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ORIGINAL ARTICLE

Late presenters among minority patients with chronic hepatitis C infection in the USA

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Abstract

Objectives Minority patients are under-screened for chronic hepatitis C (CHC) in the USA, and limited data exist for minority patients with advanced fibrosis.

Methods In this cross-sectional study, CHC patients who were prescribed direct-acting antiviral agents were divided into White patients and minority patient groups. Primary measurements were the mean fibrosis scores and percentages of patients with stage III–IV fibrosis (late presenters) for the two groups.

Results Among the 1421 patients with self-reported ethnicity, 697 were White patients, and 724 were minority patients (484 Hispanic, 175 Black, 65 Asians). Compared to the White, minority patients had significantly higher mean fibrosis score ($p < 0.001$) and a higher percentage of late presenters ($p < 0.001$). In subgroup analyses, the mean fibrosis scores for Hispanic, Black and Asian patients were 2.58 ± 1.38, 2.28 ± 1.41 and 2.28 ± 1.40, respectively.

Conclusions Minority populations with CHC in the USA experience disparities in access to treatment in the early stages of liver fibrosis. Public health strategies are necessitated to address the inequality, as late presenters are at risk of hepatocellular carcinoma.

Keywords Chronic hepatitis C · Late presenters · Liver fibrosis · Minority health disparity · Direct-acting antiviral agents · Treatment access

Abbreviations

CHC	Chronic hepatitis C
HCV	Hepatitis C virus
DAAs	Direct-acting antivirals
DM	Diabetes
HTN	Hypertension
CKD	Chronic kidney disease
GT	Genotype
HCC	Hepatocellular carcinoma
APRI	Aspartate aminotransferase-to-platelet ratio index

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Introduction

Globally, an estimated 71 million people have chronic hepatitis C infection (CHC), and approximately 399, 000 people die each year from hepatitis C-related cirrhosis and hepatocellular carcinoma (WHO Hepatitis C Update 2017). Treatment of CHC with the direct-acting antivirals (DAA's) in patients with minimal or no hepatic fibrosis provides not only a significant reduction in the incidence of decompensation and hepatocellular cancer (HCC) but also high cure rates. In addition to disease-specific outcomes, patient-reported outcomes, including the quality of life and work productivity, are also improved (Younossi et al. 2018; WHO Combating hepatitis B and C to reach elimination by 2030 2016). By 2030, the target of the World Health

Organization (WHO) Global Health sector is to reduce the viral hepatitis-related mortality by 65%. Therefore, detecting the CHC patients at an earlier stage of liver fibrosis is crucial to achieving the WHO goal (WHO Combating hepatitis B and C to reach elimination by 2030 2016).

More importantly, the incidence of HCC remains significantly high if a patient's disease has progressed to stage III or IV fibrosis before DAA treatment. Current AASLD guidelines recommend life-long surveillance of HCC in patients with advanced fibrosis (AASLD, HCV guidelines 2020). It is, therefore, critical to providing treatment to CHC before the development of advanced fibrosis. Mauss, S. et al. defined late presenters as those who present with advanced fibrosis, i.e., METAVIR stage III or IV, with no previous effective treatment for CHC (Mauss et al. 2017).

Within the USA, several factors may alter access to health care in minority patients when compared to White patients. The majority of minority patients are Hispanic, Black and Asian ethnicities. These patients may be under-screened for CHC for various reasons, including socioeconomic status and cultural barriers (Feldman et al. 2017). According to the Kaiser Family Foundation, there is a higher percentage of Medicaid recipients in the minority group in 2016. A total of 57% of Medicaid recipients were the minority, including Black 18%, Hispanic 30% and others 9% (Kaiser Family Foundation 2020). In most states, Medicaid patients have restrictions on CHC treatment based on the prescriber type. The prescriber is required to be a specialist (gastroenterology, hepatology, infectious diseases or liver transplantation), and treatment decisions can be made by a non-specialist after consultation with a specialist (The State of Medicaid Access, National Summary Report 2016). Another obstacle may be the language barrier and unfamiliarity with the US healthcare system, which can hinder access to CHC treatment (Falla 2017). Because of all the aforementioned barriers, there will be disparities in access to CHC treatment in minority groups, which ultimately leads to negative outcomes.

Before the availability of DAA regimens during the peg-interferon era, two extensive studies with patients enrolled before 2012, have reported late presenters of CHC patients and compared the minorities versus White cohort in the USA with conflicting results. In the study by Moorman et al., there was a higher percentage of patients with advanced fibrosis in the minority cohort compared to the White cohort. Butt et al. reported White race had been associated with advanced fibrosis and cirrhosis when compared to the minority cohort (Moorman et al. 2015; Butt et al. 2015). However, data are very limited after the introduction of DAA therapy for the treatment of CHC. We designed this cross-sectional study to better understand the healthcare disparity in the minority group. The aim of this study is to investigate and compare the mean liver fibrosis scores and percentage of late presenters between minority and White cohort before receiving DAA therapy.

