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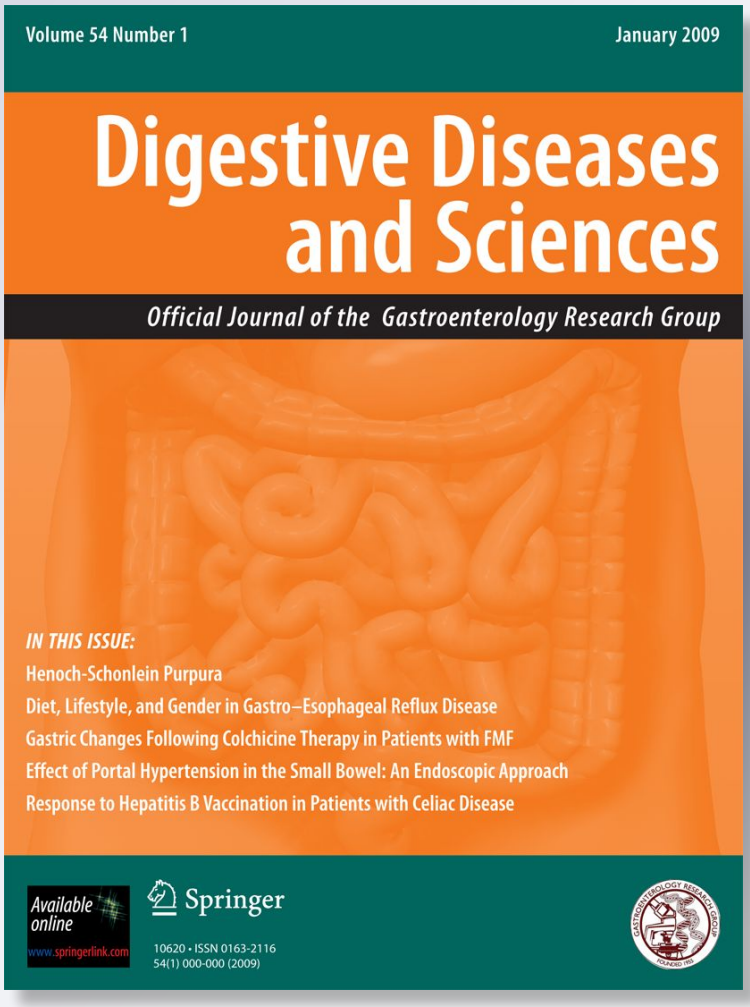

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ORIGINAL ARTICLE

Histological Versus Clinical Cirrhosis in Chronic Hepatitis C: Does Race/Ethnicity Really Matter?

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Abstract Liver fibrosis progression in hepatitis C virus (HCV) infection has been in part associated with race/ethnicity. Little is known of the frequency of clinical cirrhosis in Asian patients in the US.

Aim To compare histological and clinical features of chronic hepatitis C (CHC) in a multiethnic cohort of patients.

Methods Retrospective query of an *electronic* medical registry for CHC patients evaluated from 1999 to 2005. Histological cirrhosis was defined as advanced METAVIR fibrosis score at biopsy. Clinical cirrhosis was defined as any of: varices, ascites, or splenomegaly. Liver cirrhosis was defined as either histological or clinical cirrhosis. Chi-square tests, *t* tests, and logistic regression method were used for data analysis.

Results Six hundred and ninety-two patients were categorized into four racial-ethnic groups: 292 Caucasian (C), 145 Hispanic (H), 121 African American (AA), and 134 Asian (As) patients. Median age of *AA* (54 years) and As (53) was higher than C (52), or H (50) ($p < 0.05$). H patients had a higher percentage of alcohol abuse (60%) than AA and C (42–44%) and As (14%; $p < 0.0001$). Body mass index (BMI) was significantly lower in Asians compared to all other groups ($p < 0.0001$). Features of the metabolic syndrome were common, ranging from 28% in As to 72% in H patients. Liver cirrhosis was found in 53% H, 35% C, 29% As, and 19% AA. In multivariable analysis, only alcohol abuse, BMI, diabetes mellitus (DM), and age were significantly associated with liver cirrhosis. There was a trend for AA to have less cirrhosis, either histological or clinical ($p = 0.08$).

