

# Liver Disease Monitoring Practices After Hepatitis C Cure in the Underserved Population

Nicole J. Kim,<sup>1,2</sup> Catherine Magee,<sup>2</sup> Cassie Cummings,<sup>1,2</sup> Helen Park,<sup>1,2</sup> and Mandana Khalili<sup>1-3</sup>

Recent hepatitis C virus (HCV) guidelines recommend disease monitoring and hepatocellular carcinoma (HCC) screening in patients with advanced fibrosis after a sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy. However, data on practice patterns in this setting is lacking. We aimed to characterize disease monitoring and HCC screening practices post-SVR in an underserved HCV-infected cohort. Records of 192 patients who received DAA therapy at the San Francisco safety-net health care system between January 2014 and January 2016 with  $\geq 12$  months of follow-up post-SVR were reviewed. Patient characteristics were median age 58 years, 61.5% men, 39.1% White (23.4% Black, 16.7% Latino, 16.2% Asian), 78.1% English proficient, 48.9% intravenous drug use, 53.2% alcohol use, and 41% advanced (F3 and F4) fibrosis (26.6% with decompensation, 11.4% with HCC). Median post-SVR follow-up time was 22 months. A higher proportion of patients with advanced fibrosis attended liver clinic visits (mean,  $1.94 \pm 2.03$  versus  $1.12 \pm 1.09$  visits;  $P = 0.014$ ) and had liver imaging (41.4% versus 9.73%;  $P < 0.001$ ) post-SVR, but there was no difference in alanine aminotransferase (ALT) testing (72.2% versus 66.4%;  $P = 0.40$ ) compared to those without advanced fibrosis. However, 20% with advanced fibrosis had no HCC screening while 35% with no advanced fibrosis had liver imaging. Three patients with cirrhosis developed new HCC. **Conclusion:** Although the majority of patients with advanced fibrosis in this underserved cohort received post-SVR monitoring, gaps in HCC screening were identified and new cases of HCC occurred during a short follow-up. This highlights the importance of incorporating recently enhanced guidelines to optimize post-SVR monitoring, especially in difficult to engage populations. (*Hepatology Communications* 2018;2:1274-1283).

Chronic HCV infection affects up to 185 million people worldwide,<sup>(1)</sup> making its prevention and associated disease burden a major public health issue. Individuals with HCV cirrhosis have up to an 8% annual risk of developing HCC,<sup>(2)</sup> and liver cancer is now the fourth leading cause of cancer-related death in the world.<sup>(3)</sup> In 2015, HCV was responsible for 21% of global deaths related to liver cancer and 31% of North American deaths related to liver cancer.<sup>(4)</sup> Consequently, preventing liver disease progression

among individuals with HCV is critical to reducing HCC incidence and mortality.

The use of DAA therapy has improved HCV cure rates, with over 92% SVR rates at 12 weeks posttherapy for most HCV genotypes.<sup>(5)</sup> However, the risk of liver disease progression and HCC, although reduced, are not eliminated after achieving SVR. Recent data from Australia and Spain found that rates of fibrosis progression and cirrhosis were significantly lower (2%-7% versus 28%-30%) among patients who achieved SVR

*Abbreviations:* ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; SVR, sustained virologic response.

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after HCV therapy compared to nonresponders after 10-12 years of follow-up.<sup>(6,7)</sup> Nevertheless, patients with HCV cirrhosis continue to have a 2% annual risk of disease progression after SVR.<sup>(8)</sup> Likewise, after interferon-based therapy, the risk of developing HCC was reduced but persistent at 1.5%-5%.<sup>(9,10)</sup> Large cohort studies of U.S. veterans have since found that this risk of HCC is no different after DAA therapy, although achieving SVR does reduce the absolute risk of HCC by 70%.<sup>(11,12)</sup> Thus, given the persistent risk of disease progression and HCC even after HCV cure in those with advanced liver disease, the European Association for the Study of the Liver and American Association for the Study of Liver Diseases have recommended ongoing post-SVR disease monitoring that includes HCC screening using ultrasounds at 6-month intervals among patients with advanced fibrosis.<sup>(13,14)</sup> Expert opinion has also recommended ongoing clinic visits every 3-6 months for close follow-up.<sup>(15)</sup>