Methods

Study design, setting and patient selections

This is a cross-sectional study on patients with CHC mono-infection from 13 different states in the USA. All patients with HCV mono-infection who filled their DAA prescriptions through the Quality Specialty pharmacy network (http://www.qualityspecialtypharmacy.com/) between 2017 and 2018 were included in the study. Data were extracted from the records retained by the special pharmacy. Since the pharmacy network does not have its own IRB, the IRB clearance was submitted to the Solutions IRB for the current study. The Solutions Institutional Review Board approved the study with IRB ID: 2018/07/14, and the informed consent was exempt. Solutions IRB (https://www.solutionsirb.com/) is a private commercial AAHRPP fully accredited Institutional Review Board. They include a team of experienced reviewers supporting researchers with IRB services. They provide IRB review for all levels and all types of studies, including clinical trials, social–behavioral, international, medical device, nonsignificant risk and non-investigational new drug studies.

The major exclusion criteria included the following; missing clinical data, un-specified ethnicity from self-report generated by patients; age younger than 18; the history of DAA therapy; and the history of diagnosis with liver diseases other than CHC. Subject data were extracted from electronic and/or paper medical records submitted from the physician's office during the process of applying preauthorizations of DAA therapy from insurance companies. The patient data were de-identified at the local branch of Quality Specialty pharmacy before submission to our central site for analysis. For data analysis and comparison, subjects enrolled in the current study were stratified based on their ethnicities into two groups of the White and the minority groups. Secondly, the patients in the minority group were further divided into three subgroups, which included Black, Asian and Hispanic.

Patient assessments and study endpoints

Pretreatment baseline characteristics, laboratory studies, baseline HCV viral load and liver fibrosis staging (scores 0 to 4) by serum markers, FibroScan/elastography or biopsy were assessed. The laboratory tests for study patients were mainly performed through Quest Diagnostic Laboratory, LabCorp Laboratory and Bio-reference Laboratory. The

lower limit of detection for HCV RNA was 20 IU/mL by using the COBAS TaqMan polymerase chain reaction assay according to laboratory manuals. The fully automatic biochemical analyzer assessed the alanine aminotransferase (ALT) levels in these laboratories. All patient clinical data and laboratory test results were collected within 6 months of fibrosis assessment as required by insurance companies for the preauthorization of treatment.

The primary endpoints were assessments of the mean fibrosis scores and percentages of late presenters in the White and minority groups for comparison. Late presenters in our study were defined as patients presenting to medical care with advanced liver disease caused by CHC with significant fibrosis: $\geq$ F3 assessed by serum markers of APRI (aspartate aminotransferase-to-platelet ratio index) score > 1.5 (≤ 0.5 indicates little or no fibrosis), or fibrotest > 0.59 (0.00 to 0.58: no fibrosis to moderate fibrosis), or by transient elastography > 1.37 s (< 1.37: no significant fibrosis), or FibroScan > 9.5 kPa (< 9.5 kpa: mild to moderate fibrosis), or by liver biopsy $\geq$ METAVIR stage F3 (F0-F2: no fibrosis to portal fibrosis with few septa) with no previous DAA treatment. The secondary assessment included performing subgroup analysis of mean fibrosis scores and the percentage of late presenters in individual ethnicities in the minority cohort with the comparison to the White cohort. In addition, predictors of advanced fibrosis in the minority cohort were further analyzed.

Statistical analysis

The SPSS statistics software package (IBM SPSS statistics version 25, USA) was used for statistical analysis. Frequencies and percentages were used to summarize categorical variables. Fisher's exact test or Chi-squared test was used when comparing data between and within groups. Depending on the underlying distribution of the data, descriptive values were expressed as means $\pm$ standard deviations. Student's t test was used to assess continuous variables between groups. All tests were two-tailed with a 95% confidence interval, and the $p = < 0.05$ was considered significant. Multivariate logistic regression was performed only in variables with a $p = < 0.05$ in univariate analysis.

Results

Clinical features of the study patients

Among the 1558 consecutive eligible patients with CHC mono-infection who received treatment evaluation between 2017 and 2018, one hundred and thirty-seven patients met the exclusion criteria, and 1421 patients were included in the study (Fig. 1). Stratifying by the self-reported ethnicity, six-hundred and ninety-seven patients (49%, $n = 697/1421$) were White patients, and seven-hundred and twenty-four (51%, $n = 724/1421$) were minority patients. The majority of enrollees were from three states (New York, California and Florida), although a total of 13 states across the USA contributed patients to the current cohort. A significantly higher number of males were included in the minority cohort compared to the White cohort ($p = 0.031$). The mean age of the patients in the entire cohort was 60.35 ± 12.13 and did not differ significantly between the two groups. Genotype 1a and 1b were present in 80.9% of the study patients, and the distribution of genotypes between the cohorts was uneven ($p = < 0.001$). A significant difference was observed between the two groups regarding medical comorbidities, including diabetes (DM), hypertension (HTN), chronic kidney disease (CKD), anxiety disorder and depression. Compared to the Whites, patients in the minority cohort tend to have significantly more patients with DM ($p = 0.001$), HTN ($p = < 0.001$) and CKD ($p = 0.003$), although there were significantly fewer patients with anxiety ($p = 0.001$) and depression ($p = 0.004$) in the cohort. Also, a significantly lower platelet count ($p = 0.013$) was observed in the minority group (Table 1).

