

## ACCEPTED MANUSCRIPT

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

Ynto S. de Boer<sup>\*1,2</sup>, Alessio Gerussi<sup>\*3,4</sup>, Floris F. van den Brand<sup>\*1</sup>, Guan-Wee Wong<sup>2</sup>, Neil Halliday<sup>3,5</sup>, Rodrigo Liberal<sup>2</sup>, Joost P.H. Drenth<sup>6</sup>, Douglas Thorburn<sup>3</sup>, Gerd Bouma<sup>1</sup>, the Dutch Autoimmune Hepatitis Study Group (DAIHG<sup>\*\*</sup>) and Michael A. Heneghan<sup>2</sup>

1. Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers - VU University Medical Center, Amsterdam, The Netherlands

2. Institute of Liver Studies, King's College Hospital, Denmark Hill, London, London, UK

3. Sheila Sherlock Liver Centre and UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, UK

4. Department of Medicine, University of Udine, Udine, Italy

5. Institute of Immunity and Transplantation, Division of Infection and Immunity, University College London, Royal Free Hospital, London, UK

6. Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

\* These authors contributed equally, \*\* Full list of contributors at the bottom of the manuscript

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**Corresponding author and guarantor of the article:** Prof. Michael A. Heneghan, Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK. E-mail: michael.heneghan@nhs.net

\*\*Dutch Autoimmune Hepatitis Study Group collaborators: N.M. van Gerven, U. Beuers, K.J. van Erpecum, H.R. van Buuren, J.W. den Ouden, J.T. Brouwer, J.M. Vrolijk, R.C. Verdonk, B. van Hoek, G.H. Koek, M.M.J. Guichelaar, E. Bloemena, C.M.J. van Nieuwkerk, T.C.M.A. Schreuder, E.J. van der Wouden, J.J.M. van Meyel, L.C. Baak, P.H.G.M. Stadhouders, M. Klemt-Kropp, M.A.M.T. Verhagen, A. Bhalla, J.Ph. Kuijvenhoven

**Abbreviations:**

AASLD – American Association for the Study of Liver Diseases

AIH – autoimmune hepatitis

ALT – alanine-aminotransferase

ALP – alkaline phosphatase

AMA – anti-mitochondrial antibodies

ANA – anti-nuclear antibodies

AST – aspartate-aminotransferase

CI – confidence interval

EASL – European Association for the Study of the Liver

HCC – hepatocellular carcinoma

HLA – human leukocyte antigen

IAIHG – International Autoimmune Hepatitis Group

INR – international normalised ratio

IQR – interquartile range

IU/L – international units / liter

LKM-1 – liver kidney microsome-1 antibodies

MELD – model for end-stage liver disease

SD – standard deviation

SLE – systemic lupus erythematosus

SMA – anti-smooth muscle antibodies

UK – United Kingdom

USA – United States of America

## Abstract

### Introduction & Aims

Small studies have found that black patient with autoimmune hepatitis (AIH) patients 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%) ( $P<.001$ ). 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% CI, 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

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## Introduction

Autoimmune hepatitis (AIH) is a rare, chronic progressive immune-mediated inflammatory disorder of the liver that affects children and adults.<sup>1, 2</sup> It is characterized by female predominance, hypergammaglobulinaemia, circulating autoantibodies and interface hepatitis on liver biopsy.<sup>1</sup> Clinical presentation ranges from asymptomatic biochemical liver abnormalities to acute liver failure or cirrhosis.<sup>1, 3, 4</sup> Genetic factors play a role in the natural history of AIH; white *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.<sup>5-7</sup> A few studies reported differences in disease presentation and outcome between different ethnic groups.<sup>8-12</sup> In two studies from the USA and the UK 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.<sup>9, 10</sup> A recent population based analysis found that black AIH patients have a higher rate of hospitalisation and death during hospitalisation than white patients.<sup>13</sup> The difference in presentation and outcome between black and non-black patients may in part be genetically driven,<sup>14, 15</sup> 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 centre 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 multicentre study.

