Essays on economic evaluation of efficiency in health care interventions

Natàlia Pascual Argente

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Dr. Jaume Puig Junoy (UPF Barcelona School of Management)

DEPARTMENT OF EXPERIMENTAL AND HEALTH SCIENCES

UNIVERSITAT POMPEU FABRA

In appreciation

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Abstract

The objective of this work is the evaluation of the impact of new direct acting antivirals for Hepatitis C as a case of disruptive healthcare innovation that challenged healthcare systems. Two systematic reviews address cost-utility analyses of new therapies and productivity costs of Hepatitis C. Then we present an assessment of clinical guidelines update at a European level from 2016 to 2018 and the method addresses methodological issues identified as lacking in previous works. Specifically, the Markov model included productivity cost measurement and real drug acquisition costs. The results confirm that European update on Hepatitis C treatment recommendations was efficient as it yielded health gains and savings on the cost side. Economic evaluation can be useful not only to assess healthcare innovations, but also as an efficiency test of clinical decisions.

Resum

L'objectiu d'aquest treball és l'avaluació de l'impacte de nous antivirals d'acció directa per a l'hepatitis C com a innovació sanitària disruptiva que va desafiar els sistemes sanitaris. Dues revisions sistemàtiques analitzen els estudis de cost-utilitat de les noves teràpies i els costos de productivitat de l'hepatitis C. A continuació s'avalua l'actualització de les recomanacions clíniques a nivell europeu entre el 2016 i el 2018 i el mètode inclou qüestions metodològiques que s'han identificat com a mancances en treballs anteriors. En concret, el model Markov incorpora els costos de productivitat i els costos reals d'adquisició dels medicaments. Els resultats confirmen que l'actualització europea sobre les recomanacions de tractament contra l'hepatitis C va ser eficaç, ja que va generar guanys en salut i estalvis en costos. L'avaluació econòmica pot ser útil no només per avaluar les innovacions sanitàries, sinó també com a test d'eficiència de les decisions clíniques.

Introduction

1.1 The revolution of Hepatitis C therapies

Hepatitis C virus (HCV) infection affects the liver and leads to chronic disease which can end in cirrhosis, end-stage liver disease and hepatocellular carcinoma in a slow decade-lasting progress. Chronic hepatitis C (CHC) is a global health problem affecting more than 70 million representing 1% of the world population[1]. Once a patient is diagnosed of HCV infection, genotype, level of fibrosis and cirrhosis status condition disease progression. Virus infection is classified by genotype (1 to 8) being the most common genotypes (GT) 1 and 3, which account for almost 70% of cases. Levels of fibrosis are measured in the METAVIR score from F0 to F4, where F0 corresponds to no fibrosis in the liver and F4 to cirrhosis. Cirrhosis is classified as compensated or decompensated. Related mortality represented more than 400,000 deaths in 2015[1]. Epidemiology varies across regions, with higher prevalence in Central and Eastern Europe (3%) than in Western Europe (1%)[2].

The objective of CHC treatment is to cure the infection, which is attained when reaching sustained virological response (SVR). SVR is defined with undetectable HCV RNA or at least 24 weeks after treatment is completed. SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of complications, as hepatocellular carcinoma can occur after eradication of the viral infection, and they may finally require a liver transplant.

Before the approval of new direct acting antivirals (DAAs), the current treatment consisted in a combination of peg-interferon (PEG-IFN) and ribavirin (RBV), which lead to a SVR of 40% to 50%. However, treatment options were ineffective due to the limited efficacy of treatment in various genotypes, treatment-related adverse

effects that limited adherence to treatment[3]. Adverse effects were the first cause of non-treatment initiation and discontinuation as they could affect any patient and comprised a number of intolerable adverse effects, such as haemolytic anaemia, flu-like symptoms, and psychiatric disturbances[4,5].

New DAAs replaced previous standard of care with dual (PEG-IFN+RBV) and triple therapy (adding first-generation DAAs boceprevir (BOC) or telaprevir (TVR) to PEG-INF+RBV). Second-generation DAAs appeared in 2013 and rapidly replaced previous therapies. Sofosbuvir (SOF) was the first second-generation DAAs and it was followed by multiple alternatives and combinations with higher efficacy rates that allowed Hepatitis C to become a curable disease, even for difficult-to-treat patients[6]. After 2015, new DAAs for hepatitis C reached almost 100% efficacy, halved treatment durations to as little as 12 weeks, and avoided almost all side effects, which could impair patients' quality of life and lead to treatment discontinuation.

New DAAs appearing since 2013 have been one of the most relevant examples of new pharmaceuticals changing the management of a chronic and prevalent disease in the world. Notably, they enabled a global strategy by the World Health Organization for hepatitis C eradication by 2030[7].

1.2 New DAAs for Hepatitis C: challenging access

The case for new DAAs of Hepatitis C is an example of a health breakthrough posing great challenges to healthcare budgets. Their additional therapeutic value was not questioned, as they were a vast are a vast improvement on the previously available ones. However, high prices together with hepatitis C prevalence rates made new DAAs unaffordable for healthcare systems after their market launch. Even at initially published list prices around 100,000 USD per treatment[8]

sofosbuvir-based regimens were proven to be efficient compared to previous therapies[9].

In this context payers addressed the access and affordability issues by negotiating private discounts and rebates directly with manufacturers[9] while simultaneously designing strategic plans to a progressively expand population coverage. Macro-level (policy) healthcare decision-makers designed plans to progressively incorporate these new drugs as they all became available in a short period of time[10,11].

Compared to other pharmaceutical innovations, the efficacy of new DAAs was not questioned but in less than two years new competitors entered the market (some of them improved combinations of SOF). At this point, Hepatitis C turned into a public health priority in Europe and cost-effectiveness assessment became crucial to increase evidence to distinguish which treatments could offer best value for money to the health care systems. In theory, when analysing value for money societies seek to understand how health inputs (resources) yield health outcomes (valuable health improvements) and then choose among those input combinations that provide greater health benefits.

In the last decades health care innovations have improved health outcomes and contributed to a rise in healthcare budgets at the same time[12]. Increasing healthcare expenditure might not always be a guarantee for better health even if efficacy of the new technology has been confirmed. There might be important differences between efficacy under ideal conditions and effectiveness under real ones and the efficiency of the innovation will depend on its incremental health to costs ratio compared to a relevant comparator.

At the same time there has been an increase in new drugs entering the market bearing high prices (mostly in oncology and rare diseases)[13]. However, the benefits

of new pharmaceuticals on patients' health and quality of life vary widely[14] and they may be considered insufficient with regards to their price. The evaluation of effective yet expensive new treatments is essential for HTA agencies under the new DAAs for HCV context.

1.3 Economic evaluation of health interventions

Economic evaluation (EE) is a method used to assess health technology innovations as a part of the broad appraisal process known as health technology assessment (HTA). HTA is aimed at ensuring sustainability of health systems[12] by contributing to better resource allocation and decision making in health in a context of increasing needs (and technologies) and limited resources. Health care technologies understood in a broad sense comprise not only new drugs or devices but also new interventions, programs, and procedures. Unfortunately, innovations in health cannot be always considered breakthrough, meaning they provide "substantial improvement over available therapy on a clinically significant endpoint". Even if they do, costs might challenge access.

In EE value of new interventions is more important than price. Although value has not been uniformly defined in healthcare[15], EE define value in terms of the comparative cost-benefit ratios of competing therapies. Cost-effectiveness analyses (CEA) consider both costs and benefits of a health care intervention in comparison with a relevant alternative and provide evidence for optimal spending with regards to efficiency (health-benefit to cost ratio)[16]. The term CEA commonly includes cost-utility analyses where the measure of health impact changes from natural units (effectiveness) to quality-adjusted life years (QALY). The efficiency of a new treatment is defined in terms of its incremental cost per QALY compared to the alternative[17].

Efficiency assessment of new health technologies can lead the way on managing conflicting objectives such as population access to new treatments and public health expenditure control on the short run and the promotion of innovation in the long run. However, EE has developed at different speeds. Some countries (i.e. United Kingdom, Sweden, Australia, Canada) have CEA as a well-stablished criterion and compulsory requirement to prioritize investments and portfolio of services in their health systems[18]. Others like Spain are still on their way towards such an explicit and evidence-based scheme in health priority setting[19,20].

The increasing impact of EE of health interventions has been accompanied by a growing set of methodological standards aimed at providing a reference case when conducting CEA. Current state of the art recommendations on best practices recommended that all CEA apply a societal perspective so that all costs, not only direct medical costs, are included. EE need to consider absenteeism, productivity loses, and earnings lost due to illness, provided they may have a greater significance in total burden of illness. Apart from using a societal perspective, methodological standards consider that CEA should always use prices of health resources which reflect their true social opportunity cost and use preferences of the general population[21].

1.4 An efficiency test for clinical decisions

Traditionally, CEA has been applied to compare treatments or drugs and it is still unusual in evaluating clinical decisions made at a macro level. After drug authorizations considering risk to benefit issues, clinical guidelines define the use of a health technology in the real healthcare settings, which may condition effectiveness. Physicians act as the agents of patients as they can understand the likely health impacts of available therapies, but they are recognized as managers of scarce resources by society.

Although clinical recommendations might not be mandatory to follow, they can shape the range of acceptable treatment alternatives on a particular health problem. Notably, some of them, including those for HCV treatment by the European Association for the Study of the Liver (EASL), have explicitly integrated cost-effectiveness in their assessment frameworks[22–24]. Clinical guidelines can incorporate cost and cost-effectiveness considerations which are usually based on single treatment CEA, but they are rarely evaluated as an intervention.

This thesis assesses the EASL guidelines for HCV treatment in the context of EE of healthcare interventions. In the race towards HCV eradication, this work contributes to improve the cost-effectiveness evaluation tools that can be applied to clinical recommendations regarded as an intervention. Although eradication is still on the agenda[25,26], this case can be easily repeated in the future of health innovations and it is important that stakeholders use already available tools in any decision making process to test the efficiency of decisions that shape the impact of new technologies in the healthcare context.

The first chapter allows us to explore the available evidence on the true social cost of HCV by analysing the impact of non-healthcare costs, including mainly the costs of reduced productivity at work (absenteeism and presenteeism) and productivity losses due to premature deaths.

The second chapter assesses published cost-utility analyses of second-generation DAAs with a focus on modelling characteristics, included costs and cost-effectiveness ratios. This work identifies the strengths of Markov models used in CEA of HCV therapies and outlines main areas of improvement, mainly the inclusion of non-healthcare costs and the use of real drug acquisition prices.

The third chapter focuses on analysing EASL update on HCV treatment recommendations from 2016 to 2018, when multiple second-generation DAAs

were rapidly introduced. An enhanced Markov model considering the social cost of HCV and real drug acquisition allows us to conclude that EASL guidelines in 2018 were efficient compared to those from 2016 as they enabled a gain in QALY and savings in costs.

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1. CHAPTER 1

Natàlia Pascual-Argente, Jaume Puig-Junoy & Anna Llagostera-Punzano (2018) Non-healthcare costs of hepatitis C: a systematic review, Expert Review of Gastroenterology & Hepatology, 12:1, 19-30, DOI: 10.1080/17474124.2017.1373016

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REVIEW

Non-healthcare costs of hepatitis C: a systematic review

Natàlia Pascual-Argente [a,b], Jaume Puig-Junoy [a,b] and Anna Llagostera-Punzano[b]

[a]UPF Barcelona School of Management, Pompeu Fabra University, Barcelona, Spain; [b]Department of Economics and Business. Center for Research in Health and Economics (CRES-UPF), Pompeu Fabra University, Barcelona, Spain

ABSTRACT

Introduction: There is an increasing interest in the indirect (or non-healthcare) costs of hepatitis C virus (HCV).

Areas covered: Systematic review of original studies on the non-healthcare costs of HCV published in English or Spanish between January 2000 and March 2017. 19 studies addressing non-healthcare cost of HCV were included in the analysis. All studies but one contain treatments with monotherapy or dual therapy prior to the recent introduction of innovative and highly effective direct acting antivirals (DAAs). Five studies estimate the incremental non-healthcare cost of HCV with a control group, which is regarded as high-quality methodology. The incremental annual non-healthcare costs of HCV in untreated patients compared with non-HCV patients are €4,209 in the US, and taking data from 5 European countries costs range from €280 in the UK to €659 in France.

Expert commentary: Available studies may be underestimating the true burden of non-healthcare costs for HCV as they are all partial studies, mainly including absenteeism and premature mortality estimates. Moreover, there is a need for studies addressing non-healthcare costs of HCV in settings where new treatments with DAAs have been implemented, as they are probably changing the current and future burden of the disease.

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Absenteeism; cost of illness; hepatitis C; indirect costs; non-healthcare costs; presenteeism; systematic review

1. Introduction

Hepatitis C virus (HCV) infection is the world's leading cause of liver disease. After infection, it is estimated that 15–45% of patients will clear the virus spontaneously but 55–85% will progress to chronic hepatitis C (CHC) [1]. CHC progresses to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease where the only treatment option is a liver transplant. It is estimated that around 142 million people in the world were affected by HCV in 2015, which represents a 18% increase from 2005 [2]. HCV is characterized by its heterogeneity in genotypes and it disproportionately affects males [3]. Globally, HCV-related diseases are responsible for 492.000 deaths per year [4].

Until 2011, dual therapy with peg-interferon and ribavirin was the standard of care in HCV treatment. In 2011, first-generation direct-acting antivirals (DAAs) were launched (boceprevir and telaprevir) which substantially improved SVR rates [5]. In 2014, second-generation DAAs allowed a significant shift in HCV treatment efficacy (>95%) and widened patient eligibility, thanks to reduced toxicity and adverse events [6].

The main goal of new treatments with DAAs is to cure HCV. This translates in achieving SVR, which stops disease progression and brings health improvements [7–12]. In 2016, the World Health Organization estimated that more than a million patients had been already treated with DAAs, specially in high-income countries [13].

Healthcare costs have merited prior attention in the economic burden of HCV literature, especially in recent years [14–29]. In addition to healthcare costs, social costs also include productivity losses due to premature deaths and work absenteeism or presenteeism (reduced productivity without absence from work), costs of formal or informal care and other non-healthcare costs [30]. There is no doubt on the paramount importance of productivity losses and premature mortality attributable to HCV. The exclusion of productivity costs may substantially affect total costs (or savings) of any HCV-related intervention [31].

To date, we found only one published systematic review of the non-healthcare costs of HCV which considers the period 1985–2010 [32]. This review is limited to the USA and finds only four studies published after the year 2000 [33–36]. Authors do not report information on methodology in order to understand variation in results. Even so, they conclude that in most studies the non-healthcare cost was greater than the estimates of healthcare costs. In an earlier nonsystematic review of the economic burden of HCV [37] three studies including non-healthcare costs are found [34,38,39]. These studies find that around two-thirds of HCV costs can be attributed to indirect or productivity costs. A systematic review on the economic burden of chronic liver disease for the period 2004–2013 [40] identified three studies estimating non-healthcare costs (two for the USA and one for a group of European countries). Despite reporting incomplete non-healthcare costs, premature mortality was the main contributor to the social burden of HCV.

