CME

# Prevalence of Cirrhosis in Hepatitis C Patients in the Chronic Hepatitis Cohort Study (CHeCS): A Retrospective and Prospective Observational Study



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OBJECTIVES: **The severity of liver disease in the hepatitis C virus (HCV)-infected population in the United States remains uncertain. We estimated the prevalence of cirrhosis in adults with chronic hepatitis C (CHC) using multiple parameters including liver biopsy, diagnosis/procedure codes, and a biomarker.**

METHODS: **Patients enrolled in the Chronic Hepatitis Cohort Study (CHeCS) who received health services during 2006–2010 were included. Cirrhosis was identified through liver biopsy reports, diagnosis/procedure codes for cirrhosis or hepatic decompensation, and Fibrosis-4 (FIB-4) scores ≥5.88. Demographic and clinical characteristics associated with cirrhosis were identified through multivariable logistic modeling.**

RESULTS: **Among 9,783 patients, 2,788 (28.5%) were cirrhotic by at least one method. Biopsy identified cirrhosis in only 661 (7%) patients, whereas FIB-4 scores and diagnosis/procedure codes for cirrhosis and hepatic decompensation identified cirrhosis in 2,194 (22%), 557 (6%), and 482 (5%) patients, respectively. Among 661 patients with biopsy-confirmed cirrhosis, only 356 (54%) had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for cirrhosis. Older age, male gender, Asian race, Hispanic ethnicity, genotype 3 infection, HIV coinfection, diabetes, history of antiviral therapy, and history of alcohol abuse were independently associated with higher odds of cirrhosis (all, $P<0.05$). Conversely, private health insurance coverage, black race, and HCV genotype 2 were associated with lower odds of cirrhosis.**

CONCLUSIONS: **A high proportion of patients with biopsy-confirmed cirrhosis are not assigned ICD-9 codes for cirrhosis. Consequently, ICD-9 codes may not be reliable as the sole indicator of the prevalence of cirrhosis in cohort studies. Use of additional parameters suggests a fourfold higher prevalence of cirrhosis than is revealed by biopsy alone. These findings suggest that cirrhosis in CHC patients may be significantly underdocumented and underdiagnosed.**

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/ajg

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## INTRODUCTION

The health care and economic burden of chronic hepatitis C virus (HCV) infection in the United States relates primarily to liver disease severity. Recent estimates suggest that 1% of the noninstitutionalized civilian population in the United States is chronically HCV infected, corresponding to ~2.7 million individuals (1). Progression of chronic hepatitis C (CHC) to cirrhosis occurs over a period of several years (2). The identification

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of patients with cirrhosis may have significant implications pertaining to the management of CHC and health resource utilization (3).

A recent multicohort natural history model of CHC projected an increase in the proportion of CHC patients with cirrhosis from 25% in 2010 to 45% in 2030 (4). A subsequent retrospective cohort study of a national sample of veterans in the United States reported an increase in the prevalence of HCV-related cirrhosis from 9% in 1996 to 18.5% in 2006 and an increase in the prevalence of decompensated cirrhosis from 5% to 11% over the same period (5). Both studies postulated that the aging of the HCV-infected population and duration of HCV infection accounts for the increase in the prevalence of cirrhosis; others have shown that this progression to cirrhosis is significantly associated with Hispanic ethnicity, socioeconomic status, and metabolic factors (e.g., hepatic steatosis, obesity, insulin resistance, and diabetes) (6–14).

Although these published estimates of cirrhosis prevalence highlight the significant burden of cirrhosis associated with chronic HCV infection, they may nevertheless underestimate the true prevalence of cirrhosis. This notion is supported by our recent observation that estimated that at least two-thirds of all HCV-infected individuals who died in 2010 were likely to have had unrecognized premortem indications of chronic liver disease (15). Previous estimates of the prevalence of cirrhosis have included patients whose cirrhosis was confirmed by liver biopsy or defined based on the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for cirrhosis or hepatic decompensation in patient records (5,16,17). These estimates may have failed to capture a substantial proportion of patients with cirrhosis because liver biopsy is not routinely performed in clinical practice. Moreover, preferential diagnostic coding for the underlying HCV infection over the code for cirrhosis may result in erroneous estimates.

