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Changes in characteristics of hepatitis C patients seen in a liver centre in the United States during the last decade

N. Talaat, S. Yapali, R. J. Fontana, H. S. Conjeevaram and A. S. Lok *Division of Gastroenterology and Hepatology, University of Michigan Health System, Ann Arbor, MI, USA*

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SUMMARY. With the approval of 2 direct-acting antivirals (DAAs) in 2011 and anticipation of interferon (IFN)-free regimens, more hepatitis C virus (HCV) chronically infected patients are now seeking treatment. To describe the characteristics of newly referred HCV patients in 2011–2012 (Era-2) and compare them to those seen in 1998–1999 (Era-1). Retrospective data were collected from HCV patients newly referred to our tertiary liver clinics. Advanced liver disease was defined as cirrhosis (based on histology or Aspartate aminotransferase–platelet-ratio index (APRI) >2), hepatic decompensation or hepatocellular carcinoma (HCC). A total of 1348 patients (538 in Era-1, 810 in Era-2) were included. Compared to Era-1, Era-2 patients were older (median age 56 *vs* 45 years), more likely to be black (17.2% *vs* 11.6%) and had a longer interval between diagnosis and referral (median 4 *vs* 2 years). Genotype (GT) 1 predominated in both Eras with a significant increase in GT1a from 39.9% in Era-1 to 53.8% in Era-2. A higher per cent of patients in Era-2 were treatment experienced, but 77% had never received treatment. Era-2 patients were more likely to have advanced disease at referral (61.6% *vs* 51.5%, $P < 0.001$), with an eightfold higher prevalence of HCC (21.6% *vs* 2.6%, $P < 0.001$). HCV patients newly referred in recent years were older, predominantly infected with GT1a and had more advanced liver disease yet only a quarter had received HCV treatment. Reduction in HCV disease burden will require development of treatment regimens targeted towards patients in the current Era as well as increase in diagnosis and referral of patients for treatment.

Keywords: hepatitis C, hepatitis C treatment, hepatocellular carcinoma.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health problem. Worldwide, it is estimated that 170 million persons are chronically infected with HCV [1]. The Centers for Disease Control and Prevention estimates that 3.2 million persons in the United States (US) are chronically infected with HCV resulting in 10 000–12 000 deaths per year [2–4]. Most of these people acquired HCV infection in the 1960s and 1970s, and many are now presenting with complications of cirrhosis and hepatocellular carcinoma (HCC) 3–5 decades after their initial infection [5].

Achievement of sustained virologic response (SVR) to antiviral therapy is associated with improved morbidity and mortality [6–9]. With the rapid development of direct-acting antiviral agents (DAAs), it is anticipated that 12-week courses of interferon-free regimens with SVR rates of 90% or higher will soon be available to most HCV patients in whom cirrhosis has not yet developed [10–12]. Experience with interferon-free DAA regimens in patients with cirrhosis is limited, and available data indicate that SVR rates are lower with some regimens [12–14]. Therefore, early diagnosis and referral for treatment are important.

It is estimated that less than 50% of persons chronically infected with HCV in the US are aware of their infection [15–17]. To improve the rate of diagnosis, the US Centers for Disease Control and Prevention recently recommended a 1-time HCV testing of persons born between 1945–1965, a birth cohort with an HCV prevalence five times higher than those born earlier or later [18]. Numerous studies showed that even among those who had been diagnosed, only a small per cent of patients with chronic hepatitis C (11.6–21%) have received and completed antiviral therapy

Abbreviations: AASLD, American Association for the Study of Liver Disease; ALT, Alanine aminotransferase; APRI, Aspartate-aminotransferase-platelet-ratio index; AST, aspartate aminotransferase; DAA, Direct Acting Antivirals; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IFN, interferon; INR, international normalized ratio; PEG-IFN, pegylated-interferon.

Correspondence: Anna S. Lok, MD, Division of Gastroenterology and Hepatology, University of Michigan Health System, 1500 East Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109, USA. E-mail: aslok@umich.edu

[15–17,19]. Complexity of treatment regimens, frequent and sometimes serious adverse events, lack of health insurance coverage, contraindications due to medical or psychosocial comorbidities and low SVR rates are the common reasons cited for the low uptake of treatment [19–22].