Conclusions Using only histology, liver cirrhosis was significantly underestimated. In our cohort, severity of CHC was not clearly affected by race when alcohol use and features of the metabolic syndrome were taken into consideration. However, there was a trend for African Americans to have lower cirrhosis rates.

Keywords HCV · Fibrosis · Cirrhosis · Race · Ethnicity · Hepatocellular cancer

Background

The progression of hepatic fibrosis in chronic hepatitis C (CHC) has been estimated using a single liver biopsy [1]. Based on these estimated measures, fibrosis progression appears to be in part determined by race/ethnicity [2–5]. In particular, Hispanics have been found to have more significant histological liver disease [2, 5], while African Americans have shown lower levels of fibrosis compared to Caucasians [3]. In the UK, cirrhosis was found to be more common in Asian patients; however, the majority of these patients were from the Indian subcontinent [4]. Little is known of the frequency of histological and clinical cirrhosis in Asians patients with CHC in the US. Most Asians

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residing in the US have East Asian ethnic origins (China, Japan, Korea, Philippines) and Southeast Asia (Vietnam). The aim of this study was to compare histological and clinical features of hepatitis C in a US cohort of CHC patients, which included significant numbers of patients of East/Southeast Asian descent.

Methods

We conducted a retrospective query of an electronic database for CHC patients evaluated between 1999 and 2005 in an academic hepatology practice. We used the Organ Transplant Tracking Record (OTTR^{TM}), which contains detailed demographic (including BMI), laboratory, imaging and procedure reports, dictated reports, as well as data on patient outcomes. Our group uses OTTR^{TM} as an electronic data storage system that is used for all patients seen by our group, including general hepatology and gastroenterology patients.

The main hepatology clinic is located in San Francisco, but 14 outreach clinics serve a patient population covering Northern California, Central and Coastal California, as well as Nevada. All clinics contributed patients to the database. Our referral clinics evaluate general hepatology patients, including early patients for possible therapy or enrollment in clinical studies and also patients with advanced disease for liver transplant (OLT) evaluation. We had no way of evaluating the referral patterns from local physicians to our hepatology practice, in terms of liver disease severity, according to clinic location.

The decision to obtain a liver biopsy belonged to the clinician and the patients: typically all patients were offered a biopsy unless either contraindicated by coagulopathy, or if the presence of ascites, varices, imaging, and laboratory studies make the diagnosis obvious to the clinician. Thus, not all patients had a liver biopsy.

We excluded patients who were positive for HIV, HBV, and those who had died or had received a liver transplant at the time the CHC database was established in January 2006.

All authors were involved in the writing and critical review of the manuscript. All authors except the statistician were involved in data gathering, according to the following predetermined rules.

Clinical cirrhosis was defined as the finding of any of the following three clinical parameters in the medical record:

- varices by endoscopy or imaging study,
- ascites (clinically or by imaging),
- splenomegaly (clinically or by imaging).

In some patients, data were missing or unavailable. Thus we established the following rules:

if any of the three clinical parameters was positive, the diagnosis was ruled *clinical cirrhosis*,
if two out of the three were unknown and the other negative, or if all three were unknown, the diagnosis was ruled *unknown*.
if two out of the three were negative and the third unknown, the diagnosis was ruled *negative for cirrhosis*.

Histological cirrhosis was defined (according to the Metavir classification) as either advanced stage 3.5 (3–4 fibrosis stage out of a possible 4 on the written pathology report) or 4 out of 4. This was derived from the original pathology report. No effort was made to re-read the slides, as retrieving slides from numerous outreach pathology laboratories would have been difficult, and additionally introducing further bias, according to the rate of retrieval.

Liver cirrhosis was defined as either histological or clinical cirrhosis. The percentage of patients with liver cirrhosis was derived using as the denominator the number of patients with no more than one (1) unknown portal HTN variable (Table 2).

Our patients filled out a questionnaire including self-assessment of race ethnicity, state or country of birth, and parents' country of origin. This was the basis for our race/ethnicity classification. Accordingly, four race/ethnicity categories were defined: Caucasians (C), African Americans (AA), Asians (As), and Hispanics (H). Of the Asian group, 134 were subcategorized into Chinese (53), Vietnamese (24), Japanese (15), Korean (5), Filipino (3), and Burmese or Pacific Islanders (3); 31 were of unknown descent.

