Factors predicting staging and treatment initiation for patients with chronic hepatitis C infection: insurance a key predictor

Janet Lin1, Cammeo Mauntel-Medici1, Anjana Bairavi Maheswaran1, Sara Baghikar1, Oksana Pugach2, Ellen M. Stein1, Michelle T. Martin3, Hai Nguyen2

1Department of Emergency Medicine, College of Medicine, University of Illinois at Chicago, 808 S. Wood Street, Chicago, IL 60612, USA
2Institute for Health Research and Policy, University of Illinois at Chicago, 1747 W. Roosevelt Road, Chicago, IL 60608, USA
3Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, IL 60612, USA
Address correspondence to Anjana Bairavi Maheswaran, E-mail: amahes5@uic.edu.

ABSTRACT

Background Chronic hepatitis C (HCV) infection affects over 2.4 million Americans and accounts for 18 000 deaths per year. Treatment initiation in this population continues to be low even after introduction of highly effective and shorter duration direct-acting antivirals. This study assesses factors that influence key milestones in the HCV care continuum.

Methods Retrospective time-to-event analyses were performed to assess factors influencing liver fibrosis staging and treatment initiation among individuals confirmed with chronic HCV infection at University of Illinois Hospital and Health Sciences System between 1 August 2015 and 24 October 2016 and followed through 28 January 2018. Cox regression models were utilized for multivariable analyses.

Results Individuals tested at the liver clinic (hazard ratio [HR] = 2.03; 95% confidence interval [CI]: 1.19–3.46) and at the federally qualified health center (HR = 3.51; 95% CI: 2.19–5.64) had higher instantaneous probability of being staged compared with individuals tested at the emergency department (ED) or inpatient setting. And probability of treatment initiation increased with advancing liver fibrosis especially for Medicaid beneficiaries (HR = 1.64; 95% CI: 1.35–1.99).

Conclusions The study demonstrates a need for improving access for patients with early stages of the disease in order to reduce HCV-related morbidity and mortality, especially those tested at nontraditional care locations such as the ED or the inpatient setting.

Keywords chronic disease, management and policy

Introduction

Hepatitis C virus (HCV) infection is a public health problem affecting 4.1 million Americans.1 Approximately 50–85% of individuals who contract HCV develop chronic infection (2.4 million Americans), a leading cause of end-stage liver disease and accounts for over 18 000 preventable deaths per year.2–4

Milestones in the HCV care continuum include: positive HCV antibody (Ab) screening, detectable confirmatory RNA testing (current infection), liver fibrosis staging (fibrotic changes in the liver scored with values between F0 and F4), treatment initiation, treatment completion and sustained virologic response (undetectable HCV RNA 12 weeks following treatment completion).

The advent of interferon free direct-acting antivirals (DAA) regimens with high cure rates in 2013 was perceived as a solution to the growing epidemic.5 However, disparities continue to exist in treatment initiation rates. This study explored clinical- and patient-level factors to better understand why these disparities exist, particularly with regard to staging and treatment initiation in the HCV care continuum.
Study setting
This study was conducted at the University of Illinois Hospital and Health Sciences System (UIH), which primarily serves a low-income, minority patient population, including communities with high prevalence of HCV in Chicago. Chicago’s population is majority Caucasians (33%) followed by African Americans (30%) and Hispanics (29%). African Americans carry the majority of the disease burden for HCV. Also, 90% of Chicago’s population has health coverage with 26% of them covered through Medicaid. UIH serves the majority of its HCV patients through its outpatient liver clinic and affiliated federally qualified health center (FQHC).

Study inclusion and exclusion criteria
Patients 18 years of age or older were included in the study if their first detectable HCV RNA test at UIH was performed between 1 August 2015 and 24 October 2016. Patients were excluded from the study if they had been staged or initiated on HCV treatment prior to the study period.

Methods
This retrospective study utilized time-to-event analyses to evaluate the factors influencing staging and treatment initiation among a cohort of chronically infected HCV patients screened at UIH.