An analysis of the systematic reviews mentioned above reveals a notable gap in our knowledge of the true social cost of HCV. This work seeks to update more exhaustively

CONTACT Natàlia Pascual-Argente natalia.pascual@upf.edu Universitat Pompeu Fabra, C. Ramon Trias Fargas 25-27, edifici Jaume I, Barcelona 08005, Spain

and extensively the available knowledge on non-healthcare costs of HCV with more recent cost-of-illness studies and economic evaluations. We present an up-to-date systematic review at an international level and analyze the methods used in these studies.

2. Methods

This systematic review on the non-healthcare costs of HCV covers the period from January 2000 to March 2017. The following databases were searched: PubMed, York CRD database, Cochrane Library, EconLit, Index Medicus Español (IME) and Índice Bibliográfico Español en Ciencias de la Salud (IBECS). References in previous published reviews were also reviewed, as well as Google Scholar. The search strategy in PubMed used the following keyword combination: *cost* OR resource* OR economic* OR expenditure* OR informal care* OR social cost* OR indirect cost* OR presenteeism* OR absenteeism* OR productivity loss* AND hepatitis C*. The same structure was adapted to search the remaining databases.

We included cost-of-illness studies and economic evaluations published in English or Spanish, without any geographical restrictions. We reviewed titles and abstracts to exclude articles published before 2000, nonhuman studies, those published in languages other than English and Spanish, non-original articles (review articles, editorials and opinion pieces or letters, and papers on methodological aspects and texts not published in scientific journals) and those not directly related to HCV. A second exclusion was made by reviewing full texts by two of the authors to exclude artides that did not constitute a cost-of-illness study or an economic evaluation of HCV, and cost-of-illness studies and economic evaluations that did not calculate non-healthcare costs.

Both the first and the second revision of articles were reviewed by two of the authors independently and discrepancies were addressed with a full-text revision and resolved by discussion.

All cost figures from the selected studies were adjusted and converted to 2015 Euros by applying the GDP deflator [41] and currency exchange rates [42]. When data for several countries were reported, we computed the average of their GDP deflators.

3. Results

The initial search yielded a total of 6077 articles and after 1001 duplicates 5076 titles and abstracts were reviewed. The first exclusion yielded 1719 articles that underwent an independent examination by two of the authors using full texts. In this second revision, 1700 articles were excluded for not being a cost-of-illness study or not including non-healthcare costs, leaving 19 articles that were finally included in our analysis (Figure 1).

3.1. Synthesis of the literature

The main characteristics regarding context, population, method, and non-healthcare costs in the 19 selected studies are summarized in Table 1. We found ten studies from the USA [34–36,39,43–48], two from a group of five European Union countries (France,

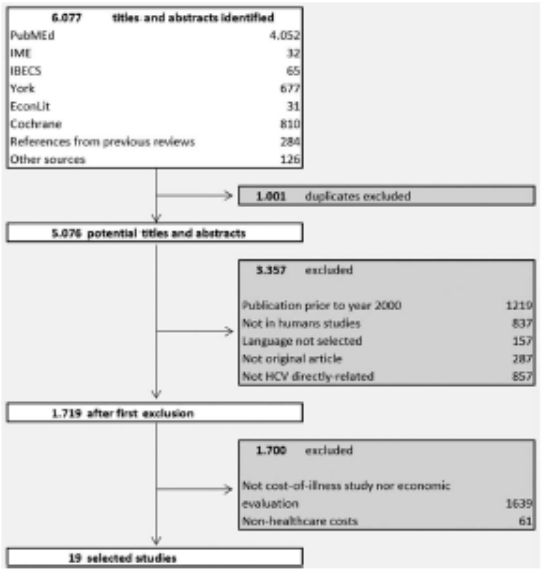

Figure 1. Flow diagram of the literature search.

Germany, Italy, Spain. and the UK) [49,50], and the rest from Australia [51], Iran [52], Italy [53], South Korea [54], Spain [55], Switzerland [38], and the UK [56]. Six of them were published between 2000 and 2009 [34,35,38,39,45,51], five between 2010 and 2014 [36,43,44,49,56], and the remaining eight were published between 2015 and March 2017 [46–48,50,52–55].

Eight studies only include adult populations [34,43,44,46–49,51], seven more include adults and minors [38,39,45,50,52,54,56], and four studies do not specify the age of the population included [35,36,53,55]. With regard to the labor market participation of the population, only in ten studies the working labor force is included [36,43,46–51,55,56], in five both the active and the inactive population are included [38,39,44,52,53] and in the remaining studies the employment status is not specified [34,35,45,54].

The societal perspective is used in 16 studies, two studies restrict the perspective to that of the employer [43,48] and another uses that of a private payer [47]. The prevalence epidemiological approach used to estimate the non-healthcare costs of HCV is applied in 17 studies, while the studies for Australia [51] and Italy [53] use the incidence approach.

The selected studies can also be distinguished depending on the type of cost measurement they use: six studies (32%) do not estimate the cost attributable solely to HCV, but rather the total non-healthcare cost of HCV patients [43,46,50,52–54]. This means they may include non-healthcare costs that cannot always be attributed directly to HCV but rather to other diseases or health problems suffered by patients with HCV. Neither of these studies includes a control group with an HCV-free population to estimate the incremental cost of the illness. The other 13 studies estimate the incremental cost attributable to HCV. Of these 11 studies, 8 estimate the incremental cost of HCV directly without a control group

Table 1. Main characteristics of the selected studies.

Type of variable	Variable	Characteristic	Number of articles	Percentage
CONTEXT	Country	United States	10	53
		5 European countries	2	11
		Australia	1	5
		Iran	1	5
		Italy	1	5
		South Korea	1	5
		Spain	1	5
		Switzerland	1	5
		United Kingdom	1	5
	Year of publication	2000–2004	5	26
		2005–2009	1	5
		2010–2014	5	26
		2015–2017	8	42
POPULATION	Age group	Only adults[a]	8	42
		Adults and minors	7	37
		Not specified	4	21
	Activity group	Active	10	53
		Active + Inactive	5	26
		Not specified	4	21
METHOD	Perspective	Society	16	84
		Employer	2	11
		Private payer	1	5
	Epidemiological focus	Prevalence	16	89
		Incidence	2	11
	Cost analysis	Total cost per patient	6	32
		Incremental cost without control group	8	42
		Incremental cost with control group	5	26
COST MEASUREMENT AND VALUATION	Non-healthcare costs	Labor losses due to absence from work	18	95
		Labor losses due to presenteeism	6	32
		Lost leisure time	2	11
		Premature deaths	8	42
		Formal care	1	5
		Informal care	2	11
		Disability	3	16
	Valuation method non-healthcare costs (labor losses)	Human capital approach	19	100
	Measurement of aggregate costs	Per patient	11	58
		National annual total	12	63

[a]Adults are considered as being 18 years and older.

[34,35,38,39,45,51,55,56]. This is done by attributing the measure of each of the resources used by the patients to the disease (sum of resources considered as being specific to a diagnosis of HCV). The authors rule out the consumption of resources that, according to some criterion, are considered not to correspond to this disease. The five remaining studies (26%) estimate the incremental cost of HCV on the basis of resource consumption corresponding to a group of HCV patients and a control group comprising patients without this disease [36,44,47–49]. The cost-of-illness studies that use a control group are of two types: those that employ a regression model to estimate the incremental effect of HCV and those that calculate the mean difference between a group with HCV and another peer group (matched control) without the disease [57]. Studies that use regression models can either identify patients with a diagnosis of HCV and then use the coefficients estimated in the regression to estimate the incremental cost of HCV or else build a matched control and then estimate the individual coefficients for HCV. The latter method is considered the gold standard [57] among cost-of-illness studies.

Two studies [47,49] employ the matched control method, estimating the incremental cost of hepatitis C as the mean difference between the two groups. The other three studies [36,44,48] are from the USA and combine the identification of a matched cohort with the regression and get the best estimate of the incremental cost of HCV.

Non-healthcare costs due to absenteeism (labor losses caused by absence from work) are included in all the selected studies except one [55], while only six studies [34,44,46,49,50,56] include presenteeism-related costs (lower productivity without absence from work) and only two studies [34,45] include the valuation of lost leisure time. Eight studies [34,38,39,45,51,54–56] include the cost of premature deaths. Two studies include formal care costs [54,58] and one of them also includes informal care costs [54]. Three studies include disability costs [47–49]. Other non-healthcare costs (missed school days, private transport, etc.) are not included in any of the selected studies. The human capital approach for assessing productivity losses was used in all studies.

Table 2. Summary of characteristics and results of the estimation of non-healthcare costs per HCV patient (in euros patient/year, 2015).

Study population	Cost measurement	Country	Author (year of publication)	Study period	Perspective	Estimated costs per patient by component					Estimated total cost per patient			Observations
						Labor losses due to absenteeism	Labor losses due to presenteeism	Lost leisure time	Premature mortality	Other costs	Labor losses (Human capital method)	Non-healthcare costs/ healthcare costs	Sample size group with HCV	
WITHOUT TREATMENT	Total cost of HCV patient	US	**Brook et al. (2011)**	2004	Employer	1358	–	–	–	–	1358	–	1223	Employees with chronic HCV. Costs adjusted for socioeconomic and health characteristics.
		US	**El Khoury et al. (2012)**	2010	Society	2053	7999	–	–	–	10,052	0.45	306	Untreated HCV patients. Costs adjusted using regression models.
		5 EU countries	**Vietri et al. (2013)**	2010	Society	1364	5398	–	–	–	6761	6.87	65	Untreated (treatment-naïve) employees with HCV.
		US	**Younossi et al. (2015)**	2013	Society	1151	3419	–	–	–	4570	–	N/A	Employees with chronic HCV.
	Incremental cost of HCV	US	**El Khoury et al (2012)**	2010	Society	1035	3688	–	–	–	4723	0.65	306	Untreated HCV patients. Costs adjusted using regression models.
		5 EU countries	**Vietri et al (2013)**	2010	Society	753	2170	–	–	–	2922	6.50	65	Untreated (treatment-naïve) employees with HCV.
		Germany	**Younossi et al (2016)**	2013	Society	X	X	–	–	–	464	–	629	Untreated HCV patients.
		France	**Younossi et al (2016)**	2013	Society	X	X	–	–	–	659	–		
		Spain	**Younossi et al (2016)**	2013	Society	X	X	–	–	–	402	–		
		Italy	**Younossi et al (2016)**	2013	Society	X	X	–	–	–	379	–		
		UK	**Younossi et al (2016)**	2013	Society	X	X	–	–	–	280	–		

(*Continued*)

Table 2. (Continued).

Study population	Cost measurement	Country	Author (year of publication)	Study period	Perspective	Estimated costs per patient by component: Labor losses due to absenteeism	Labor losses due to presenteeism	Lost leisure time	Premature mortality	Other costs	Estimated total cost per patient: Labor losses (Human capital method)	Non-healthcare costs/ healthcare costs	Sample size group with HCV	Observations
WITH TREATMENT	Total cost of HCV patient	US	**Brook et al. (2011)**	2004	Employer	1739	–	–	–	–	1739	–	441	Employees with chronic HCV.
		South Korea	**Shon et al. (2016)**	2008–11	Society	X	–	–	X	X	734	0.72	48,704	Treated patients with HCV.
		Iran	**Zare et al. (2016)**	2015	Society	X	–	–	–	X	5616	1.18	200	Treated patients with HCV.
WITH AND WITHOUT TREATMENT	Total cost of HCV patient	Italy	**Marcellusi et al. (2015)**	2013	Society	X	–	–	X	–	2678–27,083	–	296,131	Treated and untreated patients with HCV.
		US	**Su et al. (2010)**	2001–07	Society	1443	–	–	–	–	1443	0.13	1494	Employees with HCV. Costs adjusted for sodoeconomic and health characteristics.
		5 EU countries	**Vietri et al. (2013)**	2010	Society	2149	5791	–	–	–	7940	6.57	138	Employees with HCV.
	Incremental cost of HCV	US	**Baran et al. (2015)**	2001–13	Employer	X	–	–	–	X	675 – 3316	0.03–0.13	1386	Employees with HCV.
		US	**Su et al. (2010)**	2001–07	Society	497	–	–	–	–	497	0.06	1494	Employees with HCV. Costs adjusted for sodoeconomic and health characteristics.
		US	**Tandon et al. (2015)**	2001–11	Private payer	73	–	–	–	324	396	0.09	2532	Employees with HCV.
		5 EU countries	**Vietri et al. (2013)**	2010	Society	828	2315	–	–	–	3116	5.97	138	Employees with HCV.

HCV: hepatitis C virus; N/A: not applicable (simulation model).
The total cost may not coincide with the sum of the components when the two have been estimated independently using regression models.

In the following sections, the results of the selected studies are discussed separately per non-healthcare HCV cost result type: per-patient or aggregate (national/population) estimates.

3.2. Non-healthcare costs per patient

Table 2 summarizes the characteristics of 11 studies in this review that estimate the total non-healthcare cost and/or the incremental non-healthcare cost of HCV per patient for a treated or untreated population with HCV [36,43,44,46–50,53,54,58]. They all estimate absenteeism costs using the human capital method, but three of them quantify the transfers or subsidies due to absenteeism borne by the employer or insurer [43,47,48]. Four studies [44,46,49,50] estimate the impact of presenteeism, one includes premature mortality costs and formal/informal care [54]. Informal care is also included in another study [58] and disability costs are included in three of them [36,47,48]. Thus, the selected literature on the costs per patient does not include complete estimates of the true non-healthcare costs of HCV. Only absenteeism is included in these studies.

For untreated HCV patients, the annual cost per patient considering studies which include both absenteeism and presenteeism estimates ranges from €4570 [46] to €10,052 [44]. Of these costs, the cost due to absenteeism is estimated to range from €1151 [46] to €2053 [44] per year in the USA and is €1151 in a study for five European countries [49]. The costs of presenteeism range from €3419 [46] to €7999 [44] in the USA, and are €5398 in EU countries [49]. To calculate presenteeism costs, the Work Productivity and Activity Impairment questionnaire [59] is mostly used and the method presented by Lofland et al. [60], assuming that the value of the weekly productivity loss for presenteeism is a percentage of lost work when work was attended, is applied. For this type of patient (untreated), three studies calculate the incremental cost of HCV, and are therefore considered to be of higher quality. They estimate a total cost ranging from €280 to €2922 in European countries [49,50] and of €4723 for the USA [44]. In these studies, the same pattern as in the non-incremental type of studies is found, with presenteeism costs more than doubling the costs of absenteeism.

For treated HCV patients, no available study considers the incremental non-healthcare cost per patient. Three studies report a total cost per HCV patient of €1739 [43] in the USA (only includes absenteeism), €734 [54] in South Korea (includes absenteeism, premature mortality and caregiver costs), and €5616 [58] in Iran (includes absenteeism and caregiver costs).

Studies which do not differentiate between treated and untreated patients, total cost per HCV patient is found to be €1443 in the USA [36], €7940 in selected EU countries [49] and between €2678 and €27,083 in Italy (this study calculates indirect costs per disease stage: CHC, cirrhosis, HCC and death). One of them differentiates between absenteeism (€2149) and presenteeism (€5791) costs [49]. The incremental per patient costs of HCV range from €396 (including absenteeism and disability costs) and €497 [36] (including only absenteeism) in the USA, to €3116 (including absenteeism and presenteeism) for 5 EU countries [49] and €3316 (including absenteeism and disability) in the USA [48]. Only one of them distinguishes between costs arising from absenteeism and presenteeism: €814 and €2277, respectively [49]. These estimates point to the pattern seen in other studies, whereby the costs of presenteeism more than double those of absenteeism.

