

Predictors of Treatment in Patients with Chronic Hepatitis C Infection—Role of Patient Versus Nonpatient Factors

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Treatment with interferon and ribavirin is effective in patients with chronic infection with hepatitis C virus (HCV). Previous data indicate that treatment rates are suboptimal. We sought to identify patient and provider-level predictors of treatment receipt in HCV by conducting a retrospective cohort study of 5701 HCV patients in a large regional Veteran's Administration (VA) healthcare network. We also determined the degree of variation in treatment rates attributable to patient, provider, and facility factors. Three thousand seven hundred forty-three patients (65%) were seen by a specialist and 894 (15.7%) received treatment. Treatment rates varied from 6% to 29% across the 5 facilities included in the analysis. Patients were less likely to receive treatment if they were older [RR, 0.55; 95% CI, 0.45, 0.67), single (RR, 0.77; 95%CI, 0.67, 0.88), had hepatic dysfunction (RR, 0.73; 95%CI, 0.66, 0.89), had normal alanine aminotransferase (ALT) (RR, 0.73; 95%CI, 0.59, 0.89), had HCV genotype 1 (RR, 0.78; 95%CI, 0.71, 0.86), were African American with genotype 1 (RR, 0.78; 95% CI, 0.71, 0.86), or were anemic (RR, 0.70; CI, 0.60, 0.89). In addition, patients evaluated by less experienced providers were 77% less likely to receive treatment than those evaluated by more experienced providers. The patient, provider, and facility factors explained 23%, 25%, and 7% of variation in treatment rates, respectively. **Conclusion:** These data suggest that although patient characteristics are important predictors of treatment in HCV, a significant proportion of variation in treatment rates is explained by provider factors. These potentially modifiable provider-level factors may serve as high-yield targets for future quality improvement initiatives in HCV. (HEPATOLOGY 2007;46:1741-1749.)

Chronic hepatitis C virus infection (HCV) is a prevalent and expensive condition affecting more than 1.3% of the U.S. population at a cost of over \$700 million annually.¹⁻³ HCV is the leading cause of cirrhosis,

hepatocellular cancer, and death of liver disease in the United States and is the primary indication for liver transplantation worldwide.^{3,4} The economic burden of HCV is multiplied by the negative impact of HCV on health-related quality of life.⁵ Treatment with interferon and ribavirin is effective and results not only in reducing liver disease progression, but also improving health-related quality of life among patients with sustained viral response.⁶⁻⁹

Given the burden of illness, several professional societies have published evidence-based guidelines defining the best practices and standards of treatment in HCV. These include the American Association for the Study of Liver Disease, the National Institutes of Health, the American Gastroenterology Association, and the Veterans Administration (VA).¹⁰⁻¹³ Despite these well-disseminated guidelines, recent data indicate deficits in HCV care. Several reports demonstrate that antiviral treatment rates among HCV patients are lower than 30%, generally attributed to the high prevalence of treatment contraindications.¹⁴⁻¹⁸ However, even among patients otherwise eligible for treatment, the reported treatment rates range from 45% to 75%, suggesting that factors other than treatment contraindications may be important determinants of treatment receipt.^{14-16,18} Recent studies suggest

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HCV, hepatitis C virus; ICD-9, International Classification of Diseases version 9; PCP, primary care provider; PCR, polymerase chain reaction; RR, relative risk; VA, Veterans Administration.

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that patients' refusal to receive treatment and nonadherence to evaluation protocol may explain the low treatment rates among eligible patients.¹⁴⁻¹⁶ However, it is possible that treatment rates in HCV also depend on factors outside of the patient, such as healthcare provider factors.¹⁹ This hypothesis has not been previously investigated.

It is critical to examine how patient and provider factors differentially impact treatment rates in HCV. Identifying these sources of variation can determine how each level of care impacts outcomes and thus provide a blueprint to determine how quality improvement initiatives should be optimally proportioned across these levels.^{20,21} Without this information, the quality initiative development process can be potentially haphazard and arbitrary.^{20,21} In short, the targeted use of quality improvement initiatives, based on the descriptive data highlighting the primary sources of variation in the delivery of care, may enhance the cost-effectiveness of otherwise expensive interventions by maximizing a tailored approach to quality initiative development.

In light of this, we sought to evaluate the role of patient and provider level factors in determining the rates of antiviral treatment among treatment-eligible patients with HCV. Because HCV patients and providers operate within treating facilities, any analysis of process of care would be incomplete without considering the role of treating facilities in the rates of antiviral treatment. Therefore, we also sought to understand whether any of the variance in HCV treatment might be explained by treating facility-level. Based on the literature in other areas on medicine, we hypothesized that nonpatient (provider and facility) levels would explain more than 50% of explained variation in the rates of antiviral treatment.^{19,22-27} We further hypothesized that the treating experience of the provider would be the most important predictor of treatment receipt.²² To test our hypotheses, we performed multivariable analyses in a demographically diverse group of patients with HCV, estimated the rates and predictors of HCV treatment, and determined the degree of variation in treatment rates attributable to patient, provider, and facility factors.

