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Race/Ethnicity is an Independent Risk Factor for Autoimmune Hepatitis Among the San Francisco Underserved

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Abstract

Although autoimmune hepatitis (AIH) is more common in women and affects people of all races/ethnicities, there is currently limited information regarding the relationship between race/ethnicity and AIH, especially in the context of underserved populations. We aim to evaluate the relationship between race/ethnicity and AIH and better characterize its clinical features among different racial groups. We conducted a 15-year retrospective analysis, from January 2002 to June 2017, of patients seen at Zuckerberg San Francisco General Hospital (ZSFG). Sixty-three AIH patients and 2049 non-AIH controls were eligible for the study. The main predictor of interest was race/

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Disclosure Statement

1. Author's declaration of personal interests:

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ethnicity, and the main outcome of interest was AIH diagnosis; other secondary measures recorded include clinical features such as ALT, bilirubin, and biopsy fibrosis at presentation. In a multivariable model adjusting for age and sex, we found that black (OR 9.6, 95% CI 1.8 to 178), Latino (OR 25.0, 95% CI 5.3 to 448), and Asian/Pacific Islander (API) (OR 10.8, 95% CI 2.2 to 196) race/ethnicity were associated with increased odds of an AIH diagnosis compared to the white reference group. Among people of color with AIH, there were no significant differences in baseline ALT (p = .45), total bilirubin at presentation (p = .06), fibrosis at presentation (p = .74), and hospitalization (p = .27). Race/ethnicity is an independent risk factor for AIH. The clinical features of AIH did not differ significantly among black, Latino, and API patients.

Keywords

autoimmune liver disease; liver; outcomes research; liver fibrosis; race/ethnicity

Introduction

Autoimmune hepatitis (AIH) is an inflammatory liver disease with varied clinical presentations that predominantly affects women.[1,2] Accurate diagnosis of AIH is critical, as prompt treatment can prevent the progression of fibrosis and the need for liver transplantation.[3–5] The importance of treatment is highlighted by the 10-year survival rate of less than 30% without treatment, compared to the 10-year transplant-free survival rate of 85–95% with treatment.[6–8] Lifelong treatment is often necessary, as relapse rates are approximately 80% within 3 years of therapy withdrawal.[9]

However, these data are largely based on studies of white patients in quaternary health settings; there are limited studies of AIH in patients of other races/ethnicities, especially in low-resource settings.[10–13] Compared to white patients, black patients appear to have a more severe disease course in the setting of AIH.[12,14,15] In addition, the prevalence of AIH may vary by race/ethnicity. In a study from New Zealand the ethnicity-specific prevalence of AIH was higher among whites than Maori, Pacific Islanders, and Asians.[16] Epidemiologic studies have also suggested that the incidence and prevalence of AIH are lower in the Asia-Pacific region than in Europe and America.[17]

Examining AIH in various populations will allow for better understanding of critical differences in prevalence, incidence and severity of the disease.[18,19] However, it remains to be determined if AIH is more common in certain racial/ethnic groups in the United States. Moreover, as underserved populations are especially at risk for health disparities and include a high prevalence of racial/ethnic minorities, a letter understanding of the relationship between race/ethnicity and AIH is an important step in reducing related health disparities in this population.

In this study, we examined AIH in the patient population at the Zuckerberg San Francisco General Hospital (ZSFG). Based on observed clinical trends, we determined whether the risk of AIH differed among the ethnic groups served by the hospital. Our aims were to determine if race/ethnicity is a risk factor for AIH and to determine if the presentation and clinical course of AIH differ by race/ethnicity.

Methods

This was a single-center analysis of 63 AIH patients and 2,049 control patients at ZSFG, an urban county hospital that serves indigent and under-resourced communities in San Francisco. The center is racially and ethnically diverse, with less than a quarter of the patient population identifying as white.[20] The electronic health record was searched retrospectively using ICD-9 and ICD-10 codes for AIH from January 2002 to June 2017. Patients were also tracked prospectively as they presented to the Liver Clinic at ZSFG, from 2013–2017. To be included in our study, patients needed one of the following: 1) ICD code for AIH and receiving treatment for AIH, or 2) a simplified AIH score[21] or International Autoimmune Hepatitis Group (IAIHG) score[22] of “probable” or “definite”, or 3) a clinical diagnosis of AIH documented in the medical record by a gastroenterologist/hepatologist. Unmatched controls were obtained by randomly selecting patients 18 years and older, seen at ZSFG between 2002–2017, who did not have an ICD code for AIH.

