Real World Cost-of-Illness Evidence in Hepatitis C Virus: A systematic review

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Abstract

Background The introduction of direct-acting antivirals (DAAs) represents a potential clinical cure for hepatitis C virus (HCV) infection. Identification of costs associated with different stages of untreated disease through cost-of-illness (COI) evaluation helps inform policy decisions and cost-effectiveness analyses (CEAs). This study's objective was to review published real-world costs for patients with HCV to estimate the COI across different stages of disease progression.

Methods A literature search of EMBASE, Scopus, and PubMed from January 1, 2010 to August 31, 2019 was conducted to identify real-world evidence related to HCV. Data extraction included citation details, population, study type, costing method used, currency and inflation adjustments, and disease-specific costs. Standardized costing method categories (sum all medical, sum diagnosis specific, matching, regression, other incremental, and other total) were assigned. The risk of bias was assessed at the outcome level for influence on costs attributable to HCV.

Results The search strategy identified 278 studies, with 31 included in the final review after inclusion and exclusion criteria were applied. Retrospective cohorts (77%) and cross-sectional analyses (16%) were most frequently encountered. Sum Diagnosis Specific was the most common costing method (39%), followed by Regression (32%). Of the 31 studies analyzed, 35% included costs that would be included in a societal model. Costs were identified for various stages and complications related to HCV disease progression. Several studies included were determined to have a high (48%) or moderate risk (42%) of bias related to COI estimates.

Conclusion Cost estimates for formal, informal, and non-health care services were identified in this review, but several challenges still exist in fully quantifying HCV burden. Future modeling studies including cost inputs should critically evaluate the risk of bias based on costing methods and data sources.

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Key Points for Decision Makers

Real-world evidence for the costs associated with hepatitis C virus exists for formal, informal, and non-health care services, enabling both health sector and societal perspective research approaches to determine cost-effectiveness.

Many cost estimates may have a moderate or high risk of bias and should be critically evaluated and adjusted prior to inclusion as an economic model input.

1 Introduction

1.1 Chronic Hepatitis C

Chronic hepatitis C virus (HCV) infection has a global impact, with an estimated prevalence between 1 and 3% depending on country and region [1]. Pharmacological innovations in the past decade, marked by the discovery of effective direct-acting antivirals (DAAs), have provided therapeutic options that frequently lead to a clinical cure, defined as sustained virologic response (SVR) [2–4]. The high cost of DAA treatment has spurred controversy regarding affordability as well as a significant number of cost-effectiveness analyses (CEAs) investigating the value of these new medication regimens [5–7]. Identification of costs associated with different stages of the untreated disease helps to inform the numerator for the resulting incremental cost-effectiveness ratio. Dorothy Rice’s seminal paper published in 1967 helped spur the growth of cost-of-illness (COI) research to inform policy decisions and economic analyses [8]. As we focus on any particular disease, such as hepatitis C, the COI methods used may play an important role in what costs are included, where in the course of the disease these costs occur, the reliability of estimates, and who bears the financial or economic burden [9–11].

1.2 Cost-of-Illness Methods

In two previous systematic reviews of published COI studies across all diseases, costing methods (sum all medical, sum diagnosis specific, matching, regression, other incremental, and other total) have been categorized and described to aid in the interpretation and application of COI results [12, 13]. Sum All Medical and Sum Diagnosis Specific may be generally described as relatively simple costing approaches that identify patients with a given diagnosis and include all medical costs or all costs related to the diagnosis in question [14]. Matching, Regression, Other Incremental, and Other Total may be generally described as more complex approaches to costing as they attempt to address potential confounding and bias in COI estimates [14]. In the case of HCV, a hypothetical COI study might identify all patients recruited through a substance-abuse program. A simple costing method may describe that population accurately but may bias the cost estimate attributable to HCV by not considering other variables observed in that patient sample compared to the full HCV population. Rather than dismiss Sum All Medical or Sum Diagnosis Specific methods, these predominantly descriptive approaches may still be useful depending on the research question of the study. For the purposes of this review, all costing approaches may be informative, but

should be assessed in the context of the question of COI attributable to HCV disease.

1.3 Study Objectives

The aim of this study was to systematically review all published studies that captured real-world costs for patients with HCV to estimate the COI of HCV across different stages of disease progression. Additionally, this study aims to describe the study methods used to estimate the COI and provide recommendations for future economic evaluations for HCV and its treatment.

