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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

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Abstract

Background—Most cost-effectiveness analyses of hepatitis C (HCV) therapy focus on the benefits of reducing liver-related morbidity and mortality.

Objectives—Our objective was to assess how cost-effectiveness estimates of HCV therapy can vary depending on assumptions regarding the potential impact of HCV therapy on non-hepatic mortality.

Methods—We adapted a state-transition model to include potential effects of HCV therapy on non-hepatic mortality. We assumed successful treatment could reduce non-hepatic mortality by as little as 0 % to as much as 100 %. Incremental cost-effectiveness ratios were computed comparing immediate treatment versus delayed treatment and comparing immediate treatment versus non-treatment.

Results—Comparing immediate treatment versus delayed treatment, when we included a 44 % reduction in nonhepatic mortality following successful HCV treatment, the incremental cost per quality-adjusted life year (QALY) gained by HCV treatment fell by 76 % (from US$314,100 to

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Author contributions AJL had full access to all aspects of this study from inception and is the study's guarantor. Coauthor contributions include: study concept and design (AJL, SDH); acquisition of data and modeling (AJL, HWC); analysis and interpretation of results (AJL, HWC, PRS, SDH); drafting of the manuscript (AJL, HWC); critical revision of the manuscript for important intellectual content (PRS, SDH); obtained funding (SDH); study supervision (SDH). All authors have approved the final version of the manuscript. The authors gratefully acknowledge the help of Fujie Xu during this study.

Compliance with Ethical Standards

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US$76,900) for patients with no fibrosis and by 43 % (from US$62,500 to US$35,800) for patients with moderate fibrosis. Comparing immediate treatment versus non-treatment, assuming a 44 % reduction in non-hepatic mortality following successful HCV treatment, the incremental cost per QALY gained by HCV treatment fell by 64 % (from US$186,700 to US$67,300) for patients with no fibrosis and by 27 % (from US$35,000 to US$25,500) for patients with moderate fibrosis.

Conclusion—Including reductions in non-hepatic mortality from HCV treatment can have substantial effects on the estimated cost-effectiveness of treatment.

1 Introduction

Hepatitis C virus (HCV) infection is associated with increased patient morbidity and mortality [1–5]. In a large sample of people with HCV infection in the USA with a median age of 52 years, the annual probability of all-cause mortality was estimated to be 0.014 among individuals with minimal liver disease and 0.073 among individuals with severe liver disease [6]. By contrast, among the US general population the annual probability of mortality for an individual aged 51–55 years was estimated to be 0.005 [7]. Other studies [5, 8] have found all-cause mortality among people with HCV infection to occur between 15 and 23 years earlier than comparison groups of people without HCV infection.

All-cause mortality among people with HCV infection can be the result of either hepatic or non-hepatic (i.e., non-liver-related) factors. Understanding the different sources of mortality is important from the clinical perspective, for modeling disease burden, and for cost-effectiveness (CE) analyses. The majority of HCV modeling studies explicitly account for hepatic-related mortality events [9], such as those due to decompensated cirrhosis or hepatocellular carcinoma. In contrast, these studies are more diverse in their modeling of non-hepatic mortality, also referred to as “background” mortality. Some studies assume HCV-infected individuals experience background mortality at the same age-adjusted rate as the general population [10, 11]. Some studies assume HCV-infected individuals have higher background mortality rates than the general population, but that successful HCV treatment does not affect this mortality rate [12, 13]. Still other studies assume HCV-infected individuals have higher background mortality rates and that successful HCV treatment reduces this mortality rate [14–16].

Evidence suggests that successful therapy for HCV can reduce a portion of the excess non-hepatic mortality associated with HCV [17–19]. Our study explored the implications of including potential reductions in non-hepatic mortality for the assessment of CE of HCV therapy. We estimated CE assuming HCV-infected individuals have a higher background mortality rate, a portion of which can be reduced following successful HCV treatment.

