

Similarities in Hepatitis C Patient Profiles Over a Decade in an Urban GI Clinic

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ABSTRACT

INTRODUCTION: There is considerable uncertainty with respect to predicting the liver disease status of African American (AA) patients with Hepatitis C seen in the current era of highly effective direct acting anti-virals (DAA). This uncertainty is due to the complex interplay between the identification of patients early in their disease progression by screening, the fact that many AA patients failed earlier interferon based therapy, duration of the HCV viremia in AA patients, the possible variation in disease course in AA as compared to other races, and potential early mortality of AA patients due to liver disease. Understanding the evolution of HCV infection as defined by comparing previous and current patient populations provides information relevant to both therapeutic and health costs decisions.

METHODS: We selected patients from a 24 month period between

2002 and 2003 (Epoch 1; $n = 414$) to compare with patients seen in the same GI clinic between 2012 and 2013 (Epoch 2; $n=405$). Epoch 1 was the beginning of the peg-interferon and ribavirin treatment era and Epoch 2 reflects the patient population seen when DAA therapy was first available.

RESULTS: Epoch 2 patients were older (59.7 vs 50.3 years) with a similar gender distribution (55% vs 59% male). Consistent with the change in clinic demographics, more AA patients were seen in Epoch 2 (89%) as compared to Epoch 1 (77%). There was no significant difference between hepatic fibrosis as assessed by APRI (1.1 vs 0.9) or FIB-4 (2.4 vs 2.6) but there was an increase in intermediate degree of fibrosis as defined by liver biopsy. The majority of Epoch 2 patients were still naïve to treatment (96% Epoch 1 vs 61% Epoch 2) and a similar proportion had cirrhosis (15% Epoch 1 vs 17% Epoch 2) at the time of first visit in the different time periods.

CONCLUSIONS: The patients in Epoch 2 from this urban GI referral clinic are older and the majority of them had not been treated or had not responded to treatment. This age demographic continues to reflect patients who were likely infected during the 1960's-1980's which is when HCV infection became widespread. Epoch 2 patients also do not have more advanced liver disease as defined either by significant fibrosis or cirrhosis as compared to Epoch 1. Possible explanations include that Epoch 2 patients' disease was detected earlier by surveillance, progressed very slowly to advanced liver disease, or had a high mortality that resulted in a decline in patients with advanced disease. The role of access to therapy in patients not treated remains to be determined and the increased effectiveness of DAA are predicted to increase the number of AA patients seeking and accepting treatment.

Key words: Viral hepatitis; Hepatitis C; African Americans; Fibrosis; Cirrhosis

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BACKGROUND

In the United States there is a reported prevalence of approximately 2.7-3.9 million people chronically infected with HCV (antibody to HCV present with HCV RNA positive)^[1-3]. The true prevalence when underreported populations are taken into account likely is between 5-7 million people^[1]. Chronic Hepatitis C (CHC) is often an asymptomatic infection that can go years undetected, indeed the majority of chronically infected patients are not aware of their infection^[3,4]. In an effort to increase screening, the U.S. Centers for Disease Control and Prevention recommends a 1-time HCV testing of persons born between 1945-1965^[5]. As of 2007, chronic HCV

Table 1 Changes in Demographics over a 10 year period.

	Epoch 1 (2002-3)	Epoch 2 (2012-3)	
Total Patients	N = 414	N = 405	
Male	245 (59%)*	224 (55%)	
Race			
African American	324(78%)	359 (89%)	<i>p</i> < 0.0001
Caucasian	78 (19%)	21 (5%)	
Other	12 (3%)	25 (6%)	
Age (years)	50 +/- 8**	60+/- 8	<i>p</i> < 0.0001
BMI *(kg/m ²)	28 +/- 7	29 +/- 6	
Genotype			
1	311 (75%)	362 (89%)	<i>p</i> < 0.001
2	22(5%)	13 (3%)	
3	21 (5%)	8 (2)	
4	3 (1%)	0	
Unknown	57 (14%)	22 (5%)	
Sub-Genotype 1			NS
1a	194 (47%)	161 (40%)	
1b	121 (29%)	112 (28%)	
Unknown	99 (24%)	132 (32%)	
Co-morbidities			
Renal Disease	42 (10%)	43(11%)	
Cardiovascular	200 (48%)	256 (63%)	<i>p</i> < 0.05 ***
Diabetes	81 (20%)	87 (22%)	
Psych/Neuro	37 (10%)	43 (10%)	
Number Biopsied			
Number Biopsied	255 (62%)	75 (19%)	
Number previously treated			
AA (<i>n</i> = 324/313)****	1%	8%	<i>p</i> < 0.001
Cau (<i>n</i> = 78/19)	23%	21%	

* number of patients and % total; **+/- standard error of mean; ***primary due to increase in hypertension; ****number in epoch1/ number in epoch 2; excludes patients with an unclear past treatment history.