The studies that show cost results per patient and those that present the incremental cost are alike in having highly diverse results regarding the relative importance of non-healthcare costs versus healthcare costs. The eight studies that calculate both types of costs [36,44,47–49,52–54] indicate that non-healthcare costs can be 0.03 [48] to 6.87 [49] times healthcare costs. However, the type of costs included in each ratio's numerator (non-healthcare costs) and denominator (healthcare costs) influences its interpretation. The studies by Su et al. [36], El Khoury et al. [44], Shon et al. [54], Tandon et al. [47], and Baran et al. [48] present much lower estimates of non-healthcare costs than for healthcare costs for the USA and South Korea. Su et al. [36] include absenteeism in non-healthcare costs and healthcare and prescription drug costs as direct costs. The study by El Khoury et al. [44] includes the cost of presenteeism within the non-healthcare costs and the totality of the healthcare costs (hospitalizations, emergency visits, doctor visits), although it only refers to patients who have been diagnosed with HCV but have not yet been treated. Shon et al. [54] include all direct medical costs and absenteeism, caregiver and premature mortality in the non-healthcare costs. Tandon et al. [47] and Baran et al. [48] include all direct medical costs and absenteeism and disability as non-healthcare costs. On the contrary, Vietri et al. [49] report non-healthcare cost as being several times higher than that of healthcare cost, both for diagnosed patients who have not yet started treatment and for patients receiving treatment. This may be explained by the fact that drug costs are not included in healthcare costs (only physician visits, emergency room visits, and hospitalizations) and also that they do include presenteeism costs in the non-healthcare costs.

Variation in non-healthcare costs per patient has only been addressed in five studies. These costs are greater for the working-age male population [54]. Disease severity is the most studied variable for assessing non-healthcare costsvariation [47,48,52,53], but the results of these studies are not comparable since they use different classifications of severity. Nonetheless, these studies share that non-healthcare costs are increasing in disease severity and that this increase is not as pronounced as with healthcare costs.

3.3. Population non-healthcare costs

Table 3 summarizes the characteristics of the eleven studies estimating the total population cost [34,35,38,39,45,50,51,53–56]. Eight of them provide a general estimate of the incremental non-healthcare cost of HCV for a country (or region) without a control group and three of them report the total non-healthcare costs for patients with HCV [50,53,54]. These studies mainly include the costs arising from work absenteeism and premature deaths.

Total non-healthcare costs of patients with HCV range from €26.6 million to €190.5 million in a study for five EU countries [50] (it includes absenteeism and presenteeism costs). Total

Table 3. Summary of characteristics and results of the estimation of annual population HCV non-healthcare costs (in million euros, 2015).

Country	Author (year of publication)	Study period	Perspective	Costs valued					Estimated total population cost	Non-healtHCVare costs/ healtHCVare costs	Sensitivity analysis	Observations
				Labor losses due to absenteeism	Labor losses due to presenteeism	Lost leisure time	Premature mortality	Other costs	Labor losses (Human capital method)			
Australia	**Shiell and Law (2001)**	1998	Sodety	1.8	–	–	13.5 (35.1[b])	–	15.0 (38.9[b])	–	Discount rate	Discount rate of 5%
Italy	**Marcellusi et al. (2015)**	2013	Sodety	x	–	–	x	–	652.8 (374.9–1006.6)	1.54	One way to all parameters	HCVV prevalence was the most significant parameter
Spain	**Oliva-Moreno et al. (2015)**	2007	Sodety	–	–	–	245.0 (194.5–336.2)[c]	–	–	–	Attributable fraction, discount rate, productivity growth rate	Discount rate of 3%
Spain	**Oliva-Moreno et al. (2015)]**	2011	Sodety	–	–	–	178.8 (144.8–237.1)[c]	–	–	–	Attributable fraction, discount rate, productivity growth rate	Discount rate of 3%
US	**Leigh et al. (2001)**	1997	Sodety	3969.9[a]	x	657.4	x	–	4627.3 (3552.6–5689.3)[c]	2.03	Mortality, morbidity and earnings	-
US	**Ruhl et al. (2008)**	2004	Sodety	x	–	x	1865.6	-	1973.9	1.67	–	Discount rate of 4%
US	**Sandler et al. (2002)**	1996–98	Sodety	63.8	–	–	–	–	–	–	–	Cost of CHCV by time dedicated to healtHCVare use
US	**Wong et al. (2000)**	2010–19	Sodety	2623.9[d]	–	–	6676.7[d]	–	9300.6[d]	–	–	–
UK	**Patruni and Nolte (2013)**	1995	Sodety	212.6 (98.6–431.0)		–	30.3 (14.4–59.7)	–	242.8(113.0–490.0)	–	Incidence, earnings, percentage under treatment, discount rate	Discount rate of 3.5%
UK	**Patruni and Nolte (2013)**	2015	Sodety	271.8 (101.2–560.5)		–	108.4 (47.4–208.0)	–	380.3 (148.6–768.4)	–	Incidence, earnings, percentage under treatment, discount rate	Discount rate of 3.5%
South Korea	**Shon et al. (2016)**	2008–11	Sodety	x	–	–	x	x	85.2	0.72	–	–
Switzerland	**Sagmeister et al. (2002)**	1998	Sodety	25.6	–	–	x	–	–	–	–	–
Germany	**Younossi et al. (2016)**	2013	Sodety	x	x	–	–	–	53.8 (43.3)[e]	–	Earnings	–
France	**Younossi et al. (2016)**	2013	Sodety	x	x	–	–	–	73.4 (58.8)[e]	–	Earnings	–
Spain	**Younossi et al. (2016)**	2013	Sodety	x	x	–	–	–	97.4 (77.9)[e]	–	Earnings	–

(*Continued*)

Table 3. (Continued).

Country	Author (year of publication)	Study period	Perspective	Costs valued					Estimated total population cost		Non-healthHCVare costs/ healthHCVare costs	Sensitivity analysis	Observations
				Labor losses due to absenteeism	Labor losses due to presenteeism	Lost leisure time	Premature mortality	Other costs	Labor losses (Human capital method)				
Italy	**Younossi et al. (2016)**	2013	Society	x	x	–	–	–	190.5 (152.4)[a]		–	Earnings	–
UK	**Younossi et al. (2016)**	2013	Society	x	x	–	–	–	26.6 (21.3)[a]		–	Earnings	–

CHC chronic hepatitis C. x: costs included but without cost information by component.
[a]Includes costs of presenteeism and premature mortality.
[b]Cost estimate without applying discount rate.
[c]Lower and upper bounds in the sensitivity analysis.
[d]Annual mean for the study period.
[e]Sensitivity analysis assuming a 20% reduction in earning of HCV patients.

costs of €85.2 million are estimated in South Korea [54] (including absenteeism, premature mortality and caregiver costs) and the highest estimate of €652.8 million is found for Italy [53],

When estimating the aggregate incremental cost (without a control group), seven studies [34,35,38,39,45,51,56] include the costs resulting from absenteeism. Another seven studies [34,38,39,45,51,55,56] consider in some way the indirect costs of premature mortality. Only two [34,45] consider the cost of lost leisure time.

The annual incremental non-healthcare costs are €15.0 million (€38.9 million without applying a discount rate) in Australia [51], of which €1.8 million is due to absenteeism and €13.5 million (€35.1 million without applying a discount rate) are attributed to premature mortality. The study for Spain [55] only estimates the cost of premature deaths to be €245.0 million in 2007 and €178.8 million in 2011. In the USA, the estimates range from €1973.9 million [45] to €9300.6 million [39]. Of these costs, between €63.8 million [35] and €3969.9 million [34] are attributed to absenteeism, between €1865.6 million [45] and €6676.7 million [39] to premature mortality, and €657.4 million [34] is the only estimate for lost leisure time. In the UK, costs amount to an annual total of €242.8 million in 1995, of which €212.6 million are attributed to absenteeism plus presenteeism and €30.3 million is due to premature deaths. In 2015, the estimate rises to a total incremental €380.3 million, of which €271.8 million are attributed to absenteeism plus presenteeism, and €108.4 million to premature deaths. In a study for Switzerland [38], only differentiated data for the incremental non-healthcare cost of HCV associated with absenteeism, is reported and stands at €25.6 million.

The premature mortality attributable to HCV cannot be calculated directly from records of cause of death, as HCV is usually recorded as the cause of death only in deaths due to CHC. Even so, a fraction of deaths due to cirrhosis, HCC and HIV are attributable to HCV [61], so it is essential to perform estimates of the attributable fraction. The nine studies that estimate the cost of premature mortality [34,38,39,45,51,53–56] present major differences in the selection of HCV-related causes of death and do not always report in the risks attributable to HCV (see Table 4). Only three studies [34,39,55] provide information on the fraction of deaths attributable to each of the causes associated with HCV.

Within this group of studies, four studies also calculate healthcare costs. Two for the USA [34,45] indicate that non-healthcare costs are between 1.67 [45] and 2.03 [34] times higher than healthcare costs. In Italy [53], this figure is lower (1.54) and the study for South Korea reports a lower weight for non-healthcare costs than for healthcare costs (0.72) [54].

Estimates of HCV-related mortality and morbidity at population level face notoriously high uncertainty, which affects the cost-of-illness estimation. Even so, only six studies take into account this variability by means of sensitivity analysis (see Table 3). The most complete studies consider variations in the attributable fraction, the discount rate and the productivity growth rate [55] or the impact of uncertainty in incidence, earnings, percentage of the population under treatment and discount rate [34,53,55,56].

Table 4. Attributable risk fractions (%) in the estimation of premature mortality due to HCV.

Study	Country/study period	Cirrhosis	Hepatocellular carcinoma	HIV/AIDS	Other liver diseases
Oliva-Moreno et al. (2015)	Spain/2007–11	40 (35–50)	60 (50–70)	15 (10–20)	60 (50–70)
Leigh et al. (2001)	US/1997	30	30	–	100
Wong et al. (2000)	US/2010–19	36–42	33	–	36–41

Only showing studies reporting them.

4. Conclusion

This review found a growing improvement in the number and quality of the studies addressing the non-healthcare cost of HCV. This systematic review has found 19 studies published in 2000–2017 which estimate the non-healthcare cost of HCV. In spite of the heterogeneity of the estimates and the criteria used in the various studies, there are some notable coincidences with regard to the relative and absolute importance of the non-healthcare cost of HCV.

The incremental non-healthcare cost of HCV in untreated patients compared to HCV-free individuals exceeds €4000 per patient for US estimates and stands between €280 and almost €3000 for European estimates. In all the studies estimating the cost per patient of presenteeism (the cost due to productivity loss without absence from work), it more than doubles that of absenteeism. Premature mortality due to HCV may constitute its main non-healthcare cost, at least when the costs of presenteeism are not taken into account. When the costs of presenteeism are included alongside those of absenteeism, the relative importance of the cost of premature mortality within non-healthcare costs may decrease. It is noteworthy to note that in the period reviewed, no estimate of the complete non-healthcare cost of HCV has been published to date. Evidence of high methodological quality for the incremental non-healthcare cost of HCV remains limited.

5. Expert commentary

The present article updates and expands the only systematic literature review of the non-healthcare cost of HCV published during the last decade, which only included the USA and covered the period up to 2010 [32]. Despite the progressive increase in the number of artides published, this analysis found some limitations arising from the methodology and design of these studies.

First, different population characteristics are found: age and work status, level of severity, treatment of HCV, and length of observation period. We found five studies reporting non-healthcare costs by disease severity, age or gender [47,48,52–54]. Studies on HCV healthcare costs have found age, disease severity, body mass index, gender, SVR achievement, and METAVIR score to be good predictors of these costs [17,25,62–64]. Work impairment has also been found to be most affected by both patient reported outcomes (energy, well-being, worry) and clinical aspects (cirrhosis, anxiety, depression, fatigue) [65]. Therefore, in order to understand the different estimates of non-healthcare costs, one must control for the population-of-study characteristics.

Differences in study design (counterfactual choice, epidemiological focus), identification approach, and resource assessment (non-healthcare costs included, and method of assessing non-healthcare resources) were also identified. On the one hand, the level of detail when reporting non-healthcare costs could be improved, although this problem does not only affect HCV cost-of-illness studies [31]. On the other hand, the counterfactual of the study determines whether the final result is the total cost of the HCV patients – including any non-healthcare cost regardless of its relation to HCV – or the cost of the HCV itself (incremental cost of the disease) [66]. In the former, the study will not be a cost-of-illness study as such but rather a study of the cost of the patients with this disease, together with other health problems that may or may not be associated with HCV. In the absence of a counterfactual (i.e. there is none or it has not been made explicit), it will not be possible to establish the incremental cost of HCV in relation to the HCV-free population. In the latter, studies that use a control group with an HCV-free population as a counterfactual, estimate the incremental cost generated by the disease in comparison with its absence, either by comparing averages (matched control) or by means of some type of multiple regression analysis that makes it possible to estimate the additional or incremental contribution to the healthcare and non-healthcare cost involved in a diagnosis of HCV.

Eight of the twelve incremental cost studies do not explicitly use any control group to estimate the incremental cost [34,35,38,39,45,51,55,56]. Instead, they only measure the differential consumption of resources directly attributable to HCV. This method is less precise than explicitly using two population groups – an intervention group with HCV and a control group without HCV. This method calls for very precise information systems enabling the researcher to appropriately identify the reason for each non-healthcare cost incurred by patients. However, in these studies, a clear and transparent criteria for attributing absenteeism and presenteeism to HCV was not found, which represents a notable limitation to the validity of the estimates. Estimates of the incremental non-healthcare cost of HCV are more precise when they come from studies with a control group, which afford the possibility of using statistical significance tests and confidence intervals of the estimates of incremental costs per person. In this review we found five studies of this type, all of them published after 2010: four from the USA [36,44,47,48] and only one of them for EU countries [49]. This fact may indicate a temporal trend toward a methodological improvement in the quality of evidence on the cost of HCV.

In some of the studies of the cost of HCV per patient, the number of individuals included in the control group is small [44,49]. This threatens the validity of the results, which may vary substantially depending on the social and healthcare characteristics of the patients selected. With regard to studies

on the general cost of HCV, in most studies the absence of a suitable sensitivity analysis providing an insight into the impact of uncertainty about the morbidity and mortality of HCV patients and the valuation of their paid and unpaid time on the base-case estimates represents an even more serious limitation.

Last, it is essential to highlight the limitation imposed by the fact that all of the studies but one correspond to a time prior to the market entry of innovative, highly effective, high-cost drugs (DDAs) which may cause substantial changes in both healthcare and non-healthcare costs. Yet, studies included in this review may give an idea on the potential of DAAs in reducing non-healthcare costs of HCV. In fact, cost estimation before new DAAs represents the maximum indirect benefit than could be expected from DAAs and also the excluded potential benefits when, as is usual, indirect costs are not included in their cost-effectiveness analyses.

6. Five-year view

The analysis of the studies included in this review highlights the need for studies of the cost of HCV to include both comprehensive healthcare costs and in particular non-healthcare costs (productivity losses due to absenteeism but also presenteeism in the case of working age individuals; cost of formal and informal care; and missed school days in the case of children) if their results are to be useful for healthcare and public policymakers. These studies should include a sufficiently large and representative population of HCV patients, without giving undue weight to patients in advanced stages of the disease or with major complications. They should also estimate the incremental cost attributable to HCV, preferably by means of a control group without HCV, combining a matched control with the group with HCV and the estimation of costs attributable to HCV by means of regression models.