The Fibrosis-4 (FIB-4), a simple noninvasive index based on readily available demographic and laboratory parameters, has been previously validated as being able to accurately predict advanced fibrosis in HCV-infected patients with and without HIV coinfection (18–20). We have previously shown the FIB-4 index to be superior to other serum marker indices of liver fibrosis (e.g., the aspartate aminotransferase-to-platelet ratio index (APRI) and the aspartate aminotransferase-to-alanine aminotransferase ratio) in its ability to differentiate between mild-to-moderate and advanced fibrosis for CHC patients in the Chronic Hepatitis Cohort Study (CHeCS) cohort, a large, geographically and racially diverse cohort receiving routine care at four large US health-care systems (21,22). A subsequent study in the same cohort validated the FIB-4 index for both CHC and chronic hepatitis B and determined optimal cutoff values for differentiating between F0–F2 (no to moderate fibrosis), F3 (advanced fibrosis), and F4 (cirrhosis) (23). In the present study, we sought to estimate the prevalence of cirrhosis among CHC patients in the CHeCS cohort based on an expanded set of parameters that included FIB-4 as well as liver biopsy results and the presence of diagnosis or procedure codes for cirrhosis and various manifestations of hepatic decompensation.

## METHODS

### Study population

The CHeCS cohort—a dynamic, prospective, longitudinal, observational, multicenter cohort—and the process used for cohort selection have been previously described (22). Adults ≥18 years of age who met CHeCS electronic identification criteria, whose CHC infection was confirmed through chart abstraction, and who received any type of health service between 1 January 2006 and 31 December 2010 at any of the four health systems participating in the CHeCS (Geisinger Health System, Danville, PA; Henry Ford Health System, Detroit, MI (coordinating center); Kaiser Permanente Northwest, Portland, OR; and Kaiser Permanente, Honolulu, HI) were included in this study. Patients were excluded if they were coinfected with the hepatitis B virus, if they had achieved a sustained viral response to therapy, or if they were liver transplant recipients.

The CHeCS study protocol was approved at each participating site between October 2009 and February 2010 by an institutional review board approved by the Federal Office for Human Research Protections.

### Data collection and analysis

Data pertaining to routine care through the end of 2010 were collected from the electronic health record and supplemented with individual chart review; these included patient demographics, medical encounters, laboratory results, diagnoses, and procedures including liver biopsy results (22). Data regarding the source of infection were collected through a patient survey, with patients being permitted to select more than one likely source of infection. Self-reported data from the same survey were used to determine the date of infection. Data on household income were estimated from US census data based on geocoded addresses. Data on antiviral treatment were collected by chart abstraction and included any available documentation of treatment received at outside facilities. Data on HCV genotypes were collected from laboratory records. History of alcohol abuse was determined on the basis of presence of an ICD-9-CM diagnosis code related to past or present alcohol abuse (291.0–291.9, 303.00–303.93, 305.00–305.03, or 980.0) in the patients' medical records. Coinfection with HIV was determined by the presence of HIV antibodies or a detected HIV RNA level on quantitative or qualitative testing. Diabetes comorbidity was defined on the basis of the Charlson/Deyo comorbidity subscore for diabetes, defined as the presence of an ICD-9-CM diagnosis score for diabetes (250.xx) in the medical record (24).

Cirrhosis was identified from four sources: (i) liver biopsy reports (Metavir stage 4 or, if cirrhosis had not been staged, the narrative diagnosis by a pathologist); (ii) presence of at least one ICD-9-CM diagnosis code for cirrhosis (571.2 and 571.5); (iii) presence of at least one ICD-9-CM diagnosis or procedure code or Current Procedural Terminology (CPT) code associated with a manifestation of hepatic decompensation (**Table 1**); and (iv) FIB-4 index score. In addition, APRI was used in a sensitivity analysis. The FIB-4 and APRI indices were calculated as previously described (18,23,25). For FIB-4, a cutoff value of ≥5.88 that has been previ-

**Table 1. Diagnosis/procedure codes for manifestations of hepatic decompensation**

| Condition | ICD-9-CM and CPT diagnosis and procedure codes |
|---|---|
| Liver cancer | 155.0, 155.1, 155.2 |
| Liver failure with hepatorenal syndrome | 572.4 |
| Hepatic encephalopathy | 572.2 |
| Portal hypertension/portal decompression procedures | 572.3<br>37140, 37160, 37180, 37181, 37182, 37183 |
| Esophageal varices complications and procedures | 456.0, 456.20<br>43204, 43205, 43243, 43244, 43400, 43401<br>42.91, 44.91, 96.06 |
| Other GI hemorrhage (selected) | 530.7, 530.82, 578.0, 578.1, 578.9 |
| Ascites/paracentesis procedures | 789.5, 789.59<br>49080, 49081<br>54.91 |
| Other sequelae of chronic liver disease | 572.8 |

