Dig Dis Sci (2012) 57:2995–3003
DOI 10.1007/s10620-012-2233-1

ORIGINAL ARTICLE

The Burden of Untreated Hepatitis C Virus Infection: A US Patients' Perspective

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Received: 17 February 2012 / Accepted: 2 May 2012 / Published online: 5 June 2012
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Abstract
Background Hepatitis C virus (HCV) infection is widespread and associated with high economic costs and reduced quality of life, but the impact of untreated HCV infection on patient outcome is not well understood.
Aims To estimate the impact of untreated HCV infection on work productivity, daily activity, healthcare use, economic costs, and health-related quality of life (HRQoL).
Methods Respondents to the 2010 US National Health and Wellness Survey ($n = 75{,}000$) reporting physician diagnosis of HCV infection but not current or previous treatment (patients) were matched to respondents without HCV infection (controls) by use of propensity scores. Those reporting infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) were excluded. Self-reported work impairment, activity impairment, healthcare resource use, and HRQoL were compared between patients and controls. Indirect and direct costs were estimated.
Results A total of 306 patients met inclusion criteria. Patients were more impaired at work than controls, with overall work impairment of 26 % versus 15 %, respectively ($P < 0.001$), mostly because of presenteeism in both groups. Annual productivity losses were estimated at $10,316 per employed patient compared with $5,469 per control ($P < 0.001$). Patients used more healthcare, with all-cause healthcare costs estimated at $22,818 per patient annually, compared with $15,362 per control ($P < 0.001$). HRQoL and activity impairment were also worse among patients than controls.
Conclusions Untreated HCV infection is associated with substantial economic costs to society, through loss of productivity and increased use of healthcare resources, and with impaired well-being of the patient.

Keywords Hepatitis C virus · Work impairment · Indirect costs · Direct costs · Health-related quality of life

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Introduction

Hepatitis C virus (HCV) infection is a blood-borne illness affecting over 3 million Americans and approximately 160 million people worldwide [1]. In the early stages of infection, symptoms such as fatigue, abdominal pain, fever, and jaundice may be observed; most often, however, it is asymptomatic and therefore undetected [2]. Some patients will clear the infection on their own, but approximately 75 % go on to develop chronic infection [3].

If left untreated, chronic HCV infection puts patients at increased risk for cirrhosis, liver failure, and hepatocellular carcinoma (HCC), which are associated with high morbidity and mortality [4, 5]. Chronic HCV infection is already responsible for more liver transplantations than any other causes, and HCV-related deaths are estimated to be at least 10,000 per year in the US, with the rate expected to increase in the coming decades as the long-term consequences of chronic infection become manifest [5–7].

Until recently, the standard of care for HCV infection consisted of dual therapy with pegylated interferon and ribavirin [8, 9], which has enabled many patients to achieve sustained virologic response (SVR), defined as the absence of HCV RNA in serum by a sensitive test at the end of treatment and six months later. Such patients have effectively been cured of HCV, and are at much lower risk of cirrhosis and liver cancer than patients who do not achieve SVR [10]. However, the decision of whether to treat has been complicated by the high incidence of adverse events and the uncertain outcome of treatment, especially among patients infected with genotype 1, the most resistant to dual therapy and the most common type in US patients. Published data suggest overall treatment of approximately 12–27 % [11, 12] and SVR of less than 50 % for genotype 1 prevalent in the US [13]. Recent advances in treatment for this strain have resulted in better efficacy [14–17], which is likely to encourage more patients and their physicians to opt for treatment. This makes understanding the economic and humanistic implications of leaving HCV infection untreated especially important for policy makers.

Previous research has documented a significant burden of HCV infection on work productivity [18, 19], use of healthcare resources and related costs [9, 19–22] and health-related quality of life (HRQoL) [23–25]. However, the burden of the HCV infection when left untreated is not well understood. Studies have commonly relied on samples which may not be representative of the HCV population in general [23] or ignored treatment status [18, 24], both of which are important limitations. Conclusions based on unrepresentative samples may not generalize to the broader population, and the relationship between treatment and outcomes is complex. Dual therapy with peginterferon and ribavirin is associated with its own burden and limited efficacy, whereas successful treatment is associated with subsequent improvements in HRQoL and liver function [26, 27].