Data were extracted from the electronic health record (EHR) (CERNER, Cerner Corporation, Kansas City, MO) through automated reports and manual chart abstraction. Data included socio-demographic information (age, gender, race, ethnicity, marital status and primary insurance type), clinical and laboratory information (date and location of detectable RNA test, date, result and methodology of staging, instance of preliminary screening for HCV Ab immediately prior to RNA confirmation at UIH during the study and regimen, start date and duration of treatment) and behavioral and mental health information (history of alcohol use, substance use, depression, anxiety, psychosis, bipolar or trauma-related mental health disorders). The study focused on this specific set of mental health disorders because they were consistently coded in the EHR and easily accessible for extraction. This study was approved by University of Illinois at Chicago Institutional Review Board.

The two outcomes were assessed using separate models. We considered the first instance of fibrosure, fibroscan or biopsy done by a liver specialist during the study period as achieving the outcome of staging. Also, those with documented fibrosis score but unknown staging methodology and those with documented cirrhosis upon imaging were deemed eligible to be included in the staged sample with appropriate fibrosis scores. Outcome of treatment initiation was defined as starting any DAA regimen. Time to event was defined as the number of days from entry into the study until the subject achieved the outcome. The overall follow-up period was ∼2.5 years (1 August 2015 to 28 January 2018).

The date of detectable HCV RNA test was considered T0, and T1 was the date of either achieving the outcome, death or last follow-up. The difference between T1 and T0 was the follow-up time in days for the individual. Subjects were considered censored if they died or were lost to follow-up during the study, or if the study ended before they achieved the outcome. For the bivariate analysis, Kaplan–Meier estimates were generated as a nonparametric estimator of survivor function. These estimates were used to determine median survival times, hazard rate and cumulative hazard and were compared across levels of covariates. P values of the log-rank test were used to determine the statistical significance of the bivariate association of a covariate and outcome.

For multiple model selection, we conducted backwards elimination using a conservative P value of 0.2. Age, gender and race/ethnicity were selected a priori and retained throughout model selection.

The final model for the staging outcome included: age, gender, race/ethnicity, preliminary screening for HCV Ab at UIH immediately prior to RNA confirmation, RNA testing location as well as history of drug dependency, depression, anxiety, other mental health conditions and self-reported history of ever substance use. The final model for the treatment initiation outcome included age, gender, race/ethnicity, history of drug dependency, self-reported history of alcohol use, marital status, primary insurance type, liver fibrosis stage as a continuous variable conforming to parsimonious modeling principle and an interaction term between fibrosis stage and primary insurance type.

All selected covariates satisfied proportional hazard assumption, and hence, Cox proportional hazard model was utilized for final analyses. P values of the Score and Likelihood Ratio tests were used to analyze the possible association of the covariates with the outcomes and to obtain the hazard ratio (HR) adjusted for the covariates. Analysis was performed using SAS 9.4 software.

Results
The overall sample included 303 patients who met inclusion criteria. The majority of the patients were born between 1945 and 1965 (76%), were male (65%) and non-Hispanic African Americans (60%). Mean age of the sample was 56 ± 10 years.
The majority of patients were insured through Medicaid (66%). Almost half of the sample self-reported ever alcohol use (54%) and ever substance use (48%), which is higher compared with the general population, and 33% had a diagnosis of drug dependence or alcohol use documented as an ICD-10 diagnosis code in their EHR. Furthermore, 13% of the sample had a diagnosis of depression or anxiety disorder documented, which was lower than expected in this population. In total, 86% of the sample had liver fibrosis staging completed, and 45% of those patients had initiated treatment (Table 1). Among those staged, 80% were staged using the fibrosure test, 5% through fibroscan and <1% through liver biopsies.

Liver fibrosis staging outcome
For this outcome, 13% of the sample was censored and the median survival time was 11 days (Table 1). In the fully adjusted model, those who had a history of psychosis, bipolar or trauma-related mental health disorders had a 62% higher instantaneous probability of getting staged compared with those who did not have a history of these conditions, $P < 0.05$. Those who had their preliminary screening for HCV Ab at UIH had a 24% lower instantaneous probability of getting staged compared with those who had their preliminary screening elsewhere, $P = 0.048$. Also, those who had their confirmatory testing at the outpatient liver clinic and at the FQHC, had 2 and 3.5 times higher instantaneous probability of having the outcome, $P = 0.01$ and $< 0.0001$ respectively, compared with those tested in the inpatient or emergency department (ED) setting (Table 2).