Table 2 Change in Viral Disease Status between Patients over a 10 Year Period.

	Epoch 1				Epoch 2				t-test
	number	Value	STD	SEM	number	Value	STD	SEM	
Viral Load	327	1.2 × 10 ⁶	4.0 × 10 ⁶	0.2 × 10 ⁶	267	5.1 × 10 ⁶	49.3 × 10 ⁶	0.5 × 10 ⁶	<i>p</i> < 0.0005
ALT	373	77	63	3	334	61	47	3	<i>p</i> < 0.0005
AST	376	70	55	3	333	56	44	2	<i>p</i> < 0.0005
Albumin	327	3.9	0.6	0.03	321	3.8	0.48	0.03	<i>p</i> < 0.05
Platelets	374	211	81	4	319	207	74	4	NS
Fibrosis									
Metavir	255	1.72	1.4	0.87	75	2.07	1.15	0.13	<i>p</i> < 0.05
APRI	357	1.09	1.23	0.07	304	0.89	1.16	0.067	<i>p</i> < 0.05
FIB-4	331	2.38	2.14	0.12	304	2.56	2.65	0.15	<i>p</i> = 0.34

infection resulted in more deaths than those attributed to HIV^[2]. One explanation for this is the well-known evolution of chronic hepatitis C to complications such as cirrhosis, hepatocellular carcinoma (HCC) and death from liver failure. In a recently reported study, the development of HCC approached 25% over an average period of 9 years in non-treated African Americans seen in our GI clinic^[6]. Mortality for HCV positive AA patients seen consecutively in a prospective study in our clinic between 1995 and 2008 was 20% with average age at death of 56 years and time to death of 6 years from the first visit^[7]. While this suggests that patients seen in the earlier era were identified when they had more advanced liver disease, it is unclear whether patients seen in the current era will have more advanced liver disease at first visit. This study is of import since the majority of patients seen in our clinic are AA and these patients were less likely to respond to the interferon based therapies available prior to the current DAA era^[8,9]. It is also anticipated that more patients will be seeking treatment with the introduction of DAA, due to their improved tolerability and efficacy^[12]. Based on recent studies, it has been shown that when they receive treatment, AA patients are noted to have better adherence to the DAAs than has been historically observed with previous HCV treatment regimens^[12,13].

The goal of our study was to compare the characteristics of patients recently referred to the GI clinic in the time period between 2012-2013 to those seen 10 years previously in the time period from 2002-2003. Our hypothesis was that the recent patients would be older and have more advanced liver disease.

METHODS

Using electronic medical records databases of patients seen in an academic urban GI practice between 1995 and 2013, we selected patients from a 24 month period between 2002 and 2003 (Epoch 1) to compare with patients seen between 2012 and 2013 (Epoch 2). Epoch 1 was selected as a time when patients were treated with peg-interferon and ribavirin (*n* = 414). Epoch 2 was chosen to reflect the advent of the DAA (*n* = 405). Data collected included demographics, liver function tests, HCV relevant results (genotype, viral load), imaging, EGD, biopsy results and treatment history. Genotype subclassing was more commonly assessed in Epoch 2 patients than in Epoch 1 patients. AST Platelet Ratio Index (APRI), and FIB-4 were used to define the degree of fibrosis in patients.

