Health care costs associated with hepatitis C: A longitudinal cohort study

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BACKGROUND: Disease-specific estimates of medical costs are important for health policy decision making.
OBJECTIVE: To identify predictors of health care costs associated with hepatitis C virus (HCV) seropositivity across disease phases.
METHODS: HCV laboratory tests from the BC Centre for Disease Control were linked to administrative data pertaining to health services and drugs dispensed to estimate costs among case subjects and controls. The case group comprised HCV seropositive individuals (n=20,001), and the control group comprised single-tested, HCV seronegative persons (n=70,752) identified between January 1997 and December 2004. Subject observation time was assigned to the three following disease phases: initial phase (after diagnosis), late phase (late-stage liver disease) and predeath phase (12 months before death). Case subjects and controls were matched for age, sex and a propensity score within each phase to determine the net cost attributable to HCV seropositivity, and were adjusted for demographic and clinical factors.
RESULTS: Costs increased with disease progression, with hospitalization being the highest cost component in all phases. Initial and late phase net costs (2005 Canadian dollars) were $1,850 and $6,000 per patient per year, respectively. Costs among case subjects were driven by age, comorbidities, mental illness, illicit drug use and HIV coinfection. While predeath case subject and control costs were virtually the same, costs were high and case subjects died at a younger age.
CONCLUSION: HCV seropositivity is associated with increased medical costs driven by viral sequelae and medicosocial vulnerabilities (ie, mental illness, illicit drug use and HIV coinfection). Cost mitigation and health outcome improvements will require broad-based prevention programming to reduce vulnerabilities and HCV treatment to prevent disease progression, respectively.

Key Words: *Cost of illness; Health economics; Hepatitis C; Liver disease; Net costs; Vulnerable populations*

Les frais de santé associés à l'hépatite C : Une étude de cohorte longitudinale

HISTORIQUE : Il est important d'évaluer les coûts médicaux liés à une maladie donnée pour prendre des décisions en matière de politiques de santé.
OBJECTIF : Déterminer les prédicteurs des coûts de santé associés à la séropositivité au virus de l'hépatite C (VHC) lors des diverses phases de la maladie.
MÉTHODOLOGIE : Les tests de laboratoire du VHC du *Centre for Disease Control* de la Colombie-Britannique étaient liés à des données administratives relatives aux services de santé et aux médicaments dispensés pour évaluer les coûts chez les sujets atteints et les sujets témoins. Le groupe atteint se composait de personnes séropositive au VIH (n=20 001) et le groupe témoin, de personnes séronégatives au VHC ayant subi un seul test de dépistage (n=70 752) dépistées entre janvier 1997 et décembre 2004. La période d'observation des sujets était divisée en trois phases pathologiques : phase initiale (après le diagnostic), phase tardive (maladie hépatique de phase tardive) et phase terminale (12 mois avant le décès). Les sujets atteints et les sujets témoins étaient appariés selon l'âge, le sexe et un indice de propension dans chaque phase pour déterminer les coûts nets attribuables à la séropositivité au VHC, le tout rajusté selon des facteurs démographiques et cliniques.
RÉSULTATS : Les coûts augmentaient avec l'évolution de la maladie, l'hospitalisation constituant l'élément de coût le plus élevé à toutes les phases. Les coûts nets de la phase initiale et de la phase tardive (en dollars canadiens de 2005) s'élevaient à 1 850 $ et à 6 000 $ par patient par année, respectivement. Les coûts chez les sujets dépendaient de l'âge, des comorbidités, de la maladie mentale, de la consommation de drogues illicites et de la co-infection par le VIH. Les coûts liés aux sujets en phase terminale et aux sujets témoins étaient virtuellement les mêmes, mais les coûts étaient élevés et les sujets atteints mouraient plus jeunes.
CONCLUSION : La séropositivité au VHC s'associe à une augmentation des coûts médicaux attribuable aux séquelles virales et à des vulnérabilités médicosociales (c'est-à-dire, maladie mentale, consommation de drogues illégales et co-infection par le VIH). Pour atténuer les coûts et améliorer les issues de santé, il faudra respectivement instaurer des programmes de prévention généralisés afin de réduire les vulnérabilités et traiter le VHC de manière à éviter l'évolution de la maladie.

An estimated 243,000 Canadians are infected with hepatitis C virus (HCV), approximately 20% remain undiagnosed and approximately 7900 are newly infected each year mostly as a result of illicit drug use (1,2). Three-quarters of those who acquire HCV become chronically infected, and 14% to 19% will develop cirrhosis within 20 years, leading to liver failure, hepatocellular carcinoma and death (3,4). The burden of HCV is expected to increase because new infections and the progression of liver disease in those already infected outpace the rate of spontaneous and treatment-induced viral clearance (5).

The direct costs of HCV infection are associated with physician services, hospitalization, diagnostic testing, antiviral therapy and treatment of liver disease; these costs vary according to disease stage (5-7). Published studies (7-9) have reported high costs for HCV-related hospital-based services, particularly among patients with comorbid illnesses such as HIV infection. To date, cost estimates have been limited by the lack of HCV uninfected control groups required to determine the HCV-related or net costs of infection. In addition, HCV costing has not addressed cost differences according to disease stage. Net costing and phase of care approaches have been used

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extensively in measuring cancer costs, and comprehensive cost estimates are equally important for planning HCV prevention and care programs (10-13).

Using linked laboratory and administrative data, we estimated the net costs of HCV infection over three phases of illness: the initial phase (after diagnosis), late phase (late-stage liver disease) and predeath phase (12 months before death) among residents of British Columbia (BC) undergoing serological testing for HCV. The net costs were calculated as the mean costs for HCV antibody-positive cases minus those of matched anti-HCV-negative controls. We also determined predictors of costs among the case subjects to elucidate health care cost drivers.

METHODS

The costs of care among individuals undergoing serological testing for HCV were determined from the three following data sources: HCV laboratory testing data from the BC Centre for Disease Control (BCCDC, Vancouver, BC); the BC Linked Health Database, which stores information on publicly insured physician services, inpatient hospital services (including hospital discharge abstract data), outpatient diagnostic and laboratory services, outpatient clinics and same-day surgery; and data regarding prescription drug use from PharmaNet, which captures prescriptions dispensed from community and hospital outpatient pharmacies in BC for which at least a portion was publicly funded.

