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MAJOR ARTICLE

All-Cause Mortality and Progression Risks to Hepatic Decompensation and Hepatocellular Carcinoma in Patients Infected With Hepatitis C Virus

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Background. A key question in care of patients with chronic hepatitis C virus (HCV) infection is beginning treatment immediately vs delaying treatment. Risks of mortality and disease progression in "real world" settings are important to assess the implications of delaying HCV treatment.

Methods. This was a cohort study of HCV patients identified from 4 integrated health systems in the United States who had liver biopsies during 2001–2012. The probabilities of death and progression to hepatocellular carcinoma, hepatic decompensation (hepatic encephalopathy, esophageal varices, ascites, or portal hypertension) or liver transplant were estimated over 1, 2, or 5 years by fibrosis stage (Metavir F0–F4) determined by biopsy at beginning of observation.

Results. Among 2799 HCV-monoinfected patients who had a qualifying liver biopsy, the mean age at the time of biopsy was 50.7 years. The majority were male (58.9%) and non-Hispanic white (66.9%). Over a mean observation of 5.0 years, 261 (9.3%) patients died and 34 (1.2%) received liver transplants. At 5 years after biopsy, the estimated risk of progression to hepatic decompensation or hepatocellular carcinoma was 37.2% in stage F4, 19.6% in F3, 4.7% in F2, and 2.3% in F0–F1 patients. Baseline biopsy stage F3 or F4 and platelet count below normal were the strongest predictors of progression to hepatic decompensation or hepatocellular carcinoma.

Conclusions. The risks of death and progression to liver failure varied greatly by fibrosis stage. Clinicians and policy makers could use these progression risk data in prioritization and in determining the timing of treatment for patients in early stages of liver disease.

Keywords. hepatitis C; hepatic decompensation; hepatocellular carcinoma; mortality; cirrhosis.

Patients with chronic hepatitis C virus (HCV) infection are at risk for progressive hepatic fibrosis and cirrhosis, leading to hepatic decompensation (ie, hepatic encephalopathy, esophageal varices, or ascites) and hepatocellular carcinoma (HCC) [1, 2]. Decedents with HCV infection listed among causes of death on their death certificates died at an age >20 years younger than decedents without HCV infection [3, 4]. Thus, there is an urgent need for effective interventions in HCV-infected patients at most risk of immediate morbidity and mortality. The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) treatment guidance that was published in 2014 conferred "highest" priority to patients with Metavir stage F3 (advanced fibrosis), Metavir stage F4 (compensated cirrhosis), liver transplant, or severe extrahepatic hepatitis C, and "high" priority to those at

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Metavir stage F2 (moderate fibrosis) or with certain coinfections or comorbidities [5].

Previously, pegylated interferon plus ribavirin was the standard treatment for chronic HCV infection, and sustained virologic response (SVR) was only achieved in about 50% of patients infected with genotype 1a and 1b, the usual genotypes seen in the United States [6, 7]. SVR achieved on interferon-based regimens has been shown to be associated with resolution of liver disease and prevention of long-term complications in patients without cirrhosis; however, achievement of SVR after the development of cirrhosis greatly reduces but does not completely eliminate the risk of HCC [8, 9]. With the recent introduction of oral, curative, but highly expensive antiviral drugs [10], a priority research question is comparative benefits and harms of treating patients with HCV infection at the time of diagnosis vs waiting to treat only those patients who show early signs of progression of liver disease or other manifestations of HCV infection [11]. Furthermore, since some payers introduced policies to limit access to treatment in reaction to the high cost of newer regimens, there has been an ongoing debate regarding whether delaying therapy is justifiable, and thus, data about the progression of untreated early-stage HCV infection from large and diverse cohorts are critical [12, 13].

We describe all-cause mortality and progressing risks among cohort patients chronically infected with HCV according to fibrosis stage determined by liver biopsy at beginning of observation. The 1, 2, and 5-year risks of progression to liver complications in the absence of successful treatment were estimated in a large cohort with enrollment from population-based healthcare systems. These risk estimates may help inform decisions about the timing of antiviral treatment and about prioritizing antiviral treatment among patients according to liver fibrosis stage and other selected clinical factors.