RESULTS

Epoch 2 patients were older (60 vs 50 years), but had a similar distribution of gender, BMI, and co-morbidities to Epoch 1 patients (Table 1). The majority of patients in both epochs were AA and genotype 1. Although more patients had been previously treated prior

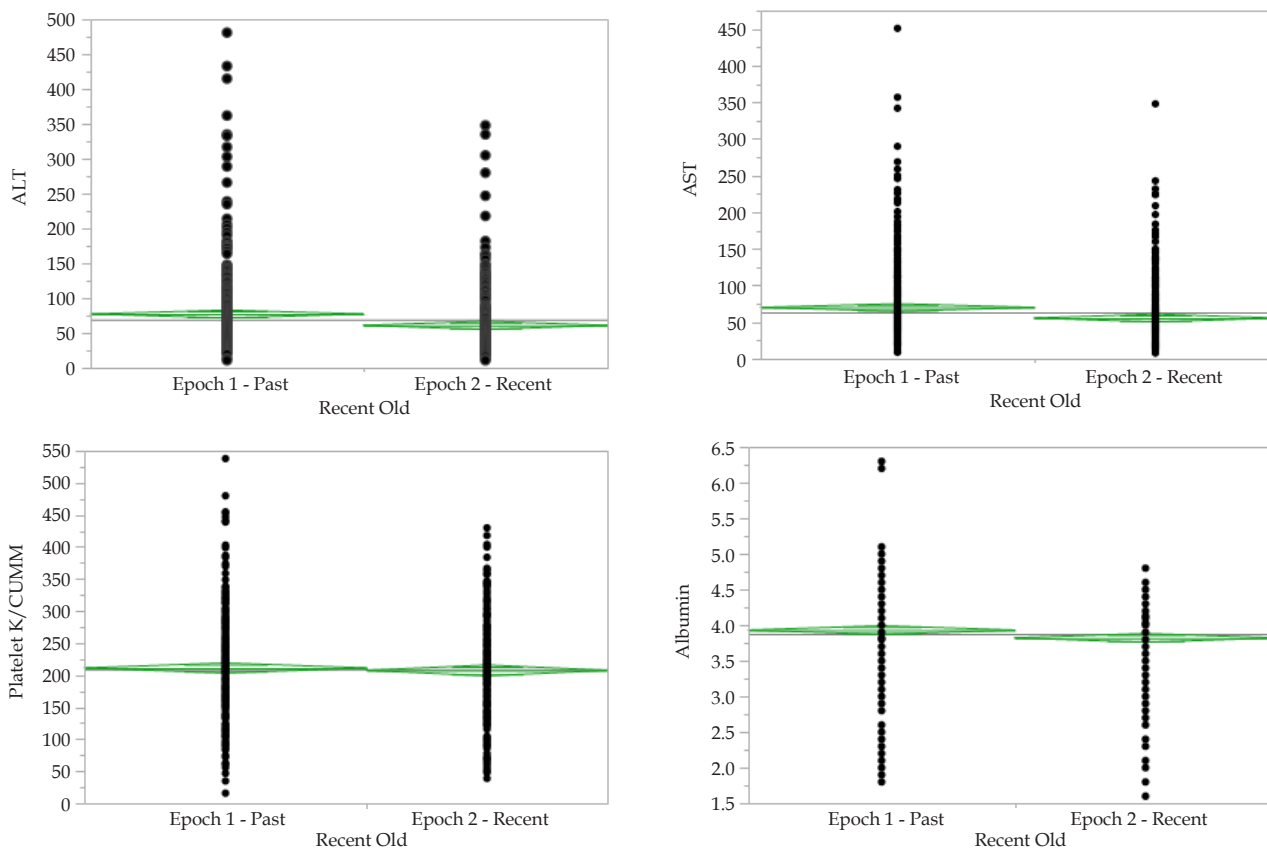


Figure 1 Serum laboratory values which are associated with liver function were evaluated in patients in both Epochs. ALT, AST, Platelet count and Albumin were all slightly lower but the wide range of values between patients suggests that on an individual patient basis, there was not a significant increase in liver disease as defined by overall laboratory values.

