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Long-Term Liver Disease, Treatment, and Mortality Outcomes Among 17,000 Persons Diagnosed with Chronic Hepatitis C Virus Infection: Current Chronic Hepatitis Cohort Study Status and Review of Findings

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INTRODUCTION

Accurately delineating the progression and rates of liver disease and death in patients with chronic viral hepatitis infection requires following many affected patients for a long period. The Chronic Hepatitis Cohort Study (CHeCS), an ongoing dynamic, retrospective/prospective observational cohort study, was launched in 2008 to study the natural history of chronic viral hepatitis with and without antiviral treatment in the United States.[1] It is one of the largest cohorts of “real world” chronic hepatitis patients in the world. CHeCS currently includes a geographically and demographically diverse population of more than 4300 persons with chronic hepatitis B virus (HBV) infection and more than 17,000 persons with chronic hepatitis C virus (HCV) infection. Major objectives of the study are to determine the health burden and mortality associated with chronic viral hepatitis, monitor the implementation and effectiveness of recommended screening and care practices, understand the costs and potential savings of appropriate care and treatment, monitor access to care and treatment, and better understand the epidemiology of currently infected persons. This report summarizes CHeCS HCV cohort study findings to date and updates the clinical experience among current cohort patients.

METHODS

Criteria for inclusion and composition of the CHeCS cohort as well as details of the database created have been summarized in previous reports.[1–4] Briefly, the cohort was based on analysis of electronic health records (EHR) and administrative data of about 2.7 million patients aged ≥18 years who had a clinical service (ie, outpatient or inpatient, emergency department, or laboratory) visit provided on or after January 1, 2006 at 1 of 4 integrated health care systems: Geisinger Health System in Danville, Pennsylvania that serves approximately 2.6 million Pennsylvania residents in 44 counties; Henry Ford Health System in Detroit that serves more than one million southeastern Michigan residents; Kaiser Permanente-Northwest in Portland, Oregon that serves approximately 500,000 members; and Kaiser Permanente of Honolulu, Hawaii that serves about 220,000 persons or approximately one-sixth of Hawaii residents. The study protocol was approved by an Institutional Review Board registered with the Department of Health and Human Services Office for Human Research Protections at each participating site.

Extensive review, by algorithm, was undertaken to specify and characterize chronic patients with HBV and HCV. Patients were identified principally by laboratory results and secondarily by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) criteria.[1–4] Health system patients seen since 2006 who have met cohort eligibility criteria have been enrolled in the cohort; during 2014 to 2016, only newly eligible patients with HCV prescribed direct-acting antiviral (DAAs) were enrolled as a subset of the cohort, with data collection on the remainder of 2014 to 2016 eligible (untreated) patients planned for 2018. For all enrolled patients, once chronic viral hepatitis infection is confirmed by data abstractors[1,4] or an electronically available test that detects hepatitis C nucleic acid, all electronically available retrospective EHR and administrative data on medical encounters, diagnoses, procedures, hepatitis treatment, and laboratory tests

back to the first health system visit are collected. Collection of prospective longitudinal follow-up data continues for all HCV cohort patients.

Electronically available data were supplemented with individual EHR chart review of text fields by trained data abstractors. Data on hepatitis treatment, external laboratory tests, and biopsy results were abstracted following a standard procedure and manual.[1,4] Abstractors reviewed all charts for patients enrolled based on 2006 to 2008 data collection. Because of capacity and funding constraints, patients newly identified as meeting HCV cohort criteria after these dates were selected by simple random sampling (enhanced by cohort-based adaptive criteria for the year 2012)[2] for chart abstraction as funding allowed.[3] In 2014, retrospective and prospective records for all patients prescribed HCV therapy and those coinfected with HBV were abstracted as well to enhance ascertainment of treatment data. Of all 17,893 enrolled in the CHeCS at the 4 health systems, 11,858 (66%) have had extensive chart abstraction. Behavioral data were collected from a one-time cross-sectional survey in 2011 to 2012.[5] To enhance ascertainment of deaths among cohort patients and obtain causes of death from death certificate data, each health system performs a yearly comparison of the records of patients with no health system contact in the previous 2 years, or with a known date of death, with the most recent National Death Index, Social Security Death Index, or electronic state death registries.[1,6] An algorithm to detect decompensated cirrhosis through *ICD-9* codes was developed and validated with chart review by gastroenterology fellows using standard diagnosis guidelines provided by a senior hepatologist.[7]

Current patient demographic and clinical status as of January 1, 2016 among 2006 to 2013 HCV cohort-eligible patients are presented as well as a review of CHeCS publications to date.