2 Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [15].

2.1 Search Strategy

On August 31, 2019, we conducted a literature search to identify COI studies related to HCV infection using EMBASE, Scopus, and PubMed. The phrase “cost of illness” was found in the Medical Subject Headings (MeSH) for PubMed and Emtree headings for EMBASE and was combined with “hepatitis C” for these databases. The “explode” function was enabled within EMBASE to enable a broader search of the Emtree headings. For Scopus, a combination of “cost of illness” and “hepatitis C” was used to search abstract/title/keywords. Searches in all three databases were limited to the period 2010–present. The term “cost of illness” was used over the more generic “cost” heading to narrow the search within health economics. See the “Online Supplement” in the electronic supplementary material for more information on the review search strategies.

2.2 Selection Criteria

Studies were included if they were full-text original research or systematic reviews utilizing real-world observations to estimate the costs related to HCV. Therefore, modeling studies that simulated cost estimates or burden-of-illness studies solely focused on epidemiology with no costs reported were excluded. Studies were also excluded if HCV costs were aggregated with other liver diseases (hepatitis A or B) where the HCV-specific costs were unknown.

Abstract screening was completed by all three authors, with two votes required for all abstracts. Any disagreements were discussed by the full research team until full consensus was reached. Full-text articles were retrieved and reviewed

by one author (TJM), and all exclusions at the full-text step required agreement from the full research team.

2.3 Data Extraction

Data extraction included article citation details (year, authors, title), country of HCV patients observed, population characteristics, sample size (if applicable), study description, study years included, presence of societal costs (yes/no), description of costing method, costing method category, analysis type, results (detail), funding source, currency and inflation costs adjustments, and disease-specific costs reported. Costing method categories were defined previously in a systematic review of COI studies for all diseases

by Onukwugha et al. [13]. For extraction of HCV costs, all health sector and societal perspective costs were extracted as reported by the study authors. Health sector and societal perspective costs were identified based on formal, informal, and non-health impact definitions provided by the Second Panel on Cost-Effectiveness in Health and Medicine [16] (Table 1).

2.4 Evidence Synthesis

To compare costs reported across studies, all costs were converted to United States dollars (USD) and inflated to December 31, 2019 using the Bureau of Labor Statistics Consumer Price Index (CPI) for medical care services [17].

Table 1 Hypothetical impact inventory for cost-effectiveness analyses in hepatitis C [51]

Sector	Type of impact	Perspective	
		Health care	Societal
Formal health	Direct medical costs (medications, laboratory testing, inpatient, outpatient, etc.)	Yes	Yes
	Direct health effects (longevity, health-related quality of life, adverse events, etc.)	Yes	Yes
Informal health	Indirect costs (patient and caregiver time related to care, transportation, etc.)	NA	Yes
Non-health	Labor market earnings lost (absenteeism)	NA	Yes
	Productivity loss (presenteeism)	NA	Yes

NA not applicable

Fig. 1 Health state model representing natural progression of liver disease for patient with hepatitis C

Costs extracted were stratified by health states commonly used in economic evaluation for DAAs in HCV (Fig. 1). Due to the expected heterogeneity of costing methods, authors determined a priori to present costs reported without combining multiple studies. Exploratory bivariate analyses were conducted to determine any associations between key variables. Costing methods were further categorized as simple (sum all medical, sum diagnosis specific) and complex (regression, matching, multiple) for comparison [14]. Additionally, analysis types were categorized as simple (descriptive statistics) and complex (regression, matching, multiple) for comparison.

2.5 Risk of Bias Assessment

In accordance with PRISMA recommendations, we assessed the risk of bias within included studies at the outcome level, which required a consensus from the full research team. Specifically, the authors considered how study methods may have influenced costs attributable to HCV for the purposes of this review. Qualitatively, we described the potential sources of bias and rated studies as being at low, moderate, or high risk of bias. The costing method categorization aided in the risk of bias assessment, as more complex costing methods

(e.g., Matching, Regression, and Other Incremental) may reduce certain types of bias in the resulting cost appropriated to disease [13, 14]. Authors reached agreement that studies reporting descriptively with little to no statistical adjustments for cost estimates, no reported method of incorporating price inflation, or unadjusted cost sources (e.g., wholesale acquisition costs for drug prices, hospital charges rather than actual paid amounts) would produce a high risk of bias. Meanwhile, studies that attempted to control for some of these factors, but not all, would be rated as having moderate risk. Source of funding was discussed as a potential source of bias; however, the authors agreed it was difficult to assess bias based on funding source and felt more weight should be given to the stated methods. Therefore, funding source was not included in the final assessment of risk of bias. Based on this categorization, a risk of bias rating was proposed by one reviewer (TJM) with rationale described prior to group discussion. Proposed ratings and rationale were reviewed and discussed by all three authors for final risk of bias ratings requiring unanimous consent. Exploratory bivariate analyses were conducted to assess risk of bias and other key variables (e.g., inclusion of societal costs, presence of industry funding, US/other). All statistical analyses were performed in R version 3.5.3 [18].