Key issues

- The non-healthcare costs attributable to HCV infection are composed of productivity losses due to absenteeism or presenteeism, lost leisure time, premature mortality and caregiver care due to the disease.
- The 19 studies discussed in this review partially estimate the non-healthcare costs, but evidence of a high methodological quality for the incremental non-healthcare cost of HCV is still limited.
- The annual incremental healthcare cost of HCV for untreated patients in comparison with HCV-free individuals is estimated to be over €4,000 per patient in the US and between €280 and around €3,000 in Europe.
- The costs arising from presenteeism more than double those arising from absenteeism as a consequence of the disease.
- Prior to the recent introduction of innovative, highly effective DAAs, it is observed that the estimated non-healthcare costs of HCV at a general or population level tend to be considerably higher than the healthcare costs, the main non-healthcare cost of HCV being attributable to premature mortality.
- Future studies should focus in assessing incremental non-healthcare costs of HCV using a control group with data for new DAAs.

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ORCID

Natàlia Pascual-Argente http://orcid.org/0000-0003-2980-366X
Jaume Puig-Junoy http://orcid.org/0000-0003-1695-3108

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2. CHAPTER 2

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REVIEW

Cost-utility analysis of second-generation direct-acting antivirals for hepatitis C: a systematic review

Jaume Puig-Junoy [a,b,c], Natàlia Pascual-Argente [b,c], Lluc Puig-Codina[b], Laura Planellas[d] and Míriam Solozabal[d]

[a]Department of Economics and Business (UPF), Pompeu Fabra University, Barcelona, Spain; [b]UPF Barcelona School of Management, Pompeu Fabra University, Barcelona, Spain; [c]UPF Center for Research in Health and Economics (CRES-UPF), Pompeu Fabra University, Barcelona, Spain; [d]Real-World Insights, IQVIA, Barcelona, Spain

ABSTRACT

Introduction: High prices of second-generation direct-acting antivirals (DAAs) in the treatment of chronic hepatitis C virus (HCV) patients led to reimbursement decisions based on cost per quality-adjusted life year (QALY).

Areas covered: We performed a systematic review of cost-utility analyses (CUA) comparing interventions with second-generation DAA therapies with no treatment, and with previous therapies for chronic HCV patients until July 2017. A total of 36 studies were included: 30 studies from the perspective of the healthcare payer, 3 from the societal perspective, and 3 did not report the perspective. For genotype 1, the highest number of ICER comparison corresponds to sofosbuvir (SOF) triple therapy and SOF-based combinations which reported a cost per QALY systematically ranging from negative to lower than US $100,000 when compared with no treatment or dual therapy or Simeprevir triple therapy.

Expert commentary: Selected studies may be overestimating the true cost per QALY of second-generation DAAs in the treatment of HCV, mainly because of neglecting non-healthcare costs, using official list prices which are higher than actual transaction prices and not adopting the long run drug price in a dynamic approach. In addition, the impact of important price reductions of several DAAs in recent years on cost per QALY should be considered.

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Cost-effectiveness; cost-utility; direct acting antivirals; hepatitis C; quality-adjusted life years; systematic review

1. Introduction

Hepatitis C virus (HCV) infection is the main cause of liver disease in the world. After infection, it is estimated that 15–45% of patients will clear the virus spontaneously but 55–85% will progress to chronic hepatitis C (CHC) [1]. CHC progresses to cirrhosis, hepatocellular carcinoma, and to end-stage liver disease where the only treatment option is liver transplant. It is estimated that around 158 million people in the world were affected by HCV in 2016 [2]. HCV is found all over the world, it is characterized by its heterogeneity in genotypes (GT) and by disproportionately affecting more males than females. HCV is associated with an important morbidity, mortality, and economic burden. Globally, HCV-related diseases are responsible for 489,000 deaths per year [3].

Until 2011 dual therapy with pegylated interferon (PEG) and ribavirin (RBV) was the standard of care in HCV treatment. In 2011, first-generation direct-acting antivirals (DAAs) were launched, boceprevir (BOC) and telaprevir (TEL), which substantially improved sustained virological response (SVR) rates. Triple therapy (BOC or TEL with PEG + RBV) importantly improved SVR rates for treatment-naïve (TN) or treatment-experienced (TE) GT 1 patients but treatment remained suboptimal for many patients. Since 2014, second-generation DAAs dual/triple therapies and all-oral DAA therapies have allowed a significant shift in the HCV treatment efficacy, starting with simeprevir (SMV), and sofosbuvir (SOF) and followed by, or in some cases combined with, daclatasvir (DCV), dasabuvir (DSV), ledipasvir (LDV) and paritaprevir-ombitasvir-ritonavir (POR). These innovations have reduced the duration of treatment and widened patient eligibility thanks to reduced toxicity and adverse events. The main goal of new treatments with DAAs is to cure HCV infection, which translates into achieving SVR, as it stops disease progression and brings health improvements [4,5]. However, the high price and heavy budget impact of new 2nd generation DAA for chronic HCV infection is the main factor limiting their use in many health systems, even in high-income countries.

The very high prices of new DAA treatments for HCV have attracted a high public concern and controversy on access and prioritization, in parallel with an increasing role of reimbursement decisions stemming from public and private insurers based on the added value of health gains [6]. Cost-utility analysis (CUA) appropriately measures the value of incremental innovation in the treatment of chronic HCV by estimating the incremental cost per quality-adjusted life year (QALY) [7].

To date, five relevant systematic reviews of cost-effectiveness in the treatment of chronic HCV with second-generation DAAs has been published between 2015 and 2017 [4,8–11]. These reviews only include studies published until August [4] or September 2015 [9,10], or August 2016 excluding GT 1 [11], or are limited to US studies [10]. As a result, except for

CONTACT Jaume Puig-Junoy jaume.puig@upf.edu Universitat Pompeu Fabra, C. Ramon Trias Fargas 25-27 edifici Jaume I, 08005 Barcelona

Chhatwal et al. [10], they include null or very limited evidence on second-generation DAAs other than SOF, and null evidence on all-oral DAA therapies; also, only one of them focuses merely on methodological approaches [4]. Comparisons included in these surveys are limited to interventions with seconnd-generation DAAs versus no treatment, dual therapy or 1st generation triple therapies. To fill these gaps, we performed a systematic review of CUA studies published until July 2017 comparing interventions with dual/triple second-generation DAAs (SOF, SMV, POR) and SOF-based all-oral combinations of DAAs versus no treatment, dual therapy (PEG + RBV), first-generation triple therapy (BOC/TEL + PEG+ RBV), and other second-generation DAA therapies in chronic HCV patients. This review focused on the CUA and modeling features, costs and incremental cost per QALY.

2. Methods

The research question (in PICO format: Population, Intervention, Comparison, Outcome), as well as the inclusion and exclusion criteria are reported in Table 1.

2.1 Search strategy

Published CUA studies on second-generation DAAs for HCV treatment were searched in the electronic databases Medline (Ovid), EBM Reviews-NHS Economic Evaluation Database (Ovid), Embase (Ovid), Pubmed, Cochrane Library, York CRD Database, and EconLit from January 2011 until July 2017. References in the selected studies and previously published reviews were screened by hand. Records and full-texts were independently screened by at least two of the reviewers (LP-C, LP, MS) and disagreements were addressed with a full-text revision and solved by discussion by a fourth and fifth reviewers (JP-J, NP-A). Four authors extracted the data (NP-A, LP-C, LP, MS), another author (JP-J) checked the completeness and correctness of the data, and disagreements were resolved by discussion. In the search strategy, terms 'hepatitis C', 'hepacivirus', 'quality-adjusted life years', 'qaly' were combined in the search codes.

Table 1. PICO question and inclusion/exclusion criteria.

PICO question
P Defined target group of HCV patients of the general population
I HCV treatments with at least a 2nd generation DAA
C All HCV treatment combinations
O Incremental cost-utility ratio (cost per QALY gained)
Inclusion criteria
Defined target group of HCV patients of the general population
Interventions include at least a 2nd generation DAA
Decision analytic model (mathematical model) evaluating both costs and health consequences
Outcome expressed as cost per QALY
Original CUA published in English or Spanish
Published studies in full text
Exclusion criteria
Purely descriptive studies
Reviews of cost-effectiveness analyses
Treatment of HCV in selected populations (e.g. incarcerated, HIV co-infected patients, children and younger people only, older than 65 years only, immigrants only))
CUA studies on a specific disease phase (e.g. transplantation, cirrhotic patients)

P: population; I: intervention; C: comparison; O: outcome; CUA: cost-utility analysis; DAA: direct-acting antiviral; HCV: hepatitis C virus; HIV: human immunodeficiency virus; QALY: quality-adjusted life year.

2.2 Inclusion and exclusion criteria

Table 1 lists the inclusion and exclusion criteria used to assess studies that evaluate chronic HCV treatments with new DAAs. We included complete CUA studies published in English and Spanish without any geographical restriction for HCV treatment strategies including second-generation DAAs for a defined target group of HCV patients of the general population, being TN and/or TE patients. We excluded CUA studies only including treatment of HCV in selected populations (e.g. incarcerated or HIV co-infected patients) and those only including patients in a specific disease phase (e.g. only cirrhotic or post-liver transplantation). We reviewed titles and abstracts to exclude those studies which are not original research, those with content not addressed (pharmacological drugs, population or treatments addressed in this systematic review), those with population not addressed, and those with no abstract or full-text availability. A second exclusion was made by reviewing full texts to exclude articles that did not constitute a full CUA, reviews, those not including second-generation DAAs, those not reporting the study population, and those not written in English or Spanish.

2.3 Information extraction process

Relevant information on the selected studies was included in evidence tables covering main CUA features (country, perspective, target population, intervention/comparator, time horizon, discounting rates, currency/year, and funding sources), modeling features (modeling approach, cycle length, within cycle correction, uncertainty/sensitivity analysis, and model validation), resources and costs included (categories of health care costs and non-health care costs, types of drug prices, sources of information for health-care use and drug prices), and base-case ICERs classified by HCV GT and TN versus TE as the main outcome of each selected comparison. All ICERs from included studies were extracted and included in the analysis except those comparisons: (i) reporting results for only cirrhotic groups; (ii) those only reporting aggregate results for mixed GT; (iii) comparisons of SOF-based all-oral combinations versus other SOF-based combinations; and, (iv) interventions with all-oral combinations second-generation DAAs not based on SOF, SMV, or POR.

Interventions were classified as second-generation DAA dual and triple therapies or all-oral DAA combination therapies. Information on five second-generation DDA dual/triple interventions was extracted: POR-based, SMV-based (SMV + DCV), SOF-based dual (SOF + RBV) and SOF-based triple (SOF + PEG + RBV) therapies. All-oral DAA combination therapies were classified as SOF-based (SOF + LDV/DCV/SMV), SMV-based (SMV + DCV), POR-based, and other combination therapies. Comparators of those second-generation DAA treatments were classified as: no treatment, dual therapy (PEG + RBV), triple therapies with first-generation DAAs (BOC + PEG + RBV and TEL + PEG + RBV), dual/triple therapies with second-generation DAAs, and all-oral DAA combination therapies (SOF-based and others).

Modeling approaches were classified as cohort state-transition models (STM), individual STM, and discrete event simulation models (DES). Uncertainty/sensitivity analyses were classified as being deterministic (DSA) and probabilistic sensitivity analysis (PSA). Conducting both DSA and PSA is recommended by the ISPOR-SMDM Modeling Good Research Practices Task Force [12]. Also, regarding model validation, four categories were considered: internal validation, face validation, cross-validation, and external validation. All cost figures from the selected studies were adjusted and converted to 2016 US dollars by applying GDP deflator [13] and currency exchange rates [14]. When data for several countries was reported, we computed the average of their GDP deflators.

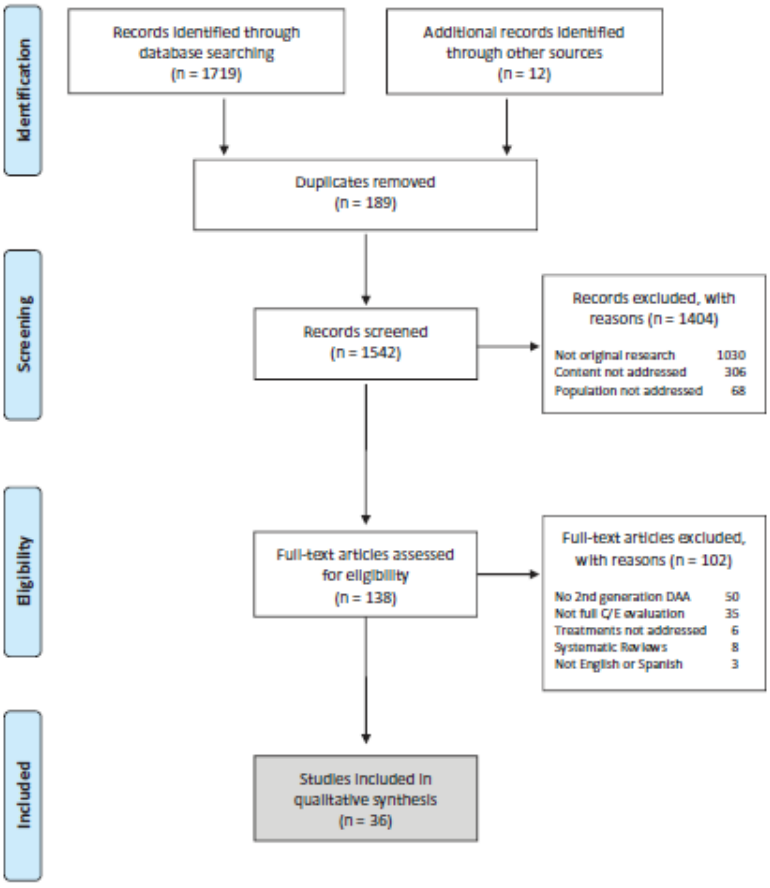
3. Results

3.1 Overview of studies

The flow diagram of the search process is shown in Figure 1. A total of 1731 records were obtained from the systematic literature search and 1542 records were screened after duplicates were removed. The first exclusion yielded 138 articles that underwent an independent examination by the authors using full texts. In this second revision, 102 articles were excluded for not being second-generation DAA studies, not being a CUA evaluation, DAA treatments not addressed, being reviews or not being written in English or Spanish. A total of 36 studies were ultimately included in the systematic review [15–50].

The main characteristics regarding context, population, research question/objective, method, and funding in the 36 selected studies are summarized in Table 2. Table 3 gives detail on the main characteristics of the 36 studies included in this review: 13 (36.1%) are from the United States, 4 are from the United Kingdom, 3 are from Japan and Spain, 2 are from Italy, Germany, and Canada; the remaining 7 studies correspond to single, one-off studies in different countries. Most of the studies, 28 (77.8%) out of 36, were published in 2015 and 2016.

Regarding treatment status of the target population of these studies, TN patients were included in 32 of them (88.9%), 20 included TE patients (55.6%), and 3 studies did not report treatment status. Population with GT 1 was



Source: adapted from Moher et al, 2009 [59]

Figure 1. Systematic literature search depicted in PRISMA 2009 flow.
Source: adapted from Moher et al. [51]

Table 2. Characteristics of the selected studies (n = 36).