RESULTS

Study Source Population

Among the 1.6 million adults in the 4 health systems as of the end of 2009 from which the initial CHeCS cohort was drawn, only 57% of predicted patients with HCV had been identified from testing and less than half of those with 2 or more abnormal alanine aminotransferase (ALT) levels had received HCV testing.[8] In this initial study source population, only 61% of persons with a positive HCV antibody test had documentation of a follow-up RNA test indicative of clinical follow-up by the end of 2011.[9] The current cohort is sourced from more than 2.8 million patients aged ≥18 years with health care utilization during 2006 to 2013 at the 4 participating health systems.

Mortality Data

CHeCS analyses revealed high rates of morbidity and mortality in the era before the availability of DAA therapy. Analyses of mortality 2006 to 2010 found very high death rates, about 2.5% to 3.5% per year.[1] Mean age of death was 59 years, 15 years younger than in age-adjusted nationally representative data, with an age-adjusted mortality for liver disease 12 times higher than the national average.[6] This study also found that only 19% of all CHeCS decedents, and just 30% of those with deaths attributed to liver disease, had HCV

listed on their death certificates, even though most had biopsy, biomarker, or other evidence of advanced liver disease. Applying this to the 20,000 death certificates a year listing HCV indicates that more than 100,000 patients with HCV a year are dying of or with HCV: this is an estimate projected only from those who have been diagnosed. In current data, achievement of sustained viral response to therapy (SVR) was associated with a reduction in all-cause mortality and risk of death, but continued mortality risk was associated with severe fibrosis and cirrhosis, and older age.[10] Further analyses showed that although prevalence of cirrhosis has increased over the past decade, particularly among non–white patients, overall mortality may be decreasing.[11]

Hospitalization Data

Compared with other patients in the health systems from which the cohort was drawn in the pre-DAA era, patients with HCV overall not only were more likely to be hospitalized from liver-related conditions but also had an approximately 3.7-fold higher likelihood of all-cause hospitalization, with 27.4 hospitalizations per 100 person-years versus 7.4 per 100 person-years for other health system patients.[12] However, the relatively small number of patients with HCV who achieved SVR following treatment in the pre-DAA era experienced a posttreatment reduction in all-cause hospitalization of about 25%.[13] These findings highlight the incremental costs and health care burden of patients with chronic HCV infection.

Advanced Liver Fibrosis and Hepatocellular Carcinoma

CHeCS analyses showed that serum/blood assays (eg, ALT, aspartate aminotransferase [AST], and platelet count) and patient age can be calculated in an index (FIB-4 or aspartate aminotransferase platelet ratio index [APRI] score) that accurately distinguishes advanced fibrosis and cirrhosis from no to moderate levels of hepatic fibrosis as measured by liver biopsy, to reduce the need for doing biopsy.[14,15]

As of 2012, almost one-fifth of CHeCS patients had been diagnosed “late,” that is, with advanced liver disease concurrent with their initial HCV diagnosis, despite many years of prior engagement with the health care system; these patients had high rates of hospitalization (59%) and mortality (33%), highlighting the severe consequences of missed opportunities for earlier diagnosis.[16] In this analysis, advanced liver disease was defined as having one or more of the following: a biopsy indicating cirrhosis; FIB-4 score >5.88 predictive of biopsy stage F4[15]; or an *ICD-9* or procedure code indicating liver transplant, hepatocellular carcinoma (HCC), liver failure, hepatic encephalopathy, portal hypertension, esophageal varices, other gastroesophageal hemorrhage, ascites, or other sequelae of chronic liver disease. Among data from biopsied CHeCS patients before 2013, analyses showed that about two-thirds of currently active patients would meet criteria for urgent HCV treatment based on American Association for the Study of Liver Diseases/Infectious Diseases Society of America/International Antiviral Society-USA guidelines,[17] and among these patients, there were substantial rates of disease progression to hepatic decompensation, HCC, liver transplant, and death.[18] Patients and their providers may not be aware of advanced liver fibrosis despite the substantial (29%) prevalence as measured by biopsy, noninvasive markers, and/or diagnoses consistent with cirrhosis or hepatic decompensation.[19] Of note, in this study only 46% of even those patients with biopsy-confirmed cirrhosis were not