Assessment of the fibrosis stages and late presenters

The primary assessment was done by analyzing the liver fibrosis staging (scores 0 to 4) between the White and the minority cohorts. Compared to the White cohort, a significantly higher mean fibrosis score was presented in the minority cohort (2.15 ± 1.39 vs. 2.48 ± 1.39; $p < 0.001$). Additionally, a significantly higher percentage of patients was late presenters in the minority group (41% [286/697] vs. 51.4% [372/724]; $p < 0.001$) (Fig. 2).

Subgroup data analyses were also performed as the secondary assessment (Table 2). When comparing the White cohort from Hispanic and Blacks, a significant difference was observed with gender, DM, HTN and CKD. When comparing the White cohort vs. Hispanics and the Asians, a significant difference was seen in patients with anxiety and depression. Also, a significant difference was noted with the mean platelet counts ($p = 0.001$) and BMI ($p = 0.043$) between the White and the Hispanic cohorts. A significant difference was noted with the insurance coverage of the Black cohort vs. White Cohort ($p = 0.019$).

For histological assessment of the subgroups, when compared to the White cohort, a significantly higher mean fibrosis score was presented in the Hispanic cohort

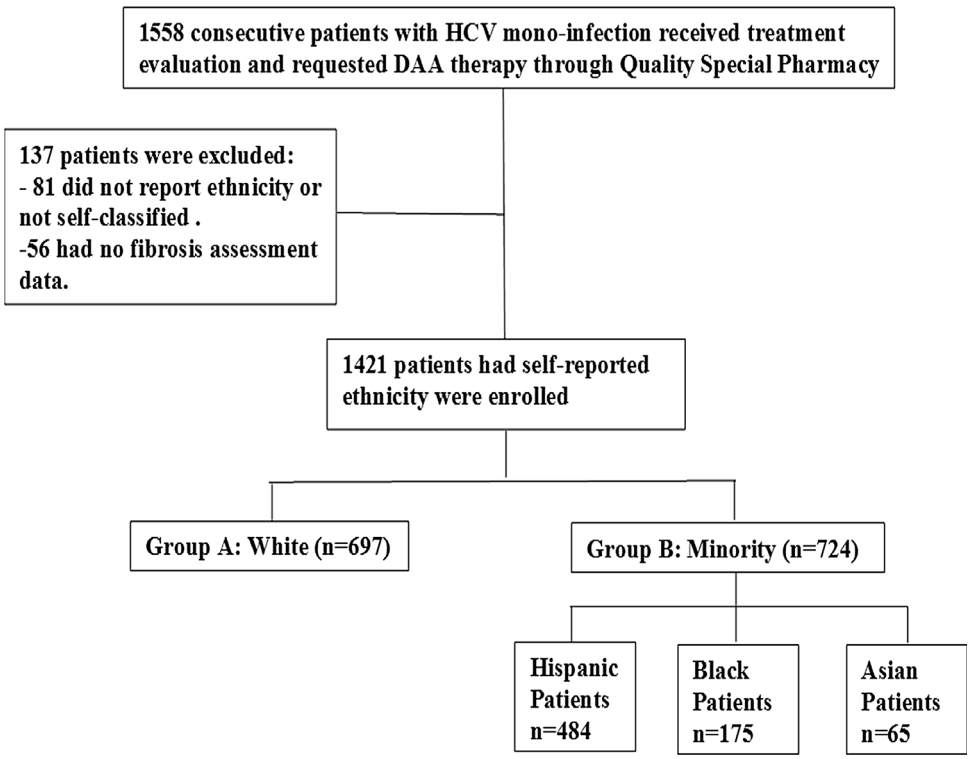

Fig. 1 Patient recruitment. Among the 1558 patients evaluated, 1477 were enrolled. Patients were divided into White and minority (Hispanic, Black and Asian). USA, 2017–2018. HCV: Hepatitis C Virus, DAA, Direct-acting antivirals

(2.15 ± 1.39 vs. 2.58 ± 1.38 ; $p < 0.001$). Additionally, a significantly higher percentage of patients were late presenters in the Hispanic cohort (41% [286/697] vs. 54.5% [264/484]; $p < 0.001$). When comparing the White to Black cohorts, no significant difference was noted with the mean fibrosis scores (2.15 ± 1.39 vs. 2.28 ± 1.40; $p = 0.262$) and the percentage of late presenters between two groups. Similarly, when comparing the White to Asian cohort, no significant difference was noted with mean fibrosis scores (2.15 ± 1.39 vs. 2.28 ± 1.39; $p = 0.474$) and late presenters between two groups. In Blacks and Asians, even though the mean fibrosis scores were numerically higher than Whites and showed the trends, it was not statistically significant. It was likely due to the fact that only limited numbers of patients enrolled were into these two subgroups.

