Assessing the effect of potential reductions in non-hepatic mortality on the estimated cost-effectiveness of hepatitis C treatment in early stages of liver disease

Supplemental Appendix

Contents

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

Appendix A – Additional materials and methods

We adapted a cost-effectiveness model that was initially developed to address HCV treatment strategies in earlier stages of liver disease (Figure 1) [1]. Briefly, this modified Markov model computes life-cycle costs and quality-adjusted life-years for patients at different stages of liver disease, where liver disease is staged according to the Metavir fibrosis scale, where stage F0, F1, F2, F3, and F4 represent, respectively, no fibrosis, minimal/mild fibrosis, moderate fibrosis, severe fibrosis, and compensated cirrhosis. Incremental cost-effectiveness ratios (ICERs) were calculated comparing immediate treatment of a 55-year-old genotype 1 patient versus delaying treatment until liver disease progressed to the next Metavir stage. The three stages of liver disease that were considered for immediate treatment included no fibrosis (F0), minimal/mild fibrosis (F1), and moderate fibrosis (F2). Computed ICERs compared treatment at F0 versus treatment at F1, treatment at F1 (vs F2), and treatment at F2 (vs F3). HCV treatment was assumed to be a generalized regimen of direct-acting antivirals at a cost of $100,000 per patient. Patient population compartments included: diagnosed, first treatment, first failed treatment, second treatment, second failed treatment, recovered, decompensated cirrhosis, liver cancer, and liver transplant (main text, Figure 1).

We adapted the original cost-effectiveness model by stratifying non-hepatic mortality by HCV-infection status. We assumed that HCV infection increased all non-hepatic mortality by 117% in the base case. We assumed that successful treatment of HCV could reduce non-hepatic mortality between 0 and 100%, with a focus on 44% which was computed from three available sources in the literature [2-4] (i.e., a successful treatment reduced the 117% increase by 44%).

The entire base case parameterization of the cost-effectiveness model is presented in Table A1, additional details and source material for these parameters can be found in a previous study [1]. Disease progression rates were estimated from data collected by the Chronic Hepatitis Cohort Study (CHeCS) [5]. Age-based mortality probabilities with and without additional non-hepatic mortality are

presented in Table A2. Rates with additional non-hepatic mortality were further stratified by assumed percent reductions in mortality that followed successful HCV treatment. The increased values for the age-based mortality probabilities constituted the primary difference between the adapted model used in this study and the original model used in previous studies [1].

Table A1. Parameter values used in the cost-effectiveness model.

Parameter description	Relevant fibrosis or ESLD stage(s)	Values
State transitions		
Annual probability of a liver disease stage transition among patients with active HCV infection	0 to 1	0.063
	1 to 2	0.081
	2 to 3	0.089
	3 to 4	0.133
Probability of a successful treatment among treatment-eligible patients	0, 1, 2, 3, 4	0.900
Annual probability of developing ESLD for patients with HCV infection	4 to HCC	0.019
	4 to DC	0.046
Annual probability of developing ESLD for patients without HCV infection	4 to HCC	0.005
	4 to DC	0.004
Annual probability of liver transplant	HCC, DC to LT	0.023
Annual probability of liver-related death while in a given ESLD compartment	HCC (year 1)	0.707
	HCC (years 2+)	0.162
	DC (year 1)	0.281
	DC (years 2+)	0.281
	LT (year 1)	0.107
	LT (years 2+)	0.049
Increase in the probability of a non-liver related mortality among patients with active HCV infection	0, 1, 2, 3, 4, HCC, DC, LT	0.790
Discount rate		0.03
Costs		
Annual costs for non-treatment medical expenses among HCV+ patients	0, 1, 2, 3	503
	4	1,686
Annual costs for non-treatment medical expenses among HCV- patients	0, 1, 2, 3	407
	4	1,686
Annual costs for non-treatment medical expenses among patients with ESLD	HCC (year 1)	27,389
	HCC (year 2+)	25,196
	DC (year 1)	10,853
	DC (year 2+)	11,992
	LT (year 1)	147,935
	LT (year 2+)	9,977
Annual treatment costs	0, 1, 2, 3, 4	86,302
QALYs		
Annual QALYs among HCV-uninfected patients in a given liver disease stage	0, 1, 2, 3	0.88
	4	0.73
Multiplier for HCV-infected patients	0, 1, 2, 3	0.98
	4	0.98
Multiplier for patients with end stage liver disease	HCC	0.52
	DC	0.82
	LT	0.90

Abbreviations: HCV, hepatitis C virus; ESLD, end stage liver disease; HCC, hepatocellular carcinoma; DC, decompensated cirrhosis; and LT, liver transplant.

Table A2. Probabilities of non-hepatic mortality by age group.

