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ORIGINAL RESEARCH

A Cascade of Care of Patients with Hepatitis C Infection in a Rural State

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Introduction:	The substance misuse epidemic has fueled an increase in hepatitis C virus (HCV) infections. Despite the availability of sensitive screening and curative treatment, relatively few people are aware of their diagnosis and engaged in care. In this study, we aimed to identify local gaps in HCV care and inform strategies for improvement.
Methods:	In this retrospective study, we assessed adult patients seen at a tertiary care center from 2015 to 2019 and who were eligible for HCV screening based on recommendations from the Centers for Disease Control and Prevention. Inclusion criteria were birth from 1945 to 1965, long-term dialysis treatment, alanine aminotransferase greater than 35 U/L for 6 months or more, and/or a diagnosis of opioid use disorder (OUD), HIV/AIDS, or hepatitis B virus (HBV) infection. We summarized the HCV cascade of care with descriptive statistics and used logistic regression to identify factors associated with HCV screening.
Results:	We identified 4948 patients eligible for HCV screening, of whom 47% were female, 54% were male; 7% were Black, 83% were White, and 10% were Other/Unknown; and 87% were born between 1945 and 1965. Among the patients, 2791/4948 (56%) were screened and 124/2791 (4%) were identified to have chronic HCV infection, of whom 12/124 (10%) were linked to care, ever treated, and cured. Patients with HCV included 63/124 (51%) with OUD and 65/124 (52%) with HBV coinfection. All risk factors for HCV were independently associated with HCV screening, except OUD (aOR, 1.2; 95% CI, 0.9-1.6; P = .28).
Discussion:	We identified multiple gaps in the HCV cascade of care at our institution. Our findings, paired with data from the Veterans Health Administration and national research, indicate a need for more comprehensive strategies for HCV screening and intervention.
Conclusions:	Our findings will help to direct strategies for improving HCV detection and subsequent enrollment into care, particularly for patients with OUD.
Keywords:	hepatitis C virus, Hepatitis C screening, continuum of care, opioid use disorder, quality improvement

epatitis C virus (HCV) infection is a major cause of morbidity and mortality globally and is one of the common contributors to chronic liver disease and liver transplantation in the United States (US).¹⁻³ An estimated 185 million people are living with HCV worldwide,⁴ and about 4.1 million people with current or past HCV infection live in the

US.⁵ Furthermore, the current substance misuse epidemic in the US is fueling new infections, leading to a nationwide increase in prevalence.^{6,7} In 2019, the Centers for Disease Control and Prevention (CDC) estimated more than 57, 000 new infections in the US, a 21% increase from the 2015 estimate.⁸ Rural states, such as Maine, have been disproportionately burdened by HCV⁹ and have experienced unprecedented increases in recent years. Based on the 2018 Maine CDC's surveillance report, there has been a 314% increase

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in HCV incidence between 2013 and 2018, from 0.9 to 2.9 per 100000 people.¹⁰

A major challenge in the control of HCV is its silent progression from acute infection to chronic disease. Chronic HCV is generally a slowly progressive disease characterized by persistent hepatic inflammation and chronic infection. Most people with HCV infection are asymptomatic and often learn of their infection only after their disease has progressed to chronic liver diseases, cirrhosis, hepatocellular carcinoma, or liver failure. After infection, 15% to 45% of people infected with HCV spontaneously clear the virus without any treatment in the first 6 months. However, the remaining 55% to 85% of people will develop a chronic infection. Of those with chronic HCV, the risk of cirrhosis is about 20% to 30% over 25 to 30 years. And with a diagnosis of cirrhosis, patients are at risk of hepatic decompensation, hepatocellular carcinoma, and liver-related death.11-14

