

Racial disparity in age and genotype defines urban hepatitis C patient profiles in the recent direct-acting antiviral era

Abstract

Introduction: Hepatitis C virus (HCV) infections are a national health issue despite highly effective therapy and screening of the high prevalence age cohort. Since an increase in younger patients may be occurring, we evaluated HCV patients seen in our urban clinic for their demographics and treatment history.

Methods: EMR charts of all 601 patients with a diagnosis of HCV seen in Wayne Health Clinics in 2019 were reviewed.

Results: The HCV patients were predominantly African American (AA) (85%) with most yet to be treated (73%). AA patients were older than non-AA patients (63 vs 51 years), had a greater likelihood of HCV genotype 1 (94% vs 60%) and had lower ALT values. Patients were seen and treated by both Gastroenterology (73%) and Infectious Disease (27%) physicians and SVR rates were greater than 95%. Fibrosis, as determined by serological biomarkers, was improved in AA patients who had achieved viral clearance (SVR) as compared to those who were untreated.

Conclusions: AA patients were older and more likely to have genotype 1, and with less inflammation (ALT) as compared to Non-AA patients. The data confirms the continuing need to ensure linkage to all HCV patients to prevent additional HCV transmission and future liver disease manifestation. While fibrosis in our population correlates with age, there was a significant number of older AA patients with minimal fibrosis. Further evaluation of these patients may reveal a more recent acquisition versus a slower development of fibrosis over time.

Keywords: racial disparity, African Americans, hepatitis c, direct acting anti-virals, linkage to care, age disparity

Volume 12 Issue 6 - 2021

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Received: October 22, 2021 | **Published:** December 20, 2021

Abbreviations: DAAs, direct-acting antivirals; HCV, hepatitis C virus; AA, African American; EMR, electronic medical records; SAS, statistical analysis software; ID, infectious diseases; CDC, centers for disease control

Introduction

Highly effective and safe direct-acting antivirals (DAAs) against hepatitis C virus (HCV) significantly improved HCV treatment rates. These new therapies, in combination with the U.S. Preventive Services Task Force (USPSTF) recommendation to screen for HCV individuals born between 1945 and 1965 (age cohort; 54-79 years of age in 2019), were expected to reduce the number of actively infected patients.¹⁻⁴ While the number of treated patients has increased, the number of untreated, infected patients continues to be significant.⁵⁻¹³

A study of predominantly African American (AA) patients in our university medical practice, during the interferon era (2002-2003) and prior to the introduction of DAAs (2012-2013), confirmed that the AA population was within the age cohort for our patients through 2013.⁵ While this aging cohort has traditionally represented the bulk of patients with HCV, the possibility that younger patients will be identified in recent populations is an important area of investigation.⁶

New infections with HCV continue to occur in the United States, with an estimated 2.4 million Americans living with HCV in 2018. The opioid epidemic appears to be an important contributor for the

increase in younger populations being infected with HCV.⁷ This has been associated with HCV infections and may be contributing to an increasing challenge for the eventual eradication of HCV. Support of this observation is found in multiple reports of an increase in HCV in younger individuals between 2006 and 2019, although many of these studies had significantly fewer AA as compared to non-AA patients.⁸⁻¹³ These observations are further confounded with respect to identification and linkage to care by the fact that many of these increases may be in underserved patient populations.¹⁴⁻¹⁷

The aim of this study was to characterize the 2019 HCV patient population seen in our predominately African American urban GI clinic. The project was designed to assess the demographics and treatment status of the population, given that second generation DAA's have been available since 2014 and HCV screening guidelines focusing on the aging cohort population have been in effect for several years. Also, since 2008, Medicaid guidelines have covered treatment of all patients with HCV regardless of fibrosis levels, thereby removing many cost barriers to treatment. This should have led to an increase in the number of treated patients both prior to and during clinic visits in 2019.

Materials and methods

The study was approved by the Wayne State University Institutional Review Board (WSU IRB approval number 093313M1E).