Treatment initiation outcome
Of the 262 patients who were staged, 11 were excluded from the study since they could not contribute to the time to event analyses. Five patients were excluded because they were staged and initiated on treatment on the same day. Six patients who made up the ‘uninsured’ category, none of whom initiated treatment, were also excluded. The final sample included 251 patients (96%).

For this outcome, 53% of the sample was censored and the median survival time was 426 days (Table 1). In the fully adjusted model, fibrosis stage was found to be a significant effect modifier of the association between primary insurance type and treatment initiation. Higher fibrosis stage was associated with a 64% higher instantaneous probability of treatment initiation for patients on Medicaid compared with patients covered by Medicare or private insurance, $P = 0.01$. Furthermore, those who were married had two times higher instantaneous probability of initiating treatment compared with those who were single, $P = 0.004$ (Table 2).

Discussion
Main findings of this study
This study illuminates disparities across the HCV care continuum with regard to staging and treatment initiation.

Early diagnosis and treatment can help limit HCV-related morbidity and mortality and associated health costs. However, evidence suggests that 35% of patients seeking HCV treatment are denied coverage by their payor. Private and public payors, except Medicare, have reimbursement policies that are multifactorial but based partly on the extent of liver damage, which prevents access to treatment for individuals with low-to-moderate liver damage. This study explored the moderating effect of liver fibrosis stage on the relationship between insurance and treatment initiation and found that the effect was significant.

Additionally, the difference in the effect of insurance on treatment initiation was exacerbated at lower fibrosis stages, demonstrating that certain payors make it more difficult for patients with less advanced disease to access treatment. Medicare beneficiaries were more likely than their Medicaid counterparts to initiate treatment, and this effect did not vary by fibrosis stage (Table 2). The likelihood for treatment initiation increased at higher fibrosis stages for Medicaid beneficiaries (Fig. 1).

In Illinois, Medicaid finances health care delivery through either a fee-for-service (FFS) system or a managed care organization (MCO). Until November 2018, in the FFS system, only beneficiaries with significant liver damage (F3 or F4) qualified for treatment, provided they also meet the sobriety and prescriber restrictions. And, most MCOs that Medicaid contracts with also have their own restrictions, adding another layer of complexity that impacts access for patients on these insurance plans. This explains why treatment initiation was lower among Medicaid beneficiaries in our sample, particularly among those with nascent liver damage.

In contrast, Medicare part D does not restrict access to treatment based on liver fibrosis stage and 98% of the part D plans cover DAAs with coinsurance or copayment, which explains why Medicare beneficiaries had higher treatment initiation rates compared with other insurance beneficiaries in our sample.

This study also explored factors that influence the likelihood of staging. The higher prevalence of people staged using the fibrosure test in the study sample was expected since the test is more readily accessible when compared with fibroscan, which is only available in the outpatient liver clinic. In our study, patients with a history of psychosis, bipolar or trauma-related mental health disorders were more likely to be staged than those who did not report these conditions.
Table 1  Distribution of socio-demographic, behavioral, mental health and clinical variables in the sample including median survival time