Predictors of advanced fibrosis

In order to identify the risk factors associated with the advanced fibrosis in minority cohort, the univariate and multivariate analysis was performed. Patients were divided into two subgroups, which were the advanced fibrosis (F3–F4) and early fibrosis (F0–F2) fibrosis groups. Using the patients with advanced fibrosis as cases and those with early fibrosis as controls, we analyzed the non-histological parameters and compared them between the two groups. A statistically significant difference was observed with age, gender, baseline ALT levels, prior treatment history with interferon-based regimens, DM and HTN in the univariate analysis. Based on the risk factors identified from univariate analysis, we performed a multivariate logistic regression to assess the independent risk factors. Among the variables above, only the age ($p = < 0.001$), gender ($p = < 0.001$), ALT level ($p = < 0.001$) and comorbidity of hypertension ($p = 0.002$) were significantly associated with the advanced fibrosis in minority patients (Table 3).

Discussion

In this large US cohort study, late presenters with advanced fibrosis were investigated and compared between the minority and the White cohorts. We observed that there are a significantly high mean fibrosis scores and a significantly higher percentage of late presenters in the minority cohort when compared to the White cohort. The independent risk factors associated with the advanced fibrosis in the minority group were increasing age, male gender, high AST levels and the medical comorbidity of hypertension. At the population level, measurements of advanced CHC-related liver disease are essential to evaluate the impact of CHC screening recommendations and the effectiveness of linkage to care. The data are crucial to healthcare resources planning and harm reduction to the target population in the

Table 1 Characteristics of White and minority population. (USA, 2017–2018)

Characteristics	Total cohort $N = 1421$	White $n = 697$	Minority $n = 724$	P value
Age (years)				
< 50, *n* (%)	222 (15.6%)	109 (15.6%)	113 (15.6%)	0.987
≥ 50, *n* (%)	1199 (84.4%)	588 (84.4%)	611 (84.4%)	
Mean ± SD	60.47 ± 12.16	59.94 ± 12.28	60.98 ± 12.03	0.106
Sex				
Male	844 (59.4%)	394 (56.5%)	450 (62.2%)	0.031
Female	577 (40.6%)	303 (43.5%)	274 (37.8%)	
BMI (kg/m^2)				
> 30	238 (16.7%)	100 (14.3%)	138 (19.0%)	0.106
20–30	472 (33.2%)	238 (34.1%)	234 (32.3%)	
< 20	50 (3.5%)	24 (3.4%)	26 (3.5%)	
Data not recorded	661 (46.5%)	335 (48.0%)	326 (45.0%)	
Mean ± SD	27.18 ± 6.95	26.80 ± 6.98	27.52 ± 6.91	0.139
Fibrosis				
F0, F1, F2	763 (53.7%)	411 (59%)	352 (48.6%)	< 0.001
F3, F4	658 (46.3%)	286 (41%)	372 (51.4%)	
Mean score	2.32 ± 1.40	2.15 ± 1.39	2.48 ± 1.39	< 0.001
Place of residence				
New York	789 (55.5%)	384 (55.0%)	405 (55.9%)	0.001
California	314 (22.0%)	128 (18.3%)	186 (25.7%)	
Florida	224 (15.7%)	133 (19.0%)	91 (12.6%)	
Other states	90 (6.3%)	48 (6.8%)	42 (5.8%)	
Patient did not specify	4 (0.28%)	4 (0.5%)	0 (0.0%)	
Genotype				
1a	802 (56.4%)	381 (54.6%)	421 (58.1%)	< 0.001
1b	343 (24.1%)	177 (25.3%)	166 (22.9%)	
Mixed 1a/1b	23 (1.6%)	12 (1.7%)	11 (1.5%)	
2	101 (7.1%)	57 (8.1%)	44 (6.0%)	
3	94 (6.6%)	56 (8.0%)	38 (5.2%)	
4, 5, 6	53 (3.7%)	10 (1.4%)	43 (5.9%)	
Undetermined	5 (0.35%)	4 (0.5%)	1 (0.1%)	
Insurance				
Medicaid	164 (11.5%)	84 (12.0%)	80 (11.0%)	0.385
Medicare	945 (66.5%)	450 (64.5%)	495 (68.3%)	
Commercial	276 (19.4%)	143 (20.5%)	133 (18.3%)	
Unknown data	36 (2.5%)	20 (2.8%)	16 (2.2%)	
ALT (IU/L)				
> 40	752 (52.9%)	363 (52.0%)	389 (53.7%)	0.204
< 40	477 (33.5%)	248 (35.5%)	229 (31.6%)	
Data not recorded	192 (13.5%)	86 (12.3%)	106 (914.6%)	
HCV RNA (IU/mL)				
< 800,000	469 (33.0%)	225 (32.2%)	244 (33.7%)	0.657
> 800,000	916 (64.4%)	451 (64.7%)	465 (64.2%)	
Data not recorded	36 (2.5%)	21 (3.0%)	15 (2.0%)	
Platelet (× 1000/ml)	195.04 ± 74.58	200.54 ± 72.42	189.43 ± 76.38	0.013
Treatment history				
Naïve	1234 (86.9%)	604 (86.7%)	630 (87.1%)	0.789
Experience	186 (13.1%)	93 (13.3%)	93 (12.9%)	