2 Background

2.1 Clinical Evidence for HCV-Caused Non-Hepatic Mortality

Recent evidence has documented the substantially higher rates of all-cause mortality among patients with hepatitis C [1, 6, 8, 20, 21] and strong associations between eradication of HCV infection (or sustained virologic response) and reductions in all-cause mortality [1–3, 22]. While this general trend has been well documented, estimating and understanding the

exact mechanisms and proportional contributions of these varied, potential causes of mortality among HCV-infected individuals remains more elusive [23]. HCV infection has been linked to a variety of nonhepatic morbidities, including Hodgkin's lymphoma [24], gestational diabetes [25], cardiovascular disease [19, 26], non-liver cancers [27], renal disease, and stroke [28]. Many studies of non-hepatic disease burden among people with HCV infection also tend to focus on particular groups, such as HIV and HCV co-infected patients [29, 30], diabetics [31], and blood donors [32]. However, at least three large empirical studies have focused on relatively more general populations [17–19].

These three studies [17–19] provide the basis for the parameterization later used in this study. Each of these studies estimated statistically significant effects of HCV-infection status on the outcome of non-hepatic mortality (also called extrahepatic mortality or non-liver-related mortality). The characteristics of the study samples varied across the studies. In terms of geography, study sites included the USA [17], Taiwan [18], and Scotland [19]. El-Kamary et al. [17] investigated a sample of people with HCV infection that were majority male (70%) and non-Hispanic white (64%). The Taiwanese sample investigated by Lee et al. [18] had an approximately even distribution of males and females. Like the US study, the Scottish study sample was also majority male (70%) [19]. The geographic diversity of these studies lends weight to their findings and, when combined, they are less likely to be biased by characteristics that are idiosyncratic to a particular region. This diversity also gives the current study some assurance that our use of results pooled from across these studies captures a relatively broad range of potential individual characteristics and attributes.

2.2 Non-Hepatic Mortality in HCV Cost-Effectiveness Models

One recent review suggested that many CE modeling studies may be underestimating HCV treatment CE due to the omission of non-hepatic morbidity and mortality [33]. To better quantify the current status of the HCV modeling literature, we augmented our review of literature with a targeted, systematic approach to identify recent HCV modeling studies, from 2010 to 2016, and to assess the implementation (if any) of non-hepatic mortality associated with people who have HCV infection (Table 1). Our search criteria initially identified 126 records from PubMed and after a review of each abstract, a total of 57 modeling studies were retained and closely examined for their implementation of non-hepatic mortality. Additional details on the systematic review methods are available in the supplemental appendix.

The majority of studies (67%) assumed that HCV-infected individuals have the same background mortality rate as the general population and this rate does not change after successful HCV therapy. Smaller proportions of studies assumed that background mortality was higher among specific sub-groups of the HCV-infected population (9%) or was higher among the entire HCV-infected population (11%), but these elevated mortality rates were not affected by successful HCV therapy. The fourth group of studies reviewed in Table 1 captures those studies (14%) that implemented elevated non-hepatic mortality rates and assumed that a proportion of these non-hepatic mortalities were reduced following successful HCV therapy. The extent to which initially-elevated, non-hepatic mortality rates

were reduced following successful hepatitis C treatment varied across these studies from 41 to 100%.

3 Methods

3.1 Model Overview

We adapted a state-transition model to include potential effects of HCV therapy on non-hepatic mortality [11]. This modified Markov model computes life-cycle costs and quality-adjusted life-years (QALYs) for patients at different stages of liver disease, where liver disease is staged according to the Metavir fibrosis scale, with stages F0, F1, F2, F3, and F4 representing, respectively, no fibrosis, minimal/mild fibrosis, moderate fibrosis, severe fibrosis, and compensated cirrhosis. The model represents the clinical experience of a 55-year-old genotype 1 patient who has been diagnosed with HCV. An age of 55 years was selected because it reflects individuals from the approximate midpoint of the 1945–1965 birth cohort [11, 34].

We calculated incremental cost-effectiveness ratios (ICERs) for HCV treatment at the three earliest stages of liver disease: no fibrosis (F0), minimal/mild fibrosis (F1), and moderate fibrosis (F2). We used two different comparison scenarios to calculate the ICERs. First, we calculated ICERs for immediate treatment versus delaying treatment until liver disease progressed to the next Metavir stage, such that ICERs were computed for treatment at F0 versus treatment at F1, treatment at F1 (vs. F2), and treatment at F2 (vs. F3). Second, we calculated ICERs for immediate treatment versus non-treatment, such that ICERs were computed for immediate treatment at F0, F1, and F2 versus scenarios where no treatment occurred.

