Estimating the Prognosis of Hepatitis C Patients Infected by Transfusion in Canada between 1986 and 1990

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Objective. *To develop a natural history model for chronic hepatitis C virus (HCV) infection to determine allocation of compensatory funds to Canadians who acquired HCV through the blood supply from 1986 through 1990.* ***Methods.*** *A Markov cohort simulation model for HCV prognosis was developed, using content experts, published data, posttransfusion look-back data, and a national survey.* ***Results.*** *The mortality rate in transfusees is high (46% at 10 years), although HCV-related deaths are rare. Only 14% develop cirrhosis at 20 years (95% confidence interval, 0%–-44%), but 1 in 4 will eventually develop cirrhosis, and 1 in 8 will die of liver disease.* ***Conclusions.*** *This unique application of Markov cohort simulation and epidemiologic methods provides a state-of-the-art estimate of HCV prognosis and has allowed compensation decisions to be based on the best available evidence.* ***Key words:*** *hepatitis C; Markov model; decision making.* ***(Med Decis Making 2004;24:20–29)***

Prior to 1990, many individuals developed posttransfusion hepatitis, mostly from hepatitis C. In 1990, a serologic test for hepatitis C virus (HCV) became available to screen donated blood. Between the period of 1986 and 1990, however, blood banks in the United States tested blood for alanine transaminase and hepatitis B surface antibody (anti-HBs) to decrease the risk of posttransfusion hepatitis. This "surrogate marker" testing was never implemented in Canada or Britain. If it had been, many Canadians who acquired HCV from transfusion or by secondary infection between 1 January 1986 and 1 July 1990 might have remained free of infection. On 27 March 1998, the federal, provincial, and territorial governments of Canada set aside $CDN1.1 billion to compensate these individuals.

The proposed compensation scheme linked payment to the severity of HCV-related liver disease. To ensure sufficient funds for potential claimants, governments and plaintiffs asked experts to estimate the prognosis of infected individuals. Because these estimates were widely divergent, both parties approached the Canadian Association for the Study of the Liver (CASL), an impartial body with no stake in the outcome of compensation negotiations, to produce the best possible estimate of the natural history of HCV. In November of 1998, CASL approached individuals with expertise in hepatitis C epidemiology, hepatitis C clinical care, and decision analysis to estimate the prognosis of the HCV-infected individuals.

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METHODS

Developing the Model

Disease models have 2 key components: model structure and model parameters. "Structure" refers to health states represented in the model and allowable transitions between them. "Parameters" include probability values assigned to transitions between health states.

After reviewing existing models of the natural history of HCV,[1–5] the group chose to adapt and revise the well-known and widely accepted Markov state transition model[6] of Bennett and Wong.[1,2] In this type of model, a set of health states representing the natural history of the disease and relevant to the research question is defined. At the beginning of the simulation, the cohort whose prognosis is being modeled is allocated among health states. Time elapsed is divided into cycles, and transitions among health states are modeled with each time cycle. Time spent in each health state is recorded, so that the cumulative proportion of the original cohort that enters each health state can be calculated.

We adopted the general structure of the Bennett/Wong model, including health states that characterize chronic HCV infection, treatment and treatment response, development of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and death. Structural changes from the original model included the aggregation of separate health states representing decompensated cirrhosis ("ascites," "refractory ascites," "variceal hemorrhage," "hepatic encephalopathy") into a single health state ("decompensated cirrhosis"). In addition, the "mild chronic hepatitis" health state in the original model was changed to a "chronic HCV infection" health state to incorporate all patients with persistent HCV infection, whether liver inflammation was present or not. We constructed a separate set of health states for each 10-year age stratum, resulting in a 90-state model to predict the prognosis of the entire transfused cohort (Figure 1). The model was programmed in DecisionMaker 7.0 (Pratt Medical Group, Boston).