Type of variable	Variable	Characteristic	Number of articles	Percentage
CONTEXT	Country	United States of America	13	36.1
		United Kingdom	4	11.1
		Japan	3	8.3
		Spain	3	8.3
		Italy	2	5.6
		Germany	2	5.6
		Canada	2	5.6
		Others	7	19.4
	Year of publication	2017	3	8.3
		2016	13	36.1
		2015	15	41.7
		2014	5	13.9
TARGET POPULATION	Treatment status	Treatment naïve	32	88.9
		Treatment experienced	20	55.6
		Not reported	3	8.3
	Genotype	GT 1	32	88.9
		GT 2	12	33.3
		GT 3	14	38.9
		GT 4	9	25.0
		GT 5	4	11.1
		GT 6	3	8.3
RESEARCH QUESTION/OBJECTIVE	Intervention	Second-generation DAA dual/triple therapy		1.2
				1.2
		• DCV-based	1	16.7
		• POR-based	1	44.4
		• SMV-based	6	52.8
		• SOF-based		58.3
				16.7
		• SOF + RBV	15	
		• SOF + PEG + RBV	19	
		All-oral DAA combination therapy		
		• SOF-based	21	
		• Other	6	
	Comparator	Dual therapy (PEG + RBV)	26	72.2
		First-generation triple therapy		44.4
				50.0
		• BOC + PEG + RBV	16	25.0
		• TEL + PEG + RBV	18	13.9
				2.8
		Second-generation DAA dual/triple therapy	9	50.0
		All-oral DAA combination therapy		
		• SOF-based	5	
		• Other	1	
		No treatment	18	
METHOD	Perspective	Health care payer	30	83.4
		Societal	3	8.3
		Not reported	3	8.3
	Time horizon	Lifetime	33	91.6
		Others	3	8.3
FUNDING	Funding	Government	9	25.0
		Non-profit	2	5.6
		Pharmaceutical Industry	21	58.3
		Pharmacy Payer	1	2.8
		Not provided	1	2.8
		None	2	5.5

ASV: asunaprevir; BOC: boceprevir; DAA: direct-acting antiviral; DCV: daclatasvir; PEG: pegylated-interferon; POR: paritaprevir-ombitasvir-ritonavir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; TEL: telaprevir

analyzed in 32 studies (88.9%), GT 3 in 14 (38.9%), GT 2 in 12 (33.3%), GT 4 in 9 (25%), GT 5 in 4 (11.1%), and GT 6 in 3 (8.3%). The most common analyzed interventions were SOF-based with all-oral DAA combination therapies (n = 21), SOF-based triple therapy (n = 19) and SOF-based dual therapy (n = 15). The most common comparators of these interventions were: dual therapy (n = 26), no treatment (n = 18), TEL triple therapy (n = 18), and BOC triple therapy (n = 16). The perspective of the healthcare payer was adopted in 30 studies (83.4%), and only 3 [25,28,34] adopted the societal perspective (8.3%). About 33 studies (91.6%) adopted a lifetime time horizon in the modeling approach. Only one study did not report using a discount rate for costs [16], 2 studies did not discount benefits in the base case scenario [24,35], and only one study used a different discount rate for costs and QALYs in the base

Table 3. Summary of the main CUA features.

Author (year of publication) [References]	Country	Perspective	Target population	Time horizon	Discount rate (Costs, QALYs)	Currency (year)	Funding
Alavian et al. [15]	Iran	Health care payer	GT1; 50 years	Lifetime	7.2%, 3%	U.S. Dollars (2014)	Government
Arshad et al. [16]	U.S.A	Health care payer	GT1; 50 years; TN	Lifetime	No discounting	U.S. Dollars (–)	Government
Chen et al. [17]	China	Health care payer	GT1; 50 years; TN, TE	Lifetime	3%,3%	U.S. Dollars (2014)	Non-profit
Chhatwal et al. [18]	U.S.A	Health care payer	GT1–4; – ; TN, TE	Lifetime	3%, 3%	U.S. Dollars (2014)	Government
Cure et al. [19]	UK	Health care payer (and social services)	GT1-6; – ; TN, TE	Lifetime	3.5%, 3.5%	UK Pounds (2011)	Pharmaceutical Industry
Cure et al. [20]	Italy	Health care payer	GT1-6 ;TN, TE	Until 80 years	3%, 3%	Euro (-)	Pharmaceutical Industry
Fraser et al. [21]	South Africa	Health care payer	GT5; 52 years; TN	Lifetime	5%, 5%	U.S. Dollars (2015)	Non-profit centre and Pharmaceutical Industry
Gimeno-Ballester et al. [22]	Spain	Health care payer	GT3; 50 years; TN	Lifetime	3%, 3%	Euro (2015)	None
Gimeno-Ballester et al. [23]	Spain	Health care payer	GT1; 54 years; TN	Lifetime	3%, 3%	Euro (2015)	None
Gissel et al. [24]	Germany	Health care payer	GT1; – ; TN;	Lifetime	3%, 0%	Euro (2014)	Pharmaceutical Industry
Hagan et al. [25]	U.S.A	Society	GT1; 50 years; TN, TE	Lifetime	3%, 3%	U.S. Dollars (2013)	Government
Johnson et al. [26]	UK	Health care payer	GT1; 40/45 years; TN, TE	Lifetime	3.5%, 3.5%	UK Pounds (2013)	Pharmaceutical Industry
Kuwabara H et al. [27]	Japan	Health care payer	GT1; 55 years; TN	Lifetime	3%, 3%	Japanese Yen (2014)	Pharmaceutical industry
Leleu H et al. [28]	France	Society	GT1-6; – ; TN, TE	Lifetime	2.5%, 2.5%	Euro (2013)	Pharmaceutical Industry
Linas et al. [29]	U.S.A	Health care payer	GT2-3; 48/54 years; TN, TE	Lifetime	3%, 3%	U.S. Dollars (2013)	Government
McEwan et al. [30]	Japan	Not reported	GT1; TE	Lifetime	2%,2%	Japanese Yen (-)	Pharmaceutical Industry
McEwan et al. [31]	UK	Health care payer	GT1, GT4; 50 years; TN, TE	Lifetime	3.5%, 3.5%	UK Pounds (2013)	Pharmaceutical Industry
McEwan et al. [32]	Japan	Not reported	GT1; 70 years	Lifetime	2%,2%	Japanese Yen (-)	Pharmaceutical Industry
Moshyk et al. [33]	Canada	Health care payer	GT3; 50 years; TN, TE	Lifetime	5%, 5%	U.S. Dollars (-)	Pharmaceutical Industry
Najafzadeh et al. [34]	U.S.A	Society	GT1-3; 50 years; TN	Lifetime	3%, 3%	U.S. Dollars (2014)	Pharmacy payer
Ollendorf et al. [35]	U.S.A	Health care payer	GT1-3; 60 years; TN, TE	20 years	3%, 0%	U.S. Dollars (2013)	Non-profit
Petta et al. [36]	Italy	Health care payer	GT1; 50 year; TN	Lifetime	3%, 3%	Euro (2013)	Pharmaceutical Industry
Pfeil et al. [37]	Switzerland	Health care payer	GT1-4; TN, TE	Lifetime	3%, 3%	Swiss Franc (2014)	Pharmaceutical Industry
Rein et al. [38]	U.S.A	Health care payer	GT1-4; 20 years or older	Lifetime	3%, 3%	U.S. Dollars (-)	Government
Saab et al. [39]	U.S.A	Health care payer	GT1; 52 years; TN, TE	1 year and lifetime (up until 100 years)	3%, 3%	U.S. Dollars (2013)	Pharmaceutical industry
Saab et al. [40]	U.S.A	Health care payer	GT1,4; 53.6 years; TN; TE	Lifetime	3%, 3%	U.S. Dollars (2015)	Pharmaceutical Industry
San Miguel et al. [41]	Spain	Health care payer	GT1-3; 50 years; TN, TE	Lifetime	3%, 3%	Euro (2013)	Not reported
Stahmeyer et al. [42]	Germany	Health care payer	GT1; 40 and 45 years; TN, TE	Lifetime	3%, 3%	Euro (2015)	Pharmaceutical Industry
Vargas et al. [43]	Chile	Health care payer	GT1, 54 years, TN	46 years	3%, 3%	U.S. Dollars (2014)	Pharmaceutical Industry
Westerhout et al. [44]	UK	Health care payer	GT1; 50 years; TN, TE	Lifetime	3.5%, 3.5%	UK Pounds (2013)	Pharmaceutical Industry
Wong et al. [45]	Canada	Health care payer	GT1-4; 50 years; TN, TE	Lifetime	5%, 5%	U.S. Dollars (2015)	Government
Younossi et al. [46]	U.S.A	Health care payer	GT1; 52 years; TN, TE	Lifetime	3%, 3%	U.S. Dollars (2014)	Pharmaceutical Industry
Younossi et al. [47]	U.S.A	Health care payer	GT1; 52 years; TN	Lifetime	3%, 3%	U.S. Dollars (2015)	Pharmaceutical Industry
Younossi et al. [48]	U.S.A	Health care payer	GT1; 52 years; TN	Lifetime	3%, 3%	U.S. Dollars (2015)	Pharmaceutical Industry
Zhang S et al. [49]	U.S.A	Not reported	GT1-3; 52 years; TN	Lifetime	3%, 3%	U.S. Dollars (2014)	Government
Zhao et al. [50]	Singapore	Health care payer	GT1; 50 years; TN	Lifetime	3%, 3%	U.S. Dollars (2015)	Government

case [15]. A total of 21 studies reported funding from the pharmaceutical industry (58.3%), 9 from government/public payer (25%), 2 from non-profit organizations (5.6%), and 2 reported not receiving any funding.

3.2 Method and modeling approach

Table 4 gives an overview of the main method and model features of the included studies. Cohort STM was the most common approach ($n = 35$): 31 used a Markov model, 2 used a Montecarlo simulation [29,38], and 2 did not specify the STM type [35,45]. Only one study used a DES model [34].

The most common cycle length was 1 year ($n = 25$), while only two studies used one week as the cycle length [18,45]. Only 9 of the included studies reported using within cycle correction. We found that 6 studies addressed the issue of uncertainty by means of only a DSA [16,19,25,35,47,48], 3 studies conducted only a PSA [15,24,31], and the remaining 27 studies (75%) conducted both DSA and PSA (Table 4).

About, 10 out of the 36 selected studies do not provide evidence of any form of model validation (27.8%), 8 provide evidence of face validation (22.2%) and other 8studies provide evidence of internal validation (22.2%). The most common form of model validation is cross-validation (23 out of 36, 63.9%), and the less common form is external validation (only 5 studies, 13.9%) [17,18,26,33,34].

3.3 Costs

All studies included in this review induded healthcare costs, but none included the indirect or non-healthcare costs of treating HCV (productivity losses due to premature deaths and work absenteeism and presenteeism, costs of formal and informal care and other non-healthcare costs), even if they claimed to use a social perspective [25,28,34] For example, Hagan et al. [25] stated that they use a societal perspective but only *'direct costs of treatment-related drugs, medical care, and adverse events, as well as continued CHC related medical care for subjects who failed treatment'* were considered.

The cost analysis of healthcare resources use is not complete at least in one study [16]. Treatment costs calculated in Arshad et al. [16] are only drug costs: *'The model also does not take into account hospital expenses, biopsies and other lab work'*. Healthcare resource use categories or cost components other than drugs (hospitalization, outpatient visits, lab tests, emergency visits, and other healthcare services) accounted in base-case scenarios are either partially or not specifically reported in a large number of studies using summary cost data from the literature. Some of them only report having accounted for *'direct medical costs'* [45], and many studies report including *'drugs, monitoring and adverse effects'* or they simply report accounting for *'health-state specific costs'*. Thirty-five studies exclusively used a gross-costing approach [52] to valuing average resources used in the treatment of chronic HCV patients for the time spent in a health-state or for certain episodes of treatment (e.g. adverse events, monitoring, etc). Only a British study [19] reports the use of micro-costing (each resource is estimated, and a unit cost derived for each one [53]), a more precise approach than gross-costing, but only for the cost of monitoring patients in the intervention and comparator strategies. Gross-counting cost estimates were taken exclusively from literature in 14 studies; in other 14 set of studies previous literature was combined with expert opinion; 5 studies used previous literature plus a local database from healthcare providers [22,23,25,41,50]; and only 2 studies fully used a local provider database [15,17]. None of the included papers reported resource use and unit costs separately.

Regarding drug prices used in the base-case scenarios of these studies, 20 out of 36 (55.6%) did not explicitly report if they used prices are ex-factory, wholesale or retail prices. About 10 studies explicitly reported having used wholesale prices, three studies reported the use of ex-factory prices [20,33,36], 2 studies reported the use of retail prices [18,50], and another 1 reported the use of acquisition costs from the perspective of the healthcare payer [15]. In two cases, the price of the new intervention drug corresponded to the price observed in an early access program [28,41]. The widespread international use of confidential discounts on acquisition prices of new and expensive drugs by healthcare payers has only been taken into account in two studies [18,20]. A US study applied an average 11% discount on ex-factory prices [18]. An Italian study reported that according to a *'reimbursement agreement with the Italian reimbursement agency, we assumed that 24 weeks of treatment with SOF had the same price as 12 weeks of treatment'* [20]. In contrast, two Spanish studies [23,41] applied not specified *'discounts'* on official generic or used *'actual prices'* instead of official ones.Seven studies (19.4%) did not report the source used to obtain drug prices employed in the CUA. In two cases, the reported source of drug prices was press news [23,24]. In one case the authors simply reported the use of *'real life data'* [50], and two other studies used *'assumptions'* as price source [43]. The most common source of drug prices used in these studies are published official price lists (25 studies, 69.4%), such as the *Bot Plus Database* [22] and a *Health Ministry Database* [23] for Spain; the *Lauer Taxe* list for Germany [24,42]; the *Firstdatabank* list [18], a health insurance price list [30], and the *RedBook* list [29,39,40,46–48] for the United States; the *British National Formulary* [26] and the *Index for Medical Specialties* [30,34] for United Kingdom; the *Bluebook* [27] and the *Drug Price List of the Japanese National Health Insurance* [32,36] for Japan; the *RAMPQ* list for Canada [33]; a list of pharmaceutical specialties of the *Swiss Federal Office of Public Health for Switzerland* [37], etc. In 5 out of the 25 studies (20%) that reported the use of a published list, this list was not identified in the paper [46–48].

3.4 Incremental cost-effectiveness ratios

Incremental cost-per-QALY ratios for SOF, SMV, and POR comparisons for GTs 1, 2, 3, and 4 are summarized in Tables 5–8. Evidence for GT 5 and GT 6 was limited and is briefly commented. For each comparison, in Tables 5–8 we report the number of base case ICERs retrieved from the selected papers, and the lowest and highest base-case ICER in 2016 US dollars for TN and TE groups of patients,

Table 4. Summary of the modeling approach.