Patients and Methods

We conducted a retrospective cohort study of HCV patients who sought care at 5 large tertiary care VA facilities in Southern California between January 1, 2000 and December 31, 2005.

Data Sources

We used the administrative and clinical data in the VA Southern California Network data warehouse. The database includes information from each of the 5 VA Medical Centers of the Southern California Network (Los Ange-

les, Las Vegas, San Diego, Loma Linda, and Long Beach) and their affiliated clinics. The database includes separate files for patient demographics, outpatient clinic and inpatient utilization, vital signs, pharmacy utilization, and laboratory data.

Study Subjects

Because only those patients with documented viremia are eligible for antiviral treatment, we defined an HCV patient as a subject with at least 1 of the following positive HCV tests: qualitative polymerase chain reaction (PCR), quantitative PCR, or genotype. We defined patient's treating facility as the most frequently visited site during the 5-year study period. To better assure that the treating clinic was accountable for patient's care, we only included subjects if they had 2 or more visits/year to the treating facility. We defined treatment exclusions based on the contraindications specified in the American association for the Study of Liver Disease and VA guidelines and excluded patients who met any of these exclusions.^{10,13} Table 1 lists the operational definitions for all treatment exclusions. We used a combination of ICD-9 codes,²⁸ laboratory data, and pharmacy data to define the presence or absence of a medical condition. We employed a pre-specified hierarchical strategy to identify treatment-eligible patients as portrayed in Fig. 1. In short, we first identified patients who might be eligible for treatment during at least 1 year of follow-up. Because this strategy was likely to be sensitive but not overly specific in identifying patients who might be treatment eligible and because 1 year of follow-up may not be long enough for treatment evaluation and initiation in HCV, we further limited our cohort to those patients who had 2 or more eligible years of follow-up at the treating facility.

Study Outcomes

Our primary outcome was receipt of antiviral treatment. However, to capture the full spectrum of care process in HCV from primary care (PCP) to specialists to antiviral treatment, we first examined receipt of specialty evaluation among all treatment-eligible patients. In the second step, we analyzed receipt of antiviral treatment in patients who had a contact with the specialists. We defined specialty evaluation based on whether the patient was seen in specialty clinics (gastroenterology or hepatology clinic, codes 307, 454). We defined HCV treatment as a prescription of interferon or pegylated interferon.

Predictors

Patient factors included sociodemographic characteristics (age, race, household income, copay requirement, marital status); propensity to use healthcare (number of

Table 1. Contraindications for HCV Treatment

| Criteria | Operational definitions |
|---|---|
| Absolute contraindications | |
| Major, uncontrolled depressive illness | ≥1 inpatient OR ≥3 outpatient ICD 9 codes of depression |
| Renal, heart, and lung transplant | ≥1 ICD 9 code (inpatient or outpatient) for renal, heart, and lung transplant |
| Autoimmune hepatitis | ≥1 ICD 9 code of autoimmune hepatitis |
| Untreated hyperthyroidism | TSH ≥0.5 mU/L ×2 >3 months apart |
| Severe hypertension | ≥1 ICD 9 code for malignant hypertension or hypertension with complications OR diastolic blood pressure ≥130 mmHg ×2 >1 month apart |
| Severe heart failure (CHF) | ≥1 inpatient ICD9 code of CHF OR ≥2 outpatient ICD9 codes with: (a) BNP>200 pg/mL, (b) prescription of digoxin, hydralazine+nitrate, or aldosterone antagonist, or (c) ≥1 code for cardioverter/defibrillator |
| Significant coronary artery disease (CAD) | ≥1 inpatient ICD9 code of CAD OR coronary revascularization procedure OR ≥2 prescriptions for isosorbide dinitrate or nitroglycerine ≥90 days apart |
| Poorly controlled diabetes | ≥2 HbA1c ≥9% OR ≥2 ICD9 codes for diabetes + complications ≥ 1 month apart |
| Severe chronic obstructive pulmonary disease (COPD) | ≥1 inpatient ICD9 code for COPD with: (a) ≥1 ICD9 code for respiratory failure, or (b) ≥1 PaCO ₂ of > 50 mm Hg |
| Relative contraindications | |
| Current illicit drugs/alcohol use | ≥1 inpatient OR ≥2 outpatient ICD9 codes for drug/alcohol dependence/abuse OR ≥1 positive blood test for illicit drugs/alcohol |
| HIV co-infection | ≥1 ICD9 code OR ≥1 positive blood test for HIV |
| Chronic renal disease (ESRD) | ≥1 ICD9 code for ESRD OR creatinine >3mg/dL >3 months apart |
| Decompensated cirrhosis | ≥1 ICD 9 code for ascites, varices, encephalopathy, liver cancer, hepatorenal |
| Liver transplant recipients | ≥1 ICD 9 code for liver transplantation |
| Severe psychiatric disease | ≥1 inpatient ICD9 code for bipolar disorder, anxiety, PTSD, schizophrenia |