Data linkage followed a multistep, anonymized process as outlined by the BC Ministry of Health and College of Pharmacists of BC (14,15). The present study was approved by the University of BC (Vancouver) and the University of Toronto (Toronto, Ontario) ethics review boards.

Since April 1, 1992, 95% of all of BC's HCV antibody tests (anti-HCV) have been performed at the BCCDC laboratory (16). Anti-HCV testers were eligible if they underwent at least one anti-HCV test during the study period (January 1, 1997 to December 31, 2004), had a valid personal health number, and provided their sex and date of birth. Case subjects were selected from seropositive individuals, while controls were selected from seronegative individuals who were tested only once within the study period. Observation time began at the time of the first positive anti-HCV test for case subjects, and the single negative anti-HCV test for controls, and ended either at death or the end of the study period.

Using the perspective of the BC Ministry of Health, the major components of publicly insured direct medical costs were used. These included physician services, inpatient and outpatient hospital services, outpatient diagnostic and laboratory testing, and outpatient prescription drugs. All costs were based on publicly paid service fees on the date of service delivery adjusted to 2005 Canadian dollars using the Statistics Canada consumer price index for BC.

The services of physicians practising in settings that do not submit encounter data, laboratory tests performed by the BCCDC laboratory, cancer treatments, costs related to continuing care (extended care and homecare) or emergency services were not available in the present linked dataset. Also unavailable were medications provided in other settings (eg, physician offices, clinics or emergency departments), those administered to hospitalized patients; those used to treat HIV/AIDS, cancer, transplant or renal disease; over-the-counter medications; and prescriptions for federally insured patients (eg, federal employees, persons in correctional institutions and Aboriginal peoples) (14).

Three phases of HCV infection were defined based on disease natural history: initial, late and predeath. Case subjects whose observation time was not associated with hospital procedures or diagnostic codes for late-stage liver disease or death were assigned to the initial phase; case subject observation time associated with a hospital diagnosis or procedure code (5) relating to late-stage liver disease (decompensated cirrhosis, liver cancer, variceal bleeding, encephalopathy, ascites or transplant [Appendix 1]) were assigned to the late phase; and the predeath phase was the 12 months preceding death from any cause. The phased approach considered costs and patterns of care at clinically meaningful points, and was appropriate because health care needs and services change with disease progression (13). However, these phases do not represent precise clinical disease stages.

Because persons at risk for HCV infection are often concurrently at risk for other social, economic and health-related problems (ie, mental illness, substance-use disorders, poverty, and coinfection with other blood-borne and sexually transmitted infections), it is important to control for the effect of these factors on resource use (17-19). Case subjects were matched with up to four control subjects based on age, sex and propensity score (20).

Propensity scores for each subject were calculated based on a general comorbidity score (Deyo-Charlson comorbidity index), socioeconomic quintile, rural residence and disease-specific comorbidities (21,22). Disease-specific comorbidities were defined by the presence of medical services plan or hospital discharge diagnoses, or service/procedure codes associated with HIV, hemophilia, illicit drug use, alcohol use and mental illness in the year before cohort entry (Appendix 2). The propensity score was then used a priori to match cases and controls to reduce bias (23).

Case subjects in each phase were 'greedy matched' with up to four controls based on the propensity score, sex and age (±5 years) (24). Each phase consisted of a unique cohort and was analyzed separately. Case subjects who contributed observation time to multiple phases were rematched to controls at entry into each phase (Figure 1). While some subjects may have contributed observation time to multiple phases, there was no overlap or duplication of case or control observation time and costs across phases. Controls were not matched to more than one case subject within a given phase. The quality of the match between case subjects and controls was evaluated using descriptive statistics on all variables for each phase and compared using standardized differences (25).

Because case subjects and controls were matched, cost differences represent the net cost or cost attributable to HCV seropositivity adjusted for demographic and clinical factors. Generalized estimating equation models, in which case-control pairs were treated as clusters, were used to generate mean and net case and control costs per 100 days for each phase and cost category. Service component and total costs for each subject in each phase were divided by the subject's observation time in the disease phase, standardized to a cost per 100 patient days and converted to annual costs. Finally, for HCV cases, predictors of total cost were identified using multiple linear regression with logarithmically transformed cost data to correct for skewness (26).

