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Late diagnosis of hepatitis C virus infection in the Chronic Hepatitis Cohort Study (CHeCS): missed opportunities for intervention

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Abstract

To determine stage of liver disease at initial diagnosis of hepatitis C virus (HCV) infection, we analyzed data from the Chronic Hepatitis Cohort Study (CHeCS), a large US observational study. We examined the temporal relationships of initial HCV infection diagnosis with cirrhosis--defined by liver biopsy or mean FIB-4 score >5.88--and time to onset of cirrhotic decompensation in electronic medical records. We determined time in health system prior to HCV diagnosis and rates of hospitalization and death following HCV diagnosis. Of 14,717 patients with chronic HCV seen during 2006–2011, 6,166 (42%) had a definable time of initial HCV diagnosis. Of these, 1,056 (17%) patients met our definition for “late diagnosis” with either cirrhosis concurrent with initial HCV diagnosis (n=550), a first diagnosis of hepatic decompensation before or within 12 months after initial HCV diagnosis (n=506), or both (n=314). Patients with late diagnosis had an average of 6 years in the health system before their HCV diagnosis. In a comparison with patients without late diagnosis, hospitalization (59% vs 35%) and death (33% vs 9%) were more frequent among patients with late diagnosis. Among all who died, mean (median) time from initial HCV diagnosis to death was 4.8 (4.2) years.

Conclusion—Many CHeCS patients had advanced liver disease concurrent with their initial HCV diagnosis despite many years of engagement with the health care system, and these patients had high rates of hospitalization and mortality.

Keywords

hepatitis C; late diagnosis; cirrhosis; hepatic decompensation; hospitalization; mortality

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Because hepatitis C virus (HCV) infection is usually asymptomatic until the development of liver failure, early identification of these asymptomatic persons is needed for timely interventions to avert progression to severe liver disease and death. While hepatitis C care is rapidly evolving with increasingly more effective and better-tolerated antiviral therapies, treatment after the onset of cirrhosis and its complications may still involve higher cost and persistence of liver injury. Data from recent large studies estimate that, of over 3 million persons with chronic HCV infection in what Dr. Howard Koh, current US Assistant Secretary for Health has dubbed the “Silent Epidemic,” only about 50% have been tested and identified as infected, 40% have received specialist evaluation, about 7–11% treated, and about 5–6% treated successfully[1]. In 2012 CDC recommended a one-time test for all persons born between 1945 and 1965[2], the group that accounts for approximately three-fourths of all HCV infections in the United States as a cost-beneficial approach to improve identification of the many persons not otherwise targeted for testing as the result of previously established risk-based testing strategies.

We sought to determine the frequency and outcomes of late diagnosis of HCV infection after the onset of advanced liver disease prior to 2012 in the Chronic Hepatitis Cohort Study (CHeCS), a large observational cohort study of persons with chronic viral hepatitis who receive care at four US healthcare systems.

Methods

CHeCS is a ‘dynamic’ multi-center observational study conducted at four large, integrated health care systems located in the United States, and represents a geographically, ethnically and clinically diverse cohort of patients with chronic hepatitis B and C. The data collected are solely based on routine clinical care and thus representative of the uncontrolled health care environment of the “real world” clinical setting. Criteria for inclusion and composition of the CHeCS cohort have been summarized in a previous report[3]. Briefly, the initial cohort was created based on analysis of electronic health records (EHRs) and administrative data of over 2.3 million patients 18 years or older who had a clinical service (i.e., outpatient or inpatient, emergency department, or laboratory visit) provided between 2006–2011 at one of four sites: Geisinger Health System, Danville, PA; Henry Ford Health System, Detroit, MI; Kaiser Permanente-Northwest, Portland, OR; and Kaiser Permanente-Honolulu, Hawaii. The study protocol was reviewed and approved by an institutional review board at each participating site.

Patients were considered confirmed chronic hepatitis C cases based principally upon laboratory and secondarily on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) criteria. Electronic health record (EHR) data and administrative data were collected for each cohort patient and supplemented with individual chart review by trained data abstractors, who also reviewed and verified chronic HCV infection from EHR data. Data collected included patient demographics, medical encounters, treatment data, and laboratory, radiology, and biopsy results. Complete observation time for each patient was determined to be time from first evidence of HCV infection in the EHR, including retrospective data prior to 2006, until last health system encounter or 31 December 2011.

