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Mortality among Persons in Care with Hepatitis C Virus Infection--The Chronic Hepatitis Cohort Study (CHeCS), 2006–2010

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Summary: Using US health system data from an observational cohort study, HCV is under-documented on death certificates. Only 19% of those with known HCV infection had HCV listed on their death certificate although two-thirds had pre-mortem indications of chronic liver disease.

Abstract:

Background: Numbers of deaths in hepatitis C virus (HCV)-infected persons recorded on US death certificates have been increasing, but actual rates and causes of death in them have not been well elucidated.

Methods: Disease-specific, liver- and non-liver-related, mortality for HCV-infected patients in an observational cohort study, the Chronic Hepatitis Cohort Study (CHeCS) at four US health care systems, were compared with Multiple Cause of Death (MCOD) data in 12 million death certificates in 2006-2010. Pre-mortem diagnoses, liver biopsies, and FIB-4 scores (a non-invasive measure of liver damage) were examined.

Results: Of 2,143,369 adult patients seen at CHeCS sites in 2006-2010, 11,703 (0.5%) had diagnosed chronic HCV infection, and 1,590 (14%) died. CHeCS decedents were born from 1945-1965 (75%), white (50%), and male (68%); mean age of death was 59 years, 15 years younger than MCOD deaths. The age-adjusted mortality rate for liver disease in CHeCS was twelve times higher than the MCOD rate. Before death, 63% had medical record evidence of chronic liver disease, 76% had elevated FIB-4 scores, and of those biopsied 70% had moderate or worse liver fibrosis. However, only 19% of all CHeCS decedents and only 30% of those with recorded liver disease had HCV listed on their death certificates.

Conclusions: HCV infection is greatly under-documented on death certificates. The 16,622 persons with HCV listed in 2010 may represent only one-fifth of about 80,000 HCV-infected persons dying that year, at least two-thirds of whom (53,000 patients) would have pre-mortem indications of chronic liver disease.

Background:

Chronic hepatitis C virus (HCV) infection is estimated to infect 2.7-3.9 million persons in the United States.[1] Recent research indicates that the reported numbers of deaths recorded with HCV on the death certificate have been increasing and now supersede HIV infection as a cause of death.[2,3] Of deaths from 1999-2007 with HCV infection listed as a primary or underlying cause of death, 57% had chronic liver disease as a cause [2] but many also had extra-hepatic manifestations.[4] Presence of HCV may potentially accelerate the disease process in heart disease,[5-7] diabetes,[8,9] various malignancies,[10,11] and genitourinary conditions.[12,13]

In this study, we looked at hepatic and extra-hepatic causes of death for a cohort of hepatitis C-infected patients in care in the United States. We used data from a large ongoing cohort study of over 11,000 HCV patients at four US health systems. Our goal was to analyze rates and causes of death for those with known pre-mortem HCV infection and compare these to national death data.

Methods:

Algorithms for inclusion in the Chronic Hepatitis Cohort Study (CHeCS) were developed and applied to the electronic health record with the goal of capturing the greatest number of verifiable chronic hepatitis C cases. Criteria for inclusion and composition of the CHeCS cohort have been summarized in a previous report.[14] Briefly, the initial cohort was created based on analysis of electronic health records (EHRs) and administrative data of adult patients who had a service provided between January 1, 2006 and December 31, 2010 at one of four sites: Geisinger Health System, Danville, PA (GHS); Henry Ford Health System, Detroit, MI (HFHS); Kaiser Permanente-Northwest, Portland, OR (KPNW); and Kaiser Permanente-Honolulu, Hawaii (KPHI).

Patients were considered confirmed cases based upon laboratory and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) criteria. Trained data abstractors reviewed and verified chronic HCV infection from EHR data. EHR and administrative data were collected for each cohort patient and supplemented with individual chart review by trained data abstractors. Data collected included patient demographics, medical encounters, laboratory results, and deaths from all causes that occurred or were reported to the health system facilities during 2006-2010. Each health system compared cohort patient records to the National Death Index (NDI), Social Security Death Index (SSDI), or electronic state death registries to enhance death ascertainment through 2010; the KPNW site was able to compare records through 2009. All three systems are central databases that provide similar information, although from different sources. The SSDI obtains information from the Social Security Administration whereas the NDI confirms mortality through a standardized process from state vital statistics offices.[15] The KPNW site matched data with the electronic state death registry and HFHS and GHS matched their data to the SSDI. The KPHI site matched their data against the NDI. All sites downloaded causes of death available in those data sources for the matches that were identified; the downloaded information was believed to be a complete list of all causes contained on the death certificate. Cause of death information was not available for patients who were known to be deceased via information obtained from the electronic health record or through survey contact attempts but without a match in the utilized death indices. The proportion of deaths with missing data was analyzed by site.