To prepare for the launch of interferon-free regimens, we examined the characteristics of hepatitis C patients newly referred to our liver clinics in 2011/2012 and compared them with patients seen in 1998/1999. We hypothesized that compared to the 1990s, HCV patients seen in recent years are older, have more advanced liver disease, are more likely to be treatment experienced and are enriched for HCV genotypes and subgenotypes that are more refractory to treatment. If these hypotheses are confirmed, the SVR rates of interferon-free regimens in clinical practice may be substantially lower than those in registration trials.

METHODS

We conducted a retrospective study of consecutive adult patients (older than 18 years) with hepatitis C, newly referred to the liver clinics (general hepatology clinic, liver transplant clinic and liver tumour clinic) at the University of Michigan Health System (UMHS) in 1998/1999 (before the approval of pegylated interferon) and 2011/2012 (around the time of approval of two protease inhibitors – telaprevir and boceprevir). We used ICD-9 codes (070.44, 070.54, 070.70, 070.71, 155.0, 155.2, 571.5 and 571.9) to identify patients with chronic hepatitis C. Chronic HCV patients were defined as patients who had positive HCV RNA test result or positive hepatitis C antibody (anti-HCV) test result and evidence of chronic liver disease. Medical records were reviewed using the electronic medical record search engine (EMERSE) developed at the University of Michigan. The study protocol was approved by our institutional review board. Of a total of 1580 potentially eligible patients, 1348 were included in the analysis and 232 were excluded (Fig. 1).

The following data were recorded: (i) demographics, duration from diagnosis to first clinic visit, treatment status (treatment naïve *vs* any prior treatment with interferon-based therapy), and clinical status (compensated *vs* clinical decompensation *vs* HCC) at the time of presentation; (ii) laboratory values: hepatic panel (albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin), platelet count, international normalized ratio (INR) within 3 months of the first clinic visit; HCV RNA level within 12 months of the first clinic visit and HCV genotype at any point in time; (iii) liver imaging results within 6 months of the first clinic visit; and (iv) liver histology within 12 months of the first clinic visit (unless historical biopsy showed cirrhosis).

Advanced liver disease was defined as cirrhosis (compensated or decompensated without HCC) or HCC (regardless of the presence or absence of clinical decompensation or cirrhosis). HCC was diagnosed by histology or radiology per the American Association for The Study of Liver Diseases (AASLD) guidelines [23]. Decompensated cirrhosis was defined as history or presence of hepatic encephalopathy, ascites or variceal bleeding. Compensated cirrhosis was diagnosed based on histology (Ishak fibrosis score ≥5) and for the patients who did not have a liver biopsy an AST–Platelet Ratio Index (APRI) >2 [24].

Statistical analyses

Data were recorded in an electronic database (Research Electronic Data Capture [REDCap]) and transferred into SPSS software version 21 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Depending on the year of presentation, patients were grouped into two eras, Era-1 (for those first seen in 1998 & 1999) and Era-2 (for those first seen in 2011 & 2012). Descriptive statistics, medians and interquartile ranges (IQR) were calculated for continuous data, and frequencies and percentages were calculated for categorical data. For comparisons between groups, student t-test and Mann–Whitney tests were used for continuous variables and chi-square test for categorical variables. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of patients at the time of presentation

Of the 1348 patients included, 538 patients were seen in Era-1 and 810 in Era-2. Table 1 summarizes the characteristics of the patients at the time of presentation.

Demographics

Compared to Era-1, patients seen in Era-2 were older; median age was 56 years *vs* 45 years ($P < 0.001$). Figure 2 shows a shift in age distribution of patients seen in the two Eras with 77.3% of those seen in Era-2 *vs* 25.1% in Era-1 being 50 years or older at presentation ($P < 0.001$). Most patients were White, but there were more Blacks (17.2% *vs* 11.6%) and patients of other races (5.2% *vs* 2.9%) in Era-2 than in Era-1 ($P = 0.003$) (Table 1). Roughly two-thirds of the patients were men with no difference between the two Eras.

Interval between diagnosis and presentation

Compared to Era-1, the median interval between diagnosis and evaluation at our clinic was double in Era-2, 4 *vs* 2 years ($P < 0.001$). Only 39.5% of patients in Era-1 and 27.0% in Era-2 were seen within 1 year of diagnosis ($P < 0.001$).