For ICD-9 codes, we used the AHRQ Clinical Classification System to classify all patient ICD9 codes into the relevant diagnosis.²⁸ Given the recent recommendations regarding considering patients with normal ALT for treatment, we did not exclude patients with normal ALT. We instead used ALT as a regressor in the multivariable models. We also included patients' laboratory parameters (including blood counts and liver function tests) in the model. With the exception of transplant receipt and autoimmune hepatitis, all exclusions were applied per year of follow-up. Specific ICD9 and CPT codes used to define the contraindications are available from the authors on request.

clinic visits); HCV-related characteristics (HCV genotype, diagnosis of cirrhosis, liver function, alanine aminotransferase [ALT] level, viral load, and blood counts); and comorbidity-related characteristics (renal function, psychiatry illness, and comorbidity count). Table 2 provides the full list of patient factors and their method of categorization. Because low treatment rates in African American patients may be explained by the high prevalence of

genotype-1 HCV, we also entered an interaction term between race and genotype in the model.²⁹ Provider factors included provider type, clinical experience, and continuity of primary care. We identified provider type based on the clinics where PCP (clinic codes 323, 322, 348, 350) and specialists (clinic codes 307, 454) provided care for the study cohort. For each patient, we selected 1 PCP and 1 specialist based on the number of times a patient was

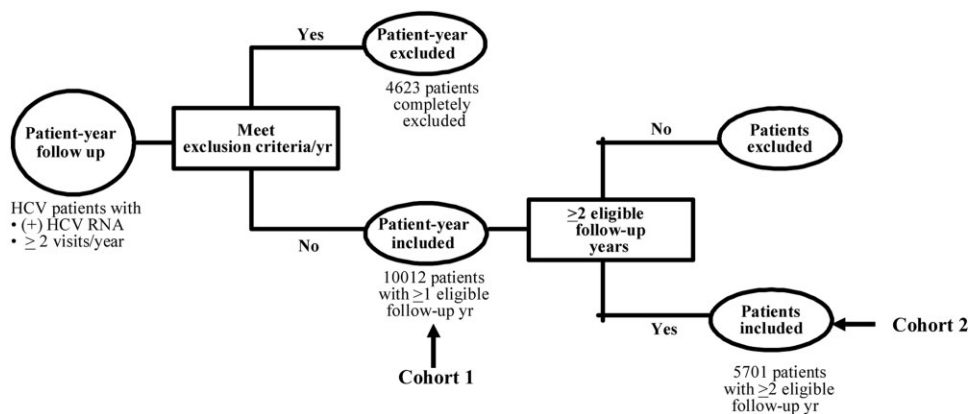


Fig. 1. Algorithm for identifying treatment-eligible patients. Figure 1 displays the hierarchical algorithm for identification of treatment-eligible patients. We used a patient-year as a unit and determined presence of exclusion criteria (listed in Table 2) during each year of patient follow-up. We excluded patients for the year in which they met any of the exclusion criteria. As a result, our first cohort (cohort 1) consisted of patients who might be eligible for treatment during at least 1 year of follow-up. Because this strategy was likely to be sensitive but not overly specific in identifying treatment-eligible patients, we then limited the cohort to patients who did not have any prespecified exclusion criteria for at least 2 years of follow-up (cohort 2). We conducted primary analysis using cohort 2 and then performed sensitivity analysis using cohort 2 as the study population.

Table 2. Sample Characteristics

| Variable | Distribution |
|--|--------------------|
| Patient-Level Factors | |
| Demographics | |
| Age in years, (mean, SD) | 52.6 (8.6) |
| Race, (%) | |
| Caucasian | 22 |
| AA | 13 |
| Other | 6 |
| Missing | 59 |
| Median annual household income, % ^a | |
| <30,000 | 14 |
| 30,000-50,000 | 57 |
| 50,000-70,000 | 22 |
| >70,000 | 7 |
| Copay (%) ^b | |
| Not required | 75 |
| Required | 25 |
| Marital status (%) | |
| Single (unmarried) | 24 |
| Married | 26 |
| Other | 50 |
| Propensity to use healthcare | |
| Number of clinic visits, median (IQR) | 9 (5, 15) |
| Clinical variables | |
| HCV genotype (%) ^c | |
| Type 1/4 | 76 |
| Type 2/3 | 24 |
| Uncomplicated cirrhosis (%) ^d | 7 |
| Compromised liver function (%) ^e | 2.5 |
| High ALT (%) ^f | 45 |
| Liver biopsy (%) | 16 |
| Highest viral load, median (IQR) | 700K (347K, 1047K) |
| Serum creatinine in mg/dL, mean (SD) | 1.0 (1.7) |
| Blood count, mean (SD) | |
| Lowest hemoglobin (mg/dL) | 14.0 (2.0) |
| Lowest white blood cell count/mm ³ | 5.9 (1.9) |
| Lowest platelet count/mm ³ | 200 (76) |
| Psychiatric comorbidity (%) ^g | |
| Depression | 16 |
| PTSD/anxiety | 17 |
| Psychosis/bipolar disorder | 4 |
| Comorbidity count, mean (SD) ^h | 0.4 (0.6) |
| System-level factors | |
| Provider level | |
| Primary care provider (PCP) | |
| Number of PCPs | 1026 |
| Experience, N seen/year, median (IQR) | 16 (7, 26) |
| Continuity of care by PCP, median (IQR) | 1.8 (1.3, 2.4) |
| Specialty care provider | |
| Number of specialty providers | 161 |
| Experience, N seen/year, median (IQR) | 47 (7,165) |
| Treating experience, N received treatment/N seen, median (IQR) | 0.14 (0.04, 0.22) |
| Facility level, N (%) | |
| Facility 1 | 42.5 |
| Facility 2 | 15 |
| Facility 3 | 18.5 |
| Facility 4 | 13 |
| Facility 5 | 11 |

Abbreviations: IQR, interquartile range; HCV, hepatitis C; ALT, alanine aminotransferase; SD, standard deviation.

