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REVIEW

Economic burden of hepatitis C-associated diseases in the United States

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SUMMARY. There are approximately 100 drugs in development to treat hepatitis C. Over the next decade, a number of new therapies will become available. A good understanding of the cost of hepatitis C sequelae is important for assessing the value of new treatments. The objective of this study was to assess the economic burden data sources for hepatitis C in the United States. A systematic literature search was conducted to identify studies reporting the costs of hepatitis C sequelae in the United States. Over 400 references were identified, of which 50 were pertinent. The costs were compiled and adjusted to 2010 constant US dollars using the medical component of the consumer price index (CPI). The cost of liver transplants was estimated at $201 110 ($178 760–$223 460), hepatocellular carcinoma (HCC) at $23 755–$44 200, variceal haemorrhage at $25 595, compensated cirrhosis at $585–$1110, refractory ascites at $24 755, hepatic encephalopathy at $16 430, sensitive ascites at $2450, moderate chronic hepatitis C at $155, and mild chronic hepatitis C at $145 per year per person. All studies were traced back to a handful of publications in the 1990s, which have provided the basis for all sequelae-based cost estimates to date. Hepatitis C imposes a high economic burden. Most cost analysis is more than 10 years old, and more research is required to update the sequelae costs associated with HCV infection.

Keywords: cost, direct cost, hepatitis C, sequelae.

INTRODUCTION

Chronic hepatitis C is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) and a major indication for liver transplantation [1]. The burden of the disease is expected to increase in the United States as the hepatitis C virus (HCV)-infected population ages [2].

There are approximately 3.9 million (MM) HCV-infected persons in the United States and 12 000 die annually from HCV-related liver disease [3]. A high proportion of US patients became infected in the 1960s and 1970s as injection recreational drug users. Now approaching or older than 60 years of age, they represent a cohort that is expected to develop significant liver disease [4]. It is projected that compensated cirrhosis and HCC will increase by over 80 per cent from the year 2000 to the year 2020. Over the same period, it is estimated that decompensated cirrhosis would increase over 100 per cent and that liver-related deaths would increase by 181 per cent [5].

Understanding the economic burden of diseases relating to HCV infection has value in itself. It is also important as a baseline for policy and resource allocation decisions as well as determining the cost effectiveness of new therapies. Given the wide selection of sources available on this topic, the focus of this study was to systematically review published literature and develop baseline costs for future work on this topic in the United States.

METHODOLOGY

To investigate the costs associated with HCV infection sequelae, the progression of the disease was researched (Fig. 1). Then, a systematic review of the literature was conducted to identify studies reporting the cost of HCV infection sequelae. Indexed articles were identified by searching in PubMed using the following terms: '(liver transplantation OR chronic hepatitis C OR HCC OR HCC OR chronic liver disease OR cirrhosis OR ascites OR variceal haemorrhage OR hepatic encephalopathy OR fulminant hepatitis) AND (cost OR treatment cost OR economic burden)' OR 'hepatitis C AND

Abbreviations: AGA, The American Gastroenterological Association; CDA, centre for disease analysis; CHC, chronic hepatitis C; CPI, consumer price index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDdb, investigational drug database; MM, million; NAMCS, national ambulatory medical care survey; NHAMCS, national hospital ambulatory care survey; NHDS, national hospital discharge survey; NIH, national institute of health; PCR, polymerase chain reaction; RNA, ribonucleic acid; US, United States.

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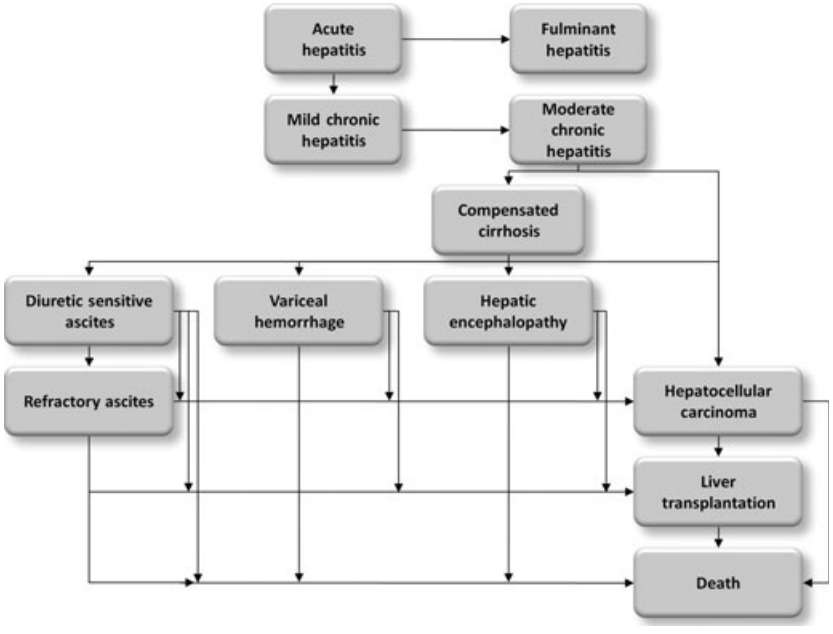

Fig. 1 Simplified hepatitis C sequelae progression.