As patients were selected for cohort eligibility based on health service encounters from 2006-2010, the start of observation for death rate calculation was January 1, 2006. Observation time was truncated at the earlier of December 31, 2010 or date of death. Demographics, including age, race, sex, site, household income based upon geo-coded addresses from census tract data, and insurance status, were analyzed. Because the size of the cohort fluctuates based on new entrants and losses (death or loss to follow-up), we calculated average cohort size for the five years of observation as denominator for analyses.

To calculate all-cause death rates among persons in the CHeCS hepatitis C cohort, we divided the number of deaths by the total number of adult patients seen at the four participating CHeCS health systems during 2006-2010. We calculated disease-specific death rates by grouping mortality codes from the ICD, Tenth Revision (ICD-10) which is used in the United States to record data about cause of death from death certificates,[16] and compared them to the US Multiple-Cause-of-Death (MCOD) database using the following fifteen categories: HCV, liver-related non-alcohol, alcohol-related liver disease, liver cancer, other hepatitis, HIV, non-liver cancer, circulatory, respiratory, diabetes, genitourinary, injuries/trauma, mental/behavioral disorders, digestive (non-hepatic), other (including eye, ear, musculoskeletal, gynecologic, endocrine-non-diabetes, etc). We coded HCV infection as B18.2 and B17.1; Liver-related non-alcohol as K71-K77; Alcohol-related liver disease as K70; liver cancer as C22 and D37.6; Other hepatitis as B94.2 and B15-B19 (except B16, and B18.1); and Non-liver cancer as C00-C97 (excluding C22) and D40-D48.

For the comparative analysis of CHeCS rates with MCOD rates, we standardized CHeCS all-cause and disease-specific death rates to the age distribution of the U.S. Census population in 2008, since it was the median year of our study period. For the calculation of MCOD rates, using the same time period, age criteria, and ICD-10 groupings, we classified a death as belonging to that group if the associated ICD-10 codes were listed as the underlying cause of death or one of the multiple causes of death in the record axis. MCOD mortality rates were calculated by dividing the average number of deaths for each category by the average number of persons in the U.S. Census population. The statistical difference between CHeCS and MCOD mortality rates was assessed using the Pearson Chi-Square test, and a p-value of less than 0.05 was considered statistically significant. To examine the likelihood of having a death with the group-specific category listed as a cause of death in the CHeCS cohort relative to the general U.S. population, we calculated the relative risk and 95% confidence intervals (CI) for each of the fifteen groups. Mean age for CHeCS and MCOD data was also calculated by cause of death with the statistical significance noted by each category.

We analyzed the EHRs of cases to determine if they had ICD-9-CM diagnosis codes indicating chronic liver disease. Cases who had at least one ICD-9-CM code for liver transplantation, hepatocellular carcinoma, liver failure, hepatic encephalopathy, portal hypertension, esophageal varices, ascites, gastrointestinal hemorrhage, or other sequelae of chronic liver disease during a health service encounter from 2006-2010 were considered to have chronic liver disease.

In addition to ICD-9 codes, we examined liver biopsy rates and results in the CHeCS HCV patients. As most infected persons do not have a biopsy, we also analyzed pre-mortem FIB-4 scores, calculated from aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and patient age, to validate our definition of chronic liver disease. [17, 18] These indices are a validated noninvasive serum- based biomarker of liver fibrosis, and a score of 2.0 or higher identifies 88% of those with at least moderate fibrosis or a higher stage of liver fibrosis. [19] For all deaths, we selected the FIB-4 score closest to death and if more than one score was present on the date closest to death, the mean FIB-4 score of that date was calculated.

Results:

Of 2,143,369 adult patients in four participating health systems with encounters during 2006-2010, 12,531 met the chronic hepatitis C cohort criteria; for purposes of calculating rates in this dynamic cohort, the mean cohort size over the five years was 11,703 patients. Of persons with HCV, 1,590 (14%) died during 2006-2010. Of all decedents with HCV, 953 (60%) were aged 45-59; 50% were white; 1068 (68%) were men and 675 (45%) were middle income (Table 1). Seventy-five percent (1,195) of deaths among those with HCV were among patients born from 1945-1965. Overall, cause of death information was missing from 10% (154/1,590) of cases: 3% (6/208) from KPNW, 3% (4/124) from KPHI, 12% (119/1024) from HFHS, and 11% (25/235) from GHS.