All patients with HCV over the age of 18 with at least one visit to the WSU gastroenterology or infectious disease clinics in 2019 were identified by their ICD-10 code and included in the study. After all patients were identified, they were evaluated via retrospective chart review of their electronic medical records (EMR). Using a study-defined and password protected case report form, the EMR charts were reviewed to confirm HCV infection and gather information including demographics (age, gender, race, BMI), laboratory studies (liver enzymes, platelets, coagulation studies, HCV genotype), fibrosis assessment by FibroScan, and treatment history. Fibrosis was also evaluated using serum based calculations of the AST Platelet Ratio Index (APRI= ((AST value /AST upper limit)/Platelet Count) x 100) and FIB-4 (FIB-4= (Age(years) x AST)/(Platelet Count x Sqrt(ALT)).

Linkage to care was assessed by determining whether patients who were seen, but not treated, in 2019 were subsequently treated in the first six months of 2020. Statistical analysis was performed using JMP software from SAS. Data was entered into the JMP statistical software program from Statistical Analysis Software (SAS). Numeric data was plotted and evaluated using ANOVA and character data evaluated using Pearson’s chi-square analysis. Statistically significant differences were defined as a p value <0.05.

Results

Demographics

There were 601 patients with documented HCV infection with at least one visit to gastroenterology (GI) or infectious diseases (ID) clinics in 2019. Most patients were African American (AA) (85%) and male (66%). Most patients had not received any treatment at their first 2019 visit (n= 439; 73%). The demographics and relevant laboratory values for all patients and untreated patients are presented in Tables 1 & 2. The most striking racial disparity was seen with patients’ age. AA patients were older than non-AA patients in both the total and untreated patient populations. As shown in the plots representing the age of untreated patients (Figure 1), this was true for both genders, with non-AA females being significantly younger in both populations. Based on the shaded area in the upper graph in Figure 1, which represents the patients in the CDC screening age cohort, and in the mosaic plots in the lower graph in Figure 1, significant numbers of non-AA patients were younger than the age cohort (8% AA vs 50% non-AA; p<0.0001). As shown in Tables 1 and 2 and Figures 1, although non-AA females were the minority in the population, they were the group with the most patients less than 54 years of age.

Table 1A Demographics, Laboratory Values and Fibrosis by Race and Gender of All HCV Patients

	AA Male(n=337)	AA Female(n=176)	Non-AA Male(n=57)	Non-AA Female(n=31)	P value; ANOVA or Pearson
Age	63(0.46) [#]	62(0.65)	55(1.13)	43(1.45)	p=0.0001
Out of Age Cohort(<54)	6.5%	12.5%	37%	74%	p=0.0001
BMI	27(0.33)	30(0.46)	26(0.8)	29(1.13)	p=0.0001
Albumin	4.07(0.02)	3.88(0.03)	4.18(0.06)	4.2(0.08)	P=0.001
PT	10.9(0.06)	11.0(0.08)	10.9(0.14)	10.6(0.19)	P=0.25
Platelets	227(4.3)	232(5.8)	210(10)	260(14.1)	p=0.048
AST	43.4(1.5)	45.5(2.0)	50.9(3.5)	41.3(4.9)	p=0.22
ALT	41.2(1.6)	36.8(2.2)	62.1(3.9)	48.7(5.4)	p=0.0001
APRI	0.56(0.03)	0.67(0.05)	0.75(0.09)	.47(0.12)	p=0.11
FIB-4	2.24(0.12)	2.88(0.17)	2.23(0.30)	1.32(0.40)	P=0.012
FibroScan	9.8(0.93)	12.6(1.1)	13.0(2.2)	9.0(3.5)	P=0.19

(values in parentheses is standard error of the mean)

Table 1B Demographics, Laboratory Values and Fibrosis by Race and Gender of Untreated HCV Patients

	AA Male(n=243)	AA Female(n=130)	Non-AA Male(n=43)	Non-AA Female(n=23)	P value; ANOVA or Pearson
Age	63(0.6) [#]	61(0.8)	53(1.3)	38(1.8)	P=0.0001
Out of Age Cohort(<54)	8%	15%	44%	87%	P=0.0001
BMI	26(0.4)	30(0.5)	25(0.9)	27(1.3)	P=0.0001
Viral Load	4.7 M	2.72 M	2.5M	2.1M	P=0.83
Genotype 1(%)	94%	94%	68%	53%	P=0.0001
Albumin	4.0(0.03)	3.8(0.04)	4.2(0.07)	4.3(0.09)	P=0.001
PT	10.9(0.08)	11.0(0.09)	10.8(0.17)	10.3(0.24)	P=0.02
Platelets	227(5.0)	236(6.8)	220(12.1)	267(16.5)	P=0.09

Table Continued...