The availability of the recent post-SVR monitoring guidelines has therefore provided an opportunity for enhanced monitoring practices in HCV care. However, there may be barriers to adhering to these guidelines in certain populations. In the United States, underserved patient populations are disproportionately affected by HCV and face high rates of coexisting mental health and substance use.<sup>(16,17)</sup> Recommended disease monitoring, such as laboratory testing, clinic visits, and imaging studies for HCC screening, may be particularly challenging in this population despite high SVR rates of 97% using DAA therapies, similar to reports from other HCV populations.<sup>(18)</sup> To date, there are limited data on current post-SVR monitoring and HCC screening practices in the DAA era,<sup>(19)</sup> and no data are available from potentially difficult to engage and underserved populations. Thus, in this study, we

aimed to address this gap by characterizing and evaluating current liver disease monitoring practices in a cohort of underserved patients infected with HCV who achieved SVR after DAA therapy.

## Patients and Methods

### PATIENTS AND OUTCOMES

Records of all patients with HCV infection who had achieved SVR with DAA therapy at the San Francisco safety-net health care system liver specialty clinic between January 2014 and January 2016 were reviewed. Data was collected through medical record review until September 2017 and included demographic, clinical (including medical and psychiatric comorbidities), and imaging studies. Patients with at least 1 year of post-SVR follow-up were included in data analyses and were categorized into having advanced or no advanced liver fibrosis prior to initiation of DAA therapy. Advanced fibrosis pretherapy was defined as F3 or F4 based on liver biopsy, FibroTest, or imaging studies confirming presence of cirrhosis. *De novo* HCC was defined as a new liver imaging reporting and data system (LI-RADS) 4-5 liver lesion on either magnetic resonance imaging (MRI) or computed tomography (CT) abdominal scan after receipt of HCV treatment. Post-SVR monitoring was captured and included clinic visits, laboratory testing, and imaging studies. Clinic visits included primary care and liver clinic visits. We defined timely laboratory monitoring as at least two or more ALT tests during the follow-up period. Timely liver imaging (or HCC screening for patients with advanced fibrosis) was defined as at least two or more liver imaging (ultrasound, CT abdomen, or MRI abdomen) during the follow-up period. Analysis

#### ARTICLE INFORMATION:

From the <sup>1</sup>Department of Medicine, University of California San Francisco, San Francisco, CA; <sup>2</sup>Department of Medicine, Division of Gastroenterology and Hepatology, Zuckerberg San Francisco General Hospital, San Francisco, CA; <sup>3</sup>Liver Center, University of California San Francisco, San Francisco, CA.

#### ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Mandana Khalili, M.D., M.A.S.  
University of California San Francisco  
San Francisco General Hospital  
1001 Potrero Avenue, Building 5, Suite 3-D

San Francisco, CA 94110  
E-mail: Mandana.Khalili@ucsf.edu  
Tel: +1-415-206-4766

of post-SVR liver imaging practices excluded those with diagnosis of HCC before therapy. This study was approved by the Committee of Human Research at the University of California San Francisco.

## STATISTICAL ANALYSIS

Descriptive analysis, including frequency (%) for categorical variables and median (interquartile range [IQR]) or mean (SD) for continuous variables was used to summarize patient characteristics as well as posttherapy monitoring and screening practices. The chi-square test (or Fisher's exact test, as appropriate) was used for categorical variables, and the Mann-Whitney rank sum test was used for continuous variables. Logistic regression modeling was used for univariate and multivariate analyses to identify factors associated with lack of timely clinical visits, laboratory testing, and HCC screening separately among patients with advanced fibrosis while controlling for age, sex, and race. Statistical significance was defined as  $P < 0.05$  (two-sided). Analyses were done using Stata version 15 statistical software (Stata Corp LP, College Station, TX).

## Results

A total of 192 patients met the inclusion criteria for the study and were included in the analysis. The patients were followed for up to 38 months post-SVR with a median follow-up time of 22 months (IQR, 17-26.5 months). Patient characteristics are summarized in Table 1. The median age was 58 years (IQR, 51-63 years), 61.5% were men, 39.1% were White (23.4% Black, 16.7% Latino, 16.2% Asian, and 4.7% other race), and 21.9% lacked English language proficiency. Overall, 30.7% had two or more medical comorbidities: 41.1% had a psychiatric comorbidity, 2.1% had hepatitis B virus (HBV) coinfection, and 1.6% had human immunodeficiency virus (HIV) coinfection. Nearly half of the patients had a history of intravenous drug use, and more than half had prior or current alcohol use.