There is also much variation in estimates of the monetary cost of productivity impairments and resource utilization in HCV [19–21]. Several analyzed only the year after diagnosis [20, 21], which may be a year of unusually high costs—especially among those undergoing treatment [9, 28]—rather than the costs in a typical year. They also excluded patients who were unemployed or not commercially insured, which is likely to be a substantial portion of the overall HCV population.

Because of these shortcomings, the economic and humanistic burden of treatment-naïve patients is not well understood. The objective of this study was to quantify the burden of HCV infection in treatment-naïve patients from a broadly representative sample of US adults, including estimates of direct and indirect costs.

Methods

Data from the 2010 US National Health and Wellness Survey (NHWS; Kantar Health, New York, NY, USA) were used. This is an annual, cross-sectional survey of 75,000 US adults aged 18 years and older. The NHWS includes questions about more than 150 diagnosed medical conditions, experience with prescription treatments for those conditions, health-related attitudes and behavior, use of healthcare resources, and health outcomes. Outcomes are assessed by use of validated scales embedded within the survey, including the SF-12v2 [29] for measuring health-related quality of life (HRQoL) and the Work Productivity and Activity Impairment questionnaire [30] for assessing impairment at work and in daily activity, discussed in greater detail below. Potential respondents to the NHWS were recruited from an existing consumer panel of approximately three million US residents. The consumer panel recruited its members by use of opt-in emails, co-registration with panel partners, e-newsletter campaigns, and online banner placements. All panelists explicitly agreed to be a panel member, registered with the panel through a unique email address, and completed an in-depth demographic registration profile. A stratified random sampling framework (with quotas based on gender, age, and race/ethnicity) was implemented within this panel to construct a sample for the NHWS that matches the US census according to age, gender, and ethnicity. Response to the survey was 16 %. The 2010 NHWS was approved by the Essex Institutional Review Board (Lebanon, NJ, USA) and all respondents provided informed consent.

Exclusion criteria for this study were self-report of HIV, AIDS, or Hepatitis B virus infection. HCV infected patients who reported current or previous treatment for HCV were also excluded.

Because HCV infected patients are known to differ significantly from the general population, a propensity scoring method was used to match individuals without HCV infection (controls) to those with HCV infection [31]. Age, gender, race/ethnicity (white, black, Hispanic, or other), sexual orientation (heterosexual, homosexual, bisexual, or decline to answer), education (high school graduate vs. not high school graduate), household income (<25 K, 25 to <50 K, 50 to <75 K, 75 K+), possession of health insurance, number of non-liver comorbidities, currently smoke cigarettes (yes/no), exercise in last 30 days (yes/no), alcohol use (yes/no), and BMI (underweight, normal, overweight, obese, or decline to answer) were included in a logistic regression to predict self-reported HCV infection. Each HCV infected patient was matched with a control subject whose probability of HCV infection, as estimated by the regression model (propensity score), was nearest, by use of a SAS macro (greedy matching algorithm). The greedy matching algorithm is one of the most widely used algorithms in propensity score matching analysis and enables each case to be matched with the most suitable control available at that point in the matching process [32].

Outcome Variables

The Work Productivity and Activity Impairment (WPAI) questionnaire was used to measure the impact of health on employment-related activity [30]. The WPAI is a six-item validated instrument that provides three measures of impairment: absenteeism (the percentage of work time missed in the past seven days because of one's health), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment of daily activities because of one's health in the past seven days). Only respondents who reported being employed full-time, employed part-time, or self-employed provided data for absenteeism, presenteeism, and overall work impairment. All respondents provided data for activity impairment. Absenteeism was calculated by dividing the number of work hours a patient missed in the past week because of his or her health by the total number of hours a patient could have worked (the number of hours he/she did work plus the number of hours missed because of his/her health). Presenteeism was computed from a patient's rating of his or her impairment while at work in the past seven days from 0 ("Health problems had no effect on my work") to 10 ("Health problems completely prevented me from working"), which was then divided by 10 and converted to a percentage, with a range from 0 to 100 %. Overall work impairment was measured by adding absenteeism and presenteeism to determine the total percentage of lost work time. Activity impairment was derived from a patient's rating of impairment of daily activities in the past seven days on a 0 ("Health problems had no effect on my daily activities") to 10 ("Health problems completely prevented me from doing my daily activities") scale. This value was then divided by 10 and converted to a percentage, with a range from 0 to 100 %.