Study data were collected and managed using REDCap electronic data capture tools hosted at UCSF.[23] This study was approved by the Institutional Review Board at UCSF.

The primary predictor variable was race/ethnicity and was reported in the electronic medical records as white, black, Latino, Asian-Pacific Islander, and Other. The primary outcome variable was a diagnosis of AIH as defined above. Secondary outcome variables were concomitant autoimmune disorders, liver histology and laboratory results at diagnosis, AIH medications received, treatment response, hospitalization for AIH, liver transplant, and death. Antinuclear antibody (ANA) titers were determined by the ZSFG clinical laboratory by indirect fluorescent antibody assay using human epithelial (HEp-2) cells. Anti-smooth muscle antibodies (ASMA) and antimitochondrial antibodies (AMA) were sent for analysis by Associated Regional and University Pathologists (ARUP) Laboratories. Both ASMA levels and AMA levels were determined by ELISA. Because many patients were not tested for liver kidney microsome (LKM) antibodies, this variable was not included in the analysis. Concomitant autoimmune disorders were extracted from the patients’ past medical history in the EMR. Liver histology results were obtained from clinical notes or the pathology report, if available. ZSFG pathologists use a 4-point system for inflammation and fibrosis (the Batts-Ludwig system) and a 3-point scale for steatosis. The presence of cirrhosis at the time of presentation was based on histology and clinician assessment per the patients’ medical record. Decompensation was defined as the presence of hepatic encephalopathy, ascites, variceal bleeding, or hepatocellular carcinoma. AIH treatment response was evaluated by ALT six months after treatment initiation. The date of treatment initiation was determined by review of the electronic medical record. All lab values were recorded within 3 months before or after diagnosis, with pre-treatment values closest to diagnosis preferred. To compare clinical presentation and outcomes among races/ethnicities, we excluded patients with missing data.

Time to steroid discontinuation was measured from the time of steroid prescription to time of discontinuation, including patients who self-discontinued their medications. Discontinuation was considered an event for patients who had discontinued steroids for at

least 6 months (rather than a temporary discontinuation). Patients were censored if they were lost to follow-up or still taking steroids up to June 2017.

Hospitalization for AIH was defined as an admission for a complication of AIH, including elevated liver enzymes, jaundice, or hepatic decompensation.

All statistical analyses were performed using R[24] in RStudio (version 1.0.136). For the primary analysis of race/ethnicity and AIH diagnosis, a univariate chi-squared test assessed differences between the racial/ethnic composition of AIH patients and control patients. Multivariable logistic regression was then used to determine the effect of race/ethnicity as a predictor of AIH diagnosis, controlling for age and sex. For the secondary analysis of clinical data among different racial/ethnic groups, the nonparametric Kruskal-Wallis test and Fisher's exact tests were used. Log-rank tests were performed for time-to-event analyses. For each outcome variable, patients were excluded if the required data for the analysis were not available.

Results

A total of 67 patients with AIH received care at ZSFG from January 2003 to June 2017. Four were excluded for inadequate or incorrect diagnostic information, leaving 63 patients available for the primary analysis.