	AA Male(n=243)	AA Female(n=130)	Non-AA Male(n=43)	Non-AA Female(n=23)	P value; ANOVA or Pearson
AST	45(1.7)	47(2.3)	50(4.1)	41(5.6)	P=0.45
ALT	42(1.7)	38(2.4)	60(4.1)	49(5.6)	P=0.0001
APRI	0.65(0.05)	0.72(0.07)	0.68(0.12)	0.46(0.16)	P=0.34
FIB-4	2.36(0.15)	2.78(0.21)	1.97(0.37)	1.07(0.49)	P=0.009
FibroScan	9.4(1.0)	12.6(1.4)	10.9(2.4)	7.8(3.6)	P= 0.266

(values in parentheses is standard error of the mean)

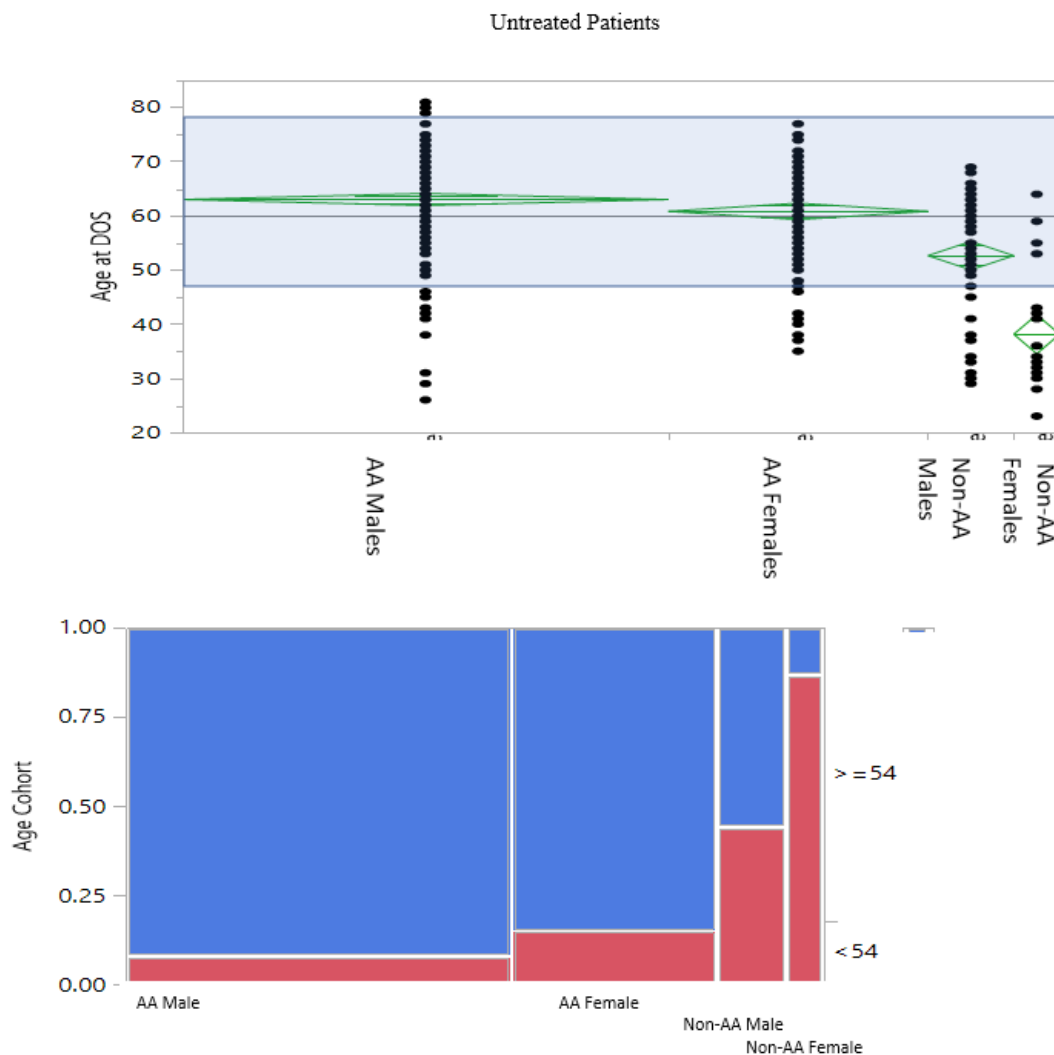


Figure 1 Age at first visit by gender and race of untreated HCV patients (n= 439) Non-AA HCV patients were younger than AA patients (p<0.0001). The shaded area in the upper graph represents patients who are in the CDC age screening cohort (age 54-79 in 2019). The lower figure is the patient’s age expressed as a mosaic plot. The data is older age cohort (≥54 years of age in 2019) or the younger age cohort (<54). The width of the bars is proportional to the size of the group. The y-axis represents proportion of patients in each group. The Pearson chi square significance is p<0.001 for both populations.

HCV infection and race

