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ORIGINAL RESEARCH ARTICLE

The Costs of Hepatitis C by Liver Disease Stage: Estimates from the Veterans Health Administration

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Abstract

Background The release of highly effective but costly medications for the treatment of hepatitis C virus combined with a doubling in the incidence of hepatitis C virus have posed substantial financial challenges for many healthcare systems. We provide estimates of the cost of treating patients with hepatitis C virus that can inform the triage of pharmaceutical care in systems with limited healthcare resources.

Methods We conducted an observational study using a national US cohort of 206,090 veterans with laboratory-identified hepatitis C virus followed from Fiscal Year 2010 to 2014. We estimated the cost of: non-advanced Fibrosis-4; advanced Fibrosis-4; hepatocellular carcinoma; liver transplant; and post-liver transplant. The former two stages were ascertained using laboratory result data; the latter stages were ascertained using administrative data. Costs were obtained from the Veterans Health Administration's activity-based cost accounting system and more closely represent the actual costs of providing care, an improvement on the charge data that generally characterizes the hepatitis C virus cost literature. Generalized estimating equations were used to estimate and predict costs per liver disease stage. Missing data were multiply imputed.

Results Annual costs of care increased as patients progressed from non-advanced Fibrosis-4 to advanced Fibrosis-4, hepatocellular carcinoma, and liver transplant (all $p < 0.001$). Post-liver transplant, costs decreased significantly ($p < 0.001$). In simulations, patients were estimated to incur the following annual costs: US $17,556 for non-advanced Fibrosis-4; US $20,791 for advanced Fibrosis-4; US $46,089 for liver cancer; US $261,959 in the year of the liver transplant; and US $18,643 per year after the liver transplant.

Conclusions Cost differences of treating non-advanced and advanced Fibrosis-4 are relatively small. The greatest cost savings would be realized from avoiding progression to liver cancer and transplant.

1 Introduction

Over the past 6 years, there has been a multitude of new and highly effective medications to treat hepatitis C virus (HCV) [1–6]. While unit prices of medications are high, recent evidence indicates that the new medications (danoprevir, faldeprevir, and most notably, sofosbuvir) for HCV are cost effective [7–10]. Thus, while these medications are associated with increased costs, they provide a health benefit that is acceptably proportionate to their additional costs.

While these new medications are cost effective, they may not be affordable. For example, the list price of a 12-week course of sofosbuvir, the recommended dose for HCV genotype 1 or 4 infection, is US $84,000 [11]. In response, private and public insurance providers have expressed concerns over their ability to cover the costs of these high-priced drugs [12–17], especially given the large size of the HCV population. In 2002, there were approximately 3.2 million

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Key Points for Decision Makers

Despite their efficacy, the high costs of new hepatitis C virus (HCV) medications render it impracticable to treat all patients. Proper allocation of limited healthcare resources requires an understanding of costs incurred throughout the HCV disease trajectory, especially the cost implications of treating those at later, more complicated stages of the disease.

To date, published estimates about the cost of HCV were based on charges, which are both inexact and overestimate the costs of care. This study uses activity-based cost accounting data, providing a better indication of the actual costs of care. This study also provides estimates of the cost of HCV per liver-disease stage.

Taken together, these methodological changes improve on the accuracy of previously published cost estimates. Estimates can be used by decision makers seeking to allocate limited healthcare resources in the face of the increasing incidence of HCV.

people living with chronic HCV in USA [18]; treating all of these patients using sofosbuvir is estimated to cost over US $300 billion [19, 20]. Thus, the high price of these drugs leads to a larger-than-usual budget impact for new drug technologies. Adding to these challenges, the incidence of HCV has more than doubled from 2004 to 2014, largely associated with injection drug use and the opioid epidemic [21]. It will therefore be expensive and likely resource prohibitive to treat all patients with HCV simultaneously.