METHODS

Data Source

We analyzed data from the Chronic Hepatitis Cohort Study (CHeCS). CHeCS is a "dynamic" observational study conducted at 4 large, integrated healthcare systems located in the United States, and represents a geographically, ethnically, and clinically diverse cohort of patients with chronic hepatitis B and C [14]. The data collected are solely based on routine clinical care and thus representative of the uncontrolled healthcare environment of the real-world clinical setting. Criteria for inclusion and composition of the CHeCS cohort have been summarized in a previous report [14]. In brief, the CHeCS cohort was created based on analysis of electronic health records (EHR) and administrative data of >2.7 million patients aged 18 years or older who had a clinical service (ie, outpatient or inpatient, emergency department, or laboratory test) provided between 1 January 2006 and 31 December 2012 at 1 of 4 sites: Geisinger Health System in Danville, Pennsylvania, which serves approximately 2.6 million Pennsylvania residents; Henry Ford Health System in Detroit, Michigan, which serves >1 million southeastern Michigan residents; Kaiser Permanente Northwest in Portland, Oregon, which serves approximately 500 000 members; and Kaiser Permanente of Honolulu, Hawaii, which serves about 220 000 persons or approximately one-sixth of Hawaii residents.

Patients were identified principally by laboratory and secondarily by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) criteria. EHR data and administrative data were supplemented with individual chart review by trained data abstractors, who also reviewed and verified chronic HCV infection. Once HCV infection was confirmed, all available retrospective and prospective data annually through 2012 were abstracted. Abstractors follow a standard abstraction manual and collect data about patients' demographics, medical encounters, treatment data, and laboratory, radiology, and biopsy results.

Study Participants

We limited our analysis to HCV-monoinfected patients who had at least 1 liver biopsy performed between 2001 and 2012. Patients with human immunodeficiency virus or hepatitis B, those who achieved SVR before biopsy, or those with <90 days of follow-up were excluded. To determine progression probabilities, patients who had developed decompensation or HCC prior to or within 90 days after biopsy were excluded. For patients who received antiviral treatment for HCV during the observation period, we only included the observation time prior to the date when the first HCV RNA test became negative or undetectable. Because the purpose of this analysis was to estimate the risk for disease progression among patients who were still infected with HCV, patients' observation time after the negative HCV RNA test (technically no longer infected) was excluded. The observation periods were further restricted to the first liver biopsy that occurred after the diagnosis of chronic HCV infection. The first biopsy during the observation period was the starting point for analysis (baseline). In CHeCS, liver biopsies are performed as part of routine clinical practice, and reports from pathologists are standardized: Fibrosis scores from different scoring systems (International Association for the Study of the Liver, Batts-Ludwig, Metavir, Ishak, Knodell, Scheuer) were mapped to a F0–F4 equivalency scale and ranked as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis [15].

Clinical Endpoints

In our analysis, liver transplant was based on *ICD-9-CM* diagnosis and Current Procedural Terminology (CPT) codes of

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996.82, 50.5, 50.51, 50.59, 47135, 47136, or V42.7. Decompensation conditions of hepatic encephalopathy, esophageal varices with bleeding, ascites, or hepatorenal syndrome were defined as the first occurrence of *ICD-9* diagnosis or CPT codes in following groups: hepatic encephalopathy (572.2), portal hypertension (572.3, 37140, 37160, 37180, 37181, 37182, 37183), esophageal varices with bleeding (456.0, 456.20, 42.91, 44.91, 96.06, 43204, 43205, 43243, 43244, 43400, 43401), ascites (789.5, 789.59, 54.91, 49080, 49081), or liver failure with hepatorenal syndrome (572.4). These conditions were used by others [16]; we also conducted a pilot study comparing the selected *ICD-9*/CPT codes with independent chart review by 2 gastroenterology fellows, which validated that these codes could reliably determine whether or not a CHeCS patient had decompensation. Cases of primary HCC and diagnosis dates were derived from validated tumor registry reports [17]. To ascertain mortality status, each health system matched cohort patient records to the most recent National Death Index, Social Security Death Index, or electronic state death registries to find out the date of death [18].

Statistical Methods

We examined the demographic and clinical characteristics at time of the first biopsy, defined as the baseline. We calculated the Charlson/Deyo comorbidity index score from diagnosis codes in inpatient, outpatient, and claims data during the year when the biopsy was performed [19]. Differences in patients' clinical outcomes by fibrosis stage following biopsy were analyzed by the Fisher exact or χ^2 test for categorical variables, and nonparametric tests for the continuous variables. Mortality and probability of progression were estimated by the Kaplan–Meier method. The time during which a patient was at risk for hepatic decompensation or HCC was defined as the time from the date of biopsy to the date of diagnosis of decompensation, HCC, death, liver transplant, first negative test for HCV RNA after treatment, or last contact, whichever was earliest. In calculating the cumulative incidence of decompensation or HCC, the occurrence of death or transplant was considered as competing risks. We also performed a proportional hazards model to determine factors independently associated with progression to decompensation or HCC among patients whose fibrosis stage was F2 or above.