(cost of illness OR economic burden OR markov OR (disease progression AND model)'. In addition, the HCV database at the Center for Disease Analysis [6], which contains over 2700 indexed and nonindexed sources from 1985 to 2010, was searched using the same terms. Furthermore, references cited within the articles were reviewed. This last step proved to be important as it not only provided new references, but also identified all studies that relied on the previous work. The scope of the search was global to identify ex-US studies that also analysed US-based data.

Cost data were categorized annually and were converted to 2010 US dollars using the medical component of the consumer price index which captured the change in prices and inflation over time [7]. The service component of the index was used for adjusting the liver transplantation cost while the commodity component was used for all other costs such as chronic hepatitis C, ascites, and cirrhosis. The top-down costs were not adjusted to 2010 US dollars. These estimates incorporated two components: incremental medical cost and number of visits and/or hospital days. The latter depended on the number of cases in a year, which could not be adjusted to 2010 values.

Given that most cost studies were traced back to a single source, a weighted average mean approach was not applied here. Instead, the 2010 adjusted cost for the original study was reported along with minimum and maximum values for other published data that significantly differed.

RESULTS

Over 400 references were identified, of which 50 were pertinent to this work. Of the original 400, approximately 50% did not contain specific cost data. Another 12.5% were specific to the treated population on the current standard of care (interferon or pegylated interferon plus ribavirin) and did not examine the costs of sequelae. Another 12.5% of the articles were too broad (e.g., all liver diseases) or too specific (e.g., HIV co-infected population). Of the remaining 25%, half, or 50 articles, were applicable to the US population, and the rest were specific to other countries.

Disease progression

A number of studies reported the disease progression for HCV infection summarized in Fig. 1 [8–14].

After infection with HCV, the acute phase lasts for 6 months, when roughly 15–45% per cent will spontaneously clear the infection [13,15]. A very small proportion will develop fulminant hepatitis, which may rapidly lead to death [13]. Acute infections will transition from mild to moderate chronic hepatitis C [11–14]. Fibrosis develops and when severe enough, the patient becomes cirrhotic. Initially, the cirrhosis is restricted sufficiently that the liver is able to compensate for the damage and provide normal functioning. Decompensated cirrhosis arises when conditions secondary to liver failure develop.

Individuals with compensated cirrhosis can develop ascites, which is the accumulation of fluid in the abdomen owing to high portal venous pressure. Initially, the condition responds to diuretic medications. For some patients, the condition becomes unresponsive, resulting in diuretic refractory ascites. Other cirrhotics can develop variceal haemorrhage, which is bleeding from enlarged veins in the oesophagus caused by high portal venous pressure. Hepatic encephalopathy, which is loss of cognitive function owing to

rising toxin levels in the bloodstream, is another sequela. Persons with chronic hepatitis C can also develop HCC, the primary cancer of the liver.

Liver transplantation is a well-accepted treatment for end-stage liver disease as well as for HCC in some cases. The procedure is expensive for several reasons. Extensive patient diagnostics are required. Donor liver procurement requires deployment of surgical teams. The surgery is interdisciplinary, complex, and long. Need for surgical reintervention and use of medication are high. Readmission is often required. Use of live donors has increased the number of available donor organs, but it has also increased patient costs [8,16–18].

Economic burden

Two approaches were reported for estimating the economic burden of hepatitis C: top-down and bottom-up. In the top-down approach (Table 1), the national estimates for medical spending were used to calculate the total cost [19–23]. The National Hospital Discharge Survey (NHDS), National Ambulatory Medical Care Survey (NAMCS), and National Hospital Ambulatory Medical Care Survey (NHAMCS) data sets were used to estimate inpatient hospital stays, physician office visits, emergency room visits, and hospital outpatient visits, respectively. The average length of stay and total days of care by disease were obtained from these databases, which were used in calculating indirect costs. Direct cost associated with hepatitis C was estimated at \$694–\$1660 million per year, HCC (all causes) at \$261–\$978 million per year, HCC (hepatitis C only) at \$140 million per year, and chronic liver diseases and cirrhosis at \$1421 million per year. These cost estimates were in different years, as shown in Table 1, making direct comparison difficult.