Nearly all of the parameter estimates were updated. We used several data sources to revise and supplement the original parameter estimates. We reviewed the parameter estimates used in previous natural history models and performed systematic electronic searches of bibliographic databases, supplemented by hand searches of reference lists of retained articles and reviews of investigators' files. We consulted a Health Canada report to obtain estimates of the number of posttransfusion HCV infections occurring between 1986 and 1990.[7] The CASL provided a report of a workshop on the natural history of hepatitis C.[8] We received data describing the mortality experience of transfusion recipients from the provincial Departments of Health in British Columbia, Saskatchewan, Prince Edward Island, and Nova Scotia and from the British Columbia Blood Recipient Notification Project.[9] Transplant data were obtained from the Multiple Organ Retrieval Programme, the transplant program of the University Health Network, Toronto (Dr. Les Lilly, personal communication, 2 March 1999), and the Canadian Organ Replacement Registry. Finally, we surveyed 13 Canadian hepatologists to determine their antiviral therapy practice.

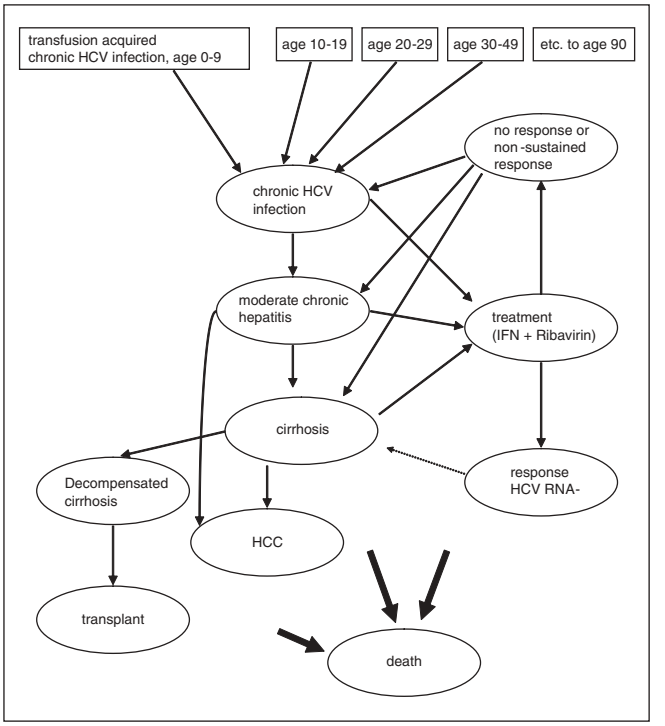

Figure 1 Markov cohort model. All members of the posttransfusion cohort enter the model in the "chronic HCV infection" stage. Separate models are evaluated for each 10-year age stratum. The simulation continues until all members have entered the "death" stage.

When multiple data sources were available to estimate a single parameter, data were summarized in evidence tables and presented to the entire panel. The panel provided a consensus judgment on which studies should be included in the data synthesis based on the criteria of clinical similarity of the study group to the posttransfusion cohort whose prognosis was being estimated and methodologic adequacy.

Mean rates or probabilities, standard errors, and 95% confidence intervals were calculated for studies that met the panel's inclusion criteria. To generate summary pooled mean rates, we weighted each individual study by the inverse variance of its rate estimate as described in Rothman and Greenland.[10] This method weights each study according to the precision of its rate estimate; precision is determined by sample size and mean duration of follow-up.[10–14] When a 95% confidence interval could not be estimated directly from the data, a plausible range was estimated by consensus and used in Monte Carlo simulations.

Analytic Method

We predicted prognosis using a Markov state-transition model. Cumulative proportions of individuals entering each health state were tabulated using the baseline estimates for each parameter. To estimate the degree of uncertainty associated with each of these estimates, Monte Carlo simulation was performed using the 95% confidence interval or plausible range for each estimate. We assumed that the probability-density function for most probability and utility estimates followed a beta distribution,[15–17] although selected parameters (e.g., transfusion-related mortality) were modeled using a normal distribution. We assumed that the baseline value represented the mean of this distribution and the plausible range represented the 95% confidence interval.

Model Data

The individual data elements that were synthesized for this study are described in detail in a monograph available from the authors. A brief description of some of the key probabilities follows.