Of the 192 patients, 113 (58.9%) patients had no advanced fibrosis while 79 (41.1%) patients had advanced fibrosis prior to HCV therapy. Pretherapy advanced fibrosis status was determined based on liver biopsy in 27.8% ( $n = 22$ ), FibroTest in 10.1% ( $n = 8$ ), and liver imaging in 62% ( $n = 49$ ) of patients. Of the 79 patients with advanced fibrosis, 81%

( $n = 64$ ) had cirrhosis; of these, 32.8% ( $n = 21$ ) had liver decompensation and 14% ( $n = 9$ ) had HCC pretherapy. Median post-SVR follow-up time was similar in those with or without advanced fibrosis (22 versus 21 months;  $P = 0.80$ ). Patients with advanced fibrosis were older (median age, 60 versus 57;  $P = 0.007$ ), had higher body mass index (BMI) levels (median, 28 versus 26;  $P = 0.004$ ), and higher ALT levels (median, 71 versus 55;  $P = 0.036$ ) than patients without advanced fibrosis (Table 1).

## POST-SVR MONITORING AND LIVER IMAGING PRACTICES BY FIBROSIS STAGE

Patients with advanced fibrosis had a higher number of liver specialty clinic visits post-SVR than those without advanced fibrosis (mean,  $1.94 \pm 2.03$  versus  $1.12 \pm 1.09$  visits;  $P = 0.014$ ), whereas the number of primary care clinic visits were similar in the two groups (mean,  $5.62 \pm 5.51$  versus  $5.26 \pm 6.91$  visits;  $P = 0.25$ ) (Table 2). However, there was no difference in the proportion of patients who received timely laboratory testing (at least two or more ALT tests, 72.2% versus 66.4%;  $P = 0.40$ ) among those with and without advanced fibrosis. Approximately 41% of patients with advanced fibrosis received timely liver imaging (at least two or more during the follow-up period), but 10% of those without advanced fibrosis also received two or more liver imaging tests. Among a subgroup of patients with advanced fibrosis and at least 24 months of follow-up, 19.4% ( $n = 6$ ) had at least four or more liver imaging tests.

Among patients with advanced fibrosis, 6.3% ( $n = 5$ ) had no clinic visit (primary care or liver clinic), 7.6% ( $n = 6$ ) had no ALT testing, and 20.3% ( $n = 16$ ) had no liver imaging during the study period (Fig. 1). On the other hand, 35.4% ( $n = 40$ ) of patients without advanced fibrosis had liver imaging during the study period.

## FACTORS ASSOCIATED WITH LACK OF TIMELY MONITORING AND HCC SCREENING POST-SVR AMONG PATIENTS WITH ADVANCED FIBROSIS

Among patients with advanced fibrosis, no demographic, medical or psychiatric comorbidity, or laboratory factors were significantly associated with either