Insurance data were also captured and patients were categorized as having Medi-Cal (Medicaid program), Blue Cross or private insurance (including HMO, PPO etc.), other insurance (including Medicare) and no insurance. This classification was an attempt to establish whether insurance, as a proxy for socioeconomic status, was a variable associated with outcomes.

Alcohol abuse was either absent or present, based on a diagnosis of abuse or dependence, according to the chart notes by the hepatologist as well as social workers' consultations in the context of OLT evaluation. Diabetes was either present or absent, based on its inclusion in chart notes. The diagnosis of hepatocellular cancer (HCC) was made by chart review and included either histological confirmation, or a hypervascular mass appearing on imaging (Tri- or quadriphasic CT, contrast-enhanced MRI, or blush on angiography) that is compatible with HCC, or an alpha-fetoprotein (AFP) level >500 ng/ml. We calculated percentages using the number of patients with known data as the denominator.

Statistical Analysis

We used the Chi-square test to compare distributions of categorical variables across the five racial-ethnic groups. We used the analysis of variance (ANOVA) method to compare distributions of interval-scale variables across race/ethnicity. We used the logistic regression method to examine the association between the presence of cirrhosis and host characteristics including race/ethnicity, age, gender, diabetes, BMI, alcohol dependence, and socioeconomic status. We used type of medical insurance (Medi-Cal/no insurance, other) as a proxy for socioeconomic status. Age was categorized into seven groups as follows: ≤40, 41–45, 46–50, 51–54, 55–59, 60–69, ≥70 years. BMI was dichotomized as under versus 30 and above (definition of obesity). All computations were performed using the statistical software StatView and SPSS. Two-sided p values less than 0.05 were considered statistically significant.

Subject Protection

The CPMC Institutional Review Board gave permission to perform this study and waived the need for written consent.

Results

A total of 692 patients were categorized into four racial-ethnic groups: 292 Caucasian (C), 145 Hispanic (H), 121 African American (AA), and 134 Asian (As) patients. Demographics and insurance data are summarized in Table 1.

The median age of AA (54.2 years) was significantly higher than either C (51.7) or H (50.4; $p < 0.05$).

The percentage of males varied from 43% (Asians) to 55% (C and AA; Table 1). The only statistically significant difference was that there were more C males (55%) versus As ($p = 0.02$). In terms of insurance, 189 had Blue Cross/private insurance (26%), 166 had Medi-Cal (23%), 292 had other insurance (41%) and 66 had no insurance listed (9%). The presence of alcoholism or alcohol abuse/dependence was different in the four ethnic groups, and was statistically lower in Asians compared to all other ethnic groups ($p < 0.0001$; Table 1).

BMI was significantly lower in Asians (mean 25) compared to all other groups. Caucasians had a lower BMI (mean 28) than H (31) and AA (30; Table 1). The prevalence of either diabetes or obesity (metabolic syndrome) was high in all groups and ranged from 28% in As to 72% in H patients (Table 1). Asians were statistically less likely to have features of the metabolic syndrome compared to all other groups except C (Table 1).

Favorable HCV genotypes (gt 2, 3) were less frequent in As and AA (Table 2). A liver biopsy was performed significantly more often in C (66%), compared to all other groups (Table 2). Inflammatory scores (grading 0–4) were significantly lower in As versus AA ($p = 0.04$) and H ($p = 0.05$). They were significantly higher in H versus C ($p = 0.003$). Fibrosis scores (staging 0–4) were also significantly higher in H versus C ($p = 0.001$).

Overall, 158 of 692 patients (22.8%) were determined to have liver cirrhosis: 87 (12.5%) had only clinical cirrhosis, 27 (4%) had only histological cirrhosis, and 44 (6%) had both. Thus, greater than half of cirrhotics (87/158) were diagnosed solely on clinical grounds without a liver biopsy. Of these 87, the diagnosis of cirrhosis was based on one parameter of portal hypertension (see "Methods") in 53 (60%), on two parameters in 28 (32%), and on three parameters in six (8%) patients.