CPT, Current Procedural Terminology; GI, gastrointestinal; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

ously validated as being predictive of cirrhosis in this cohort (23) was used, whereas cutoff values of >1.0, >1.5, and >2.0 were used for the APRI index. The most recent values for aminotransferase levels and platelet counts that had been collected within 7 days of each other were used. Aminotransferase levels and platelet counts taken during antiviral therapy were excluded as therapy can influence these parameters. A second sensitivity analysis that excluded laboratory values collected while patients were hospitalized was performed in order to eliminate the potential influence of spurious platelet and/or aminotransferase derangements during hospitalization.

### Statistical methods

Logistic regression—univariate, followed by multivariable modeling—was used to compare the demographic and clinical characteristics of patients with and without an indication of cirrhosis (by any of the four methods). Variables with $P$ value of <0.05 were retained in the final multivariable model.

## RESULTS

### Population characteristics

**Table 2** shows the demographic characteristics of the study population ($n$=9,783). The mean age of the patients was 55±10.9 years at the time of most recent follow-up. More than one-half of them were white males and a majority (94%) were insured. Of all patients, 43% had at least one liver biopsy report during follow-up, 17% of whom had a recent biopsy <2 years old. The median follow-up time was 6.4 years.

**Table 2. Population characteristics**

| Characteristic | *N*=9,783 |
|---|---|
| Age[a] *(mean, s.d.)* | 55.0 (10.9) |
| *Age category*[a] | |
| ≤40 years | 807 (8%) |
| >40 to <50 years | 1,464 (15%) |
| >50 to <60 years | 4,513 (46%) |
| ≥60 years | 2,999 (31%) |
| Male sex | 5,752 (59%) |
| *Race* | |
| Asian | 311 (3%) |
| White | 5,963 (61%) |
| Black | 2,267 (23%) |
| Pacific Islander/Hawaiian | 190 (2%) |
| Native American | 177 (2%) |
| Unknown | 875 (9%) |
| Hispanic ethnicity | 366 (4%) |
| *Median annual household income*[b] | |
| <$15,000 | 253 (3%) |
| ≥$15,000 to <$30,000 | 1,877 (19%) |
| ≥$30,000 to <$50,000 | 4,424 (45%) |
| ≥$50,000 to <$75,000 | 2,147 (22%) |
| ≥$75,000 | 548 (6%) |
| Missing | 534 (6%) |
| *Insurance status*[b] | |
| Medicaid | 1,256 (13%) |
| Medicare | 2,281 (23%) |
| Private | 5,623 (57%) |
| None | 289 (3%) |
| Unknown | 334 (3%) |
| Any HCV antiviral therapy | 3,586 (37%) |
| *HCV genotype* | |
| 1 | 4,687 (48%) |
| 2 | 830 (8%) |
| 3 | 613 (6%) |
| Other | 117 (1%) |
| Unknown | 3,536 (36%) |
| History of alcohol abuse | 2,262 (23%) |
| HIV coinfection | 319 (3%) |
| Diabetes (Charlson/Deyo comorbidity subscore) | 967 (10%) |

HCV, hepatitis C virus.
[a]At the time of most recent follow-up through 31 December 2010.
[b]At the time of enrollment into Chronic Hepatitis Cohort Study (CHeCS).

**Table 3. Proportion of patients with cirrhosis indicated vs. not indicated**

| | *N* (%); *n*=9,783 |
|---|---|
| Cirrhosis not indicated | 6,995 (71.5) |
| *Cirrhosis indicated by FIB-4 scores, liver biopsy, or diagnostic/procedure codes for cirrhosis or manifestations of hepatic decompensation* | 2,788 (28.5) |
| By FIB-4 ≥5.88 | 2,194 (22.4) |
| By liver biopsy | 661 (6.8) |
| By diagnostic/procedure codes (for cirrhosis or manifestations of hepatic decompensation) | 751 (7.7) |
| By ICD-9-CM diagnostic codes for cirrhosis | 557 (5.7) |
| By ICD-9 diagnostic codes/CPT codes for manifestations of hepatic decompensation | 482 (4.9) |
| By APRI >1.0[a] | 1,825 (18.7) |
| By APRI >1.5[a] | 1,488 (15.2) |
| By APRI >2.0[a] | 1,231 (12.6) |

APRI, aspartate aminotransferase-to-platelet ratio index; CPT, Current Procedural Terminology; FIB-4, Fibrosis-4; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

[a]APRI scores served as additional criteria for determination of cirrhosis in sensitivity analyses.