Since most patients were not treated, it was possible to evaluate viral titers and HCV genotype of untreated patients that were seen in 2019. Viral titers were not significantly different by race or gender (Table 2). Viral genotypes, however, were significantly different by

race, as defined by the percentage of patients with genotype 1 (94% for AA vs 60% for non-AA). Table 3 & Figure 2 which presents the complete genotype distribution, genotypes 2 and 3 were the primary genotypes that account for the difference between AA patients and non-AA patients.

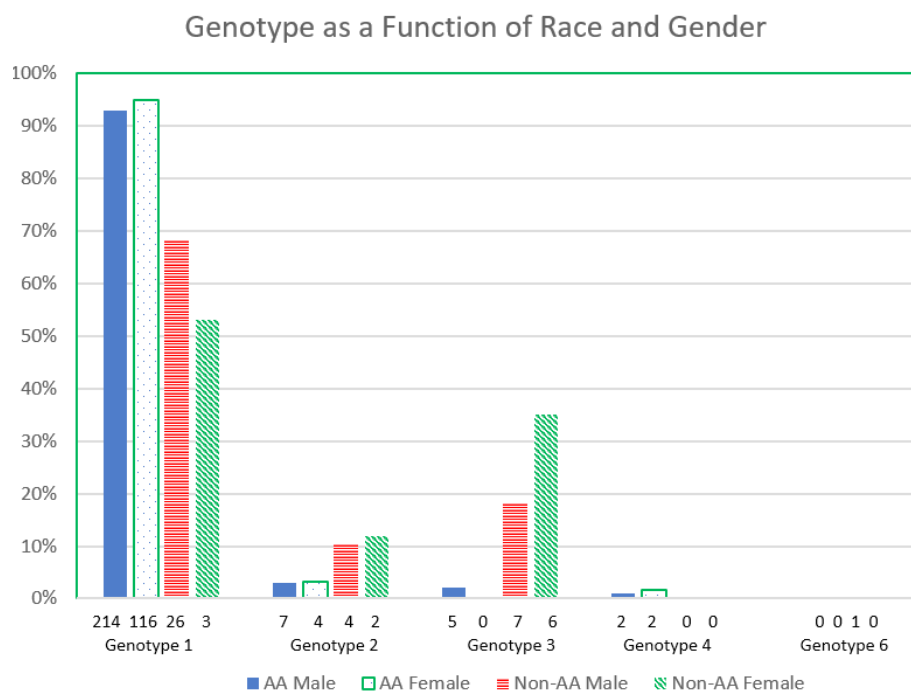


Figure 2 Genotype as a function of race and gender for untreated patients. The four groups of patients (AA Male, AA Female, Non-AA Male, and Non-AA female) were plotted as a function of the percent of patients with each of the 5 genotypes measured in the population. The number of patients in each group is presented on the x-axis above the genotype legends. Genotypes 2 and 3 were more likely to be found in non-AA patients as compared to AA patients ($p < 0.0001$).