Number and Age of HCV-Infected Individuals

We used the estimate of the number and age distribution of HCV-infected individuals from a Health Canada Report.[7] This estimate, which used number of transfusions and per-unit risk of HCV infection to predict the number infected, has a unimodal age distribution with a peak at age 67. It estimates that approximately 2% of the cohort is aged 10 to 14 years, 4% is aged 25 to 29, 6% is aged 50 to 54, 10% is aged 60 to 64, and 17% is aged 65 to 69. Proportions then gradually decline with advancing age, such that only 8% of the cohort is older than 80 years, until 7% are aged 80 to 84 and only 1% are older than 90 years. In contrast, a look-back program from British Columbia that attempted to trace all transfusions between 1986 and 1990 observed twin peaks of HCV infection at ages 30 to 34 (approximately 13% of the cohort) and 65 to 69 (8% of the cohort). Compared with the Health Canada Report estimate, it has higher proportions of the cohort in the younger age groups (15–49 years) and lower proportions in the older age groups (50–90 years). The British Columbia look-back group includes individuals who acquired HCV through other means, including injection drug use, but were nonetheless transfusion recipients. It includes, therefore, individuals whose HCV infection predated transfusion.

Because our intention was to model outcomes in those infected through transfusions, we used the estimate in the Health Canada Report, realizing that it is difficult in practice to ascertain the means by which HCV was acquired. Thus, our prediction of the prognosis of individuals who were infected through the blood supply may require some adjustment for application to all HCV-positive individuals who received a blood transfusion.

Excess Mortality in Transfusion Recipients

Predicting the prognosis of HCV-infected patients requires determining the number who remain alive and still at risk of HCV-related complications at any given time. The mortality rates for the Canadian population are not applicable because several studies have shown that transfused patients have a much higher mortality rate than the general population, which is mainly attributable to the illness for which transfusion is indicated.[18–22] We obtained our baseline estimate of excess transfusion-associated mortality from the study of Vamvakas and Taswell[18] (Table 1). This study reported a 10-year overall death rate of 52% among all individuals transfused in Olmsted County, Minnesota, in 1981 (n = 802), somewhat higher than the 39.8% mortality rate (at 9.75 years) reported in the British Columbia look-back study. However, the latter's lower rate may be due to less restrictive transfusion practice in Canada than in Olmsted County and therefore a (theoretically) lower burden of comorbidity among the British Columbia patients and also due to a failure to capture approximately 5% of short-term deaths in the look-back study.[7] We computed excess non-HCV mortality rates from Vamvakas and Taswell's study by estimating hazard rate ratios of annual instantaneous mortality, (Vamvakas and Taswell v. life table) for males and females in 3 age strata (<40, 40–64, 65+). A revised life table and survival function was estimated for the

Table 1 Summary of Probabilities

	Age/Time	Baseline Rate	Low	High	Source
Mortality among transfusion recipients					
10-year cumulative mortality, entire transfused cohort		0.520	0.323	0.575	Vamvakas and Taswell[18]
Chronic HCV infection					
Remission		0.002	0.001	0.004	Bennett and others[1]
Moderate chronic hepatitis		0.041[a] × constant			Derived
Moderate chronic hepatitis					
Cirrhosis		0.073[a] × constant			Pooled analysis (Table 2)
Hepatocellular carcinoma		0.0001	0.0000	0.0020	Consensus judgment
Cirrhosis					
Decompensated cirrhosis		0.046	0.038	0.054	Pooled analysis[34–37]
Hepatocellular carcinoma		0.017	0.013	0.022	Pooled analysis[34–37]
Decompensated cirrhosis					
Death		0.138	0.074	0.202	Fattovich and others[34]
Transplant		0.033	0.017	0.049	Calculated
Hepatocellular carcinoma					
Death		0.860	—	—	Bennett and others[1]
Liver transplantation					
Death	Year 1	0.169	0.127	0.210	Pooled analysis[38,39]
Death	Year > 1	0.034	0.024	0.043	Pooled analysis[38,39]
Proportion of posttransfusion hepatitis C patients identified					
Prior to 1989		0.30	0.20	0.40	Laboratory Centre for Disease Control estimate
Of remainder, contacted in look-back		0.85			British Columbia look-back program
Tested for hepatitis C virus (HCV), given contact		0.60			Consensus judgment
Overall probability of HCV test		0.52	0.27	0.77	Calculated
Liver biopsy					
Proportion alive in 1999 getting liver biopsy	> 65	0.10	0	0.20	Consensus judgment
	≤ 65	0.60	0.40	0.80	Consensus judgment
Mortality of liver biopsy		0.0002	0.0001	0.0003	Consensus judgment
Proportion treated with antiviral therapy post-1999	≥ 65	0	0	0	Practice survey
Mild chronic hepatitis	< 65	0.317	0.261	0.372	Practice survey
Moderate chronic hepatitis	< 65	0.450	0.387	0.513	Practice survey
Cirrhosis	< 65	0.396	0.337	0.455	Practice survey
Sustained response post–interferon/ribavirin therapy					
Mild chronic hepatitis		0.361	0.286	0.436	Pooled analysis[40,41]
Moderate chronic hepatitis		0.432	0.376	0.488	Pooled analysis[40,41]
Cirrhosis (chronic HCV fibrosis)		0.208	0.042	0.374	Pooled analysis[40,41]
Posttransfusion HCV infections in Canada	1986	4501			Remis report[7]
	1987	3882			
	1988	3425			
	1989	3046			
	1990a[1]	852			
	1990b	524			