assigned *ICD-9* codes for cirrhosis, suggesting that cirrhosis may be underdocumented and underdiagnosed.

Given the inherent challenge in identifying when patients with longstanding HCV infection become cirrhotic and at risk for HCC, CHeCS investigators devised a simple clinical scoring system to estimate the 1-, 3-, and 5-year probabilities of developing HCC before and after SVR, based on APRI score, age, sex, alcohol abuse history, and prior (interferon-based) treatment history (Xing and colleagues 2017).[20] Patients who were male, were older (ie, aged >50 years), had higher APRI scores (including post-SVR values), had a history of alcohol abuse, and had a history of interferon treatment failure had the highest probability of HCC.[20] In an earlier CHeCS study, failure of interferon-based therapy was associated with increased rates of HCC.[21] The same study found that those with genotype 3 did have a greater risk of HCC than those with genotype 1. SVR appeared to induce long-term regression of hepatic fibrosis based on FIB-4 scores collected over 10 years; patients receiving no treatment or with treatment failure had progressive increases in FIB-4 scores.[22] In this study, men and patients with HCV genotype 3 infections had higher FIB-4 scores than women or patients with HCV genotype 2 infections. Additional studies found that highly elevated ALT (>2 times the upper limit of normal) was significantly more common in patients with genotype 3 and that FIB-4 scores indicative of cirrhosis were most common in the patients with genotypes 4 and 6, with overall cohort distribution of genotypes and subtypes more variable than suggested by previous national-level estimates and single-center studies.[23]

Nonhepatic Comorbidities

Substantial comorbidities, such as kidney disease,[24] diabetes, and coronary artery disease, [25,26] are likely to affect clinical course and may complicate HCV care management. Although the prevalence of severe renal impairment and diagnosed extrahepatic manifestations was low (about 2%), mild to moderate renal impairment was common (about 33%) in patients with HCV, across all levels of hepatic fibrosis.[24] In addition to the expected excess of liver cancers that was 48.6 times higher than the national average, investigators found significantly elevated age-adjusted incidence of pancreatic, kidney, non-Hodgkin lymphoma, and lung cancers in the CHeCS cohort over a comparable nationally representative comparison group.[27]

Contributions to National Disease Estimates

Significant national disease estimates incorporated data from CHeCS and other sources. Based on information from CHeCS and the National Health and Nutrition Examination Study as well as other sources, investigators were able to estimate the rate at which US residents were tested for HCV, referred for specialist care, treated and achieved SVR before the availability of DAAs.[28] Only about half of the chronic cases had been identified, and of these, only 5% to 6% were successfully treated. CHeCS data were also used to estimate the number of people infected with HCV in 2014 in the United States who would qualify for immediate treatment according to 2014 treatment guidance, finding that as many as 813,000 persons nationwide were in need of urgent treatment.[29] Similar analyses determined that immediate treatment of HCV-infected patients with moderate and advanced fibrosis appears

to be cost-effective, and immediate treatment of even patients with minimal or no fibrosis can be cost-effective.[30]

Access to Care

Analyses of access to care from the pre-DAA era showed that only 57% had ever received liver specialist care with high variation in rates by health system[31] and that many patients lacked recommended protection against other forms of viral hepatitis: 35% had been neither tested nor vaccinated for hepatitis A and 32% neither tested nor vaccinated for hepatitis B.[32] Recently updated data as of 2016 showed that a little over one-half the cohort appeared susceptible to either infection.[33]