HCV treatment was assumed to be a generalized regimen of direct-acting antivirals at a cost of US$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 (Fig. 1). Additional details on the model structure and an extended discussion of the model parameters are available in the supplemental appendix. Because all data were obtained from secondary sources without patient-level information, this study was exempt from human subjects review and approval.

3.2 Non-Hepatic Mortality Conceptual Framework

This study accommodated additional non-hepatic mortality in two distinct steps. First, we increased the background mortality rate for all individuals in the model, both individuals with ongoing HCV infection and individuals whose infections have been resolved following treatment. Since hepatic causes of death are explicitly included elsewhere in the model, increasing the background mortality rate largely represents an increase in the rate of non-hepatic mortality. This first step is an attempt to make mortality rates more realistic for an HCV-infected population, which have demographics and behaviors associated with mortality rates that are higher than those of the general population. This type of non-hepatic mortality modeling has been done by Elbasha et al. in a sensitivity analysis [13] and done by others in

their base case analyses [12]. This first step, taken in isolation, does not assume that successful HCV treatment has any effect on these higher background mortality rates.

The second step in our modification was to reduce the background mortality following a successful HCV treatment. We assumed a portion of the increased background mortality is attributable to, or caused by, HCV infection. Non-hepatic mortality can be caused by a number of factors that are potentially the result of, or made more severe by, an HCV infection. These non-hepatic mortalities may include those associated with HIV-infection [29], vascular disease [35], and diabetes [36]. Other types of non-hepatic mortalities can be caused by other factors, such as high-risk behaviors that may include alcohol abuse, injection drug use, or smoking; or socio-economic conditions that are associated with reduced utilization of health care. With respect to their influence on an individual's likelihood of non-hepatic mortality, these other factors (behaviors and socio-economic status) may be less likely to change following a successful HCV treatment than the group of factors that include vascular disease and diabetes. As such, in the model we make a distinction between the background mortality that may be reduced following a successful HCV treatment and the background mortality that is less likely to be affected by a successful HCV treatment. The portion of background mortality that can be reduced following successful HCV treatment was based on three previous studies looking at non-hepatic mortality among HCV-infected individuals [17–19] (Table 2).

The distinction between step one and step two is subtle but important. Many modeling studies make no adjustment of background mortality [10, 11]. Other studies essentially only implement step one [12, 13], and still other studies implement both step one and step two [14–16].

3.3 Non-Hepatic Mortality Parameterization

The estimates for increased background mortality among HCV-infected individuals and for the reduction in non-hepatic mortality following successful HCV treatment were identified from three published empirical studies [17–19]. Pooled estimates that combine the results of the multiple studies were computed using the generic inverse-variance approach [37, 38]. More information on the calculation of pooled estimates is available in the supplemental appendix. The empirical studies reported hazard ratios for the association of HCV-infection status and nonhepatic mortality for two distinct models (Table 2). One model was age- and sex-adjusted, and we interpret this hazard ratio to represent deviations in background mortality from the general population that were due to any cause. The other model was a fully-adjusted model, which included a large number of relevant covariates in addition to age- and sex-related covariates. We interpreted the hazard ratio from the fully-adjusted model to better represent deviations in background mortality that were due specifically to HCV infection. In this way, the HCV-associated background mortality measured by the fully-adjusted models constitutes a subset of the HCV-associated background mortality measured by the age- and sex-adjusted models. By dividing the hazard ratio from the fully-adjusted model by the hazard-ratio from the age- and sex-adjusted model, we compute the portion of background non-hepatic mortality that is attributable to HCV infection. In the

modified CE model, this is the portion of non-hepatic background mortality that is reduced following successful HCV treatment.

We calculated the pooled hazard ratio from the age- and sex-adjusted models from El-Kamary et al. [17] and Innes et al. [19] to be 2.17 [95% confidence interval (CI): 1.72–2.74] (Table 2). Based on this result, we increased the background mortality rate by 117%, which corresponds to an estimated hazard ratio of 2.17. We calculated the pooled hazard ratio from the fully-adjusted models to be 1.52 (95% CI: 1.32–1.74). Based on this result, we assumed the increase in background mortality rate attributable to HCV infection would be 52%, which corresponds to an estimated hazard ratio of 1.52. Combining these two results, the percent-reduction in non-hepatic mortality following successful HCV treatment was estimated to be 44% (=52%/117%).