The age-adjusted CHeCS mortality rate in these HCV-infected patients was 12,854 per 100,000 persons compared to the MCOD mortality rate of 1,046 per 100,000 persons. The age-adjusted mortality rate for all liver disease categories in CHeCS was higher than the national MCOD rate; for example, alcohol-related liver disease was 6 times greater while other hepatitis was 86 times higher than the national rate (Table 2). The most frequently cited cause of death was non-alcohol related liver disease; it was listed for 32% of all deaths (513 /1,590). The CHeCS mortality rate among persons with non-alcohol related liver disease was 669 vs. 51 per 100,000 for alcohol-related liver disease. In addition, all age-adjusted death rates from extra-hepatic causes were higher than the national MCOD rates; the highest rates were seen with genitourinary causes, mental/behavioral disorders, and diabetes (Table 2). Of 1,590 deaths, only 12 (1%) were due to intentional self-harm, 93 (6%) due to sepsis due to any cause, and none were due to overdose/poisonings.

Despite confirmed chronic HCV infection, only 19% (306/1,590) had HCV infection listed on the death certificate. HCV was not listed for the majority of deaths across disease categories whether liver or non-liver related. The total number of deaths listed as liver-related was 47% (752/1,590), but of these, only 41% (306/752) had HCV listed as a cause of death. By type of liver-related death, HCV was listed for 36% (183/513) of those with non-alcohol related liver disease, 27% (13/49) of those with alcohol-related liver disease, 31% (53/169) of those with liver cancer, and only 9% (6/70) of those with "other" hepatitis (Figure; Table 3). Even among 156 (10%) of decedents who had a liver transplant before death, HCV was only listed on 46 (29%) of death certificates.

We looked at all ICD-9-CM diagnosis and procedure codes in the EHR prior to death for all cases. Of the 1,590 CHeCS patients with HCV who died, 1,002 (63%) had pre-mortem ICD-9-CM diagnosis codes indicating chronic liver disease. Also, of the 1,590 deaths, 76% had a FIB-4 score greater than 2.0 (moderate fibrosis) and 60% had a FIB-4 score greater than 4.0 (cirrhosis). Comparing liver and non-liver related causes of death, 752 (46%) had a liver-related cause of death with a median FIB-4 score of 7.98 -- 94% > 2.0, 79% > 4.0-- indicating moderate fibrosis or cirrhosis respectively. Of 838 (53%)

with no liver-related cause of death, median FIB-4 score was 3.11 also indicative of advanced liver fibrosis. [30]

To further determine the level of liver disease in this population, we examined biopsy stage for those with a previous liver biopsy. Although biopsy results were only available for 17% of cases (266/1,590), performed a mean of 4.3 years before death, 185 (70%) had a biopsy stage equal to or greater than 2 (moderate fibrosis). Of those with a biopsy, 57% (152/266) had liver disease documented on their death certificates vs. 43% (114/266) who died of non-liver causes.

The overall mean age of death was 59 for CHeCS cases and 74 years for MCOD cases and was statistically significantly lower for all disease categories (Table 4). Those with non-hepatic causes of death in the CHeCS population had a mean age of death that was 11-19 years younger when compared to national data, with the exception of the few (40) patients with HIV- and HCV coinfection whose age was slightly lower (52 vs 48 yrs respectively) at time of death.

We conducted a review of the records from one site to confirm the accuracy of our results. We verified our cause of death data completeness against the original death certificate obtained from the EHR for all 84 patients from Henry Ford Health System who died of liver-related illness without HCV listed as a cause of death. Among these patients we found 99% (83/84) agreement between the EHR records and death certificates regarding cause of death information.

Discussion:

Data from this study suggests a much greater role of HCV on mortality in the United States than has been previously understood based on analyses of death certificate data. The data in this paper document and contradict prevalent views that, perhaps because of its long incubation period (30 years), HCV infection is an indolent infection that is not of urgent concern. Originally intended as a study of causes of death in approximately 1,600 well-characterized decedent HCV patients in the CHeCS, we

found that only 19% had HCV listed on their death certificates, and only in 30% of death certificates in which liver disease had been noted. Even among the 156 HCV-infected CHeCS patients who had a liver transplant before death, only 46 (29%) had had HCV noted on their death certificate. As there were 16,622 death certificates in the US listing HCV as an underlying or contributing cause of death in 2010, we extrapolate that only one-fifth of those with HCV who die are having HCV recorded on their death certificates. Thus, our analysis suggests that at least 80,000 persons with HCV may have actually died in 2010. Given that 63% of the well-characterized CHeCS patients had medical records (ICD 9 codes) indicating pre-mortem liver disease--and 76% had FIB4 scores indicative of substantial or more liver damage—this suggests that total US deaths contributed to by HCV total at least 53,000.