Table 1 continued

Characteristics	Total cohort $N = 1421$	White $n = 697$	Minority $n = 724$	P value
Comorbidity				
DM	242 (17.0%)	95 (13.6%)	147 (20.3%)	0.001
HTN	467 (32.8%)	197 (28.2%)	270 (37.2%)	< 0.001
Dyslipidemia	114 (8.0%)	59 (8.4%)	55 (7.5%)	0.554
CKD	57 (4.0%)	17 (2.4%)	40 (5.5%)	0.003
Anxiety	215 (15.1%)	128 (18.3%)	87 (12.0%)	0.001
Depression	224 (15.7%)	130 (18.6%)	94 (12.9%)	0.004

Minority includes self-reported Hispanic, Black and Asian ethnicities. DM—diabetes mellitus, HTN—hypertension, CKD—chronic kidney disease, HCV— hepatitis C virus

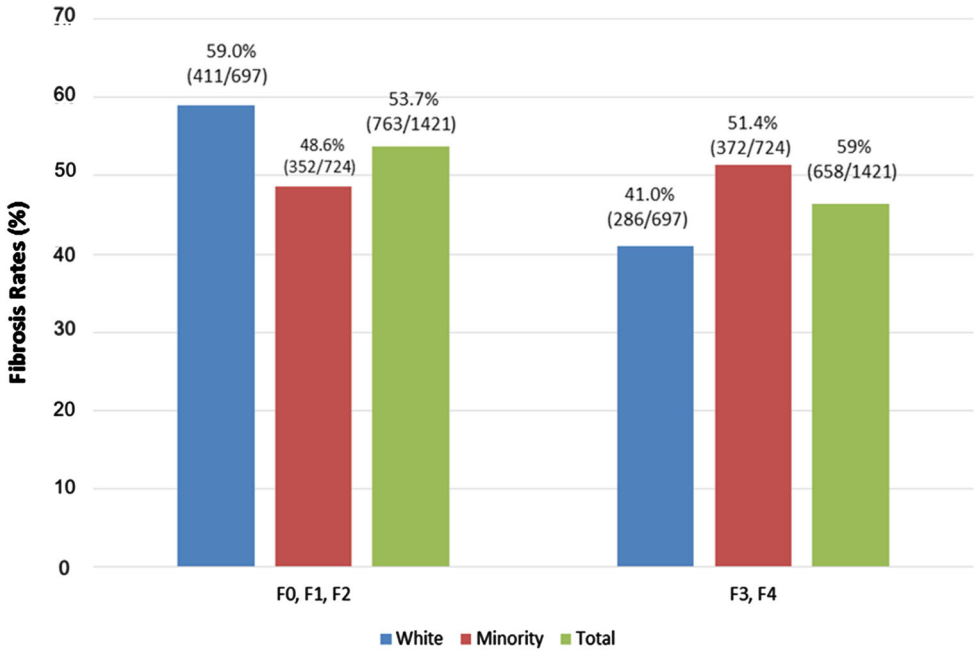

Fig. 2 Comparison of early fibrosis (F0–F2) and advanced fibrosis (F3, F4) in the White, minority and the total cohort. USA, 2017–2018. F0, F1 and F2: No fibrosis, mild and moderate fibrosis F3, F4: Advanced fibrosis

context of CHC infection. To our knowledge, the current study represents the largest studied cohort in the published literature to date after the availability of the DAA regimens. The data highlight the healthcare disparity of minority patients with CHC and provide independent risk factors for advanced fibrosis, which aid clinicians in classifying patients for early intervention and formulate the plan to monitor the disease progression. More importantly, our study aims to provide evidence and rationality on driving a change in healthcare policy, which impacts minority patients with CHC.

Before the availability of the DAAS, there were two studies with a reasonable sample size to investigate the late presenters among the minority patients. An observational Chronic Hepatitis Cohort Study (CHeCS) by Moorman et al. enrolled patients from 2006 to 2011, reported that many patients had advanced liver disease concurrent with their initial HCV diagnosis in the general cohort. In addition, a significantly high percentage of the minority population was presented with cirrhosis (late presentation) compared to the Whites. Late presenters had higher rates of hospitalization and mortality compared to those diagnosed at an earlier stage of liver disease (Moorman et al. 2015). These findings of late presenters in the minority cohort in the setting of interferon therapy were congruent with our observations in minority cohort in the context of DAA therapy, although the DAAs have much less adverse events compared to interferon-based treatment.