Patient Survey

The extensive cross-sectional survey of almost 5000 HCV-infected CHeCS patients during 2010 to 2011 provided a novel source of data on risk behaviors, physical and psychosocial functioning, demographics, and clinical history. About half of surveyed patients reported past injection drug use, 34% were current smokers, 18% had abused alcohol in the previous year, 30% met criteria for current depression, and one-quarter were in poor physical health.[5] Achieving a 12-week SVR was found to be protective for depression. A substantial proportion reported having been tested for HCV only after clinical indications that their infection had progressed and became symptomatic.[34]

Current Analyses

Current analyses focus on the impact of and access to new therapies and comorbidities, including their reversal with current effective therapies. For instance, to test the hypothesis that antiviral treatment may have an impact on long-term extrahepatic outcomes, investigators examined incidence of type 2 diabetes and found that SVR significantly reduces this incidence in analyses controlling for demographic and clinical factors, including race and body mass index.[25] In addition, among patients under treatment for type 2 diabetes, the achievement of SVR led to reduced rates of end-stage renal disease and acute coronary syndrome, and to temporary reductions in hemoglobin A1c levels.[26] Additional studies are examining health outcomes by survey self-reported behavioral risks and measures of physical and psychosocial functioning[35] as well as describing substantial rates of depression and alcohol misuse whether measured by *ICD-9* code or survey.[36] In 2016, the prevalence of HBV current coinfection (1.1%) and past resolved infection (40% of tested, 15% of entire cohort as more than half were untested) was similar to other US studies, with no hepatitis B reactivation identified in almost 700 (31%) of CHeCS patients with a history of (mostly resolved) hepatitis B infection who were treated with DAAs.[37] Despite improvements in care, barriers remain: black race, Medicaid coverage, and care at one of the sites were associated with noninitiation of DAA therapy during 2014 to 2015.[38] In addition, the prevalence of consistent surveillance for HCC (screening at least every 6 months) in cirrhotic patients with chronic HCV infection remains low (11.8%) (Abara WE, Spradling P, Zhong Y, et al. Surveillance for hepatocellular carcinoma in a cohort of cirrhotic patients chronically infected with hepatitis C virus, 2006–2014. Submitted for publication, 2018).

Current Hepatitis C Virus Cohort Status

From more than 2.8 million adult patients seen during 2006 to 2013 at participating sites, 23,603 were identified that met criteria for potential inclusion before chart review. Patients whose chronic HCV status was ruled out or could not be confirmed were excluded.[1–3] Of 17,893 patients finally included in the cohort, comparing the 12465 (70%) sampled for chart review with the 5428 (30%) whose charts were not abstracted showed that differences were small and not statistically significant. Among those sampled for data abstraction, 61% were men, mean year of birth was 1961, and mean FIB-4 score was 3.3; among those not sampled and abstracted, 60% were men, mean year of birth was 1956, and mean FIB-4 score was 3.4.

As of the beginning of 2016, cohort patients had been observed for an average of 6 years and 22% (3871) had died, ranging from 13% to 31% by site; most deaths were among those born between 1945 and 1964 (Table 1). Three percent (555) had undergone liver transplant (ranging from 3% to 4% by site). Nineteen percent (3378) of the total cohorthadachievedSVRafterantiviraltherapy.AchievementofSVRvariedwidelybydemographic factors, with lowest rates among those with lowest census tract estimated income, nonprivate insurance, black race, and the oldest age group (born ≤1944). The 50% (8906) of cohort patients who remained infected because of either no treatment or treatment failure had a mean observation time of 7.5 years (see Table 1). In Table 2, the demographic and clinical characteristics of patients who were still infected by the beginning of 2016 are shown by study site. Mean age of these patients ranged from 50 to 61 years. Overall, 6.9% (612) patients had received a diagnosis of decompensated cirrhosis or portal hypertension, 1.3% (115) had received a diagnosis of HCC, and 44.5% (3963) had a prior unsuccessful treatment attempt. Of these persons still infected at last follow-up, 27.0% (2400) had no health system visits during 2014 to 2016 after the availability of DAA therapy, but did not appear in the death registries.