Author, year (of publication), [References]	Modeling approach	Cycle length	Within cycle correction	Uncertainty/ sensitivity analysis	Model validation
Alavian et al. [15]	Cohort STM (Markov model)	1 year	No	PSA	NR
Arshad et al. [16]	Cohort STM (Markov model)	1 year	No	DSA	NR
Chen et al. [17]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Face validation, external validation
Chhatwal et al. [18]	Cohort STM (Markov model)	1 week	No	DSA and PSA	Cross validation, external validation
Cure et al. [19]	Cohort STM (Markov model)	3 months for the first 2 years,1 year after that	Yes	DSA and PSA	Face validation, internal validation, cross-validation
Cure et al. [20]	Cohort STM (Markov model)	3 months for the first 2 years, 1 year after that	Yes	DSA and PSA	Cross-validation
Fraser et al. [21]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Face validation, cross-validation
Gimeno-Ballester. [22]	Cohort STM (Markov model)	4 months	Yes	DSA and PSA	NR
Gimeno-Ballester et al. [23]	Cohort STM (Markov model)	3 months	Yes	DSA and PSA	Internal validation
Gissel et al. [24]	Cohort STM (Markov model)	1 year	No	PSA	Cross-validation
Hagan et al. [25]	Cohort STM (Markov model)	1 year	No	DSA	NR
Johnson et al. [26]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Internal validation, cross-validation, external validation
Kuwabara et al. [27]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Cross-validation
Leleu et al. [28]	Cohort STM (Markov model)	3 months for the first two years, 1 year after that	No	DSA and PSA	NR
Linas et al. [29]	Cohort STM (Monte Carlo simulation)	1 month	No	DSA and PSA	NR
McEwan et al. [30]	Cohort STM (Markov model)	1 year	No	DSA	Interval validation, cross-validation.
McEwan et al. [31]	Cohort STM (Markov model)	1 year	Yes	PSA	Internal validation
McEwan et al. [32]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Cross-validation
Moshyk et al. [33]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Cross-validation, external validation
Najafzadeh et al. [34]	DES	1 year	No	DSA and PSA	Cross-validation, external validation
Ollendorf et al. [35]	Cohort STM	1 year	No	DSA	NR
Petta et al. [36]	Cohort STM (Markov model)	1 year	Yes	DSA and PSA	Cross-validation
Pfeil et al. [37]	Cohort STM (Markov model)	1 year	Yes	DSA and PSA	Face validation, cross-validation, internal validation
Rein et al. [38]	Cohort STM (Monte Carlo simulation)	1 year	No	DSA and PSA	NR
Saab et al. [39]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Face validation, cross validation
Saab et al. [40]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Cross-validation
San Miguel et al. [41]	Cohort STM (Markov model)	3 months	Yes	DSA and PSA	Face validation, cross validation
Stahmeyer et al. [42]	Cohort STM (Markov model)	1 month for one and a half years, 2 months for the next two cycles. After 2 years, 1 year cydes.	No	DSA and PSA	Cross-validation
Vargas et al. [43]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Face validation, cross-validation, internal validation,
Westerhout et al. [44]	Cohort STM (Markov model)	1 year	Yes	DSA and PSA	Cross-validation
Wong et al. [45]	Cohort STM	1 week	No	DSA and PSA	Cross-validation
Younossi et al. [46]	Cohort STM (Markov model)	1 year	No	DSA and PSA	Face validation, internal validation, cross-validation
Younossi et al. [47]	Cohort STM (Markov model)	1 year	No	DSA	NR
Younossi et al. [48]	Cohort STM (Markov model)	1 year	No	DSA	Cross-validation
Zhang et al. [49]	Cohort STM (Markov model)	1 year	No	DSA and PSA	NR
Zhao et al. [50]	Cohort STM (Markov model)	1 month	No	DSA and PSA	Cross-validation

including only non-cirrhotic or mixed populations. In this section, only comparisons with three or more base-case ICERs for the same patient group will be analyzed. From the included studies, we have retrieved 144 ICERs for GT 1, 31 for GT 2, 40 for GT 3, 14 for GT 4, and 2 for GT 5. In total, 231 were retrieved and analyzed.

3.4.1 Genotype 1

Dual therapy with SOF + RBV was only analyzed in TN patients with GT 1 in four comparisons (Table 5). Both the lowest and the highest base-case ICER of SOF dual therapy compared to dual therapy (PEG + RBV), the standard of care previous to the approval of SOF, were higher than US$50,000.

Table 5. Summary of incremental cost per QALY in the treatment of chronic hepatitis C patients. Genotype 1.

		Treatment Naïve			Treatment experienced		
Intervention	Comparator	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]
SOFOSBUVIR							
SOF dual therapy (SOF + RBV)	Dual therapy (PEG + RBV)	3	134,317 [45]	215,870 [50]	-	-	-
	First generation triple therapy (BOC/ TEL + PEG + RBV)	1	1,239,022 [50]	1,239,022 [50]	-	-	-
SOF triple therapy (SOF + PEG + RBV)	No treatment	4	2,159 [39]	95,526 [37]	1	17,321 [39]	17,321 [39]
	Dual therapy (PEG + RBV)	11	6,769 [47]	41,476 [50]	3	3,423 [39]	29,574 [20]
	First generation triple therapy (BOC/ TEL + PEG + RBV)	20	−30,994 [47]	76,963 [50]	4	−25,108 [39]	82,325 [20]
	Simeprevir (SMV + PEG + RBV)	2	−10,433 [39]	−5,468 [39]	2	−43,113 [39]	36,370 [42]
SOF-based all-oral second generation DAAs (SOF + LDV/DCV/SMV)	No treatment	6	−17,138 [46]	243,145 [40]	4	−6,050 [46]	287,718 [40]
	Dual therapy (PEG + RBV)	11	−13,426 [47]	124,561 [50]	5	21,894 [17]	90,202 [45]
	First generation triple therapy (BOC/ TEL + PEG + RBV)	15	−49,359 [47]	214,145 [50]	3	−14,974 [46]	34,457 [42]
	Simeprevir (SMV + PEG + RBV)	3	−39,596 [46]	19,061 [31]	1	−29,731 [46]	−29,731 [46]
	SOF dual (SOF + RBV)	2	−142,428 [46]	−112,813 [42]	1	−86,161 [46]	−86,161 [46]
	SOF triple (SOF + PEG + RBV)	3	−120,546 [42]	80,599 [31]	2	−11,621 [46]	13,653 [42]
	POR	1	497,889 [42]	497,889 [42]	1	−197,817 [42]	−197,817 [42]
SIMEPREVIR							
SMV triple therapy (SMV + PEG + RBV)	No treatment	2	461 [27]	175,786 [40]	1	283,139 [40]	283,139 [40]
	Dual therapy (PEG + RBV)	4	−8,370 [27]	49,410 [45]	2	10,977 [44]	22,839 [45]
	First generation triple therapy (BOC/ TEL + PEG + RBV)	5	−64,265 [47]	3,483 [47]	2	−62,079 [44]	−28,315 [44]
SMV-based all-oral second generation DAAs (SMV + DCV)	First generation triple therapy (BOC/ TEL + PEG + RBV)	2	36,104 [23]	43,318 [23]	-	-	-
Paritaprevir/Ombitasvir/Ritonavir							
POR-based all-oral second generation DAAs	No treatment	1	127,105 [40]	127,105 [40]	1	157,881 [40]	157,881 [40]
	Dual therapy (PEG + RBV)	5	−4,127 [47]	32,016 [45]	4	14,401 [26]	17,068 [45]
	First generation triple therapy (BOC/ TEL + PEG + RBV)	4	−35,554 [47]	50,099 [50]	-	-	-

BOC: boceprevir; DAA: direct-acting antivirals; DCV: daclatasvir; ICER: incremental cost–effectiveness ratio; LDV: ledipasvir; SOF: sofosbuvir; PEG: pegylated interferon; POR: paritaprevir/ombitasvir/ritonavir; QALY: quality adjusted life year; RBV: ribavirin; SMV: simeprevir; TEL: telaprevir. Number of base case ICERs included: 144 (from 22 studies).

Table 6. Summary of incremental cost per QALY in the treatment of chronic hepatitis C patients. Genotype 2.

		Treatment naïve			Treatment experienced		
Intervention	Comparator	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]
SOFOSBUVIR							
SOF dual therapy (SOF + RBV)	No treatment	9	3,127 [29]	248,088 [29]	7	6,410 [19]	487,837 [29]
	Dual therapy (PEG + RBV)	10	34,566 [19]	708,208 [34]	4	10,585 [19]	131.867 [18]
SOF triple therapy (SOF + PEG + RBV)	Dual therapy (PEG + RBV)	-	-	-	1	19,612 [45]	19,612 [45]

ICER: incremental cost–effectiveness ratio; SOF: sofosbuvir; PEG: pegylated interferon; QALY: quality adjusted life year; RBV: ribavirin. Number of base case ICERs included: 31 (from 9 studies).

Notwithstanding, the highest number of comparisons correspond to triple therapy SOF + PEG + RBV with 47 reported ICERs. The 5 ICERs comparing triple therapy SOF + PEG + RBV in TN and TE patients with no treatment and the 14 ICERs comparing it with dual therapy (PEG + RBV) are lower than US $50,000 even for the highest base case estimates; even the four ICERs for those two comparisons in TE patients are notably lower than US$50,000. For the 24 ICERs comparing SOF triple therapy with first-generation triple therapy (BOC/ TEL + PEG + RBV), the lowest ICERs are negative and the

highest ones are lower than US$100,000. The four comparisons of SOF triple therapy with SMV triple therapy, another second-generation DAA, showed negative ICERs (SOF triple therapy was dominant) or lower than US$50,000. Fifty-eight base-case ICERs compared SOF-based combinations with second-generation DAAs (SOF + LDV/DCV/SMV): the lowest base-case ICERs are negative in all comparisons except one, and the highest base-case ICERs are under US$100,000 in comparisons with SMV triple therapy, with SOF dual and triple therapy, and with first-generation triple therapy only for TE patients.

SMV triple therapy compared to previous treatments (dual therapy and first-generation triple therapy) showed a lowest and highest base-case ICERs negative or lower than US$50,000. POR-based combinations of all-oral second-generation DAA compared to previous dual therapy and first-generation triple therapy also showed negative ICERs or around US$50,000.

3.4.2 Genotype 2

For HCV patients with GT 2 (Table 6), our review showed sixteen comparisons of SOF dual therapy (SOF + RBV) with no treatment and fourteen comparisons with dual therapy (PEG + RBV). The ICERs of all these comparisons showed a high range of variation: lowest base-case ICERs were under US $50,000, but higher base-case ICERs were well above US $100,000.

3.4.3 Genotype 3

For HCV patients with GT 3 (Table 7), our results showed 21 comparisons of SOF dual therapy (SOF + RBV) with no treatment and with dual therapy (PEG + RBV). All comparisons with no treatment showed a lowest and highest base-case ICERs lower than or around US$50,000, except the highest base-case ICER for TE patients which is higher than US$100,000. Comparisons of SOF dual therapy with dual therapy (PEG + RBV) showed a lowest and highest ICERs clearly higher than US$50,000. SOF triple therapy (SOF + PEG + RBV) compared to dual therapy (PEG + RBV) showed lowest ICERs lower than US$50,000 and highest ICERs lower than US$100,000 in the ten comparisons reported in Table 7 for TN and TE patients. The four comparisons of SOF-based all-oral combinations of second-generation DAAs (SOF + LDV/DCV/SMV) showed a lowest ICER under between US$50,000 and US$100,000, but the highest ICER is clearly above US$100,000.

3.4.4 Genotype 4, 5, and 6

For HCV patients with GT 4 (Table 8), 12 comparisons for SOF treatment and 2 for POR treatment are reported in Table 8. We report three comparisons between SOF triple therapy and dual therapy with the lowest ICER under US$50,000 and the highest ICER lower than US$100,000. For those included studies analyzing GT 5 and 6, only one study [21] reported individualized result for GT 5. In this study, a SOF-based combination (SOF/LDV) dominated dual therapy (PEG + RBV) and also dominated SOF triple therapy (SOF + PEG + RBV).

4. Discussion

We systematically reviewed CUAs for the treatment of HCV patients with 2nd generation DAA, introduced in late 2013, compared to previous treatments by providing information about their methodological and modeling approaches, and about their cost analysis and incremental costs per QALY estimated in the base-case scenarios. This assessment included 36 studies published in just 3 years and 231 base-case ICERs from the performed comparisons, and we summarized heterogeneity in these ICERs by GT and TN versus TE patients. The present review updates and expands the scope of previously published five systematic reviews [4,8–11] of cost–effectiveness studies evaluating second-generation DAA treatments for HCV patients. At difference with previous reviews, we do not restrict our interest to one drug (SOF) [9] or some GTs [10,11] or the United States [8] or only to the modeling approaches [4].

Despite the important number of CUAs published since 2014, this analysis found several limitations derived from the economic evaluation method and the modeling techniques of the included CUAs which may bias estimated ICERs and that pose difficulties to inter-study comparisons. Regarding the main CUA features, despite some published papers claimed to present ICERs from a societal perspective, none of the selected studies really used the societal perspective, given that none of them included non-health care or indirect costs. This may result in an underestimation of the true burden of HCV, and therefore, in an overestimation of treatment impact on the use of social resources. A previous review of studies of non-healthcare costs of HCV concluded that future studies should focus on assessing incremental non-healthcare costs of HCV using a control group and with data for new DAAs [54]. Also, the results from a previous CUA for first-generation DAAs in the Netherlands showed the relevance of non-healthcare costs in order to obtain unbiased ICER estimates [55].

Regarding modeling features, two main limitations have been pointed out in our review. First, despite what ISPOR's good practice recommendations on transparency and validation [56] provide, more than one-fourth of the selected papers did not provide information on any form of model validation, and only a a few of them performed an external validation of the results. Second, even though limitations of using DSA are known [57], a higher proportion (one out of six studies) than in a previous review [4] solely used DSA. Also, the impact of the sensitivity analysis on outcome variables has been poorly reported in many papers: lower and higher figures around the base-case ICER estimate were presented in numerical terms only in a reduced number of 36 studies, being not reported or only graphically reported in others. These problems in addressing uncertainty in CUA studies makes it difficult to analyze intra-study variations in the estimated ICER, and may reduce confidence on their results to decision makers.Our review is also subject to some limitations that recommend caution in interpreting the results and ask for more research. First, our report is based only on information from published papers. Second, information retrieved from the studies in this paper is only partial, given that treatment outcomes and health-state

Table 7. Summary of incremental cost per QALY in the treatment of chronic hepatitis C patients. Genotype 3.

		Treatment naive			Treatment experienced		
Intervention	COMPARATOR	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]
SOFOSBUVIR							
SOF dual therapy (SOF + RBV)	No treatment	5	21,023 [20]	277,775 [29]	6	24,717 [20]	52,602 [37]
	Dual therapy (PEG + RBV)	7	89,993 [49]	188,639 [37]	3	74,637 [37]	127,380 [41]
SOF triple therapy (SOF + PEG + RBV)	No treatment	1	274,148 [29]	274,148 [29]	4	13,275 [19]	85,476 [29]
	Dual therapy (PEG + RBV)	6	31,977 [19]	74,174 [37]	4	16,199 [37]	59,957 [41]
SOF-based all-oral second generation DAAs (SOF + LDV/DCV/SMV)	No treatment	-	-	-	1	36,706 [45]	36,706 [45]
	Dual therapy (PEG + RBV)	4	73,251 [22]	401,404 [34]	-	-	-

DAA: direct-acting antivirals; DCV: dadatasvir; ICER: incremental cost–effectiveness ratio; LDV: ledipasvir; SOF: sofosbuvir; PEG: pegylated interferon; POR: paritaprevir/ombitasvir/Ritonavir; QALY: quality adjusted life year; RBV: ribavirin; SMV: simeprevir. Number of base case ICERs included: 40 (from 10 studies).