## Methods

Three well-established and updated databases of patients with AIH attending the Institute of Liver studies at King's College Hospital, London, between 1971 and October 2015, The Royal Free Hospital, London between 1982 and December 2016, and the multicentre Dutch Autoimmune Hepatitis Study Group cohort (DAIHG) between 2006 and August 2016 were

reviewed. The King's College Hospital and the Royal Free Hospital are 2 of 7 liver transplant centres in the UK. These liver units treat local patients, but both have large national and international referral practices.<sup>16</sup> The DAIHG cohort data was updated in 6 academic centres, including all 3 Dutch transplant centres, and 10 general referral hospitals.<sup>17</sup> 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 IAIHG scoring system (564 UK and 421 Dutch AIH patients). We compared the black and white patient groups in relation to clinical, laboratory 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.<sup>17, 18</sup> All patients were treated according to standardized protocols published previously.<sup>19, 20</sup> Response to treatment and relapse were defined in accordance with the revised IAIHG criteria.<sup>21</sup> 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 and/or by contacting the attending physicians or general practitioners/family doctors. In the Dutch cohort, liver transplantation rates were assessed by cross-checking the clinical record data with the transplantation list from all three 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 centres. In all participating transplant centres, no donor organs were obtained from executed prisoners or other institutionalized persons.

### Statistical analysis

Statistical analysis was performed with IBM SPSS 22.0 (IBM, Armonk, NY, USA) and Graphpad Prism 7.02 (GraphPad Software, La Jolla, CA, USA). Demographic and therapy-specific data are given descriptively as mean and standard deviation (SD) and median and 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  $\chi^2$ -test or Fisher's exact test. A P-value of  $<0.05$  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 black patients (12%) and 496 white patients (88%). Black patients presented at a younger age (median 38 vs 44 years,  $P=0.05$ ), but the proportion of female gender (77 vs 79%,  $P=0.7$ ), IAIHG scores (20 vs 20,  $P=0.15$ ) and transaminases (median 551 vs 586 IU/L,  $P=0.9$ ) were similar between both groups. There were no differences in ANA, SMA and LKM positivity (Supplementary table 1). Median international normalised ratios (INR) for prothrombin time levels were higher (1.3 vs 1.2,  $P=0.051$ ) and albumin levels were lower (32.1 vs 34.4 g/L,  $P=0.017$ ) in black patients. Black patients more

often had concomitant SLE (10 vs 2%,  $P=0.003$ ) than white patients, but mean IgG levels were similar (29.3 vs 27.4 g/L,  $P=0.3$ ). The median follow-up and associated treatment exposure was shorter in the black patients than white patients (103 [IQR 41-149] vs 126 months [IQR 58-202],  $P=0.01$ ). The response to standard therapy was significantly lower in black patients than white patients (81% vs 93%,  $P=0.005$ ). Twenty black patients (34%) and 144 white patients (32%) had cirrhosis at diagnosis ( $P=0.8$ ). Twelve black patients (18%) and 38 white patients (8%) underwent liver transplantation ( $P=0.007$ ). Sixteen black patients (24%) and 67 white patients (14%) reached the combined end-point of liver-transplantation and liver-related death ( $P=0.029$ ).

#### Netherlands cohort

The Netherlands cohort consisted of 20 black patients (5%) and 401 white patients (95%). Black patients presented at a younger age (median 38 vs 46 years,  $P=0.05$ ), but the proportion of female gender (75 vs 77%,  $P=0.8$ ), IAIHG scores (20 vs 18,  $P=0.3$ ) and median transaminase levels (378 vs 492 IU/L,  $P=0.2$ ) were similar between both groups. There were no differences in ANA, SMA and LKM positivity (Supplementary table 2). Median INR levels (1.1 vs 1.1,  $P=0.7$ ) and mean albumin levels (35.8 vs 36.2 g/L,  $P=0.7$ ) were similar in black and white patients respectively. Black patients more often had concomitant SLE (10 vs 2%,  $P=0.08$ ) and had higher mean IgG levels (40.4 vs 27.6 g/L,  $P=0.001$ ). Two black patients (13%) and 56 white patients (19%) had cirrhosis at diagnosis ( $P=0.7$ ). The median follow-up and associated treatment exposure were similar in both groups (181 [IQR 133-212] vs 178 [IQR 139-239] months,  $P=0.7$ ). The response to standard therapy were similar in both groups (100 vs 89%,  $P=0.1$ ). One-hundred-eighty-five (38%) patients were managed at a transplant centre, whereas the majority of patients was treated at general (37%) or non-transplant academic referral (25%) hospitals. Black patients were less often managed at transplant (3 [15%] vs 155 [39%],  $P = 0.03$ ) or academic referral centres (9 [45%] vs 256 [64%]  $P = 0.09$ ). The rate of biopsy proven cirrhosis was 19%, which was not related to transplant (21%) or academic referral centre (21%). The rates of liver-related



death and liver transplantation for all patients were significantly higher in the transplant centres than in the general and academic centres ( $n = 24$  [15%] vs  $n = 12$  [5%],  $P = <0.001$ ). No black patients and 11 white patients (3%) underwent liver transplantation ( $P=1.0$ ). Three black patients (15%) and 33 white patients (8%) reached the combined end-point of liver-transplantation and liver-related death ( $P=0.2$ ).