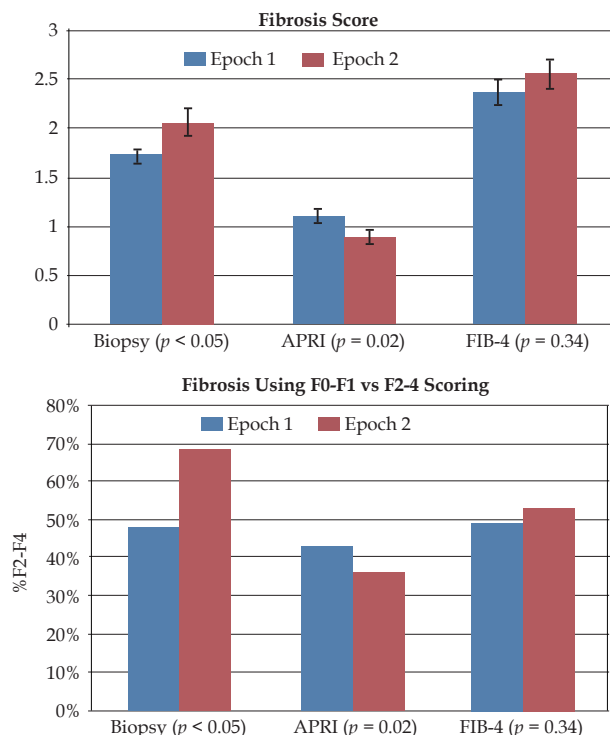


Figure 2 Fibrosis comparison between Epochs using both numeric and categorical assessment. Fibrosis was assessed either by numerical value (upper) or category (lower). Using Student's *t*-test (top), biopsy results suggest that there is a possible increase in advanced fibrosis in the recent Epoch as compared to the past. APRI and FIB-4 were less different. When categorizing the patients into minimal fibrosis (F0-F1) vs significant fibrosis (F2-F4), again biopsy results also suggested an increase in significant fibrosis in the recent patients compared to the past.

to the first visit in Epoch 2, racial disparity for treatment was more apparent in Epoch 1 as compared to Epoch 2 (Table 1).

The possibility that the patients in Epoch 2 had significantly more advanced liver disease was evaluated in multiple ways. These included, comparing albumin levels, platelet counts, HCV RNA levels in serum and assessment of fibrosis/cirrhosis by biopsy, imaging, and biochemical evaluations (APRI and FIB-4) (Table 2, Figures 1-3). Although the serum viral levels were higher in Epoch 2 patients, there was minimal variation in the levels of other individual serum markers of liver disease (Figure 1 and Table 2). Since the patient numbers were large, The mean values were statistically lower number for four typical liver function parameters (ALT, AST, Albumin, Platelets) in Epoch 2 patients, however the wide range in values suggests a similar distribution in liver disease status between the two Epochs (Figure 1). Liver biopsy was performed in 255 Epoch 1 patients and 75 Epoch 2 patients. Average fibrosis score was greater in Epoch 1 patients (Figure 2 $p < 0.05$), due predominately to an increase in patients with intermediate fibrosis (Figure 3 $p < 0.001$). Using surrogate markers such as APRI, FIB-4 and ultrasound assessment of the liver, patients in Epoch 2 were not significantly or minimally different with respect to average fibrosis, fibrosis by category (F0-F1 vs F2-F4), or cirrhosis (Figure 2 and 3).

The absence of cirrhosis was consistent between the Epochs (85% Epoch 1 vs 83% Epoch 2) and this finding was observed regardless of the assessment method. In the non-cirrhotic Epoch 2 patient group, 208 out of 319 had viral loads less than 6 million. When non-cirrhotic patients with low viral load and no previous treatment were identified, there were 125 patients (31%) eligible for the shorter term 8 week treatment suggested for sofosbuvir/ledipasvir^[11].