Although previously suggested strategies include the selection of patients according to their severity of liver disease [22], recent US guidelines recommend near-universal treatment for patients with chronic HCV [23]. Despite these guidelines, certain state-based US healthcare programs did restrict HCV treatment based on liver disease severity and drug or alcohol use [24–26]. The high cost of HCV medications may be driving such restrictions; HCV treatment is a clear example of the tension between cost effectiveness and affordability. Thus, health systems domestically and worldwide will need to carefully consider how to allocate resources to HCV treatment vs. other interventions. Such decisions will require accurate information about the impact of treating HCV early in the course of illness vs. the costs of delaying treatment to patients with more advanced liver disease.

An understanding of how to best allocate resources to treat patients with HCV depends on understanding the costs of care required throughout the disease trajectory and its complications, including hepatocellular carcinoma and liver transplantation. These data are important for all payers as they plan their future budgets, as even those that are not able to afford to provide patients with HCV with new directly acting antiretroviral treatments will still incur the downstream costs associated with progression to more severe liver disease stages. Previous work has found that outpatient care [27, 28] and pharmacy [27–30] are the two biggest drivers of healthcare claims for patients with HCV, and that healthcare charges increase dramatically as HCV progresses into advanced liver disease (defined as decompensated cirrhosis, hepatocellular carcinoma, or liver transplant) [28].

While informative, there are three limitations to the current state of HCV cost literature that we improve upon with this work. First, existing studies have been limited by the cost information present in their datasets, which consist of charged amounts or settled claims. Charges are inexact and overestimate the true costs of care, while claim data include profits along with the costs of care. Our work utilizes the activity-based cost accounting data in the Veterans Health Administration (VA) to estimate the actual cost of treating each liver disease stage, thus improving greatly on the accuracy of previously published cost estimates. Second, previous studies have used claims data employing *International Classification of Diseases, Ninth Revision* (ICD-9) codes to indicate diagnoses of HCV-related liver disease [27–29, 31, 32]. However, ICD-9 codes may not always capture a patient's true illness or severity of illness, either because of incomplete coding of disease [33–36] or because ICD-9 codes are not specific enough to capture varying levels of severity of disease [37–39]. This may be particularly problematic for assessing the degree of liver fibrosis. Our work leverages the extensive laboratory result data present in the VA to estimate the cost per stage of fibrosis. Third, patients with HCV often have mental health or substance abuse comorbidities, both of which are generally under-identified in administrative or claims data owing to a lack of proper healthcare coverage available for these conditions. The VA, however, has a strong commitment to treating mental health and substance abuse; these comorbidities can be ascertained from VA datasets. Our work adjusts for these comorbidities to isolate healthcare costs that are due to HCV.

2 Patients and Methods

Cohort members were identified by an HCV RNA test confirming the presence of HCV. We obtained data from the VA Corporate Data Warehouse, which holds the results of VA laboratory tests conducted since 2000. Veterans entered the cohort in 2010, or on the date of the first positive HCV result, whichever was later. Patients with human immunodeficiency virus co-infection, identified as a positive human immunodeficiency virus western blot or a human

immunodeficiency virus viral load test with detectable virus, were excluded. Liver disease stage was assessed by dichotomizing the Fibrosis 4 (FIB-4) score using the threshold of 3.25, the level associated with high probability of advanced fibrosis [40, 41]. Patients below this threshold were considered to have non-advanced FIB-4; those with values above this threshold were considered to have advanced FIB-4. We used ICD-9 CM diagnosis codes to identify hepatocellular carcinoma and a history of liver transplant, and ICD-9 CM procedure codes to identify liver transplants. The ICD-9 CM codes for all diagnoses used in this study can be found in the "Appendix". Patient-years post-sustained viral response were excluded from the dataset.