Due to its asymptomatic nature, early diagnosis of HCV relies on screening tests. Before April 2020, the CDC recommended screening at-risk populations, which included people who had a history of injection drug use, ever received blood products, long-term hemodialysis treatment, persistently elevated alanine aminotransferase (ALT) levels, or a diagnosis of HIV/AIDS or hepatitis B virus (HBV) infections. The CDC also recommended screening children born to women infected with HCV. In addition, the CDC recommended screening people with recognized exposure to HCV infectious sources in occupational settings, such as health care, emergency medical, and public safety workers after a needle stick and sharp injuries, or mucosal exposure to blood infected with HCV.15 As of April 2020, the CDC now recommends one-time HCV testing of all adults aged 18 years or older. Also, pregnant women should be tested during each pregnancy, and people with continued risks, such as those who inject drugs, must be tested regularly.¹⁶ Unfortunately, there is nationwide underperformance in screening people with HCV infection in the US. Among people living with chronic HCV in the US, only 50% are diagnosed and aware of their status.17

Before the advent of direct-acting antiviral (DAA) therapies, HCV treatment required longer durations and had substantial side effects and low treatment-success rates. Cure rates with the old treatment

regimens was approximately 50% or lower among people with genotype 1 infections, which is the most common type in the US.^{18,19} The new DAA therapies require shorter duration of treatment, have favorable side-effect profiles, and have high cure rates (> 90% in clinical trials), irrespective of prior treatment experiences or genotype.^{20,21} Despite the availability of such effective interferonfree HCV treatment that significantly decreases morbidity and mortality, fewer than half of patients infected with HCV are aware of their diagnosis, and even fewer persons diagnosed with HCV are enrolled in HCV care.^{22,23}

Some of the barriers of HCV screening identified in prior studies include lack of knowledge about HCV infection, poor access to health care, fear of stigma, and comorbidities, such as substance use disorder and mental illness.²⁴⁻²⁶ On the other hand, studies of HCV care pathways showed that comprehensive HCV screening, communicating with patients with HCV about their diagnoses, and subsequent assessment of liver fibrosis were associated with improved outcomes. Such pathways included an order set with multiple levels of reflex testing, as well as an HCV care coordinator and a multidisciplinary team approach.27 Another study showed that the rate of HCV screening improved by 10-fold over a 2-year period through engaging leadership in communities and health care facilities, developing and sustaining a healthy workforce, developing policies and procedures for increased access to testing and treatment, and optimizing clinical information systems.28

Due to all the challenges discussed above, there are gaps along the HCV cascade of care. The framework for the HCV cascade of care represents a logical sequence of HCV care across a continuum, from HCV-antibody screening to HCV RNA confirmatory testing, linkage to subsequent care, treatment, and retention in care. Thus, the framework helps to evaluate and identify gaps along the HCV continuum of care. Most published studies on the HCV cascade of care reflected clinical practice before 2014, when liver biopsy was needed to start treatment and DAA therapies were not available. This study reflects clinical practice after the advent of DAA therapies and during an era when biopsy was not required for fibrosis assessment. Our study goals were to (1) identify gaps in the HCV continuum of care in a rural state, (2) compare regional and national HCV cascades

of care, and (3) inform future intervention targets and strategies for HCV care delivery in the setting of the newer therapies and recent HCV guidelines.