To evaluate possible selection biases for liver biopsy, we compared demographic and clinical characteristics (measured <90 days of HCV diagnosis) in patients who did and did not have biopsy after diagnosis. To make the observation period comparable between these 2 groups, this comparison was made in a subgroup of patients whose HCV diagnosis was first made during 2009–2012.

The study protocol was reviewed and approved by an institutional review board at each CHeCS participating site.

RESULTS

Patient Characteristics

Among 9912 HCV-monoinfected patients enrolled in CHeCS, 3091 (31%) persons had at least 1 biopsy performed during 2001–2012. Although 621 patients had 2 or more biopsies, the results from any repeated biopsy were not considered. After applying the study exclusion criteria, a total of 2799 patients were included in this analysis.

Based on each patient's first biopsy result, the classification by fibrosis stage was as follows: 309 (11.0%) were at Metavir stage F0, 724 (25.9%) at F1, 849 (30.3%) at F2, 509 (18.2%) at F3, and 408 (14.6%) at F4. Demographic characteristics were different between the groups (Table 1): The mean age was 50.7 years overall, and was 48.2 years among F0–F1 patients, compared with 53.0 years among those with F4 ($P < .0001$); the proportion of men increased significantly as biopsy stage advanced (52.0% in F0–F1 to 68.9% in F4) (Table 1). Most patients were white, and more than one-half of the patients had private insurance. As expected of HCV patients in the United States, the majority (at least 66.5%) of patients were genotype 1. The proportions of patients who had comorbidities, abnormal liver and renal function tests, and low platelets grew with increasing fibrosis stage, and in the F4 group, only about half (55.9%) did not have any Charlson comorbidity diagnosed (Table 1).

Progression Risks and All-Cause Mortality

Mean observation time after biopsy was about 5.0 years in all stage groups (Table 2). During this observation period, more than half (54.1%) of patients had treatment prescribed and 24.0% had 2 or more courses of treatment attempted; the observation time was truncated for 910 persons at the time when their first HCV RNA test was negative after treatment. Risks of all adverse clinical outcomes approximately doubled with each increase in fibrosis stage (Table 2). No one with baseline F0–F1 developed HCC. In contrast, among the baseline F4 group, 8.8% developed HCC, 26.5% decompensated, 4.9% had a transplant, and almost one-quarter had died by the end of observation (Table 2).

We plotted the progression to initial HCC or decompensation over the first 7 years after baseline biopsy (Figure 1*A*), and there were significant differences in the cumulative incidence by baseline fibrosis stage. We also examined the time to initial HCC and hepatic decompensation events separately (Figure 1*B* and 1*C*). No diagnoses of HCC were observed among baseline F0–F1 patients (Figure 1*B*), but otherwise the 2 cumulative incidence curves by baseline stage showed similar patterns over time. Clearly, the overall progression risks were much lower in F0 and F1 patients (gaps were small between these 2 groups) (Figure 1*A*).

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Table 1. Demographic and Clinical Characteristics of Hepatitis C Virus–Infected Patients at the Time of Biopsy, by Biopsy-Determined Liver Fibrosis Stage