Patient classification and study definitions

The date of initial HCV diagnosis was defined as the earliest of: electronic health record report of a positive laboratory test; an HCV-related diagnostic or procedure code or patient report via survey. To allow for adequate observation time, our analyses were restricted to patients who had their initial HCV diagnosis at least 6 months after their first visit to the health system and who were observed for at least 12 months after diagnosis. A few patients with HBV co-infection were excluded from this analysis to minimize confounding.

We determined the proportion of patients with an initial HCV infection diagnosis concurrent with cirrhosis, defined as having a liver biopsy indicating cirrhosis or mean Fibrosis-4 (FIB-4) score[4–9] >5.88 [9] during the period of time from 3 months prior to 12 months post initial HCV diagnosis. A mean fibrosis score ≤1.21 during this period was considered to indicate no cirrhosis, and mean scores >1.21 but ≤ 5.88 were considered mainly to include those with mild to moderate fibrosis but not sufficiently characterized for analysis[8,9].

We also determined the proportion of patients with first diagnoses indicating hepatic decompensation (ICD9 or procedure codes indicating liver transplant, hepatocellular carcinoma, liver failure, hepatic encephalopathy, portal hypertension, bleeding esophageal varices, other gastroesophageal hemorrhage, ascites, and other sequelae of chronic liver disease [codes listed in Table 1 footnote])[10] by proximity to time of initial HCV diagnosis. We compared self-reported location and reasons for initial HCV testing by group, among those patients who were sampled for survey and responded. CHeCS survey methods and participation rates have been described previously [3,11].

Patients were considered to have had “late” diagnosis with cirrhosis or its complications at initial HCV diagnosis by having either cirrhosis concurrent with initial HCV diagnosis, a cirrhotic decompensation diagnostic code prior to or concurrent with initial HCV diagnosis, or both. We compared demographic factors among patients with and without late diagnosis (Table 1). We also compared all-cause hospitalization and mortality outcomes and length of contact with the healthcare system prior to diagnosis among those with and without late diagnosis (Table 2).

Statistical methods

We performed multivariate analysis to compare categories of demographic and clinical variables. SAS (SAS Institute Inc. Cary, North Carolina, USA) procedure GENMOD was applied to calculate odds ratios adjusted for birth cohort, sex, race, Hispanic ethnicity, geocensus tract estimated household income and health insurance with 95% confidence intervals and Wald Chi-Square test to calculate p-values, and for tests of trend the Cochran-Armitage trend test was applied (Table 1). For comparison of outcomes among patients with versus without late diagnosis, we calculated incidence ratios for hospitalization and death with 95% confidence intervals and p-value with Chi-Square test; SAS procedure FREQ was applied for comparisons of percentages and procedure TTEST was used to compare means and p-values (Table 2).

Results

Of 14,717 patients with one or more visits to a CHeCS clinic during 2006–2011, 6,166 (42%) met the inclusion criteria for observation bracketing the time of initial HCV diagnosis. Of these, 3,925 (64%) had either a liver biopsy or laboratory data available for calculation of a FIB-4 score (alanine aminotransferase [ALT], aspartate aminotransferase [AST], platelet count and patient age[4–9]) during the period of time from 3 months prior to 12 months post initial HCV diagnosis. Among these patients, 707 (18%) had cirrhosis concurrent with initial HCV diagnosis, 1,362 (35%) had no cirrhosis at the time of initial HCV diagnosis, and 1856 (47%) were "indeterminate" (no biopsy and 1.21> FIB-4 <5.88) at that time. In a sub-analysis limited to the 2767 (70%) of the analytic cohort born from 1945–1965, 790 (29%) had cirrhosis at initial diagnosis.

Eleven percent (663) of the 6,166 patients meeting analysis inclusion criteria had their first diagnosis of hepatic decompensation either prior to or within 12 months of their initial HCV diagnosis. An additional 406 (7%) developed hepatic decompensation within one to five years, and 326 (5%) had such a diagnosis >5 years after their initial HCV diagnosis. A sub-analysis restricted to the 4294 patients born between 1945–1965, for whom routine one-time HCV screening is now recommended by CDC[2] and the US Preventive Services Task Force[12], revealed nearly identical percentages with cirrhosis or hepatic decompensation within one to five years and >5 years after their initial HCV diagnosis.