The AIH cohort had an average age of 49.2 years (18 – 91 years old) and was 84.1% female (Table 1). Latinos were the largest group, comprising 46% of the AIH patients, while whites comprised only 6%. The median ALT for all patients at presentation was 201 U/L, median bilirubin was 0.9 mg/dL, IgG was 2060 mg/dL, and INR was 1.2. Index liver biopsy information was available for 45 patients (71%). For 2 patients, only fibrosis information was available through clinic notes noting biopsies from outside hospitals. For 7 patients with fibrosis staging, the pathology report did not include a specific inflammation grade. Mean biopsy inflammation and fibrosis using the Batts-Ludwig scoring system were 2.8 and 2.1, respectively. Six patients (13% of all biopsies graded for steatosis) had evidence of steatosis (> 0 on 3-point scale) on the initial biopsy. Sixteen patients (25%) had evidence of cirrhosis upon diagnosis of AIH. ANA was positive in 49 patients (77%). Twenty-seven AIH patients (43%) had at least 1 concomitant autoimmune disorder; of these 27 patients, 12 patients (44%) had primary biliary cholangitis, 8 patients (30%) had systemic lupus erythematosus, 5 patients (19%) had rheumatoid arthritis, 4 patients (15%) had Sjögren's syndrome, 2 patients (7%) had ulcerative colitis (UC), 2 patients (7%) had antiphospholipid antibody syndrome, 1 patient (4%) had type 1 diabetes mellitus, and 1 patient (4%) had immune thrombocytopenic purpura. Of the two patients with UC, neither had evidence of bile duct involvement on radiological assessment but one had a diagnosis of primary sclerosing cholangitis. Thirty-seven (59%) patients received prednisone and azathioprine for induction. Eight patients (13%) received mycophenolate mofetil and 4 patients (6%) received budesonide. Twelve patients received no treatment: 10 patients had other diagnoses or risks that did not indicate AIH-specific treatment and 2 patients were not treated because they had normal LFTs. 8 patients had no available data. Approximately six months after treatment initiation, the median ALT was 38. Twenty-three out of 63 patients (37%) were hospitalized for AIH over

230.5 total years of follow-up. Eleven patients (17%) experienced a decompensating event. Seventeen patients (27%) of patients were taking corticosteroids 1 year after initiation of treatment, but the majority (94%) of these patients were on budesonide or prednisone 10 mg daily or less. Two patients (3%) had a liver transplant, and 1 patient (2%) died of a liver-related complication.

Univariate analysis of our primary outcome showed a significant difference in the racial/ethnic distribution of those diagnosed with AIH compared to controls from the overall population who received medical care at ZSFG ($p < .01$) (Table 1). Multivariable analysis of the primary outcome found that the odds of being diagnosed with AIH is significantly higher in people of color than white patients in our hospital system, i.e. race/ethnicity was a significant variable in the logistic regression of factors associated with an AIH diagnosis (Wald test, $p < .01$) (Table 2). After controlling for age and sex, the odds of a diagnosis of AIH were significantly higher when the patients were black, Latino, or Asian Pacific Islander compared to white. The odds of a diagnosis of AIH were 9.6 times higher for black patients compared to white patients (95% CI 1.8 to 178, $p = .03$). The odds of a diagnosis of AIH were 25.0 times greater for Latino patients compared to white patients (95% CI 5.3 to 448, $p < .01$). The odds of an AIH diagnosis were 10.8 times greater for API patients compared to white patients (95% CI 2.2 to 196, $p = .02$).

For the secondary analysis, white ($n = 4$) and “Other” ($n = 1$) AIH patients were excluded due to small sample size and missing data. Only one white patient and one “Other” patient had available data. Therefore, 58 patients were included in the secondary analysis of clinical data (Table 3). Individual patients with missing data were also excluded from the relevant analyses.

At presentation, the median ALT among black, Latino, and API AIH patients were 308, 182, and 189 U/L respectively ($p = .45$) (Fig. 1). Treatment response was not clearly different between racial/ethnic groups, as the ALT level six months after treatment initiation were similar among all groups ($p = .20$) (Fig. 1). Median total bilirubin at presentation among black, Latino, and API AIH patients were 2.8, 0.7, and 1.1 mg/dL respectively ($n = 52$, $p = .06$) (Fig. 2). Liver biopsy inflammation and fibrosis did not differ significantly by race/ethnicity ($p = .09$, $p = .74$ respectively) (Fig. 3). There was no significant difference in time to steroid discontinuation by race/ethnicity ($p = 1.00$) (Fig. 4).

There was no significant difference in hospitalizations among black, Latino, and API patients with AIH ($p = .27$). Medication regimens also did not differ significantly among the groups, as measured by budesonide and mycophenolate mofetil use ($p = 0.85$, $p = 0.11$ respectively). The number of decompensating events was similar between racial/ethnic groups ($p = .65$) (Table 3).

