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Health state utility values measured using the EuroQol 5-dimensions questionnaire in adults with chronic hepatitis C: a systematic literature review and meta-analysis

A. M. Buchanan-Hughes[1] · M. Buti[2,3] · K. Hanman[1] · B. Langford[1] · M. Wright[4] · L. A. Eddowes[1]

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Abstract

Purpose Chronic hepatitis C infection and its treatment can considerably affect patients' health-related quality-of-life (HRQoL). This study aimed to identify and summarise the current evidence base for health state utility values (HSUVs) in patients with chronic hepatitis C infection, generated using the EuroQol 5-dimensions (EQ-5D) questionnaire.

Methods MEDLINE, Embase, the Cochrane Library and EconLit were searched from database inception through 31 August 2017. Eligible studies reported HSUVs elicited using the EQ-5D questionnaire in adults with chronic hepatitis C infection. Study quality and risk of bias were assessed.

Results Of 1480 records identified, 26 studies were included. The most commonly defined health states described different stages of chronic hepatitis C infection and specific liver-related disease states, including METAVIR score, compensated and decompensated cirrhosis, hepatocellular carcinoma and liver transplantation. Patients with higher METAVIR scores tended to have lower EQ-5D scores compared to patients with lower METAVIR scores. Patients that achieved sustained virologic responses tended to have higher EQ-5D scores compared to those that did not. A meta-analysis conducted on three studies confirmed that patients with decompensated cirrhosis have significantly lower HSUVs than patients with compensated cirrhosis [mean difference − 0.11 (95% CI − 0.19 to − 0.04)], implying worse HRQoL. However, there was not sufficient evidence to compare how different treatments for chronic hepatitis C infection affect EQ-5D scores.

Conclusions This study provides a summary of EQ-5D HSUVs for patients with chronic hepatitis C infection, and demonstrates that clinically important disease stages associated with treatment decisions are associated with differences in HRQoL.

Keywords EQ-5D · HCV · Hepatitis C · QoL · Quality of life · Utility

Introduction

The hepatitis C virus (HCV) epidemic affects approximately 2.35% of the global population, with the World Health Organization (WHO) reporting an estimated 71 million chronically infected patients and 399,000 deaths attributable to HCV per year [1, 2]. Patients may initially experience relatively mild symptoms such as weight loss and fatigue; however, approximately 55 to 85% of patients will progress to chronic infection [1, 3]. Over several years, chronically infected patients are likely to develop severe and debilitating conditions such as cirrhosis and hepatocellular carcinoma (HCC) [4].

Until recently, many patients with hepatitis C were treated with interferon-based regimens. These regimens are only efficacious in an estimated 40 to 70% of patients and are associated with side effects including influenza-like symptoms and

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✉ A. M. Buchanan-Hughes
amy.buchanan-hughes@costellomedical.com

[1] Costello Medical Consulting Ltd, Cambridge, UK

[2] Hospital Universitario Valle Hebron, Barcelona, Spain

[3] Ciberehd del Instituto Carlos III, Madrid, Spain

[4] University Hospital Southampton NHS Foundation Trust, Southampton, UK

depression, which can considerably affect patients' health-related quality of life (HRQoL) [4]. The relatively recent introduction of direct-acting antiviral (DAA) agents has offered patients treatments that are safer, better tolerated and more effective. DAAs are also associated with shorter treatment durations, which may reduce the number of side effects patients experience [5].

It is known that patients with chronic and progressive diseases place a high value on their mental and social wellbeing, as well as physical health, hence HRQoL is of considerable importance in the chronic hepatitis C-infected patient community [6]. Due to the chronic nature of HCV and, until recently, the limited number of efficacious treatment options, many patients experience worsening liver disease and declining HRQoL over time. Decreased HRQoL associated with HCV can lead to a higher disease-related burden for patients as well as increased indirect costs due to factors such as low medication adherence and poor psychological wellbeing [4, 7].

HRQoL is a complex patient-reported outcome (PRO) that has become increasingly important and valued by regulatory bodies such as the European Medicines Agency [8]. Greater knowledge of HRQoL, using a measurement scale that is widely used across studies in chronic hepatitis C, may contribute to the identification of treatment gaps or of patient subgroups most in need of effective and well-tolerated therapies. This may lead to improvements in health care services and disease prevention strategies [9].