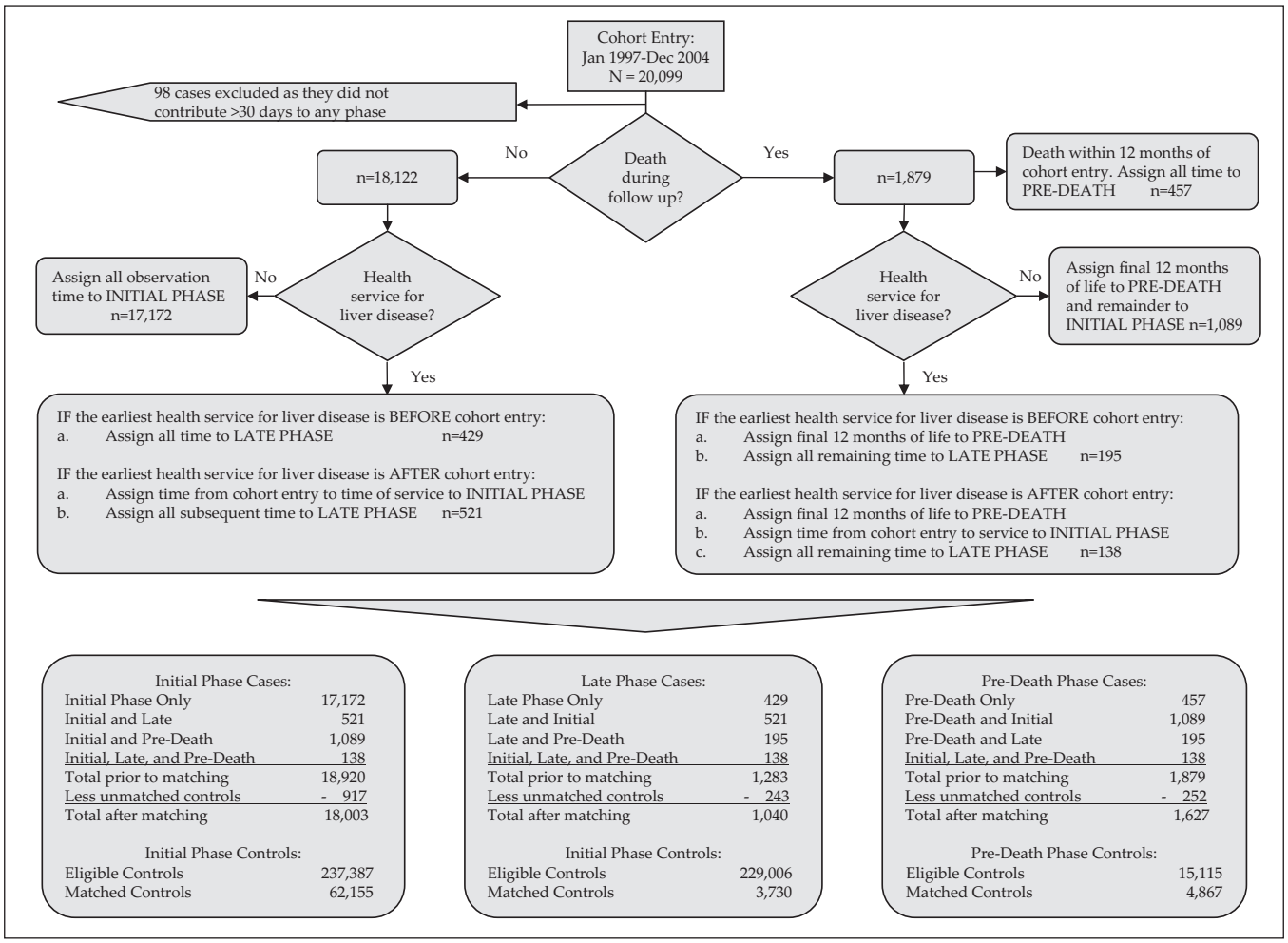

Figure 1) *Outcome of phase allocation and case-control matching. Dec December; Jan January*

RESULTS

Phase allocation and case-control matching resulted in 20,001 unique HCV cases (Figure 1). Of the case subjects, 18,058 (90%) contributed time to only one disease phase, 1805 (9%) to two phases and 138 (1%) to all three phases. The final numbers of matched cases were 18,003, 1040 and 1627 for the initial, late and predeath phases, respectively. Thus, the vast majority of observation time was related to the initial phase. Many case subjects who contributed person-time to the initial, late and predeath phases (917, 243 and 252, respectively) could not be matched with suitable controls. Unmatched cases were younger and had very high propensity scores related to multiple markers of vulnerability (ie, HIV, poverty, flags for addictions, mental illness and high Deyo-Charlson comorbidity index).

Table 1 summarizes sociodemographic and clinical characteristics, and overall matching between case subjects and controls across the disease phases. Despite intensive efforts to evenly match cases and controls, several attribute variables could not be evenly distributed and demonstrated standardized differences (sd) of greater than 0.10. For example, codes for mental health were higher among cases than controls across all phases (initial phase sd=0.20; late phase sd=0.19; and predeath phase sd=0.17). Comorbidities were higher in late phase cases than in controls (sd=0.58). Flags for illicit drug use were higher among cases than controls in the initial phase and predeath phase (initial phase sd=0.31; predeath phase sd=0.30). Finally, the mean ages of the initial, late and predeath phase cases were 43, 55 and 56 years, respectively. Predeath phase cases were younger than their matched controls (56.1 years versus 60.7 years, sd=0.26).

Table 2 summarizes health resource use. Total costs increased across disease phases, largely due to hospitalization. Increases in hospitalization correlated with reduced prescription drug costs from 26% of total costs in the initial phase to 4% in the predeath phase, in which drug costs while in hospital were included in overall hospitalization costs. Therefore, BC spent approximately $1,068/100 patient-days or $3,900/person/year and $3,013/100 patient-days or $11,000/person/year for initial and late phase patient care, respectively. Approximately one-half of these costs relate to HCV infection or related risks. For cases in the predeath phase, BC spent $10,281/100 patient-days or $37,530/person/year, which was virtually identical to the health-related costs of the controls during their final year of life.

Table 3 summarizes the net costs and CIs according to disease phase and service category. Net costs increased from $507/100 patient-days (95% CI $473 to $540) or $1,850/year in the initial phase, to $1,642/100 patient-days (95% CI $1,302 to $1,983) or $6,000/year in the late phase. Predeath costs were $22/100 patient-days or $80/year lower in case subjects than controls (95% CI –$972 to $929); however, given the CIs, no cost differences were observed for this disease phase.

TABLE 1
Baseline characteristics of matched cases and controls, and unmatched cases