#### Combined cohort

The combined study population comprised of 985 patients (736 definite AIH and 259 probable AIH, black:  $n=88$ , white  $n=897$ ). Black patients presented at a younger age than white patients (median 38 vs 45 years,  $P=0.007$ ), but had similar gender distribution and IAIHG post-treatment scores as well as auto-antibody positivity (Table 1). Black patients had higher IgG levels (mean 31.0 vs 27.5 g/L,  $P=0.04$ ) and they had a higher rate of SLE (10% vs 2%,  $P<0.001$ ). 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 vs 27.4 g/L,  $P=0.055$ ). The prevalence of cirrhosis at baseline was similar in both groups (29% vs 27%,  $P=0.5$ ) in the 822 AIH patients (84%) 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 %,  $P<0.001$ ). The INR ratios were similar in black and white patients, whereas the albumin levels were significantly lower (mean 32.8 vs 35.1 g/L,  $P=0.005$ ) in black patients. Both black and white patients were treated with steroids as standard induction therapy (99% vs 95%,  $P=0.2$ ) and had a similar exposure to azathioprine as maintenance therapy (75% vs 81 %,  $P=0.2$ ; Table 2). Black patients had a similar clinical response rates to standard therapy compared to white patients (86 % vs 91 %,  $P=0.2$ ) and also comparable occurrence of at least one relapse (57% vs 50%  $P=0.3$ ). 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 ( $P=0.018$ ). Overall, there was no significant difference in the rate of use of second-line therapies (17% vs 11%,  $P=0.1$ ).

## Outcome

The median duration of follow-up in the combined cohort was shorter in the black than in the white patients (127 months [IQR: 48-173] vs 152 months [IQR: 91-223],  $P < 0.001$ ). 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 (0.018/10 patient years vs 0.022/10 patient years). The rate of transplantation and liver related death was significantly higher in the black patients in the UK cohort ( $P = 0.029$ ), 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% respectively,  $P = 0.002$ ), but overall mortality was similar between the two groups (11% vs 15%,  $P = 0.3$ ). Log-rank survival analysis showed an impaired combined transplant-free and liver-related mortality for black patients in the combined UK and Dutch cohorts ( $P < 0.001$ , Figure 2A). This was primarily driven by the UK cohort ( $P < 0.001$ , Figure 2B-C) as the Dutch cohort did not reveal a significant association ( $P = 0.4$ , Figure 2D). This suggests that the difference in rates of cirrhosis between the UK and Dutch patients (32% vs 19%,  $P < 0.001$ ) 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 [HR] 2.4, 95%-confidence interval 1.4-4.0,  $P = 0.001$ , Table 3), independent of age, cirrhosis at diagnosis and SLE in the multivariate analysis. Incorporation of transplant centre 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 centres in the UK and 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 to white

patients. We also demonstrated that these outcomes occurred in healthcare 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 to 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.<sup>22</sup> In both countries and healthcare 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 were higher in black patients compared to 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 factor, although we could not reliably address this issue. Lim et al. 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.).<sup>8</sup> These data suggest that current treatment regimens may be inadequate for black patients, and therefore future studies should focus on the development of different treatment protocols stratified according to race to address this issue.<sup>23, 24</sup> Importantly, this study also confirms that race also impacts on the natural history of the disease, since black patients were more likely to have progressive disease requiring liver transplantation. We propose three possible explanations for this outcome. Firstly, and although this was a multicentre 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, academic, and less frequently at transplant hospitals, whereas the UK cohort consisted of two transplant