^aUsing ZIP codes, we linked the VISN-22 data to the national census data and derived patients' median household income.

^bWe derived co-payment status using a previously described scheme based on means test (indicator of income) and amount of service connection variables in VISN-22 data warehouse.

^cThe genotype proportions in the table are among patients who received a genotype test. Fifty-four percent of the cohort did not undergo genotype testing during the study time frame. We grouped viral genotype as genotypes 1 or 4 (more resistant to antiviral treatment), and genotypes 2 or 3 (more susceptible to antiviral treatment).

^dWe defined compensated cirrhosis based on presence of 1 inpatient or 2 outpatient cirrhosis-related ICD9 codes ≥ 6 months apart.

^eWe defined compromised liver function as 2 of 3 laboratory results—low albumin (<3.0 mg/dL), high bilirubin (>2.0 mg/dL), or high INR (>1.2).

^fHigh ALT defined as ALT ≥ 40 IU/mL $\times 2 > 6$ months apart.

^gWe categorized psychological disorders into 3 variables: (1) depression, (2) posttraumatic stress or anxiety disorder, and (3) psychosis or bipolar disorder.

^hFor assessment of comorbidity, we estimated the number of comorbidities included in the Deyo score (Deyo RA, et al. *J Clin Epidemiol.* 1992;45:613-619).

The definitions of provider variables are provided in the text.

seen by the provider and the HCV experience of the provider. We defined provider "experience" in HCV as the number of HCV patients evaluated per year, and derived this variable for both the PCPs and specialists. In addition, we measured a specialist's treatment-related experience by the ratio of the number of patients treated over the number of total patients seen by that specialist. As previously described by Brookhart et al.,³⁰ we excluded providers who evaluated fewer than 5 HCV patients per year. Thus, our analysis focused on providers who regularly evaluate HCV patients. We further determined the continuity of primary care by estimating the ratio of number of primary care visits/number of primary care providers seen as previously described. We included a categorical variable for 5 facility identifiers in the primary analyses. Because our study included only 5 facilities, we were unable to examine specific facility-level factors. However, we estimated the group-level impact of facility factors in treatment evaluation and receipt, as detailed below.