### Indication of cirrhosis

Of the 9,783 patients in the cohort, cirrhosis was indicated by at least one method in 2,788 patients (28.5%) (**Table 3**). Of these, 2,194 (22.4%) had FIB-4 scores ≥5.88, 661 patients (6.8%) were diagnosed with cirrhosis by liver biopsy, and 751 patients (7.7%) had diagnostic/procedure codes for cirrhosis or manifestations of hepatic decompensation (of whom 557 patients (5.7%) and 482 patients (4.9%) had diagnostic or procedure codes for cirrhosis and hepatic decompensation, respectively). Cirrhosis was indicated exclusively by FIB-4 scores in 1,727 patients (17.6%) and was indicated by all methods (FIB-4 score, liver biopsy, and presence of a diagnostic/procedure code for cirrhosis or hepatic decompensation) in only 221 patients (2.3%). Notably, of the 661 patients with cirrhosis identified by biopsy, only 356 (53.9%) also had ICD-9-CM/CPT codes for cirrhosis or manifestations of hepatic decompensation (**Supplementary Table S1** online).

Among the 2,194 patients whose FIB-4 scores were ≥5.88, only 357 patients (16%) had been diagnosed with cirrhosis by liver biopsy results, whereas 326 patients (15%) had ICD-9-CM/CPT codes for cirrhosis or manifestations of hepatic decompensation. When APRI scores >1.0, >1.5, and >2.0 were also taken into consideration, cirrhosis was indicated in 1,659 (75.6%), 1,402 (63.8%), and 1,186 (54.0%) patients, respectively; cirrhosis remained indicated solely by FIB-4 scores in only 433 patients (19.7%) (**Supplementary Table S2**). Of the 2,194 patients with cirrhosis indicated by FIB-4 scores ≥5.88, only 788 patients (36%) had a biopsy performed at any time (**Supplementary Table S3**). Of these 788 patients, 357 patients (45%) had a biopsy indicating cirrhosis (concordance), whereas cirrhosis was not indicated in the remaining 431 patients (55%). Discordance between cirrhosis indicated by FIB-4 scores and by biopsy was seen in only 431 of the 2,194 patients (19.6%).

We explored the possibility that this discordance may have been due to the performance of the biopsy significantly earlier than the FIB-4 score calculation. The discordance could indicate that the FIB-4 score represents a true progression to cirrhosis during the time interval between the two tests. We therefore analyzed differences in the timing of the FIB-4 relative to the timing of the biopsy in the 788 patients who had cirrhosis as indicated by FIB-4 scores and had a biopsy performed, comparing patients showing concordance with those showing discordance with regard to the two measures. We compared the elapsed time of the earliest indication of cirrhosis by FIB-4 scores from the time of biopsy. The median elapsed time from biopsy to FIB-4 was 37.9 months among the patients with concordance and 46.8 months in patients with discordance (including negative times in cases where the biopsy was performed after FIB-4 scores were calculated). Although the differences between the two groups was not significant based on a nonparametric Wilcoxon test, it is possible that a cirrhotic FIB-4 score measured almost 4 years after a noncirrhotic biopsy could indeed represent progression to cirrhosis.

### Sensitivity analysis

In the second sensitivity analysis, exclusion of FIB-4 scores from lab values collected during hospitalizations resulted in a reduction in the number of patients with FIB-4 scores ≥5.88 from 2,185 (22%) to 1,757 (18%). There was a corresponding decrease in the overall number of patients with an indication of cirrhosis by at least one of the methods from 2,788 (28%) to 2,422 (25%).