Indirect costs were estimated by use of the procedure described by Lofland and colleagues to infer costs from the WPAI by use of a human capital approach [33]. Each patient's absenteeism and presenteeism was converted into an estimate of hours of lost productivity per year by multiplying the weekly value by 50, the customary number of weeks worked annually by US employees. This yearly figure was then multiplied by an hourly wage to monetize the lost productivity. As the NHWS does not collect information on personal income, the hourly wages used in the calculations were estimated by using the 2010 median weekly income figures from the US Bureau of Labor Statistics (BLS), stratified by age and gender [34]. The median weekly income figures from the BLS were divided by 40, the number of hours in a conventional work week.

Healthcare resource use was assessed as the number of reported visits in the last 6 months to traditional healthcare providers, the emergency room (ER), and the number of times hospitalized for the patient's own medical condition. Healthcare providers include general practitioners/family practitioners, internists and dentists, and more specialized physicians. Self-reported values were doubled to obtain an annual estimate. Direct costs were estimated by multiplying each patient's annualized healthcare use by the average 2010 cost of each type of service as reported in the Medical Expenditure Panel Survey (MEPS) [35], stratified by age (18–44, 45–64, or 65 and older). The MEPS is a large US government survey study assessing healthcare resource use and cost. The unit cost within the database represent the payments made to healthcare providers according to the type of service, including both out-of-pocket payments by the patient and contributions from insurance. Full details of determination of costs within MEPS are available online (http://meps.ahrq.gov).

The Medical Outcomes Study 12-Item Short Form Survey Instrument, revised edition (SF-12v2) was used to assess HRQoL [29]. This is a multipurpose, generic HRQoL instrument comprising 12 questions selected from the SF-36 health survey [36]. Details of development, norming, and scoring algorithms are given elsewhere [29]. This analysis included three metrics derived from the scale: physical component summary score (PCS), assessing physical health; mental component summary score (MCS), assessing mental health; and SF-6D, a preference-based measure for health using general population values [37]. MCS and PCS scores are interpreted as normal scores, with a mean of 50 and a standard deviation of 10 for the US population. A review of minimum clinically important differences (MCID) in MCS and PCS scores found typical clinically validated MICD for these scales to be 3–5 points [38]; 3–5 points also represents effect sizes proposed as criteria for MCID [39, 40]. Differences of 0.03 on the SF-6D are often regard as the MCID [41].

Statistical Analysis

SPSS 19.0 was used for the analysis. Mean and standard deviation were calculated for all continuous measures, and frequency distributions were scrutinized for skewness and kurtosis. Frequencies and percentages were computed for categorical variables. Differences between the groups were analyzed by using χ^2 tests for categorical variables and t tests for continuous, normally distributed variables, which included the MCS, PCS, and SF-6D scores. Mann–Whitney U tests were conducted for variables with non-normal distributions, which included work and activity impairment variables, healthcare resource use, and both direct and indirect costs. An alpha error of 5 % was used for all null hypothesis tests.

Results

A total of 306 respondents reported a physician diagnosis of HCV with no treatment ever received. An additional 73,586 did not report HCV, or infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)/AIDS, and served as an unmatched control group. Table 1 shows that the demographic characteristics of treatment-naïve HCV patients differed in a variety of ways from unmatched non-HCV controls. HCV patients versus non-HCV subjects were older (53 vs. 48 years old, $P < 0.001$), more likely to be male (64 vs. 48 %, $P < 0.001$), and less likely to be heterosexual (86 vs. 91 %, $P < 0.01$) or to live with a partner (46 vs. 60 %, $P < 0.001$). HCV infected patients were also less likely to have graduated from high school (95 vs. 97 %, $P < 0.05$), to be employed (40 vs. 55 %, $P < 0.001$), or to have health insurance (73 vs. 83 %, $P < 0.001$) than non-HCV subjects in the NHWS, and tended to have lower household income. They also had poorer health habits, being less likely to be normal weight (23 vs. 31 %, $P < 0.01$) and more likely to be obese (37 vs. 33 %, $P < 0.05$), smoke cigarettes (44 vs. 19 %, $P < 0.001$), and less likely to exercise (57 vs. 65 %, $P < 0.01$). They were less likely to drink alcohol (56 vs. 65 %, $P < 0.001$), although more than half reported doing so. They also suffered from more non-liver co-morbid health conditions (0.78 vs. 0.37, $P < 0.01$). As expected, they were also much more likely to suffer from cirrhosis (3.9 vs. 0.1 %, $P < 0.001$) or liver cancer (0.7 vs. 0.0 %, $P < 0.001$).