We used both VA and community care data to capture the total costs of care from a health system perspective. Community care represents care authorized by the VA but provided in the community; veterans are able to seek such care when the VA is unable to provide care or it is infeasible to do so, such as a liver transplant. To estimate costs of VA-provided services, we used managerial cost accounting (formerly decision support system) data. Managerial cost accounting is an activity-based cost accounting system and reflects the actual direct and overhead costs of care provided. Community care costs were obtained from paid claims. We evaluated inpatient, outpatient, and non-HCV pharmacy costs. Hepatitis C virus costs were excluded from the main analyses because the purpose of this work is to produce cost estimates that can be used by healthcare systems seeking to populate their own HCV triage decision models; those models should have as inputs the specific costs each system pays for HCV medications. For example, the VA enjoys volume-based drug discounts on drugs but does not generally obtain rebates for drug prices; other healthcare systems may experience opposite cost scenarios. All costs were inflated to 2014 dollars using the Consumer Price Index.

We estimated the relationship between annual total costs of care for patients with HCV and liver disease stage using generalized estimating equations. Standard errors from the generalized estimating equations are corrected to reflect the correlation between annual observations of the same patient as well as the variation attributable to multiple imputation of missing data. Generalized estimating equations models have the additional advantage that their parameters can be used to predict the dependent variable without retransformation bias. Modified Park Tests revealed the need for gamma distribution and a Box-Cox regression determined that a log link function was appropriate because of the skewness of cost data.

We adjusted for a variety of comorbidities; given the slow progressing nature of HCV, patients with more advanced liver disease may also have more comorbidities. In the absence of including these comorbidities, we would erroneously attribute the cost of frequently co-occurring conditions to HCV and thus overestimate the costs of more advanced liver disease stages. Comorbidities were assessed by evaluating VA and community care claims from Fiscal Year (FY) 2009 to 2014. Medical and mental health comorbidities were included as covariates indicating the count of each comorbidity type; this produced the model that best fit the data with respect to the root mean squared error, mean absolute error, and residuals at the extreme of the distribution. We tested other models using individual covariates and their interactions; these models provided an inferior fit of the data. Mental health comorbidities and medical comorbidities were specified as indicator rather than numeric variables owing to the non-linearity of marginal comorbidity costs (e.g., a person with four comorbidities will not experience double the logged healthcare costs of a person with two comorbidities). The VA is a national healthcare system, and the costs of care vary across the VA as a result of geographic differences in wages. We thus included the Medicare Wage Index as a covariate to adjust for these geographic wage differences, and predicted a national average cost by setting the wage index equal to 1.00.

Some patients were missing covariate data because of a lack of contact with the VA healthcare system. We handled missing data in two ways. First, for patients with chronic disease who were missing that indicator for subsequent years, values were carried forward. For example, a patient with a dementia diagnosis in 2010 was considered to have dementia in all subsequent years of the analysis, regardless of whether he/she had a code for dementia in subsequent years. After using this method for chronic disease, approximately 7% of remaining annual observations had at least one missing covariate. We next imputed values for these remaining missing covariates using multiple imputation with chained equations [42], relying on the current year's data as well as the previous years' clinical data when available. Regressions were estimated over ten imputations and standard errors of regression parameters were adjusted to reflect the variation between these multiple regressions.

The purpose of this modeling endeavor was to estimate the mean annual costs of a HCV-positive patient per liver disease stage, after adjusting for comorbidities. We thus used regression model results to predict the cost incurred by patients in five different stages of liver disease stages: non-advanced FIB-4; advanced FIB-4, hepatocellular carcinoma, liver transplant, and history of liver transplant. In estimating these costs, we maintained all other covariate values at their observed value for the individual, rather than estimating costs at the mean level of comorbidities of the cohort. Our approach thus estimates the cost per liver disease stage while accounting for the distribution of comorbid conditions in the cohort. The uncertainty in the prediction of the mean cost per liver disease stage was estimated by finding mean values

through 1000 bootstrapped samples. The resulting standard error of the mean reflects the uncertainty due to the distribution of covariates in the cohort as well as variation due to multiple imputation of missing values. All analyses were conducted in SAS Version 9.4 (SAS, Cary, North Carolina USA). This protocol was approved by the Stanford University Institutional Review Board.