**TABLE 1. PATIENT CHARACTERISTICS PRIOR TO HEPATITIS C THERAPY IN PATIENTS WITH AND WITHOUT ADVANCED FIBROSIS**

Characteristic	All Patients (N = 192)	No Advanced Fibrosis (n = 113)	Advanced Fibrosis (n = 79)	P Value*
Median age (IQR)	58 (51-63)	57 (50-63)	60 (57-64)	0.007
Male (%)	118 (61.5)	64 (56.6)	54 (68.4)	0.10
Race (%)				0.16
White	75 (39.1)	42 (37.2)	33 (41.8)	
Black	45 (23.4)	29 (25.7)	16 (20.3)	
Latino	32 (16.7)	15 (13.3)	17 (21.5)	
Asian	31 (16.2)	23 (20.4)	8 (10.1)	
Other	9 (4.7)	4 (3.5)	5 (6.3)	
English speaking (%)	150 (78.1)	87 (77.0)	63 (79.8)	0.65
Insurance type (%)				0.78
Uninsured	10 (5.2)	6 (5.3)	4 (5.1)	
Public	175 (91.2)	102 (90.3)	73 (92.4)	
Other	7 (3.7)	5 (4.4)	2 (2.5)	
Median BMI (IQR)	27 (23-30)	26 (22-29)	28 (24-31)	0.004
HBV (%)	4 (2.1)	4 (3.5)	0	0.15
HIV (%)	3 (1.6)	1 (0.9)	2 (2.5)	0.57
Two or more medical comorbidities <sup>†</sup> (%)	59 (30.7)	36 (31.9)	23 (29.1)	0.46
Psychiatric disease (%)	79 (41.1)	45 (39.8)	34 (43.0)	0.66
Substance use (%)				
Intravenous drug use (ever)	94 (48.9)	51 (45.1)	43 (54.4)	0.21
Current alcohol use	27 (14.1)	16 (14.2)	11 (13.9)	0.96
Prior alcohol use	75 (39.1)	39 (34.5)	36 (45.6)	0.12
Cirrhosis (%)	64 (33.3)	0	64 (81.0)	<0.001
Decompensated	21 (10.9)	0	21 (26.6)	<0.001
HCC (%)	9 (4.7)	0	9 (11.4)	<0.001
Median ALT (IQR)	60 (38-92)	55 (37-76)	71 (43-111)	0.036
Median Log <sub>10</sub> HCV viral load (IQR)	6.1 (5.6-6.4)	6.1 (5.6-6.5)	6.1 (5.4-6.4)	0.71
Genotype (%)				0.551
1	133 (69.3)	76 (67.3)	57 (72.2)	
2	27 (14.1)	19 (16.8)	8 (10.1)	
3	21 (10.9)	11 (9.7)	10 (12.7)	
Other	11 (5.7)	7 (6.2)	4 (5.1)	

\* $P < 0.05$  considered significant. <sup>†</sup>Medical comorbidities included diabetes, cardiac disease, hypertension, hyperlipidemia, chronic kidney disease, lung disease, non-HCC malignancy, and thyroid disorders.

**TABLE 2. CLINICAL AND LABORATORY MONITORING AND LIVER IMAGING PRACTICES IN PATIENTS WITH AND WITHOUT PRETHERAPY ADVANCED FIBROSIS**

Characteristic	No Advanced Fibrosis (n = 113)	Advanced Fibrosis (n = 79)	P Value*
Mean number of primary care visits (SD)	5.26 (6.91)	5.62 (5.51)	0.25
Mean number of liver clinic visits (SD)	1.12 (1.09)	1.94 (2.03)	0.014
Patients with two or more ALT testing (%)	75 (66.4)	57 (72.2)	0.40
Patients with two or more liver imaging (%) <sup>†</sup>	11 (9.73)	29 (41.4)	<0.001

\* $P < 0.05$  considered significant. <sup>†</sup>Excludes patients diagnosed with HCC pretherapy.



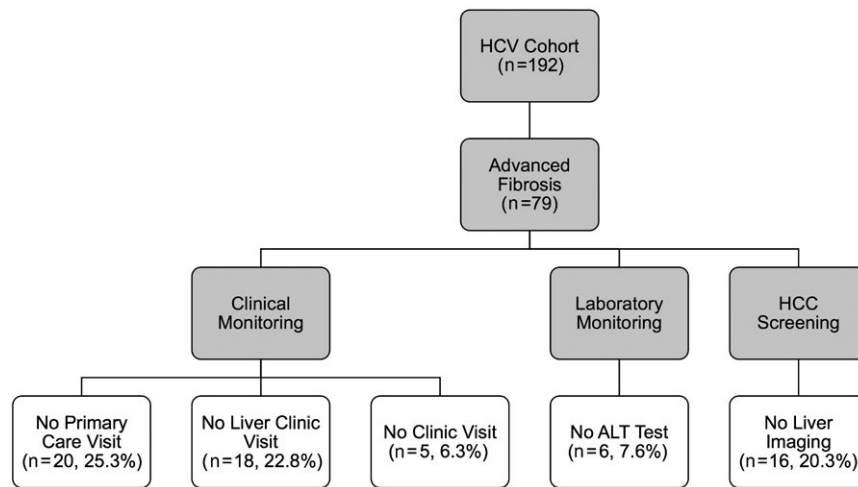


FIG. 1. Post-SVR monitoring practices among patients with advanced fibrosis.

the lack of clinic visits or timely ALT testing (Table 3). With respect to HCC screening, only the presence of cirrhosis was significantly associated with a reduced likelihood of lacking timely liver imaging (odds ratio [OR], 0.07; 95% confidence interval [CI], 0.01-0.56;  $P = 0.012$ ) on univariate analysis. This finding remained significant even after controlling for age, sex, and race on multivariate analysis (OR, 0.06; 95% CI, 0.01-0.53;  $P = 0.011$ ).