Black patients with AIH had higher median values for ALT, IgG, INR, total bilirubin, biopsy inflammation at presentation, and had a greater percentage of patients hospitalized and with other concomitant autoimmune diseases, though none of these differences were statistically significant (Table 3). These values and all other clinical features, treatment, and outcome variables analyzed did not differ significantly by race/ethnicity.

Discussion

In this study, the racial/ethnic composition of the AIH cohort was significantly different from that of the hospital system. Our main result suggests that among the underserved, AIH disproportionately occurs in people of color. Though AIH affecting people of color has been described in other centers, this is the first study to use a control group to verify this phenomenon. Our findings are in line with previous studies describing large populations of Latino, Asian, and black patients with AIH.[11,14,25–27] However, this contrasts with a New Zealand study which found a higher ethnicity-specific incidence in Caucasians than Asian and Maori populations.[16] Though our findings show no significant differences in the clinical course of AIH among black, Latino, and API patients, we note several interesting observations. First, the trend of black patients having more severe (but not statistically significant) presentations corroborate other studies.[12,14,15,28] Second, we found that 31% (n = 9) of our Latino cohort had cirrhosis at presentation, while a prior cohort from Mexico found that 56% of their patients had cirrhosis at presentation.[29] Latinos have been found to be less likely to achieve remission and have poorer outcomes, which our results do not replicate.[26,30] Third, bilirubin was the only finding approaching significance in our study, similar to a single-center study from New York, where total bilirubin was significantly higher among black patients with AIH.[15] Prior regional multiethnic AIH cohorts have conflicting results, but generally find a trend towards poorer outcomes in people of color.[31,27,32] Many prior studies have focused on comparing two ethnic groups, with white patients as the reference. [14,27] Importantly, several communities of color are represented in our study. It is interesting that while we found AIH is diagnosed more in people of color, there were no significant differences when the clinical course and outcomes between people of color are compared. This may speak to equality of health care quality and access in our safety-net system.

Our observed relationship between race/ethnicity and AIH is in accord with the larger narrative of other autoimmune conditions preferentially affecting people of color. For example, Black and Latino patients are at higher risk for both systemic lupus erythematosus and rheumatoid arthritis, and experience a more severe manifestation of these diseases.[33–37] Some studies have suggested a link between genes and autoimmune susceptibility in certain ethnic groups.[38–40] However, the health disparities that exist in different autoimmune diseases are not known to be secondary to genetic differences, and are likely due to the many race- and socioeconomic-based disparities often faced by these patients.[34,41] Even after controlling for socioeconomic factors, race/ethnicity is found to be a key determinant of poor outcomes in autoimmune diseases.[36] There are important differences in incidence, prevalence and outcomes of autoimmune diseases in communities of color, and our study echoes the importance of increasing representation of people of color in future studies and trials.[42,43]

The main strengths of our study are the racial/ethnic diversity of our population, the fact that our cohort reflects a vulnerable and underserved population, and the large control group of non-AIH patients available for comparison. Epidemiologic studies have provided limited data about the prevalence of AIH in different ethnic groups, particularly in Latino populations, whereas our patient population is predominantly Latino. Additionally, there are

currently no studies that analyze variation in response to treatment between different racial/ethnic groups as we do.[25]

The main limitation of our study was sample size; we excluded the few white patients in our cohort from our analysis of presentation and outcomes because of missing data. As a result, we could not compare the clinical features of AIH in people of color to white patients, as has been done in other studies. We did not detect any statistically significant differences among blacks, Latinos, and APIs with regards to presentation, treatment, and outcomes. This negative result may be due to a lack of statistical power. Additionally, this study was performed at a single center, and may be difficult to generalize to other populations. Another limitation of our study was its retrospective design involving the evaluation of multiple measurements, increasing the likelihood of a Type I error, though none of our secondary analyses show significant findings. Race/ethnicity is captured by self-report in electronic medical records by other autoimmune studies assessing racial disparities.[31,44] However, these broad, pre-defined categories preclude a more nuanced analysis of patients who are not perfectly described by the given racial/ethnic choices. Nevertheless, this is the largest study to date assessing AIH among an ethnically diverse, underserved population with a large control group for comparison.