Using biopsy readings only, H were statistically more likely to have histological cirrhosis (40%) compared to C (19%, $p = 0.004$), AA (17%, $p = 0.02$) and Asians (13%, $p = 0.005$). Using histological plus clinical data, H patients were more likely to have liver cirrhosis (31/59, 53%) compared to C (90/259, 35%, $p = 0.02$) AA (18/93, 19%, $p < 0.0001$) or As (19/66, 29%, $p = 0.01$; Table 2). C were also more likely to have liver cirrhosis compared to AA ($p = 0.006$).

Thus, using clinical data, the percentage of liver cirrhosis was now less markedly different in Hispanic versus

Table 1 Demographics and comorbidities in the four race/ethnicity groups

	Caucasian (C) ($n = 292$)	Hispanic (H) ($n = 145$)	African American (AA) ($n = 121$)	Asian (As) ($n = 134$)
Median age (years)	51.7 (23–81)	50.4 (24–76)	54.2 (35–74)	52.8 (28–91)
Males (%)	55	53	55	43
Medi-Cal insurance (% known)	51/266 (19%)	42/133 (32%)	44/110 (40%)	20/117 (17%)[#]
Mean BMI (SD)	28 (6)[#]	31 (6)	30 (7)	25 (4)[♠]
Alcohol abuse/known data (%)	97/233 (42%)	38/63 (60%)	41/93 (44%)	9/66[♠] (14%)
Metabolic/known	88/250 35%	59/82* 72%	53/117** 45%	21/74 28%

[#] $p < 0.05$ versus H and AA; [♠] $p < 0.0001$ versus all other groups; * H versus C or As $p < 0.0001$; ** AA versus As $p = 0.02$; Note for alcohol abuse: H versus As $p < 0.0001$, versus C = 0.01

Table 2 Virological and histological data

	Caucasian (C) ($n = 292$)	Hispanic (H) ($n = 145$)	African American (AA) ($n = 121$)	Asian (As) ($n = 134$)
Genotype 2,3 (%)	61/232, 27%	22/97, 23%	6/83, 7%$^{\infty}$	15/79, 18%
Gt 1 (%)	165/232, 71%	74/97, 76%	76/83, 92%	51, 65%
Liver biopsy (%)	192 (66%)$^{\spadesuit}$	50 (35%)	52 (43%)	39 (29%)$^{\wedge\wedge}$
Inflamm mean (SD)	1.7 (1.0)	2.4 (0.9)$^{\wedge}$	2.3 (0.4)	1.3 (0.6)$^{\wedge\wedge}$
Fibrosis mean (SD)	2.0 (1.3)	2.7 (1.3)$^{\blacklozenge}$	2.2 (1.2)	2.3 (1.1)
Histological cirrhosis (% of biopsy)	37/192 (19%)$^{\#\#}$	20/50 (40%)$^{\blacktriangledown\blacktriangledown}$	9/52 (17%)	5/39 (13%)
Clinical or histo cirrhosis (liver cirrhosis)	90/259 (35%)$^{\clubsuit}$	31/59 (53%)$^{\blacktriangledown}$	18/93 (19%)	19/66 (29%)

$^{\infty}$ $p < 0.005$ versus C, H; $^{\spadesuit}$ $p < 0.0001$ versus all other groups; $^{\wedge}$ Versus Asian $p = 0.05$ and Cauc $p = 0.003$; $^{\wedge\wedge}$ $p = 0.02$ Asian versus AA; $^{\blacklozenge}$ t test; Hispanics versus C, $p = 0.001$; $^{\#\#}$ $p = 0.004$ versus Hisp only; $^{\blacktriangledown\blacktriangledown}$ $p < 0.05$ versus Cauc, AA and As; $^{\clubsuit}$ $p = 0.02$ versus Hisp; $p < 0.01$ versus AA; $^{\blacktriangledown}$ $p = 0.02$ versus C; $p \leq 0.01$ versus AA and As

Caucasian patients. Conversely, a significant difference emerged between the frequency of liver cirrhosis in C, greater than in AA ($p = 0.006$).