Fig. 2 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram. *PICOS* Population, Intervention, Comparator, Outcomes, Setting

3 Results

3.1 Overview of Studies

The search strategy identified 495 records in EMBASE, Scopus, and PubMed, yielding 278 unique studies after duplicates were removed (Fig. 2). Of the 278 unique studies, there were 35 inclusion/exclusion conflicts during title and abstract screening (12.6%) that required additional discussion for full author agreement. After title and abstract screening, 50 full-text manuscripts were assessed for eligibility. During full-text assessment, an additional 19 studies were excluded. Finally, 31 studies were included with full author agreement in the review for evidence synthesis [19–49]. Several countries were identified within the included studies, with the United States being identified the most frequently (42%, 13/31) and multiple countries identified in two or fewer studies (Fig. 3).

3.2 Methodological Heterogeneity

The most frequent study type found in this review utilized a retrospective cohort design (77%, 24/31), followed by cross-sectional (16%, 5/31). There were two previously published systematic reviews (6%) that met the inclusion criteria [28, 45]. In terms of costing method, Sum Diagnosis Specific was the most common (39%, 12/31), with Regression as the next most common (32%, 10/31). Sum All Medical (10%,

3/31) and Matching (6%, 2/31) were found less frequently, and four studies (13%) used multiple methods to estimate costs (Table 2). In addition to costing method heterogeneity, methods varied in several areas, including data sources, population focus, presence of a control group for comparison, and accounting for net paid amount for health services or medications versus charged amounts.

3.3 Societal Perspective Costs

Of the 31 studies included, 35% (11/31) included costs that would be included in a societal perspective model [16]. Absenteeism, presenteeism, patient time, caregiver time, and travel were identified costs (Table 4) associated with different stages of HCV infection [20, 28, 33, 34, 37, 41–44, 46, 49]. We did not identify any costs measured in the literature related to social services, legal or criminal justice, education, housing, environment, friction costs, or other unique societal perspective costs [16]. No associations were found between studies that reported societal costs and other key variables extracted (Table 5).

3.4 Health-State Specific Costs

Costs were identified for various stages of HCV disease progression, from no HCV (i.e., controls) through advanced liver fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver transplant (Tables 3,

Fig. 3 Countries identified within published studies identifying costs associated with hepatitis C from 2010 to present [61]