Implicit or unconscious bias very possibly underlies many health disparities, including those seen in AIH.[45] However, we were not able to detect a significant difference in time from diagnosis to treatment initiation among racial/ethnic groups (Table 3). It should be noted that our study and other studies on race/ethnicity may be difficult to interpret collectively due to the broad diversity of people grouped together in racial/ethnic categories. Autoimmune diseases have varying presentations and outcomes not only between but also within racial groups.[46]

Our findings suggest AIH to be more common in people of color, especially in the underserved/vulnerable community of San Francisco. Future studies should investigate the possible reasons behind this health disparity in AIH, as a better understanding of these differences could lead to improved AIH diagnosis and management.

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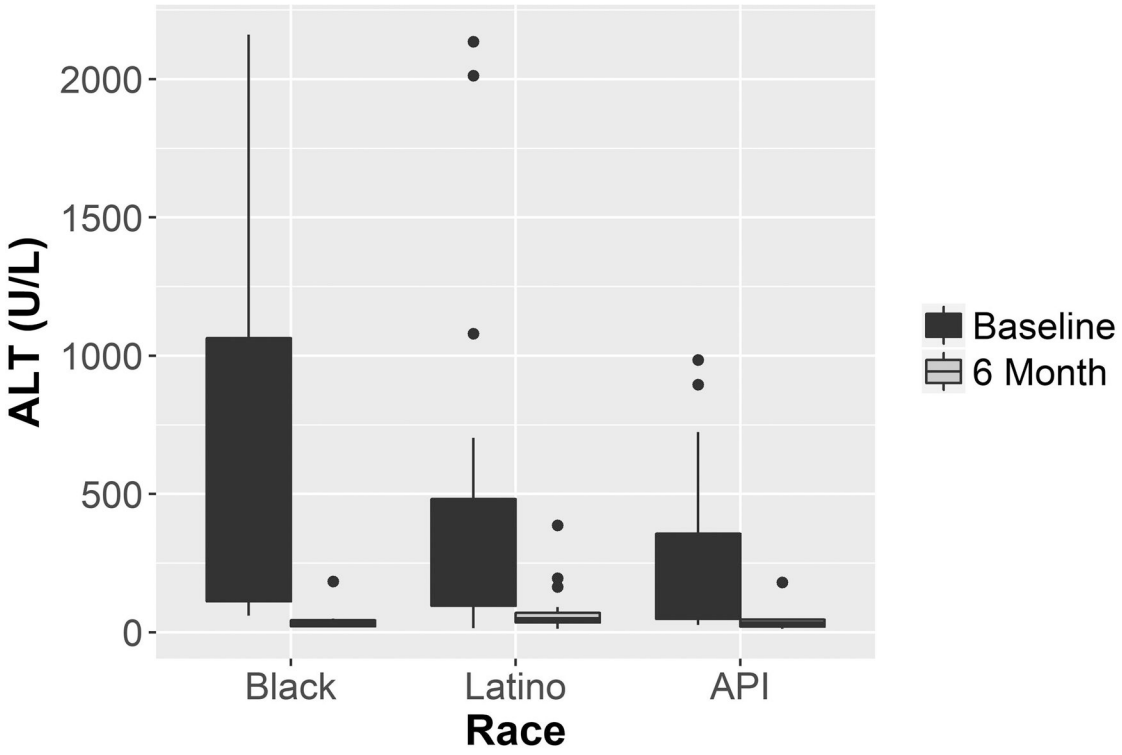

Fig. 1.

ALT at time of diagnosis and at 6 months after treatment for black, Latino, and API AIH patients (n = 52). White and other patients not shown due to small numbers. Boxplot shows 1st quartile, median, and 3rd quartile, while the lines represent the range of values excluding outliers.