Among the 6,166 HCV cohort members with data available surrounding the time of initial HCV diagnosis, 1,056 (17%) met the combined definition of late diagnosis, having either cirrhosis concurrent with initial HCV diagnosis (n=550), a first diagnosis of hepatic decompensation before or within 12 months after initial HCV diagnosis (n=506), or both (n=314). Demographic groups with the highest proportions of late diagnosis included persons with: public insurance including Medicare (26%) or Medicaid (16%) vs private insurance (13%), African-American race (25%), and older age (7% among those born after 1965, 19% among those born 1945–1965, and 29% among those born before 1945, t-test for trend p<.001) (Table 1).

Patients with late diagnosis had significantly worse health outcomes than those without: 59% (n=619) vs 35% (n=1799, chi-square p<.0001) experienced hospitalization after HCV diagnosis, and those with "late" diagnosis had hospitalization rates 3 times higher with four times more hospital days (Table 2). Deaths during the six-year period 2006–2011 were more frequent among those with vs without "late" diagnosis: 33% (n=346) vs 9% (n=480, chi-square p<.001), with a mortality incidence rate four times higher (Table 2). Among all who died, mean (median) time from initial HCV diagnosis to death was 4.8 (4.2) years.

The vast majority (90%, n=953) of patients with "late" diagnosis had inpatient or outpatient visits to the health care system a year or more prior to their initial HCV diagnosis, with an average of 6 years in the health system prior to diagnosis. These patients had a median of 10 inpatient or outpatient healthcare visits during this time, including hospitalizations for 24% (n=256, with a mean of 2 hospitalizations), and emergency department visits for 47% (n=494, with a mean of 5 visits). Only 18% of those with late diagnosis and 10% of those

without late diagnosis had a prior ALT elevation more than a year before their initial HCV diagnoses; among these patients a mean of 4 (median 3) years had elapsed between the first elevation in aminotransferases and HCV testing (Table 2).

Survey data were available for 2,410 (39%) of 6173 patients. We compared patients' responses regarding initial reasons and locations for HCV testing by time from HCV diagnosis to onset of cirrhosis or decompensation. A majority (60.4%) of all patients had initial testing performed in physician's offices, with those having onset of severe liver disease less than vs. more than two years after initial HCV diagnosis being less likely to be tested in inpatient or emergency settings (7.1% vs 16.3%). CDC risk indications[11] were the reason for testing for 13.1% of all patients, compared to clinical indications[11] for 26.0%.

Discussion

A sizeable minority of CHeCS patients had advanced liver disease concurrent with their initial HCV diagnosis despite on average more than five years of prior engagement with the healthcare systems, and these patients had a substantially higher incidence of hospitalization and mortality. Our mean (median) of 4.8 (4.2) years from HCV diagnosis to death among all those who died is consistent with a report from the Massachusetts Department of Health showing that 8,373 (11%) of 76,122 HCV cases reported between 1992–2009 died during this period, with a median of three years from first report (not including any time from diagnosis to report) to death[13]. It is striking that a quarter of African-Americans as well as those on Medicare were diagnosed late; differential delay in HCV diagnosis by race has been found in other populations as well[14].

Diagnosis codes selected to define "late diagnosis" were of sufficient severity to correspond with decompensated liver disease[10] rather than mild to moderate liver disease. This highly conservative definition of late diagnosis also likely included some patients with advanced HCV infection in the "without late diagnosis" group, particularly the 7% with a decompensation diagnosis within one to five years, and possibly the additional 5% with such a diagnosis more than five years after their initial HCV diagnosis.

We selected FIB-4 as a marker for cirrhosis in patients without biopsy data based on previous CHeCS studies showing FIB-4 to be the biomarker correlated best with fibrosis on liver biopsy[8,9]. Fibromarkers are of current interest to clinicians because they are simple to calculate and readily available during usual patient care, and are useful to screen patients with high values needing biopsy and clinical follow-up and to provide a system for categorizing stage of illness. Apart from use in a clinical setting, the markers can be easily obtained in longitudinal studies for studying disease progression and treatment effects in cohorts outside of clinical trials. Our use of a conservative FIB-4 cutoff level for "cirrhosis" could be anticipated to miss some patients with advanced fibrosis, thus leading to an underestimate of the proportion of patients with cirrhosis at diagnosis.