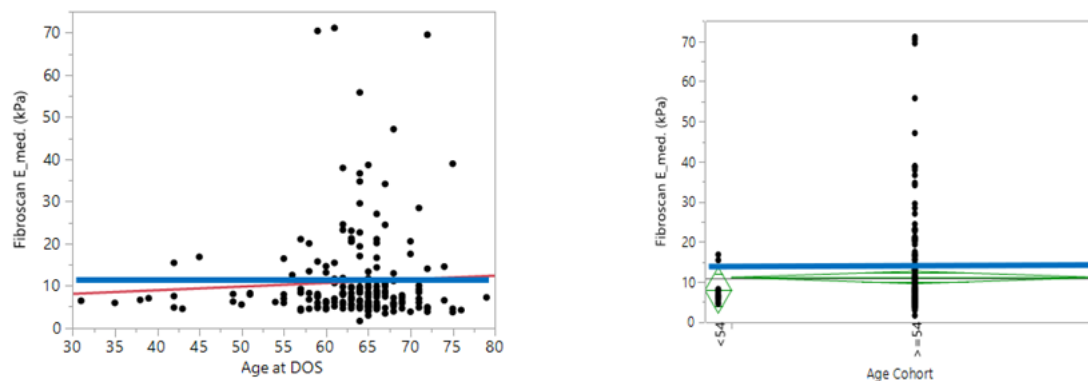
Laboratory values and fibrosis

Inflammation represented by ALT was the most significantly different laboratory value in untreated patients (Table 2). Males had higher ALT values than females of both races ($p < 0.001$). Additionally, non-AA patients had higher ALT values than AA patients ($p < 0.001$).

There was minimal difference in the APRI between the four groups of untreated patients when evaluated by race and gender (Table 2). Fib-4 was statistically lower in non-AA compared to AA patients. This difference may be accounted for by the fact that FIB-4 includes patient age in the numerator and non-AA patients were younger. No biopsies were performed in 2019 for the patients in the dataset. FibroScan, using transient elastography was performed for

most patients. The results for untreated patients are presented in Table 2. There was no statistically significant difference in fibrosis between race and gender. Since fibrosis is likely increased as a function of age and time elapsed post infection, we compared AA to non-AA patients by FibroScan and age. As shown in Figure 3, fibrosis by FibroScan is more advanced in the aging individuals, the majority of whom are in the AA group as compared to the non-AA group. This observation is true for age as a continuous variable (left panels in Figure 3) and as stratified for aging cohort (right panel Figure 3, ≥ 54) or younger cohort (< 54). A significant number of older patients had minimal fibrosis, raising questions about the time that infection was acquired and patient variability for development of fibrosis.