Table 2 Summary of included studies

Year	Authors [reference]	Study type	Country	Study years	Currency	Societal perspective	Costing method	Analysis	Risk of bias	Funding source
2016	Abergel et al. [19]	Retrospective cohort	France	2012	2013 Euro	N	Sum All Medical	Descriptive statistics	High	Industry
2015	Baran et al. [20]	Retrospective cohort	United States	2001–2013	2013 USD	Y	Regression	Regression	Moderate	Industry
2014	Bichoupan et al. [31]	Retrospective cohort	United States	2011	2012 USD	N	Sum Diagnosis Specific	Descriptive statistics	High	Industry and government
2011	Brook et al. [42]	Retrospective cohort	United States	2001–2008	2007 USD	Y	Regression	Regression	Moderate	Industry
2018	Castelo et al. [44]	Cross-sectional	Brazil	2014–2015	2016 USD	Y	Sum Diagnosis Specific	Descriptive statistics	High	Industry
2012	El Khoury et al. [45]	Systematic review	Multiple	1990–2011	2010 USD	N	Multiple	Descriptive statistics	Low	Industry
2012	Federico et al. [46]	Cross-sectional	Canada	2006–2008	2007 Canadian	Y	Regression	Regression	Moderate	Government
2014	Galbraith et al. [47]	Retrospective cohort	United States	2001–2010	2010 USD	N	Sum Diagnosis Specific	Descriptive statistics	High	Government
2012	Helsper et al. [48]	Retrospective cohort	Netherlands	2001–2010	2010 Euro	N	Sum Diagnosis Specific	Descriptive statistics	High	Government
2013	Karahasanoğlu et al. [49]	Cross-sectional	Turkey	2009–2010	2010 USD	Y	Sum Diagnosis Specific	Descriptive statistics	High	None
2017	Ki et al. [21]	Retrospective cohort	South Korea	2009–2013	2013 USD	N	Sum All Medical	Descriptive statistics	High	Industry and government
2015	Kieran et al. [22]	Retrospective cohort	Ireland	2006–2013	2011 Euro	N	Sum Diagnosis Specific	Descriptive statistics	High	None
2010	Krajden et al. [23]	Retrospective cohort	Canada	1997–2006	2005 Canadian	N	Matching	Propensity score matching, analysis of cost differences	Low	None
2019	Mattingly et al. [24]	Retrospective cohort	United States	2007–2015	2015 USD	N	Sum All Medical	Descriptive statistics	High	None
2012	Menzin et al. [25]	Retrospective cohort	United States	1999–2007	2009 USD	N	Regression	Regression	Moderate	Industry
2012	Nevens et al. [26]	Retrospective cohort	Belgium	2005–2007	2010 Euro	N	Sum Diagnosis Specific	Descriptive statistics	Moderate	Industry
2018	Park et al. [27]	Retrospective cohort	United States	2006–2013	2013 USD	N	Regression	Regression	Moderate	None
2018	Pascual-Argente et al. [28]	Systematic review	Multiple	2000–2017	2015 Euro	Y	Multiple	Descriptive statistics	Low	Government
2016	Perrone et al. [29]	Retrospective cohort	Italy	2009–2010	2010 Euro	N	Sum Diagnosis Specific	Descriptive statistics	High	None
2018	Pham et al. [30]	Retrospective cohort	United States	2014–2016	2017 USD	N	Regression	Regression	Moderate	None
2017	Reau et al. [32]	Retrospective cohort	United States	2009–2016	2016 USD	N	Multiple	Matching/regression	High	Industry
2015	Scalone et al. [33]	Retrospective cohort	Italy	2011	2011 Euro	Y	Regression	Regression	Moderate	Industry
2016	Shon et al. [34]	Retrospective cohort	South Korea	2008–2011	2011 USD	Y	Sum Diagnosis Specific	Descriptive statistics	High	Government
2017	Solid et al. [35]	Retrospective cohort	United States	2011–2012	2012 USD	N	Regression	Regression	High	Industry

Table 2 (continued)

Year	Authors [reference]	Study type	Country	Study years	Currency	Societal perspective	Costing method	Analysis	Risk of bias	Funding source
2011	Solomon et al. [36]	Retrospective cohort	United States	2001–2008	2007 USD	N	Multiple	Matching/regression	Moderate	Industry
2014	Stahmeyer et al. [37]	Retrospective cohort	Germany	2008–2011	2010 Euro	Y	Sum Diagnosis Specific	Descriptive statistics	Moderate	Industry
2014	Tandon et al. [38]	Retrospective cohort	United States	2001–2012	2012 USD	N	Sum Diagnosis Specific	Regression	Moderate	Industry
2016	Tapper et al. [39]	Retrospective cohort	United States	2003–2013	2013 USD	N	Regression	Regression	Moderate	Industry
2012	Vahedi et al. [40]	Retrospective cohort	Iran	2000–2009	2009 USD	N	Regression	Regression	High	None
2013	Vietri et al. [41]	Cross-sectional	Multiple	2010	2010 Euro	Y	Matching	Propensity score matching, analysis of cost differences	Moderate	Industry
2016	Zare et al. [43]	Cross-sectional	Iran	2015	2015 USD	Y	Sum Diagnosis Specific	Descriptive statistics	High	Government

USD US dollars

4). We did not identify costs associated with specific METAVIR fibrosis stages F0–F4, but rather costs observed by researchers were reported as either mild (F0–F2), moderate (F3), or compensated cirrhosis (F4) [50]. Health sector and societal cost estimates varied within and across natural progression health states from Fig. 1. In 2019 USD, all medical costs for non-HCV controls ranged from \$952 to \$2164 annually. Mild disease costs for all medical costs ranged from \$477 to \$5505 per year. Compensated cirrhosis all medical costs ranged from \$5162 to \$7732 per year. Decompensated cirrhosis and hepatocellular carcinoma had much greater variability for all medical costs, ranging from \$4970 to \$63,080 per year and \$4396 to \$110,495 per year, respectively. The cost of liver transplant also varied widely, ranging from \$20,127 to \$578,758 in the year of the transplant, with much smaller maintenance costs (\$7009–\$8224/year) in years > 1 year after transplant.