| Variables                              | Overall sample | Staged | Treatment initiated |
|----------------------------------------|---------------|--------|---------------------|
|                                        |               | Yes (%)| No (%) | Median survival time$^a$ in days (95% confidence interval [CI]) | Yes (%)| No (%) | Median survival time$^a$ in days (95% CI) |
|                                        | N (%)         |        |        |                                  |        |        |                                  |
| Total                                  | 303 (100)     | 262 (86.5) | 41 (13.5) | 11 (6, 24)                      | 117 (46.6) | 134 (53.4) | 426 (247, 427)                 |
| **Socio-demographic variables**        |               |        |        |                                  |        |        |                                  |
| Gender                                 |               |        |        |                                  |        |        |                                  |
| Female                                 | 107 (35.3)    | 95 (36.3) | 12 (29.3) | 12 (6, 26)                      | 46 (39.3) | 47 (35.1) | 426 (241, 241)                 |
| Male                                   | 196 (64.7)    | 167 (63.7) | 29 (70.7) | 7 (6, 34)                       | 71 (60.7) | 87 (64.9) | 404 (225, 225)                 |
| Age$^b$                                |               |        |        |                                  |        |        |                                  |
| <51                                    | 58 (19.1)     | 48 (18.3) | 10 (24.4) | 27 (5, 62)                      | 17 (14.5) | 27 (20.1) | —                              |
| ≥51                                    | 245 (80.9)    | 214 (81.7) | 31 (75.6) | 10 (6, 23)                      | 100 (85.5) | 107 (79.9) | 359 (225, 770)                 |
| Race and ethnicity                     |               |        |        |                                  |        |        |                                  |
| Non-Hispanic African American          | 181 (59.7)    | 155 (59.2) | 26 (63.4) | 12 (6, 33)                      | 72 (61.5) | 76 (56.7) | 376 (226, 226)                 |
| Non-Hispanic Caucasian                 | 42 (13.9)     | 37 (14.1) | 5 (12.2) | 7 (6, 20)                       | 15 (12.8) | 22 (16.4) | 770 (122, 122)                 |
| Non-Hispanic other                     | 40 (13.2)     | 33 (12.6) | 7 (17.1) | 35 (5, 74)                      | 14 (12.0) | 18 (13.4) | 348 (124, 124)                 |
| Hispanic                               | 38 (12.5)     | 35 (13.3) | 3 (7.3) | 6.5 (5, 27)                     | 16 (13.7) | 16 (11.9) | 247 (121, 121)                 |
| Missing                                | 2 (0.7)       | 2 (0.8) | —       | —                               | —       | 2 (1.5) | —                              |
| Marital status                         |               |        |        |                                  |        |        |                                  |
| Single                                 | 189 (62.4)    | 161 (61.5) | 28 (68.3) | 23 (6, 47)                      | 65 (55.6) | 87 (64.9) | —                              |
| Married                                | 52 (17.2)     | 48 (18.3) | 4 (9.8) | 13 (5, 34)                      | 28 (23.9) | 19 (14.2) | 151 (92, 261)                 |
| Separated or widowed or divorced       | 48 (15.8)     | 42 (16.0) | 6 (14.6) | 6 (4, 14)                       | 20 (17.1) | 22 (16.4) | 376 (253, 253)                 |