### Demographic and clinical characteristics of patients with cirrhosis

Univariate analysis of the demographic and clinical characteristics of patients with an indication of cirrhosis (by any of the four methods), compared with those without indication of cirrhosis, revealed that age, gender, race/ethnicity, median annual household income, insurance status, receipt of any HCV antiviral therapy, HCV genotype, history of alcohol abuse, HIV coinfection, and diabetes (as assessed by the Charlson/Deyo comorbidity subscore) were significantly associated with prevalence of cirrhosis in this cohort (**Table 4**). Multivariable logistic modeling for characteristics associated with cirrhosis revealed that older age, male gender, Asian race (compared with White race), Hispanic ethnicity, lack of insurance coverage or coverage by Medicare or Medicaid (compared with private insurance), history of receipt of antiviral therapy, infection by HCV genotype 3 (compared with infection by genotype 1), history of alcohol abuse, HIV coinfection, and diabetes were associated with being cirrhotic (**Table 5**). Conversely, Black race and infection with HCV genotype 2 were associated with lower odds of being cirrhotic.

### Source of infection

We collected data regarding source of infection among a subgroup of 4,218 patients who completed a survey to examine

**Table 4. Univariate logistic comparisons of demographic and clinical characteristics among patients with an indication of cirrhosis (by any method) and those without an indication of cirrhosis**

| Characteristic | No indication of cirrhosis, *n*=6,995 | Indication of cirrhosis, *n*=2,788 | *P* value[a] |
|---|---|---|---|
| Age *(mean, s.d.)* | 53.6 (11.3) | 58.5 (8.9) | <0.001 |
| *Age category* | | | <0.001 |
| ≤40 years | 771 (11%) | 36 (1%) | |
| >40 to <50 years | 1,193 (17%) | 271 (10%) | |
| >50 to <60 years | 3,103 (44%) | 1,410 (51%) | |
| ≥60 years | 1,928 (28%) | 1,071 (38%) | |
| Male sex | 3,950 (56%) | 1,802 (65%) | <0.001 |
| *Race* | | | <0.001 |
| Asian | 193 (3%) | 118 (4%) | |
| White | 4,416 (63%) | 1,547 (55%) | |
| Black | 1,485 (21%) | 782 (28%) | |
| Pacific Islander/Hawaiian | 121 (2%) | 69 (2%) | |
| Native American | 129 (2%) | 48 (2%) | |
| Unknown | 651 (9%) | 224 (8%) | |
| Hispanic ethnicity | 237 (3%) | 129 (5%) | <0.001 |
| *Median annual household income* | | | <0.001 |
| <$15,000 | 172 (2%) | 81 (3%) | |
| ≥$15,000 to <$30,000 | 1,302 (19%) | 575 (21%) | |
| ≥$30,000 to <$50,000 | 3,146 (45%) | 1,278 (46%) | |
| ≥$50,000 to <$75,000 | 1,556 (22%) | 591 (21%) | |
| ≥$75,000 | 399 (6%) | 149 (5%) | |
| Missing | 420 (6%) | 114 (4%) | |
| *Insurance status* | | | <0.001 |
| Medicaid | 887 (13%) | 369 (13%) | |
| Medicare | 1,379 (20%) | 902 (32%) | |
| Private | 4,307 (62%) | 1,316 (47%) | |
| None | 183 (3%) | 106 (4%) | |
| Unknown | 239 (3%) | 95 (3%) | |
| Any HCV antiviral therapy | 2,429 (35%) | 1,157 (41%) | <0.001 |
| *HCV genotype* | | | <0.001 |
| 1 | 3,229 (46%) | 1,458 (52%) | |
| 2 | 636 (9%) | 194 (7%) | |
| 3 | 415 (6%) | 198 (7%) | |
| Other | 85 (1%) | 32 (1%) | |
| Unknown | 2,630 (38%) | 906 (32%) | |
| History of alcohol abuse | 1,349 (19%) | 913 (33%) | <0.001 |
| HIV coinfection | 182 (3%) | 137 (5%) | <0.001 |
| Diabetes (Charlson/Deyo comorbidity subscore) | 603 (9%) | 364 (13%) | <0.001 |

HCV, hepatitis C virus.

[a]*P* values for categorical variables are based on the chi-square test, while the *P* value for the continuous variable (age) is based on the t-test (unequal variance).

whether mode of infection was associated with development of cirrhosis (indicated by FIB-4 ≥5.88, biopsy, or diagnosis codes). In univariate analysis, we found that contracting hepatitis C through occupational exposure, blood transfusion, or a medical procedure was associated with higher rates of cirrhosis, whereas exposure by injection drug use or sex with males was associated with lower rates of cirrhosis (**Supplementary Table S4**).