The indirect costs, defined as the cost of forgone earnings or production because of hospitalization, ambulatory care, premature death, and work loss because of acute or chronic infection, were often higher than the direct costs. In a 2010 study, the indirect cost associated with hepatitis C was estimated at \$490 per year per diagnosed individual [24]. In the 2008 report by the National Institute of Health (NIH) [19], the indirect cost (\$1.78 billion in 2004) for hepatitis C was 67% higher than estimated direct costs (\$1.1 billion in 2004).

In the bottom-up approach, a patient cohort model was used to estimate the total cost using the cost and transition probability for each sequela [8,9,12,25–29]. In the latter approach, the disease progression analysis used Markov models and updated transition probabilities, but the disease cost component in all studies was traced back to a handful of publications as shown in Table 2 [8,26,29]. The most frequently used study was by Bennett *et al.* [8] where the incremental cost (cost for one additional patient) was assessed in a study of 126 hospital patients at the University of Florida. Outpatient costs were estimated by applying an assumed cost/charge ratio to fee schedules and wholesale medication costs. A panel provided frequency estimates for services and medications. The study by Younossi *et al.* [26] used Medicare fee schedules and physician assessment of cost frequency to estimate the cost of chronic hepatitis C and cirrhosis.

A considerable number of studies were published on liver transplantation cost [16,30–43], which were consolidated and analysed by a recent meta-analysis [16]. The mean cost of liver transplantation was estimated at \$201 110 (2010 US dollar) with a 95% confidence interval of \$178 60–\$223 460. Subsequent years' cost was estimated at \$37 535 with a range of \$30 550–\$46 750 in 2010 dollars [8,44].

DISCUSSION

According to a database of drugs in development by Thomson Pharma [45], there are approximately 100 drugs

Table 1 Summary of top-down studies reporting total annual costs (\$MM in the reported year)

Sequela	Direct cost (\$MM)	Indirect cost (\$MM)	Total cost (\$MM)	Year	Source
Chronic liver disease and cirrhosis–all causes	1421	222	1643	1998	[21,23,54]
Hepatitis C–chronic	1065	1784	2849	2004	[19]
	694	51	745	1998	[21,54]
	1660	3370	5050	1997	[20]
HCC–all causes	261	1319	1580	2004	[19]
	978	10	988	1998	[21,55]
			241	1988	[23,56]
			509	2000	[23,56]
HCC–Hepatitis C	140	290	430	1997	[20]

TD, top-down study; BU, bottom-up study; HCC, hepatocellular carcinoma; MM, million.

Table 2 Summary of studies reporting incremental cost by sequela (in 2010 US $)

	Base 2010 cost ($/Patient/Year)	Min 2010 cost ($/Patient/Year)	Max 2010 cost ($/Patient/Year)	Notes
Mild chronic hep C	$145 [8,9,12,57]			Studies relied on Bennett *et al.* work
Moderate chronic hep C	$155 [27,57]			All studies under base case relied on Bennett *et al.* work
Compensated cirrhosis	$1110 [9,27,57]	$585 [26]		All studies under base case relied on Bennett *et al.* work
Diuretic sensitive ascites	$2450 [8,12,57]			Studies relied on Bennett *et al.* work
Refractory ascites	$24 755 [8,12,57]			Studies relied on Bennett *et al.* work
All ascites	$4690 [9,27]			Studies relied on Bennett *et al.* work
Variceal Haemorrhage –1st Year	$25 595 [8,9,12,27,57]			Studies relied on Bennett *et al.* work
Subsequent Year	$5010 [8,9,12,27,57]			Studies relied on Bennett *et al.* work
Hepatic Encephalopathy–1st Year	$16 430 [8,9,12,27,57]			Studies relied on Bennett *et al.* work
Subsequent year	$3810 [8,9,12,27,57]			Studies relied on Bennett *et al.* work
Hepatocellular carcinoma	$44 200 [8,9,12,27]	$23 755 [29]		All studies under base case relied on Bennett *et al.* work
Liver transplantation	$201 110 [16]	$178 760 [16]	$223 460 [16]	van der Hilst included all previous studies and provided mean & 95% confidence interval
Subsequent year	$37 535 [8,44]	$30 550 [8,44]	$46 750 [8,44]	Using 1993–1997 data which do not take into account the recent drop in cost of transplants

in development to treat hepatitis C. Over the next decade, a number of new therapies will become available. A good understanding of the cost of hepatitis C sequelae is important to assess the value of the new treatments.