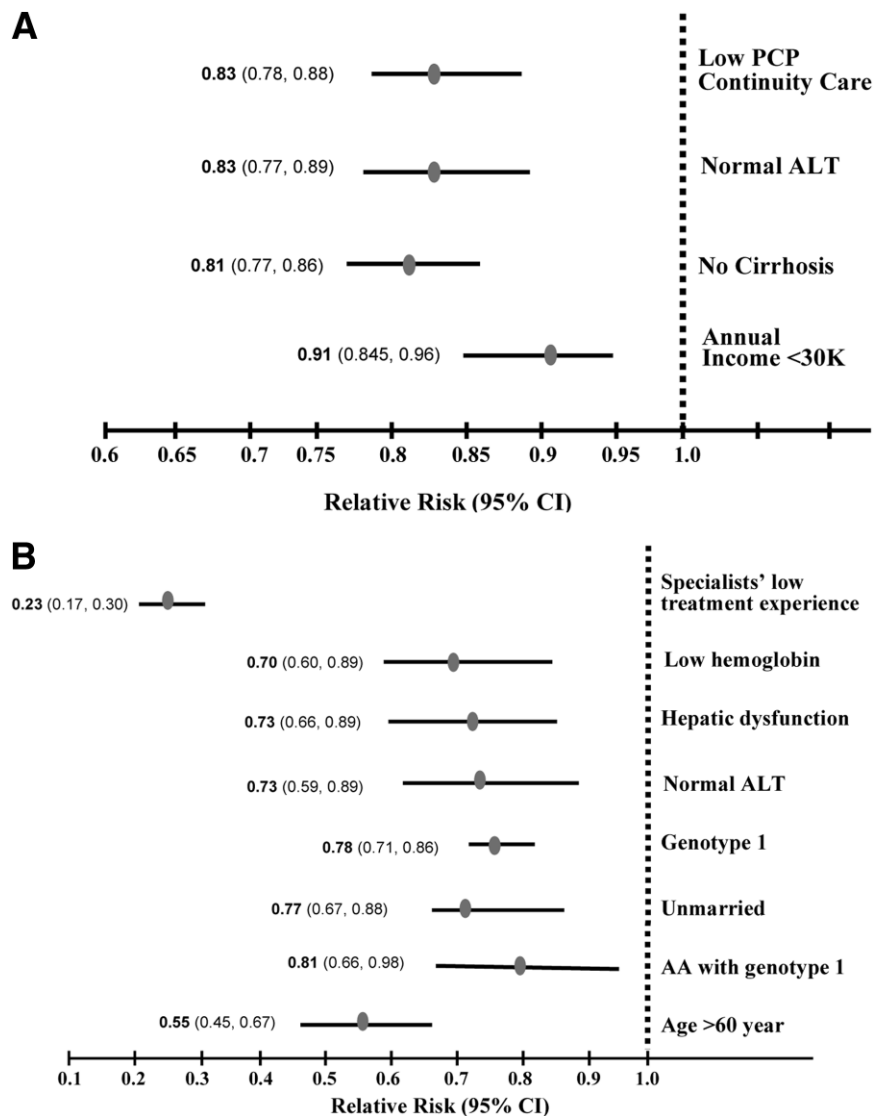
Statistical Analyses

Handling Missing Values. Demographic, healthcare use, liver disease severity, and comorbidity data were missing in fewer than 5% of patients. These patients were excluded from the analyses. Data were missing in more than half of the patients for race and HCV genotype, and in approximately 30% of patients for HCV viral load. We used a "missing" variable for patients with missing race and genotype in the primary analyses, and performed sensitivity analysis excluding these variables from the multivariable models. We did not include HCV viral load in the primary analysis. However, we then performed exploratory analysis to examine the effect of HCV viral load on the model results.

Primary Analyses. In order to capture the full spectrum of care process in HCV, we created separate multivariable logistic regression models to first estimate the probability of being seen by specialists and then estimate the conditional probability of receiving HCV treatment. Figure 2 details the variables included in both models. We calculated the relative risks (RR) and the 95% confidence intervals (CI) of receiving specialty evaluation and treatment across strata of patient and provider factors. To estimate the RR for numerical variables (for example, hemoglobin, continuity of care, and provider experience), we categorized these variables based on the empiric data and defined a value of greater than 75th percentile as high and lower than 25th percentile as low.

Sensitivity Analyses. We conducted a number of sensitivity analyses to test how robust our findings were to specifications of treatment exclusion criteria, rates of missing variables, concerns related to low treatment effi-

Fig. 2. Results of multivariable logistic regression analyses. (A) Factors associated with reduced likelihood of specialty evaluation; (B) factors associated with reduced likelihood of antiviral treatment among patients who had a contact with specialists. Results are expressed in terms of relative risks and 95% confidence intervals (CI). Although patient's treatment facility predicted both specialty evaluation and antiviral treatment rates, the results are not shown because we included treatment facilities in the multivariable models primarily to adjust for facility effect. We analyzed primary care provider (PCP) characteristics in the 1st and specialists' characteristics in the 2nd model. Because we hypothesized that patients' genotype and other laboratory data (such as hepatic dysfunction laboratories, hemoglobin, and platelet count) will primarily impact treatment decision in specialty clinics, these variables were included in the treatment model only. Other variables were similar across 2 models and included age, race, marital status, copay, median household income, number of visits/year, presence of cirrhosis diagnosis, persistently normal ALT, presence of psychiatric diagnosis (depression, anxiety, posttraumatic stress disorder, psychosis, bipolar disorder) comorbidity count, and an interaction term between race and genotype.



cacy, and patients' non-interest in treatment. We constructed models using less strict treatment exclusion criteria (cohort 1 in Fig. 1), models that excluded variables with significant missing data, as well as models limited to patients with genotype 2/3 HCV, and to those who received a liver biopsy. We hypothesized that genotype 2/3 patients would represent a subgroup in whom HCV treatment is highly effective and that receipt of a liver biopsy during treatment evaluation would act as a surrogate for patient preference and interest in treatment, respectively. To examine potential changes in clinical practice with the availability of National Institutes of Health guidelines in 2002, we stratified patients based on whether they were diagnosed before (<2002) versus after guideline dissemination (>2002).¹² Our preliminary analyses found that the rates of specialty evaluation and treatment were lower in the cohort diagnosed before (71% and 18%, respectively) versus after 2002 (56% and

11%, respectively). However, these results likely represented differential lengths of follow-up in the 2 groups. Evaluation and treatment rates ≤1 year of HCV diagnosis in the pre versus post guideline cohort were 23% and 7% versus 26% and 6.2%, respectively. In light of these data, we did not adjust for diagnosis before versus after 2002 in our primary analyses. Instead, we constructed separate multivariable models that predicted receipt of specialty evaluation and treatment within 1 year of HCV diagnosis to determine whether diagnosis in the pre-guideline versus the postguideline era independently affected HCV treatment in our study cohort.