AA Untreated Patients



Non-AA Untreated Patients

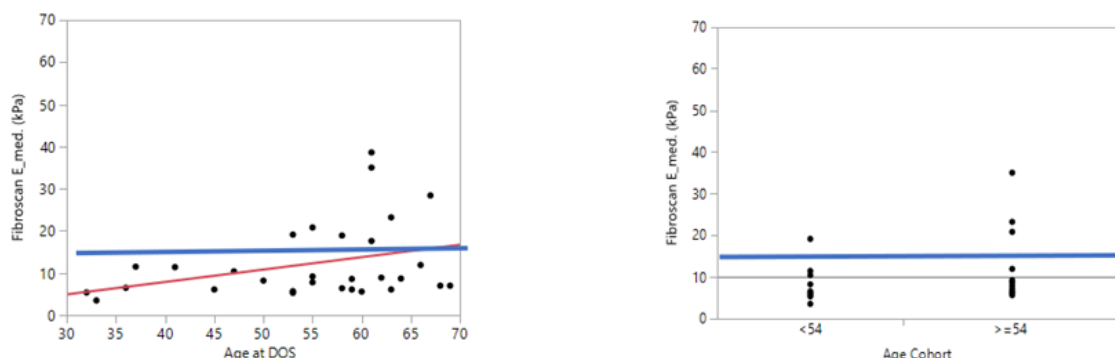


Figure 3 Fibrosis determined by FibroScan by age and race in untreated HCV Patients. The plots on the left display age as a continuous variable versus FibroScan value. The plots on the right display patients who are in the CDC age cohort (≥ 54) compared to those who are younger (<54). The blue line represents the FibroScan value (12.5 kPa) that indicates significant fibrosis and cirrhosis. The red fit line for the non-AA patients is consistent with an increase in fibrosis as a function of age (fit probability=0.043) whereas the AA patients are not statistically correlated with age. The fibrosis difference in the categorical plots for non-AA patients is statistically significant ($p=0.047$), whereas the AA patients are not.

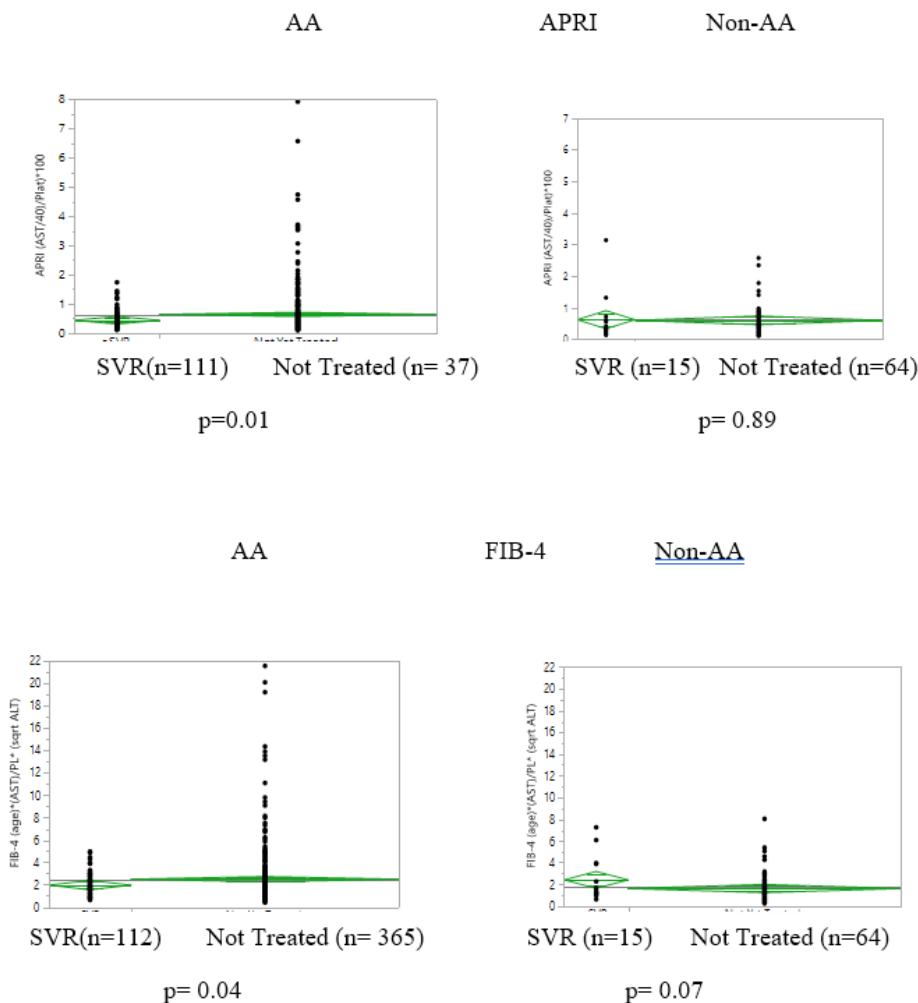


Figure 4A Comparison of laboratory assessed Fibrosis between SVR and untreated patients by race. Successfully treated HCV patients prior to 2019 compared to patients not treated at their first 2019 visit. The data is by race and the number of patients in each group are listed on the x-axis. The p values are for Student's t test between the two groups.