DISCUSSION

CHeCS has provided a wealth of highly impactful information about HCV epidemiology, outcomes such as long-term liver disease, comorbidities, and mortality, and access to and outcomes of treatment with a current cohort of almost 18,000 persons diagnosed with chronic HCV. As one measure of CHeCS's impact, per the Science Citation Index, CHeCS publications have been referenced more than 900 times by others. An early analysis of viral hepatitis testing in the health system populations from which CHeCS was drawn[8] was used as a basis for the Centers for Disease Control and Prevention (CDC) and U.S. Public Health Service *Recommendations for One-time Screening of Persons Born 1945 to 1965*, critical to the cost-effectiveness analyses that underlay and supported those recommendations. CHeCS contributions to national disease estimates include developing a national HCV care cascade to quantify the number of persons getting diagnosed and moving along the care continuum and the numerous benefits of treatment.[28] In addition, data from CHeCS were used to estimate the number of persons infected with HCV in the United States who would qualify for immediate treatment according to 2014 treatment guidance,[29] which were shared with the Center for Medicare and Medicaid Services that, in turn, advised and urged state partners to expand treatment. CHeCS studies were used for the National Academies of Sciences,

Engineering, and Medicine report on the feasibility of eliminating HCV in the United States.[39] Cost-effectiveness analyses, including data from CHeCS, are increasingly cited in the argument to treat all hepatitis C patients, including those early in infection or with no or minimal liver disease.[30] CHeCS analyses indicating that more than 100,000 HCV-infected persons per year are dying, 75% with evidence of moderate or worse liver disease,[6] dramatically changed perceptions of HCV as a benign chronic condition and highlighted the urgent need for treatment.

The lack of attribution of HCV to liver-related deaths on death certificates is particularly striking in light of current findings that mortality attributed to chronic HCV infection on death certificates recently surpassed mortality attributable to 60 other nationally notifiable infectious conditions in the United States combined.[40] In current data as of January 1, 2016, among more than 17,000 HCV cohort patients observed for an average of 6 years, the authors found that 1 in 5 had died or had achieved treatment-induced SVR, which varied widely by demographic factors, and 1 of every 2 cohort patients remained infected (ranging by site from 43% to 62%).

Although CHeCS is among the largest long-term observational studies to date of persons with chronic viral hepatitis infection, this analysis has several unavoidable limitations. Some comorbid conditions that confer high priority for HCV treatment, such as debilitating fatigue, could not be included because of lack of reliable measures. Differential mortalities by site may be due to greater number of patients with end-stage liver disease in the 2 sites with transplant centers, in Detroit and Pennsylvania. Also, results from these large integrated health systems may not be generalizable to other populations. Demographic differences between abstracted and nonabstracted cohort patients were modest, so sampling of charts for full supplementary data abstraction due to budget constraints in later years was unlikely to have introduced bias. All electronically derived data (eg, mortality dates and causes, health system laboratory results, and hospitalizations) were available for both abstracted and nonabstracted patients.

Current cohort characteristics may be rapidly changing in the current era of highly effective therapy. More than one-quarter of patients who remained HCV infected at last health system visit had no further follow-up visits during 2014 to 2016 after the availability of DAA therapy, which may indicate loss to follow-up and missed opportunity for treatment, although in some cases could also indicate change to a new health provider. Efforts are underway within all 4 health systems to reengage patients who appear lost to follow-up.

Among current cohort patients, clinical management may be complicated for the 3% who had been transplanted, and the 7% of untreated, still-infected patients who had already progressed to hepatic decompensation. Among these patients alive and without previous SVR, almost one-half had experienced treatment failure, primarily with prior interferon-based therapy, which some data suggest may confer additional morbidity risk.[20] At least 30% of cohort patients are at a high priority for treatment as defined by laboratory-derived fibrosis score; of the small proportion (20%) who underwent liver biopsy, more than 50% were stage F2 or higher. Treatment will be essential for these remaining cohort patients to avoid the substantial morbidity and mortality demonstrated in this cohort in the era before

the widespread availability of highly effective DAA therapy. More than one-half the cohort was without documented protection from hepatitis A or B infection, with potentially serious consequences in the event of exposure. CHeCS data are continuing to provide unique, population-based insights into the changing dynamics of hepatitis C in the United States.