| Unknown                                | 14 (4.6)      | 11 (4.2) | 3 (7.3) | 5 (4, 131)                      | 4 (3.4) | 6 (4.5) | —                              |
| Primary language                       |               |        |        |                                  |        |        |                                  |
| English                                | 282 (93.1)    | 244 (93.1) | 38 (92.7) | 12 (6, 25)                      | 110 (94.0) | 126 (94.0) | 426 (241, 241)                 |
| Other                                  | 21 (6.9)      | 18 (6.9) | 3 (7.3) | 7 (5, 71)                       | 7 (6.0) | 8 (6.0) | —                              |
| **Primary insurance$^†$**              |               |        |        |                                  |        |        |                                  |
| Medicare                               | 51 (16.8)     | 46 (17.5) | 5 (12.2) | 19 (5, 68)                      | 25 (21.4) | 20 (14.9) | 125 (87, 87)                  |
| Medicaid                               | 199 (65.7)    | 176 (67.2) | 23 (56.1) | 7 (6, 16)                       | 72 (61.5) | 100 (74.6) | 770 (404, 404)                |
| Private or commercial                  | 45 (14.9)     | 34 (13.0) | 11 (26.8) | 35 (6, 121)                     | 20 (17.1) | 14 (10.4) | 122 (87, 300)                 |
| Uninsured                              | 8 (2.6)       | 6 (2.3) | 2 (4.9) | 12 (4, 156)                     | —       | —       | —                              |
| Behavioral and mental health variables |               |        |        |                                  |        |        |                                  |
| **Self-reported ever alcohol use$^*$** |               |        |        |                                  |        |        |                                  |
| Yes                                    | 163 (53.8)    | 139 (53.1) | 24 (58.5) | 14 (7, 26)                      | 64 (54.7) | 70 (52.2) | 330 (208, 208)                |
| No                                     | 108 (35.6)    | 98 (37.4) | 10 (24.4) | 6 (5, 14)                       | 48 (41.0) | 49 (36.6) | 444 (169, 169)                |
| Missing                                | 32 (10.6)     | 25 (9.5) | 7 (17.1) | 49 (5, 246)                     | 5 (4.3) | 15 (11.2) | —                              |
| **Self-reported ever substance use$^{**}$** |               |        |        |                                  |        |        |                                  |
| Yes                                    | 145 (47.8)    | 127 (48.5) | 18 (43.9) | 8 (6, 23)                       | 54 (46.2) | 67 (50.0) | 572 (261, 261)                |
| No                                     | 132 (43.6)    | 118 (45.0) | 14 (34.1) | 9 (6, 27)                       | 59 (50.4) | 56 (41.8) | 253 (138, 770)                |
| Missing                                | 26 (8.6)      | 17 (6.5) | 9 (22.0) | 165 (10, 513)                   | 4 (3.4) | 11 (8.2) | 611 (121, 121)                |
| **Documented history of drug dependency$^c$** |               |        |        |                                  |        |        |                                  |
| Yes                                    | 101 (33.3)    | 79 (30.2) | 22 (53.7) | 49 (14, 83)                     | 25 (21.4) | 48 (35.8) | 335 (212, 681)                |
| No                                     | 202 (66.7)    | 183 (69.9) | 19 (46.3) | 6 (5, 12)                       | 92 (78.6) | 86 (64.2) | —                              |