Age Group	Probability [a.]	Non liver-related mortality increased by 1.17[b]	Proportional reduction in non-hepatic mortality following successful HCV treatment 0.00	0.44	1.00
18-20	0.000	0.001	0.001	0.001	0.000
20-25	0.001	0.002	0.002	0.001	0.001
26-30	0.001	0.002	0.002	0.002	0.001
31-35	0.001	0.002	0.002	0.002	0.001
36-40	0.001	0.003	0.003	0.002	0.001
41-45	0.002	0.004	0.004	0.003	0.002
46-50	0.003	0.007	0.007	0.005	0.003
51-55	0.005	0.011	0.011	0.008	0.005
56-60	0.007	0.015	0.015	0.012	0.007
60-65	0.010	0.022	0.022	0.017	0.010
66-70	0.015	0.033	0.033	0.025	0.015
71-75	0.024	0.051	0.051	0.039	0.024
76-80	0.038	0.082	0.082	0.062	0.038
81-85	0.062	0.135	0.135	0.103	0.062
86-90	0.107	0.231	0.231	0.176	0.107
91-95	0.174	0.377	0.377	0.288	0.174
96-120	0.263	0.572	0.572	0.436	0.263

[a.] Source of age-based mortality probabilities was National Vital Statistics Report [6].
[b.] Source of proportional increase in non-hepatic mortality was from pooled estimates of El-Kamary et al. [2] and Innes et al. [4].
[c.] Source of proportional reduction non-hepatic mortality among persons with resolved HCV infection was from pooled estimates of El-Kamary et al. [2] Lee et al. [3], and Innes et al. [4].

Appendix B – Systematic review methodology

We conducted a systematic review to augment our initial review of the literature to ensure as many relevant citations could be included as possible. We searched the PubMed records from January 2010 to March 2016, using the following terms and conditionals: "(hepatitis C) AND (cost-effectiveness model)". This yielded an initial list of 126 citations. The review of abstracts for these citations resulted in the exclusion of 54 records. These records were excluded because their abstracts indicated: (1) an article that was a literature review, (2) an article that was a commentary or editorial, (3) the article focused exclusively on a sub-population of the general HCV-population, such as incarcerated individuals or HIV-HCV coinfected individuals, or (4) the article was primarily an empirical study with a minimal modeling component. To clarify a point about (3), some studies were conducted to represent a general population but, as part of the model structure, they allowed for different types of individuals (such as IDUs and HIV-coinfected). These studies were retained for later review.

After the abstract review, 72 articles were retained for later review. The implementation of non-hepatic mortality could not be assessed in 15 of these studies. Of the remaining 54 studies, the majority (67%, 38/57) assumed the HCV-infected population had a non-hepatic mortality rate equal to the general population. A smaller proportion of studies assumed that HCV-infected populations have higher mortality rates than the general population. These studies either assumed (1) non-hepatic mortality was associated with a specific HCV-infected-individual characteristic, such as IDU and co-infection, or (2) non-hepatic mortality was elevated for all HCV-infected individuals and unaffected by treatment, or (3) non-hepatic mortality was elevated for all HCV-infected individuals and was reduced in all or in part following successful HCV-treatment.

Appendix C – Combining estimates of non-hepatic mortality

Pooled hazard ratio estimates were generated from three empirical studies [2-4]. Pooled estimates were computed using the generic inverse-variance approach. We utilized the meta-analysis framework described by two previous studies [7, 8]. Following those studies, the pooled estimate of the log hazard ratios, $ln(HR_P)$, for *I* studies can be estimated with:

$$ln(HR_P) = \frac{\sum_i^I \frac{ln(HR_i)}{var\left(ln(HR_i)\right)}}{\sum_i^I \frac{1}{var\left(ln(HR_i)\right)}} \quad [1]$$

The estimate of the variance of the pooled log hazard ratios for I studies, $var\left(ln(HR_i)\right)$, can be estimated with:

$$var\left(ln(HR_i)\right) = \left(\sum_i^I \frac{1}{var\left(ln(HR_i)\right)}\right)^{-1} \quad [2]$$

The log of the hazard ratios of each individual study, $ln(HR_i)$, is found by taking the natural logarithm of the hazard ratios each study, which was presented in study's respective results tables. The variance of the log of the hazard ratio for an individual study, $var\left(ln(HR_i)\right)$, can be directly estimated from the following:

$$var\left(ln(HR_i)\right) = \left(\frac{1}{E_{HCV+,i}} + \frac{1}{E_{HCV-,i}}\right) \quad [3]$$

In this equation, the counts of non-hepatic mortality events among the sample of people infected with HCV and among the sample of people without infection are represented by $E_{HCV+,i}$ and $E_{HCV-,i}$, respectively. The relationship between the variance of the log hazard ratio and a 95% confidence intervals for the natural log of the pooled hazard ratio can be expressed with the following equation:

$$var\left(ln(HR_P)\right) = \left(\frac{UPPCI_P - LOWCI_P}{3.92}\right)^2 \quad [4]$$