Consistent with demographic differences, patients with untreated HCV infection had worse outcomes than those in the unmatched control group for numerous measures. Treatment-naïve HCV infected patients had greater presenteeism, overall work impairment, and activity impairment (Table 2), and used more healthcare resources (Table 3). Estimated costs are presented in Table 4. Consistent with their greater work impairment and healthcare resource utilization, all estimated costs were significantly higher for untreated HCV infected patients than for the unmatched control group. A similar pattern of results can be seen in the HRQoL data, presented in Table 5; MCS, PCS, and health utility values are much less for untreated HCV infected patients than for unmatched controls.

Matched Controls

There were no significant differences for demographics or health behavior between the treatment-naïve HCV infected patients and propensity-matched controls (Table 1), but different outcomes remained. Mean work impairment is presented in Table 2. Employment was not included in the matching procedure, but employment was not significantly lower for respondents with untreated HCV infection (40 vs. 46 %, $P = 0.10$). The employed HCV group ($n = 121$) reported an average of 23 % impairment while at work, approximately 10 percentage points greater than employed controls ($n = 141$; 13 %, $P < 0.001$). Overall work impairment was also greater than that reported by those without HCV infection (26 vs. 15 %, $P < 0.001$), although untreated HCV infected patients did not report missing more hours of work than matched controls (5.0 vs. 2.8 %, $P = 0.09$). Activity impairment also was higher among untreated HCV infected patients, with 42 % impairment in non-work activity on average, compared with 27 % among matched controls ($P < 0.001$).

Greater use of healthcare resources was also reported among treatment-naïve HCV infected patients compared with matched non-HCV subjects (Table 3). Untreated HCV infected patients went to the ER more often (0.76 vs. 0.54 times per year, $P < 0.05$) and made more annual visits to traditional healthcare providers (12.24 vs. 8.22, $P < 0.001$). There was also a trend for untreated HCV infected patients to have more hospitalizations on average (0.42 vs. 0.25), although this did not reach statistical significance ($P = 0.07$).

Estimated costs are presented in Table 4. These were also significantly higher among the untreated HCV infection group than matched controls. For employed treatment-naïve HCV infected patients, productivity impairments were worth $10,316 per patient per year, compared with $5,469 for matched controls ($P < 0.001$). Indirect costs were primarily because of productivity lost to presenteeism in both groups, which was significantly higher among untreated HCV infected patients ($8,209 vs. $4,424, $P < 0.001$). Annual incremental costs were approximately $400, $3,100, and $3,950 dollars more for ER visits, hospitalizations, and physician visits, respectively, for untreated HCV infected patients than for matched controls. Total direct costs were $22,818 for untreated HCV infected patients and $15,362 for matched controls ($P < 0.001$). The direct costs estimated here do not include outpatient pharmacy costs, which can be substantial for HCV infected patients undergoing treatment. The average total costs were nearly $27,000 per untreated HCV infected patient per year, approximately 150 % of the total costs of the matched controls. This is an incremental cost of $9,017 per patient per year.

Finally, treatment-naïve HCV infected patients also had lower HRQoL than matched controls on all three SF-12 metrics (Table 5). Differences on MCS (43.72 vs. 48.62, $P < 0.01$) and PCS (40.20 vs. 44.89, $P < 0.01$) were more than four points lower than for those without HCV, suggesting a clinically important difference. Health utilities