## CLINICAL OUTCOMES OF PATIENTS POST-SVR

Of the 79 patients with advanced fibrosis pretherapy, 9 had a diagnosis of HCC prior to therapy, and of the remaining 70 patients without a history of HCC, 3 developed *de novo* HCC during the study follow-up period. All 3 patients with *de novo* HCC posttherapy had cirrhosis and were men; median age was 53 years (IQR, 48-72 years), 2 were White and 1 was Asian, 2 had a history of prior alcohol use, and 2 also had evidence of liver decompensation pretherapy. Additional patient comorbidities included 1 patient with diabetes, 2 with hypertension, and 1 with hyperlipidemia. The pretherapy HCV genotype assessment showed one case each of genotype 1, genotype 2, and genotype 3. None of the patients had HBV or HIV coinfections.

Among the 67 patients with advanced fibrosis without a diagnosis of HCC before or after therapy, 3% ( $n = 2$ ) developed decompensated liver disease, while 7.5% ( $n = 5$ ) died during the follow-up period. Only one death was due to further decompensation of liver

disease. The other four deaths were due to pancreatic cancer, endocarditis, respiratory failure, and opiate overdose.

## Discussion

This is the first study to evaluate post-SVR monitoring and liver imaging practices in an underserved HCV-infected population who achieved SVR after DAA therapy. We found that the majority of patients with advanced fibrosis underwent some form of clinical or laboratory monitoring post-SVR and, as suspected, received more frequent liver clinic follow-up and liver imaging than patients without advanced fibrosis. However, gaps in HCC screening and laboratory monitoring were also identified in that 20% of patients with advanced fibrosis did not have any liver imaging despite at least 12 months of follow-up and the frequency of laboratory monitoring was no different compared to those without advanced fibrosis. Furthermore, although routine imaging for patients without advanced fibrosis is not recommended, 35% of patients without advanced fibrosis received imaging during the study period. The reasons for these gaps in monitoring could not be ascertained, but aside from potential patient and provider factors, our findings may reflect changes in practice over time as more data on outcomes post-DAA therapy have become available in recent years. Nevertheless, three new cases of HCC were identified within our advanced fibrosis cohort despite a relatively short follow-up period, consistent

**TABLE 3. FACTORS ASSOCIATED WITH LACK OF TIMELY CLINIC VISIT MONITORING, LABORATORY MONITORING, AND LIVER IMAGING POST-SVR AMONG PATIENTS WITH ADVANCED FIBROSIS ON UNIVARIATE ANALYSIS**

Characteristic	Clinic Visit Monitoring		Laboratory Monitoring <sup>†</sup>		Liver Imaging <sup>‡</sup>	
	Unadjusted OR (95% CI)	P Value <sup>§</sup>	Unadjusted OR (95% CI)	P Value*	Unadjusted OR (95% CI)	P Value*
Age	1.02 (0.90-1.16)	0.71	1.03 (0.96-1.11)	0.34	1.02 (0.96-1.08)	0.61
Male	0.68 (0.11-4.33)	0.68	0.74 (0.26-2.10)	0.58	1.02 (0.37-2.76)	0.98
White race	0.92 (0.15-5.87)	0.93	0.56 (0.20-1.57)	0.27	0.96 (0.37-2.51)	0.94
English proficiency	1.02 (0.11-9.78)	0.99	0.40 (0.13-1.26)	0.12	0.57 (0.17-1.86)	0.35
Insurance						
Uninsured	Ref	-	Ref	-	Ref	-
Public	1.00	-	1.13 (0.11-11.5)	0.92	1.46 (0.19-11.0)	0.71
Other	1.00	-	3.00 (0.08-107.4)	0.55	1.00 (0.03-29.8)	1.00
BMI	0.92 (0.76-1.12)	0.42	0.96 (0.88-1.05)	0.38	0.97 (0.90-1.04)	0.42
HBV	1.00	-	1.00	-	1.00	-
HIV	1.00	-	1.00	-	0.70 (0.04-11.7)	0.80
Two or more medical comorbidities <sup>  </sup>	1.24 (0.17-9.30)	0.83	1.33 (0.50-3.59)	0.57	1.64 (0.62-4.33)	0.32
Psychiatric disease	0.88 (0.14-5.55)	0.89	1.15 (0.43-3.08)	0.79	2.33 (0.86-6.32)	0.096
Substance use						
IVDU	0.19 (0.02-1.79)	0.15	1.69 (0.61-4.65)	0.31	1.51 (0.58-3.94)	0.40
Current alcohol	1.00	-	0.53 (0.11-2.69)	0.45	0.49 (0.10-2.39)	0.38
Prior alcohol	0.89 (0.35-2.23)	0.80	1.13 (0.69-1.85)	0.62	1.11 (0.68-1.79)	0.68
Cirrhosis	0.93 (0.10-9.01)	0.95	0.50 (0.15-1.62)	0.25	0.07 (0.01-0.56)	0.012
Decompensation	1.93 (0.30-12.4)	0.49	0.52 (0.15-1.78)	0.30	0.46 (0.15-1.42)	0.18
ALT	1.00 (0.99-1.02)	0.80	1.00 (0.99-1.00)	0.40	1.00 (0.99-1.00)	0.38
Log <sub>10</sub> HCV viral load	1.04 (0.36-2.99)	0.95	1.04 (0.59-1.84)	0.89	1.20 (0.70-2.07)	0.50
Genotype						
1	Ref	-	Ref	-	Ref	-
2	1.00	-	1.84 (0.39-8.71)	0.44	2.44 (0.45-13.3)	0.30
3	1.00	-	1.32 (0.30-5.79)	0.72	1.02 (0.24-4.26)	0.98
Other	1.00	-	3.07 (0.40-23.9)	0.28	2.44 (0.24-25.2)	0.45