Our results may be a conservative estimate as recent studies indicate that only about half of all HCV-infected persons have been diagnosed with the infection.[20-22] Further, approximately 50% of all deaths in those with known HCV had liver disease listed on their death certificates. Thus, even if we exclude other diseases associated with HCV infection such as diabetes and non-Hodgkin lymphoma,[23-26] it appears that most are dying not just with HCV but in possibly from HCV. These considerations are especially important because identifying and treating HCV patients in an era of rapidly evolving and effective, curative therapies could have a major public health impact.

Often, the high mortality and burden from HCV infection are minimized because other non-HCV-related causes of death are considered to be more proximal or immediate reasons. For example, in a recent survey of New York resident physicians, over-documentation of cardiopulmonary causes of death and other inaccuracies-- both knowing and unavoidable--were reported; those surveyed believe that the current cause-of-death reporting system is generally inaccurate.[27] This study also indicates that in the HCV-infected population over 70% had pre-mortem liver disease by ICD-9-CM electronic hospital record coding, liver biopsy, or FIB-4 score. So, in addition to under-recording HCV infection, even verified pre-mortem liver disease is also under-recorded, Further, whether the death was considered HCV or non-

HCV-related, mean age of death in HCV-infected persons (59 years) was 15 years younger than for all-cause mortality in the general population (74 years), a finding similar to previous research. [28]

The mortality rate estimated from this analysis was twelve times higher than the general population; this is much higher than the two-to-five times higher mortality rates in HCV-infected vs uninfected persons seen in other studies. [29-32] Even with significant underreporting, persons who died in our cohort with non-alcohol related liver disease had 24 times the risk of death and those with liver cancer had almost 29 times the risk of death compared to over 12 million deaths in the age-matched general population. This effect was seen with extra-hepatic causes as well: compared to the general population, cases had three times the rate of injuries and genitourinary causes of death, ten times the rate of HIV, and twice the rate of mental/behavioral disorders. Other researchers have attributed higher rates of injuries/trauma as well as mental/behavioral disorders to lifestyle factors, including a previous history of substance abuse. [7,33] However, results from our death certificate data show that only 1% of CHeCS patients had suicide listed, 6% had sepsis, and none died of overdose or poisoning.

Our data represent findings from four health care systems in the United States and thus have a number of limitations. While two sites have transplant centers associated with them, we cannot measure how many patients are "attracted" to these medical centers because they have tertiary care facilities vs the fact that they are in the catchment area of these large integrated health systems. However, as only a minority (10%) of the CHECS decedents were seen at the transplant centers, these patients do not affect the overall picture. Level of care provided at a particular site should not affect the low rate of death certificate recordings of HCV (29%). Due to the variability in the definition of ICD-10 mortality codes used for chronic liver disease, we compared the codes that we used for our definition of chronic liver disease with a previously established definition. We found that for both definitions, 46% of cases were identified as having liver-related causes of death.[34] This concordance further substantiates our findings.

An additional limitation is the use of the FIB-4 index as a measure of chronic liver disease; although validated, changes to liver enzymes and platelet count may be affected by non-liver related conditions such as infection or malignancy. However, the overlap between liver disease defined by ICD-9-CM codes and FIB-4 scores correlates with the findings using the ICD-10 mortality codes indicating that there is truly underlying liver disease in patients dying with and from HCV.