For our results in this study, we assumed 44% as a base case value. To accommodate additional uncertainty around this relationship, we applied a range of 0–100% for reductions in non-hepatic mortality following a successful HCV treatment as a sensitivity analysis. For additional context, we also computed results that correspond to the unpooled estimates from each of the individual studies presented in Table 2 that were used to parameterize non-hepatic mortality. For the base case (44%), the sensitivity analysis range (0–100%), and the scenarios based on the individual unpooled studies, we calculated the cost per QALY gained by HCV treatment for patients with no fibrosis (F0), minimal/mild fibrosis (F1), and moderate fibrosis (F2).

4 Results

When comparing immediate treatment to delayed treatment and including a 44% reduction in non-hepatic mortality, the incremental cost per QALY gained by HCV treatment decreased by 67% (from US$314,100 to US$76,900) for patients with no fibrosis (F0), by 71% (from US$241,700 to US$70,800) for patients with minimal/mild fibrosis (F1), and by 43% (from US$62,500 to US$35,800) for patients with moderate fibrosis (F2). When a 100% reduction in non-hepatic mortality followed successful HCV treatment, the ICER for immediate HCV treatment fell by 89% (from US$314,100 to US$33,700) for patients with no fibrosis (F0), by 87% (from US$241,700 to US$32,300) for patients with minimal/mild fibrosis (F1), and by 67% (from US$62,500 to US$20,700) for patients with moderate fibrosis (F2).

In the scenarios where immediate treatment for HCV was compared to non-treatment, the change in ICERs due to including non-hepatic-related mortality was less dramatic than the differences found when immediate treatment (vs. delayed) was considered. When the alternative was non-treatment and a 44% reduction in non-hepatic mortality was assumed, the incremental cost per QALY gained by HCV treatment fell by 64% (from US$186,700 to US$67,300) for patients with no fibrosis (F0), by 45% (from US$81,700 to US$45,200) for patients with minimal/ mild fibrosis (F1), and by 27% (from US$35,000 to US$25,500) for patients with moderate fibrosis (F2). When the alternative was non-treatment and a 100% reduction in non-hepatic mortality followed successful HCV treatment, the ICER for HCV treatment fell by 83% (from US$186,700 to US$31,600) for patients with no fibrosis (F0),

by 69% (from US$81,700 to US$25,200) for patients with minimal/mild fibrosis (F1), and by 51% (from US$35,00 to US$17,200) for patients with moderate fibrosis (F2).

In the main sensitivity analyses, the reduction in non-hepatic mortality following successful treatment for HCV was allowed to vary from 0–100% (Fig. 2). As the percent reduction in non-hepatic mortality following successful treatment for HCV was increased, the ICER for immediate treatment versus delayed treatment decreased (Fig. 2a) and the ICER for treatment versus non-treatment decreased (Fig. 2b). This relationship was consistent across all starting levels of fibrosis. In additional sensitivity scenarios, where the model was parameterized based on unpooled estimates from each of the three source studies [17–19], results varied but were largely consistent in terms of traditional CE thresholds. The most dramatic difference in results came from the parameterization that implemented unpooled estimates from Innes et al. [19], which suggested an 80% percent reduction of non-hepatic mortality following successful HCV therapy. This scenario yielded results that were more favorable to treatment, with ICERs that were 16–20% lower than in the base case. Full results from these scenarios are available in the supplemental appendix.

5 Discussion

In this study, we adapted a CE model for treatment of HCV to accommodate higher rates of non-hepatic mortality among HCV-infected individuals and reductions in non-hepatic mortality following successful HCV treatment. We found the CE of an HCV treatment strategy was influenced by assumptions made about the relationship between HCV-infection status, successful treatment, and non-hepatic mortality. In particular, as stronger associations between successful treatment and reductions in non-hepatic mortality were assumed, the ICER values were reduced substantially. Based on our assessment of published studies, an estimated decrease in non-hepatic mortality of 44% following successful HCV treatment is plausible.