centres. Nevertheless, as advanced health care is accessible through both the National Health Service in the UK 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 USA national liver transplant registries reported that black patients were listed at younger age and had higher model for end-stage liver disease (MELD) scores than other races (Table 4.).<sup>25</sup> Secondly, socioeconomic status, healthcare access and practice, and thus quality of care are factors that must be considered comparing disease characteristics and outcomes amongst different groups.<sup>26</sup> For example, mortality differences between white and African descent North Americans with cirrhosis disappear after adjustment for socio-economic status.<sup>27</sup> 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 USA (Table 4).<sup>13</sup> Unfortunately, Wen et al. did not report on the clinical characteristics, but 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. Lastly, 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 neutropaenia<sup>28</sup> and the distribution of the Duffy antigen receptor for chemokines polymorphisms<sup>29</sup> suggest that genetic influences upon the immune system differ between populations. Previous studies have shown that genetic factors influence AIH occurrence, clinical expression and response to corticosteroid

therapy,<sup>6, 14, 30</sup> 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.<sup>5</sup> Interestingly, it has been shown that HLA-DR4 is under-represented in African Americans compared to Caucasian individuals.<sup>31</sup> The current study provides no information about HLA class II genotypes, constituting one 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 categorised 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 two different countries with accessible healthcare systems.

Future, prospective studies are required to explore the mechanism, importance and generalizability of our findings. The impact of genetic variants amongst different racial groups in Europe, and globally, upon clinical outcomes would help inform our understanding of disease biology, aetiology and risk prediction. Qualitative and quantitative exploration of the experiences of patients and access to healthcare, capturing data on, amongst others, socio-economic status, race, gender and treatment centre should be performed. The proposed IAHG retrospective and prospective registries offer a suitable starting point and further focused studies will be required.<sup>23, 24</sup>

In summary, the results of this study show that the presentation and clinical course of AIH is different in black patients compared to 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.

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## Legends

### **Table 1. Baseline characteristics of black and white AIH patients**

Abbreviations: ALT, alanine-aminotransferase; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; AST, aspartate-aminotransferase; IQR, interquartile range; IU/L, international units / liter; LKM-1, liver kidney microsome-1 antibodies; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibodies.

### **Table 2. Therapy and outcome in black and white AIH patients**

Abbreviations: HCC, hepatocellular carcinoma; IQR, interquartile range.

### **Table 3. Liver transplant and/or liver related death**

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 patients (98%) with available data for included variables. Abbreviations: HR, hazard ratio; SLE, systemic lupus erythematosus.

### **Table 4. Summary of presentation, response and outcome the literature on black race and autoimmune hepatitis**

**Figure 1.** Flowchart of selection of AIH patients in the United Kingdom and the Dutch cohort. Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

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

### **Supplementary table 1. Baseline characteristics, therapy and outcome in black and white AIH patients in the UK cohort**

Abbreviations: ALT, alanine-aminotransferase; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; AST, aspartate-aminotransferase; HCC, hepatocellular carcinoma; IQR, interquartile range; IU/L, international units / liter; LKM-1, liver kidney microsome-1 antibodies; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibodies.

### **Supplementary table 2. Baseline characteristics, therapy and outcome in black and white AIH patients in the Dutch cohort**

Abbreviations: ALT, alanine-aminotransferase; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; AST, aspartate-aminotransferase; HCC, hepatocellular carcinoma; IQR, interquartile range; IU/L, international units / liter; LKM-1, liver kidney microsome-1 antibodies; SLE, systemic lupus erythematosus; SMA, anti-smooth muscle antibodies.