(Continued)
Table 1 Continued.

| Variables                                                      | Overall sample | Staged | Treatment initiated |
|---------------------------------------------------------------|----------------|--------|---------------------|
|                                                               | N (%)          | Yes (%)| No (%)              | Median survival time<sup>a</sup> in days (95% confidence interval [CI]) | Yes (%) | No (%) | Median survival time<sup>a</sup> in days (95% CI) |
| Documented history of depression***                           |                |        |                     |                                |         |        |                                |
| Yes                                                           | 42 (13.9)      | 28 (10.7) | 14 (34.1)         | 121 (13, 316)                  | 9 (7.7) | 19 (14.2) |                                |
| No                                                            | 261 (86.1)     | 234 (89.3) | 27 (65.9)        | 7 (6, 16)                      | 108 (92.3) | 115 (85.8) | 359 (226, −) |
| Documented history of anxiety disorders***                   |                |        |                     |                                |         |        |                                |
| Yes                                                           | 40 (13.2)      | 27 (10.3) | 13 (31.7)         | 62 (31, 316)                  | 9 (7.7) | 17 (12.7) |                                |
| No                                                            | 263 (86.8)     | 235 (89.7) | 28 (68.3)        | 7 (6, 16)                      | 108 (92.3) | 117 (87.3) | 404 (236, −) |
| Documented history of other mental health diagnosis<sup>d</sup> |                |        |                     |                                |         |        |                                |
| Yes                                                           | 26 (8.6)       | 22 (8.4) | 4 (9.8)           | 21.5 (6, 91)                  | 8 (6.8) | 13 (9.7) | 681 (151, −) |
| No                                                            | 277 (91.4)     | 240 (91.6) | 37 (90.2)        | 10 (6, 24)                     | 109 (93.2) | 121 (90.3) | 404 (230, −) |
| Clinical and laboratory variables                             |                |        |                     |                                |         |        |                                |
| HIV Coinfection                                               |                |        |                     |                                |         |        |                                |
| Yes                                                           | 19 (6.3)       | 15 (5.7) | 4 (9.8)           | 26 (5, 60)                     | 8 (5.8) | 6 (4.5) | 376 (60, −) |
| No                                                            | 278 (91.8)     | 241 (92.0) | 37 (90.2)        | 11 (6, 25)                     | 106 (90.6) | 125 (93.3) | 572 (247, −) |
| Missing                                                       | 6 (1.9)        | 6 (2.3) | —                 | —                             | 3 (2.6) | 3 (2.2) | —                             |
| Prior HCV Ab test at UIH preceding RNA confirmation***       |                |        |                     |                                |         |        |                                |
| Yes                                                           | 138 (45.5)     | 107 (40.8) | 31 (75.6)        | 62 (35, 84)                   | 41 (35.0) | 63 (47.0) | —                             |
| No                                                            | 165 (54.5)     | 155 (59.2) | 10 (24.4)        | 5 (5, 6)                      | 76 (65.0) | 71 (53.0) | 376 (214, 681) |
| Location of HCV RNA test***                                  |                |        |                     |                                |         |        |                                |
| ED or inpatient unit                                          | 48 (15.8)      | 28 (10.7) | 20 (48.8)        | 124 (44, 316)                 | 5 (4.3) | 22 (16.4) | —                             |
| Outpatient liver clinic                                       | 37 (12.2)      | 34 (13.0) | 3 (7.3)           | 31 (7, 83)                    | 13 (11.1) | 20 (14.9) | 681 (178, −) |
| FQHC                                                          | 133 (43.9)     | 133 (50.8) | —                 | 5 (4, 5)                      | 70 (59.8) | 61 (45.5) | 301 (172, −) |
| Primary care clinics                                          | 85 (28.1)      | 67 (25.5) | 18 (43.9)        | 59 (35, 88)                   | 29 (24.8) | 31 (23.1) | 462 (212, −) |
| HCV genotype result                                          |                |        |                     |                                |         |        |                                |
| 1A or 1B                                                      | 210 (69.3)     | 202 (77.5) | —                 | —                            | 102 (87.2) | 93 (69.4) | 335 (214, 681) |
| 2, 3 or 4                                                    | 29 (9.6)       | 28 (10.7) | —                 | —                            | 14 (12.0) | 14 (10.4) | 261 (122, −) |
| Missing                                                      | 64 (21.1)      | 31 (11.8) | —                 | —                            | 1 (0.9) | 27 (20.1) | —                             |
| Liver fibrosis stage<sup>†††</sup>                          |                |        |                     |                                |         |        |                                |
| F0                                                           | 33 (10.9)      | 33 (12.6) | —                 | —                            | 7 (6.0) | 24 (17.9) | —                             |
| F1                                                           | 25 (8.3)       | 25 (9.5) | —                 | —                            | 4 (3.4) | 18 (13.4) | —                             |
| F2                                                           | 80 (26.4)      | 80 (30.5) | —                 | —                            | 37 (31.6) | 42 (31.3) | 770 (208, −) |
| F3                                                           | 42 (13.9)      | 42 (16.0) | —                 | —                            | 20 (17.1) | 17 (12.7) | 230 (176, 404) |
| F4                                                           | 82 (27.1)      | 82 (31.3) | —                 | —                            | 49 (41.9) | 33 (24.6) | 126 (110, 330) |
| Missing                                                      | 41 (13.5)      | —       | —                 | —                            | —       | —       | —                             |