3.5 Risk of Bias for Cost Estimates

Authors evaluated each study for risk of bias specific to the reported costs associated with HCV disease and rated the majority of studies either high risk (15/31, 48%) or moderate risk (13/31, 42%). Only three studies (3/31, 10%) were given low risk scores, two of which were systematic reviews that included multiple country estimates [23, 28, 45]. Source of study funding was discussed as a possible variable to consider for bias, but the authors preferred to report funding separately for the reader to consider rather than make any judgments based on funder (Table 2). There was no association between societal perspective costs reported and risk of bias (Table 5).

4 Discussion

This systematic review included 31 studies that reported costs associated with HCV and descriptively reported evidence across health states commonly used in the development of CEAs for treatment in this population. Additionally, we categorize costs reported according to the recommended health sector and societal perspectives and assess potential risks of bias in these cost estimates [15, 51].

One of the most significant issues that CEA researchers must consider before reconstructing the commonly used HCV Markov process tied to METAVIR stage progression is the lack of real-world evidence for costs associated with the individual stage level (F0–F4) [50]. In a prior review of modeling approaches for CEAs in HCV, Chhatwal et al. reported 97% (35/36) of published HCV models used a Markov design with 58% (21/36) built in terms of METAVIR staging [7]. Using the METAVIR framework for transitioning between health states has

Table 3 Cost-of-illness estimates for health sector perspective stratified by health state for hepatitis C

Health state	Cost type	Annual health sector cost estimates (2019 USD)	SD/SE	N	Source
No HCV	All medical	952	2007	286	[41]
	All medical	2164	4	727,588	[20]
Any active HCV	Inpatient	2915	NR	23,214	[21]
	Outpatient	1490	NR	23,214	[21]
Post-SVR	All medical	23–104	NR	28	[22]
Disease severity					
Mild (F0–F2)	All medical	5505	252	1007	[20]
	All medical	4204	NR	652	[33]
	All medical	691	NR	166	[43]
	All medical	477–684	NR	40	[22]
	Inpatient	39–1,616	NR	51	[37]
	Inpatient	5436	NR	1193	[25]
	Outpatient	3468	NR	1193	[25]
	Outpatient	2362–2889	NR	51	[37]
	Pharmacy	13,188	NR	1193	[25]
	Pharmacy	20,481–27,514	NR	51	[37]
Moderate (F3)	Pharmacy	3432	147	1007	[20]
	All medical	475–713	NR	29	[22]
	Inpatient	19–110	NR	165	[37]
	Outpatient	2362–2675	NR	165	[37]
	Pharmacy	21,765–25,810	NR	165	[37]
Compensated cirrhosis (F4)	All medical	5546	861	87	[20]
	All medical	7732	NR	222	[33]
	All medical	5162	NR	24	[43]
	Inpatient	129–859	NR	67	[37]
	Outpatient	2229–2862	NR	67	[37]
	Pharmacy	5147	739	87	[20]
	Pharmacy	19,418–26,867	NR	67	[37]
Decompensated cirrhosis	All medical	14,784	1339	256	[20]
	All medical	4970–63,080	NR	NR	[45]
	All medical	5595–20,759	NR	13	[22]
	Inpatient	7927–28,221	NR	32	[37]
	Outpatient	1395–2150	NR	32	[37]
	Pharmacy	1321–7780	NR	32	[37]
Hepatocellular carcinoma	Pharmacy	4078	338	256	[20]
	All medical	39,986	14,031	17	[20]
	All medical	20,059	NR	85	[33]
	All medical	9649	NR	10	[43]
	All medical	4396–110,495	NR	NR	[45]
	All medical	21,588–41,791	NR	27	[22]
	Inpatient	15,897	NR	7140	[21]
	Inpatient	33,744	NR	73	[25]
	Outpatient	3252	NR	73	[25]
	Outpatient	6279	NR	7140	[21]
Liver transplant (year 1)	Pharmacy	5560	1823	17	[20]
	All medical	116,665	38,724	19	[20]
	All medical	192,914–196,150	NR	33	[22]
	All medical	20,127–578,758	NR	NR	[45]
	Inpatient	72,664	NR	118	[21]
	Outpatient	8899	NR	118	[21]
Liver transplant (> 1 year)	Pharmacy	8377	2539	19	[20]
	All medical	7009–8224	NR	33	[22]
	Inpatient	9078	NR	84	[21]
	Outpatient	13,903	NR	84	[21]