Table 8. Summary of incremental cost per QALY in the treatment of chronic hepatitis C patients. Genotype 4.

		Treatment naive			Treatment experienced		
Intervention	Comparator	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]	Number of base case ICERs	Lowest base case ICER (US$, 2016) [ref]	Highest base case ICER (US$, 2016) [ref]
SOFOSBUVIR							
SOF dual therapy (SOF + RBV)	No treatment	-	-	-	1	48,640 [45]	48,640 [45]
SOF triple therapy (SOF + PEG + RBV)	Dual therapy (PEG + RBV)	3	32,980 [37]	82,695 [45]	-	-	-
SOF-based all-oral second generation DAAs (SOF + LDV/DCV/SMV)	No treatment	2	5,282 [31]	31,313 [40]	2	5,282 [31]	36,528 [40]
	Dual therapy (PEG + RBV)	1	14,539 [31]	14,539 [31]	1	5,216 [31]	5,216 [31]
	Simeprevir triple therapy (SMV + PEG + RBV)	1	39,862 [31]	39,862 [31]	1	2,161 [31]	2,161 [31]
Paritaprevir/Ombitasvir/Ritonavir							
POR-based all-oral second generation DAAs (POR + RBV; POR + DSV + RBV)	No treatment	1	16,608 [40]	16,608 [40]	1	16,253 [40]	16,253 [40]

BOC: boceprevir; DAA: direct-acting antivirals; DSV: dasabuvir; DCV: dadatasvir; ICER: incremental cost–effectiveness ratio; LDV: ledipasvir; SOF: sofosbuvir; PEG: pegylated interferon; QALY: quality adjusted life year; RBV: ribavirin; SMV: simeprevir; TEL: telaprevir. Number of base case ICERs included: 14 (from 4 studies).

utilities sources and values have not been analyzed. Third, this review is not aimed at providing evidence on which factors may explain inter study cost-per-QALY variations, such as, for example, heterogeneity related to the stage of the disease, level of fibrosis, or drug prices. Fourth, only base-case cost-per-QALY estimates were reviewed without systematically analyzing the results coming from sensitivity analyses. Fifth, this review was not intended for, and results should not be interpreted as, providing evidence on the optimal treatment strategy for HCV patients or evidence on whether a particular new treatment is cost-effective. And, sixth, it remains a task for future research to estimate the important influence of recent drug price reductions of several DAAs on the cost per QALY.

Future research on the economic evaluation of new and highly priced DAA treatments for HCV patients should devote attention to the analysis of influential parameters on the estimated ICERs in order to explain the important inter- and intra-study variation reported in this review for the same comparison and HCV population group.

5. Conclusion

For GT 1 HCV patients, the highest number of ICER comparisons reviewed in this paper corresponds to SOF triple therapy and SOF-based combination therapies, which reported ICERs systematically ranging from negative to lower than US$100,000 when compared with no treatment, dual therapy or SMV triple therapy.

Comparisons for GT 2, 3, and 4 HCV patients found highest base-case ICERs being above US$100,000. The highest base-case ICERs were higher for GTs 2–4 than for treatment of GT 1 HCV patients. In conclusion, second-generation DAA in the treatment of GT 1 patients showed highest base-case ICER lower than US $50,000 when compared to no treatment and previous dual therapy (PEG + RBV), and below US$100,000 when compared to previous triple therapy (BOC/TEL + PEG + RBV).

6. Expert commentary

The present article updates and expands the five systematic literature reviews of cost-effectiveness of second-generation

DAAs for the treatment of CHC published during the last years, which only included studies published until 2015 or were limited to US patients or only GT 1 patients [4,9–11]. In this review, we covered both method and modeling features and cost per QALY as the outcome variable of CUAs. Notwithstanding the progressive increase in the number of articles published, this analysis found some important limitations arising from the methodology and design of these studies that should deserve attention of researchers and journals as they pose limits to the policy implications of this literature.

Several factors have been identified in this review that were not addressed or did not receive enough attention in previous reviews. In our opinion, incremental treatment costs and cost-per-QALY estimates may be biased as a result.

First, the common use of a gross-costing approach (a partial micro-costing approach was used in only one study [19]) makes difficult to be sure that all differential costs among intervention and control treatment strategies have been considered (i.e. emergency visits or adverse events).

Second, combining previous literature with expert opinion (not always validated) and available databases as cost sources for non-drug healthcare resources may result in a high heterogeneity and may yield non-comparable estimates.

Third, being the results of the CUAs presumably very influenced by the high prices of the new DAA under evaluation, it is surprising to report in this review that more than one quarter of the studies did not explicitly state what type of drug price was used in the evaluation (ex-factory, wholesale, retail with or without taxes). In fact, only two papers out of 36 [28,41] reported an effort to take into account the fact that relying on a pricing list may overestimate the cost of the innovation and, thus, it may not represent actual transaction prices because of the increasing and extended use of confidential discounts on official list prices.

Fourth, none of the reviewed studies used the long run price of intervention and comparison drugs. From the social perspective, not adopting a dynamic evaluation of new drugs using the long-term average price and using the entry price for innovations and the actual price for generic comparators, after the exclusivity period for the comparator drug, overstates the cost of the pharmacological second-generation DAA treatment in the long run [7,58].

Fifth, the sources of inter- and intra-study variations are only partially described in some studies [8,9] but none of them provided a detailed and quantitative analysis of the impact of the several sources of heterogeneity on the estimated costs per QALY. Two previous review papers [10,11] tried to evaluate the influence of price variation on cost per QALY by reanalyzing the published cost-utility results assuming a linear relationship between treatment costs and ICERs. Besides other limitations, there is no evidence of this linear relationship in the economic literature between ICER and drug prices or any other model inputs (i.e. healthcare costs, quality-of-life weights, transition probabilities, etc.).

The non-healthcare costs attributable to HCV infection are composed of productivity losses due to absenteeism or presenteeism, lost leisure time, premature mortality, and caregiver care due to the disease. The extended omission of non-healthcare costs in economic evaluations of second-generation DAA may have overvalued the estimation of cost per QALY in this literature, as they are probably changing the current and future burden of the disease. This observation is reinforced by the evidence prior to the introduction of innovative highly effective medicines DAAs. It was observed that the estimated non-healthcare costs of HCV at a general or population level tend to be considerably higher than the healthcare costs, the main non-healthcare cost of HCV being attributable to premature mortality [54].

7. Five-year view

The analysis of the studies included in this review highlights the need for cost–effectiveness studies of innovative and highly priced HCV treatments in the next 5 years which include comprehensive healthcare costs and non-healthcare costs in particular, provided that results are to be useful for healthcare and decision makers. Future cost-of-illness studies should focus on assessing incremental healthcare and non-healthcare costs of HCV using a control group with real word data for new DAAs as they would be useful and complementary to cost–effectiveness studies.

The results of this review, which focused on CUAs and modeling features, costs and incremental cost per QALY, have some useful and practical implications for an improved design of cost–utility studies of second-generation DAAs for the treatment of chronic HCV, but also for the evaluation of successive improved and innovative HCV therapies more recently introduced and for those still in the pipeline. From the methodological perspective, there is an urgent need for improvement in this literature of health economics, especially regarding drug, and non-drug healthcare cost features, in order to improve transparency and reliability of incremental cost per QALY estimates.

First, high healthcare costs related to treatment and complications at the different stages of the illness and their expected budget impact deserve a more refined and precise approach to cost estimation using more frequently a micro-costing approach and providing evidence of the type of resources and their quantities used in the estimation of the cost for each health state. Second, transparency and replicability of non-drug healthcare resource estimation requires to justify the appropriateness and reliability of the extended and ad-hoc use of non-validated expert opinion and *cherry picking* on previous literature as the main sources of resource measurement. Third, regarding drug costs, CUA literature should explicitly state which type of drug price has been used (ex-factory, wholesale, retail with or without taxes), the sensitivity of the outcome measure to the price choice, and why this one was the relevant price from the selected perspective of the study. Given the well-known widespread prevalence of confidential discounts and rebates for the majority of healthcare payers, in order not to provide systematic overestimated incremental cost per QALY measures, we consider also necessary to make an effort not to rely only on official list prices in the CUA base-case scenarios. And, fourth, as it is recommended for all high-priced innovative drugs, a dynamic approach should be adopted by using the long run price of intervention and comparison drugs instead of the actual price of both, which also may lead to an overestimated ICER for these innovations. Economic evaluation models should consider the

price fall after the loss of exclusivity, which tends to be omitted even in simulations over the patient's lifetime.

Key issues

- Thirty-six cost-utility analyses (CUAs) were included to review the evidence from the current literature.
- CUAs included in this review compared interventions with second generation DAAs therapies with no treatment, and with previous therapies for chronic HCV patients for genotypes 1–4.
- Twenty studies, out of thirty-six, did not report the type of drug prices used.
- The highest number of ICER comparisons corresponds to sofosbuvir (SOF) triple therapy and SOF-based combinations.
- SOF-treatments studies for genotype 1 reported a cost per QALY in base-case scenarios were systematically ranging from negative to lower than US$100,000 when compared to no treatment or dual therapy.
- Cost per QALY base-cases found in this review for genotypes 2–4 were higher than US$100,000.
- Several limitations of method and modeling techniques of CUAs included in this review may bias estimated cost per QALY and pose severe difficulties to inter-study comparisons.

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ORCID

Jaume Puig-Junoy http://orcid.org/0000-0003-1695-3108
Natàlia Pascual-Argente http://orcid.org/0000-0003-2980-366X

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CHAPTER 3: COST-UTILITY ANALYSIS OF UPDATING GUIDELINES FOR THE TREATMENT OF HEPATITIS C

3.1 Introduction

Since 2014, new regimens for hepatitis C virus (HCV) treatment have marked a turning point in the management of chronic hepatitis C (CHC). HCV infection is the leading cause of chronic liver disease worldwide. HCV infection, which leads to CHC progression might undergo decades of progression with stages including fibrosis cirrhosis, hepatocellular carcinoma (HCC), ending with end-stage liver disease[1]. In 2015, CHC affected 71 million people and 10 million people globally and in Europe, respectively, with important variability observed across countries[2,3]. Latest prevalence estimates of HCV prevalence in Europe indicate a range of 0.1%-5.9% for 30 European countries[4]. CHC is associated with an increased premature death rate compared to the general population, even after controlling for the main risk factors (i.e. injectable drug use and HIV coinfection)[5,6]. In 2019, cirrhosis ranked 7th in the Global Burden of Disease leading causes for people aged 50-74 years. The ranking was similar to that in 1990, despite clear improvements in all-ages burden of illness along the decade[7].

Prior to 2014, the introduction of first generation direct-acting antivirals (DAAs) (i.e. boceprevir and telaprevir) improved sustained virologic response (SVR) rates; however, they had to be used in combination with previous therapy (i.e. peginterferon and ribavirin)[8]. Since 2014, new (2nd generation) DAAs substantially

improved SVR from 60-70% to more than 95% and shorter treatment durations[8,9]. Furthermore, new treatments (i.e. sofosbuvir, simeprevir, and subsequent treatments) enabled all-oral and pangenotypic regimens and improved adverse events, which led to the development of HCV eradication strategies[10]. Apart from the clinical burden of CHC, the economic burden has proven to be substantial as the disease affects direct medical costs[11–15] and indirect costs, due to decreased patient productivity and premature mortality associated with CHC[16–19].

Although many studies have analysed the cost-effectiveness of treatments based on new DAAs[20,21], limited studies conduct efficiency analyses to support clinical guidelines which affect several treatments at the same time[22]. The European Association for the Study of the Liver (EASL) updated its recommendations on treatment of HCV [23] to guide clinicians at a national level, as a significant number of new treatments were approved in a short period of time. New DAAs offered improved efficacy rates and they offered savings for health systems in the long-run but they compromised budgets in the short-run[24].

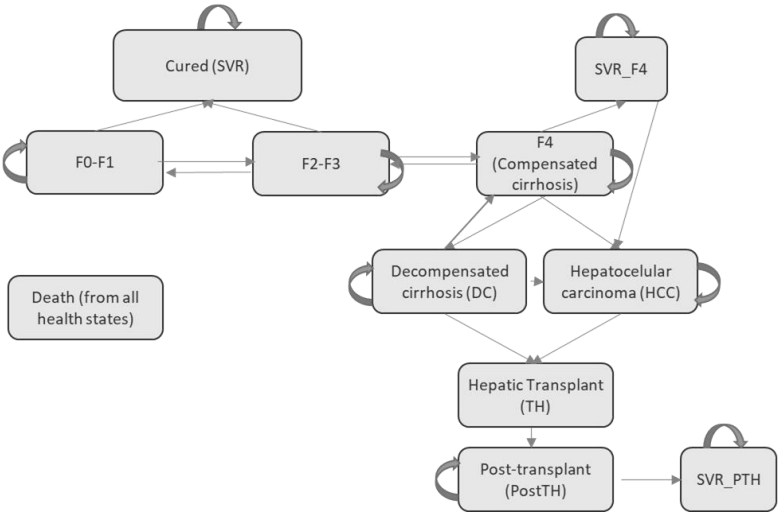
The aim of this study is to assess the efficiency of changes made in treatment recommendations of HCV, after new DAAs were introduced in the market. This study assesses the change in guidelines (EASL recommendations in 2016 vs. 2018) using Spain as a case in the European context. The study is the first evaluation detailing the impact of clinical guidelines for Hepatitis C drugs. The

study contributes to the increasing interest concerning the consideration of economic aspects in clinical guidelines development.

3.2 Methods

A cost-utility analysis (CUA) was used to assess the change in Hepatitis C clinical guidelines following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations for state-transition modelling studies for Spain. A Markov-model with a structure commonly used in economic evaluation for DAA in HCV[25] (Figure 1) was implemented to compare the EASL guidelines for 2018 [23] to 2016 [26] (Table 1). In the base case, a societal perspective (human capital approach), a lifetime time horizon, and a discount rate of 3% were applied to the case and the outcomes.

Figure 1. Markov model diagram by health states for chronic HCV



SVR: sustained virological response, F0 to F4 indicate METAVIR scores (fibrosis stage).

Table 1. EASL recommendations summary 2016 – 2018. Treatment regimens available as valuable options by HCV genotype and cirrhosis.