**Table 1 Baseline characteristics**

|  | <b>Black (n=88)</b> |          | <b>White (n=897)</b> |          | <b>p</b> | <b>n</b> |
|--|---------------------|----------|----------------------|----------|----------|----------|
| Age at diagnosis (years), median (IQR)     | 38                  | 23-49    | 45                   | 24-58    | 0.007    | 981      |
| Female, n (%)                              | 67                  | 76       | 700                  | 78       | 0.7      | 985      |
| Post-treatment IAIHG score, median (IQR)   | 20                  | 17-22    | 19                   | 17-22    | 0.9      | 941      |
| Definite post-treatment IAIHG score, n (%) | 61                  | 69       | 665                  | 74       | 0.3      | 985      |
| ALT or AST, (IU/L), median (IQR)           | 483                 | 192-932  | 539                  | 197-1080 | 0.8      | 850      |
| ALP (IU/L), median (IQR)                   | 191                 | 145-269  | 174                  | 129-252  | 0.1      | 823      |
| Bilirubin (mmol/L), median (IQR)           | 57                  | 30-165   | 55                   | 19-180   | 0.7      | 810      |
| Creatinin (umol/L), median (IQR)           | 72                  | 62-89    | 73                   | 63-85    | 0.9      | 597      |
| INR, median (IQR)                          | 1.2                 | 1.1-1.6  | 1.2                  | 1.0-1.4  | 0.082    | 634      |
| Albumin (g/L), mean (range)                | 32.8                | 16-46    | 35.1                 | 15-55    | 0.005    | 762      |
| Peak IgG (g/L), mean (range)               | 31.0                | 4.6-91.1 | 27.5                 | 4.8-89.5 | 0.043    | 748      |
| ANA positivity =>1:40, n (%)               | 58                  | 68       | 572                  | 69       | 0.8      | 909      |
| SMA positivity =>1:40, n (%)               | 47                  | 55       | 478                  | 60       | 0.4      | 890      |
| LKM-1 positivity =>1:40, n (%)             | 4                   | 5        | 44                   | 6        | 0.8      | 807      |
| AMA positivity =>1:80, n (%)               | 2                   | 2        | 30                   | 4        | 0.8      | 924      |
| SLE, n (%)                                 | 9                   | 10       | 19                   | 2        | <0.001   | 985      |
| Thyroid disease, n (%)                     | 8                   | 9        | 127                  | 14       | 0.2      | 983      |
| Hypothyroidism, n (%)                      | 7                   | 10       | 93                   | 11       |          |          |
| Hyperthyroidism, n (%)                     | 1                   | 2        | 28                   | 3        |          |          |
| Coeliac disease, n (%)                     | 0                   | 0        | 8                    | 1        | 1.0      | 983      |
| Acute presentation (< 6 months), n (%)     | 54                  | 68       | 375                  | 61       | 0.3      | 693      |
| Cirrhosis at diagnosis, n (%)              | 22                  | 29       | 200                  | 27       | 0.6      | 822      |
| Managed at transplant centre               | 71                  | 81       | 651                  | 73       | 0.1      | 985      |

**Table 2 Therapy and outcome**

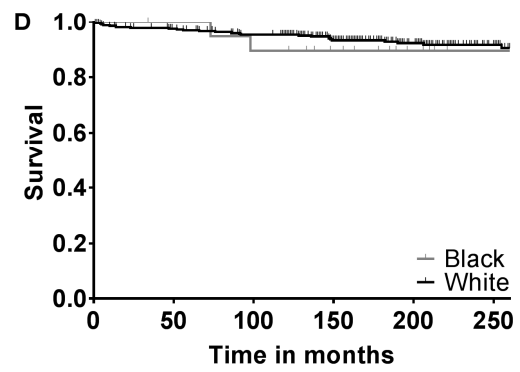
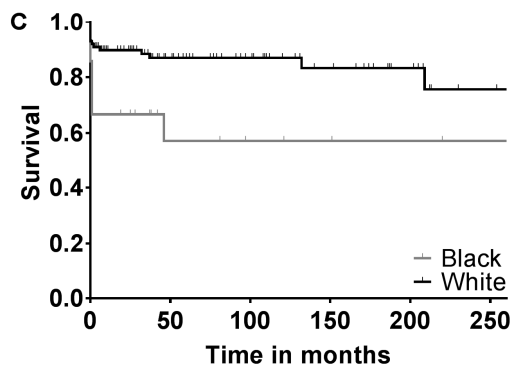
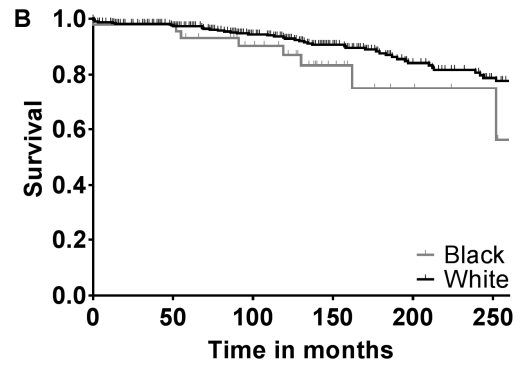
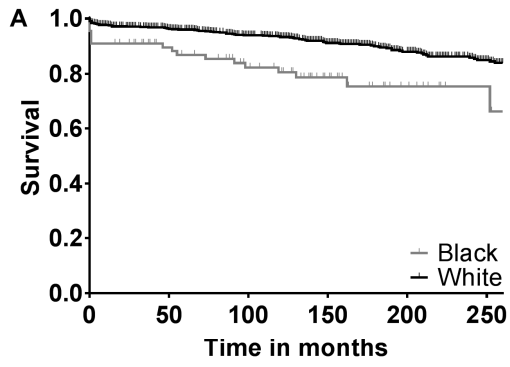
|   | <b>Black (n=88)</b> |     | <b>White (n=897)</b> |     | <b>p</b> | <b>n</b> |
|---|---------------------|-----|----------------------|-----|----------|----------|
| Therapy   |                     |     |                      |     |          |          |
| Steroids for induction, n (%)                     | 84                  | 99  | 841                  | 95  | 0.2      | 971      |
| Azathioprine for maintenance, n (%)               | 59                  | 75  | 703                  | 81  | 0.2      | 949      |
| Ever on second-line therapy, n (%)                | 13                  | 17  | 96                   | 11  | 0.1      | 953      |
|   |                     |     |                      |     |          |          |
| Response to standard therapy, n (%)               | 67                  | 86  | 773                  | 91  | 0.1      | 928      |
| Relapse, n (%)                                    | 39                  | 57  | 405                  | 50  | 0.3      | 875      |
| Number of relapses, median (IQR)                  | 1                   | 0-3 | 1                    | 0-2 | 0.018    | 815      |
|   |                     |     |                      |     |          |          |
| Outcome   |                     |     |                      |     |          |          |
| HCC, n (%)  | 2                   | 2   | 23                   | 3   | 1.0      | 973      |
| Liver transplantation, n (%)                      | 12                  | 14  | 49                   | 6   | 0.002    | 984      |
| Livertransplantation + Liver related death, n (%) | 19                  | 22  | 100                  | 11  | 0.004    | 985      |
| Overall death, n (%)                              | 10                  | 11  | 138                  | 15  | 0.3      | 985      |