	Disease phase								
	Initial			Late			Predeath		
Characteristic	Cases	Controls	Nonmatched	Cases	Controls	Nonmatched	Cases	Controls	Nonmatched
Subjects	18,003 (100)	62,155 (100)	917 (100)	1040 (100)	3730 (100)	242 (100)	1627 (100)	4867 (100)	252 (100)
Follow-up, days (mean ± SD)	1735±776	1714±780	2146±736	1478±808	1314±805	966±834	361±26	361±25	356±43
Age, years									
Mean ± SD	42.9±11.7	43.1±11.9	41.3±7.0	55.1±15.0	55.6±15.3	48.4±11.7	56.1±16.1	60.7±16.3	44.0±7.6
Median	43	43	42	52	53	48	52	60	45
0–10	106 (0.6)	417 (0.7)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.1)	1 (0.0)	0 (0.0)
11–20	233 (1.3)	947 (1.5)	1 (0.1)	3 (0.3)	12 (0.3)	1 (0.4)	0 (0.0)	7 (0.1)	0 (0.0)
21–30	1868 (10.4)	6244 (10.0)	63 (6.9)	33 (3.2)	126 (3.4)	10 (4.1)	41 (2.5)	131 (2.7)	12 (4.8)
31–40	5097 (28.3)	17,406 (28.0)	304 (33.0)	94 (9.0)	360 (9.7)	39 (16.1)	202 (12.4)	413 (8.5)	61 (24.2)
41–50	7214 (40.1)	23,999 (38.6)	485 (53.0)	350 (33.7)	1219 (32.7)	99 (40.9)	462 (28.4)	827 (17)	139 (55.2)
51–60	2264 (12.6)	8699 (14.0)	58 (6.3)	214 (20.6)	709 (19.0)	62 (25.6)	359 (22.1)	1160 (23.8)	36 (14.3)
61–70	727 (4.0)	2705 (4.4)	4 (0.4)	136 (13.1)	502 (13.5)	16 (6.6)	183 (11.3)	820 (16.8)	3 (1.2)
≥71	494 (2.7)	1738 (2.8)	0 (0.0)	210 (20.2)	802 (21.5)	14 (5.8)	378 (23.2)	1508 (31)	1 (0.4)
Sex									
Female	6467 (35.9)	22,929 (36.9)	254 (28.0)	386 (37.1)	1456 (39.0)	77 (31.8)	464 (28.5)	1634 (33.6)	78 (31.0)
Male	11,536 (64.1)	39,226 (63.1)	663 (72.0)	654 (62.9)	2274 (61.0)	165 (68.2)	1163 (71.5)	3233 (66.4)	174 (69.0)
Income quintile									
1 (low)	5907 (32.8)	19,016 (30.6)	454 (50.0)	318 (30.6)	1274 (34.2)	111 (45.9)	578 (35.5)	1349 (27.7)	133 (52.8)
2	3704 (20.6)	12,406 (20.0)	200 (21.3)	221 (22.0)	768 (20.6)	48 (19.8)	333 (20.5)	1023 (21.0)	42 (16.7)
3	2786 (15.5)	10,360 (16.7)	77 (13.8)	143 (8.4)	556 (14.9)	28 (11.6)	212 (13.0)	810 (16.6)	22 (8.7)
4	2523 (14.0)	9619 (15.5)	78 (15.2)	158 (8.5)	516 (13.8)	20 (8.3)	224 (13.8)	779 (16.0)	22 (8.7)
5 (high)	1856 (10.3)	7313 (11.8)	42 (13.1)	136 (4.6)	433 (11.6)	21 (8.7)	163 (10.0)	637 (13.1)	16 (6.3)
Missing	1227 (6.8)	3441 (5.5)	66 (6.2)	64 (7.2)	183 (4.9)	14 (5.8)	117 (7.2)	269 (5.5)	17 (6.7)
Rural flag									
No	15,646 (86.9)	54,453 (87.6)	847 (92.4)	892 (85.8)	3,143 (84.3)	207 (85.5)	1434 (88.1)	4241 (87.1)	242 (96.0)
Yes	2357 (13.1)	7702 (12.4)	70 (7.6)	148 (14.2)	587 (15.7)	35 (14.5)	193 (11.9)	626 (12.9)	10 (4.0)
Index year									
1996	–	–	–	–	–	–	51 (3.1)	145 (3.0)	7 (2.8)
1997	4071 (22.6)	13,827 (22.2)	427 (47.0)	169 (16.3)	641 (17.2)	20 (8.3)	147 (9.0)	410 (8.4)	21 (8.3)
1998	3184 (17.7)	10,520 (16.9)	262 (29.0)	135 (13.0)	510 (13.7)	25 (10.3)	174 (10.7)	542 (11.1)	22 (8.7)
1999	2640 (14.7)	8831 (14.2)	91 (9.9)	151 (14.5)	561 (15.0)	24 (9.9)	188 (11.6)	607 (12.5)	24 (9.5)
2000	2243 (12.5)	7778 (12.5)	47 (5.1)	153 (14.7)	570 (15.3)	29 (12.0)	222 (13.6)	628 (12.9)	43 (17.1)
2001	2190 (12.2)	7811 (12.6)	39 (4.3)	102 (9.8)	380 (10.2)	32 (13.2)	290 (17.8)	896 (18.4)	31 (12.3)
2002	1992 (11.1)	7177 (11.5)	40 (4.4)	136 (13.1)	480 (12.9)	32 (13.2)	272 (16.7)	846 (17.4)	39 (15.5)
2003	1683 (9.3)	6211 (10.0)	11 (1.2)	131 (12.6)	401 (10.8)	45 (18.6)	283 (17.4)	793 (16.3)	65 (25.8)
2004	–	–	–	63 (6.1)	187 (5.0)	35 (14.5)	–	–	–
Measures of comorbidity									
Deyo-Charlson comorbidity index									
0	17,498 (97.2)	61,150 (98.4)	864 (94.0)	564 (54.2)	3001 (80.5)	27 (11.2)	1270 (78.1)	3648 (75.0)	163 (64.7)
1	272 (1.5)	556 (0.9)	16 (1.7)	139 (13.4)	233 (6.2)	24 (9.9)	99 (6.1)	357 (7.3)	14 (5.6)
2	129 (0.7)	303 (0.5)	3 (0.3)	92 (8.8)	293 (7.9)	20 (8.3)	107 (6.6)	427 (8.8)	5 (2.0)
≥3	104 (0.6)	146 (0.2)	34 (3.7)	245 (23.6)	203 (12.4)	171 (70.7)	151 (9.3)	435 (8.9)	70 (27.8)
Disease-specific services flags (hepatitis C-related comorbidities)									
HIV	137 (0.8)	250 (0.4)	86 (9.4)	12 (1.2)	55 (1.5)	52 (21.5)	21 (1.3)	42 (0.9)	96 (38.1)
Mental health	6340 (35.2)	16,467 (26.6)	894 (97.5)	366 (35.2)	1670 (44.8)	206 (85.1)	545 (33.5)	1252 (30.1)	234 (92.9)
Illicit drug use	2930 (16.3)	4513 (7.3)	901 (98.3)	127 (12.2)	539 (14.5)	141 (58.3)	183 (11.2)	206 (4.2)	223 (88.5)
Alcohol use	1140 (6.3)	2179 (3.5)	185 (20.2)	129 (12.4)	541 (14.5)	152 (62.8)	154 (9.5)	303 (6.2)	66 (26.2)
Hemophilia	49 (0.3)	101 (0.2)	2 (0.2)	24 (2.3)	41 (1.1)	6 (2.5)	30 (1.8)	112 (2.3)	4 (1.6)