Additional limitations of the analysis include possible missed detection of outside-system HCV diagnoses among patients not surveyed, despite lengthy observation time from first health system encounter to first EHR evidence of HCV diagnosis. Just over one-half of

CHeCS patients with chronic HCV infection were diagnosed prior to observation and could not be included in this analysis. Patients with late diagnosis had many outpatient visits during the pre-diagnosis period, with significantly more hospitalizations and emergency room visits than those without late diagnosis, yet were less likely to report having been tested in those settings. While these are mainly persons with access to care in large health care systems, this finding would tend to bias against the results found that African-Americans, persons with lower income and those with public (Medicaid or Medicare) or no insurance were more likely to be diagnosed later.

This analysis underscores the benefits of screening to identify and treat patients prior to the development of advanced liver disease and provides insight into venues where screening for viral hepatitis can be improved to avoid missed opportunities for identification of patients with chronic HCV infection, particularly those who go on to develop serious sequelae. The availability of better tolerated and more efficacious therapies of shorter duration, including combinations of direct acting antivirals without interferon and ribavirin, may enhance opportunities for intervention in both the early and late diagnosis groups, particularly therapies that may be effective even in the setting of cirrhosis. These findings suggest missed opportunities for diagnosis and therapeutic intervention before the onset of severe liver disease when treatment involves higher cost and/or diminished health benefits.

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List of abbreviations

HCV
hepatitis C virus

CDC
Centers for Disease Control and Prevention

CHeCS
Chronic Hepatitis Cohort Study

electronic health record
EHR

FIB-4

Fibrosis-4 score

ICD9
International Classification of Diseases, Ninth Revision, Clinical Modification

ALT
alanine aminotransferase

AST
aspartate aminotransferase

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Table 1

Demographics among patients with and without "late" diagnosis of HCV[*]

Demographics		With late diagnosis[*] n=1056 (17%) n (%)	Without late diagnosis n=5117 (83%) n (%)	OR (95%CI)	[**] p-value
Age at HCV diagnosis	Mean (median)	54 (54)	47 (48)		
Birth cohort	Born after 1965	83 (6.6)	1181 (93.4)	0.49 (0.37–0.65)	<0.001
	Born during1945–1965	794 (18.5)	3500 (81.5)	ref.	
	Born before 1945	179 (29.1)	436 (70.9)	1.34 (1.05–1.72)	0.02 2-sided t-test for trend, p<.0001
Sex	Female	684 (19.4)	2881 (80.8)	ref.	
	Male	372 (14.3)	2236 (85.7)	1.15 (0.98–1.35)	0.084
Race	White	522 (13.8)	3255 (86.2)	ref.	
	Black	399 (25.0)	1200 (75.0)	1.52 (1.26–1.82)	<0.001
	Asian	30 (14.4)	179 (85.6)	0.85 (0.54–1.34)	0.849
	Hawaiian/PI	19 (16.0)	100 (84.0)	0.93 (0.51–1.69)	0.614
	American Indian/Alaska Native	12 (16.7)	60 (83.3)	1.67 (0.82–3.39)	0.213
	Unknown	74 (18.6)	323 (81.4)	1.45 (1.01–2.06)	0.116
Hispanic ethnicity		32 (15.2)	179 (84.8)	0.8 (0.49–1.28)	0.355
Household income[†]	<15,000	112 (14)	661 (86)	1.35 (0.99–1.83)	0.059
	15,000–29,000	250 (22)	909 (78)	1.08 (0.84–1.39)	0.554
	30,000–49,000	443 (12)	2167 (88)	1.03 (0.84–1.28)	0.758
	50,000–75,000	198 (16)	1040 (84)	ref.	
	>75,000	40 (14)	239 (86)	0.80 (0.53–1.21)	0.292
Insurance	None	40 (20.4)	156 (79.6)	1.47 (0.95–2.27)	0.082
	Medicaid	152 (16.3)	783 (83.7)	1.44 (1.14–1.83)	0.003
	Medicare only	154 (24.5)	475 (75.5)	1.32 (1.03–1.70)	0.028
	Medicare Plus	250 (26.3)	701 (73.7)	1.49 (1.19–1.86)	0.001
	Private	437 (13.2)	2883 (86.8)	ref.	