Variables	Overall	F0–F1	F2	F3	F4	*P* Value
Sample size	2799	1033	849	509	408	
Age at biopsy, y						
Median	51.7	50.2	51.8	53.2	52.7	
Range	15.7–79.8	15.7–75.3	18.1–76.8	20.6–74.4	30.3–79.8	
Mean (SE)	50.7 (0.2)	48.2 (0.3)	51.4 (0.3)	52.9 (0.3)	53.0 (0.4)	<.0001
Male	1650 (58.9)	537 (52.0)	507 (59.7)	325 (63.9)	281 (68.9)	<.0001
Race						
Non-Hispanic white	1872 (66.9)	687 (66.5)	575 (67.7)	348 (68.4)	262 (64.2)	
Non-Hispanic black	470 (16.8)	249 (24.1)	116 (13.7)	61 (12.0)	44 (10.8)	
Others	457 (16.3)	97 (9.4)	158 (18.6)	100 (19.6)	102 (25.0)	<.0001
Insurance type						
Private	1751 (62.6)	590 (57.1)	596 (70.2)	341 (67.0)	224 (54.9)	
Government	813 (29.0)	311 (30.1)	218 (25.7)	144 (28.3)	140 (34.3)	
None	235 (8.4)	132 (12.8)	35 (4.1)	24 (4.7)	44 (10.8)	<.0001
Median household income						
Missing	39 (1.4)	19 (1.8)	5 (0.6)	8 (1.6)	7 (1.7)	
<$30 000	490 (17.5)	227 (22.0)	122 (14.4)	63 (12.4)	78 (19.1)	
$30 000–$49 999	1362 (48.7)	517 (50.0)	393 (46.3)	245 (48.1)	207 (50.7)	
≥$50 000	908 (32.4)	270 (26.1)	329 (38.8)	193 (37.9)	116 (28.4)	<.0001
Genotype						
1	1862 (66.5)	732 (70.9)	528 (62.2)	326 (64.0)	276 (67.6)	
2	338 (12.1)	114 (11.0)	128 (15.1)	73 (14.3)	23 (5.6)	
3	219 (7.8)	48 (4.6)	71 (8.4)	41 (8.1)	59 (14.5)	
4	26 (0.9)	15 (1.5)	4 (0.5)	5 (1.0)	2 (0.5)	
Other/mixed type	13 (0.5)	1 (0.1)	9 (1.1)	3 (0.6)	0	
Missing	341 (12.2)	123 (11.9)	109 (12.8)	61 (12.0)	48 (11.8)	<.0001
Charlson comorbidity score						
0	1753 (62.6)	696 (67.4)	524 (61.7)	305 (59.9)	228 (55.9)	
1	592 (21.2)	182 (17.6)	205 (24.1)	119 (23.4)	86 (21.1)	
2	192 (6.9)	81 (7.8)	49 (5.8)	29 (5.7)	33 (8.1)	
≥3	262 (9.4)	74 (7.2)	71 (8.4)	56 (11.0)	61 (15.0)	<.0001
ALT category						
Missing	5 (0.2)	2 (0.2)	2 (0.2)	1 (0.2)		
≤ULN	1024 (36.6)	526 (50.9)	302 (35.6)	116 (22.8)	80 (19.6)	
>ULN to <2× ULN	980 (35.0)	339 (32.8)	302 (35.6)	184 (36.1)	155 (38.0)	
≥2× ULN	790 (28.2)	166 (16.1)	243 (28.6)	208 (40.9)	173 (42.4)	<.0001
AST category						
Missing	8 (0.3)	4 (0.4)	3 (0.4)	1 (0.2)		
≤ULN	950 (33.9)	546 (52.9)	280 (33.0)	79 (15.5)	45 (11.0)	
>ULN to <2× ULN	1075 (38.4)	361 (34.9)	383 (45.1)	197 (38.7)	134 (32.8)	
≥2× ULN	766 (27.4)	122 (11.8)	183 (21.6)	232 (45.6)	229 (56.1)	<.0001
Platelet count below normal	441 (15.8)	52 (5.0)	71 (8.4)	126 (24.8)	192 (47.1)	<.0001
Total bilirubin						
Missing	27 (1.0)	12 (1.2)	11 (1.3)	3 (0.6)	1 (0.2)	
Normal	2638 (94.2)	992 (96.0)	812 (95.6)	478 (93.9)	356 (87.3)	
Above normal	134 (4.8)	29 (2.8)	26 (3.1)	28 (5.5)	51 (12.5)	<.0001
International normalized ratio						
Missing	47 (1.7)	33 (3.2)	3 (0.4)	4 (0.8)	7 (1.7)	
Normal	2098 (75.0)	767 (74.2)	693 (81.6)	394 (77.4)	244 (59.8)	
Above normal	654 (23.4)	233 (22.6)	153 (18.0)	111 (21.8)	157 (38.5)	<.0001

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Table 1 continued.

Variables	Overall	F0–F1	F2	F3	F4	*P* Value
Creatinine						
Missing	43 (1.5)	24 (2.3)	14 (1.6)	2 (0.4)	3 (0.7)	
Normal	2570 (91.8)	921 (89.2)	780 (91.9)	486 (95.5)	383 (93.9)	
Above normal	186 (6.6)	88 (8.5)	55 (6.5)	21 (4.1)	22 (5.4)	.001

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SE, standard error; ULN, upper limit of normal.