a. Transfusion recipients eligible for compensation include those infected between 1986 and the early part of 1990 (1990a).

Table 2 Annual and 20-Year Probability of Developing Cirrhosis

	Mean Annual Rate	Range (Annual Rates)	95% Confidence Interval (Annual Rates)	20-Year Probability of Cirrhosis[a]
Decision models				
Bennett, Kim, Dusheiko, Shiell[1,3–5]	—	0.011–0.055	—	0.104–0.423
Prognostic studies				
I. Posttransfusion studies (n = 5)[23–27,38,39]	0.014	0.006–0.021	0.009–0.018	0.131
II. Chronic liver disease (n = 12)[26–28,55–64]	0.019	0.008–0.068	0.016–0.023	0.173
III. Retrospective analysis of historically defined transfusion associated hepatitis[a] (n = 5)[56,65–69]	0.025	0.023–0.040	—	0.221
IV. Retrospective-prospective studies of NANB and hepatitis C (n = 2)[29,31]	—	0.001–0.008	—	0.010–0.077
Pooled estimate (I + IV) excluding Crowe and others[31]	0.011	0.006–0.021	0.008–0.013	0.197

a. Under the assumption that the full cohort survives for 20 years.

entire cohort, using the age and gender distribution of the transfused cohort, and life table survival data, using the age- and sex-adjusted relative survival estimates.

Our upper-bound 10-year mortality estimate (58%) was derived from Remis and others[7] (Table 1). Because HCV-infected individuals receive much more blood than the average transfusee, and because mortality risk is a function of transfusion intensity,[18] Remis and others argued that the excess mortality risk in HCV-infected individuals was higher than in transfusees in general. Our lower-bound estimate (32.3%) (Table 1) was derived by calculating the mean excess mortality rate in prognostic studies of HCV-infected cohorts.[23–29]

Development of Cirrhosis

We identified all published decision models and studies relevant to the development of cirrhosis. Published decision models report estimates of the annual rate of progression to cirrhosis that range from 1.1% to 5.5% per year, for cumulative 20-year rates of 10% to 42%.[1,3–5] We used the taxonomy developed by Seeff[30] to aggregate individual studies characterizing the prognosis of HCV infection. Seeff identified 4 types of study. Posttransfusion studies are prospective cohort studies of individuals developing posttransfusion hepatitis. Chronic liver disease studies are prospective cohort studies of individuals identified in clinical care settings, usually at tertiary care centers. Retrospective analysis of historically defined transfusion-associated hepatitis studies are contemporary case series in which an attempt is made to ascertain the date of transfusion. Retrospective-prospective studies are those in which a posttransfusion or postinfection cohort is identified retrospectively and then prospectively followed.

Event rates were derived by dividing the number of events (cases that progress to cirrhosis) by the number of person-years in the study to arrive at a rate of progression to cirrhosis per person-year. For each study type, we averaged rates by weighting the event rate by the inverse variance of the event rate.