3 Results

Our cohort consisted of 208,090 HCV-positive patients who contributed between 1 and 5 years of data to the analysis, depending on when they were diagnosed with HCV and when they passed away. Our cohort was largely male (97.1%), between 50 and 64 years of age (80.8%), and white (60.0%), although it had a substantial proportion of black patients as well (33.9%) (Table 1). Patients had a large burden of mental or substance abuse disorders, with many patients experiencing depression (32.3%), drug dependency or abuse (24.2%), or alcohol problems (22.7%). Diabetes mellitus (22.2%) and chronic obstructive pulmonary disease (16.5%) were the most frequently occurring medical comorbidities in this cohort. Most patients in this cohort had non-advanced FIB-4 (56.4%). Very few patients underwent a liver transplant or had hepatocellular carcinoma.

The biggest drivers of total annual costs for this 2010–2014 cohort were outpatient medical visits (mean cost of US $6146), followed by inpatient medical hospitalizations (mean cost of US $3832) (Table 2). Table 2 also provides an estimate of costs of medical care and prescription drugs incurred by the cohort, exclusive of the cost of HCV antiviral treatments and the cost of behavior health services. Excluding these costs results in mean annual per-patient costs of US $11,693.

Regression models show significantly higher annual costs as patients progressed from non-advanced FIB-4 to advanced FIB-4, hepatocellular carcinoma, and then to liver transplant (Table 3). Post-liver transplant, costs decrease significantly (all p values < 0.001). Unsurprisingly, annual costs of care increased as the comorbidity burden increased, with medical comorbidities being more costly to treat than mental health or substance abuse comorbidities. Costs decreased significantly after age 65 years, when patients became eligible for Medicare-provided services. We found black patients had 2% higher costs than white patients ($p < 0.001$), but found no other racial differences in healthcare costs.

Table 3 presents results from our regression model estimating costs per liver disease stage. Each coefficient represents the proportional change in cost given a unit change in the independent variable. Thus, the coefficient of 0.27 for the indicator for advanced FIB-4 can be interpreted that individuals with advanced FIB-4 had 27% higher logged

Table 1 Cohort characteristics at baseline

Patient demographics	Cohort ($n = 208,090$)	
	(%)	n
Male	97.1	202,096
Age categories, y [mean (SD) = 56.2 (7.7)]		
Less than 50	8.3	17,254
50–54	20.0	41,522
55–59	32.7	68,060
60–64	28.1	58,500
65–69	6.5	13,550
70–74	1.9	3845
75 +	2.6	5359
Race/ethnicity		
White	60.0	124,879
Black	33.9	70,582
Asian	0.3	539
American Indian or Alaska Native	1.3	2594
Hawaiian or Pacific Islander	1.3	2630
Hispanic	5.4	11,290
Comorbidities		
Alcohol problem: drinking, abuse, or dependence	22.7	47,159
Any drug dependency/abuse	24.2	50,319
Arthritis[a]	0.9	1958
Bipolar disorder[b]	5.7	11,752
Cancer (excluding hepatocellular carcinoma)	6.5	13,443
Cancer (metastatic solid tumor)[a]	0.9	1873
Congestive heart failure[a]	3.8	7972
Chronic obstructive pulmonary disease[a]	16.5	34,417
Dementia[a]	0.4	739
Depression[b]	32.2	66,954
Diabetes mellitus[a]	22.2	46,234
Hepatitis B[a]	0.5	1044
Kidney transplant, history of[a]	0.3	558
Myocardial infarction[a]	1.4	2813
Paralysis[a]	1.0	2144
Peripheral vascular disease[a]	4.7	9736
Psychosis, other[b]	2.8	5715
Post-traumatic stress disorder[b]	16.5	34,381
Renal failure[a]	5.4	11,240
Schizophrenia[b]	4.9	10,196
Seizure[a]	0.1	127
Stroke[a]	4.2	8766
Suicide attempt[b]	0.7	1378
Transplant (other than kidney or liver)[a]	0.0	13
Liver disease stage		
Non-advanced FIB-4	56.4	117,263
Advanced FIB-4	16.6	34,493
Hepatocellular carcinoma	1.5	3156
Liver transplant	0.0	45
History of liver transplant	0.8	1684