Abbreviations: IVDU, intravenous drug use; Ref, reference.

\*Number of primary care or liver clinic visits during follow-up time. <sup>†</sup>Two or more ALT testing during follow-up time. <sup>‡</sup>Two or more liver imaging during follow-up time, excludes pretherapy HCC (n = 9). <sup>§</sup>P < 0.05 considered significant. <sup>||</sup>Medical comorbidities included diabetes, cardiac disease, hypertension, hyperlipidemia, chronic kidney disease, lung disease, non-HCC malignancy, and thyroid disorders.

with the known risk of disease progression and HCC even after HCV cure. Our findings corroborate the importance of recent recommendations for continued monitoring in this at-risk population. Future studies are needed to assess the impact of these enhanced monitoring guidelines on addressing gaps in post-SVR monitoring practices.

Recent practice guidelines and expert opinion recommend that patients with advanced fibrosis have clinic visits every 3-6 months and HCC screening every 6 months post-SVR.<sup>(13-15)</sup> In our study, patients with advanced fibrosis received more frequent liver clinic follow-up and a higher rate of liver

imaging compared to patients without advanced fibrosis. Furthermore, 72% and 41% of patients with advanced fibrosis received timely ALT testing and HCC screening, respectively. However, 6.3% and 7.6% of our advanced fibrosis cohort did not receive any clinic follow-up (primary care or specialty care) and ALT testing, respectively. Overall, these rates are similar to posttherapy monitoring rates reported among patients with chronic hepatitis B. Wu et al.<sup>(20)</sup> found that 71% and 55% of patients with chronic hepatitis B received at least once yearly laboratory testing and HCC screening, respectively. Within our own health care system, a prior study found that 51%

of patients with chronic hepatitis B had received HCC screening within the year.<sup>(21)</sup> The rate of 20% without HCC screening in this HCV cohort, however, is higher than reported (10.2%) among patients with HBV.<sup>(22)</sup>

While we did not identify any particular factor that was significantly related to the lack of timely clinic visits or laboratory testing, the presence of cirrhosis was associated with receiving timely HCC screening among patients with advanced fibrosis. Further studies are needed to evaluate the role of other unmeasured patient and any provider factors contributing to the lack of optimal monitoring post-SVR in HCV. Indeed, provider knowledge has been independently associated with suboptimal monitoring of patients in chronic HBV.<sup>(21,22)</sup> Collectively, these data suggest that adherence to disease monitoring guidelines in viral hepatitis is suboptimal, and interventions including patient and provider education along with enhanced access to care and reduced barriers are likely needed to address these gaps.