Recent modeling studies in the literature accommodated non-hepatic mortality among HCV-infected individuals in several ways. The majority of studies we identified assumed HCV-infected individuals experience non-hepatic mortality (or background mortality) at the same rate as the general population. Some studies incorporated higher levels of non-hepatic mortality among HCV-infected populations [12–16, 39, 40]. Of those studies, only a few also imposed reductions in non-hepatic mortality following successful HCV treatment [14–16, 39, 40]. Across studies that implemented a reduction in non-hepatic mortality following SVR, the magnitude of the reduction varied from 41% [14, 15] to 80% [16] to 100% [39, 40]. In this study, we conducted a set of sensitivity analyses to assess the degree to which these assumptions contribute to the outcomes of interest. This study uses a published model which originally did not account for higher rates of non-hepatic mortality among people with HCV compared to those not infected. Assuming higher non-hepatic mortality rates that are not affected by HCV treatment can increase the estimated cost per QALY gained by HCV treatment [13]. For this reason, the base case results from our previous study [11] have lower ICERs than the corresponding ICERs in this study.

Limitations of this model are described in greater detail in the supplemental appendix and elsewhere [11]. Briefly, our model was designed to investigate the clinical decision to initiate treatment immediately versus delaying treatment to a later stage in liver disease, so questions as to the CE of specific treatment regimens are not addressed. Transmission dynamics of HCV were not modeled and so treatment as a preventive intervention was not included in our estimates of CE. Due to differences in model structures, implementation of non-hepatic mortality assumptions into other models may not yield exactly the same effects as those demonstrated in this study. Our estimates for the effect of HCV-infection status on non-hepatic mortality were based on the three available studies on this topic. Given the disparity—all three of these studies identify a substantial contribution of HCV to non-hepatic mortality and the majority of HCV CE models do not account for SVR-induced changes to non-hepatic mortality—the impact of this topic is potentially substantial and additional research into the clinical, empirical, and economic aspects, along with meta-analysis across studies, is recommended.

Until recently, HCV patients with severe liver fibrosis (i.e., Metavir stages F3–F4) were considered a priority to receiving treatment [41]. The HCV treatment guidelines have since been updated so that now all patients, including those with early stages liver disease, are recommended for treatment [42]. Our study emphasizes how for patients with less severe liver disease, the consideration of non-hepatic mortality can be important for clinical decision-making. Finding that non-hepatic mortality has substantial effects on estimates of CE, these results underscore the need to better understand and more precisely quantify the relationship between HCV-infection status, treatment success, and non-hepatic disease outcomes. In the coming years, additional empirical research into the relationship between HCV-infection status and non-hepatic mortality, and morbidity, may help to make this exploratory analysis more concrete. If a strong causal relationship between HCV and non-hepatic mortality is established, particularly among patients with no fibrosis or minimal/mild liver disease, then health system payers may face additional incentives to expand HCV treatment. Our analysis illustrates that consideration of the effects of successful treatment on the reduction of non-hepatic mortality has substantial implications for CE analyses of HCV therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points for Decision Makers

HCV treatment models vary in the way they incorporate non-hepatic mortality.

Assumptions regarding reductions in non-hepatic mortality from HCV treatment can have substantial effects on estimated cost-effectiveness ratios.