METHODS

We performed a retrospective study using data collected from the electronic health record at Maine Medical Center (MMC), a tertiary care institution. The study population included all adult patients (age 18 years and older) seen at MMC's internal medicine clinics between May 2015 and May 2019. We defined eligibility for HCV screening based on the CDC's recommendations that were in place during the study period. These recommendations included any patient who (1) was not already known to be infected with HCV, (2) was born between 1945 and 1965, (3) was engaged in long-term treatment with dialysis, (4) had persistently elevated ALT (> 35 U/L) for at least 6 months, or (5) had a prior or current diagnosis of opioid use disorder (OUD), HIV/AIDS, or HBV infection. Patients under 18 years old at the time of screening or who had a diagnosis of HCV infection or treatment for HCV before May 2015 were excluded from the study. We used the International Classification of Diseases, Tenth Revision (ICD-10), and Current Procedural Terminology (CPT) codes to identify patients with an HCV diagnosis and/or laboratory tests for HCV. HCV diagnosis included acute HCV infection, chronic HCV infection, hepatitis due to HCV, liver cirrhosis due to HCV, or HCV infection otherwise non-specified. We also used ICD-10 codes to identify people eligible for HCV screening based on their clinical history of HIV infection, AIDS, acute retroviral syndrome, acute HBV infection, chronic HBV infection, hepatitis due to HBV, liver cirrhosis due to HBV, HBV infection otherwise non-specified, end stage renal disease with dependence on renal dialysis, and/or OUD (ICD-10-CM, 2016). To identify laboratory results, we used test names and CPT codes for HCV antibody, HCV antibody with reflex to polymerase chain reaction (PCR), HCV RNA PCR (with reflex to genotype), HIV 1/2 antibody/antigen, HIV RNA PCR, ALT, HBV antigen, HBV DNA PCR, and HBV core antibody tests (Appendix A). The study was reviewed by the Institutional Review Board at MMC and was deemed non-research because the work was part of a systematic quality improvement project.

To create our cascade of care, we summarized our data descriptively and determined the number of patients who (1) received at least one HCV-antibody

screening test during the study period; (2) had at least 1 positive HCV-antibody test; (3) received positive HCV confirmatory tests (measured by a positive HCV RNA PCR); (4) were linked to HCV care (documented evidence of referral to infectious diseases or gastroenterology, or evidence of treatment for HCV infection after the date of screening or confirmatory HCV RNA PCR testing); (5) were ever treated for HCV, including having documented evidence of prescriptions for HCV or HCV drugs listed in their medications list, and (6) achieved sustained virologic response (SVR; i.e., HCV test of cure) defined as HCV RNA QN PCR reported as undetected or less that the detection limit 12 weeks after completing treatment.

We calculated the cascade frequencies for the overall study population and with stratification by key demographic and clinical factors. Independent predictors of HCV screening were evaluated by logistic regression. Variables were included in the model if they were either known risk factors for HCV for which screening was recommended or if they showed a significant ($P \le .1$) association with HCV screening in univariate analysis. Presence of HBV or HIV coinfections, birth cohort, OUD, current employment, health insurance, long-term dialysis, and persistent ALT elevation were included in the regression model. In addition, we provided a graphical comparison of our HCV cascade findings against those published for the US23 and for the Veterans Health Administration (VHA).²⁹ Analyses were performed using SPSS Statistical Software version 25 (IBM SPSS Inc, Armonk, NY).

RESULTS

We identified 4948 patients who were seen at internal medicine clinics at MMC from May 2015 to May 2019 and met eligibility criteria for HCV screening. Table 1 summarizes the demographic characteristics of eligible patients and the reasons for their eligibility, which were not mutually exclusive. Of those eligible patients, 47% were female, and 54% were male; 7% were Black, 83% were White, and 10% were Other/Unknown; and 70% were age 55 years or older. Most patients were eligible for HCV screening due to their birth cohort — born between 1945 and 1965 (87%). The remaining patients were eligible for HCV screening for having one or more of the following: persistently elevated ALT (> 35 U/L) for at least 6 months (15%), hepatitis B coinfection (10%), OUD (7%), HIV/AIDS coinfection (2%), and engaged in long-term dialysis (2%).

Table 1. Demographic and Clinical Characteristicsof Patients Eligible for HCV Screening at InternalMedicine Clinics of Maine Medical Center, 2015-2019 (N = 4948)

2299 (46.5)
2649 (53.5)
182 (3.7)
1303 (26.3)
3463 (70.0)
362 (7.3)
4112 (83.1)
474 (9.5)
1727 (34.9)
979 (19.8)
1853 (37.4)
389 (7.9)
1407 (28.4)
4319 (87.3)
330 (6.7)
748 (15.1)
468 (9.5)
100 (2.0)
72 (1.6)

Abbreviations: ALT, alanine aminotransaminase.