HCV hepatitis C virus, NR not reported, SD standard deviation, SE standard error, SVR sustained virologic response, USD US dollar

Table 4 Cost-of-illness estimates for the societal perspective stratified by health state for hepatitis C

Health state	Cost type	Annual societal cost estimates (2019 USD)	SD/SE	N	Source
No HCV	Absenteeism	1830	7136	286	[41]
	Absenteeism	778	6	727,588	[20]
	Presenteeism	4818	7968	286	[41]
Any active HCV	Absenteeism	1450–2,587	NR	NR	[28]
	Absenteeism	1910	NR	1223	[42]
	Presenteeism	4309–10,081	NR	NR	[28]
Post-SVR	Patient time	191–422	NR	148	[46]
	Caregiver time	25–107	NR	148	[46]
Disease severity					
Mild (F0–F2)	Absenteeism	1197	358	1007	[20]
	Absenteeism	221–5018	NR	51	[37]
	Direct non-medical	300	NR	166	[43]
	Indirect	838	NR	166	[43]
	Patient time	1015–2062	NR	326	[46]
	Caregiver time	25–107	NR	326	[46]
	Caregiver time	45	NR	652	[33]
	Travel	218	NR	652	[33]
Moderate (F3)	Absenteeism	1049–2713	NR	165	[37]
Compensated cirrhosis (F4)	Absenteeism	874	478	87	[20]
	Absenteeism	732–5520	NR	67	[37]
	Direct non-medical	706	NR	24	[43]
	Indirect	1016	NR	24	[43]
	Caregiver	156	NR	222	[33]
	Travel	652	NR	222	[33]
Decompensated cirrhosis	Absenteeism	1616	346	256	[20]
	Absenteeism	73–716	NR	32	[37]
Hepatocellular carcinoma	Absenteeism	4291	2388	17	[20]
	Caregiver time	159	NR	85	[33]
	Caregiver time	0–2558	NR	21	[46]
	Direct non-medical	1081	NR	10	[43]
	Indirect	1703	NR	10	[43]
	Patient time	1060–4915	NR	21	[46]
Liver transplant (year 1)	Travel	701	NR	85	[33]
	Absenteeism	3343	1433	19	[20]
	Caregiver time	0–5433	NR	47	[46]
	Patient time	3258–17,280	NR	47	[46]
Liver transplant (> 1 year)	NR	NR	NR	NR	

HCV hepatitis C virus, NR not reported, SD standard deviation, SE standard error, SVR sustained virologic response, USD US dollar

been generally acceptable in HCV CEA modeling due to a large meta-analysis of disease progression based on this scoring system and the common use of fibrosis scores for clinical trial reporting [7, 52]. Modelers sourcing transition probabilities from the Thein et al. meta-analysis must then apply costs from sources that group F0–F2 (“mild”) or even F0–F3 (“non-cirrhotic”) [52]. Whether or not this modeling decision influences CEA results has not been evaluated to our knowledge.

In terms of types of costs, we found a broad range of costs covering what could be included in both health sector and societal perspective CEAs. Formal health care costs were frequently reported as “all medical,” which may include a range of services, including inpatient, outpatient, laboratory, or other direct services captured under the medical benefit. Some studies stratified these formal health care costs into inpatient, outpatient, and pharmacy. We did not identify costs specific to laboratory costs that were not rolled into

Table 5 Analyses of key variables by the presence of societal costs in included articles

Variable	Societal costs (<i>N</i> = 11)		No societal costs (<i>N</i> = 20)		<i>P</i> value*
	<i>N</i>	%	<i>N</i>	%	
Country					
US	2	18	11	55	0.066
Other	9	82	9	45	
Industry funding					
Yes	6	55	11	55	1.0
No	5	45	9	45	
Costing method					
Simple	5	45	10	50	1.0
Complex	6	55	10	50	
Risk of bias					
High	4	36	11	55	0.46
Moderate/low	7	64	9	45	