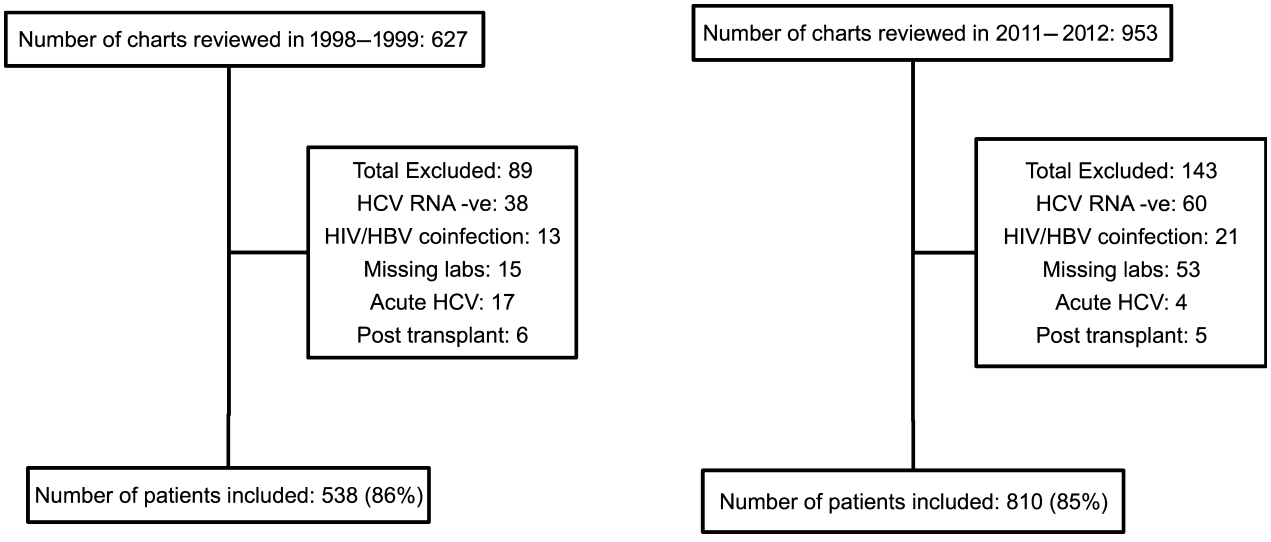

Fig. 1 Flow Diagram of Patients Evaluated in Era 1 and Era 2.

HCV genotype

Hepatitis C virus (HCV) genotype data were not available in 18.8% of patients in Era-2 and 45.5% of patients in Era-1. Unavailability of HCV genotype result among patients seen in Era-2 was largely confined to those seen in the liver tumour clinic where the physicians deemed the patients not to be HCV treatment candidates. Genotype 1 was present in 64.7% (43.7% 1a, 15.8% 1b and 5.2% unknown subtype) of patients in Era-2 and 41.8% (21.7% 1a, 13.2% 1b and 6.9% unknown subtype) in Era-1. Genotypes 2 and 3 were present in 5.2% and 6.3% of Era-1 patients and 7.5% and 7.0% of Era-two patients, respectively (Table 1). When patients with unknown HCV genotype were excluded, proportions of patients with genotype 1a increased from 39.9% in Era-1 to 53.8% in Era-2, while proportions with genotype 2 decreased from 12.6% to 6.4% and proportions with other genotypes remained stable (Fig. 3) .

Treatment status

The per cent of patients who had received HCV treatment prior to presentation at our clinic increased significantly from 17.4% in Era-1 to 23.1% in Era-2 ($P = 0.013$), but the vast majority of patients were treatment naïve. Increase in prior treatment was observed mainly in patients with advanced liver disease (19.1% *vs* 25.6%, $P = 0.043$) and those who were 50 or younger (17% *vs* 26.4% $P = 0.010$).

Stage of liver disease

Liver biopsies within 12 months of presentation for non-HCC indications were available in 293 (55.1%) patients in Era-1 and in 189 (25.2%) patients in Era-2 ($P < 0.001$). Among the patients who had liver biopsies, those in Era-2 were older, median age 55 years compared to 44 years in Era-1 ($P < 0.001$). The proportions with Ishak fibrosis 3 or 4 or Ishak fibrosis 5 or 6 in both Eras were comparable; however, a significantly lower per cent of patients in Era-2 had Ishak 0–2, 31.7% *vs* 41.3% ($P = 0.035$) (Table 1).