Table 2 shows the percentage of patients who achieved each level in the cascade of care. Data are presented as overall distribution (2a), distribution after stratified by HCV eligibility factors (2b) and stratified by demographic factors (2c). Overall (Table 2a), among the 4948 eligible patients, 2791/4948 (56%) received HCV screening. Of those screened, 210/2791 (8%) had a positive result for HCV antibody (HCV AB+). Among patients with positive HCV AB testing, 204/210 (97%) received subsequent confirmatory testing, of whom 124/210 (59%) had chronic HCV (HCV RNA+). Among patients with chronic HCV infection, only 10% were linked to care, received DAA therapy, and achieved SVR. These results are also graphically depicted in Figure 1.

https://knowledgeconnection.mainehealth.org/jmmc/vol5/iss2/1 DOI: 10.46804/2641-2225.1137 Among patients with chronic HCV, 51% had OUD, 52% had hepatitis B coinfection, and 62% had persistently elevated ALT. Patients with OUD accounted for only 7% of patients eligible for HCV screening (Table 1), but they comprised 51% of patients with chronic HCV (Table 2b). Patients with HBV (aOR, 8.8; 95% CI, 6.4-12.2; P < .001), HIV (aOR, 2.1; 95% CI, 1.2-3.5; P = .01), birth period 1945-1965 (aOR, 1.8; 95% CI, 1.4-2.3, P < .001), long-term dialysis (aOR, 1.8; 95% CI, 1.0-3.4; P = .04), Medicare insurance (aOR, 1.2; 95% CI, 1.0-1.4; P = .02), and persistently elevated ALT (aOR, 1.3; 95% CI, 1.0-1.5; P = .03) were more likely to be screened for HCV infection. On the other hand, there is no significant difference in HCV screening between patients with and without OUDs (aOR, 1.2; 95% CI, 0.9-1.6; P = .28) (Table 3). Additional data are provided in Supplemental Tables 1 and 2.

Figure 2 compares the cascade of care of patients with chronic HCV at MMC's internal medicine clinics from 2015 to 2019 to US data published in 2014 and VHA data published in 2016. At MMC, 63% of patients with chronic HCV were linked to care, 23% ever received treatment, and 9.7% achieved SVR. The national and VHA data showed a lower linkage to care, treatment, and SVR rates than MMC.

DISCUSSION

At MMC, located in rural New England, we found that just over half of all eligible patients received HCV-antibody screening tests from 2015 to 2019. Of those, fewer than 10% were linked to care, ever received treatment, and achieved SVR. Patients with OUD accounted for a small proportion of patients eligible for HCV screening but accounted for more than half of patients with chronic HCV. The current screening rate in the US is not known but given the availability of HCV-antibody testing with reflex PCR and interferon-free curative treatments with favorable side-effect profiles, our local screening rate appears low. In our study, we also found that subsequent enrollment into care after diagnosis (63%) was similar to those reported for the VHA cascade of care by Maier et al. at 59%.²⁹ This estimate is higher than the US estimate published by Yehia et al. at 38%,23 potentially because of differences in definitions of "linkage to care". Whereas Yehia et al.23 defined linkage to care as those patients with insurance access for outpatient care, we defined linkage to care as referral to treatment, because we believe referral to treatment more accurately reflects linkage to care in our local health system.