Estimate Relative Role of Patient, Provider, and Facility Factors. Although identification of individual predictors of treatment is important, these parameter estimates do not represent the "group level" impact of patient and provider factors. Moreover, we were unable to examine the impact of facility-level factors in the analyses

detailed above. To quantify the relative importance of all 3 levels of factors (i.e., patient, provider, and facility factors) in HCV treatment, we created separate multilevel logistic regression analyses.³⁰⁻³² We specified models that contained combinations of the following sets of effects and variables:

Patient observed characteristics (fixed effects)—demographics, propensity to use health care, liver disease severity

Provider observed characteristics (fixed effects)—HCV experience, treatment-related experience

Provider unobserved tendency toward low treatment (random effect)—provider unique identifier

Facility unobserved tendency toward low treatment (random effect)—facility unique identifier

For each model, we estimated a modified version of the R^2 statistic to measure the proportion of explained variation or the predictive power of the model.^{30,33} We used SAS, version 8.1 (SAS Inc., Cary, NC) for the statistical analyses.³⁴

Results

Sample Characteristics

We identified 14,275 patients with active viremia as defined by a positive qualitative PCR ($n = 5818$), quantitative PCR ($n = 10,784$), or genotype ($n = 5947$) test. Of these, 5701 (39.9%) were classified as eligible for treatment. Table 2 lists the descriptive results for the sample characteristics in treatment-eligible patients. The mean age of eligible HCV patients was 52.5 ± 8.2 years, and 99% were male. Of the patients with nonmissing race, there were 56% white and 33% African American patients in our sample. The median annual household income of more than half of our cohort was in the range of \$30K to \$50K, and most patients (76%) did not have a copayment requirement. Half of the patients were either separated or divorced. The patient cohort on average had a high propensity to use healthcare, with a mean of 12 ± 12 clinic visits per year. Of the patients who received an HCV genotype test, 75% had genotype 1 and 24% had genotypes 2 or 3. The cohort had relatively preserved hepatic function as suggested by serum bilirubin, international normalized ratio, transaminases, and platelet count, and approximately 7% patients were diagnosed with compensated cirrhosis. Sixteen percent of patients had received a liver biopsy during the course of evaluation. Despite excluding patients with severe depression and psychosis, 16%, 17%, and 4% of patients included in the cohort carried at least 2 ICD9 codes of depression, posttraumatic stress disorder, and psychosis, respectively.

There were 1026 PCPs and 161 specialists involved in the care of our HCV cohort. The PCPs saw a median of 16 HCV patients per year (interquartile range = 7, 26). Patients on average saw 1 PCP at least twice. In contrast to

the PCPs, the specialists saw a median of 47 HCV patients annually (interquartile range, 7, 165). The specialists provided treatment-related care to a median of 14% of all HCV patients under care (interquartile range, 4%-22%). The distribution of patients per treating facility is detailed in Table 2.

Predictors of Specialty Evaluation and Treatment

Of the 5701 eligible patients, 3743 (65%) were seen by the specialists, and 894 (15.7%) received treatment. Specialty evaluation and treatment rates varied from 50% to 90% and 6% to 28% across the 5 facilities, respectively. Results from the multivariable logistic regression models are displayed in Fig. 2. Patients were less likely to receive specialty evaluation if they did not have cirrhosis diagnosis (RR, 0.83; 95% CI, 0.76, 0.88), had persistently normal ALT (RR, 0.84; 95% CI, 0.79, 0.91), and had a low median household income (RR, 0.91; 95% CI, 0.85, 0.96). Although the HCV experience of the PCPs did not impact the rates of specialty evaluation, patients with lower continuity of PCP care (in other words, <25th percentile) were 27% less likely to receive specialty evaluation than patients with higher (in other words, >75th percentile) continuity of care.

Among patients evaluated in the specialty clinics, several patient-level factors were associated with lower likelihood of antiviral treatment receipt. Specifically, patients were less likely to receive treatment if they were older (RR, 0.55; 95% CI, 0.45, 0.67), were single (RR, 0.77; 95% CI, 0.67, 0.88), had hepatic dysfunction (RR, 0.73; 95% CI, 0.66, 0.89), had normal ALT (RR, 0.73; 95% CI, 0.59, 0.89), had HCV genotype 1 (RR, 0.78; 95% CI, 0.71, 0.86), or were anemic (RR, 0.70; 95% CI, 0.60, 0.89). Although African American patients with genotype 2/3 were as likely to receive treatment as whites with genotype 2/3 (RR, 0.97; 95% CI, 0.66, 1.4), those with genotype 1 were less likely to receive antiviral treatment than white patients with genotype 1 (RR, 0.81; 95% CI, 0.66, 0.98). In addition, patients treated by less experienced providers were 77% less likely to receive treatment than those treated by more experienced providers.

Sensitivity analyses with less strict treatment exclusion criteria, inclusion of viral load variable, exclusion of patients with missing race or genotype, or inclusion of HCV diagnosis before versus after 2002 did not change the direction or significance of the reported results, above (data not shown). The antiviral treatment rates were higher when we limited our analysis to treatment-eligible patients with genotype 2/3 HCV (236/608, 38.8%) and to patients who had undergone liver biopsy during HCV evaluation (443/912, 48.5%). However, there still was wide variation in treatment rates across the 5 facilities (Fig. 3A,B).