FIB-4 Fibrosis-4, *SD* standard deviation

[a]These conditions comprise the "medical comorbidities" used in regression analyses

[b]These conditions comprise the "mental health comorbidities" used in regression analyses

Table 2 Unadjusted costs per category, per patient-year (US $2014)

Costs	Mean (SD)
Outpatient cost, medical/surgical	$6146 ($9731)
Outpatient cost, behavioral health	$1701 ($4864)
Inpatient cost, medical/surgical	$3832 ($17,230)
Inpatient cost, behavioral health	$3310 ($23,279)
HCV Rx cost	$609 ($6383)
Non-HCV Rx cost	$1528 ($5370)
Total costs, excluding HCV Rx costs	$18,320 ($41,469)
Total costs, excluding HCV Rx costs and behavioral health	$11,693 ($24,150)

Total costs represent all dollars spent on the care of veterans with HCV and include costs beyond those in the medical, surgical, and behavioral health categories, including the cost of nursing home care

HCV hepatitis C virus, *Rx* prescription, *SD* standard deviation

costs than individuals without this indicator, all other factors being equal. To obtain specific cost estimates from this model, one must first add together the relevant coefficients before taking the anti-log of their sum. For example, the annual cost to treat a patient at the reference category for all covariates and with no comorbidity burden is US $4345 (2014 values) [obtained by summing the coefficients for the intercept and the wage index and taking the anti-log of the result]. However, given the non-linearities present in the data model, we used the more accurate approach of using regression parameters to simulate costs of a particular health state while holding all other covariates to each individual's original value.

Results from simulation models estimating the cost per liver disease stage can be seen in Table 4. The simulation models estimate of the total costs of a patient with HCV, including costs for behavioral healthcare. These estimates account for the differential comorbidity burden that may be associated with age-related advancement of liver disease. Patients with non-advanced FIB-4 had the lowest costs of US $17,556 per year (2014 values). Those with advanced FIB-4 had higher costs of US $20,791 per year. Patients who progressed to hepatocellular carcinoma experienced a substantial increase in costs of US $46,089 per year. Those undergoing liver transplants had the highest annual costs of US $261,959. Follow-up costs resulted in patients with a history of liver transplant incurring costs of US $18,643 annually in the years after the liver transplant procedure.

4 Discussion

To the best of our knowledge, this study represents the first time the actual costs of HCV based on laboratory-identified liver disease stage have been estimated. Our work provides estimates that can be used by health plans and providers with limited budgets to inform their allocation of HCV treatment resources, and by analysts modeling the cost effectiveness of anti-viral treatments for HCV. Our analysis focuses on the costs of treating the disease, rather than the utilization of treatment. Modelers looking to understand the treatment uptake of new HCV medications may wish to refer to two other papers evaluating the uptake and use of directly acting antivirals in the VA [43, 44].