Agmas et al.: Cascade of care for HCV infection

Cascade of care	Overall, No. (%)	HCV Ab+, No. (%)	HCV RNA+, No. (%)	
HCV screen	2791 (56.4)	-	-	
HCV AB+	210 (7.5)	210 (100)	-	
HCV RNA test	204 (4.1)	204 (97.1)	-	
HCV RNA+	124 (2.5)	124 (59.0)	124 (100)	
Linked to care	78 (1.6)	78 (37.1)	78 (63.0)	
Treated	29 (0.6)	29 (13.8)	29 (23.4)	
SVR (cure)	12 (0.2)	12 (5.7)	12 (9.7)	

Table 2. HCV Cascade of Care at Internal Medicine Clinics of Maine Medical Center, 2015-20192a. Overall Patient Distribution in the HCV Cascade of Care (N = 4948)

Abbreviations: AB, antibody; HCV, hepatitis C virus; SVR, sustained virologic response.

2b. Patient Distribution in the HCV Cascade of Care Stratified by Demographic Factors

	Sex, No. (%))	Age, y, No.	(%)		Race, No. (%)	
Cascade steps	Female	Male	18-35	35-55	≥55	Black	White	Other/ Unknown
Eligible	2299 (100)	2649 (100)	182 (100)	1303 (100)	3463 (100)	362 (100)	4112 (100)	474 (100)
HCV screen	1314 (57.2)	1477 (55.8)	122 (67.0)	696 (53.4)	1973 (57.0)	220 (60.8)	2311 (56.2)	260 (54.9)
HCV AB+	91 (4.0)	119 (4.5)	38 (20.9)	92 (7.1)	80 (2.3)	13 (3.6)	183 (4.5)	14 (3.0)
HCV RNA test	90 (3.9)	114 (4.3)	38 (20.9)	89 (6.8)	77 (2.2)	13 (3.6)	177 (4.3)	14 (3.0)
HCV RNA+	48 (2.1)	76 (2.9)	28 (15.4)	59 (4.5)	37 (1.1)	6 (1.7)	111 (2.7)	7 (1.5)
Linked to care	27 (1.2)	51 (1.9)	15 (8.2)	36 (2.8)	27 (0.8)	3 (0.8)	71 (1.7)	4 (0.8)
Treated	12 (0.5)	17 (0.6)	4 (2.2)	13 (1.0)	12 (0.3)	3 (0.8)	24 (0.6)	2 (0.4)
SVR (Cure)	4 (0.2)	8 (0.3)	0 (0.0)	5 (0.4)	7 (0.2)	3 (0.8)	9 (0.2)	0 (0.0)

Abbreviations: AB, antibody; HCV, hepatitis C virus; SVR, sustained virologic response.

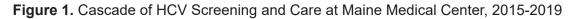
2c. Patient Distribution in the HCV Cascade of Care Stratified by HCV Screening Eligibility Factors

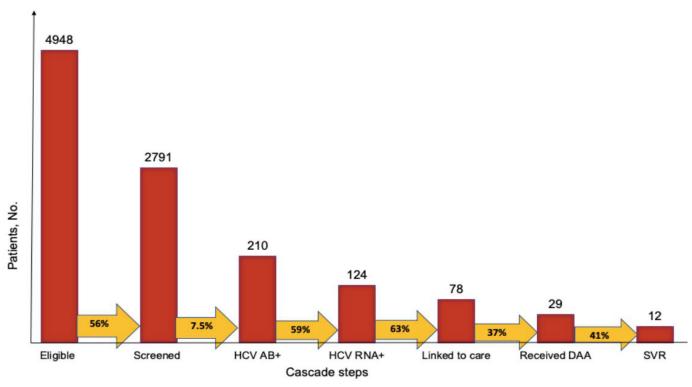
Cascade of care	Born 1945-1965, No. (%)	OUD, No. (%)	HIV, No. (%)	Dialysis, No. (%)*	Elevated ALT, No. (%)	HBV, No (%)
Eligible	4319 (100)	330 (100)	100 (100)	72 (100)	748 (100)	468 (100)
HCV screen	2441 (56.5)	197 (59.7)	78 (78.0)	53 (73.6)	446 (59.6)	422 (90.2)
HCV AB+	113 (2.6)	85 (25.8)	5 (5.0)	6 (8.3)	90 (12.0)	93 (19.9)
HCV RNA test	109 (2.5)	83 (25.2)	2 (2.0)	5 (6.9)	89 (11.9)	91 (19.4)
HCV RNA+	51 (1.2)	63 (19.1)	2 (2.0)	4 (5.6)	77 (10.3)	65 (13.9)
Linked to care	36 (0.8)	36 (10.9)	2 (2.0)	2 (2.8)	53 (7.1)	40 (8.5)
Treated	15 (0.3)	13 (3.9)	2 (2.0)	2 (2.8)	20 (2.7)	15 (3.2)
SVR (cure)	9 (0.2)	4 (1.2)	2 (2.0)	2 (2.8)	7 (0.9)	4 (0.9)