Table 1 Respondent characteristics by HCV status

	HCV group $n = 306$	Unmatched control group $n = 73{,}586$		Matched control group $n = 306$	
	n, (%)	n, (%)	P value*	n, (%)	P value†
Female	110 (35.95)	38,396 (52.18)	<0.001	122 (39.87)	0.115
Race					
White	230 (75.16)	54,393 (73.92)	0.620	216 (70.59)	0.203
Black	30 (9.80)	7,789 (10.58)	0.658	44 (14.38)	0.083
Hispanic	26 (8.50)	4,647 (6.32)	0.118	20 (6.54)	0.358
Other race	20 (6.54)	6,757 (9.18)	0.109	26 (8.50)	0.358
Married/living with partner	141 (46.08)	43,872 (59.62)	<0.001	143 (46.73)	0.871
Sexual orientation					
Heterosexual	263 (85.95)	67,426 (91.63)	0.002	264 (86.27)	0.907
Homosexual	21 (6.86)	2,327 (3.16)	<0.001	17 (5.56)	0.503
Bisexual	18 (5.88)	2,165 (2.94)	0.002	20 (6.54)	0.738
Decline to answer	4 (1.31)	2,231 (3.03)	0.080	5 (1.63)	0.737
High school graduate	291 (95.10)	71,450 (97.10)	0.038	293 (95.75)	0.699
Employed	121 (39.54)	40,678 (55.28)	<0.001	141 (46.08)	0.102
Have health insurance	223 (72.88)	61,005 (82.90)	<0.001	238 (77.78)	0.160
Annual household income					
<$25 K	103 (33.66)	13,267 (18.03)	<0.001	101 (33.01)	0.864
$25 to <$50 K	109 (35.62)	19,761 (26.85)	0.001	101 (33.01)	0.496
< $75 K	42 (13.73)	14,549 (19.77)	0.008	58 (18.95)	0.080
$75 K+	43 (14.05)	19,991 (27.17)	<0.001	38 (12.42)	0.551
Decline to answer	9 (2.94)	6,018 (8.18)	0.001	8 (2.61)	0.806
BMI					
Underweight	4 (1.31)	1,323 (1.80)	0.519	5 (1.63)	0.737
Normal	71 (23.20)	22,642 (30.77)	0.004	64 (20.92)	0.495
Overweight	112 (36.60)	23,722 (32.24)	0.103	107 (34.97)	0.673
Obese	118 (38.56)	24,174 (32.85)	0.034	129 (42.16)	0.365
Decline to answer	1 (0.33)	1,725 (2.34)	0.020	1 (0.33)	1.000
Currently smoke cigarettes	133 (43.46)	13,762 (18.70)	<0.001	130 (42.48)	0.806
Currently exercise	173 (56.54)	47,936 (65.14)	0.002	153 (50.00)	0.105
Drink alcohol	171 (55.88)	47,898 (65.09)	0.001	164 (53.59)	0.570
Cirrhosis	12 (3.92)	110 (0.01)	<0.001	0 (0.00)	<0.001
Liver cancer	2 (0.65)	22 (0.03)	<0.001	0 (0.00)	0.157
	Mean (SD)	Mean (SD)	P value*	Mean (SD)	P value†
Age	52.58 (11.78)	48.11 (16.58)	<0.001	54.3 (14.63)	0.115
Number of comorbidities (excluding liver disease)	0.78 (1.16)	0.37 (0.82)	<0.001	0.77 (1.36)	0.924

Significance tests were conducted using χ^2 tests for categorical variables and t tests for continuous variables

* Indicates significance for comparison of the HCV group with the unmatched control group

† Indicates significance for comparison of the HCV group with the matched control group

were 0.08 point lower (0.65 vs. 0.73, $P < 0.001$), which would also be considered clinically meaningful [41].

Discussion

Treatment-naïve HCV infected patients reported significantly impaired work productivity, greater impairment of non-work activity, more healthcare resource utilization, higher estimated costs, and worse health-related quality of life compared with unmatched and propensity-matched subjects without HCV infection. Overall work impairment averaged more than 25 %, well above the 15 % figure for non-HCV controls. The average employed untreated HCV infected patient loses over $10,000 worth of productivity because of ill health, nearly double that lost by either the average patient in the NHWS without HCV or propensity-matched controls. Healthcare resource use was also greater, especially for outpatient physician visits, which were nearly 50 % more frequent than for the matched controls.

Table 2 Impairment at work and in non-work activity by HCV status

	HCV group $n = 306$	Unmatched control group $n = 73{,}586$		Matched control group $n = 306$	
	Mean (SD)	Mean (SD)	*P* value*	Mean (SD)	*P* value†
Absenteeism[a]	5.03 % (16.85 %)	3.17 % (12.90 %)	0.087	2.82 % (13.13 %)	0.089
Presenteeism[a]	23.16 % (24.66 %)	14.27 % (22.56 %)	<0.001	13.06 % (21.53 %)	<0.001
Overall work[a] impairment	26.16 % (28.00 %)	16.02 % (25.04 %)	<0.001	14.91 % (24.71 %)	<0.001
Activity impairment	42.16 % (33.03 %)	23.32 % (28.80 %)	<0.001	27.29 % (30.13 %)	<0.001

Significance was tested by use of the Mann–Whitney *U* test

* Indicates significance for comparison of the HCV group with the unmatched control group