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KEY POINTS

- The Chronic Hepatitis Cohort Study (CHeCS) was established to improve the understanding of chronic viral hepatitis in “real-world” US patients and the impact of their screening, care, and treatment.
- This report summarizes CHeCS results to date and updates the clinical experience among more than 17,000 current HCV cohort patients.
- The more than 40 CHeCS publications have described access to care, status of hepatic disease, and comorbidities in this population. Current activities center on comorbidities, impact, and access to new therapies.

Table 1

Chronic Hepatitis Cohort Study hepatitis C virus cohort patient status on January 1, 2016

	Overall	Died (All Cause)	Liver Transplant[a]	Achieved SVR[b]	Still HCV Infected	HCV Status Cannot Be Determined
	N (Column%)	n *(row%)*	n *(row%)*	n *(row%)*	n *(row%)*	n *(row%)*
Variables	**17,893**	**3871 (21.6%)**	**555 (3.1%)**	**3378 (18.9%)**	**8906 (49.8%)**	**1183 (6.6%)**
Birth year						
1965 through 1984	5985 (33.4)	1054 (17.6)	190 (3.2)	1231 (20.6)	3129 (52.3)	381 (6.4)
1945 through 1964	6682 (37.3)	1882 (28.2)	292 (4.4)	1305 (19.5)	2933 (43.9)	270 (4.0)
Birth year ≤1944	1467 (8.2)	657 (44.8)	46 (3.1)	180 (12.3)	550 (37.5)	34 (2.3)
Gender						
Male	10,862 (60.7)	2684 (24.7)	420 (3.9)	1941 (17.9)	5108 (47.0)	709 (6.5)
Female	7031 (39.3)	1187 (16.9)	135 (1.9)	1437 (20.4)	3798 (54.0)	474 (6.7)
Race						
Non-Hispanic white	11,308 (63.2)	2109 (18.7)	357 (3.2)	2403 (21.3)	5518 (48.8)	921 (8.1)
Non-Hispanic black	4022 (22.5)	1247 (31.0)	115 (2.9)	544 (13.5)	1982 (49.3)	134(3.3)
Other	2563 (14.3)	515 (20.1)	83 (3.2)	431 (16.8)	1406 (54.9)	128 (5.0)
Insurance status						
Private	8824 (49.3)	1362 (15.4)	179 (2.0)	1959 (22.2)	4641 (52.6)	683 (7.7)
Medicaid	2054(11.5)	499 (24.3)	38 (1.9)	208 (10.1)	1165 (56.7)	144 (7.0)
Medicare	5538 (31.0)	1612 (29.1)	326 (5.9)	1054 (19.0)	2365 (42.7)	181 (3.3)
Other/unknown	1477 (8.3)	398 (26.9)	12 (0.8)	157 (10.6)	735 (49.8)	175 (11.8)
Income (estimated census tract geocode)						

	Overall	Died (All Cause)	Liver Transplant[a]	Achieved SVR[b]	Still HCV Infected	HCV Status Cannot Be Determined
	N (Column%)	n *(row%)*	n *(row%)*	n *(row%)*	n *(row%)*	n *(row%)*
Variables	**17,893**	**3871 (21.6%)**	**555 (3.1%)**	**3378 (18.9%)**	**8906 (49.8%)**	**1183 (6.6%)**
<$30,000	4258 (23.8)	1172 (27.5)	80 (1.9)	578 (13.6)	2137 (50.2)	291 (6.8)
$30,000 to <50,00C	8201 (45.8)	1700 (20.7)	237 (2.9)	1585 (19.3)	4110 (50.1)	569 (6.9)
≥$50,000	4850 (27.1)	872 (18.0)	212 (4.4)	1159 (23.9)	2345 (48.4)	262 (5.4)
Not available	584 (3.3)	127 (21.7)	26 (4.5)	56 (9.6)	314(53.8)	61 (10.4)
Study site						
Portland, OR	4329 (24.2)	577 (13.3)	53 (1.2)	809 (18.7)	2633 (60.8)	257 (5.9)
Honolulu, HI	1564 (8.7)	222 (14.2)	25(1.6)	292 (18.7)	969 (62.0)	56 (3.6)
Detroit, MI	7402 (41.4)	2288 (30.9)	423 (5.7)	1345 (18.2)	3158 (42.7)	188 (2.5)
Danville, PA	4598 (25.7)	784(17.1)	54 (1.2)	932 (20.3)	2146 (46.7)	682 (14.8)
Observation time in years[c]						
Median	5.9	4.8	6.6	2.9	7.5	4.4
Range	0.0–25.4	0.0–20.5	0.0–20.5	0.0–25.4	0.0–23.0	0.0–22.8
Mean (SE)	6.8 (0.0)	5.8 (0.1)	7.6 (0.2)	4.6 (0.1)	8.2 (0.1)	5.5 (0.1)