<sup>a</sup>Median survival time, in this study, is the time in days when half of the sample had an event. Estimate of median survival time or upper confidence limit is missing for certain variables for which survival curve did not drop below 0.50

<sup>b</sup>The cutoff of 51 years was chosen to include individuals born between 1945 and 1965 (the birth cohort) in one category.

<sup>c</sup>Self-reported ever substance use refers to any substance use except for alcohol.

<sup>d</sup>Documented history of other mental health diagnosis variable includes diagnosis of bipolar, psychosis and trauma-related disorders.

For the log-rank test of equality across strata for the outcome of Staging: ***P < 0.001, **P < 0.01, *P < 0.05

For the log-rank test of equality across strata for the outcome of Treatment Initiated: ††† P < 0.001, †† P < 0.01, † P < 0.05
Table 2  Results from the final model for staging and treatment initiation outcomes

| Variables (reference categories) | HRs from fully adjusted model for staging (95% CI) | HRs from fully adjusted model for treatment initiation (95% CI) |
|----------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Socio-demographic variables**  |                                               |                                               |
| Age (<51)                        |                                               |                                               |
| ≥51                              | 0.81 (0.56–1.17)                               | 1.16 (0.65–2.08)                              |
| **Gender**                       |                                               |                                               |
| ‘Male’                           |                                               |                                               |
| Female                           | 0.96 (0.73–1.25)                               | 1.25 (0.82–1.91)                              |
| **Race and ethnicity**           |                                               |                                               |
| ‘Non-Hispanic Caucasian’         |                                               |                                               |
| Non-Hispanic African American    | 1.07 (0.73–1.58)                               | 1.11 (0.62–2.0)                               |
| Non-Hispanic other               | 0.94 (0.58–1.55)                               | 1.16 (0.53–2.52)                              |
| Hispanic                         | 1.28 (0.79–2.08)                               | 1.27 (0.61–2.64)                              |
| **Marital status**               |                                               |                                               |
| ‘single’                         |                                               |                                               |
| Married                          | —                                              | 1.99 (1.24–3.20)**                            |
| Separated or widowed or divorced | —                                              | 0.88 (0.51–1.52)                              |
| Unknown                          | —                                              | 0.92 (0.33–2.57)                              |
| **Behavioral and mental health variables** |                     |                                               |
| **Self-reported ever substance use** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 1.10 (0.85–1.42)                               | —                                              |
| Missing                          | 0.64 (0.37–1.09)                               | —                                              |
| **Self-reported ever alcohol use** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | —                                              | 1.04 (0.70–1.56)                              |
| Missing                          | —                                              | 0.35 (0.13–0.90)*                             |
| **Documented history of drug dependency** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 0.76 (0.56–1.03)                               | 0.71 (0.45–1.13)                              |
| **Documented history of depression** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 0.70 (0.43–1.15)                               | —                                              |
| **Documented history of anxiety disorders** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 0.68 (0.42–1.10)                               | —                                              |
| **Documented history of other mental health diagnosis** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 1.62 (1.01–2.60)*                              | —                                              |
| **Clinical and laboratory variables** |                                              |                                               |
| **Prior HCV Ab test at UIH preceding RNA confirmation** |                                              |                                               |
| ‘no’                             |                                               |                                               |
| Yes                              | 0.76 (0.57–1.0)*                               | —                                              |
| **Location of HCV RNA test**     |                                               |                                               |
| ‘ED or inpatient unit’           |                                               |                                               |
| Outpatient liver clinic          | 2.03 (1.19–3.46)***                           | —                                              |
| FQHC                             | 3.51 (2.19–5.64)***                           | —                                              |
| Primary care clinics             | 1.23 (0.76–1.97)                               | —                                              |
| **Interaction between liver fibrosis stage and primary insurance** |                                              |                                               |
| Liver fibrosis stage while on Medicare | —                                              | 1.0 (0.72–1.40)                              |
| Liver fibrosis stage while on Medicaid | —                                              | 1.64 (1.35–1.99)*                           |
| Liver fibrosis stage while on private or commercial insurance | —                                              | 1.50 (0.90–2.51)                              |

***P < 0.001, **P < 0.01, *P < 0.05

*aSelf-reported ever substance use refers to any substance use except for alcohol.

*bDocumented history of other mental health diagnosis variable includes diagnosis of bipolar, psychosis and trauma-related disorders.
Why these conditions are associated with better staging is not known. It is possible that these individuals were engaged in structured psychiatric care and were connected to resources and support services that helped them navigate the healthcare system.

Patients who had their HCV Ab test performed at UIH were less likely to be staged compared with patients who had their screening test outside of UIH. It is possible that individuals tested outside were referred to UIH for HCV care and, in turn, entered the system already primed for staging within the HCV care continuum.

Also, those tested in the ED or inpatient setting were the least likely to be staged, whereas those tested in Mile Square were the most likely to be staged. Because Mile Square is a primary care facility, it is possible that their patients have an established relationship with a provider leading to greater likelihood for follow-up care. Patients tested in the ED or inpatient setting may not have established care within the healthcare system and hence would require additional efforts to enter the HCV care continuum.

What we already know on this topic

In the USA, between 2003 and 2010, only 50% of individuals with HCV infection were aware of their status, 7–11% were treated and only 5–6% achieved cure.12 Despite introduction of well-tolerated, shorter duration and highly effective regimens of interferon-free DAAs in 2013,5 treatment initiation rates continue to be low. A retrospective study of HCV mono-infected and HCV/HIV coinfected patients between 2011 and 2015 demonstrated that only 10.2% and 18% were initiated on interferon-free DAA treatment, respectively. However among those initiated on treatment, 91% of those with mono-infection and 97% of those with co-infection achieved cure, respectively.13 Previous studies identified socio-demographic, behavioral and clinical factors that hinder diagnosis and access to care for individuals with HCV that persist even in the interferon-free DAA era.14–16

A key barrier is payor-imposed HCV treatment restrictions based on severity of liver disease, level of viral suppression and compliance with antiretroviral treatment for HIV coinfected individuals, type of provider prescribing treatment and sobriety.17–21 Many state Medicaid programs have restricted HCV treatment access due to budget challenges.10,22 These policies are in violation of the Social Security Act by restricting access to medically necessary outpatient drugs on the basis of cost containment.23 Furthermore, HCV treatment initiation is substantially low among people who inject drugs, a population disproportionately burdened by HCV and contributing to 72% of new infections.15,24–26