The proportion of patients with advanced liver disease defined as compensated cirrhosis, decompensated cirrhosis or HCC increased from 51.5% in Era-1 to 61.6% in Era-2 ($P < 0.001$). This was mainly due to an eightfold increase in patients with HCC from 2.6% in Era-1 to 21.6% in Era-2 ($P < 0.001$) (Fig. 4). Even after excluding the subset of patients with HCC who presented to the liver tumour clinic (74 patients), there was still a sharp increase in number of HCC patients from 14 in Era-1 to 101 in Era-2 and an increase in proportion of patients with advanced liver disease from 51.5% to 57.9% ($P = 0.023$). The proportion of patients with decompensated cirrhosis in the two Eras was similar, 17.7% *vs* 16.4%. This was true even after excluding patients specifically referred for liver transplant evaluation, 9.8% *vs* 8.6%. The proportion of patients with compensated cirrhosis based on a combination of histology and APRI decreased from 31.2% in Era-1 to 23.6% in Era-2. When APRI > 2 was used as the sole criterion for diagnosing compensated cirrhosis, a similar proportion of patients in Era-1 and Era-2 met criteria for compensated cirrhosis, 21.9% (118/538) *vs* 19.9% (161/810), ($P = 0.361$).

Because patients in Era-2 were older, comparison of the proportion of patients with advanced liver disease in the two Eras was repeated after stratification for age. The proportion of patients with advanced liver disease in the two Eras was similar for patients <50 years old (47.9% *vs* 49.5%) and those ≥50 years old (62.2% *vs* 65.2%), while a marked increase in HCC from Era-1 to Era-2 was observed among the patients who were <50 years old (2.0% *vs* 20.1%) as well as those ≥50 years old (4.4% and 22.0%).

Table 1 Characteristics of the patients studied

	1998–1999 (n = 538)	2011–2012 (n = 810)	P-value*
Age			
Median (IQR), Years	45 (45–50)	56 (50–60)	<0.001
≥50 years	135 (25.1)	626 (77.3)	
Gender			
Male	349 (64.9)	512 (63.2)	0.53
Race			
White	407 (85.5)	593 (77.6)	0.003
Black	55 (11.6)	131 (17.2)	
Other	14 (2.9)	40 (5.2)	
Duration from diagnosis			
Median (IQR), Years	2 (1–4)	4 (1–12)	<0.001
Treatment status			
Experienced	93 (17.4)	180 (23.1)	0.013
Platelets (k/mm3)	163 (103–211)	162 (97–226)	0.34
Albumin (g/dL)	4.0 (3.5–4.2)	4.1 (3.6–4.4)	0.100
AST (U/L)	67 (42–108)	63 (39–104)	0.66
ALT (U/L)	84 (55–132)	59 (37–97)	<0.001
Total bilirubin (mg/dL)	0.80 (0.6–1.1)	0.7 (0.4–1.2)	0.48
HCV RNA (Log_{10} IU/mL)	6.2 (5.4–8.0)	6.1 (5.5–6.6)	<0.001
HCV Genotype (GT)			<0.001
GT-1	225 (41.8)	524 (64.7)	
GT 1a	117 (21.7)	354 (43.7)	<0.001
GT 1b	71 (13.2)	128 (15.8)	0.043
Unknown subtype	37 (6.9)	42 (5.2)	0.001
GT-2	28 (5.2)	61 (7.5)	
GT-3	34 (6.3)	57 (7.0)	
Other	6 (1.1)	16 (2.0)	
Unknown	245 (45.5)	152 (18.8)	
APRI	1.2 (0.6–3.2)	1.2 (0.6–2.8)	0.2
APRI cutoffs†	n = 288	n = 485	
>1.5	85 (29.5%)	182 (37.5%)	0.024
>2	70 (24.3%)	146 (30.1%)	0.082
Histology			
Number with biopsies‡	293 (55.1)	189 (25.2)	<0.001
Ishak fibrosis stage			
Ishak 0–2	121 (41.3)	60 (31.7)	0.035
Ishak 3–4	19 (6.5)	21 (11.1)	0.072
Ishak 5–6	145 (49.5)	103 (54.5)	0.283
Unknown	8 (2.7)	5 (2.6)	
Advanced liver disease	277 (51.5)	499 (61.6)	<0.001
Compensated cirrhosis	168 (31.2)	191 (23.6)	0.002
Clinical Decompensation	95 (17.7)	133 (16.4)	0.553
Hepatocellular carcinoma	14 (2.6)	175 (21.6)	<0.001

Results are expressed as number (%) or median (interquartile range) unless specified otherwise. †Excluding patients with biopsy showing cirrhosis, clinical decompensation or HCC. ‡Excluding patients with HCC on biopsy. *P-value: comparison between patients seen in 1998–1999 and 2011–2012.