The estimated probabilities by liver fibrosis stage over 1, 2, and 5 years are shown in Table 3. The 1-year risk for liver transplant increased from 0.1% (95% confidence interval [CI], .01–.6) among patients with baseline stage F0–F1 to 1.6% (95% CI, .6–3.4) among those with baseline stage F4. The cumulative incidence of HCC at 2 years after biopsy was 6.3% in F4, and was lower at 0.3% in F2 patients. Patients starting baseline at F4 experienced high cumulative incidence of decompensation: 33.6% by 5 years after biopsy, compared with 18.6% in F3, 3.5% in F2, and 2.3% in F0–F1 (Table 3). Further analysis showed no difference in the cumulative incidence of decompensation between patients starting at F0–F1 and those at F2 ($P = .09$, data not shown). At 5 years after baseline biopsy, all-cause mortality was 31.5% in F4, 13.7% in F3, 6.9% in F2, and 6.8% in F0–F1 patients (Table 3).

Factors Associated With Progression

We used a Cox proportional hazards model to identify patient characteristics at the time of biopsy that were independently associated with the development of HCC or decompensation; this analysis was in patients staged at F2, F3, or F4 only (Table 4). After adjusting for age, race, and other factors included in the model, higher baseline stage, higher comorbidity score, platelet count below normal, and bilirubin level above normal were significantly associated with the development of HCC or decompensation (Table 4). Of these, baseline fibrosis stage F3 (adjusted hazard ratio [aHR], 4.2) or F4 (aHR, 7.05) vs F2, and platelet count below normal (aHR, 3.45) were the strongest predictors of progression to HCC or decompensation (Table 4).

Table 2. Clinical Endpoints (First Occurrence Only) Observed During Study Follow-up, by Biopsy-Determined Liver Fibrosis Stage at Baseline

Clinical Endpoint	Overall	F0–F1	F2	F3	F4	*P* Value
Sample size	2799	1033	849	509	408	
Time after biopsy, y						
Median	5.0	4.8	5.1	4.9	5.3	
Range	0.2–12.7	0.2–12.2	0.3–12.7	0.3–12.7	0.3–12.1	
Mean (SE)	5.1 (0.1)	5.0 (0.1)	5.2 (0.1)	5.2 (0.1)	5.4 (0.1)	.04
Ever treated for HCV	1513 (54.1)	440 (42.6)	417 (49.1)	374 (73.5)	282 (69.1)	<.0001
Liver transplant	34 (1.2)	4 (0.4)	5 (0.6)	5 (1.0)	20 (4.9)	<.0001
Hepatocellular carcinoma	58 (2.1)	0	6 (0.7)	16 (3.1)	36 (8.8)	<.0001
With hepatic decompensation	35 (1.3)	0	1 (0.1)	9 (1.8)	25 (6.1)	
Hepatic decompensation[a]	201 (7.2)	18 (1.7)	22 (2.6)	53 (10.4)	108 (26.5)	<.0001
Liver failure	4 (0.1)	0	0	3 (0.6)	1 (0.2)	
Hepatic encephalopathy	25 (0.9)	0	2 (0.2)	7 (1.4)	16 (3.9)	
Portal hypertension	54 (1.9)	2 (0.2)	5 (0.6)	12 (2.4)	35 (8.6)	
Esophageal varices with bleeding	30 (1.1)	2 (0.2)	4 (0.5)	6 (1.2)	18 (4.4)	
Ascites	121 (4.3)	15 (1.5)	13 (1.5)	36 (7.1)	57 (14.0)	
All-cause mortality	261 (9.3)	66 (6.4)	50 (5.9)	50 (9.8)	95 (23.3)	<.0001

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HCV, hepatitis C virus; SE, standard error.

[a] A patient could have ≥2 hepatic decompensation conditions.