In summary, our analysis of a known HCV-infected cohort demonstrates that less than one-fifth of deaths in HCV-infected persons are coded as having HCV; this indicates a significant underestimation of the number of deaths among people with HCV and the true medical and public health impact of HCV. In this analysis, we have tried to be clear about the difference between dying *with* HCV and dying *from* HCV, but both represent a substantial public health burden. For purposes of public health, policy planning, disease modeling, and medical care, this is a huge burden that should be reported and hopefully spur public health action as curative, all-oral therapies are becoming available to treat HCV. Addressing the true impact of HCV, including of those chronically infected with HCV who are not utilizing health services, will be essential to appropriately respond to this epidemic. [35]

NOTES

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Appendix:

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Figure legend. All Causes of Death with HCV Listed as a Contributing Cause of Death in CHeCS Chronic HCV Patients, 2006-2010

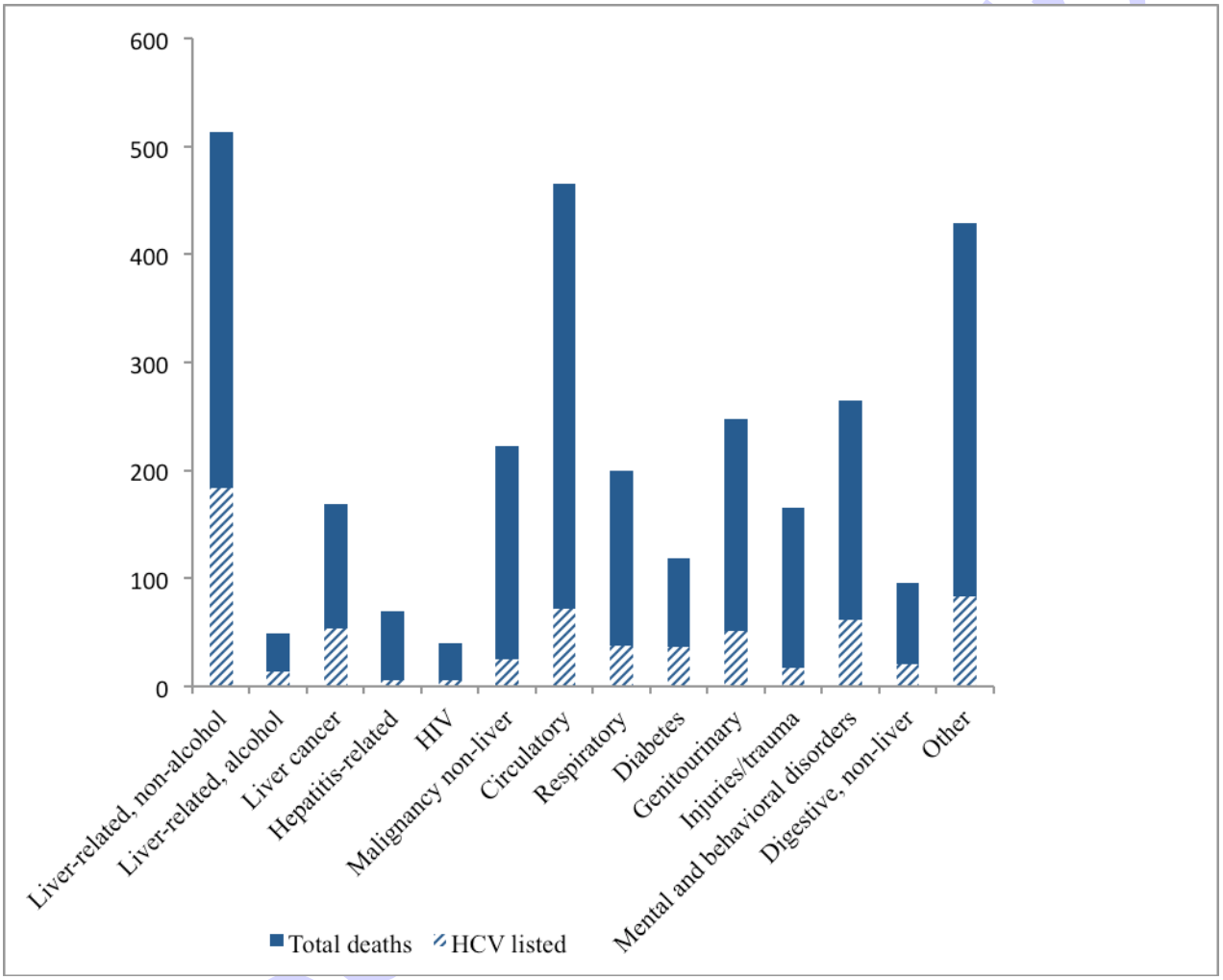

Table 1: Demographics of Deaths among 1,590 CHeCS Chronic HCV Patients, 2006-2010