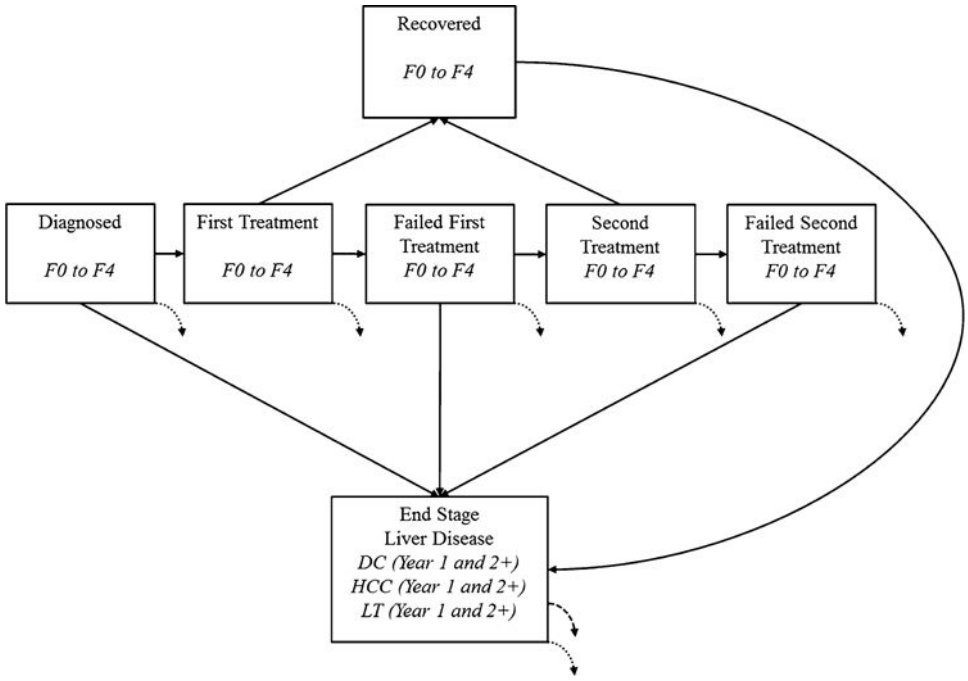

Fig. 1.

Model diagram for the cost-effectiveness of hepatitis C treatment in the early stages of liver disease. *Dotted arrows* exiting the population compartments refer to non-hepatic mortality. The *dashed arrow* exiting the end stage liver disease (ESLD) compartment refers to hepatic mortality. Transitions to ESLD compartments only occur from fibrosis stage F4. An extensive discussion of model details can be found in the appendix as well as in a previous publication [11]. *HCC* hepatocellular carcinoma (first and subsequent years), *DC* decompensated cirrhosis (first and subsequent years), *LT* liver transplant (first and subsequent years), *F0* no liver fibrosis (Metavir scale), *F4* compensated cirrhosis (Metavir scale), *ESLD* end stage liver disease

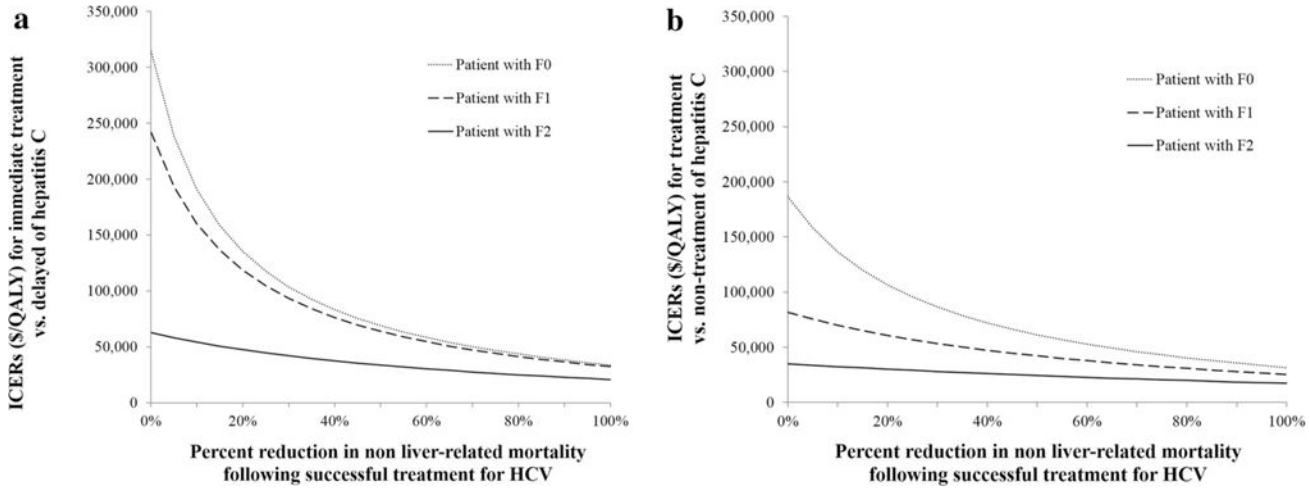

Fig. 2.