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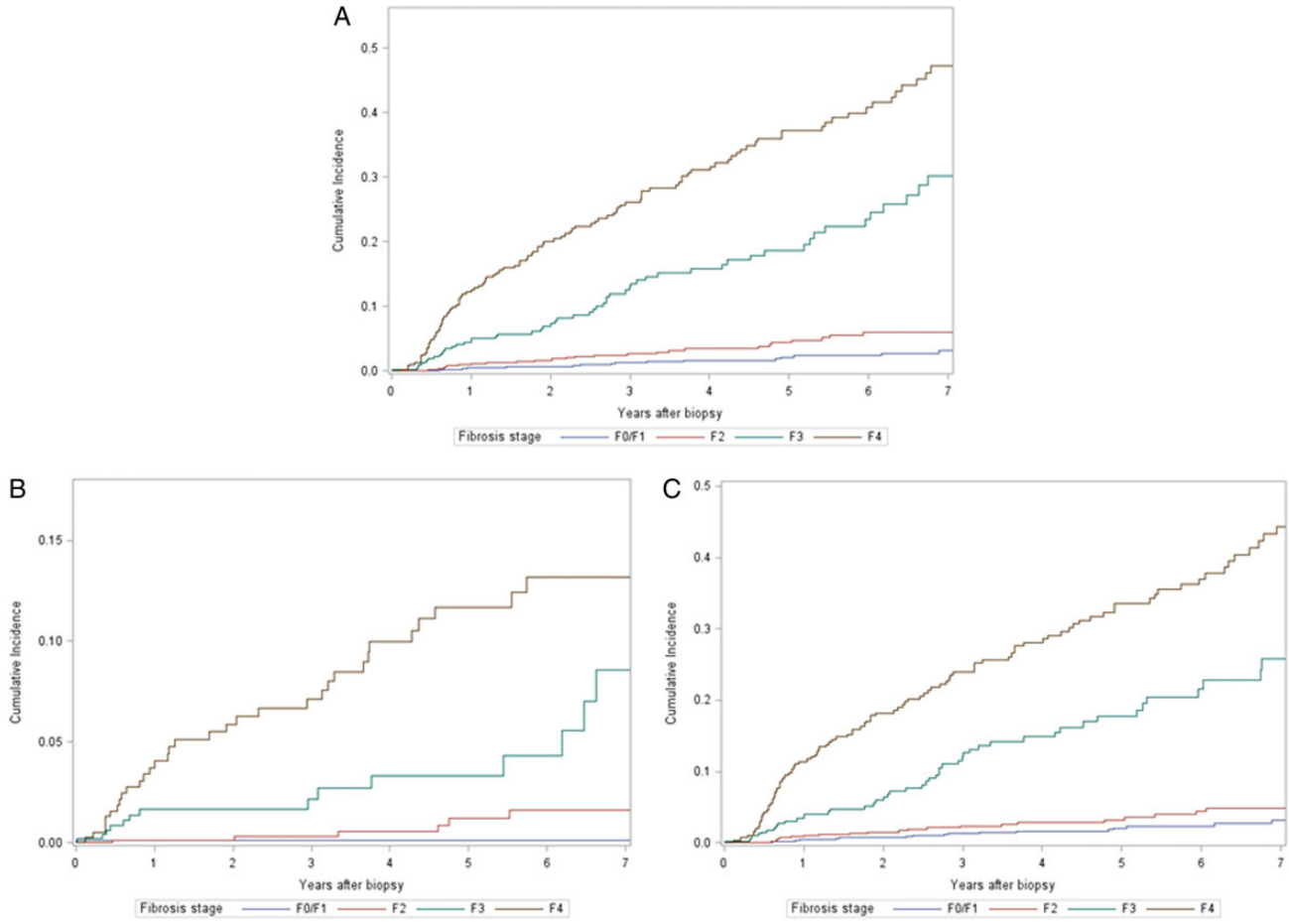

Figure 1. The cumulative incidence of developing a hepatic decompensation condition or hepatocellular carcinoma, by baseline fibrosis stage. *A*, Hepatic decompensation or hepatocellular carcinoma. *B*, Hepatocellular carcinoma only. *C*, Hepatic decompensation only.

Additional Analyses

We compared the demographic and clinical characteristic, assessed at the time of HCV diagnosis, among patients who were and were not biopsied after diagnosis. Of the 870 patients whose HCV diagnosis was first made during 2009–2012, 156 (17.9%) were biopsied at least once (Supplementary Table). The differences between the biopsied and nonbiopsied groups were relatively small, and statistically significant differences were limited to insurance type and study site: the percentage of patients who had private insurance was significantly higher in the biopsied group than the nonbiopsied group (63.5% vs 45.9%, $P < .0001$; Supplementary Table).

DISCUSSION

We observed significant progression to liver failure and death among patients with advanced liver fibrosis or cirrhosis in the absence of successful treatment. Our results emphasize that effective treatment is urgently needed in these groups of patients to preserve remaining liver function to improve survival and to reduce the risk of liver cancer and hepatic decompensation. Our risk estimates in patients with early stages of liver disease are important for cost-effectiveness analyses and policy decisions about timing of treatment [20]. Our study provides timely data for understanding the implications in the United States if HCV treatment is delayed in certain patient groups as a national debate is ongoing regarding restrictive policies for access to newer HCV therapies [13].