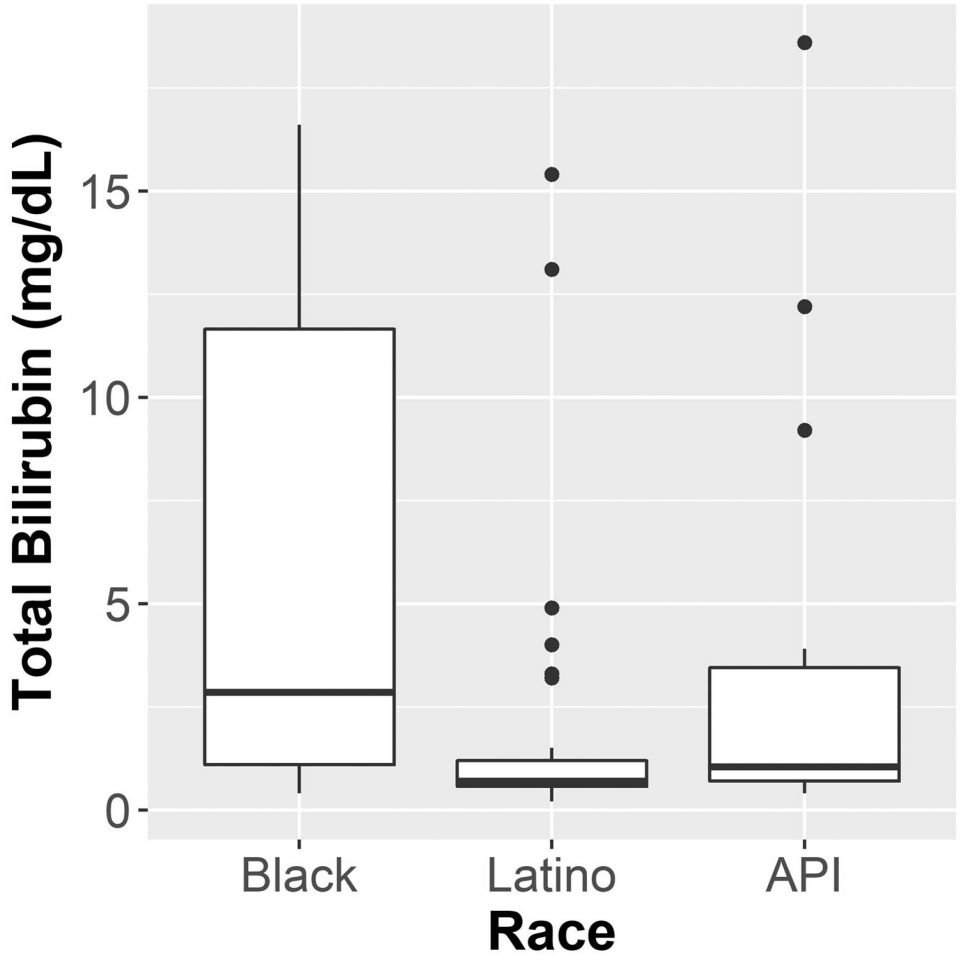

Fig. 2.
Total bilirubin at time of diagnosis for black (n = 8), Latino (n = 28) and API (n = 16) patients with AIH. Boxplot as in Fig. 1.