Our work corroborates other studies indicating that outpatient costs are the biggest driver of reimbursed charges for HCV-positive patients [27, 28]. As other work has presented charges, rather than costs, per liver disease stage (identified through ICD-9 CM codes or otherwise) [27, 28, 30–32] and uses data that are generally much older than used in our analyses, it is difficult to make other comparisons with the existing sparse HCV cost literature. Furthermore, other work has not been able to properly adjust for mental health or substance abuse comorbidities, and the costs of these commonly occurring comorbidities remained in the error term of those models. Indeed, 66% of our cohort had mental health or substance abuse comorbidities, the costs of which would be in the error term were we not able to properly identify them in the administrative data. We provide cost estimates that are more reflective of current healthcare costs, costs that are specific to liver disease stage, and costs that are adjusted for a wide range of comorbidities, thus rendering our results suitable for use in current decision analytic models.

4.1 Limitations

This analysis is subject to certain limitations. We used both laboratory results and ICD-9 CM administrative data to characterize patients' level of illness. Relying on ICD-9 CM billing codes for comorbidities may have resulted in an inaccurate capture of illness. Hepatitis C virus is a slowly progressing disease, and thus some of the costs that accrue as liver disease progresses may be due to the incidence or increasing severity of other age-related illnesses. We controlled for this to the extent possible by including age as well as a variety of age-related comorbidities, such as congestive heart failure and dementia, in our models. Our work used data from a cohort followed from FY 2010 to 2014 and excluded HCV medications; our cost estimates thus do not include the costs of the newest HCV medications. However, given our estimates of cost per liver disease stage were produced with the goal of informing rational allocation of HCV *medications*, the exclusion of these medications from cost estimates is appropriate; to include these medications in our cost totals would result in the double-counting of HCV medication costs in future decision analytic models using these estimates as inputs. Additionally, given the VA's volume-based drug discounts and lack of rebates, drug

Table 3 Estimates from cost regression models (Log costs in US $2014)

Parameter	Estimate	Standard error	95% confidence limits		*p* value
Sex (reference = male)					
Female	0.06	0.01	0.04	0.07	< 0.0001
Age, y (reference = 50 to < 55)					
Less than 50	− 0.01	0.01	− 0.02	0.01	0.3474
55–59	− 0.02	0.00	− 0.02	− 0.01	< 0.0001
60–64	− 0.02	0.00	− 0.03	− 0.02	< 0.0001
65–69	− 0.04	0.00	− 0.04	− 0.03	< 0.0001
70–74	− 0.04	0.01	− 0.05	− 0.02	< 0.0001
75 +	− 0.06	0.01	− 0.07	− 0.04	< 0.0001
Race/ethnicity (reference = white)					
Black	0.02	0.00	0.01	0.02	< 0.0001
Asian	0.05	0.02	0.00	0.10	0.0524
American Indian or Alaska Native	− 0.02	0.01	− 0.04	0.01	0.1409
Hawaiian or Pacific Islander	0.00	0.01	− 0.02	0.03	0.8386
Hispanic	0.00	0.01	− 0.01	0.01	0.7875
Comorbidity					
Alcohol problem: drinking, abuse, or dependence[a]	0.46	0.00	0.46	0.47	< 0.0001
Any drug dependency/abuse[a]	0.56	0.00	0.55	0.57	< 0.0001
Presence of 1 medical comorbidity	0.84	0.00	0.83	0.84	< 0.0001
Presence of 2 medical comorbidities	1.42	0.00	1.41	1.43	< 0.0001
Presence of 3 medical comorbidities	1.93	0.01	1.92	1.95	< 0.0001
Presence of 4 medical comorbidities	2.28	0.01	2.26	2.30	< 0.0001
Presence of 5 medical comorbidities	2.64	0.02	2.60	2.67	< 0.0001
Presence of 6 + medical comorbidities	2.85	0.03	2.79	2.91	< 0.0001
Presence of 1 mental health comorbidity	0.78	0.00	0.77	0.79	< 0.0001
Presence of 2 mental health comorbidities	1.04	0.01	1.03	1.05	< 0.0001
Presence of 3 mental health comorbidities	1.38	0.01	1.36	1.39	< 0.0001
Presence of 4 mental health comorbidities	1.63	0.02	1.60	1.67	< 0.0001
Presence of 5 mental health comorbidities	1.91	0.05	1.82	2.00	< 0.0001
Mental health comorbidity and substance abuse disorder	− 0.05	0.01	− 0.07	− 0.04	< 0.0001
Medical comorbidity and substance abuse disorder	− 0.12	0.01	− 0.13	− 0.10	< 0.0001
Mental health comorbidity and medical comorbidity	− 0.37	0.01	− 0.38	− 0.36	< 0.0001
Mental health comorbidity, medical comorbidity, and substance abuse disorder	− 0.08	0.01	− 0.10	− 0.07	< 0.0001
High FIB-4 and alcohol problem	− 0.06	0.01	− 0.08	− 0.05	< 0.0001
High FIB-4 and drug dependency/abuse	− 0.10	0.01	− 0.12	− 0.08	< 0.0001
High FIB-4 and depression	− 0.07	0.01	− 0.08	− 0.05	< 0.0001
Liver disease stage (reference = non-advanced FIB-4)					
Advanced FIB-4	0.27	0.01	0.26	0.28	< 0.0001
Hepatocellular carcinoma	0.85	0.01	0.83	0.86	< 0.0001
Liver transplant	2.14	0.11	1.91	2.36	< 0.0001
History of liver transplant	0.49	0.01	0.47	0.51	< 0.0001
Wage index	0.49	0.01	0.47	0.50	< 0.0001
Intercept	7.89	0.01	7.88	7.90	< 0.0001