		GT 1a		GT 1b		GT3	
Cirrhosis	Treatment	EASL 2016	EASL 2018	EASL 2016	EASL 2018	EASL 2016	EASL 2018
Without cirrhosis	SOF/LDV	TN (8-12) /TE (12 o 24)	TN (8-12)	TN (8-12) / TE (12)	TN (8-12) / TE (12)	Not included	Not included
	SOF/VEL	TN & TE (12)		TN & TE (12)		TN (12) & TE (12/24)+/-RIVA	TN & TE (12)
	OBV/PTV/RTV+DSV	TN & TE (12)	Not included	TN (8-12) / TE (12)	TN (8 F0-F2; 12 F3) / TE (12)	Not included	Not included
	GZR/EBR	TN & TE (12 o 16)	TN & TE (12)	TN & TE (12)	TN (8 F0-F2; 12 F3) / TE (12)	Not included	Not included
	SOF+DCV	TN (12) / TE (12 o 24)	Not included	TN & TE (12)	Not included	TN (12) & TE (12/24)+/-RIVA	Not included
	GLE/PIB	Not included	TN & TE (8)	Not included	TN & TE (8)	Not included	TN (8) & TE (12)
With cirrhosis	SOF/LDV	TN (12) /TE (12 o 24)	TN (12)	TN & TE (12)		Not included	Not included
	SOF/VEL	TN & TE (12)		TN & TE (12)			Not included
	OBV/PTV/RTV+DSV	TN & TE (24)	Not included	TN & TE (12)		Not included	Not included
	GZR/EBR	TN & TE (12 o 16)	TN & TE (12)	TN & TE (12)		Not included	Not included
	SOF+DCV	TN (12) / TE (12 o 24)	Not included	TN & TE (12)	Not included	TN & TE (24)	Not included
	GLE/PIB	Not included	TN & TE (12)	Not included	TN & TE (12)	Not included	TN (12) & TE (16)
	SOF/VEL/VOX	Not included	Not included	Not included	Not included	Not included	TN & TE (12)

Genotype (GT), European Association for the Study of the Liver (EASL), Sofosbuvir/ledipasvir (SOF/LDV), Sofosbuvir/Velpatasvir (SOF/VEL), Ombitasvir-paritaprevir-ritonavir+Dasabuvir (OBV/PTV/RTV+DSV), Grazoprevir/Elbasvir (GZR/EBR), Sofosbuvir+Daclatasvir (SOF+DCV), Glecaprevir/Pibrentasvir (GLE/PIB), Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX), treatment-naïve (TN), treatment-experienced (TE). In parentheses, treatment duration in weeks.

Target population

The study population was a hypothetical cohort of adult patients (55 years) with HCV subtypes GT1a, 1b, and 3. The patients had HCV infection with or without cirrhosis and were treatment-naïve or experienced. Only GT1 and 3 were modelled as they represent the most prevalent subtypes accounting for 70% of global HCV infections3. Number of patients and stage distribution was determined using the demographic and epidemiological data for Spain. Treatment history and cirrhosis were considered separately in the model as they influenced treatment indications and duration[23,26] (Table 1).

Treatment strategies

SVR was used to measure treatment effectiveness as it is an accepted indicator for analysing the cure rate of CHC and is related to decreased mortality[27]. Treatments and their respective durations were applied differently in 2016 and 2018 according to guidelines. DAA included in 2016 were sofosbuvir/ledipasvir (SOF/LDV), mmbitasvir-paritaprevir-ritonavir+sasabuvir (OPR+DSV), grazoprevir/elbasvir (GZR/EBR), and sofosbuvir+daclatasvir (SOF+DCV). DAA included in 2018 were SOF/LDV, sofosbuvir/velpatasvir (SOF/VEL), OPR+DCV, GZR/EBR, glecaprevir/pibrentasvir (GLE/PIB), and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). Pharmacological treatment pools were weighted according to market shares in 2016 and 2018[28].

Markov Model

Patients entered the model in health states corresponding to HCV stages F0-F4 (METAVIR score) and they progressed to cured (SVR) or decompensated cirrhosis, HCC, and transplant-related health states. Cycles were set to trimesters to capture changes in treatment durations. Efficacy data, transition probabilities, and utility values were retrieved from literature following best practices and a recent hepatitis C model review[29,30], followed by validation in an expert panel. Transition probabilities combined general and specific ones by genotype and treatment and varied according to age- and sex-adjusted mortality over time (see Tables S1, S2, S3 of the Supporting Information).

In the base case, EASL's recommended treatment strategies for 2016 and 2018 were compared and total direct and indirect costs (societal perspective, human capital approach) and quality-adjusted life years (QALY) throughout lifetime were estimated at a discount rate of 3%, following current recommendations[31,32]. A half-cycle correction was applied to health benefits and costs[33]. The model allowed for comparisons regarding patient types (naïve/experienced), drug prices (list vs. purchase price), and perspectives.

Costs

The societal perspective included indirect costs (1) due to productivity loses (human capital approach) and (2) based on the value of a life-year. The health system perspective accounted for only direct costs. Direct costs comprised drug

and management costs by health state. Recommended duration and dosage were used to compute pharmacological costs. Indirect costs for the human capital approach were estimated based on literature and expert panel information on loss of labour productivity and official data on annual salaries from the National Institute of Statistics[34] or published estimates on the value of a life year in the latter approach[35]. All costs were updated to €2019 by using the Gross Domestic Product deflator.

Sensitivity analyses

Deterministic (DSA) and probabilistic sensitivity analysis (PSA) were performed to assess uncertainty concerning base-case results. Main model parameters were checked using a ±25% variation range for the deterministic analysis. In the PSA (1000 montecarlo simulations), Dirichlet distribution for transition probabilities, Beta for utilities, and Lognormal for costs were used. Alternative discount rates (0% and 5%) were checked according to published guidelines[36].

Results

This model estimated that the EASL guidelines in 2016 for the treatment of chronic HCV yielded 22.95, 23.05, and 23.01 QALY per patient corresponding to GT1a, 1b, and 3, respectively. Concerning 2018 guidelines, resulting QALY per patient were estimated at 23.08 (GT1a), 23.14 (GT1b), and 23.03 (GT3). No relevant

differences were found by treatment history (Table 2). Estimated costs exhibited important variations in 2016 and 2018 estimations concerning genotype, perspective, and acquisition costs (Table 3). Considering the variations from a societal perspective with human capital approach (base case) and purchase prices, treatment costs in 2016 were €70,196 (GT1a), €61,106 (GT1b), and €92,752 (GT3). The treatment costs in 2018 were €48,944 (GT1a), €49,130 (GT1b), and €49,061 (GT3).

Table 2. QALYs per patient resulting from EASL Hepatitis C recommendations.

	EASL 2016	EASL 2018
QALY (overall)		
GT1a	22.95	23.08
GT1b	23.05	23.14
GT3	23.01	23.03
QALY (naïve)		
GT1a	22.95	23.07
GT1b	23.05	23.14
GT3	23.01	23.03
QALY (treatment- experienced)		
GT1a	22.95	23.09
GT1b	23.05	23.14
GT3	23.01	23.03

Table 3. Cost per patient resulting from EASL Hepatitis C recommendations in 2016 and 2018.

	EASL 2016	EASL 2018
Costs (List prices)		
GT1a		
Societal (human capital) perspective	€ 97,715	€ 74,212
Societal (life year value) perspective	€ 431,382	€ 400,250
Health system perspective	€ 57,774	€ 36,064
GT1b		
Societal (human capital) perspective		
Societal (life year value) perspective	€ 81,965	€ 73,582
Health system perspective	€ 409,389	€ 396,143
GT3	€ 43,815	€ 36,347
Societal (human capital) perspective		
Societal (life year value) perspective	€ 143,879	€ 76,251
Health system perspective	€ 475,358	€ 405,152
	€ 103,651	€ 37,440
Costs (Purchase prices)		
GT1a		
Societal (human capital) perspective	€ 70,196	€ 48,944
Societal (life year value) perspective	€ 403,862	€ 374,982
Health system perspective	€ 30,254	€ 10,796

Table 3 (continued)		
GT1b		
Societal (human capital) perspective	€ 61,106	€ 49,130
Societal (life year value) perspective	€ 388,530	€ 371,691
Health system perspective	€ 22,957	€ 11,895
GT3		
Societal (human capital) perspective	€ 92,752	€ 49,061
Societal (life year value) perspective	€ 424,231	€ 377,962
Health system perspective	€ 52,524	€ 10,250

The clinical guidelines update yielded positive gains in QALY and a significant effect on incremental costs (Table 4). Incremental QALY per patient were higher in GT1a (0.134) and GT1b (0.093) compared to GT3 (0.020). Incremental costs per patient involved savings in all scenarios, with a higher value for GT3 (€-42,274–€-46,269) compared to GT1a (€-19,458–€-28,880) and GT1b (€-11,061–€-16,840). Savings were accomplished in all genotypes, considering different acquisition costs (list vs. purchase prices) and perspectives (societal vs. health system). Consequently, the guidelines update in 2018 was dominant compared to 2016 in all scenarios.

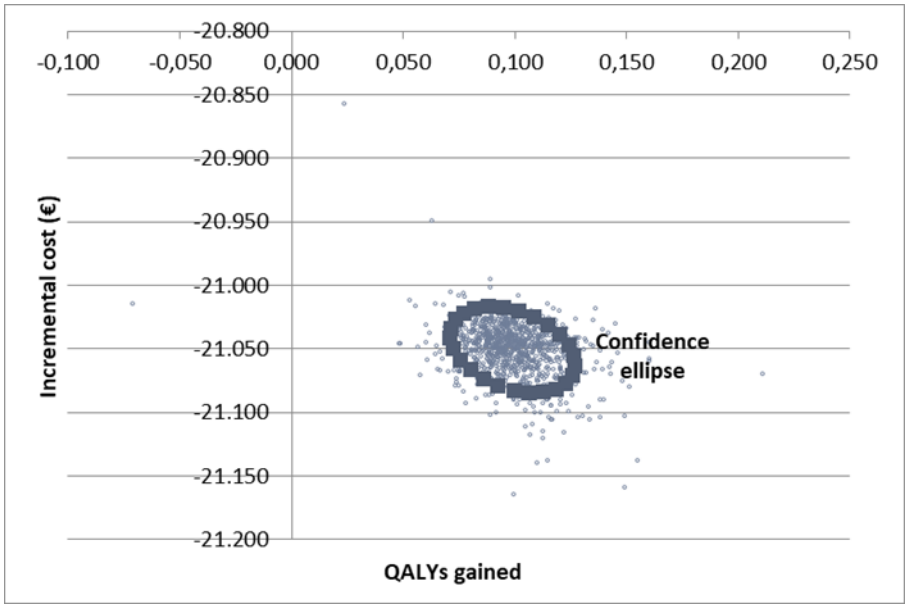
Table 4. Incremental QALY. Costs and ICER of EASL Hepatitis C treatment recommendations in 2016 and 2018 by perspective and genotype (Purchase prices. Per-patient values).

Difference (2016 to 2018)	GT1a	GT1b	GT3
QALY	0.134	0.093	0.020
Costs Societal (HC)	€ -21,252	€ -11,976	€ -43,692
ICER	dominant	dominant	dominant
Costs Soc (LYV)	€ -28,880	€ -16,840	€ -46,269
ICER	dominant	dominant	dominant
Costs HS	€ -19,458	€ -11,061	€ -42,274
ICER	Dominant	dominant	dominant

HC: human capital. HS: health system. LYV: life years value

In the DSA, the most influent parameters were transition probabilities and utility values (see Figure S1 of the Supporting Information). In the PSA, the treatment strategy included in 2018 guidelines was dominant compared to that from 2016 in 99.9% of cases, as indicated by the cost-effectiveness plane (Figure 2).

Figure 2. Incremental cost-effectiveness plane (PSA)



Discussion

This CUA compared EASL recommendations for treating HCV in 2018 with those in 2016. These findings show that the update in EASL recommendations that incorporated new DAAs for HCV treatment resulted in dominant ICER in all perspectives and genotypes considered. These results indicate that updated clinical guidelines in 2018 exerted a positive impact on health results and they led to important savings for the healthcare system. This is the first study assessing the cost-effectiveness of a change in clinical guidelines on Hepatitis C. The study results contribute to existing studies on other therapeutic areas wherein CUA is applied to compare clinical recommendations that have an impact on healthcare costs [37–39].

This study considered indirect costs related to decreased productivity in HCV patients which is seen as a measure to overcome previous CUA limitation concerning costs involved[29,40]. However, other studies about productivity costs of chronic HCV showed a lower proportion of indirect to direct costs[19,41–43], which can be attributed to the situation before new DAA were available. Recent data suggest that productivity costs improved (lowered) due to the new therapies[44], which is in line with the estimations presented here.

Different acquisition costs (list prices and purchase prices) were used in the analysis as it was found to be an important driver in HCV CUA models[45,46]. To date, few studies with purchase prices are found in literature due to transparency constraints at the government level. This posed a limitation in previous CUA on HCV drugs[25,40]. In the present study, prices were reduced at a range of 30-70% depending on the source (list vs. purchase) and DAA. The reduction is higher compared to the 25% reduction indicated by recent findings, with rebates and discounts on pharmaceutical expenditure at a country level [47]. This reduction can be potentially attributed to the favourable price-negotiations at a provider and local level for the case of HCV drugs.

Limitations of this study include, first, a possible overestimation of treatment effects due to the assumption of full adherence. Results would be affected if the guidelines update entangled changes in treatment adherences. Second, the study does not take into account the effects of screening or the effects of a possible reduction in

transmission rates thanks to generalised treatment. However, this bias has a homogenous effect on the period considered in the analysis. Lastly, the study lacks an external validation with real world data although face validity was used to assess the model. However, results can be extrapolated to countries like Spain, with a National Health System and similar prices.

Conclusions

In summary, this analysis shows that clinical recommendations on treatment of chronic HCV in 2018 contributed to the efficiency of the healthcare system in Spain as a case in Europe from societal and health system perspectives. Updating clinical guidelines resulted in better health outcomes and a cost-saving strategy considering most prevalent genotypes (GT1 and GT3). These results might be useful for the application of EE tools to clinical guidelines development alongside the development of a novel measure for health intervention. The study demonstrated that treatment strategies incorporating new DAAs regimens for HCV included in EASL guidelines in 2018 contributed to the efficiency of their health systems.

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Supporting information

Table S1. Health-state costs used in the Markov model.

Health-state costs	Value	Source
Cure	-	Expert panel
F0-F1	€ 384.89	Expert panel
F2-F3	€ 543.26	Expert panel
F4	€ 701.64	[1]
SVR-F4	€ 203.17	[1]
DC	€ 2,858.28	[1]
HCC	€ 10,889.24	[1]
TH (with follow-up)	€ 98,409.71	[1]
TH (w/o follow-up)	€ 18,392.22	[2]
PostTH	€ 44,892.09	[1]
SVRPTH	€ 203.17	Expert panel

Table S2. Health state utilities used in the model.

Health-state utilities	Value	Source
Cure	1.00	Expert panel
F0-F1	0.99	Expert panel
F2-F3	0.96	[3]
F4	0.94	Expert panel
SVR-F4	1.00	[3]
DC	0.84	[3]
HCC	0.76	[3]
TH	0.81	[3]
PostTH	0.89	[3]
SVRPTH	0.90	[3]

Table S3. Transition probabilities used in the model.

Transition probabilities*	**Value**	**Source**
From SVRF4 to		
SVRF4	0.950	Expert panel
F4	0.000	Expert panel
HCC	0.005	[1]
Death	0.045	Expert panel
From HCC to		
HCC	0.094	Expert panel
TH	0.040	[4]
Death	0.866	[4]
From TH to		
Death	0.066	[4]
PostTH	0.815	Expert panel
From PostTH to		
PostTH	0.866	Expert panel
SVRPTH	0.313	Expert panel
Death	0.071	Expert panel
From SVRPTH to		
SVRPTH	0.950	Expert panel
PostTH	0.000	Expert panel
Death	0.050	Expert panel

* Only those for the general case (used in all treatments and Genotypes) are included

References in tables S1-S3

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Figure S1. Tornado diagram (DSA).