Table 2 shows results by study design. Transition rates incorporated within published decision models for this absolutely central prognostic parameter varied widely, with the highest value being 5-fold higher than the lowest. As a result, the predicted 20-year estimates of the cumulative probability of cirrhosis ranged from 10% to more than 40%. Rates reported within individual studies also varied widely. Study design appeared to affect transition probabilities, as those studies with less robust design (e.g., chronic liver disease and retrospective analysis of historically defined transfusion-associated hepatitis studies) showing significantly higher rates of progression to cirrhosis.

Because the rate at which individuals progress to liver cirrhosis is perhaps the single most important model parameter, we carefully considered how to aggregate these disparate data. We were concerned about surveillance bias and selection bias in chronic liver disease and retrospective analyses of historically defined transfusion-associated hepatitis studies and therefore did not include these studies. We considered, but ultimately excluded, the Irish women's study[31] because we believed that a cohort that was young and fe-

male (characteristics that indicate good prognosis)[32] was too dissimilar from our mixed gender, much older posttransfusion cohort. Therefore, we aggregated the posttransfusion studies[23–27] and the Seeff study[29] to arrive at our overall estimates. From these studies, the mean annual rate of progression to cirrhosis was estimated to be 0.011 (range = 0.006–0.021, 95% confidence interval = 0.008–0.013), and the 20-year probability of cirrhosis, given survival for 20 years, was estimated to be 0.197.

Our group considered at some length incorporating factors such as mode of acquisition of HCV infection and the role of individual covariates such as alcohol consumption, obesity, hemophilic status, and HIV coinfection. We concluded that the prognostic effect of mode of acquisition remained controversial and that no specific adjustments for this factor should be incorporated. Alcohol consumption and obesity are poorly reported, especially in older prognostic studies and were therefore difficult to incorporate explicitly. However, because these factors were implicitly represented in the populations included in the prognostic studies, this represents a bias only to the extent that the distribution of covariates differs between prognostic studies and the posttransfusion cohort. Inclusion of the effects of HIV and hemophilia were deferred to future refinements of the model because of very short project deadlines.

We also considered the issue of duration of disease progression. It is not possible to ascertain from prospective studies whether patients with chronic hepatitis continue to progress after 25 years. From cross-sectional data,[32,33] we concluded that some progression to cirrhosis probably does occur beyond this time. However, in consideration of the high degree of uncertainty that surrounds its estimate, we set our model's transition rates for the long term to the same parameters used to model short-term (25 years) outcomes. This simplification may introduce a modest degree of overestimation of cumulative event rates in the long term because we were not able to adjust transition rates as the HCV cohort changes over time. As the "rapid fibrosers" develop cirrhosis, they are no longer at risk, and the mean progression rate in individuals who remain at risk falls.

Postcirrhosis Prognosis

The parameters used to describe the prognosis of individuals who develop cirrhosis and are at subsequent risk of decompensated liver disease, hepatocellular carcinoma, and liver transplantantation are described in Table 1.[1,7,18,34–41]

HCV Treatment Patterns

To estimate current and future patterns of treatment with antiviral therapies, we surveyed 15 Canadian hepatologists with a particular interest in viral hepatitis. Twelve returned completed questionnaires, for an overall survey response rate of 80%. Nine hepatologists indicated that they prescribe only combination treatment; only 3 Canadian hepatologists indicated that they would currently consider any patient for monotherapy with interferon. When responses were combined, only 1% of patients were currently being treated with interferon alone. We therefore opted to represent only combination therapy in our model. Hepatologists indicated that approximately 30% of HCV patients were not candidates for therapy because of coexisting morbidity and that 32% of patients with mild hepatitis, 45% with moderate hepatitis, and 40% with compensated cirrhosis would be treated. An updated version of this survey has been published.[42]

Treatment Efficacy

We estimated the proportion of posttransfusion recipients who had been treated. Our estimate of treatment efficacy (Table 1) was derived from a pooled analysis of the primary data set of 2 randomized controlled trials evaluating combination interferon/ribavirin therapy.[40,41] The distribution of genotypes in Canada (predominantly genotype 1I) is similar to that observed in the trial populations.[43–45]