Top-down studies use national survey results to estimate the total cost attributed to chronic liver diseases, hepatitis C, and HCC. The NHDS is an annual survey conducted by the Center for Disease Control and Prevention that collects data on the characteristics of inpatients discharged from non-Federal short-stay (<30 days) hospitals in the United States [46]. Data are collected from 239 hospitals and include demographic information and length of stay, as well as patients' diagnoses and procedures coded to International Classifications of Diseases (ICD). The NAMCS collects demographic data, reason for the visit, services provided, diagnostic procedures, diagnosis by ICD code, drugs prescribed, patient management, and planned future treatment from office based physicians [47]. The survey includes results from 1600 responding physicians and about 42 000 patient visits. The NHAMCS gathers data from hospital emergency and outpatient departments as well as ambulatory surgery centres [47]. All of the above surveys exclude Federal, military, and Veteran's administration hospitals. These surveys do have limitations. Extrapolation is carried out from a small sample. One case may be reported multiple times if it involves multiple visits, and they under-report cases that do not involve visits to hospitals, outpatient centres, or physician offices (e.g., veterans who have a higher prevalence of hepatitis C [48]). However, despite these limitations, they have been used to estimate the number of cases and duration of treatment by disease.

The studies took different approaches for estimating the associated cost. Work by Leigh *et al.* [20] started with the total national expenditure of $1035 billion on medical care in 1996, portioned it to hepatitis C based on hospital days, and adjusted it by including assumptions for outpatient visits. The NIH report relied on nationally reported costs, Medicare costs, and audit sales data for prescription drugs [19]. Hospital costs were estimated from the Healthcare Cost and Utilization Project (HCUP NIS), which collects data on hospital inpatient stays [49]. It includes data from 37 states reporting approximately 8 million hospital stays each year. The data collected include demographic, admission and discharge status, length of stay, total charges and payment source as well as diagnosis using ICD codes. In the top-down approach, billed charges were used as a surrogate for the total cost of patient services. For hospital charges, cost-to-charge ratio from the Center for Medicare & Medicaid Services [50] was used to calculate total cost. Medicare reimbursement rates were used to estimate physician charges. Prescription drug costs were estimated from audited data provided by Verispan [19]. The American Gastroenterological Association (AGA) also published a study reporting the cost burden of digestive diseases, but their study was later updated by the NIH report [19,21].

All top-down studies relied on the same data set, and yet, there was considerable variability in the projected cost (e.g., $694–$1660 million for chronic hepatitis C as shown in Table 1). The large difference in the forecast was because of two factors: methodology and number of cases over time. Not all studies used the same methodology to estimate total number of cases or cost. For example, the study by Leigh *et al.* used the ICD code for liver diseases (and adjusted for percentage that can be attributed to hepatitis C) rather than the code for hepatitis C because they felt that hepatitis C cases were under-recorded by the hospitals. In their cost estimates, they also included health care expenditure cost such as construction of new hospitals, arguing that without hepatitis C, some portion of these new expenses would not be necessary. Overall, their estimated direct cost attributed to chronic hepatitis C ($1660) in 1997 was substantially higher than estimates by the NIH ($1065) in 2004 [19,20]. Top-down studies captured costs at a particular point in time. Comparison across years and studies is feasible for diseases whose population is steady over time. However, this was not the case with HCV infection and its sequelae. As an example, HCC cases doubled between 1985 and 1998, making comparison across years difficult [23].

Comparison across top-down studies was not possible. There were too many variables changing across studies to allow direct comparison. That said, the NIH report was the gold standard in this group of studies. It was the most recent analysis, the editor was involved in the earlier AGA study and would have adjusted for the shortcoming of the earlier study, and it provided the most robust methodology. It should be noted that top-down analyses captured total costs including prescription drugs. In the NIH report, 47% of the annual cost associated with chronic hepatitis C was attributed to drug costs [19]. Top-down studies are based on a set number of cases at a point in time. Coupled with an epidemiology study, the bottom-up analysis lends itself more readily for estimating the cost of the disease burden in the absence of treatment or the economic benefits of new treatment.