Patient, provider, and health system factors are likely to influence health behavior,<sup>(23)</sup> and tailoring

interventions specific to the needs of the underserved is especially paramount in modifying health behavior in this population. Underserved populations are at risk for health disparities, and potential barriers to care include the high prevalence of comorbid medical and psychiatric disorders, substance abuse, unstable housing, limited access to transportation, and low health literacy, among others.<sup>(24-26)</sup> Further, despite expansion of health insurance coverage as a result of health care reform, a recent report highlighted the ongoing challenge of integrating clinical services between the safety-net hospitals and their community health centers, making it difficult to deliver more efficient and effective care to this population.<sup>(27)</sup> Potential strategies and opportunities to enhance post-SVR care in the underserved are summarized in Fig. 2. These strategies can be prioritized based on the practice setting and the underserved population accessing care in that setting. For example, in a previously implemented patient-centered intervention, formal patient education in this liver specialty clinic was shown to be effective in improving both HCV patient knowledge and management along with hepatitis C care coordination with primary

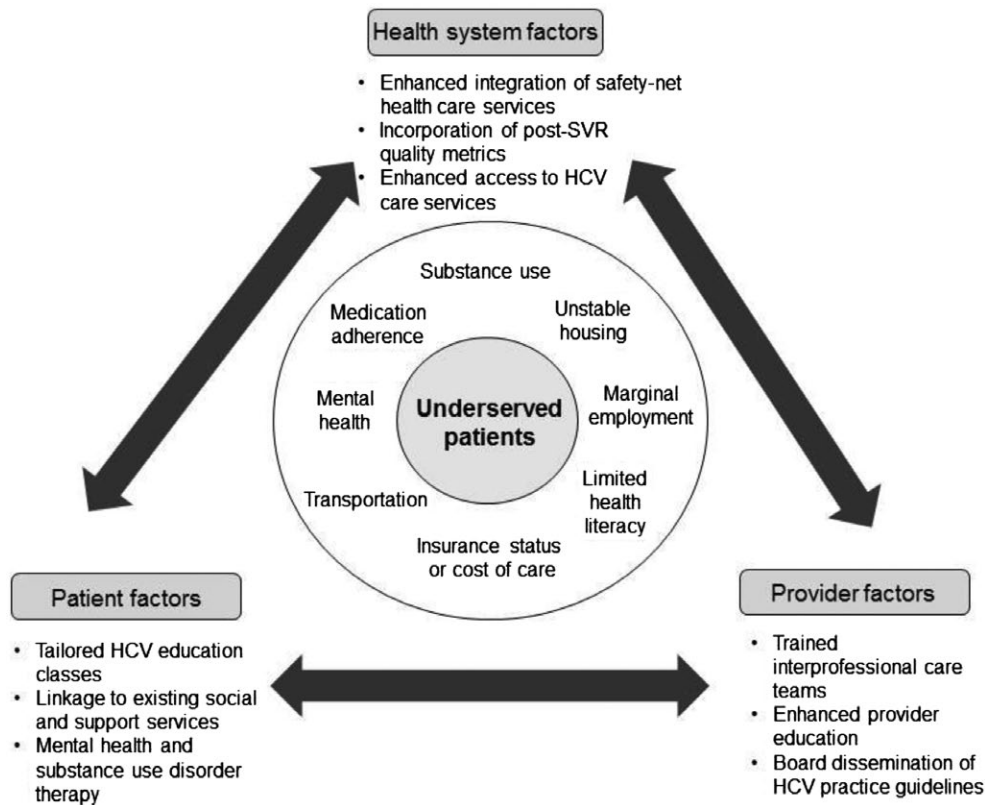


FIG. 2. Strategies to enhance post-SVR care among underserved patients.