**Table 3 Survival: Transplant and liver-related death**

|                        | UK cohort     |        | Dutch cohort  |       | Overall       |        |               |        |
|------------------------|---------------|--------|---------------|-------|---------------|--------|---------------|--------|
|                        | Univariate    |        | Univariate    |       | Univariate    |        | Multivariate  |        |
|                        | HR (95-CI)    | p      | HR (95-CI)    | p     | HR (95-CI)    | p      | HR (95-CI)    | p      |
| Black                  | 2.5 (1.5-4.4) | 0.001  | 1.6 (0.5-5.4) | 0.4   | 2.5 (1.6-4.2) | <0.001 | 2.4 (1.4-4.0) | 0.001  |
| Age                    | 1.0 (1.0-1.0) | 0.6    | 1.0 (1.0-1.0) | 0.012 | 1.0 (1.0-1.0) | 0.14   | 1.0 (1.0-1.0) | 0.049  |
| Gender                 | 0.9 (0.5-1.5) | 0.7    | 1.2 (0.5-2.7) | 0.7   | 0.9 (0.6-1.5) | 0.9    |               |        |
| Cirrhosis at diagnosis | 3.3 (2.1-5.1) | <0.001 | 1.8 (0.9-3.9) | 0.12  | 3.2 (2.2-4.5) | <0.001 | 3.1 (2.1-4.4) | <0.001 |
| SLE                    | 2.7 (1.2-6.2) | 0.02   | 1.0 (0.1-7.8) | 0.9   | 2.3 (1.1-4.9) | 0.035  | 1.9 (0.9-4.3) | 0.12   |

| Authors (y)                        | Population <i>n</i>   | Presentation  | Response   | Outcome   | Study setting                                       |
|------------------------------------|---|---|--|---|---|
| Lim et al. (2001) <sup>8</sup>     | 27 African Americans 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 whites  | One tertiary referral center                        |
| Zolfino et al. (2002) <sup>9</sup> | 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 Arabic patient. Partial or no response in 7 patients | Death or transplantation in 2 African (33%), 4 Asian (80%) and 1 (100%) Arabic patient  | One tertiary referral center                        |
| Verma et al. (2007) <sup>10</sup>  | 37 Black and 64 non-black AIH patients  | Cirrhosis and acute presentation were more common in black than nonblack patients (57% vs 38% and 76% vs 50%, respectively) | Black patients were less likely to achieve remission (76%) than nonblack patients (90%)            | Black patients had a 4-fold higher mortality rate and were referred two times more often for transplantation than nonblack patients | One tertiary referral center                        |
| Wen et al. (2018) <sup>13</sup>    | Hospitalizations for AIH in 1.463 black and 4.666 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  | US Nationwide Inpatient Sample database (2008-2012) |
| Webb et al. (2018) <sup>16</sup>   | 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                              | US and UK transplantation centers (1995-2014)       |
| Lee et al. (2018) <sup>12</sup>    | 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 ten times higher odds of AIH than whites                               | One tertiary referral center                        |





**What You Need to Know**

## Background

- Autoimmune hepatitis 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 healthcare outcomes

## Findings

- Autoimmune hepatitis patients of black background present at an earlier age than white patients
- Black autoimmune hepatitis 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 autoimmune hepatitis patients may need a more stringent therapeutic approach in order to prevent worse liver-related outcomes.