Data presented as n (%) unless indicated otherwise

TABLE 2
Mean health care costs* among cases and controls according to cost category and disease phase

	Disease phase					
	Initial		Late		Predeath	
Cost category	Cases	Controls	Cases	Controls	Cases	Controls
n	18,003	62,155	1040	3730	1627	4867
Total drug cost†, $	377	165	616	355	561	570
Nonpublicly paid portion, $	104	83	219	124	130	197
Publicly paid portion, $ (%)	273 (25.6)	82 (14.7)	397 (13.2)	231 (17.0)	431 (4.2)	373 (3.6)
MSP cost (physician and outpatient clinic services; outpatient diagnostic and laboratory services), $ (%)	307 (28.7)	203 (36.5)	687 (22.8)	338 (24.8)	1,073 (10.4)	1,124 (10.9)
Hospital cost (acute inpatient), $ (%)	446 (41.8)	232 (41.7)	1,712 (56.8)	721 (53.0)	8,667 (84.3)	8,707 (84.0)
Same-day surgery cost, $ (%)	42 (4.0)	39 (7.0)	216 (7.2)	72 (5.3)	110 (1.1)	157 (1.5)
Total cost‡, $ (%)	1,068 (100)	556 (100)	3,013 (100)	1,361 (100)	10,281 (100)	10,361 (100)

**Mean health care costs are expressed in 2005 $CAD per 100 patient days; 2005 $1 CAD = $0.83 USD; †PharmaNet files report two cost components: total drug cost (the full drug and dispensing fee) and the publicly paid portion (the portion of total drug cost that is paid by the provincial PharmaCare program). The remaining cost (nonpublicly paid portion) is generally paid by the patient at the time of receipt of the drug. It may also be paid at either the point of purchase or later reimbursed to the patient by a third-party payer. Both components are displayed to provide a more complete description of drug costs. However, only the publicly paid portion is included in these costing estimates; ‡Total cost includes only bolded categories, excluding nonpublicly paid portion of drug costs. MSP Medical services plan*

TABLE 3
Health care costs* attributable to hepatitis C according to cost category and disease phase

	Disease phase		
Cost category	Initial	Late	Predeath
Total drug cost	210 (200 to 219)	259 (199 to 319)	–9 (–55 to 38)
Publicly funded drug cost	190 (182 to 198)	165 (121 to 209)	58 (17 to 99)
MSP cost (physician and outpatient clinic services; outpatient diagnostic and laboratory services)	101 (96 to 107)	348 (288 to 408)	–50 (–126 to 26)
Hospital cost (acute inpatient)	213 (185 to 241)	987 (703 to 1,270)	14 (–885 to 912)
Same-day surgery cost	3 (1 to 5)	145 (113 to 176)	–47 (–69 to –24)
Net cost (hepatitis C-related cost)†	507 (473 to 540)	1,642 (1,302 to 1,983)	–22 (–972 to 929)
Net cost as a percentage of the mean total cost in cases, %	47.5	54.5	–0.2

**Health care costs expressed in 2005 Canadian dollars ($1 CAD = $0.83 USD) per 100 days (95% CI) unless indicated otherwise; †Net costs were generated using generalized estimating equation (GEE), and GEE modelling and rounding account for the minor cost differences in Tables 2 and 3. MSP Medical services plan*

Table 4 reports independent predictors of total costs among cases. Age and the Deyo-Charlson comorbidity index were significant cost predictors in all phases, although the pattern varied. Illicit drug use had an effect on initial and late phase costs, but not on predeath costs; mental illness was a significant predictor of costs only for the initial phase; and HIV infection was associated with increased costs in all three disease phases. There were no significant cost differences for unmatched cases in the adjusted model of costs.

A subset of case subjects had undergone HCV-RNA testing to determine whether their HCV infection was active (Table 4). In the natural history of HCV, approximately 25% of HCV infected individuals spontaneously clear HCV RNA but remain anti-HCV positive, indicating resolved infection. Among the cases, there were 8892, 627 and 450 subjects with HCV-RNA testing in initial, late and predeath phases, respectively. Of these, 81%, 84% and 81% were RNA positive, across the respective disease phases. While these individuals were classified as case subjects based on their positive anti-HCV status, those who were HCV RNA negative are known to be at very low risk of viral-related sequelae (27,28). Case subjects who did not undergo HCV RNA testing had lower costs (19% less in the initial, 13% less in the late and 15% less in the predeath disease phase).

DISCUSSION

During the initial and late disease phases, BC spent an estimated $1,850/person/year and $6,000/person/year, respectively, on direct HCV-related health care. Costs increase with disease progression and hospitalization was the largest cost component across all disease phases, followed by medical services and publicly funded drugs. While no increase in the net cost was observed for the predeath phase, two limitations need to be considered. First, PharmaNet does not capture medications used in HIV/AIDS, cancer, transplant or renal disease, and the BC Linked Health Database files do not capture cancer care costs. Thus, capture of costs relating to known causes of death in individuals infected with HCV is incomplete (29). Second, while predeath costs for cases and controls were similar, case subjects died at a significantly younger age, suggesting potential years of life lost due to HCV-related illness not accounted for by direct costing (4,30). Our findings align with previous work (8,29,31) showing higher costs and earlier mortality among HCV monoinfected and HCV-HIV coinfected individuals.