providers.<sup>(28,29)</sup> Based on our findings, this formal patient education was enhanced to further emphasize the importance of post-SVR follow-up and HCC screening. A similar patient-level strategy can easily be implemented both in the specialty and primary care setting in other safety-net health care systems. Provider-level interventions are also critical; recent reports have shown that both primary care and hepatology providers perceive significant patient-level barriers, such as substance use disorders, mental health, and history of nonadherence, to influence HCV treatment initiation.<sup>(30)</sup> Such perceived barriers are especially common among the underserved population and may play a role in post-SVR management following receipt of therapy. Therefore, cultivating positive attitudes toward post-SVR monitoring among providers by reinforcing national guidelines and improving awareness of existing resources (e.g., integrated mental health and substance use treatment, use of existing health navigators and educators) can help promote improvement in post-SVR management practices. Targeting education toward interprofessional HCV care teams may also represent a potential provider-level facilitator to enhancing post-SVR monitoring and HCC screening. In a recent study, a 1-hour online HCV course provided education to a multidisciplinary team of health and social care workers, educators, and volunteers and enhanced their knowledge and ability to engage their clients in HCV care.<sup>(31)</sup> Such interventions along with provider education and the addition of post-SVR follow-up and HCC screening as clinic quality improvement measures in those with advanced liver disease will provide multilevel opportunities to improve adherence to post-SVR best practices. Finally, the integration of multiple strategies across systems, such as a comprehensive public health approach involving reimbursement, clinical guidelines, training, and prevention education, which has already been shown to enhance access to HCV care among injection drug users, may also represent system-level opportunities to enhance post-SVR care in the larger underserved population.<sup>(32)</sup>

The importance of post-SVR monitoring is based on the persistent, albeit reduced, risk of developing HCC after HCV cure following treatment. Among 598 patients who had achieved SVR after interferon therapy in South Korea, the 5-year incidence of HCC was still 1.7%.<sup>(33)</sup> Similarly, another study of 1,094 patients found that the 5-year risk of HCC was as high as 22% among patients with advanced fibrosis.<sup>(34)</sup> With the availability of DAA therapies, additional studies have

also assessed the risk of HCC in the DAA era. Initial smaller studies suggested surprisingly high rates of HCC at 5%-9% shortly after DAA therapy.<sup>(35,36)</sup> More recent and larger studies, however, have shown that there is no difference in HCC risk between interferon and DAA therapies.<sup>(37)</sup> In a propensity score-matched study, the incidence and recurrence of HCC was not different between patients treated with interferon and interferon-free therapies.<sup>(38)</sup> In a larger retrospective study using the electronically retrieved cohort of HCV infected veterans (ERCHIVES) database, the HCC incidence was similar among patients with cirrhosis who had achieved SVR after either interferon or DAA therapy.<sup>(39)</sup> In our study, 70 of the 79 patients with advanced fibrosis did not have a diagnosis of HCC prior to therapy; of these 70 patients, 3 patients (4.3%) developed new HCC over a median follow-up of 22 months. This rate is similar to the 3.16% reported after 24 weeks post-SVR among patients with cirrhosis in Italy,<sup>(40)</sup> 4.1% after a median follow-up of 15 months post-SVR among patients with cirrhosis in Austria,<sup>(41)</sup> and 4.5% after a median follow-up of 23 months post-HCV treatment in patients with all levels of fibrosis in Japan.<sup>(42)</sup> Although our cohort size does not allow for evaluation of factors related to the development of HCC post-SVR *per se*, all 3 patients had cirrhosis prior to therapy, and 2 of these patients had decompensated disease and an abnormal metabolic profile, including diabetes, a known risk factor for HCC and HCC-related mortality.<sup>(43,44)</sup> These findings further support the importance of monitoring for disease progression and HCC among patients with advanced fibrosis, particularly in those with additional risk factors. Prospective studies with longer follow-up durations after DAA therapy can help clarify the true risk of HCC post-SVR.

Our study was limited by its retrospective single-center design and sample size. The data should also be interpreted within the context of changes in post-SVR practice guidelines over time, which may have impacted monitoring practices. Furthermore, we were unable to ascertain the indication for liver imaging among those without advanced fibrosis. Nevertheless, this is the largest report to date on post-SVR monitoring in an underserved population and highlights that while still suboptimal, a significant proportion of our higher risk patients remained engaged in care after cure.

In conclusion, we show that while many remain engaged with HCV care posttreatment, there are gaps



in disease monitoring and HCC screening in the underserved population with advanced fibrosis following cure. Although DAA therapies have revolutionized rates of HCV cure, adverse patient outcomes (e.g., HCC) can occur in those at risk within a short period of time after SVR. Addressing gaps in post-SVR monitoring in patients with advanced fibrosis are critical to reducing the burden of HCV disease, especially as HCV therapy expands to nonspecialty settings. Our findings also highlight the need for broader dissemination of post-SVR monitoring guidelines to enhance the assessment of liver disease severity prior to therapy and to subsequently tailor disease monitoring and harm reduction after cure among patients with advanced fibrosis.

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