DISCUSSION

In this study of 1348 patients with chronic hepatitis C newly referred to our liver centre, we found as expected patients seen in Era-2 (2011–2012) were older and more likely to have advanced liver disease compared to those seen a decade ago (Era-1, 1998–1999).

There were a few unexpected findings. We found that the interval between initial diagnosis and referral to our liver centre for patients seen in Era-2 was double that in

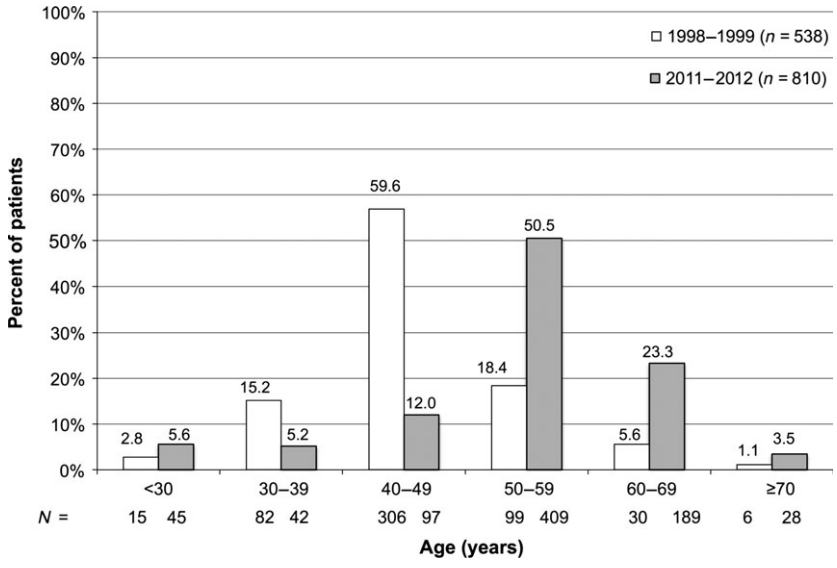

Fig. 2 Age distribution for each Era.

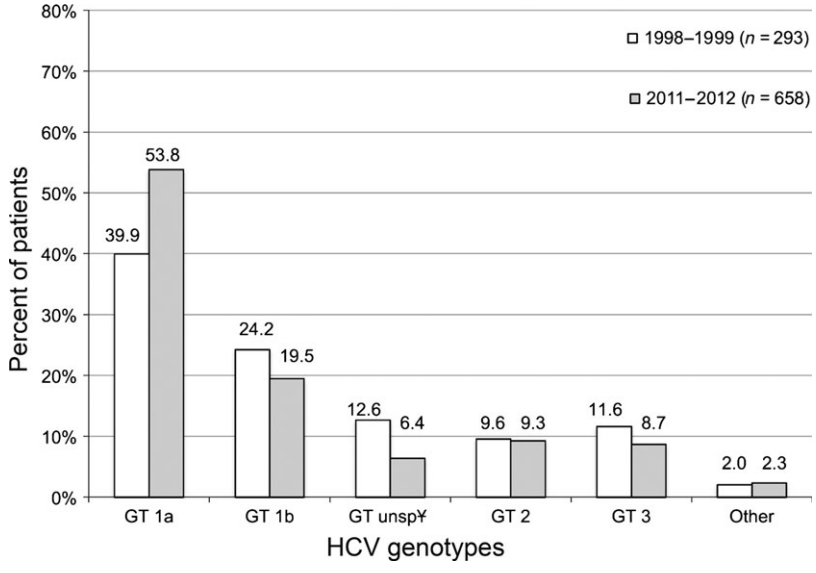

Fig. 3 Genotype distribution for each Era. Analysis limited to subset of patients with known genotype. ¥GT 1 unspecified subtype.