Approximately 14% to 19% of individuals chronically infected with HCV develop cirrhosis within 20 years, leading to liver failure, hepatocellular carcinoma and death (3,4). Thus, late and predeath disease phase case subjects reflect the relatively small proportion of HCV patients requiring medically

TABLE 4
Predictors of total health cars costs in persons with hepatitis C (HCV)

	Disease phase					
	Initial		Late		Predeath	
Characteristic	e^{β}*	95% CI	e^{β}	95% CI	e^{β}	95% CI
Age, years						
≤30	0.954	0.925–0.983	0.973	0.819–1.157	0.79	0.644–0.968
31–40 (referent)	1.00	–	1.00	–	1.00	–
41–50	1.057	1.034–1.081	1.099	0.99–1.22	1.169	1.054–1.297
51–60	1.205	1.169–1.243	1.148	1.023–1.288	1.362	1.214–1.529
61–70	1.428	1.36–1.50	1.244	1.095–1.413	1.437	1.25–1.652
≥71	1.537	1.45–1.63	1.23	1.09–1.389	1.291	1.143–1.457
Sex						
Male (referent)	1.00		1.00		1.00	
Female	1.115	1.094–1.136	1.061	0.997–1.128	1.199	1.115–1.289
Deyo-Charlson comorbidity index						
0 (referent)	1.00	–	1.00	–	1.00	–
1	1.464	1.361–1.575	1.245	1.134–1.366	1.355	1.177–1.559
2	1.603	1.44–1.785	1.359	1.22–1.515	1.363	1.185–1.569
3+	1.407	1.249–1.584	1.352	1.252–1.459	1.375	1.226–1.542
Income quintile						
1–low (referent)	1.00	–	1.00	–	1.00	–
2	0.984	0.96–1.009	0.943	0.871–1.022	1.07	0.978–1.171
3	0.973	0.946–1	0.999	0.91–1.096	0.941	0.846–1.047
4	0.956	0.929–0.984	0.969	0.884–1.062	0.948	0.854–1.053
5–high	0.944	0.914–0.975	0.961	0.873–1.059	0.929	0.825–1.046
Missing	0.95	0.915–0.986	1.058	0.93–1.203	0.906	0.794–1.033
Index year						
1996	–	–		–	1.00	–
1997	1.00	–	1.00	–	0.914	0.75–1.114
1998	0.984	0.957–1.012	1.089	0.975–1.217	0.974	0.801–1.184
1999	0.966	0.938–0.995	1.037	0.931–1.156	0.945	0.778–1.148
2000	0.98	0.95–1.012	1.026	0.921–1.144	0.981	0.811–1.187
2001	0.966	0.936–0.998	1.032	0.916–1.161	0.906	0.75–1.093
2002	0.931	0.9–0.962	0.915	0.815–1.026	0.909	0.75–1.1
2003	0.97	0.936–1.005	0.967	0.862–1.085	0.811	0.67–0.981
2004	–	–	1.293	1.127–1.484	–	–
Rural flag	0.968	0.942–0.994	0.955	0.878–1.038	0.978	0.879–1.088
Disease-specific use of health services (HCV-related comorbidities)						
Alcohol related	1.034	0.996–1.073	1.031	0.943–1.128	1.01	0.902–1.131
Hemophilia related	1.353	1.14–1.607	1.08	0.894–1.305	1.381	1.083–1.76
HIV related	1.38	1.255–1.518	1.175	1.01–1.367	1.288	1.088–1.524
Illicit drug related	1.23	1.193–1.268	1.219	1.109–1.339	1.084	0.96–1.224
Mental health related	1.224	1.195–1.255	1.075	0.996–1.161	1.046	0.958–1.141
Nonmatched cases	0.993	0.947–1.041	0.925	0.823–1.04	1.006	0.874–1.159
HCV RNA testing (polymerase chain reaction testing)						
HCV RNA negative (referent)	1.00	–	1.00	–	1.00	–
HCV RNA positive	1.08	1.044–1.116	0.985	0.882–1.1	1.048	0.881–1.247
No HCV RNA test	0.812	0.787–0.839	0.866	0.775–0.967	0.848	0.721–0.998

**e^{β} refers to the exponential of the regression coefficient interpreted as the relative change in median cost with a one-unit increase in predictor variable*

cost-intensive services. These cases represent a missed opportunity to prevent chronic HCV sequelae by using potentially curative treatment (32).

In contrast, initial phase case subjects have a special significance when one considers that the majority of prevalent cases will spend decades in this phase. Initial phase case costs increased with age, comorbid conditions, HIV infection, illicit drug use and mental illness. Nguyen et al (31) reported that physician and hospital service costs among HCV patients tended to be highest in the year following diagnosis, largely related to mental health services. Using methods similar to the present study, a Canadian research group found mental health and drug-related services to be important predictors of initial phase HCV costs for the province of Ontario (M Patterson and M Krahn, unpublished data, 2009).

In the initial phase, mental illness and illicit drug use are both risk factors for HCV acquisition and contribute to health care costs. It remains challenging to separate costs of the medical sequelae of HCV infection from acquisition-related risks and costs. Sulkowski and Thomas (19) reviewed the complex inter-relationship of HIV/HCV coinfection, illicit drug use, and mental illness and its impact on the delivery of medical

care for both infections. They determined that the higher rates of illicit drug use, mental illness and poverty confounded the assessment of the relative impact of mono- or coinfection and this was likely the case in our study. Future studies based on RNA status can further differentiate these costs. For example, the lower costs in subjects who did not undergo HCV RNA testing suggest that this test may also be a marker for access to care and treatment. In addition, we found only minor differences in costs between HCV RNA-positive or -negative cases suggesting that a substantial proportion of costs reflects the impact of mental health and addictions rather than viral sequelae. While intriguing, it is important not to over interpret these findings because the present study was not designed to assess the impact of HCV RNA status on costs.

In BC, the cost of treating HCV infection with antivirals is estimated to range from $11,000 to $20,000 per completed patient course of treatment, depending on the genotype and number of weeks of treatment (33). During the study period, a very limited number of cases underwent antiviral treatment; approximately 1% of initial and late-phase case subjects and 0.2% of predeath phase case subjects received treatment during the costing period. Overall, antiviral treatments represented 0.7% of the reported case costs; however, this is an underestimate because PharmaNet data does not provide information about treatment starts in clinical trials, prison, or via federal or private payers. It is also important to note that pegylated interferon and ribavirin only became publicly funded in BC in May 2003. While treatment-related drug costs were a relatively trivial proportion of the HCV-attributable costs in our study, these costs would be expected to rise substantially with widespread treatment.