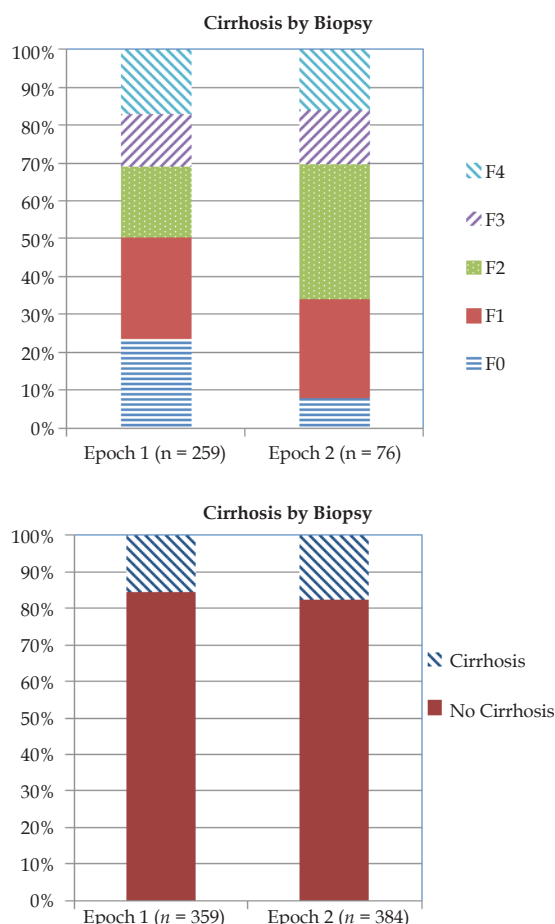


Figure 3 Cirrhosis between the two epochs was defined by biopsy or a combination of biopsy, ultrasound and APRI. A. Epoch 2 patients have different biopsy based fibrosis profiles with an increase in the intermediate fibrosis scores F2 ($p < 0.002$). There is no difference in either cirrhosis (F4) or significant fibrosis (F3). B. When defining cirrhosis by a combination of biopsy, ultrasound and/or APRI, cirrhosis was similar between the Epochs and in both Epochs cirrhosis prevalence was low (~15%).

DISCUSSION

The liver disease status of AA patients with HCV seen in the era of highly effective DAA is similar to that of patients seen 10 years previously. This study provided evidence on that issue, yet the interpretation of the characteristics of the cohorts studied does require knowledge of a complex interplay of factors. The ethnic makeup of this study is notable as AA patients are more prone to have failed earlier interferon based therapy^[8,9]. Further, AA patient populations have historically had decreased access to care and a comparatively lower likelihood for treatment when care is established^[14].

To date the impact of the increase in length of time with infection prior to treatment in AA patients has been undefined. The majority of patients in Epoch 2 had either not received treatment or had not responded to treatment for HCV. Notably, despite the increase of mean patient age by 10 years, the study did not reveal a significant increase in the fibrosis scores or the presence of cirrhosis in Epoch 2. This was an unexpected finding given the aforementioned poor treatment responses of AA patients to the standard treatment regimen of Epoch 1. Although there were marginally higher fibrosis scores and an increased presence of intermediate fibrosis (F2) in those who were biopsied in Epoch 2, it is likely those biopsied represented a higher-risk population in the setting of other modalities present in that time period for assessing the extent of liver injury.

It is possible that an increased identification of HCV-affected patients attributable to the evolution of surveillance guidelines is what led to the detection of patients with earlier stage disease in Epoch 2. Yet, as the majority of the HCV outbreak took place between roughly sixty to forty years ago, the disease likely had a longer period of time in which to progress in the older Epoch 2 cohort^[5]. This could suggest unusually slow disease progression. Another possibility is that patients whose disease evolved to a more advanced stage in the interim years had a high mortality rate and were subsequently not represented in Epoch 2. This latter possibility, when viewed together with the finding that a significant proportion of Epoch 2 patients qualified for shorter 8 week DAA treatment regimens, would significantly strengthen the argument for the cost-effectiveness of augmenting access to HCV screening and treatment, particularly in historically underserved AA populations^[8,14,15].

A HCV cohort comparison study of similar design was performed at the University of Michigan. This study showed older patients with more significant liver disease in the latter of the two cohorts^[16]. Notable differences with the UMich study include its predominately Caucasian (> 80%) patient population and its location in a liver disease based clinic^[16]. There are multiple possibilities to explain the more advanced liver disease found in the UMich study despite the similar time periods analyzed. It is possible the setting of the UMich study in a liver disease based clinic rather than a general GI clinic led to referrals of a population with more advanced disease^[16]. Another possibility may relate to the ethnic background of the respective patient populations and a difference in the natural progression of the disease within them. Prior studies suggest a more aggressive disease in AA patients potentiating a rapid progression to mortality when disease progresses^[6,7,17,18].

There are several limitations to this study. First, the relative lack of biopsies in Epoch 2 required the use of less accurate surrogate markers such as ultrasound, APRI, and FIB-4^[19]. Second, the small number of Caucasians in this study limits the statistical accuracy of race comparisons. A third limitation is that more patients in Epoch 2 could not confirm or deny previous treatment, reducing the population numbers in that group. Yet the key observation of this analysis, that current AA patients do not have significantly more advanced disease as compared to patients ten years prior, remains valid in spite of these limitations.

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