Incremental cost per quality-adjusted life-year ($/QALY) gained for hepatitis C treatment in **a** immediate treatment vs. delayed treatment scenario and **b** immediate treatment vs. non-treatment, assuming reductions in non-hepatic mortality following successful treatment. Incremental cost-effectiveness ratios compare immediate treatment at fibrosis level F2 (*black line*), F1 (*dashed line*), or F0 (*dotted line*) to a strategy of delayed treatment (**a**) and non-treatment (**b**). For example, the immediate treatment of a patient at F1 (vs. delaying treatment until that patient's liver disease progressed to stage F2 fibrosis) incurred a cost per QALY of US$241,700 when 0% of the non-hepatic mortality was reduced following a successful treatment and incurred a cost per QALY of US$63,800 when 50% of the non-hepatic mortality was reduced following a successful treatment

Table 1

Results from an expanded literature review of cost-effectiveness modeling studies for hepatitis C interventions, investigating the modeling of non-hepatic mortality following successful hepatitis C therapy, from studies published from January 2010 to March 2016

Assumptions about non-hepatic mortality among HCV-infected individuals as compared to the general population	Non-hepatic mortality affected by SVR	No. of studies	Portion of studies reviewed	Citations
Non-hepatic mortality assumed to be same as general population	No	38	0.67	[10, 11, 43–78]
Non-hepatic mortality assumed to be elevated for a subset of HCV-infected population group, such as IDUs and individuals with HIV-coinfection	No	5	0.09	[79–83]
Non-hepatic mortality assumed to be elevated for all HCV-infected individuals	No	6	0.11	[12, 13, 84–87]
Non-hepatic mortality assumed to be elevated for HCV-infected individuals and is reduced following successful treatment	Yes	8	0.14	[14–16, 39, 40, 88–90]
Total		57	1.00	
Total abstracts identified	126			
Excluded based on abstract	54			
Non-hepatic mortality status could not be determined	15			

HCV hepatitis C virus, *SVR* sustained virologic response, *IDU* injection drug user, *HIV* human immunodeficiency virus

Table 2

Associations between HCV-infection status and non-hepatic mortality from the literature

Source	Hazard ratios of HCV-positive status		
	Estimate	95 % confidence interval	
		Lower	Upper
Age- and sex-adjusted models[a]			
El-Kamary et al.	3.12	1.76	5.53
Innes et al.	1.59	1.15	2.17
Pooled[b]	2.17	1.72	2.74
Fully adjusted models			
El-Kamary et al.[c]	1.79	0.77	4.19
Lee et al.[d]	1.47	1.23	1.77
Innes et al.[e]	1.47	1.05	2.04
Pooled[b]	1.52	1.32	1.74

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *HCV* hepatitis C virus, *F0* no liver fibrosis (Metavir scale), *F1* minimal/mild fibrosis (Metavir scale), *F2* moderate fibrosis (Metavir scale), *F4* compensated cirrhosis (Metavir scale)

[a] Lee et al. [18] did not provide results for an age- and sex-adjusted model

[b] The pooled estimates were computed using the generic inverse-variance method [37, 38] as described in detail in the supplemental appendix

[c] The following covariates from El-Kamary et al. [17] were included in the fully-adjusted model: demographics (age, sex, race/ethnicity, marital status, education, poverty income ratio), lifestyle factors (alcohol consumption, smoking status, lifetime cocaine and marijuana use, lifetime number of sexual partners), body mass index, and co-morbidities/viruses (cancer, diabetes, hepatitis A antibody, hepatitis E antibody), liver function biomarkers (ALT, total bilirubin)

[d] The following covariates from Lee et al. [18] were included in the fully-adjusted model: demographics (age, sex), lifestyle factors (alcohol consumption, smoking status, betel-nut chewing), central obesity, and personal history co-morbidities (diabetes, hypertension, heart disease, and cerebrovascular disease)

[e] Innes et al. [19] reported hazard ratios associated with HCV negative status, so these hazard ratios were transformed to represent associations with HCV positive status, to make them consistent with the presentation from El-Kamary et al. and Lee et al. The following covariates from Innes et al. [19] were included in the fully-adjusted model: demographics (age, sex), behavioral factors (alcohol consumption, injection drug use, prior hospitalization for violence-related injury, prior hospitalization for drug intoxication), viral genotype, liver function tests (aspartate aminotransferase-to-platelet ratio-index, gamma-glutamyl transferase), and co-morbidities (cirrhosis status, Charlson co-morbidity index)