The two main limitations of the current study are that the predeath cost estimates did not capture all of the costs that are related to the recognized causes of HCV mortality, and that mental illness, addictions and behaviours known to correlate with the risk of HCV acquisition confound our ability to tease apart the HCV-attributable costs that relate to the risk of acquiring infection versus the consequences of the infection itself. The limitation in our ability to accurately quantify the impact of social vulnerability on costs occurs at two levels. First, valid personal health number identifiers are required for data linkage, and 14% of testers in the present study could not be linked to their administrative data; thus, a proportion of those most vulnerable were excluded from data linkage. In addition, certain case subjects could not be matched to controls because of their profound vulnerabilities (ie, HIV, poverty, flags for addictions, mental illness and high Deyo-Charlson comorbidity index). These unmatched case subjects had multiple markers of vulnerability suggesting that generalizability of the net costs to those most vulnerable is limited. The challenges in matching cases and controls speak to the nature of HCV positive testers as individuals with multiple comorbidities with a high level of health and social vulnerability. Limited capture of the costs of those most vulnerable combined with the use of seronegative single testers as controls, who might have some risk of HCV infection to justify serological testing, tends to make our cost estimates conservative.

The present study also has important strengths. The cohort was drawn from a large, comprehensive sample of anti-HCV testers in the province of BC. Detailed matching of cases and controls for such a large number of subjects would not be possible using traditional case-by-case follow-up. Both the serological data and the administrative health data were longitudinal, which enabled assessment of health resource use across time and the disease phases. Finally, we were able to base cost estimates on several sectors – not just hospitalization – and the use of control group matching provided a first estimate of HCV net costs.

HCV-related health care costs in BC are considerable and likely on par with annual provincial spending on HIV-related direct medical costs. While there are few studies with estimates of direct costs of HIV/AIDS, in 2006, Levy et al (34) and, in 2003, Krentz et al (35) reported that the total direct costs for treating HIV/AIDS in Canada was $11,196/person/year (2001 US dollars), not stratified according to disease phase. BC has reported 12,966 HIV-positive cases since 1989 (36). Not accounting for mortality or migration, this would suggest BC spends approximately $145 million/year on HIV/AIDS care, with about two-thirds of costs related to treatment.

A similar gross estimate can be made for HCV. Remis (1) estimated 9% of those Canadians living with HCV in 2007 had cirrhosis or liver failure. In BC, there were 62,214 HCV antibody positive cases reported in the Integrated Public Health Information System as of December 31, 2008 (BCCDC, unpublished data). If we apply this to the estimated $1,850/person/year and $6,000/person/year for initial and late-phase net costs, respectively, provincial spending on HCV-related health care approaches $136 million/year (assuming 89% are in initial phase [55,371×$1,850 = $102 million] and 9% are late phase [5,600×$6,000=$34 million] and 2% are in predeath phase [with no identified net costs]). Compared with HIV direct costs, a much lower proportion of costs are drug related. Future research on lifetime cost estimates of HCV is required to accurately gauge provincial and national spending on HCV.

HCV seropositivity is correlated with substantial increases in direct health care costs. Accurate costing of HCV infection will require refinements in assessing costs related to viral sequelae, and adjusting for underlying risk factors and related comorbidities. It is clear that prevention aimed at mental health and addictions, as well as HCV treatment are required to mitigate the costs and health outcomes in this population.

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Appendix 1: Late-phase conditions

Charlson comorbidity index	CCP code	ICD-10 code	ICD-9 code	Description
1NA13BA	1006	B190	0706	Unspecified viral hepatitis with hepatic coma
1NA13BABD	1006	C220	1550	Malignant neoplasm of liver, primary
1NA13BAFA	5421	C229	1552	Malignant neoplasm of liver, not specified as primary or secondary
1NA13BAX7	5421	D695	2874	Secondary thrombocytopenia

Continued on next page

Appendix 1: Late-phase conditions – CONTINUED

Charlson comorbidity index	CCP code	ICD-10 code	ICD-9 code	Description
1OA59DAGX	6219	D696	2875	Thrombocytopenia, unspecified
1OA59DAX7	6219	D731	2894	Hypersplenism
1OA59HAX7	6294	G934	3483	Encephalopathy, unspecified
1OA59LAAD	6219	I81	452	Portal vein thrombosis
1OA59LAGX	6219	I850	4560	Esophageal varices with bleeding
1OA85LAXXK	624	I859	4561	Esophageal varices without mention of bleeding
1OA85WLXXJ	6241	I864	4568	Varicose veins of other sites
1OA85WLXXK	6249	K703	5712	Alcoholic cirrhosis of liver
1OA87LA	6249	K704	5728	Other sequelae of chronic liver disease
1OA87LAAZ	6249	K720	570	Acute and subacute necrosis of liver
1OT52HA	6212	K721	5728	Other sequelae of chronic liver disease
3OT20WE	6212	K729	5728	Other sequelae of chronic liver disease
3OT40WC	6691	K766	5723	Portal hypertension
	251	K767	5724	Portal hypertension
	276	R161	7892	Splenomegaly
		R162	7891	Hepatomegaly
		R17	7824	Jaundice unspecified, not of newborn
		R18	7895	Ascites
		T86400	9968	Complications of transplanted organ
		T86401	9968	Complications of transplanted organ
		T86402	9968	Complications of transplanted organ
		T869	9968	Complications of transplanted organ
		Z944	V427	Organ or tissue replaced by transplant – liver

CCP Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; ICD International Classification of Diseases (9th and 10th Revisions)