FIB-4 Fibrosis 4

[a]Substance abuse disorder

Table 4 Total predicted costs per liver disease stage, adjusted (US $2014)

Liver disease stage	Total annual costs mean (standard error of mean)[a]
Non-advanced FIB-4	17,556 (23)
Advanced FIB-4	20,791 (43)
Liver cancer	46,089 (193)
Liver transplant	261,959 (12,699)
History of liver transplant	18,643 (23)

FIB-4 Fibrosis 4

[a]Standard error of the mean was obtained from sampling from the cohort with 1000 bootstrap replicates. This error reflects uncertainty in our estimation of the mean owing to the distribution of the covariates as well as uncertainty from the imputation of missing values

price estimates in the VA, including the differences in prices between various HCV treatments, are not generalizable outside the VA. For example, the VA pays US $770 for a single pill of Sovaldi®, compared with US $1200 for a pill at average wholesale price.

4.2 Strengths

The strengths of this analysis are two fold. First, we used laboratory result data to identify HCV-positive patients and their FIB-4 status, rather than administrative data billing codes, thus increasing the specificity of our cohort. Second, our use of VA cost data confers a great advantage; the VA's status as a non-revenue-generating system coupled with its activity-based cost accounting system allows for a better evaluation of the costs of care than does the price or reimbursement associated with health services. As VA cost data do not include profit, and profit may be unevenly distributed across disease states (e.g., the profit associated with a liver transplant is likely much higher than the profit associated with treating non-advanced fibrosis), VA cost data are higher quality inputs for HCV decision models than cost estimates from private insurers, Medicaid, or Medicare. We are thus able to more accurately represent the resources required to care for HCV-positive patients at different liver disease stages. While VA-based cost estimates do not directly generalize to non-VA systems, they also allow for *relative* comparisons of the costs of each disease state in future decision models.

5 Conclusion

The list price of HCV medications is high, ranging from US $54,600 to US $94,500 for a 12-week course of treatment. This, coupled with the increasing prevalence of HCV in the US population, means that many health plans have restrictive criteria for treatment eligibility. Improved estimates of costs of care for patients with chronic HCV will help decision makers understand the effect of liver disease progression that accompanies a delay in treatment. This work presents cost estimates per liver disease stage for a cohort of newly diagnosed HCV-positive patients in the VA. While our cost estimates are specific to the VA, they have the advantage of being actual costs rather than charges or reimbursed amounts. Furthermore, they can be used by any healthcare system seeking to evaluate the *relative* costs of different HCV treatment strategies. Our results may be especially relevant to the Medicaid program, as almost 30% of HCV-positive patients were thought to be covered under Medicaid in 2016 [45]. Results from this work can thus assist the Medicaid program and other health plan decision makers in the best allocation of limited healthcare resources to optimize outcomes amongst patients with HCV.