### Duration of infection

Data on the duration of infection were available for a subgroup of patients who completed a survey and were able to estimate when they became infected (*n*=2,389). Of these, 365 patients were indicated as having cirrhosis by FIB-4 ≥5.88, whereas 2,024 patients were determined not to have cirrhosis by FIB-4. To improve our confidence in FIB-4 as a predictor of cirrhosis, we used logistic regression analysis to examine whether, as we hypothesized, a longer duration of infection was associated with FIB-4-cirrhosis. We found that the odds of cirrhosis as indicated by FIB-4 increased with duration of infection (odds ratio=1.09 for each 5-year duration of infection; 95% Wald confidence interval 1.04–1.14, *P*<0.0001).

## DISCUSSION

This study revealed that the use of parameters in addition to liver biopsy—including a previously validated serum biomarker that serves as a surrogate for more advanced fibrosis—facilitates the identification of previously unrecognized cirrhotic CHC patients. Use of all four parameters (liver biopsy, FIB-4 scores, and diagnostic/procedural codes for cirrhosis and manifestations of hepatic decompensation) suggests a fourfold higher prevalence of cirrhosis than is indicated by biopsy alone. The estimated prevalence of cirrhosis of 25–28% in the CHC population at four health systems in the United States is in agreement with the previously modeled projection of 25% prevalence of cirrhosis in 2010 (4). These results imply that a quarter of all CHC patients under medical care may be cirrhotic, but that most have never been formally assigned this diagnosis and may be unaware of their cirrhosis. Moreover, only half of all patients with biopsy-confirmed cirrhosis are assigned an ICD-9 code for cirrhosis. Consequently, ICD-9 codes may not be reliable as the sole indicator of the prevalence of cirrhosis in cohort studies.

The present analysis corroborates earlier reports indicating that age, alcohol abuse, male gender, coinfection with HIV, and diabetes are associated with a significant increase in the risk of progression to cirrhosis (14,26–29). Our observation that Hispanic ethnicity increases the risk of progression to cirrhosis is in agreement with findings of other studies that have evaluated the role of ethnicity in the progression of hepatitis C infections to cirrhosis (6–9); similarly, our finding that African Americans are at lower risk of cirrhosis compared with Caucasians is also in agreement with findings of other studies (8,27,29,30).

**Table 5. Multivariable logistic model of characteristics associated with cirrhosis (indicated by any method)**

| Characteristic | Adjusted odds ratio (95% CI) | *P* value |
|---|---|---|
| Age category | | <0.001 |
| <40 years | 1 (reference) | |
| >40–50 years | 5.04 (3.49–7.28)* | |
| >50–60 years | 10.65 (7.49–15.15)* | |
| ≥60 years | 12.63 (8.81–18.11)* | |
| *Sex* | | 0.003 |
| Male | 1 (reference) | |
| Female | 0.86 (0.78–0.95)* | |
| *Race* | | <0.001 |
| White | 1 (reference) | |
| Asian | 1.59 (1.22–2.06)* | |
| Black | 0.81 (0.70–0.92)* | |
| Pacific Islander/Hawaiian | 1.28 (0.90–1.80) | |
| Native American | 0.97 (0.68–1.39) | |
| *Hispanic ethnicity* | | <0.001 |
| Not Hispanic | 1 (reference) | |
| Hispanic | 1.36 (1.05–1.75)* | |
| *Insurance* | | <0.001 |
| Private | 1 (reference) | |
| Medicaid | 1.80 (1.54–2.11)* | |
| Medicare | 1.73 (1.54–1.94)* | |
| No insurance | 2.14 (1.62–2.82)* | |
| *Any HCV antiviral therapy* | | <0.001 |
| No | 1 (reference) | |
| Yes | 1.43 (1.29–1.58)* | |
| *HCV genotype* | | <0.001 |
| 1 | 1 (reference) | |
| 2 | 0.74 (0.62–0.89)* | |
| 3 | 1.27 (1.04–1.55)* | |
| Other | 0.99 (0.63–1.54) | |
| *History of alcohol abuse* | | <0.001 |
| No | 1 (reference) | |
| Yes | 2.32 (2.08–2.59)* | |
| *HIV coinfection* | | <0.001 |
| No | 1 (reference) | |
| Yes | 1.86 (1.45–2.39)* | |
| *Diabetes (Charlson/Deyo comorbidity subscore)* | | <0.001 |
| No | 1 (reference) | |
| Yes | 1.39 (1.18–1.64)* | |

95% CI, 95% confidence interval; HCV, hepatitis C virus.