Treatment programs in 2012 or earlier were not effective. Although a majority of patients staged at F3 and F4 at baseline were treated for HCV, sometimes with >1 attempt, an overall 19.6% of F3 patients and 37.2% of F4 patients went on to experience hepatic decompensation or HCC within 5 years before treatment could lead to testing negative for HCV RNA. In F4 patients, the 1-year progression rate to HCC was 4.8% and to hepatic decompensation was 13.4%. Newer and more effective treatments in these patients are needed to reduce the risks of mortality and liver complications.

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Table 3. Estimated Probabilities of Developing Selected Clinical Endpoints Over 1, 2, and 5 Years, by Biopsy-Determined Liver Fibrosis Stage at Baseline

Clinical Endpoint		F0–F1	F2	F3	F4
Liver transplant					
1-year	% (95% CI)	0.1 (.01–.6)	0.1 (.01–.8)	0.2 (.01–1.1)	1.6 (.6–3.4)
	Sample size	869	637	293	276
2-year	% (95% CI)	0.1 (.01–.6)	0.1 (.01–.8)	0.6 (.1–2.3)	2.7 (1.2–5.0)
	Sample size	738	501	223	217
5-year	% (95% CI)	0.3 (.06–1.1)	0.4 (.1–1.4)	2.4 (.7–6.2)	6.5 (3.8–10.2)
	Sample size	377	270	99	105
Hepatocellular carcinoma					
1-year	% (95% CI)	0	0.1 (.01–.7)	1.7 (.7–3.3)	4.8 (2.8–7.4)
	Sample size	869	637	293	274
2-year	% (95% CI)	0	0.3 (.1–1.1)	1.7 (.7–3.3)	6.3 (3.9–9.4)
	Sample size	738	501	223	214
5-year	% (95% CI)	0	1.2 (.4–2.8)	3.3 (1.6–6.2)	11.7 (8.0–16.1)
	Sample size	377	266	99	98
Hepatic decompensation					
1-year	% (95% CI)	0.4 (.2–1.1)	1.1 (.5–2.2)	4.0 (2.4–6.3)	13.4 (10.0–17.3)
	Sample size	867	635	288	261
2-year	% (95% CI)	0.7 (.3–1.4)	1.7 (.9–3.0)	7.2 (4.7–10.5)	19.4 (15.2–24.0)
	Sample size	735	497	215	197
5-year	% (95% CI)	2.3 (1.3–3.8)	3.5 (2.1–5.5)	18.6 (13.5–24.4)	33.6 (27.7–39.5)
	Sample size	372	264	90	86
Hepatocellular carcinoma or hepatic decompensation					
1-year	% (95% CI)	0.4 (.2–1.1)	1.3 (.6–2.3)	5.0 (3.1–7.5)	14.5 (11.0–18.5)
	Sample size	867	635	288	260
2-year	% (95% CI)	0.8 (.4–1.6)	2.0 (1.1–3.4)	8.2 (5.5–11.5)	20.8 (16.5–25.5)
	Sample size	735	497	215	194
5-year	% (95% CI)	2.3 (1.3–3.8)	4.7 (3.0–7.0)	19.6 (14.4–25.4)	37.2 (31.1–43.2)
	Sample size	372	261	90	82
All-causes mortality					
1-year	% (95% CI)	1.5 (.9–2.4)	1.7 (.9–2.8)	4.8 (3.0–7.3)	8.0 (5.4–11.3)
	Sample size	869	637	293	276
2-year	% (95% CI)	2.9 (1.9–4.2)	2.4 (1.4–3.8)	6.0 (3.8–8.8)	10.7 (7.5–14.5)
	Sample size	738	501	223	217
5-year	% (95% CI)	6.8 (5.0–9.0)	6.9 (4.7–9.5)	13.7 (9.4–18.9)	31.5 (25.6–38.2)
	Sample size	377	270	99	105

Abbreviation: CI, confidence interval.

The 1-year risk of developing hepatic decompensation or HCC was 0.4% and 1.3% for F0–F1 and F2 patients, respectively, and these probabilities are less than one-tenth of the respective risks in F3 patients (5.0%) and F4 patients (14.5%); thus, our data support the guidance provided by AASLD/IDSA [5]. Although no HCC case was detected in F0–F1 patients, HCC cases were detected in F2 and F3 patients in the short term, probably because a subset of these patients may have rapidly progressed to cirrhosis. It is also possible that some patients may have been misclassified, due to biopsy sampling and/or interpretation error, and may have actually had more advanced fibrosis than indicated. Because our risk estimates were drawn from a large cohort of HCV-infected patients in real-world settings, the findings of our study are likely less affected by selection bias than the previous clinic-based studies.

