The persistence of underreporting of hepatitis C as an underlying or contributing cause of death, 2011-2017

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Abstract

Using electronic health records, we found that hepatitis C reporting on death certificates of 2,901 HCV-infected decedents from four U.S. healthcare organizations during 2011-2017 was documented in only 50% of decedents with hepatocellular carcinoma and less than half with decompensated cirrhosis. National figures likely underestimate the U.S. HCV mortality burden.

Key words: hepatitis C, multiple cause of death, underreporting

Background

In 2018, there were 15,713 hepatitis C-associated deaths reported in the United States [1]. U.S. mortality estimates are derived from death certificates and compiled nationally as multiple cause of death data [2,3]. Accordingly, accurate cause of death documentation on death certificates is essential for understanding the burden of a disease and for gauging the effectiveness of interventions to reduce its lethality. In a previous publication using U.S. healthcare data from 2006−2010, we found that hepatitis C was reported as an underlying or contributing cause of death in 19% of patients with identified hepatitis C virus (HCV) infection, and in only 30% of those with hepatitis C and advanced liver disease [4]. We hypothesized that increased provider awareness of hepatitis C since the initial study would result in more frequent death certificate reporting and sought to determine whether such a change occurred during 2011−2017.

Methods

Methods of data collection and inclusion criteria for patients with chronic hepatitis C in our cohort have been described [5]. The cohort is based on electronic health records (EHR) of adults who received services at the following health systems since 2006: Geisinger Health System (Pennsylvania); Henry Ford Health System (Michigan); Kaiser Permanente–Northwest (Oregon); and Kaiser Permanente–Honolulu (Hawaii). Patients were classified with hepatitis C based on positive HCV RNA tests and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. EHR data were supplemented with record reviews by trained abstractors to collect additional demographic and clinical information.

The study period for this analysis commenced on January 1, 2011 and ended on December 31, 2017 or date of death, whichever came first. For patients who entered care after January 1, 2011, follow-up

began at the date of first clinical service. Patients who died before January 1, 2011 and those with hepatitis B virus or human immunodeficiency infection were excluded from the analysis.

As previously, we examined causes of death from death certificates of HCV-infected decedents and the frequency that hepatitis C was documented as an underlying (i.e., initiated the train of events leading directly to death) or contributing (i.e., contributed to the fatal outcome) cause of death. We used groupings of ICD-10 codes to classify causes of death as in the previous analysis (**Supplement 1**) [4,6]. Decedents could be classified in more than one category if they had more than one cause of death. As a subanalysis, we examined coding in the EHR for severe liver disease (e.g., cirrhosis, hepatocellular carcinoma) and liver transplantation during clinical follow-up compared with hepatitis C coding on death certificates.

Cirrhosis status was defined according to several criteria we have validated and applied in previous analyses (see **Table 1** footnote) [5]. Hepatocellular carcinoma diagnoses were obtained from validated tumor registry data.

We calculated the proportion of deaths with hepatitis C (ICD-10 codes B 17.1, B18.2) listed as an underlying or contributing cause on the death certificate and compared differences in the frequency of reporting according to sociodemographic and sustained virologic response (SVR) status. The Chi-square statistic was used to examine differences in distribution frequencies and relative risks (RR) were determined according to the modified Poisson regression method. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 21,378 patients with hepatitis C were followed for a median of 6.0 years, during which 3,413 (16%) died after a median follow-up of 2.3 years; 2,901 (85%) of these decedents had death certificate data on cause of death available. The median age at death was 60.0 years. Overall, hepatitis C was listed as an underlying or contributing cause of death for 783 (27%) decedents, compared with 19% during 2006–2010. Among patients in the 2011–2017 cohort with documentation of liver-related/non-alcohol, liver-related/alcohol, or hepatocellular carcinoma as a cause of death, hepatitis C was listed on 52%, 49%, and 50% of death certificates, respectively. Hepatitis C was listed less frequently for non-liver-related causes, ranging from 9% of deaths from injuries/trauma to 36% of deaths from diabetes. Except for deaths from injuries/trauma, reported frequencies of hepatitis C on death certificates increased for all causes relative to 2006–2010, albeit marginally (**Table 1**).

Among patients with advanced liver disease according to the EHR, hepatitis C was listed on death certificates of 36% of patients with any cirrhosis, 43% of those with FIB-4 greater than 5.88, 44% of patients with decompensated cirrhosis, and 36% of decedents who had undergone liver transplantation (**Table 1**).