In another cohort study on patients receiving care at the veterans' administration (VA) hospital system conducted between 2002 and 2012, Butt et al. evaluated the rate of liver fibrosis progression in HCV infection after seroconversion based on ERCHIVES 3 database. They found the White race has been independently associated with advanced fibrosis and cirrhosis in HCV-infected patients compared to minority cohort (Butt et al. 2015). Although their findings are in contrast to our study as we found a higher percentage of advanced fibrosis and cirrhosis in the

Table 2 Subgroup analysis between different ethnicities. (USA, 2017–2018)

Characteristics	White patients $n = 697$	Hispanic patients $n = 484$	White vs. Hispanic p value	Black patients $n = 175$	White vs. Black p value	Asian patients $n = 65$	White vs. Asian p value
Age (years)							
< 50, *n* (%)	109 (15.6%)	82 (16.9%)	0.550	20 (11.4%)	0.161	11 (16.9%)	0.786
≥ 50, *n* (%)	588 (84.4%)	402 (83.1%)		155 (88.6%)		54 (83.1%)	
Mean ± SD	59.94 ± 12.28	60.73 ± 12.09	0.272	61.18 ± 10.39	0.217	62.31 ± 15.38	0.146
Sex							
Male	394 (56.5%)	304 (62.8%)	0.031	115 (65.7%)	0.028	31 (47.7%)	0.170
Female	303 (43.5%)	180 (37.2%)		60 (34.3%)		34 (52.3%)	
BMI (Kg/m^2)							
> 30	100 (14.3%)	96 (19.8%)	0.052	37 (21.1%)	0.131	5 (7.6%)	0.118
20–30	238 (34.1%)	150 (30.9%)		54 (30.8%)		30 (46.1%)	
< 20	24 (3.4%)	15 (3.0%)		7 (4.0%)		4 (6.1)	
Data not recorded	335 (48.0%)	223 (46.0%)		77 (44%)		26 (40%)	
Mean ± SD	26.807 ± 6.98	27.91 ± 7.03	0.043	27.55 ± 7.05	0.328	24.73 ± 4.83	0.065
Fibrosis							
F0, F1, F2	411 (59%)	220 (45.5%)	< 0.001	94 (53.7%)	0.208	38 (58.5%)	0.937
F3, F4	286 (41%)	264 (54.5%)		81 (46.3%)		27 (41.5%)	
Mean score	2.15 ± 1.39	2.58 ± 1.38	< 0.001	2.28 ± 1.40	0.262	2.28 ± 1.39	0.474
Place of residence							
New York	384 (55.0%)	280 (57.9%)	< 0.001	100 (57.1%)	0.398	25 (38.5%)	< 0.001
California	128 (18.3%)	124 (25.6%)		32 (18.3%)		30 (46.2%)	
Florida	133 (19.0%)	57 (11.8%)		26 (14.9%)		8 (12.3%)	
Other states	48 (6.8%)	23 (4.8%)		17 (9.7%)		2 (3.1%)	
Patient did not specify	4 (0.5%)	0 (0.0%)		0 (0.0%)		0 (0.0%)	
Genotype							
1a	381 (54.6%)	286 (59.0%)	0.020	124 (70.9%)	< 0.001	11 (6.9%)	< 0.001
1b	177 (25.3%)	109 (22.5%)		41 (23.4%)		16 (24.6%)	
Mixed 1a/1b	12 (1.7%)	6 (1.2%)		4 (2.3%)		1 (1.5%)	
2	57 (8.1%)	35 (7.2%)		1 (0.6%)		8 (12.3%)	
3	56 (8.0%)	27 (5.5%)		4 (2.3%)		7 (10.8%)	
4,5,6	10 (1.4%)	20 (4.1%)		1 (0.6%)		22 (33.8%)	
Undetermined	4 (0.5%)	1(0.20)		0 (0.0%)		0 (0.0%)	
Insurance							
Medicaid	84 (12.0%)	51 (10.5%)	0.668	18 (10.2%)	0.012	11 (16.9%)	0.394
Medicare	450 (64.5%)	322 (66.5%)		135 (77.1%)		38 (58.5%)	
Commercial	143 (20.5%)	96 (19.8%)		21 (12.0%)		16 (24.6%)	
Unknown data	20 (2.8%)	15 (3.0%)		1 (0.5%)		0 (0.0%)	
ALT (IU/L)							
> 40	363 (52.0%)	248 (51.2%)	0.285	103 (58.8%)	0.381	38 (58.4%)	0.554
< 40	248 (35.5%)	147 (30.3%)		60 (34.2%)		22 (33.8%)	
Data not recorded	86 (12.3%)	89 (18.3%)		12 (6.8%)		5 (7.6%)	
HCV RNA (IU/mL)							
< 800,000	225 (32.2%)	175 (36.1%)	0.212	49 (28.0%)	0.267	20 (30.7%)	0.741
> 800,000	451(64.7%)	300 (61.9%)		121 (69.1%)		44 (67.6%)	