Abbreviations: AB, antibody; ALT, alanine aminotransaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; OUD, opioid use disorder; SVR, sustained virologic response.

*Dialysis-dependent renal failure

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AB, antibody; HCV, hepatitis C virus; SVR, sustained virologic response

Table 3. Independent Predictors of HCV Screening Among Eligible Patients at Internal Medicine Clinics of

 Maine Medical Center, 2015-2019

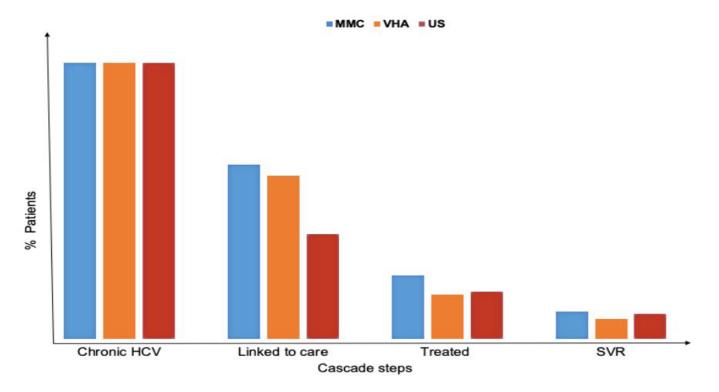
	Odds ratio (95% confidence interval) for HCV screening					
Variable [*]	Unadjusted	P value	Adjusted [†]	P value		
Current employment	0.84 (0.74-0.94)	.002	0.92 (0.80-1.07)	.28		
Insurance						
Medicare	1.26 (1.10-1.44)	<.001	1.20 (1.02-1.41)	.02		
Medicaid	1.30 (1.12-1.53)	<.001	1.06 (0.88-1.27)	.56		
Private insurance	Reference	-	Reference	-		
Risk factors	1.30 (1.12-1.53)	<.001	1.06 (0.88-1.27)	.56		
Born 1945-55	1.04 (0.88-1.23)	.68	1.82 (1.41-2.34)	<.001		
OUD	1.16 (0.92-1.45)	.21	1.19 (0.89-1.60)	.28		
HIV infection	2.79 (1.73-4.49)	<.001	2.05 (1.20-3.49)	.01		
HBV infection	8.18 (6.00-11.14)	<.001	8.80 (6.38-12.13)	<.001		
Long-term dialysis	2.18 (1.29-3.69)	.004	1.83 (1.03-3.25)	.04		
Persistent ALT	1.17 (1.00-1.37)	.05	1.25 (1.02-1.54)	.03		

Abbreviations: ALT, alanine aminotransferase; ESRD, end stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; OUD, opioid use disorder

*Independent predictors of screening were evaluated by logistic regression. Variables were included in the model if they were (1) known risk factors for HCV for which screening is recommended or (2) showed a significant ($P \le 0.1$) relationship with HCV screening in univariate analysis (Table 1).

[†]N=4948 patients who were eligible for HCV screening had complete data for all variables and were included in the adjusted analysis.