There was considerably more consistency among the bottom-up analyses. However, further research into the origins of the assumptions found that nearly all studies were using data reported by Bennett *et al.* in 1997 [8]. In this original study, the incremental cost (cost for one additional patient) was assessed in a study of 126 hospital patients at the University of Florida. Outpatient costs were estimated by applying an assumed cost/charge ratio to fee schedules and wholesale medication costs. A panel provided frequency estimates for services and medications. The fixed costs (cost of purchasing new building, equipment, etc.) were not considered. On an individual patient level, this is a safe assumption. However, at an infected population level, this approach will underestimate the total cost as the incidence of morbidities increases. Finally, this study reported the variable cost and diagnosis-related group cost. Nearly all subsequent reports used the variable cost only, which again underestimated the total cost associated with the sequelae. A couple of investigators did develop independent cost analyses, which were substantially different. A study by Younossi *et al.* [26] used Medicare fee schedules and physician assessment of cost frequency to estimate the cost of decompensated cirrhosis ($585 per year in 2010 US dollars *vs* $1110 from Bennett *et al.*). However, the same study used cost estimates from the Bennett study for HCC and liver transplantation. Kim *et al.* [29] used HCC annual costs from a 1994 NIH report based on a top-down approach. The top-down cost was $23 755 per year in 2010 US dollars *vs* $44 200 from Bennett *et al.* The cost of liver transplantation was studied by many authors [16,30–43]. A recent meta-analysis by van der Hilst *et al.* consolidated all previous work to report a total cost of $201 110 (2010 US dollar) per liver transplant with a 95% confidence interval of $178 60–$223 460 (2010 US dollar). They showed that the cost of liver transplantation was 57% higher in the United States as compared to the Organization for Economic Cooperation and Development (OECD) countries. This analysis is considered the gold standard owing to its wide scope and the robustness of the methodology. It excluded the work by Bennett *et al.*, which estimated at $174 935 (2010 dollar), lower than the range provided by the meta-analysis. The cost in subsequent years was reported by two studies [8,44]: mean of $37 535 per year in 2010 dollars with range of $30 550–$46 750. Again, the cost estimate by Bennett *et al.* ($30 550 per year) was at the lower end of the range. The higher end of the range was defined by change in cost liver transplantation over the years.

Our analysis highlights the need for more updated cost studies. The historical cost burden analyses relied on data that were over 10 years old, and may not reflect the current clinical practice. The old data most likely underestimate the current costs even after adjustment for inflation. As an example, the variable cost associated with mild chronic hepatitis was estimated at $146 per patient per year in 2010 dollars [8]. A more recent study reported that, excluding the outpatient visit, the cost of HCV antibody testing and HCV RNA PCR testing was $107 and $300, respectively, in 2006 [51]. Future studies could leverage insurance claim data, which have been shown to be an important source to reflect current standard practices [52,53].

Finally, the cost burden of hepatitis C also has an indirect cost component. A number of studies estimated the indirect cost defined as the cost of forgone earnings or production owing to hospitalization, ambulatory care, work loss owing to acute or chronic infection, and premature death [19–21,24,29]. In most cases, the indirect cost was higher than the projected direct expenses. The total annual indirect cost was estimated at $51–$3370 million in the reported year (see Table 1). At the lower end of the range, only productivity loss owing to time away from paid labour was considered [21,29]. At the high end of the range, production loss owing to early death was added. The most recent study for indirect cost was published by the NIH, which estimated the indirect cost at $2847 in 2004 [19]. Hospital and ambulatory data were used to estimate foregone earnings. Loss owing to early death was estimated using forgone lifetime earnings to age 75. Overall, hospital stays, ambulatory care, and mortality accounted for $46.6, $51.2, and $1685.7 million respectively in 2004. However, this technique underestimated the cost associated with work and leisure loss that did not result in hospitalization or physician visits. Using a completely different approach, Su *et al.* [24] estimated the indirect cost associated with disease-related absence using data from multiple large employers in the United States by comparing record of employees with and without HCV. They attributed an increase of $490 (2007 dollar) per person per year in indirect costs to HCV infection.

Over the next decade, a number of new therapies will become available to treat hepatitis C. The debate over the cost effectiveness of these new therapies will depend on the comparison of no treatment, treatment with pegylated interferon and ribavirin, and treatment with new therapies/combinations. This review reported all relevant cost studies in the United States by different categories: top-down, bottom-up, direct, and indirect. The top-down analyses could not be compared directly with bottom-up estimates, as the former represented the cost and duration and number of hospital and physician visits in a particular year while the latter focused on cost per year for each sequelae. The indirect cost, cost associated with loss of productivity and early death, can be substantially higher than direct costs—cost of physician visits, hospitalization, diagnosis, and treatment. Although bottom-up estimates are more appropriate for scenario-based cost burden analysis, most sequelae costs date back to analyses in the 1990s. Updated cost analyses would help stakeholders make informed decisions when choosing among future therapeutic alternatives.

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AC El Khoury is an employee of Merck & Co, Inc.

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