In Equation 4 the upper boundary of the confidence interval and lower boundary of the confidence interval are represented by $UPPCI_P$ and $LOWCI_P$, respectively. Equation 4 can be re-arranged as follows:

$$(UPPCI_P - LOWCI_P)^2 = var\left(ln(HR_P)\right) * 3.92^2 \quad [5]$$

The upper and lower confidence values can be replaced by a difference term, Δ_P, which represents the plus or minus distance from the mean to the boundary value of the confidence interval:

$$(2 * \Delta_P)^2 = var\left(ln(HR_P)\right) * 3.92^2 \quad [6]$$

$$\Delta_P = \frac{1}{2}\left(var\left(ln(HR_P)\right)\right)^{\frac{1}{2}} * 3.92 \quad [7]$$

Once this value of Δ_P has been calculated, the confidence interval for the log of the hazard ratio can be computed.

$$ln(HR_P) \pm \Delta_P = (UPPCI_P, LOWCI_P) \quad [8]$$

After the log of the hazard ratios and the confidence intervals of the log hazard ratios were computed, all values were exponentiated to remove the natural log term and converted into the standard hazard ratio scale. The unpooled estimates, the pooled estimates, and the count data that were used to generate the variances of the log of the hazard ratios are presented in Table C1.

Table C1. Hazard ratios on the effect of hepatitis C infection status on non-hepatic mortality from three empirical studies.

		Hazard Ratios of HCV-positive status 95% Confidence Intervals			Non-hepatic mortality event counts	
	Source	Estimate	Lower	Upper	E_{hcv+}	E_{hcv-}
Age- and sex-adjusted models	El-Kamary et al.	3.12	1.76	5.53	35	537
	Innes et al.[a]	1.59	1.15	2.17	100	62
	Pooled	2.17	1.72	2.74		
	Source	Estimate	Lower	Upper	E_{hcv+}	E_{hcv-}
Fully adjusted models	El-Kamary et al.	1.79	0.77	4.19	35	537
	Lee et al.[b]	1.47	1.23	1.77	150	2020
	Innes et al.	1.47	1.05	2.04	100	62
	Pooled	1.52	1.32	1.74		

[a.] El-Kamary et al. [2] and Lee et al. [3] reported hazard ratios where the base case condition was HCV-positive status, whereas Innes et al. reported hazard ratios where the base case condition was HCV-negative status. To simplify presentation, Innes et al. [4] hazard ratios were converted to the equivalent value, as if the base case had been HCV-positive status.

[b.] To compute the weights used in the pooled estimates, we need counts of mortality events among the HCV-positive and HCV-negative samples. In Lee et al. [3] this value was not explicit, but could be estimated based on their Figure 1. We estimated the population of HCV-positive individuals that died from non-hepatic diseases was 19.8% of the initial HCV-RNA-detectable sample, i.e., 150 of 760. Where 760 is the sample size for the HCV-RNA-detectable sample, computed as 19.6% of the HCV-antibody positive sample of 1095.

Appendix D – Special cases corresponding to empirical studies

As additional context for the base case results, we constructed sensitivity scenarios that correspond to each study we used to generate the pooled parameter values. The scenario based on El-Kamary used an initial increase in non-hepatic mortality of 212% and a reduction following SVR of 37% (= 79% / 212%). The scenario based on Lee et al. utilized the pooled estimate for the initial increase in non-hepatic mortality (since that estimate was not provided in Lee et al.) of 117% and a reduction following SVR of 40% (= 47% / 117%). The scenario based on Innes et al. used 59% as the increase in initial non-hepatic mortality and used 80% (= 47% / 59%) as the reduction in non-hepatic mortality following SVR. These parameterizations yielded the results presented in Table D1.

Table D1. Incremental cost-effectiveness ratios (ICERs) and percentage deviations from the base case for sensitivity scenarios based on unpooled values from literature sources.

Treatment strategies compared	Scenario	Increase in non-hepatic mortality	Reduction in non-hepatic mortality after SVR	Fibrosis stage of patient		
				F0	F1	F2
Immediate treatment vs. delayed treatment	Base case	117%	44%	76,929	70,756	35,843
	El-Kamary et al.	212%	37%	73,269 *-5%*	68,592 *-3%*	40,174 *12%*
	Lee et al.	117%[a]	40%	82,934 *8%*	75,893 *7%*	37,376 *4%*
	Innes et al.	59%	80%	64,619 *-16%*	59,392 *-16%*	28,736 *-20%*
Immediate treatment vs. non-treatment	Base case	117%	44%	67,342	45,167	25,468
	El-Kamary et al.	212%	37%	69,554 *3%*	50,744 *12%*	30,271 *19%*
	Lee et al.	117%[a]	40%	71,803 *7%*	47,220 *5%*	26,157 *3%*
	Innes et al.	59%	80%	53,493 *-21%*	35,595 *-21%*	20,401 *-20%*

Note(s): Values in italics underneath the ICER value is the percentage deviation from the base case value.

[a.] This value is the pooled estimate because Lee et al. did not present an age- and sex-adjusted model.

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