Author Contributions RGM contributed to the study design, data interpretation, and writing of the manuscript, and is the overall guarantor of this work. PB contributed to the study conceptualization and design, data interpretation, and writing of the manuscript. JL contributed to the data acquisition and analyses, and writing of the manuscript. DO contributed to the funding, study conceptualization, and data interpretation. SA and JGF contributed to the data interpretation.

Compliance with Ethical Standards

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Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Conflict of interest Risha Gidwani-Marszowski, Douglas K. Owens, Jeanie Lo, Jeremy D. Goldhaber-Fiebert, Steven M. Asch, and Paul G. Barnett have no conflicts of interest that are directly relevant to the content of this article.

Data Sharing The datasets generated during and/or analyzed during the current study are not publicly available because of Veterans Health Administration regulations. Persons who are not approved by the project's institutional review board are prohibited by the Veterans Health Administration from viewing the underlying data. Additionally, the Veterans Health Administration requires all its data to remain on its own secure servers.

Appendix

Comorbidity International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnosis codes

Comorbidities	ICD-9 CM diagnosis codes
Alcohol problem: drinking, abuse, or dependence	291.x, 303.0x, 303.9x, 305.0x, and where the fifth digit is not equal to '3'
Any drug dependency/abuse	292.x, 304.0x–304.9x, 305.2x–305.9x, and where the fifth digit is not equal to '3'
Arthritis	725.x, 446.5x, 710.0x–710.4x, 714.0x–714.2x, 714.8x
Bipolar disorder	296.0x, 296.4x–296.8x
Cancer (excluding hepatocellular carcinoma)	140.x–172.x, 174.x–194.x, 195.0x–195.8x, 200.x–208.x, 238.6x, and excluding 155.x
Cancer (metastatic solid tumor)	196.x–199.x
Congestive heart failure	428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x–425.9x
Chronic obstructive pulmonary disease	490.x–505.x, 416.8x, 416.9x, 506.4x, 508.1x, 508.8x
Dementia	290.x, 294.1x, 331.2x
Depression	311.x, 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 293.83, 296.90, 296.99, 301.12
Diabetes	250.0x–250.9x
Hepatitis B	070.22, 070.23, 070.32, 070.33
Kidney transplant, history of	V42.0x, 996.81
Myocardial infarction	410.x, 412.x
Paralysis	342.x, 343.x, 334.1x, 344.0x–344.6x, 344.9x
Peripheral vascular disease	440.x, 441.x, 093.0x, 437.3x, 447.1x, 557.1x, 557.9x, V43.4x, 443.1x–443.9x
Psychosis, other	297.0x–297.3x, 297.8x–298.4x, 298.8x, 298.9x
Post-traumatic stress disorder	309.81x
Renal failure	582.x, 585.x, 586.x, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 583.0x–583.7x, 588.0x, V42.0x, V45.1x, V56.x
Schizophrenia	295.x
Seizure	345.01, 345.11, 345.41, 345.51, 345.61, 345.71, 345.81, 345.91
Stroke	430.x–438.x, 362.34
Suicide attempt	E950.x–E959.x
Transplant (other than kidney or liver)	996.83–996.87, V42.84
Liver disease stage	
Non-advanced FIB-4	FIB-4 score < 3.25
Advanced FIB-4	FIB-4 score ≥ 3.25
Hepatocellular carcinoma	155.0x
Liver transplant	50.51x, 50.59x
History of liver transplant	V42.7x

FIB-4 Fibrosis 4

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