There were significant differences in comparative frequency of hepatitis C reporting on death certificates according to study site, race, annual income, and insurance status (P<.001 for all), but not sex or SVR status (**Supplemental Table 2**). Detroit was used as the reference site; hepatitis C was reported for 22% of deaths. In comparison, hepatitis C was reported for 45% [RR 1.77] of deaths at the Honolulu site, 44% [RR 1.73] of deaths at the Portland site, and 25% [RR 0.87] of deaths at the Danville site. The Kaiser Permanente-affiliated Honolulu and Portland sites were more likely to have hepatitis C reported as a cause or contributing factor of death while there was no significant difference in reporting between Detroit and Danville.

Relative to Whites, who had hepatitis C listed for 30% of deaths, reporting was significantly lower among Black decedents (19% [RR 0.62]), and higher among decedents of Hispanic (47% [RR 1.57]) and Asian (41% [RR 1.38]) descent. Compared to decedents with annual income <$15,000, the likelihood of reporting hepatitis C associated with death increased as income increased (23% [RR 1.86], 27% [RR 2.18], 30% [RR 2.38] for annual income ranges of $15,000-$30,000, >$30,000-$50,000, and >$50,000, respectively) (*P*<.001, Cochran-Armitage Trend Test). Finally, compared with Medicaid recipients (22%), decedents with Medicare plus supplemental coverage (35% [RR 1.58]) and those with private insurance (31% [RR 1.41]) were more likely to have hepatitis C reported on death certificates.

Discussion

During 2011−2017 there were several well-publicized advances with respect to hepatitis C control, including expanded testing recommendations [7], largescale national awareness campaigns [https//www.cdc.gov/knowmorehepatitis/about-kmh.htm], and the release of direct acting antiviral medications that cure HCV infection in nearly all recipients. Moreover, contemporaneous publications documented an increased mortality burden attributable to hepatitis C [8,9].

We found that hepatitis C reporting on death certificates of patients with identified HCV infection increased modestly during 2011−2017 from our earlier assessment (19% to 27% overall). Reporting increases were more pronounced among decedents with liver-related vs. non-liver-related causes of death. However, hepatitis C was listed as an underlying or contributing cause of death in only 50% of decedents with hepatocellular carcinoma, less than half of those with decompensated cirrhosis, and approximately one-third of patients who had liver transplantation. We also found that decedents less likely to have hepatitis C documented were Black, or had lower annual income, or were not privately insured, characteristics often associated with healthcare disparities. In such situations, reduced engagement with primary care or specialty providers might favor a hepatitis C diagnosis falling “under

the radar." In contrast, HCV-infected decedents with hepatitis C reported were more likely affiliated with the two Kaiser Permanente sites, which suggests that more cohesive and centralized care delivery systems (such as staff-model health maintenance organizations) may be better equipped to exercise policies and procedures that favor consistency and accuracy in reporting multiple causes of death.

An increase in the frequency of reporting of a diagnosis on death certificates does not necessarily indicate better reporting. Some conditions, such as heart disease, have been subject to overreporting [10]. With respect to hepatitis C, it is important to differentiate whether persons die *from* rather than *with* HCV infection. Hepatitis C is particularly challenging in this respect. Given the relationship of HCV infection with several extrahepatic conditions [11], infected persons may suffer from its effects in the absence of severe liver disease. With our HCV-infected cohort, however, it seems more plausible that underreporting was the prevailing tendency, since over half of decedents with indisputable end-stage liver disease had no death certificate documentation of hepatitis C.

Nonetheless, our findings may not be generalizable to hepatitis C decedents in other U.S. settings, and 15% of our decedents lacked death certificate data; thus, it is difficult to assess the degree to which underreporting of hepatitis C on a larger scale might affect national mortality estimates. However, given the geographic and demographic diversity of our cohort, it is likely that such underreporting is not uncommon and, consequently, that national figures underestimate the actual mortality burden of hepatitis C. Our data also lacked specificity regarding the setting in which deaths occurred (e.g., at home vs. facility); thus, we could not determine whether such factors might affect cause of death documentation.

Appeals to the medical community for measures to improve death certificate reporting are not new [12]. Ideally, such measures are applied at an early, formative stage of the medical career [13]. For practicing clinicians, the Centers for Disease Control and Prevention offers online training to improve reporting accuracy [https://www.cdc.gov/nchs/training/improving_cause_of_death_reporting]. Promotion and further study of such accuracy are critical to inform policies, target public health resources, and reduce disparities in mortality.