Era-1. Increased familiarity of primary care physicians and gastroenterologists with hepatitis C and its treatment during the past decade may have prompted these physicians to evaluate and/or treat patients with hepatitis C in their clinics and only refer those with more advanced liver disease who had failed to respond or were unable to tolerate available therapies. Approved treatment for hepatitis C in 1998–1999 consisted of standard interferon and ribavirin with SVR rates of 16–28% and 66–69% for patients with genotype 1 and 2/3 infection, respectively [25]. Pegylated interferon was approved for treatment of hepatitis C in 2001 and two protease inhibitors – telaprevir and boceprevir – were approved for genotype 1 infection in 2011. Triple therapy with either telaprevir or boceprevir with pegylated interferon and ribavirin improved SVR rates to 68%-75% for treatment naïve patients with genotype 1 HCV [26,27]. We found that patients referred to our liver centre in 2011–2012 were more likely to have received prior antiviral therapy, but most (77%) remained treatment naïve despite a median delay of 4 years from the time of diagnosis. Thus, delay in referral in most patients was not due to time spent on prior treatment that failed. Other reasons that may have contributed to the delay in referral and treatment include the low experience level and insufficient knowledge among health-care providers caring for HCV patients [28–30], lack of insurance coverage [20], presence of underlying medical or psychiatric illness that might be a contraindication for interferon and difficulty commuting to specialist clinics [31]. Failure of patients and providers to recognize that hepatitis C is largely an asymptomatic disease until patients develop hepatic decompensation may also have contributed to delays in referral. Finally, it is possible that patients were 'warehoused' while waiting for the approval of telaprevir and boceprevir;

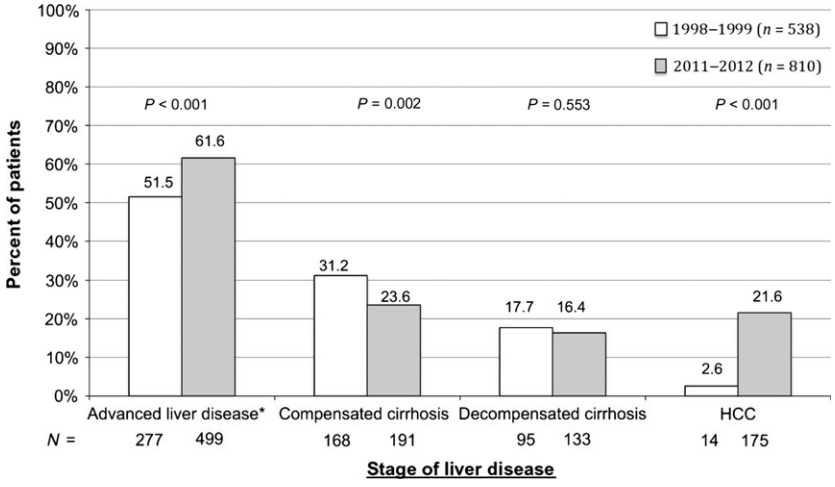

Fig. 4 Prevalence of advanced liver disease for each Era. *Combination of compensated cirrhosis, clinical decompensation and hepatocellular carcinoma (HCC).

however, the number of patients seen in the first half of 2011 was not different from that seen in the second half of 2011, 48% *vs* 52%. The delay in referral might have contributed to progression of liver disease accounting for a higher per cent of patients with advanced liver disease in Era-2.

We observed a significant increase in uptake of treatment among patients age less than 50, but not in those 50 years and older although most of the latter were only 50–59 years old. Given the ageing of the HCV patient population in the US with the vast majority now in the 50s and 60s, it is concerning if physicians feel that these patients are too old to be considered for HCV treatment. We hope the availability of shorter courses of treatment that are interferon-free and possibly ribavirin-free will diminish those concerns because these older patients who had been infected for 30 years or longer are at the greatest risk of cirrhosis and HCC. However, the high cost of new DAAs may prevent access of patients to interferon-free regimens.

In accordance with our hypothesis, we found an enrichment of more difficult to treat HCV genotype and subgenotype in Era-2. Genotype 1a was more prevalent in Era-2 compared to Era-1 (43.7% *vs* 21.7%, $P < 0.001$) when all patients were analysed and also when the analysis was limited to those with known genotypes: 53.8% *vs* 39.9% ($P < 0.001$). Our finding is important because while some DAAs have pan-genotype activity, others have lower barrier to resistance with genotype 1a HCV and lower SVR rate, and some DAA combination therapies are developed for patients with genotype 1b infection only [32].