Univariate Analysis

In univariate analysis, race/ethnicity, type of medical insurance, age, presence of alcohol abuse, presence of diabetes mellitus, and BMI >29 were each significantly associated with the presence of cirrhosis. The association with gender was of borderline significance ($p = 0.09$), with males having a higher risk for cirrhosis. The presence of cirrhosis was unrelated to either genotype or viremia (data not shown).

Multivariate Analysis

A logistic regression model was run and the results are displayed in Table 3. When histological and/or clinical cirrhosis were considered, this analysis showed that only four parameters were independently associated with cirrhosis: age, alcohol abuse, DM, BMI >29. The effect of race was reduced to a trend for AA to have less cirrhosis, either histological or clinical ($p = 0.08$).

Table 3 Multivariable logistic regression: testing for (independent) association with cirrhosis in the presence of the other variables in the model

How cirrhosis diagnosed	Clinically	Histologically	Either clinically or histologically
Race/ethnicity	<0.001	0.047	**0.081**
Gender	0.11	0.23	0.15
Age	0.003	0.18	**0.007**
Type of insurance	0.24	0.36	0.14
Alcohol abuse	0.002	0.043	**<0.0001**
Diabetes	0.021	0.011	**0.002**
BMI >29	0.46	0.056	**0.078**

Bold value indicates more significant variables

p values are based on the likelihood ratio test associated with the logistic model

Hepatocellular Carcinoma (HCC) Data

HCC was diagnosed in 19 patients (Table 4). The HCC patients were significantly older (median 61 years) than those without (51 years, $p < 0.0001$) and 18/19 (95%) were diagnosed in cirrhotics either clinically or histologically. One Asian patient had no biopsy, no clinical evidence of portal hypertension, and normal platelets, but AST/ALT >1.

Fifty-two percent of patients had AFP <100. One patient died in the time since the study was undertaken and six additional patients were lost to follow-up. Only two patients (10%) were placed on the transplant list. The percentage of HCC was higher in As compared to C ($p = 0.002$). When the percentage was calculated using the number of patients with liver cirrhosis as the denominator, AA and As had more HCC diagnosis than C ($p < 0.001$).

Anti-HB core antibodies were available in 14 HCC patients. Asians (4/5, 80%) were more likely to be positive than other races (5/9, 56%) but the difference was not statistically significant. Interestingly, the percentage of HCC diagnosed in patients with either clinical or histological cirrhosis were higher in the groups with the lowest rates of cirrhosis, As (42%) and AA (33%) compared to H (10%) or C (2%; Table 4).

Discussion

In this paper, we have challenged the concept of assessing hepatitis C progression by looking at histological fibrosis scores alone [1]. A number of patients with advanced liver disease do not undergo biopsy and are not included in prognostic estimates. Thus we decided to evaluate our

Table 4 HCC data in different race-ethnicities

	Caucasian (C) ($n = 292$)	Hispanic (H) ($n = 145$)	African American (AA) ($n = 121$)	Asian (As) ($n = 134$)
HCC diagnosis	2 (1%)	3 (2%)	6 (5%)	8 (6%)
HCC/cirrhosis (clinical + histo)	2/90 (4%)	3/31 (10%)	6/18 (33%)	8/19 (42%)

patients with hepatitis C looking at both histological fibrosis and clinical evidence of portal hypertension (ascites, varices, or splenomegaly), which is typically accepted as being associated with liver cirrhosis. For that purpose, we looked at biopsy-derived liver fibrosis scores and defined cirrhosis as stage 3.5–4 on the Metavir scale, but in addition we defined clinical cirrhosis as the presence of either ascites, varices, or splenomegaly. Further, we aimed at uncovering differences among race/ethnic groups in terms of the prevalence of liver cirrhosis diagnosed either histologically or clinically, as defined above.

First, we found that in this real-life cohort, a diagnosis of cirrhosis was most often made on clinical grounds alone (55%) rather than by histology alone (18%). Thus, using only a histological definition, a significant underestimate of advanced liver disease occurs. However, the main goal of the study was to compare clinical features generally associated with cirrhosis across race/ethnicity groups.