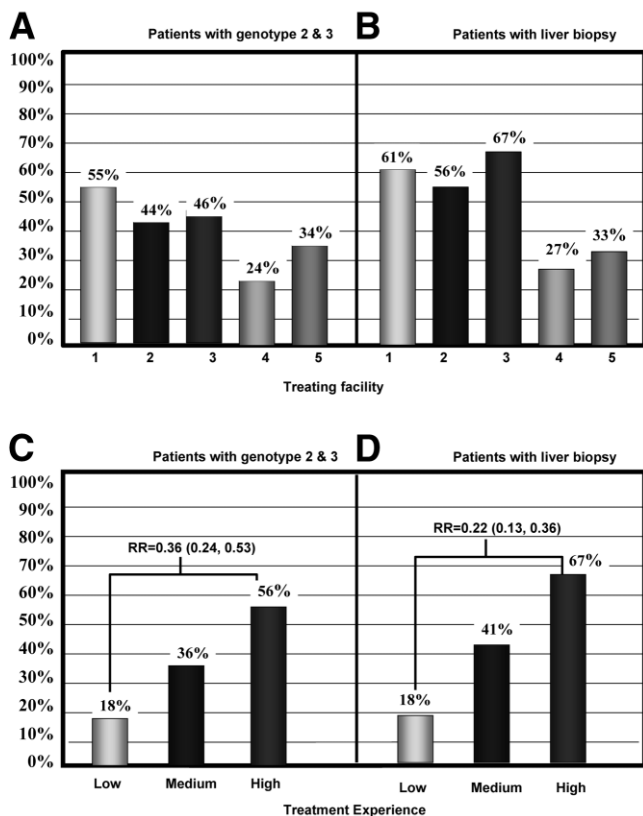


Fig. 3. Results of sensitivity analyses. Variation in antiviral treatment rates across treatment facility and across provider treating experience in patients with genotype 2/3 (A, C) and in patients with liver biopsy (B, D), respectively. (C, D) Relative risk (RR) with 95% confidence interval (CI) of treatment receipt in patients seen by less experienced providers compared with those seen by more experienced providers after adjusting for patient and facility-level variables. In the sensitivity analysis limited to patients with liver biopsy, the magnitude, direction, and statistical significance of regression coefficients for patient level factors were similar to those observed in the primary analysis (Fig. 2). Only provider experience and treatment facility were significantly associated with treatment receipt in the sensitivity analysis limited to genotype 2/3 patients.

Also as shown in Figure 3C and D, provider experience-related differences in treatment rates persisted both in genotype 2/3 and in patients who had undergone a liver biopsy after adjusting for all the prespecified patient-level variables. The rates of specialty evaluation (RR, 1.07; 95% CI, 0.98, 1.17) and treatment (RR, 0.80; 95% CI, 0.66, 1.1) did not improve in our study cohort after the dissemination of HCV clinical guidelines in 2002.

Relative Role of Patient, Provider, and Facility Factors in HCV Treatment

Table 3 presents the estimated values of R² for each multilevel model considered in patients who were seen by specialists. The full model with patient, provider, and facility effects yielded an adjusted R² of 0.440, therefore explaining an estimated 44% of the variation in treatment rates. Patient factors alone explained for 23% of the vari-

Table 3. Relative Role of Patient, Provider, and Facility Factors in Hepatitis C Treatment

| Model and Effects | R ² |
|--|----------------|
| Full model | |
| Patient, provider, and facility effects | 0.440 |
| Patient effect | |
| Patient effects | 0.230 |
| Healthcare delivery system effect | |
| Provider effect (random, that is, propensity to treat) | 0.258 |
| Provider effect (fixed, that is, treatment experience) | 0.162 |
| Facility effect | 0.069 |
| Provider and facility effects | 0.271 |

R² statistic measures the amount of explained variation of a given model. Fixed effects represent the measured variables included in the model. Random effects represent the unmeasured propensity to treat.

ation in treatment rates. Although provider factors explained greater than 25% of the variation in patient treatment, only 16% of variation was captured by the measured provider characteristics (that is, provider experience). Facility effects explained 7% of variation in the data. Combined together, provider and facility factors, in other words, nonpatient factors, explained 27% of the variation in patient receipt of antiviral treatment. The relative importance of patient, provider, and facility factors did not change in models predicting specialty evaluation among eligible patients with 26%, 29%, and 18% variation explained by each category, respectively.

Discussion

Our analysis has 2 key findings: First, we found that antiviral treatment rates are low among patients who may be eligible for treatment and that these rates vary greatly. Specifically, our analysis revealed that less than 16% of eligible patients received antiviral treatment during the study duration and that treatment rates varied across several patient characteristics (for example, older patients and African American with genotype 1 less likely to receive treatment than younger patients and whites with genotype 1, respectively), providers' experience gradient (for example, patients seen by less experienced providers less likely to receive treatment than those seen by more experienced providers), and across treatment facilities (for example, treatment rates varied from 6% to 28%). Even in patients in whom treatment is highly effective (that is, those with genotype 2 or 3) and in patients more likely to be interested in pursuing treatment (that is, those who underwent a liver biopsy) treatment rates were lower than 50% and varied significantly across providers' experience and treatment facilities. The rates of evaluation and treatment prescription did not improve in our study cohort after the dissemination of HCV clinical guidelines in 2002. These results highlight the mismatch between evi-