Table 2 (continued)

Characteristics	White patients $n = 697$	Hispanic patients $n = 484$	White vs. Hispanic p value	Black patients $n = 175$	White vs. Black p value	Asian patients $n = 65$	White vs. Asian p value
Data not recoded	21 (3.0%)	9 (1.8%)		5 (2.8%)		1 (1.5%)	
Platelet (x1000/ml)	200.54 ± 72.42	184.28 ± 77.8	0.001	201.09 ± 76.04	0.937	193.30 ± 70.03	0.486
Treatment history							
Naïve	604 (86.7%)	418 (86.5%)	0.955	157 (89.7%)	0.278	55 (84.6%)	0.645
Experience	93 (13.3%)	65 (13.5%)		18 (10.3%)		10 (15.4%)	
Comorbidity							
DM	95 (13.6%)	104 (21.4%)	< 0.001	38 (21.7%)	0.006	5 (7.6%)	0.173
HTN	197 (28.2%)	174 (35.9%)	0.005	78 (44.5%)	< 0.001	18 (27.6%)	0.969
Dyslipidemia	59 (8.4%)	27 (5.5%)	0.059	25 (14.2%)	0.017	3 (5.0%)	0.287
CKD	17 (2.4%)	27 (5.5%)	0.005	10 (5.7%)	0.023	3 (5.0%)	0.283
Anxiety	128 (18.3%)	63 (13.0%)	0.014	21 (12.0%)	0.051	3 (5.0%)	0.005
Depression	130 (18.6%)	68 (14.0%)	0.040	23 (13.1)	0.100	3 (5.0%)	0.004

DM—diabetes mellitus, HTN—hypertension, CKD—chronic kidney disease, HCV—hepatitis C virus

minority cohort, the study population also differed as it involved the VA system. The authors have pointed out that there was a higher prevalence of alcohol and drug abuse in their CHC cohort when compared to those non-infected. Also, the difference in the results could be related to the availability of DAAs. Although the patients who receive DAAs experience much less adverse events, the cost of DAA treatment is extremely high when compared to interferon-based regimens. Patients in the VA system have equal access to the medications as they are all under the same coverage, while patients in the community have many barriers to access DAA treatment, including but not limited to insurance restrictions. Our findings are relevant to the current real-world setting of healthcare for CHC patients in the country as patients in the study were contributed by 13 different states in the USA from both academic and community treatment centers or clinics after the availability of DAA treatment. The findings have the potential to aid in changes regarding healthcare policy on minority care. Our data provide clinical evidence of the disparity in minority healthcare of patients with CHC and the ground for eliminating the access restriction for DAA treatment in Medicaid recipients with CHC.

In terms of predictors of advanced liver fibrosis early study done by Poynard, T., et al. suggested that male gender and older age were independent risk factors (Poynard et al. 2001). We found similar findings in the minority cohort. Also, the association of hypertension with advanced fibrosis is an interesting new finding in our study. Hypertension and insulin resistance have been independently associated with advanced forms of non-alcoholic fatty liver disease (NAFLD), which in turn can progress to advanced liver fibrosis, cirrhosis and liver failure (Butt et al. 2015; Dixon et al. 2001). It is possible that the synergetic effects of NAFLD and CHC may have been associated with advanced fibrosis. Our data are limited to delineate the relationship between NAFLD and CHC as most patients did not have complete workup of NAFLD, while they were receiving treatment evaluation for DAA therapy.

The reasons for the late presentation with advanced fibrosis in the minority cohort are likely from barriers in multiple aspects of health care. In a study done by Kuniholm et al. on the awareness of hepatitis C seropositivity screening in the Hispanic population, data were compared with the insured and those without insurance. Uninsured patients were over five times less likely to be aware of having HCV-related liver disease (Kuniholm et al. 2016). Treatment access in the minority cohort with DAAs was low in a recent study by Wong, R.J. et al. The lowest rates of treatment were seen among Hispanics and those with Medicaid insurance, which is concerning given these are particularly vulnerable populations for advanced fibrosis (Wong et al. 2018a, b). A real-world study from the TRIO network also shows significant barriers to access the DAAs in Medicaid recipients. Almost half of the non-start patients with liver histology data had advanced fibrosis scores (F3 or F4). Medicaid was the primary insurance of nearly half

Table 3 Analyses of predictors for advance fibrosis in the minority group. (USA, 2017–2018)