The most prominent finding of this study was the marked increase in advanced liver disease from 51.5% in Era-1 to 61.6% in Era-2. This was largely due to an eightfold increase in HCC in Era-2 compared to Era-1. While this sharp increase might be due to referral bias because of the establishment of a multidisciplinary liver tumour clinic at our institution in 2008, a significant increase in per cent of patients with advanced liver disease persisted even after exclusion of patients who presented to the liver tumour clinic. Analysis of the national database also showed a 19-fold increase in prevalence of HCV-related HCC between 1996 and 2006 [33,34]. Our finding that the marked increase in proportion of patients with HCC was observed not only among those older than 50 but also in younger patients is concerning. It is not clear whether these patients have more rapidly progressive liver disease, greater exposure to carcinogens or longer duration of infection. Given that obesity and diabetes are independent risk factors for HCC, it is possible that the growing obesity epidemic may also play a role in the recent increase in HCC.

There were limitations to this study. First, this is a retrospective chart review study and therefore it was not possible to determine the reasons behind the low uptake of HCV treatment and the delay in referral. Second, while our goal was to include all new hepatitis C patients seen during the study period, a small per cent (15%) were excluded because of the unavailability of laboratory data within the specified window. Third, the establishment of a new multidisciplinary HCC clinic during the interval between the two Eras might have increased referrals of patients with HCC thus inflating the increase in number of patients with HCC in the recent era, but only 42% of the HCC patients seen in Era-2 were directly referred to the liver tumour clinic, and a fivefold increase in HCC was still observed after exclusion of those seen in the liver tumour clinic. Fourth, a higher proportion with known genotype data in Era-2 might have contributed to the increase in genotype 1a in recent era, but an increase in genotype 1a in Era-2 persisted when the analysis was limited to the subset with known genotype data. Fifth, due to the lack of liver

biopsies in many patients, we had to rely on a combination of histology and APRI to determine which patients have compensated cirrhosis and the decrease in performance of liver biopsy in Era-2 might have resulted in underestimation of the number of patients with compensated cirrhosis. While APRI has been shown to be specific for detection of cirrhosis its sensitivity is only 17–76% [35]. Unfortunately, elastography was not available at our centre. Finally, observations in a tertiary liver clinic may not apply to HCV patients in the community.

In summary, our study showed that HCV patients newly referred to a tertiary liver centre in the U.S. in 2011 and 2012 were older, had a longer duration between diagnosis and referral to liver clinics, were more likely to be infected with genotype 1a HCV and more likely to have advanced liver disease, in particular HCC, compared to those seen a decade ago. Despite being diagnosed for a longer period of time and having access to care, three-quarters of the HCV patients seen in 2011–2012 had not received any treatment. Reduction in HCV disease burden will require development of treatment regimens targeted towards patients in the current Era (>50 years, predominantly genotype 1a and advanced liver disease), improvement in early diagnosis and referral of infected patients to appropriate centres for treatment, and reduction in costs of newly approved DAAs, otherwise implementation of screening programs and availability of highly efficacious treatment regimens will have little impact on disease burden.

AUTHOR CONTRIBUTIONS

N. Talaat and S. Yapali contributed to the study concept and design; acquisition of data; analysis and interpretation of data, literature review, and drafting of this manuscript; A. S. Lok contributed to the study concept and design, supervised the conduct of the study and analysis of the data, and edited this manuscript. Robert J. Fontana and Hari S. Conjeevaram contributed to interpretation of data and editing of this manuscript. All authors have reviewed and approved the final version of this manuscript.

FINANCIAL DISCLOSURES

Nizar Talaat, Suna Yapali, and Hari S. Conjeevaram have nothing to disclose. Anna S. Lok had received research grants from Bristol-Myers Squibb, AbbVie, Gilead Sciences, Idenix and Merck and had served on advisory board for Gilead Sciences, Merck and Janssen. Robert J. Fontana had received research grants from Bristol-Myers Squibb, Vertex and Gilead and served as consultant for Tibotec and GlaxoSmithKline.

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