[a] Liver transplant status identified by at least one of the following *ICD-9* diagnosis or procedure codes: 996.82, 50.5, 50.51, 50.59, 47135, or 47136.

[b] Defined as having more negative HCV RNA tests at least 12 wk after treatment as evidenced by available EHR laboratory data or provider documentation.

[c] Observation defined as time from the first diagnosis of hepatitis C within the health system to the date of the first endpoint (death, liver transplant, SVR) or last encounter in the health system.

Table 2

Demographic and rliniral characteristics of natients still infected with hepatitis C virus in 2016 [a] by Chronic Hepatitis Cohort Study site

Variables	Overall N = 8906 (Column %)	CHeCS Study Site			
		Portland, OR n = 2633 (29.6%)	Honolulu, HI n = 969 (10.9%)	Detroit, MI n = 3158 (35.4%)	Danville, PA n = 2146 (24.1%)
Age (median on 1/1/16)	58.8	58.8	61.0	61.4	49.9
Birth year					
1965 through 1984	2294 (25.8)	573 (21.8)	114(11.8)	475 (15.0)	1132 (52.7)
1945 through 1964	6062 (68.1)	1949 (74.0)	779 (80.4)	2365 (74.9)	969 (45.2)
Birth year ≤1944	550 (6.2)	111 (4.2)	76 (7.8)	318 (10.1)	45 (2.1)
Male	5108 (57.4)	1556 (59.1)	610 (63.0)	1867 (59.1)	1075 (50.1)
Previous treatment attempt [b]					
Yes	3963 (44.5)	945 (35.9)	466 (48.1)	1430 (45.3)	1122 (52.3)
No	4943 (55.5)	1688 (64.1)	503 (51.9)	1728 (54.7)	1024 (47.7)
Genotype distribution					
Genotype 1	4010 (77.2)	980 (69.7)	533 (74.5)	1735 (84.6)	762 (74.8)
Genotype 2	565 (10.9)	219 (15.6)	94 (13.1)	135 (6.6)	117 (11.5)
Genotype 3	498 (9.6)	176 (12.5)	79 (11.0)	146 (7.1)	97 (9.5)
Genotype 4, 5, or 6	97 (1.9)	30 (2.1)	8 (1.1)	33 (1.6)	26 (2.6)
Genotype mixed	22 (0.4)	2(0.1)	1 (0.1)	2 (0.1)	17 (1.7)
Had liver biopsy during 2004–15	1764(19.8)	741 (28.1)	226 (23.3)	418 (13.2)	379 (17.7)
Latest biopsy stage distribution [c]					