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Ethical Considerations: The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects. The study protocol was approved and is renewed annually by the institutional review board at each participating site.

CDC 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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References

[1] CDC. Viral Hepatitis Surveillance – United States. Available at https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm. Accessed October 2, 2020.

[2] CDC. Mortality data, underlying cause-of-death public-use data files. Available at: www.cdc.gov/nchs/products/elec_prods/subject/mortucd.htm.

[3] Centers for Disease Control and Prevention. National Death Index. Available at: http://www.cdc.gov/nchs/ndi.htm.

[4] Mahajan R, Xing J, Liu SJ, et al. Mortality among persons in care with hepatitis C virus infection--the Chronic Hepatitis Cohort Study (CHeCS), 2006-2010. *Clin Infect Dis* 2014;58:1055-61.

[5] Moorman AC, Rupp LB, Gordon SC, et al. 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. Infect Dis Clin North Am 2018;32:253-268.

[6] World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 2. 2. Geneva: WHO; 2004. p. 1-125.

[7] CDC. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *MMWR* 2012;61(RR04):1-18.

[8] Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; 156:271–278.

[9] Ly KN, Hughes EM, Jiles RB, et al. Rising Mortality Associated with Hepatitis C Virus in the United States, 2003–2013. *Clin Infect Dis* 2016;62(10):1287–1288.

[10] Al-Samarrai T, Madsen A, Zimmerman R, et al. Impact of a hospital-level intervention to reduce heart disease overreporting on leading causes of death. *Prev Chronic Dis* 2013;16:E77.

[11] Spearman CW, Dusheiko GM, Hellard M, et al. Hepatitis C. *Lancet* 2019;394:1451–66.

[12] Messite J, Stellman SD. Accuracy of death certificate completion: the need for formalized physician training. *JAMA* 1996;275:794–610.

[13] Hemans-Henry C, Greene CM, Koppaka R. Integrating Public health–oriented e-learning into graduate medical education. *Am J Public Health* 2012;102:S353–S356.

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Table 1. Frequency of hepatitis C listed as an underlying or contributing cause of death on death certificates according to cause of death, and liver disease status ascertained from electronic health records (EHR), among confirmed hepatitis C patients, Chronic Hepatitis Cohort Study, 2006–2010 and 2011–2017.

Cause of death according to death certificate	2006–2010 Mahajan et al.		2011–2017	
	Deaths (N)	n (% of N) with hepatitis C listed on death certificate	Deaths (N)	n (% of N) with hepatitis C listed on death certificate
All causes	1,590	302 (19)	2,901	783 (27)
Any liver-related cause	731	250 (34)	1,578	810 (51)
Liver-related, non-alcohol	513	185 (36)	999	520 (52)
Liver-related, alcohol	49	13 (27)	134	66 (49)
Hepatocellular carcinoma	169	52 (31)	445	224 (50)
Non-liver cancer	222	24 (11)	444	89 (20)
Circulatory	465	70 (15)	1,003	231 (23)
Respiratory	200	38 (19)	547	137 (25)
Diabetes	118	37 (31)	228	82 (36)
Genitourinary	248	52 (21)	503	126 (25)
Injuries/trauma	165	16 (10)	390	35 (9)
Mental/behavioral	265	61 (23)	650	208 (32)
Digestive (extrahepatic)	96	20 (21)	196	67 (34)
Others	429	82 (19)	922	267 (29)
Liver disease status according to EHR				
No evidence of cirrhosis			1,252	183 (15)
Cirrhosis* by any method of ascertainment			1,649	600 (36)
FIB-4 > 5.88			856	364 (43)
Diagnostic/procedure code for decompensation			1,013	443 (44)
Liver transplantation			190	69 (36)

See **Supplement 1** for International Classification of Diseases, Tenth Revision (ICD-10) codes used to classify causes of death.

*Cirrhosis was defined in the EHR according to any of the following criteria: a) Fibrosis-4 (FIB-4) score of >5.88; b) Liver biopsy equivalent to Metavir F4 or transient elastography results >12.5 kPa; or c) ICD-9-CM/ICD-10-CM and Current Procedural Terminology codes consistent with cirrhosis or hepatic decompensation (**Supplement 1**). These classification criteria for cirrhosis were not in use in the 2006-2010 analysis and thus cannot be applied to the **Table**.

Mahajan et al. *Clin Infect Dis* 2014;58:1055-61