[*] Late diagnosis defined as having either a biopsy indicating fibrosis or a FIB-4 score >5.88 [8,9] during the time period from three months prior up to twelve months post initial HCV diagnosis, or: during the time period from prior to up to twelve months post initial HCV diagnosis having an ICD9 diagnosis or procedure code indicating liver transplant (996.82, 50.5, 50.51, 50.59, 47135, 47136), hepatocellular carcinoma (155.0 155.1 155.2), liver failure (572.4), hepatic encephalopathy (572.2), portal hypertension (572.3, 37140, 37160, 37180, 37181, 37182, 37183), esophageal varices (456.0, 456.20, 43204, 43205, 43243, 43244, 43400, 43401, 42.91, 44.91, 96.06), other gastroesophageal hemorrhage (530.7, 530.82, 578.0, 578.1, 578.9), ascites (789.5, 789.59, 49080, 49081, 54.91), or other sequelae of chronic liver disease (572.8).

** SAS (SAS Institute Inc. Cary, North Carolina, USA) procedure GENMOD was applied to calculate odds ratios adjusted for birth cohort, sex, race, Hispanic ethnicity, geocensus tract estimated household income and health insurance with 95% confidence intervals and Wald Chi-Square test to calculate p-values. For the test of trend a two-sided Cochran-Armitage trend test was applied.

† Yearly household income estimated from census tract geocode

Table 2

Outcomes and prior healthcare among patients with and without "late" diagnosis of HCV*

		With late diagnosis* n=1056 (17%)	Without late diagnosis n=5117 (83%)	Incidence Risk Ratio (95% Confidence Interval)	p-value**
Years of observation after initial HCV dx	Mean (median)	5.7 (5.0)	4.7 (3.7)		p<.001
Hospitalization					
Hospitalized at least once after initial HCV diagnosis	n (%)	619 (58%)	1,799 (35.2%)		p<.001
Total hospitalizations after HCV diagnosis	n/100 person-years (p-y)	64.1	19.7	3.2 (3.1–3.4)	p<.001
Total hospital days after HCV diagnosis	n/100 p-y	403.1	102.9	3.9 (3.9–4.0)	p<.001
Deaths during the six-year period 2006–11	n (%)	346 (32.8%)	480 (9.4%)		p<.001
	n/100 p-y	6.7	1.8	3.8 (3.2–4.2)	p<.001
Years from HCV diagnosis to death	mean (median)	3.4 (2.2)	5.8 (5.5)		p<.001
Prior healthcare					
Years in health system prior to HCV diagnosis	mean (median)	5.7 (5.0)	4.7 (3.7)		p< 0.001
Any inpatient or outpatient healthcare system visit more than one year prior to HCV diagnosis	n (%)	953 (90%)	4,428 (87%)		p < 0.001
Ever emergency room visit in this period	n (%)	494(47%)	1,565 (31%)		p < 0.001
Number of emergency room visits	mean (median)	4.6 (2)	3.2 (2)		p< 0.001
Ever hospitalized in this period	n (%)	256 (24%)	783 (15%)		p< 0.001
Number of hospitalizations	mean (median)	2.4 (1)	1.7 (1)		p< 0.001
ALT ever elevated in this period	n (%)	194 (18%)	496 (10%)		p < 0.001
Years from first ALT elevation to HCV dx	mean (median)	4.1 (3.2)	3.8 (3.0)		p < 0.001

* Late diagnosis defined as having either a biopsy indicating fibrosis or a FIB-4 score >5.88 [8,9] during the time period from three months prior up to twelve months post initial HCV diagnosis, or: during the time period from prior to up to twelve months post initial HCV diagnosis having an ICD9 diagnosis or procedure code indicating liver transplant (996.82, 50.5, 50.51, 50.59, 47135, 47136), hepatocellular carcinoma (155.0 155.1 155.2), liver failure (572.4), hepatic encephalopathy (572.2), portal hypertension (572.3, 37140, 37160, 37180, 37181, 37182, 37183), esophageal varices (456.0, 456.20, 43204, 43205, 43243, 43244, 43400, 43401, 42.91, 44.91, 96.06), other gastroesophageal hemorrhage (530.7, 530.82, 578.0, 578.1, 578.9), ascites (789.5, 789.59, 49080, 49081, 54.91), or other sequelae of chronic liver disease (572.8).

** For comparison of rates of hospitalization and death per person-year incidence ratios were calculated with 95% confidence intervals and p-value with Chi-Square test. SAS procedure FREQ was applied for comparisons of percentages and procedure TTEST was used to compare means and p-values.