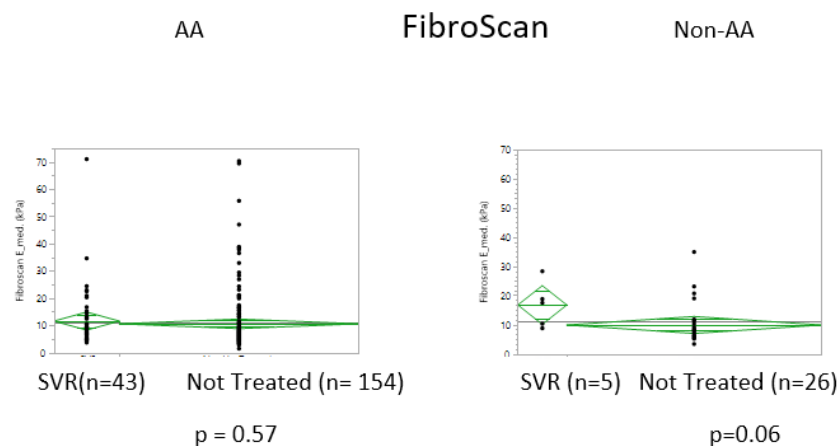


Figure 4B Comparison of FibroScan measured fibrosis between SVR and untreated patients by race. Successfully treated HCV patients prior to 2019 compared to patients not treated at their first 2019 visit. The data is by race and the number of patients in each group are listed on the x-axis. The p values are for Student's t test between the two groups.

Treatment

There was no racial disparity among AA and non-AA patients in terms of treatment status at the time of the first clinic visit in 2019 (23% vs 22% not treated). If patients had been treated, they were very likely to have achieved viral clearance (>95% SVR). Overall, of the patients who had not been treated at their first visit, only 146 out of 439 (33%) were subsequently treated in 2019 or the first 6 months of 2020.

In contrast to the management of HCV patients in the interferon era exclusively by hepatologists, patients in 2019 were seen and treated by both gastroenterology (73%) and infectious disease specialists (27%).¹⁸ The primary combination DAAs used were ledipasvir and sofosbuvir (Harvoni), glecaprevir and pibrentasvir (Mavyret), and sofosbuvir and velpatasvir (Epclusa), with SVR rates for all three being greater than 95%.

Fibrosis and treatment response

Patients who achieve SVR have better outcomes than patients who are not treated.¹⁹ It is not clear, however, whether this is due to an interruption of the progression of fibrosis or whether an actual reversal of fibrosis occurs. Patients who achieved SVR were compared to untreated patients to evaluate differences in fibrosis. Lower fibrosis by APRI and FIB-4, but not FibroScan, was seen in AA SVR patients, but not in non-AA patients (Figure 4 a,b). An important caveat to this observation is that, unlike the interferon-based therapies, DAAs can be used in patients with cirrhosis. Of the patients treated in 2019, 28% had advanced fibrosis or cirrhosis (F3 or F4 as defined by FibroScan).

Discussion

Our urban clinic population-based study of HCV infected patients was comprised of primarily African American patients. Although this population continues to be dominated by patients in the CDC defined age cohort (born between 1915 and 1965), there were still significant numbers of younger patients. In this younger cohort, the most striking difference was the greater percentage of non-AA patients, specifically with respect to female gender. These findings contrasted with the aging cohort, or “Baby Boomers,” in the AA population. An unexpected observation revealed that AA patients continued to have dominance of genotype 1 (94%), while non-AA patients were more likely to have genotype 2 and 3.

The findings of race and age disparity were also unexpected. The extent of involvement of racial diversity in the opioid epidemic is unknown. Unlike the AA population that is dominated by the age cohort, the young age of the non-AA patients stands out compared to young patients in the AA population. This contribution of age to the genotype distribution in non-AA patients is unclear from this study.