† Indicates significance for comparison of the HCV group with the matched control group

[a] Sample sizes for work impairment are 121 for HCV infected patients and 141 for matched controls

Table 3 Annual healthcare resource use by HCV infected patients and controls

	HCV group $n = 306$	Unmatched control group $n = 73{,}586$		Matched control group $n = 306$	
	Mean (SD)	Mean (SD)	*P* value*	Mean (SD)	*P* value†
Emergency room visits	0.76 (1.80)	0.38 (1.81)	<0.001	0.54 (1.92)	0.023
Hospitalizations	0.42 (1.23)	0.22 (1.82)	0.006	0.25 (0.92)	0.071
Physician visits	12.24 (15.91)	7.63 (11.64)	<0.001	8.22 (11.06)	<0.001

Significance was tested by use of the Mann–Whitney *U* test

* Indicates significance for comparison of the HCV group with the unmatched control group

† Indicates significance for comparison of the HCV group with the matched control group

Table 4 Estimated costs in HCV infected patients and controls

	HCV group $n = 306$	Unmatched control group $n = 73{,}586$		Matched control group $n = 306$	
	Mean (SD)	Mean (SD)	*P* value*	Mean (SD)	*P* value†
Direct costs					
ER visits	$1,179.48 ($2,773.58)	$535.80 ($2,511.35)	<0.001	$803.00 ($2,903.74)	0.020
Hospitalization	$7,085.71 ($20,990.48)	$3,391.89 ($27,418.50)	<0.001	$3,970.54 ($14,511.52)	0.057
Physician visits	$14,553.29 ($18,921.80)	$8,978.92 ($13,913.17)	<0.001	$10,588.10 ($14,578.54)	0.002
Total direct costs	$22,818.48 ($34,372.73)	$12,906.61 ($33,907.66)	<0.001	$15,361.64 ($26,142.77)	0.001
Indirect costs[a]					
Lost to absenteeism[a]	$2,106.92 ($9,860.54)	$1,033.41 ($4,920.45)	0.020	$1,044.75 ($5,062.12)	0.086
Lost to presenteeism[a]	$8,209.08 ($10,983.09)	$4,367.20 ($7,959.81)	<0.001	$4,423.81 ($7,811.91)	<0.001
Total indirect costs[a]	$10,316.00 ($14,582.01)	$5,403.65 ($9,905.91)	<0.001	$5,468.56 ($10,143.52)	<0.001
Overall total costs	$26,897.69 ($36,410.05)	$15,886.15 ($35,192.95)	<0.001	$17,881.47 ($27,545.37)	<0.001

Significance was tested by use of the Mann–Whitney *U* test. Totals were estimated by use of separate regressions, and may differ from the sum of component parts

* Indicates significance for comparison of the HCV group with the unmatched control group

† Indicates significance for comparison of the HCV group with the matched control group

[a] Sample sizes for indirect costs are 121 for HCV infected patients and 141 for matched controls

Direct costs were even larger than the productivity losses, averaging nearly $23,000 per patient per year, approximately $10,000 more than for the average survey respondent, and approximately $7,500 more than for matched controls. Average incremental cost for each untreated HCV infected patient was approximately $9,000 compared

Table 5 Health-related quality of life by HCV status

	HCV group $n = 306$	Unmatched controls $n = 73{,}586$		Matched controls $n = 306$	
	Mean (SD)	Mean (SD)	*P* value*	Mean (SD)	*P* value†
Mental component summary (MCS)	43.72 (12.07)	48.41 (10.92)	<0.001	48.62 (11.41)	<0.001
Physical component summary (PCS)	40.20 (12.89)	48.46 (10.61)	<0.001	44.89 (11.28)	<0.001
Health utility (SF-6D)	0.65 (0.14)	0.75 (0.14)	<0.001	0.73 (0.14)	<0.001

Significance tests were conducted by use of independent-samples *t* tests

* Indicates significance for comparison of the HCV group with the unmatched control group

† Indicates significance for comparison of the HCV group with the matched control group

with matched controls. It is important to remember these costs do not include the cost of HCV treatment, or the adverse events associated with it.