RESULTS

Perhaps the most striking result of our analysis is the importance of coexisting disease in the mortality rate of HCV-positive transfusion recipients. The disease that led to the transfusion nearly doubles the likelihood of dying at 10 years, relative to the general population (Table 3). Up to 10 years posttransfusion, hepatitis C contributes little to overall mortality, but over the next 10 years (years 10 to 20), HCV-related mortality rises 8-fold. During the subsequent 10 years (years 20 to 30), hepatitis C–related mortality doubles. These results are consistent with the slowly evolving disease progression of hepatitis C.

The average life expectancies for all individuals receiving a transfusion (20.6 years) and acquiring HCV infection (18.1 years) are much shorter than that of age- and gender-matched cohorts (25.6 years). Cirrhosis developed in only 25% of the cohort, but it shortened their life expectancy substantially.

Table 3 Cumulative Probability of Hepatitis C Virus (HCV)-Related Outcomes, 1986–1990 Posttransfusion, HCV-Infected Cohort (in percentages)

	Years Posttransfusion			
	10	20	30	Lifetime
Entire 1986–1990 post-transfusion HCV-infected cohort				
HCV-related cirrhosis	5.6	13.4	18.9	24.9
Decompensated cirrhosis	0.7	3.2	6.1	11.2
HCV-related death	0.3	2.5	5.6	12.3
All-cause mortality				
General population	24.5	48.9	67.5	—
Transfused	46.1	59.7	72.4	—
HCV-infected only	46.4	61.7	76.3	—
	Years from 1999			
Posttransfusion HCV cohort, living in 1999				
HCV-related cirrhosis	11.8	20.2	—	29.4
Decompensated cirrhosis	3.5	7.7	—	14.9
HCV-related death	2.9	7.3	—	16.9
All-cause mortality				
General population	24.5	48.9	67.5	—
Transfused	46.1	59.7	72.4	—
HCV-infected only	46.4	61.7	76.3	—

The high probability of dying from the disease that necessitated the transfusion, the advanced age of the posttransfusion cohort, and the slow progression of hepatitis C reduces the number of transfusees that survive long enough to develop complications. Thus, only 14% of this cohort will develop cirrhosis after 20 years. Older patients are likely to die before developing complications from hepatitis C, whereas younger patients with a longer life expectancy have a higher risk of developing complications from hepatitis C that then shorten their lives.

The prognosis of HCV-infected individuals alive in 1999 with respect to liver disease is, paradoxically, worse than that of the overall cohort (Table 3). These patients have had viral hepatitis for 10 years, so many have already developed some liver fibrosis that may progress to cirrhosis. Second, all-cause annual mortality falls dramatically in those alive in 1999 because they have survived the excess mortality related to the disease that led to the transfusion.

Table 4 Monte Carlo Simulations (in percentages)

	Mean Value	Standard Deviation	95% Confidence Interval
20-year probability of cirrhosis	13.9	15	0–44
Lifetime probability of cirrhosis	26.2	19	0–64
20-year probability of liver death	2.5	28	0–8
Lifetime probability of liver death	12.3	72	0–27

Monte Carlo simulations (Table 4) highlight the fact that our long-term projections included a significant amount of uncertainty. At 20 years, 14% are predicted to develop cirrhosis, but the 95% confidence interval extends from 0% to 44%. Similarly, the 95% confidence interval surrounding the lifetime probability of liver death (12%) extends from 0% to 27%. Further model details and outputs, including age-related outputs, are available on request from the authors.