While the improved HCV cure rate in the age cohort population after the advent of DAA therapy might predict a decline in untreated older AA patients in the clinic, the age cohort continues to dominate the AA population.^{3,4} It is unclear from this study why this population did not decline because of mortality from liver disease or other comorbidities that dominate our underserved population. One unexplored possibility is that the age cohort of HCV patients may have been considerably underestimated in the AA community.

The Centers for Disease Control and Prevention (CDC) and USPSTF have also made recent recommendations for one-time screening of all patients above the age of 18 for HCV, as opposed to risk-based screening. The extension of screening to all adults may have also contributed to the increasing incidence in the younger population. Alternatively, this increase may just reflect significant numbers of patients who exhibit risk-based behavior and were identified through risk-based screening.^{2,18} This study did not assess whether the younger screening cohort recommendation, risk-based assessment, or laboratory abnormalities (i.e. elevated transaminases) triggered the HCV assessment visit.

The emergence of younger patients in our HCV population has implications for the importance of screening all patients 18 years and above, especially in the primary care setting where most patients are likely to be detected. Patient outreach and increasing patient awareness are also vital components of increasing detection, as most patients with chronic HCV do not exhibit symptoms until they develop significant fibrosis or cirrhosis. They would remain contagious and could unknowingly infect others. Earlier detection of HCV and linkage to care can prevent the progression to fibrosis and cirrhosis, which in turn will help decrease healthcare expenditures for decompensated cirrhosis and liver transplantation.

In our study, we found that we still fail to initiate treatment in many of our patients. The fact that fewer patients may have initiated treatment and followed up in 2020 could be explained by the

COVID-19 pandemic. However, these findings will need to be further elucidated in the future. We hypothesize that a more relevant issue is the length of time from identification of HCV infection via viral testing to initiation of treatment. It is possible that treating earlier (i.e. prior to complete a clinical assessment via ultrasound, FibroScan, and current labs) would result in more patients being treated.^{20,21}

There was a lower rate of fibrosis in younger patients compared to the older cohort. This difference was not as pronounced as anticipated, as significant numbers of older AA patients still had minimal fibrosis. This could be due to a later age of HCV contraction and decreased exposure time. An increased prevalence of fibrosis risk factors in the younger cohort with alcohol consumption and obesity could also account for increased fibrosis in younger patients. Future studies that address the impact of other risk factors on fibrosis in this patient cohort are warranted.

As a retrospective study, there are possibilities for the introduction of selection, recall, or misclassification biases, as well as unidentified confounding factors. Attempts were made to offset any risk of bias with carefully defined inclusion criteria, using clear definitions and cutoffs for the variables in the data collection, and ensuring that all data was collected in a similar way using a defined case reporting form. We also had a large sample size which lent to our findings being adequately powered. Lastly, our study was conducted at a single center with a population of primarily AA patients in an urban setting. Our findings may not be extrapolated to the general population, which is comprised of non-AA patients, private health insurance, and is in suburban or rural settings. Prospective studies with more diverse cohorts in various settings are warranted.

Conclusions

Our study revealed a trend toward younger non-AA females presenting with HCV genotype 2 or 3 infection. AA HCV-infected patients were older and more likely to have genotype 1, and with less inflammation (ALT) as compared to Non-AA patients. While fibrosis in our population correlates with age, there was a significant number of older AA patients with minimal fibrosis. Further evaluation of these patients may reveal a more recent acquisition versus a slower development of fibrosis over time.

In our patient population, there was a low rate of treatment for HCV in patients who were diagnosed. This could possibly be attributed to the COVID-19 pandemic and the hesitancy of patients to seek non-emergent medical care during that time. However, there are other possible contributing factors which would need to be elucidated.

Given the trend toward a younger cohort of HCV infected patients as well as a continued low treatment rate, it is important to offer a one-time HCV screen for all patients above the age of 18 with linkage to care. It is also critical to find a means to ensure infected patients are identified and treated immediately, rather than via a prolonged liver status assessment prior to treatment. Our data confirms the continuing need to ensure linkage to all HCV patients to prevent additional HCV transmission and future liver disease manifestation.

Acknowledgments

None.

Conflicts of interest

Authors declare that we have no conflicting interests.

Funding

None.

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