**Table 1. Baseline characteristics, therapy and outcome of UK AIH patients**

|  | Black (n=68) |          | White (n=496) |          | p     | n   |
|--|--------------|----------|---------------|----------|-------|-----|
| Age at diagnosis (years), median (IQR)             | 38           | 22-48    | 44            | 22-58    | 0.05  | 560 |
| Female, n (%)                                      | 52           | 77       | 391           | 79       | 0.7   | 564 |
| Post-treatment IAIHG score, median (IQR)           | 20           | 17-22    | 20            | 18-23    | 0.15  | 520 |
| ALT or AST, (IU/L), median (IQR)                   | 551          | 209-1044 | 586           | 199-1125 | 0.9   | 517 |
| ALP (IU/L), median (IQR)                           | 194          | 146-291  | 183           | 136-273  | 0.3   | 501 |
| Bilirubin (mmol/L), median (IQR)                   | 75           | 31-184   | 69            | 21-225   | 0.9   | 506 |
| Creatinin (umol/L), median (IQR)                   | 75           | 65-89    | 73            | 63-88    | 0.5   | 313 |
| INR, median (IQR)                                  | 1.3          | 1.1-1.6  | 1.2           | 1.0-1.5  | 0.051 | 428 |
| Albumin (g/L), mean (range)                        | 32.1         | 16-45    | 34.4          | 20-55    | 0.017 | 480 |
| Peak IgG (g/L), mean (range)                       | 29.3         | 4.6-71.7 | 27.4          | 4.8-89.7 | 0.3   | 525 |
| ANA positivity =>1:40, n (%)                       | 42           | 65       | 312           | 65       | 0.9   | 542 |
| SMA positivity =>1:40, n (%)                       | 40           | 61       | 299           | 63       | 0.7   | 538 |
| LKM-1 positivity =>1:40, n (%)                     | 3            | 5        | 29            | 6        | 0.8   | 545 |
| AMA positivity =>1:80, n (%)                       | 2            | 3        | 19            | 4        | 1.0   | 545 |
| SLE, n (%)   | 7            | 10       | 11            | 2        | 0.003 | 564 |
| Thyroid disease, n (%)                             | 7            | 10       | 93            | 19       | 0.092 | 562 |
| Hypothyroidism, n (%)                              | 7            | 10       | 69            | 17       |       | 562 |
| Hyperthyroidism, n (%)                             | 0            | 0        | 19            | 5        |       | 562 |
| Coeliacs disease, n (%)                            | 0            | 0        | 6             | 1        | 1.0   | 562 |
| Acute presentation (< 6 months), n (%)             | 43           | 67       | 267           | 58       | 0.2   | 521 |
| Cirrhosis at diagnosis, n (%)                      | 20           | 34       | 144           | 32       | 0.8   | 509 |
| Managed at transplant centre                       | 68           | 100      | 496           | 100      | NA    | 564 |
| Therapy  |              |          |               |          |       |     |
| Steroids for induction, n (%)                      | 65           | 100      | 480           | 99       | 1.0   | 551 |
| Azathioprine for maintenance, n (%)                | 41           | 70       | 375           | 80       | 0.064 | 528 |
| Ever on second-line therapy, n (%)                 | 12           | 21       | 63            | 13       | 0.13  | 532 |
| Response to standard therapy, n (%)                | 47           | 81       | 424           | 93       | 0.005 | 514 |
| Relapse, n (%)                                     | 25           | 52       | 191           | 46       | 0.4   | 462 |
| Number of relapses, median (IQR)                   | 1            | 0-3      | 0             | 0-1      | 0.09  | 403 |
| Outcome  |              |          |               |          |       |     |
| HCC, n (%)   | 2            | 3        | 21            | 4        | 1.0   | 552 |
| Liver transplantation, n (%)                       | 12           | 18       | 38            | 8        | 0.007 | 563 |
| Liver transplantation + Liver related death, n (%) | 16           | 24       | 67            | 14       | 0.029 | 564 |
| Overall death, n (%)                               | 5            | 7        | 75            | 15       | 0.09  | 564 |