DISCUSSION

Several countries, including Ireland, France, Sweden, and New Zealand, have compensation programs for individuals thought to have acquired HCV infection through the blood supply. As the result of legal judgments, the National Health Service in Britain and the Hungarian government have been required to offer compensation to individuals with transfusion-acquired HCV infection.[46,47] Compensation programs have attracted public debate on the need for "no fault" compensation schemes for medical misadventure and the relative roles of government and the courts in assuming responsibility for settling compensation claims.[48–50] The specific value attached to HCV infections by compensation programs ($90,000 [Canada], $US10,700 [Hungary], £87,000 [United Kingdom]) is also of interest, in that the dollar value of compensation judgments represents an explicit societal valuation of an important health outcome. It is of particular interest to compare these figures to implicit valuations of HCV infections associated with the adoption of new blood-screening methods. Nucleic acid amplification testing, recently implemented by blood services in many developed countries, costs $CDN1.5 to 4.0 million/case of HCV prevented,[51,52] suggesting that the social value of

Table 5 Stage-Based Compensation Schedule for HCV-Infected Class Members

Level	Medical Condition	Maximum Cumulative Payment as Compensation for Damages	Fixed Payments as Compensation for Damages	Loss of Income	HCV Drug Therapy	Uninsured Treatment, Medication, and Out-of-Pocket Expenses	Care Costs
6	Liver transplant, decompensation, or HCC, BCL, SMC, RF	$225,000	$100,000	Yes	$1000/month	Yes	Up to $50,000 per year
5	Cirrhosis or PCT, TCP, GN	$125,000	$65,000	Yes	$1000/month	Yes	No
4	Bridging fibrosis	$60,000	No further fixed payment	Yes	$1000/month	Yes	No
3	Nonbridging fibrosis or compensable HCV drug therapy	$30,000–$60,000	$30,000 if income support waived	Only if $30,000 fixed payment waived	$1000/month	Yes	No
2	HCV PCR+	$30,000	$20,000	No	NA	Yes	No
1	HCV Ab+	$10,000	$10,000	No	NA	Yes	No

Note: HCV = hepatitis C virus; HCC = hepatocellular carcinoma; BCL = B-cell lymphoma; SMC = symptomatic mixed cryoglobulinemia; RF = renal failure requiring dialysis due to glomerulonephritis; PCT = unresponsive porphyria cutanea tarda causing disfigurement or disability; TCP = unresponsive thrombocytopenia; GN = glomerulonephritis not requiring dialysis; PCR = HCV polymerase chain reaction test, indicating the presence of HCV virus in the blood; Ab+ = presence of anti-HCV antibodies in the blood, indicating previous, but not necessarily current, infection with HCV; NA = not applicable.

blood-transmitted HCV infection, at least from the perspective of agencies responsible for the safety of the blood supply, may have changed in the context of public attention and litigation surrounding the issue of blood safety.

Canada's compensation program is unique in that it explicitly links the amount of compensation to the stage of HCV-related liver disease. The prognostic model described in this article was used to develop the compensation schedule described in Table 5 (http://www.hepc8690.ca). A revised version of this model linked to fibrosis stage is currently being calibrated using data gathered from individuals currently coming forward for compensation. The model will be used in an iterative way in coming years to ensure the sufficiency of the $CDN1.1 billion fund over the life expectancy of the remaining members of the posttransfusion cohort.

Our model offers useful predictions and new insights into the natural history of posttransfusion hepatitis C. It illustrates the importance of transfusion-related mortality in the first 10 years. It is mainly in the individuals who survive the first 10 years posttransfusion that the slowly evolving effects of hepatitis C have a chance to affect mortality. Our model demonstrates that the prognosis of HCV is not benign: Ultimately 1 in 4 will develop cirrhosis, and 1 in 8 will die from HCV-related causes. These rates are significantly higher than those quoted in narrative reviews.[53,54]

One of the limitations of our model is the uncertainty of our projections beyond 25 years due to our lack of understanding of the longer-term prognosis of the disease. Other limitations are lack of applicability of these projections to children, hemophiliacs, or patients co-infected with HIV, in whom progression rates to cirrhosis and competing mortality rates differ.

In our forecasts, we are projecting not only disease-specific prognoses but also Canadian practice patterns, including response to notification programs, rates of liver biopsy, antiviral therapy, and transplantation. Current practice in Canada may not be generalizable to other countries and will certainly change.

Limitations notwithstanding, this effort has allowed public representatives to direct compensation where it is most needed by employing a compensation scheme linked to disease stage. It has reduced the risk of premature fund depletion by placing compensation decisions on a reproducible, evidence-based foundation and represents a unique application of clinical epidemiology and decision modeling to a practical public policy problem.

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