*Adjusted odds ratio is statistically significant at alpha = 0.05 level.

Our finding that HCV infection acquired through blood transfusion is associated with higher rates of cirrhosis is in agreement with earlier retrospective studies that reported more aggressive histological inflammatory activity and a higher risk of hepatic decompensation in patients with transfusion-acquired hepatitis C (31,32). Our observation that duration of infection is a significant risk factor for the development of cirrhosis as assessed by FIB-4 corroborates earlier reports that showed duration of infection to be an independent predictor of advanced fibrosis in hepatitis C-infected individuals (33,34). Our observation that the duration of infection is positively associated with a higher likelihood of FIB-4-indicated cirrhosis also suggests that the FIB-4 test is a reliable predictor of cirrhosis. Finally, our observations that infection with HCV genotype 3 increases the risk of cirrhosis compared with infection with genotype 1, and that infection with HCV genotype 2 is associated with a lower risk for cirrhosis, are consistent with the recently-reported findings of Kanwal *et al.* (35). That HCV viral genotype influences response to antiviral therapy has been long recognized, but the finding that genotype actually affects liver disease progression is a recent finding that has significant implications regarding the modeling of this viral epidemic.

Our study has significant strengths, including the large size and diversity of the cohort (22,36). The cohort is drawn from four large integrated health systems that serve almost 4 million individuals in five geographically and racially distinct states. This study is unique because it used an expanded set of parameters (liver biopsy, the serum fibrosis marker FIB-4, and the presence of diagnostic/procedure codes for cirrhosis and manifestations of hepatic decompensation) to identify CHC patients with cirrhosis. The FIB-4 index employed in our study has been extensively validated in this large cohort for its ability to predict the lower and upper ends of the liver fibrosis spectrum (F0–F2 and cirrhosis, respectively) in both patients with hepatitis B virus infection and HCV infection (23). The FIB-4 cutoff value of 5.88 that we used to identify cirrhosis in this study is conservative. In the original validation study of FIB-4 in this cohort, a value of 1.81 differentiated fibrosis stages 3–4 from fibrosis stages 0–2. Accordingly, use of this lower cutoff would have identified an even higher proportion of CHC patients with advanced fibrosis, some with cirrhosis but with FIB-4 between 1.81 and 5.88. It must be emphasized, however, that this study reports period prevalence of cirrhosis between 2006 and 2010, and not the prevalence at a single point in time.

Our study has inherent limitations. The FIB-4 index is based on laboratory values (alanine and aspartate aminotransferase values and platelet counts) that may fluctuate over time, and such natural fluctuations may occur during the course of HCV infection. However, we used the most recently available aminotransferase levels and platelet counts collected within 7 days of each other, rather than peak values, reducing the likelihood that we captured spurious elevations. Furthermore, we excluded laboratory values collected while a patient was receiving antiviral therapy in order to eliminate any influence of therapy on these laboratory values. Our sensitivity analysis also excluded

laboratory values collected from hospitalized patients who may have had spurious platelet count or aminotransferase values during hospitalization for reasons unrelated to their liver disease. Although the FIB-4 score has been shown to have an area under the receiver operating characteristic curve value of 85% in predicting cirrhosis in our cohort (23), it is not diagnostic and does not identify cirrhosis in patients with low or normal transaminase levels and those who have normal platelet counts. Although we would have liked to combine this noninvasive test score with an assessment of liver stiffness to improve the test performance, the observational nature of our study precluded the collection of liver stiffness data. Moreover, liver stiffness tests had not been approved at the time of conduct of our study. Finally, the CHeCS cohort represents patients known to health systems and diagnosed with CHC; thus, our estimate of cirrhosis prevalence cannot be extrapolated to the undiagnosed HCV-infected population or to infected patients who have not had encounters with the health-care system.