Characteristic	Number (%)	
Age, years		
18-29	15 (1)	
30-44	68 (4)	
45-59	953 (60)	
60-74	420 (26)	
75+	134 (8)	
Age by Birth Year		
Born before 1945	335 (21)	
Born from 1945- 1965		1195 (75)
Born after 1965	60 (4)	
Sex		
Male	1086 (68)	
Female	504 (32)	
Race		
White	790 (50)	
Black	551 (35)	
Hispanic	35 (2)	
Asian	38 (2)	
Hawaiian/PI	18 (1)	
NH- Unknown	152 (10)	
Site		
Kaiser Permanente- Northwest (Portland, Oregon)		208 (13)
Kaiser Permanente- Honolulu, Hawaii		124 (8)
Henry Ford Health System, Detroit, Michigan		1024 (64)
Geisinger Health System- Danville, Pennsylvania		235 (15)
Median household income		
<15,000	64 (4)	
>=15,000-30,000	401 (27)	
>=30,000-<50,000		675 (45)
>=50,000-<75,000		298 (20)
>=75,000	69 (5)	
Insurance status		
Medicaid	226 (15)	
Medicare only	62 (4)	
Medicare Plus	566 (37)	
Private	550 (36)	
None		113 (7)

Table 2: Comparison of Age-Adjusted Mortality Rates in the 1,590 CHeCS Chronic HCV Patients Compared with the Multiple Cause of Death (MCOD) Data (N= 12,249,640) by Causes of Death, 2006-2010

	Annual Mortality Rate per 100,000 Person-Years		
Cause of Death	**CHeCS**	**MCOD**	**Relative risk (95% CI)***
HCV	414.3	6.8	61.4 (60.4-62.3)
Liver-related, non-alcohol	669.3	27.4	24.4 (24.2-24.6)
Liver-related, alcohol	50.9	8.2	6.20 (6.1-6.3)
Liver cancer	250.0	8.7	28.80 (28.3-29.2)
Hepatitis-related (unspecified)	72.4	0.8	86.10 (82.4-90.1)
HIV	50.6	5.2	9.80 (9.6-10.0)
Cancer, except liver cancer	344.6	269.2	1.28 (1.28-1.29)
Circulatory	827.2	582.2	1.42 (1.42-1.43)
Respiratory	370.8	268.1	1.38 (1.38-1.39)
Diabetes	179.0	101.1	1.77 (1.76-1.78)
Genitourinary	435.3	116.1	3.75 (3.73-3.77)
Injuries/Trauma	289.2	99.9	2.90 (2.88-2.91)
Mental and behavioral disorders	426.1	189.0	2.25 (2.25-2.26)
Digestive (extra-hepatic)	160.0	51.0	3.14 (3.12-3.16)
Other	680.9	361.9	1.88 (1.88-1.89)

+Total number of deaths equals 1,590. Cases could have more than one listed cause of death, so total will be greater than 1,590. A mean mortality rate from 2006-2010 was calculated for CHeCS and MCOD data. Data was age-standardized to the census population in 2008.
*All p values <.0001

Table 3: All Causes of Death with HCV Listed as a Contributing Cause of Death in the CHeCS Chronic HCV Patients, 2006-2010

Cause of Death (CHeCs patients)	Total deaths	HCV listed on death certificate (%)
Liver-related, non-alcohol	513	183 (36)
Liver-related, alcohol	49	13 (27)
Liver cancer	169	53 (31)
Hepatitis-related	70	6 (9)
HIV	40	5 (13)
Cancer, except liver cancer	222	25 (11)
Circulatory	465	72 (15)
Respiratory	200	38 (19)
Diabetes	118	36 (31)
Genitourinary	248	51 (21)
Injuries/Trauma	165	17 (101)
Mental and behavioral disorders	265	62 (23)
Digestive (extra-hepatic)	96	20 (21)
Other	429	83 (19)

Table 4: Comparison of Mean Age in Years for CHeCS Chronic HCV Patients and the MCOD Data, by Causes of Death, 2006-2010

	Mean age, years		
Cause of Death	**CHeCS**	**MCOD**	**P value**
Overall	59	74	0.0001
HCV	58	57	0.046
Liver-related, non-alcohol	57	63	0.0001
Liver-related, alcohol	54	56	0.01
Liver cancer	60	68	0.0001
Hepatitis-related	56	59	0.029
HIV	52	48	0.0006
Cancer, except liver cancer	61	72	0.0001
Circulatory	61	77	0.0001
Respiratory	61	77	0.0001
Diabetes	59	74	0.0001
Genitourinary	60	77	0.0001
Injuries/Trauma	54	57	0.0001
Mental and behavioral disorders	57	76	0.0001
Digestive (extra-hepatic)	59	75	0.0001
Other	59	76	0.0001