*Significance level $P < 0.05$

the broader medical cost category. In terms of informal health costs, time (both patient and caregiver) and travel costs related to care were identified. The only non-health costs identified in articles included in our study were related to absenteeism and presenteeism. To our knowledge, when considering the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force on value assessment, several elements of value described by Lakdawalla et al. have not been evaluated in the context of HCV [53]. When engaging HCV patients directly through qualitative interviews, advisory boards, focus groups, or Delphi panels, many patients report concerns that are difficult to measure in an observational study, such as impact on relationships, fear of harming others, financial stress, insurance issues, or stigma [54–57]. It may be difficult for researchers to accurately capture and quantify the real-world costs of some of these components reported by patients and attribute causality to HCV infection, leaving many of these constructs out of CEA designs [58].

Another area of concern for COI and CEA research in HCV was the use of list prices of drugs or hospital charges to estimate costs rather than determine an estimated net price actually paid by payers [20, 32, 42, 47, 59]. If CEA studies in HCV apply inflated disease costs without discounts to health states and use net drug prices (an estimated cost less than wholesale acquisition cost) for DAA treatment, the incremental cost of treatment may appear more favorable. Consistency in the approach for costing of the treatment, comparator, and health states may provide less chance of bias for incremental analyses, but having transparent net prices across the board to compare would be ideal.

The costing and analysis approaches described by articles included in this review demonstrate the heterogeneity in two of the most important research decisions made when conducting a COI analysis. Many researchers exploring COI make methodological decisions specific to answering a more narrow research question, and while these methods may be appropriate for the major question in the publication, the methods selected may present sources of bias for the health economists that seek to use these results to model a different question. There is nothing inherently wrong with any specific costing or analytical approach in a COI study, but the methods should be fit for purpose. Additionally, assessing the risk of bias for COI estimates can be quite challenging, as several factors may contribute to the direction or magnitude of bias. For example, a COI study using observational data failing to account for common sources of bias (e.g., selection bias, censoring, drug pricing discounts) may create both overestimation and underestimation problems. At the very least, economic modelers should attempt to qualitatively evaluate the potential bias for each input and then quantitatively account for the bias through thorough sensitivity and scenario analyses [60].

Future areas of research for the COI of HCV may consider ways to quantify the dynamic nature of HCV and the interactions of individuals in a population. Additionally, the psychosocial complexity of the disease warrants further investigation into extrahepatic manifestations, such as anxiety or depression. With highly effective treatments helping more patients reach SVR, we now have more opportunities to observe the post-SVR experience, which may inform costs and health effects for the post-SVR health state and re-infection transition probabilities for Markov-based modeling approaches in HCV infection. Currently, very few cost estimates have been reported on post-SVR, and we anticipate this to change over the next few years.

This systematic review had a few limitations that readers should consider. First, we focused on real-world evidence reporting costs, which eliminated any modeling approaches to estimate COI. Modeling costs may help provide estimates where current gaps exist or where real-world observational analyses are not feasible; however, we determined the potential methodological considerations for modeling costs were beyond the scope of this review and were covered previously by Chhatwal et al. [7]. We also focused our search on studies that were included in the “cost of illness” paradigm rather than more broadly including any study that mentioned “costs,” as we aimed to compare studies with specific economic evaluation methods. Additionally, a majority of studies originated in the USA where costs may differ significantly from other international sites due to differences in pricing and health care system structure. Another limitation of this review is that we focused on full manuscripts,

excluding posters or conference abstracts. Due to the in-depth review and assessment of costing methods, we felt full manuscripts were necessary for appropriate evaluation. Finally, our assessment of risk of bias was reported for each study, but we did not quantitatively adjust cost estimates reported by each study outside of the currency and inflation conversions. We recognize that many cost estimates may be biased above or below the true costs, and we recommend any CEA researchers using this review to consider the costs we identified, costing methods used, and bias assessment all in the context of the specific research questions in their analyses.

5 Conclusions

Several observational studies capturing costs associated with HCV were identified in this review. Cost estimates for formal, informal, and non-health care services have been observed in HCV, but several challenges still exist in quantifying the full disease burden. These results showed significant heterogeneity in identification of all medical, inpatient, outpatient, pharmacy, and other direct and indirect costs associated with HCV infection. While there was no significant difference in risk of bias, comparing high versus low in the studies reviewed, future modeling exercises using real-world cost inputs should critically evaluate the risk of bias based on costing methods and data sources used and adjust their models accordingly.

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Data Availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Compliance with Ethical Standards

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