Then, we assessed the prevalence of severe liver disease according to racial groupings. Without taking other variables into account, this was different across races, particularly when histology alone was examined. In accordance with published literature [2–5], we found the prevalence of histological cirrhosis to be greatest in Hispanics (40%), compared to Caucasians (19%), AA (17%), and As (13%; Table 2). However, some of these differences were less significant. When clinical cirrhosis was also evaluated, in particular, the difference between prevalence of liver cirrhosis in H (53%) and C (35%) was reduced ($p = 0.02$). On the other hand, a statistically significant difference in liver cirrhosis between C (35%) and AA (19%) emerged ($p = 0.006$).

We also noted that for all ethnic groups except AA, seeking evidence of ascites, varices, or splenomegaly increased the percentage of patients diagnosed with cirrhosis. This was particularly evident in the C and As group where the prevalence of cirrhosis increased from 19 to 35% ($p = 0.0003$) and 13 to 29% ($p = 0.09$) respectively, using the above clinical criteria. This illustrates that relying on histology alone, with a bias in patient selection for liver biopsy, may have led to spurious differences previously reported in the literature [2, 5, 6].

We found that clear-cut risks for liver disease were very common in this cohort, and were also unequal across race/ethnicity groups, particularly a history of alcohol abuse/dependence and parameters associated with the metabolic syndrome (Table 1). Moreover, using a logistic regression model, we confirmed that age and alcoholism are important variables significantly and independently associated with cirrhosis [1]. We also confirmed that the presence of DM and a BMI >29 also have strong independent associations with liver cirrhosis [7, 8].

East Asian populations with CHC have not been studied in the US. In London, Asian patients (mainly from Pakistan and Bangladesh) were thought to have higher rates of histological cirrhosis, however, the clinically advanced group was not represented, as the study was based on histology alone. However, in that particular study, age and alcohol abuse were also significantly associated with cirrhosis [4]. Our Asian population was of a different origin, and when age, alcohol use and features of the metabolic syndrome were taken into consideration, the rates of cirrhosis in Asians were similar to other ethnicities (Table 2). In fact, in the present cohort, we could only document a trend for AA patients to have lower rates of cirrhosis, despite a significant percentage of patients with DM or BMI >29. Our logistic regression analysis showed that race/ethnicity was not strongly associated with liver cirrhosis ($p = 0.08$). On the other hand, this study was retrospective, leading to several potential biases.

We do not know why some patients did not undergo a liver biopsy. It appears that the lowest rates of biopsy were found in H (35%) and As (29%). Although there is no a priori reason why H or As patients without a biopsy would have had significantly more or less cirrhosis than those who did undergo a biopsy, it is possible that if more biopsies would have been available, results may have been affected.

Interpretation of chart review may have been imperfect. As an example, not all patients had a glucose tolerance test. Therefore, the prevalence of insulin resistance was almost certainly underestimated. However, we have no reason to suspect that such an additional diagnosis, above and beyond a diagnosis of diabetes, would have been so different across races as to change the results significantly.

We were not able to evaluate lipid parameters or blood pressure to more accurately define the metabolic syndrome. However, we feel that evaluating two key parameters (DM

and BMI) was sufficient to confirm the point that the metabolic syndrome increases the risk of fibrosis progression. Indeed, we found that controlling for this important variable largely abolished the impact of race/ethnicity on the prevalence of liver cirrhosis.

Finally, we found that the rates of HCC were also unequal across race-ethnic groups. The two groups with lower cirrhosis rates had the highest percentages of HCC using cirrhosis as the denominator. Because of the small numbers, we are unable to conclude whether these differences are real.

In summary, we found that cirrhosis is often diagnosed without liver biopsy in clinical practice. Racial differences found by evaluating histology alone were less apparent when expanded criteria for the diagnosis of cirrhosis were applied. Furthermore, when we used multivariable analysis, known prognostic parameters such as age, alcohol use, and parameters of the metabolic syndrome were much more significant risks for cirrhosis than race/ethnicity. The exception was the finding of a trend for lower rates of cirrhosis in African Americans. Further studies comparing race-ethnic groups with corrections made for age as well as the presence of alcohol abuse and the metabolic syndrome would be important to confirm our findings.

Conflict of interest The authors report no conflicts of interest.

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