Figure 2. Comparison of the HCV Cascade of Care at MMC, the VHA, and in the US. VHA data was extracted from Maier et al. 2016,²⁹ and US data was extracted from Yehia et al. 2014.²³



HCV, hepatitis C virus; MMC, Maine Medical Center; SVR, sustained virologic response; US, United States; VHA, Veterans Health Administration.

The VHA has a robust linkage to care system and maintains a registry of HCV patients known as the HCV Clinical Case Registry.^{15,29} Maier et al. defined linkage to care as patients who were in the HCV Clinical Case Registry and had HCV listed in their electronic health record.²⁹

Treatment data from MMC showed slightly higher treatment rates than the VHA²⁹ and US,³⁰ but SVR rates were similar to these existing data sources. Although the VHA and US comparison data reflect clinical practice before 2014, our data reflects clinical practice after 2015. Also, the availability of HCV AB tests with reflex to PCR and new treatment options in recent years may contribute to the observed differences.

Highly effective interferon-free therapies became available after the introduction of oral DAA therapies. Yet, HCV diagnosis and treatment uptake in the US, particularly in rural areas, is lagging behind³¹ the World Health Organization's target of 90% diagnosed and 80% treated by 2030.³² All 3 data sources (MMC, VHA, and US) show an underperformance of HCV screening and subsequent enrollment into care, indicating the need for a more comprehensive intervention strategy.

Unfortunately, the incidence of HCV continues to increase in the epidemic of substance use disorder in the US.⁷ There are several factors identified from prior published data for the low uptake. Of those factors, lack of awareness about HCV infection; barriers to receiving testing and treatment, such as distance from HCV clinics in rural areas and lack of telehealth options; and ongoing substance use disorder and mental health issues are some of the many reasons for the gaps in HCV care.^{17,33} Even though investigating the causes of low uptake for HCV screening is not within the scope of this study, all the key risk factors we assessed are independently associated with HCV screening, except patients with OUD. Our findings indicate an area of public health importance that needs intervention to increase HCV screening and enrollment into care, particularly in people with substance use disorder.

We found that patients with OUD accounted for less than 7% of patients eligible for HCV screening,

but more than 50% of people with chronic HCV infection. These results indicate that OUD (which may involve use of injection drugs) is a major contributor to HCV infection. In our study, only 6% of patients with chronic HCV and OUD ever received treatment and achieved SVR. This finding highlights that HCV intervention programs should consider substance use disorder when planning strategies of linkage and retention in care. Suggested strategies include, but are not limited to, (1) educating and training providers about the updated HCV-screening and treatment guidelines; (2) providing molecular HCV testing and treatment at point-of-care to reduce phlebotomy barriers;³⁴ (3) reducing referrals to specialty care and expanding HCV treatment through primary care offices with support of electronic consults and Extension for Community Healthcare Outcomes (Project ECHO);³⁵ (4) collaborating with harm-reduction services, peer navigators, and addiction medicine clinics for linkage and/or point-of-care services;36-38 and (5) using innovative ways to increase access to HCV care, such as providing HCV screening at syringe service programs and health services via TeleHealth.39

There were some limitations to this study. This study was done at a single center and included only patients seen in internal medicine clinics. We were unable to capture other types of substance use disorder (e.g., stimulants), so we may have underestimated the role that substance misuse plays in chronic HCV infection at MMC. Our data also lacks information about the time between HCV diagnosis and treatment, as well as treatment outcomes of patients referred to providers outside MMC. Children and pregnant women were not included in this study. Notably, since we completed this study, HCV-screening recommendations were revised to include screening all adults 18 years and older for HCV at least once in their lifetime. As a result, more recent screening rates may differ.

CONCLUSIONS

Our study identified gaps in the continuum of HCV care at multiple levels. In the era of DAAs, our results provide insight about opportunities for intervention to improve the HCV cascade of care, particularly for people with OUD. These results can be used to develop strategies to work toward HCV microelimination strategies, particularly in rural areas.

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Conflicts of Interest: None

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