Characteristics	Total $N = 724$	F0–F2 $n = 352$	F3-F4 $n = 372$	Univariate *P* value	Multivariate *P* value
Age (years)					
< 50	113 (15.6%)	81 (23%)	32 (8.6%)	< 0.001	< 0.001
≥ 50	611 (84.4%)	271 (77%)	340 (91.4%)		
Mean ± SD	60.73 ± 11.98	57.70 ± 13.01	64.09 ± 10.11	< 0.001	
Gender					
Male	450 (62.2%)	199 (56.5%)	251 (67.5%)	0.002	<0.001
Female	274 (37.8%)	153 (43.5%)	121 (32.5%)		
BMI (Kg/m^3)					
> 30	138 (19.0%)	76 (21.5%)	62 (16.6%)	0.061	
20–30	234 (32.3%)	104 (29.5%)	130 (61.8%)		
< 20	26 (3.5%)	16 (4.5%)	10 (2.6%)		
Data not recorded	326 (45.0%)	156 (44.3%)	170 (45.6%)		
Mean ± SD	27.44 ± 7.09	27.45 ± 7.91	27.58 ± 5.78	0.846	
Genotype					
1a	421 (58.1%)	200 (56.8%)	221 (59.4%)	0.634	
1b	166 (22.9%)	90 (25.5%)	76 (20.4%)		
Mixed 1a/1b	11 (1.5%)	6 (1.7%)	5(1.3%)		
2	44 (6.0%)	20 (5.6%)	24 (6.4%)		
3	38 (5.2%)	18 (5.1%)	20 (5.3%)		
4,5,6	43 (5.9%)	18 (5.1%)	25 (6.7%)		
Undetermined	1 (0.1%)	0 (0.0%)	1 (0.2%)		
ALT (IU/L)					
> 40	389 (53.7%)	152 (43.1%)	237 (63.7%)	< 0.001	< 0.001
< 40	229 (31.6%)	145 (41.1%)	84 (22.5%)		
Data not recorded	106 (914.6%)	55 (15.6%)	51 (13.7%)		
Mean ± SD	64.60 ± 55.54	54.79 ± 55.21	74.98 ± 55.00	<0.001	
HCV RNA (IU/mL)					
< 800,000	244 (33.7%)	117 (33.2%)	127 (34.1%)	0.826	
> 800,000	465 (64.2%)	227 (64.4%)	238 (63.9%)		
Data not recorded	15 (2.0%)	8 (2.2%)	7 (1.8%)		
Treatment history					
Naïve	630 (87.1%)	319 (90.6%)	311 (83.8%)	0.006	0.065
Experience	93 (12.9%)	33 (9.4%)	60 (16.2%)		
Comorbidity					
DM	147 (20.7%)	58 (16.4%)	89 (23.9%	0.011	0.075
HTN	270 (38.1%)	105 (29.8%)	165 (44.3%)	< 0.001	0.002
Dyslipidemia	55 (7.8%)	22 (6.2%)	33 (8.8%)	0.181	
CKD	40 (5.6%)	17 (4.8%)	23 (6.1%)	0.417	
Anxiety	87 (12.3%)	45 (12.7%)	42 (11.2%)	0.560	
Depression	94 (13.3%)	45 (12.7%)	49 (13.1%)	0.870	

DM—diabetes mellitus, HTN—hypertension, CKD—chronic kidney disease, HCV—hepatitis C virus

of non-starts (Younossi et al. 2016). Vutien, P. et al. reported a cohort of 76,335 insured CHC patients and showed that significant racial disparities with minorities being associated with lower treatment rates, and the race remained an independent predictor even after adjusting for socioeconomic status, other demographic factors and

medical/psychiatric comorbidities (Vutien et al. 2016). In addition, a study by Wong, A. et al. has demonstrated that the impact of comorbidity was higher in minority patients with CHC. Compared to the White, Hispanic patients with two or more metabolic risk factors had an 89% higher risk of developing HCC and a 60% higher risk of developing hepatic decompensation (Wong et al. 2018a, b).

The major strength is assessing the real-world comparison of mean fibrosis scores and late presenters in the White and Minority cohort in a large sample size dataset representing a variety of clinical settings. This study identified not only vulnerable groups for advanced fibrosis but also risk factors for late presentation. Our data provide substantial evidence for public health authorities to gain a better understanding of minority disparity in CHC care, so the strategic plan of educating patients and providers as well as resource allocation from payers can be carried out. These data will also contribute to the knowledge of the epidemiological information, including genotype distribution with clinical features and presentation of CHC in the minorities. Limitations of our study include those using a cross-sectional design and a relatively limited sample size in Black and Asian groups. Besides, NAFLD has not been investigated in the current study as the risk factor for late presenters, although we have compared the BMI and comorbidities, including DM among different ethnic groups. Also, alcohol consumption, as a predictor for the liver fibrosis, was not assessed in our study population.

The summary of our data demonstrated that minority patients have significantly higher mean fibrosis scores and a higher percentage of late presenters (advanced fibrosis) when compared to White patients. Late presenters remain at an increased risk of progression to liver decompensation and hepatocellular carcinoma. As a result, public health interventions are warranted to address this disparity in minorities.

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Conflict of interest Dr. Pan received grants from Gilead. He also serves as a consultant or advisor for Gilead and speaker for Gilead, Abbvie and Intercept. Other authors have nothing to be disclosed.

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