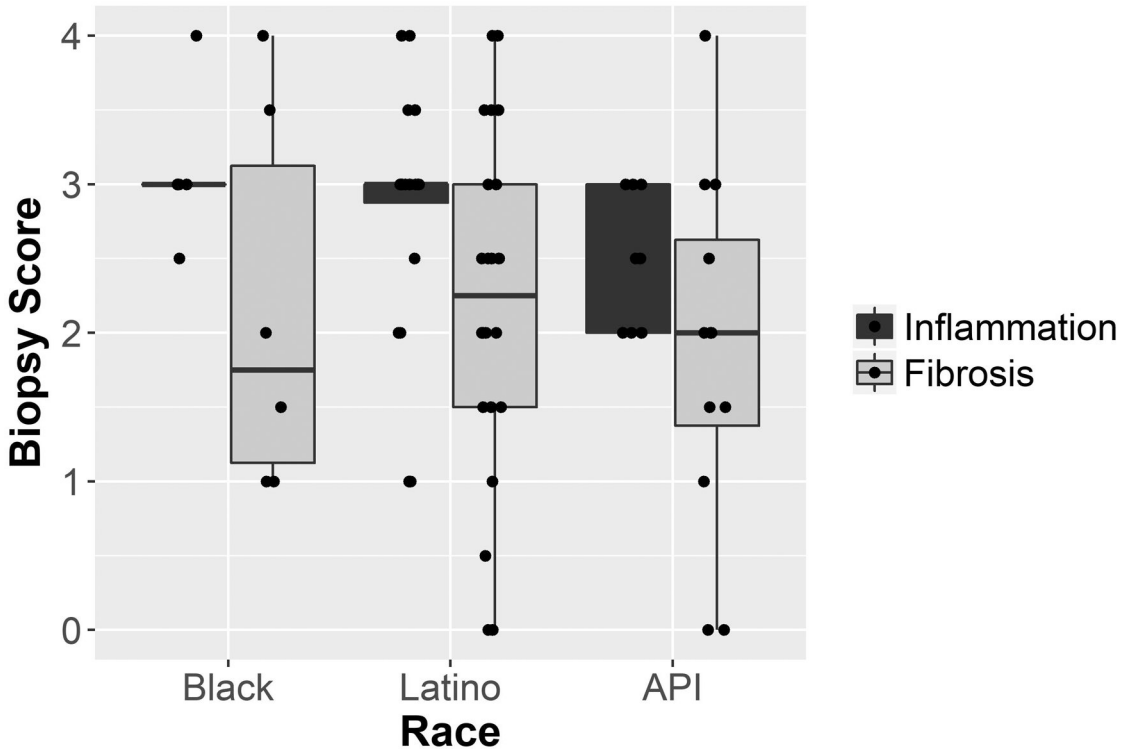

Fig. 3.

Biopsy data showing inflammation grade (n = 35) and fibrosis stage (n = 44) for black, Latino, and API AIH patients. Individual patients' values are overlaid on top of the box plots. Boxplot as in Fig. 1.