Appendix 2: Disease-specific comorbidities

ICD-10 code	Description
Alcohol abuse	
Z714	Alcohol abuse counselling and surveillance
Y573	Alcohol deterrents causing adverse effect in therapeutic use
Z502	Alcohol rehabilitation
Y919	Alcohol involvement, not otherwise specified
Z721	Alcohol use
I426	Alcoholic cardiomyopathy
K703	Alcoholic cirrhosis of liver
K700	Alcoholic fatty liver
K702	Alcoholic fibrosis and sclerosis of liver
K292	Alcoholic gastritis
K704	Alcoholic hepatic failure
K701	Alcoholic hepatitis
K709	Alcoholic liver disease, unspecified
G721	Alcoholic myopathy
G621	Alcoholic polyneuropathy
K860	Alcohol-induced chronic pancreatitis
X65	Intentional self-poisoning by and exposure to alcohol
F100	Mental and behavioural disorders due to use of alcohol, acute intoxication
F101	Mental and behavioural disorders due to use of alcohol, harmful use
F102	Mental and behavioural disorders due to use of alcohol, dependence syndrome
F103	Mental and behavioural disorders due to use of alcohol, withdrawal state
F104	Mental and behavioural disorders due to use of alcohol, withdrawal state with delirium
F105	Mental and behavioural disorders due to use of alcohol, psychotic disorder
F106	Mental and behavioural disorders due to use of alcohol, amnesic syndrome
F107	Mental and behavioural disorders due to use of alcohol, residual and late-onset psychotic disorder
F108	Mental and behavioural disorders due to use of alcohol, other mental and behavioural disorders
F109	Mental and behavioural disorders due to use of alcohol, unspecified mental and behavioural disorder
Z8640	Personal history of alcohol abuse
HIV	
Z717	HIV counselling
B24	HIV disease
R75	Laboratory evidence of HIV
Z21	Asymptomatic HIV infection status
F024	Dementia in HIV disease
Hemophilia	
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
Drug abuse	
Z715	Drug abuse counselling and surveillance
Z722	Drug use
Z8641	Personal history of drug abuse
F110–149	Mental and behavioural disorders due to opioids, cannabinoids, sedatives, hypnotics, cocaine, various presentations
F160–169	Mental and behavioural disorders due to stimulants, hallucinogens, various presentations
F190–199	Mental and behavioural disorders due to multiple drug use and use of psychoactive substances, various presentations
R782	Finding of cocaine in blood

Appendix 2: Disease-specific comorbidities – CONTINUED

ICD-10 code	Description
R783	Finding of hallucinogen in blood
R781	Finding of opiate drug in blood
R784	Finding of other drugs of addictive potential in blood
R788	Finding of other specified substances, not normally found in blood
R785	Finding of psychotropic drug in blood
R789	Finding of unspecified substance, not normally found in blood
T407	Poisoning by cannabis (derivatives)
T405	Poisoning by cocaine
T401	Poisoning by heroin
T408	Poisoning by lysergide (LSD)
T403	Poisoning by methadone
T400	Poisoning by opium
T406	Poisoning by other and unspecified narcotics
T409	Poisoning by other and unspecified psychodysleptics (hallucinogens)
T402	Poisoning by other opioids
T404	Poisoning by other synthetic narcotics
T436	Poisoning by psychostimulants with abuse potential
Mental illness	
F04	Organic amnesic syndrome, not induced by alcohol and other psychoactive substances
F050	Delirium not superimposed on dementia, so described
F051	Delirium superimposed on dementia
F058	Other delirium
F059	Delirium, unspecified
F060–F066	Organic mental disorders, various (not drug induced)
F070	Organic personality disorder
F071	Postencephalitic syndrome
F072	Postconcussional syndrome
F078	Other organic personality and behavioural disorders due to brain disease, damage and dysfunction
F079	Unspecified organic personality and behavioural disorder due to brain disease, damage and dysfunction
F09	Unspecified organic or symptomatic mental disorders
F21	Schizotypal disorder
F24	Induced delusional disorder
F28	Other nonorganic psychotic disorders
F29	Unspecified nonorganic psychosis
F39	Unspecified mood (affective) disorder
F54	Psychological and behavioural factors associated with disorders or diseases classified elsewhere
F55	Abuse of nondependence-producing substances
F59	Unspecified behavioural syndromes associated with physiological disturbances and physical factors
F61	Mixed and other personality disorders
F69	Unspecified disorder of adult personality and behaviour
F99	Mental disorder, not otherwise specified
F200–F209	Schizophrenia, various presentations
F220	Delusional disorder
F228	Other persistent delusional disorders
F229	Persistent delusional disorder, unspecified
F230	Acute polymorphic psychotic disorder without symptoms of schizophrenia
F231	Acute polymorphic psychotic disorder with symptoms of schizophrenia
F232	Acute schizophrenia-like psychotic disorder
F233	Other acute predominantly delusional psychotic disorders
F238	Other acute and transient psychotic disorders
F239	Acute and transient psychotic disorder, unspecified
F300	Hypomania
F301	Mania without psychotic symptoms
F302	Mania with psychotic symptoms
F308	Other manic episodes
F309	Manic episode, unspecified
F310–F319	Bipolar affective disorders, various presentations
F319–F323	Depressive disorders, by severity, various presentations
F328–F334	Other depressive episodes, by frequency, various presentations
F338–F339	Other recurrent depressive disorders, various presentations
F340	Cyclothymia
F341	Dysthymia
F348	Other persistent mood (affective) disorders
F349	Persistent mood (affective) disorder, unspecified
F380	Other single mood (affective) disorders
F381	Other recurrent mood (affective) disorders
F388	Other specified mood (affective) disorders
F400–F402, F408–F409	Phobias, various
F410	Panic disorder (episodic paroxysmal anxiety)
F411–F413, F418–F419	Anxiety disorders, various
F420–F422, F428-F429	Obsessive compulsive disease, various
F430–F432, F438–F439	Acute stress disorders, various
F440–F449	Dissociative disorders, various
F450–F454, F458–F459	Somatoform disorders, various
F480–F481, F488–F489	Neurotic disorders, various
F500–F509	Eating disorders, various
F515–F529	Sleeping and sexual disorders, various
F530–F531, F538–F539	Puerperal mental disorders, various
F600–F609	Personality disorders, various presentations
F620-F621, F628–F629	Enduring personality change, various
F630–F633, F638–F639	Habit and impulse disorder, various
F640–F642, F648-F649	Gender identity disorders, various
F650–F659	Multiple disorders of sexual preference
F660–F662, F668–F669	Psychosexual relational disorders, various
F680–F681, F688	Other specified disorders of adult personality and behaviour
F900–F901, F908-F909	Hyperkinetic disorders, various
F910–F913, F918-F919	Conduct disorders, various
F920	Depressive conduct disorder
F928	Other mixed disorders of conduct and emotions
F929	Mixed disorder of conduct and emotions, unspecified
X60–X84	Intentional self-harm, various methods
X7400–X7401, X7408–X7409	Intentional self-harm, various methods

ICD International Classification of Diseases, 10th Revision

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