Retrospective studies evaluating the economic impact of CHC, and Markov models evaluating the cost effectiveness of newer anti-HCV therapies, have typically relied on ICD-9 codes to identify and stratify patients on the basis of disease severity (17,37–40). Our finding that only one-half of all patients with biopsy-confirmed cirrhosis have ICD-9 codes assigned to them suggests that estimates of the economic burden reported by these retrospective studies and Markov models may be very conservative. Moreover, these cost-effectiveness models are based on baseline estimates of the prevalence of cirrhosis. If the actual prevalence is higher than the current estimates, as is suggested by the results of our study, these models will need to be revised accordingly, which may result in significantly different findings with regard to the cost-effectiveness of the newer antiviral therapy regimens.

In conclusion, our study suggests that the prevalence of cirrhosis in CHC patients is higher than would be diagnosed through the use of liver biopsies and ICD-9 codes alone. Prospective studies of the natural history of CHC have reported the development of cirrhosis in 7–16% of patients over 8–16 years of follow-up (41–44), whereas retrospective–prospective studies with exposure intervals of 9–45 years have reported progression to cirrhosis in 0.3–15% of CHC patients (45–51). Our study also reveals that less than one-half of all CHC patients (43% in our cohort) underwent liver biopsy, and that use of additional parameters including FIB-4 scores and ICD-9/CPT codes for cirrhosis and hepatic decompensation likely facilitated a more accurate estimate of the prevalence of cirrhosis in a CHC population. Accurate estimation of the prevalence of advanced fibrosis or cirrhosis has significant implications for patient care and health-care policy. There has been recent interest in the use of noninvasive modalities including elastography and blood tests for the diagnosis of liver fibrosis in patients with hepatitis C, and the use of these noninvasive modalities in lieu of liver biopsy has been widely discussed (52,53). Our findings suggest that the use of FIB-4 and APRI scores facilitates more accurate estimation of the prevalence of cirrhosis in CHC patients than would be possible through the use of biopsy alone. Serum markers such as FIB-4 and APRI scores, which are easily calculable with online tools that use readily available demographic and laboratory parameters (54), could prove clinically useful if included as part of the comprehensive clinical profile of CHC patients. Cirrhosis has likely been underdiagnosed in the past because of patient reluctance to undergo liver biopsy. Use of these noninvasive modalities will help address this underdiagnosis and provide more reliable estimates of the true prevalence of advanced fibrosis. Knowledge of the actual prevalence of advanced fibrosis will also help inform clinical decision making regarding screening for sequelae of CHC, timing of initiation of antiviral therapy, and follow-up counseling. Our findings are the first in the United States to attempt an accurate estimate of the prevalence of cirrhosis in the CHC patient population at large. These findings heighten awareness of the health-care burden imposed by advancing HCV disease progression in the US population.

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## CONFLICT OF INTEREST

**Guarantor of the article**: Stuart C. Gordon, MD.

**Specific author contributions:** Study concept and design: S.C.G., M.L., and L.B.R.; acquisition of data: S.C.G., M.L., L.B.R., J.A.B., V.V., and M.A.S.; analysis and interpretation of data: S.C.G., M.L., L.E.L., and L.B.R.; critical revision of the manuscript for important intellectual content: S.C.G., L.E.L., L.B.R., S.D.H., A.C.M., P.R.S., E.T., F.X., J.A.B., V.V., M.A.S., N.O.-T., and M.L; statistical analysis: M.L. and N.O.-T.; obtained funding: S.C.G., S.D.H., and A.C.M.; administrative, technical, or material support: L.B.R. and N.O.-T.; study supervision: S.C.G., S.D.H., M.L., L.B.R., and A.C.M.; approval of the final draft to be submitted for publication: S.C.G., L.E.L., L.B.R., S.D.H., A.C.M., P.R.S., E.T., F.X., J.A.B., V.V., M.A.S., N.O.-T., and M.L.

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LIVER

## Study Highlights

**WHAT IS CURRENT KNOWLEDGE**

- ✓ The prevalence of chronic hepatitis C (CHC)-related cirrhosis is uncertain.
- ✓ Previous studies may underestimate the true prevalence of cirrhosis in CHC patients.

**WHAT IS NEW HERE**

- ✓ Use of additional parameters to identify cirrhosis suggests a fourfold higher prevalence compared with liver biopsy alone.
- ✓ A significant proportion of patients with biopsy-confirmed cirrhosis are not assigned International Classification of Diseases, Ninth Revision (ICD-9) codes for cirrhosis.

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## APPENDIX

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