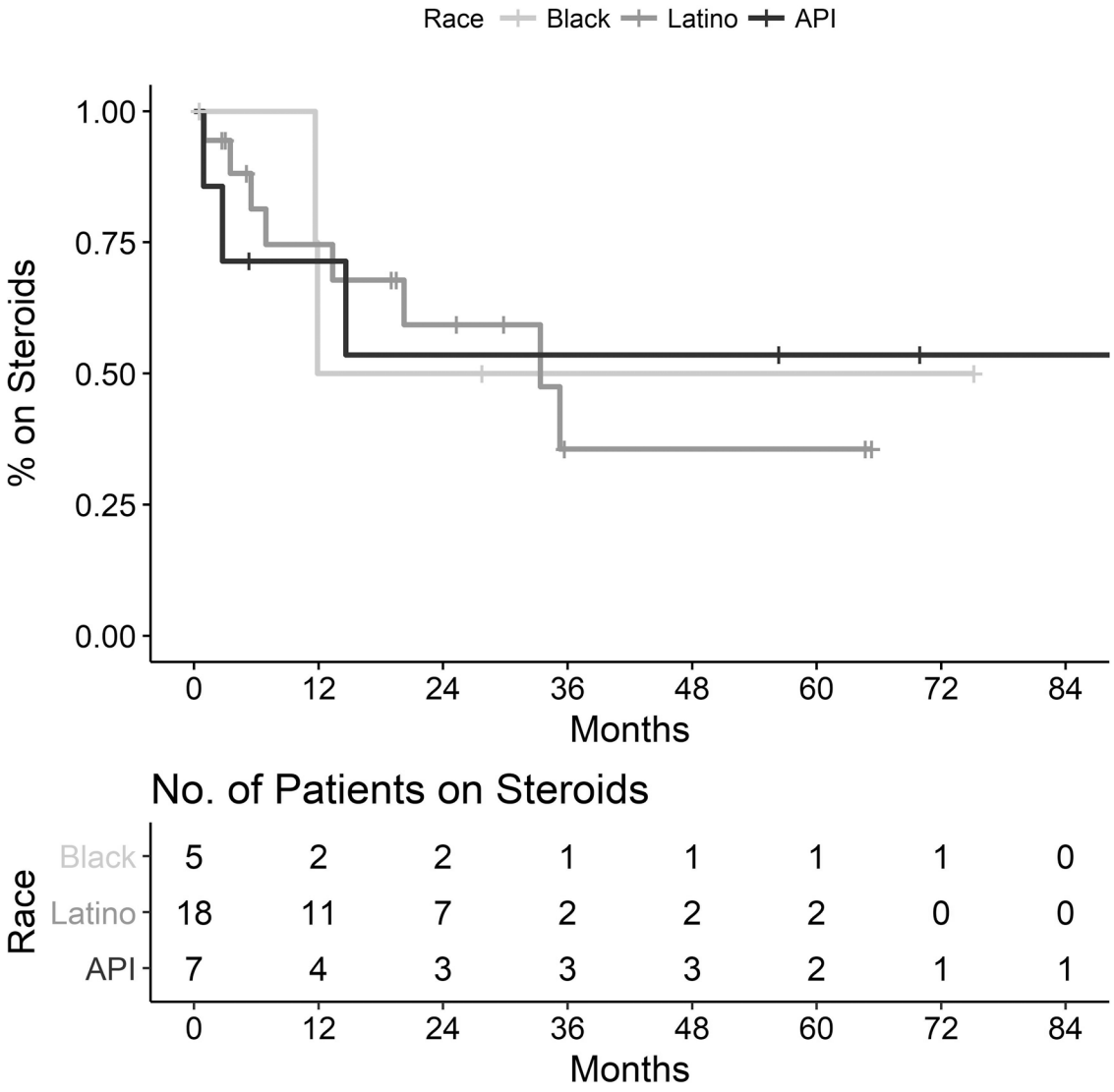

Fig. 4.

Time-to-event analysis comparing duration of steroid treatment for black, Latino, and API patients with AIH (p = 1).

Table 1.

Patient Characteristics

	Group		
	AIH	**Control**	**p-values**
Total Patients	63	2049	
Age at Diagnosis	49.2	45.8	0.72
% Female	84.1	48.1	< .01
Race (%)			< .01
White	4 (6.3)	398 (19.4)	
Black	10 (15.9)	382 (18.6)	
Latino	39 (46.0)	370 (18.1)	
API	19 (30.2)	456 (22.3)	
Other	1 (1.6)	379 (18.5)	
Unknown	0 (0.0)	64 (3.1)	

Table 2.

Multivariable Model of Factors Associated with AIH Diagnosis

	Adjusted OR	95% CI	p-values
Race			
White	REF	REF	REF
Black	9.6	(1.8, 177.5)	0.03
Latino	25.0	(5.3, 448.3)	< .01
API	10.8	(2.2, 195.8)	0.02
Other	0.9	(0.0, 22.1)	0.92
Sex			
Male	REF	REF	REF
Female	5.8	(2.9, 13.4)	< .01
Age	1.0	(1.0, 1.0)	0.10

Table 3.

Differences in the Presentation and Outcomes between Black, Latino, and API Patients with AIH

Measurements	Total (n = 58)	Black (n = 10)	Latino (n = 29)	API (n = 19)	p-values
Presentation					
ALT (U/L)	198	308	182	189	0.45
IgG (mg/dL)	2040	2988	1960	1895	0.12
ANA	1:640	1:640	1:640	1:640	0.93
ASMA	32	63	37	20	0.11
AMA	5.7	8.3	5.1	5.9	0.98
INR	1.2	1.3	1.1	1.1	0.58
Total Bilirubin (mg/dL)	0.8	2.8	0.7	1.1	0.06
Biopsy Inflammation Grade *	2.8	3.1	2.8	2.4	0.09
Biopsy Fibrosis Stage *	2.1	2.2	2.2	1.9	0.74
Biopsy Steatosis Grade *	0.1	0.0	0.1	0.2	0.65
Treatment/Outcomes					
ALT 6 mo. after Treatment Initiation (U/L)	38	33	46	31	0.20
Hospitalization (%)	39.3	60.0	39.3	27.8	0.27
Decompensation (%)	18.2	20.0	14.3	23.5	0.65
Concomitant Autoimmune Disease (%)	35.4	50.0	30.8	35.7	0.65
Budesonide Use (%)	10.3	10.0	13.8	5.3	0.85
Mycophenolate Use (%)	10.3	20.0	13.8	0.0	0.11
Time from Diagnosis to Treatment (Days)	13.0	3.0	34.5	9.5	0.11

* Mean values presented; **all other values are median values** unless otherwise designated.