Consistent with previous studies of chronic HCV infection, we found HCV diagnosis had a significant impact on a range of outcomes. The magnitude of these effects was comparable with those in other studies which relied on different data sources or inclusion criteria. Our analysis of self-reported work productivity found that absenteeism was approximately 80 % higher for untreated HCV infected patients, similar to a recent analysis of the Human Capital Management Services Research Reference Database, although the values for the patients and controls were half of those reported in that study [19]. Absenteeism figures reported here are also similar to those in an analysis of the 2009 NHWS data that did not exclude HCV patients on the basis of treatment status [18]. Our results for presenteeism and overall work impairment show a greater [20] decrement in the HCV group than the 2009 data, however, perhaps because of the inclusion of successfully treated patients in that analysis. We are not aware of another study estimating the indirect costs of work productivity loss, which were substantial among the employed patients. The impact of HCV on direct costs reported here is consistent with a recent analysis of untreated HCV infected patients in the Ingenix database, which found all-cause medical expenditure to be approximately $19,000 per year in 2007 dollars, not including pharmacy costs [9]. It is, however, higher than another recent analysis, which is, in part, likely to be because of the inclusion of patients achieving SVR in that sample [12]. The HRQoL burden is slightly larger than that reported in previous studies of HCV infected patients which did not exclude currently or previously treated patients [24], suggesting that studies which include treated patients may underestimate the impact of HCV infection.

Although these analyses revealed an impact of HCV on a broad range of health outcomes, not every metric was significantly affected. Treatment-naïve HCV infected patients were much more impaired while at work, but did not miss significantly more work than controls. Part of this could be lack of sensitivity of the WPAI, because the recall period is only seven days, and even those who miss a substantial amount of work per year are relatively unlikely to miss work in a given week. A previous study using an employer database revealed a significant, but relatively subtle, impact of HCV on work attendance, and a larger impact on productivity [19]. Likewise, untreated HCV infected patients had more physician visits and use of the ER. The difference in hospitalizations was not statistically significant, although the magnitude of the difference—68 % higher among patients than controls—suggests this null result may be because of small sample size and the resulting lack of statistical power rather than comparable rates of hospital admission.

Limitations

Our use of propensity matching ensures that none of the observed differences in outcomes between HCV infected patients and controls are the result of demographic or health history variables included in the matching analyses. The matching procedure did not include co-morbid psychiatric conditions in the equation, and such disorders are more prevalent among untreated HCV infected patients [42]. To determine whether the increased costs among HCV infected patients observed in this study could be attributed to greater mental illness, we used a pair of generalized linear models incorporating both HCV status and mental illness (among other variables) to predict direct and indirect costs. HCV status significantly predicted both types of cost, although mental illness was also associated with higher costs, indicating that psychiatric comorbidities are not sufficient to explain the difference between groups reported here. We suggest future research explore the relationship between mental illness and the burden of HCV infection.

It is also important to note that because of the survey methodology, it was not possible to verify HCV diagnosis. Nevertheless, as noted above, many of the findings coincide with that of the literature, suggesting our HCV sample is similar to that of other, clinically verified HCV samples. Further, if actual HCV infected patients were in the control group (because they were not aware of their disease status) then the results of this study would be likely to underestimate the burden of HCV. This study did not assess reasons for healthcare resource utilization but, given the propensity score methodology, the assumption was made that the additional resources used by the HCV group were because of the virus itself, because none of the assessed demographic or non-HCV health history variables differed between the groups.

Our measurement of work productivity losses through the WPAI ensured we were able to assess impairment using a well-validated measure across a broader range of occupations than would be available using objective measurements. However, self-reported productivity measures may provide larger estimates of impairment than would objective measures [43]. Likewise, our estimates of direct and indirect costs assume the wages and unit costs used in the calculations are representative of the wages and costs of the individuals included in this study, and so may under or overestimate the true impact of the disease.

A final limitation to consider is the Internet-survey methodology. It remains unclear if patients who did not complete the survey differ in meaningful ways from those who did. However, it seems unlikely that a selection bias explains the difference between patients and controls in our study, as selection would have to exert markedly different effects in HCV infected patients than in other respondents to create the differences reported here.

Conclusions

Untreated HCV infection is a costly illness, both economically and in terms of quality of life. The economic cost to society of impaired work productivity and increased use of healthcare resources is substantial, and there is a significant impact on both mental and physical health. The results of this study highlight the economic and humanistic burden that HCV can cause to patients and society if left untreated.

Acknowledgments This analysis was conducted by Kantar Health and was funded by Merck and Co.

Conflict of interest AEK was an employee of Merck and Co. at the time the study was conducted, JV is an employee of Kantar Health, and GP works for Merck and Co. as a contractor.

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