dence-based guidelines and clinical practice in HCV and underscore the importance of quality improvement efforts to narrow this gap. Second, we found that provider factors explained as much, if not more, multivariate adjusted variation in specialty evaluation and in treatment rates as patient factors. For example, despite adjusting for wide range of known patient level predictors of treatment such as age, race, liver disease severity, and comorbidity, we still found important differences across provider experience gradient and across facilities. These data suggest that individual providers vary in how they manage HCV patients who are eligible for treatment. Our results, therefore, highlight the need to systematize care. This goal may be achieved by integrating evidence base into clinical practice through strategies such as provider education (for example, small group, problem-based training sessions), provider feedback, and close collaboration of primary care and specialty providers with clear definitions of respective roles. Moreover, because approximately half of the provider effect is still unmeasured after accounting for provider experience, unmeasurable provider factors, such as provider knowledge, attitude, and beliefs toward treatment may be important determinants of treatment in HCV. An in-depth understanding of the association between providers' treatment-related perceptions and treatment decisions through structured interviews may facilitate the goal of making HCV care more consistent across the healthcare delivery system.

Several patient characteristics are known to impact treatment rates in HCV. For example, in recent population-based studies, Butt et al.,³⁵ Bini et al.,¹⁴ and Backus et al.³⁶ found several patient factors to be strongly associated with lower treatment rates in HCV patients. These included old age, nonwhite race, absence of cirrhosis diagnosis, and low ALT, among others—all similar to the patient factors identified in our analysis. The fact that we and others found similar patient-level predictors of treatment provides convergent validity to our findings. Regardless of these corroborating data, the identified patient level factors (such as age, race, genotype) may not be amenable to change. Identification of these predictors, therefore, may not have similar policy implications as associated with the quantification of non-patient-level factors' impact.

In addition to examining the role of non-patient-level factors in HCV treatment, our analysis has several other strengths. First, we relied on positive viral test to identify patients with HCV and did not include patients with only HCV-related International Classification of Diseases version 9 (ICD-9) codes. As a result, we minimized any ascertainment bias in classifying patients with HCV. Second, our analysis relies on data from a demographically diverse group of patients in 5 large healthcare systems and follows patients

from primary care to specialty care to treatment receipt. Unlike the previously published studies of treatment rates among eligible patients with HCV, our study does not suffer from the potential selection bias associated with recruitment limited to tertiary care clinics. Third, we had access to broad array of data sources, allowing us to capture and adjust for the full range of patient-level variables that might affect the receipt of treatment among treatment-eligible patients. These included sociodemographic characteristics, treatment contraindications, propensity to use health care, and stage of liver disease, among others.

Our analysis has several limitations. First, we relied on the preexisting clinical and administrative data for estimates of patient characteristics. Because the administrative data are entered for record-keeping reasons, absence of ICD-9 codes does not mean that patients did not have the given diagnoses. We tried to address this limitation of secondary data analysis by specifying a combination of ICD-9 codes, laboratory data, and pharmacy data to define the presence or absence of a condition—a strategy known to be more accurate than relying on ICD-9 codes alone. Second, our hierarchical strategy for identifying treatment-eligible HCV patients was likely to be specific but not overly sensitive. We therefore conducted a pre-specified sensitivity analysis using less strict exclusion criteria. The fact that the predictors of treatment in this sensitivity analysis were similar to the estimates from our primary analysis provides support for the robustness of our results. Third, several unmeasured patient characteristics could have biased our results. Specifically, we could not determine patients' or providers' concerns related to low treatment efficacy and patients' preference for treatment. However, we conducted separate sensitivity analyses to address these limitations, as detailed previously. We were also unable to ascertain the stage of patients' fibrosis. However, it is unlikely that this missing variable can completely explain the difference between the observed and expected treatment rates, especially in genotype 2/3 patients. Fourth, our data were derived from a VA system that predominantly serves male patients. Thus, the results may not be generalizable to patients in other healthcare systems and to female patients with HCV. However, whereas the electronic data sources within the VA permit comprehensive evaluation of process of HCV care, similar quality assessment efforts in the non-VA healthcare systems may be difficult without an advanced information system. Fifth, we could not examine individual treating facility level factors. However, given the relatively small amount of variation explained by treating facilities in the multilevel models, identification of individual facility predictors may not be of a high yield in the current analysis.

As HCV makes the transition to a treatable disease, understanding where best to direct resources to improve care becomes increasingly important. Our analysis found that provider-level factors explain a significant part of the variation in treatment rates among treatment-eligible HCV patients, indicating that patient-level factors are not the sole determinant of treatment decisions. Our results are important because they suggest that one way to make inroads into the problem of suboptimal treatment in HCV is to focus on provider-level changes—not just patient-level factors. These initial assessments are particularly relevant in this era of optimizing the quality of care provided to patients with HCV and may act as the link in the broader translational framework developed by the Institute of Medicine.³⁷

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