Variables	Overall N = 8906 (Column %)	CHeCS Study Site			
		Portland, OR n = 2633 (29.6%)	Honolulu, HI n = 969 (10.9%)	Detroit, MI n = 3158 (35.4%)	Danville, PA n = 2146 (24.1%)
Metavir F0/1	724(45.5)	248 (34.8)	60 (28.3)	201 (57.8)	215 (67.4)
Metavir F2	518 (32.6)	332 (46.6)	68 (32.1)	85 (24.4)	33 (10.3)
Metavir F3	186 (11.7)	91 (12.8)	42 (19.8)	35 (10.1)	18 (5.6)
Metavir F4	163 (10.2)	41 (5.8)	42 (19.8)	27 (7.8)	53 (16.6)
Latest FIB-4, score category[11,12,d] during 2004–2015					
<1.6	4005 (49.2)	1088 (46.1)	359 (41.1)	1204 (42.4)	1354 (65.8)
1.6–2.5	1855 (22.8)	630 (26.7)	224 (25.6)	712 (25.1)	289 (14.0)
2.5 to <3.25	720 (8.9)	194 (8.2)	94 (10.8)	306 (10.8)	126 (6.1)
≥3.25	1554(19.1)	450 (19.1)	197 (22.5)	618 (21.8)	289 (14.0)
Latest APRI score category[11,12,e] during 2004–2015					
<1.5	6852 (82.3)	1971 (82.2)	710 (80.2)	2362 (79.4)	1809 (87.3)
≥1.5	1476 (17.7)	426 (17.8)	175 (19.8)	611 (20.6)	264(12.7)
Viral load from latest test[f]					
<1.5 million	2249 (54.0)	378 (39.6)	306 (61.3)	813 (52.9)	752 (63.9)
>1.5 to <6 million	1192 (28.6)	312 (32.7)	132 (26.5)	453 (29.5)	295 (25.1)
≥6 million	726 (17.4)	265 (27.7)	61 (12.2)	271 (17.6)	129 (11.0)
Decompensated cirrhosis or portal hypertension[g]					
Yes	612 (6.9)	183 (7.0)	70 (7.2)	237 (7.5)	122 (5.7)
No	8294 (93.1)	2450 (93.0)	899 (92.8)	2921 (92.5)	2024 (94.3)

Variables	Overall N = 8906 (Column %)	CHeCS Study Site			
		Portland, OR n = 2633 (29.6%)	Honolulu, HI n = 969 (10.9%)	Detroit, MI n = 3158 (35.4%)	Danville, PA n = 2146 (24.1%)
HCC[h]					
Yes	115 (1.3)	35 (1.3)	12 (1.2)	50 (1.6)	18 (0.8)
No	8791 (98.7)	2598 (98.7)	957 (98.8)	3108 (98.4)	2128 (99.2)
Platelet count below normal[i]					
Yes	1872 (21.6)	466 (18.3)	167 (17.8)	827 (27.0)	412 (19.5)
No	6790 (78.4)	2079 (81.7)	772 (82.2)	2240 (73.0)	1699 (80.5)
HIV coinfection	293 (3.3)	65 (2.5)	17 (1.8)	150 (4.7)	61 (2.8)
Ever had hepatitis B surface antigen or HBV DNA test	5847 (74.4)	1682 (72.8)	708 (85.9)	2007 (71.7)	1450 (75.1)
Among those tested, one or more tests positive	94(1.3)	25(1.5)	2 (0.2)	38 (1.9)	29 (2.0)
Charlson comorbidity score (excluding liver diseases)[j]					
0	5824 (65.4)	1710 (64.9)	652 (67.3)	1969 (62.3)	1493 (69.6)
1	1347 (15.1)	445 (16.9)	153 (15.8)	409 (13.0)	340 (15.8)
2 or more	1735 (19.5)	478 (18.2)	164(16.9)	780 (24.7)	313 (14.6)

[a] Among patients alive but without documented liver transplant or SVR as of January 1, 2015.

[b] Treatment defined as having been prescribed at least 1 day of antiviral therapy.

[c] Biopsy reports from different scoring systems (International Association for the Study of the Liver, Batts-Ludwig, Metavir, Ishak, Knodell, Scheuer) were mapped to an 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.[1]

[d] Among 8928 (93%) patients with available laboratory data for calculation of FIB-4, excluding laboratory results during hospitalization.

[e] AST/platelet ratio, calculated among 8829 (93%) patients with available same-day AST and platelet count data, excluding laboratory results during hospitalization.

[f] Among 6631 (70%) patients with available viral load data.

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[g] The development of decompensated cirrhosis was ascertained based on the presence of an *ICD-9* diagnosis or procedure codes in the 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), liver failure with hepato-renal syndrome (572.4).

[h] Primary HCC as determined from validated tumor registry reports.[27]

[i] Among 9289 (97%) patients with available platelet count data.

[j] Calculated from standard diagnosis codes, while omitting liver diseases in inpatient, outpatient, and claims data[5] during the last 2 y of observation before January 1, 2015.

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