Evidence also suggests that there are significant racial and ethnic disparities in HCV disease burden and treatment initiation in the US population.27,28 In 2017, the rate of
infection was highest among American Indians/Alaska Natives at 2.9 per 100,000 and that among non-Hispanic African Americans and Hispanics was 0.5 and 0.4 per 100,000, respectively, whereas only representing 1%, 13% and 18%, respectively, of the general US population.29 However, treatment initiation is higher among non-Hispanic Whites compared with African Americans, Hispanics and other minority population in the USA.27

**What this study adds**

While several barriers to HCV care have been described in the literature, this study is the first to use time to event methodology to explore the impact of clinical- and patient-level factors on milestones in the HCV care continuum: time to liver fibrosis staging and treatment initiation. To our knowledge, this is also the first study to analyze the effect of the interaction between liver fibrosis stage and insurance on treatment initiation. Findings of this study will add to the body of knowledge on barriers to HCV staging and treatment initiation and inform strategies in improving access to care for individuals who face the greatest impediments along the HCV care continuum.

**Limitations of this study**

There were several limitations to this study. First, this was a retrospective cross-sectional analysis using secondary data from the EHR; thus, not all variables were available to us. For the same reasons, we were also not able to perform further analysis to understand why factors like marital status of the patient had an impact on the outcomes and were unable to assess system- and provider-level barriers to staging and treatment initiation. Additionally, data were extracted using both automated queries and manual chart review. Though the percentage of data pulled through manual review was small (<25%), it could have introduced bias into the data. Some patients were referred to care outside of UIH owing to insurance coverage, which contributed to omitted cases. We excluded six patients making up the uninsured category from the second model since none initiated treatment; this prevented us from drawing insights on this unique group who might have differed from the insured population. Also, since the completion of our study, many of the state Medicaid programs have eliminated stringent treatment initiation restrictions based on liver fibrosis staging, which we believe played a role in the differential treatment initiation rates by insurance type observed in our data. Despite these limitations, our findings provide significant insights.

**Public health implications**

HCV is a public health crisis and was the leading cause of infectious disease death in the USA prior to the COVID-19 pandemic, despite the availability of highly effective treatment. There has been a drastic increase in acute cases and neonatal cases owing to the opioid epidemic and increase in injection drug use.30,31 In light of this trend, the US Preventive Services Task Force revised its screening recommendations recently to include screening for all adults aged 18–79 years.32 The updated recommendations will increase the number of individuals diagnosed and in turn the number of individuals seeking access to treatment. In order to best prevent morbidity and mortality, HCV treatment should be initiated at the earliest time possible, when the patient is at the lowest fibrosis stage. This is reflected in recent recommendations for universal treatment for HCV patients by the Centers for Disease Control and Prevention (CDC) and American Association for the Study of Liver Diseases.33 This study highlights some of the key barriers that impede early treatment, especially the role that insurance plays in delaying treatment, and the need for facilitating improved follow-up care for those diagnosed in the ED (a healthcare venue most frequented by those vulnerable to acquiring the infection). The findings strongly encourage universal access to treatment to end the epidemic.

Medicaid beneficiaries bear a disproportionate burden of the disease and, as our study suggests, also the population with poor access to treatment.34 However, there is some promising news on the horizon. Between 2017 and 2019, 28 state Medicaid programs, including Illinois Medicaid, removed restrictions on treatment initiation based on liver fibrosis stage. Therefore, 38 states now have no fibrosis restrictions, 19 states scaled back prescriber restrictions and 11 states relaxed sobriety requirements.35,36 Furthermore, compared with 2017 when 52% of the state Medicaid programs were graded poorly by the National Viral Hepatitis Roundtable and the Center for Health Law and Policy Innovation of Harvard Law School for their HCV treatment access, only 15% of the states received poor grades in 2019.35 This recent policy development warrants future studies to evaluate the difference in treatment initiation among Medicaid beneficiaries following removal of restrictive treatment initiation policies.

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**Conflict of interest**

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