The baseline liver fibrosis was staged by biopsy, which is traditionally viewed as the gold standard in staging liver fibrosis. Our stage-specific estimates based on biopsy results should be highly relevant to alternative staging approaches, such as transient elastography, which is increasingly used to guide patient management. Given that repeated biopsy is not practical, long-term monitoring of patients with lesser degrees of fibrosis

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Table 4. Patient Characteristics Associated With Progression Risks to Hepatocellular Carcinoma or Hepatic Decompensation

Characteristics at Time Biopsy	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Age, y	**1.02 (1.00–1.04)**	1.01 (.99–1.02)
Male sex	1.30 (.97–1.75)	1.03 (.76–1.40)
Race		
Non-Hispanic white	Reference	Reference
Non-Hispanic black	0.90 (.60–1.37)	0.75 (.45–1.25)
Others	1.11 (.79–1.56)	0.70 (.45–1.05)
Site		
Kaiser Permanente Northwest, Portland, OR	0.61 (.42–.87)	1.17 (.75–1.82)
Kaiser Permanente, Honolulu, HI	0.97 (.65–1.44)	1.26 (.76–2.09)
Henry Ford Health System, Detroit, MI	Reference	Reference
Geisinger Health System, Danville, PA	1.32 (.86–2.05)	0.79 (.48–1.29)
Stage of liver fibrosis		
F2	Reference	Reference
F3	**5.29 (3.36–8.34)**	**4.17 (2.60–6.70)**
F4	**11.78 (7.75–17.89)**	**7.05 (4.41–11.28)**
Charlson comorbidity score		
0	Reference	Reference
1	**1.73 (1.25–2.41)**	**1.80 (1.28–2.53)**
≥2	**2.62 (1.89–3.65)**	**2.05 (1.44–2.91)**
Genotype (limited to 3 genotypes)		
1	Reference	. . .[a]
2	0.85 (.53–1.35)	
3	1.35 (.86–2.14)	
ALT category		
Normal	Reference	Reference
Above normal	1.31 (.95–1.81)	0.84 (.59–1.19)
Platelet count		
Normal	Reference	Reference
Below normal	**6.40 (4.84–8.45)**	**3.45 (2.52–4.72)**
Bilirubin level		
Normal	Reference	Reference
Above normal	**4.12 (2.88–5.88)**	**2.31 (1.56–3.41)**

Statistically significant associations are highlighted in bold.

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HI, Hawaii; MI, Michigan; OR, Oregon; PA, Pennsylvania.

[a] Not included in the multivariate model due to sample sizes by specific genotype and missing information.

using noninvasive methods of transient elastography and FIB-4 score should be further studied [15, 21].

Our study has several limitations. First, although we used more reliable sources for HCC events and death, the occurrences of decompensation and liver transplant were ascertained by *ICD-9*/CPT codes. Based on our validation study in CHeCS patients, the subset of *ICD-9*/CPT codes we used can correctly identify decompensation in 81.7% of cases. Our estimates of progression to HCC are not precise, due to small numbers of cases in subgroups, but are consistent with the literature [22–24]. However, the progression risks to hepatic decompensation are on the high side compared with the risks reported by Dienstag et al [24] and Bruno et al [22], suggesting that a portion of the occurrences identified by *ICD-9*/CPT codes might include rule-out or suspected diagnoses. Second, the selection of patients for biopsy was not random and may have been based on clinical status, desire to ascertain treatment eligibility, or access to specialty care. However, in a group of patients newly diagnosed with HCV infection, we did not find any differences in clinical factors predictive of liver disease progression between patients who did and did not undergo biopsy. Finally, although CHeCS patients were geographically, clinically, and demographically diverse, the prevalence of comorbidity and behavioral factors such as alcohol abuse in CHeCS patients may not be generalizable to all HCV-infected persons who have been diagnosed.

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The trend of increasing morbidity associated with advanced liver diseases in the United States [25] may be rapidly changed if access to care and effective treatment become widely available for persons who are at high risk of morbidity and mortality. This natural history study provides real-world data about the probability of, time to, and risk factors for HCV-related morbidity and mortality. These timely data can help evidence-based decision making by clinicians and policy makers about HCV management, and can help inform the debate regarding the comparative benefits and harms of treating HCV patients at the time of diagnosis vs waiting to treat only those patients who show early signs of progression of liver disease (eg, F2) or other manifestations of the infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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