**Table 2. Baseline characteristics, therapy and outcome in the Dutch cohort**

|   | <b>Black (n=20)</b> |           | <b>White (n=401)</b> |          | <b>p</b> | <b>n</b> |
|---|---------------------|-----------|----------------------|----------|----------|----------|
| Age at diagnosis (years), median (IQR)            | 38                  | 27-50     | 46                   | 28-59    | 0.2      | 421      |
| Female, n (%)                                     | 15                  | 75        | 309                  | 77       | 0.8      | 421      |
| Post-treatment IAIHG score, median (IQR)          | 20                  | 16-22     | 18                   | 16-21    | 0.3      | 421      |
| ALT or AST, (IU/L), median (IQR)                  | 378                 | 166-526   | 492                  | 185-1604 | 0.2      | 333      |
| ALP (IU/L), median (IQR)                          | 170                 | 87-212    | 158                  | 117-236  | 0.8      | 322      |
| Bilirubin (mmol/L), median (IQR)                  | 39                  | 17-131    | 40                   | 14-128   | 0.9      | 304      |
| Creatinin (umol/L), median (IQR)                  | 62                  | 55-78     | 73                   | 63-83    | 0.2      | 292      |
| INR, median (IQR)                                 | 1.1                 | 1.1-1.2   | 1.1                  | 1.0-1.3  | 0.7      | 206      |
| Albumin (g/L), mean (range)                       | 35.8                | 26-46     | 36.2                 | 15-54    | 0.8      | 282      |
| Peak IgG (g/L), mean (range)                      | 40.4                | 19.6-91.1 | 27.6                 | 7.4-75.3 | 0.001    | 223      |
| ANA positivity =>1:40, n (%)                      | 16                  | 80        | 260                  | 75       | 0.8      | 367      |
| SMA positivity =>1:40, n (%)                      | 7                   | 35        | 179                  | 54       | 0.1      | 352      |
| LKM-1 positivity =>1:40, n (%)                    | 1                   | 6         | 15                   | 6        | 1.0      | 262      |
| AMA positivity =>1:80, n (%)                      | 0                   | 0         | 11                   | 3        | 1.0      | 379      |
| SLE, n (%)  | 2                   | 10        | 8                    | 2        | 0.08     | 421      |
| Thyroid disease, n (%)                            | 1                   | 5         | 34                   | 9        | 1.0      | 421      |
| Hypothyroidism, n (%)                             | 0                   | 0         | 24                   | 6        |          | 421      |
| Hyperthyroidism, n (%)                            | 1                   | 5         | 10                   | 3        |          | 421      |
| Coeliacs disease, n (%)                           | 0                   | 0         | 2                    | 1        | 1.0      | 412      |
| Acute presentation (< 6 months), n (%)            | 11                  | 69        | 108                  | 69       | 1.0      | 172      |
| Cirrhosis at diagnosis, n (%)                     | 2                   | 13        | 56                   | 19       | 0.7      | 313      |
| Managed at transplant centre, n (%)               | 3                   | 15        | 155                  | 39       | 0.03     | 421      |
| Therapy   |                     |           |                      |          |          |          |
| Steroids for induction, n (%)                     | 19                  | 95        | 361                  | 90       | 0.7      | 420      |
| Azathioprine for maintenance, n (%)               | 18                  | 90        | 328                  | 82       | 0.5      | 421      |
| Ever on second-line therapy, n (%)                | 1                   | 5         | 33                   | 8        | 1.0      | 421      |
| Response to standard therapy, n (%)               | 20                  | 100       | 349                  | 89       | 0.1      | 414      |
| Relapse, n (%)                                    | 14                  | 70        | 214                  | 55       | 0.2      | 413      |
| Number of relapses, median (IQR)                  | 2                   | 0-4       | 1                    | 0-2      | 0.038    | 412      |
| Outcome   |                     |           |                      |          |          |          |
| HCC, n (%)  | 0                   | 0         | 2                    | 1        | 1.0      | 421      |
| Liver transplantation, n (%)                      | 0                   | 0         | 11                   | 3        | 1.0      | 421      |
| Livertransplantation + Liver related death, n (%) | 3                   | 15        | 33                   | 8        | 0.2      | 421      |
| Overall death, n (%)                              | 5                   | 25        | 63                   | 16       | 0.3      | 421      |