The EuroQol 5-dimensions (EQ-5D) questionnaire is a generic preference-based instrument that assesses HRQoL across five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) [10]. It is often the method of choice for cost–utility analyses and is the preferred method for a number of health technology assessment (HTA) bodies, including the National Institute for Health and Care Excellence (NICE) [11]. The generic health states generated by the EQ-5D are valued by applying societal preference weights that generate a health state utility value (HSUV), which reflects the preference that individuals express for a health state, anchored at 0 (death) and 1 (full health) [12]. HSUVs can be combined with life expectancy to generate quality-adjusted life years (QALYs), a vital measure included in cost–utility analyses [13].

Due to the importance of cost–utility analyses in decisions about reimbursement, it is crucial that the most robust and clinically appropriate estimates of HSUVs measured in adults with chronic hepatitis C infection are used in cost–utility analyses of new treatments. Therefore, this systematic literature review (SLR) aimed to identify and summarise the current evidence base for HSUVs, measured using the EQ-5D questionnaire, in the chronic hepatitis C-infected patient population.

Methods

Search strategy

The SLR and update were conducted and reported in accordance with a pre-specified protocol and PRISMA guidelines [14]. The published literature was searched via the databases MEDLINE, MEDLINE In-Process and Embase (via Ovid SP), the Cochrane Library (via the Wiley platform) and EconLit (via EBSCO). The literature was searched from database inception to 19 February 2016, and for the subsequent update, from 19 February 2016 to 31 August 2017. When possible, search terms included combinations of free-text terms and database-specific subject headings relating to HCV and HRQoL (Supplementary Tables 1 to 3).

The bibliographies of identified meta-analyses, economic evaluations and HTAs were hand-searched, along with abstract books from relevant congresses and the EQ-5D online database [15]. Available abstract books that were hand-searched are presented in Supplementary Information 1.

Eligibility criteria

Relevant studies included adult humans with chronic hepatitis C infection of any genotype; patients were permitted to have human immunodeficiency virus (HIV) or hepatitis B coinfection and to have received any treatment or none. HSUVs were required to have been measured using the EQ-5D questionnaire or mapped to the EQ-5D. Longitudinal and cross-sectional study types published in the English language were included.

Study selection

The titles and abstracts of articles from the electronic database searches were screened by two reviewers using the pre-specified eligibility criteria. When the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. The full-texts of articles fulfilling the inclusion criteria during the title/abstract review stage were retrieved and independently screened for inclusion by two reviewers. For cases in which the article did not give enough information to be sure that it met the inclusion criteria, the article was excluded to ensure that only relevant articles were ultimately included. During the title/abstract and full-text review stages, any disagreements were resolved by discussion until a consensus was met. If necessary, discrepancies were arbitrated by a third reviewer.

Data extraction and quality assessment

Data from included studies were extracted independently by two reviewers into a pre-specified grid, with discrepancies resolved by a third reviewer. Data on population demographics, recruitment methodology, country the study was conducted in, sample size, health state descriptions, EQ-5D HSUVs and HSUV elicitation methods were captured. Two independent reviewers determined the quality of each included study by considering factors such as sample size, population demographics, methodology used to calculate HSUVs, and whether or not baseline EQ-5D values were reported for longitudinal studies. Guidance from the NICE Decision Support Unit's report on the identification, review and synthesis of HSUVs from the literature, for use in economic evaluations, was considered to evaluate the quality and relevance of each included study [16].

Meta-analysis

The feasibility of conducting a meta-analysis was considered if two or more studies reported HSUVs for at least two health states for the same liver-related condition (e.g. compensated and decompensated cirrhosis). In this study, a meta-analysis was ultimately performed for three studies that reported HSUVs for both compensated cirrhosis and decompensated cirrhosis [17–20]. HSUVs, standard deviations (SDs), 95% confidence intervals (CIs), subgroup cohort sizes, as well as gender, age and ethnicity demographics were extracted.

The meta-analysis was conducted using fixed-effect and random-effects models in R (version 3.2.2). As a measure of the effect of cirrhosis, the mean difference between change in HSUVs for patients with compensated and decompensated cirrhosis was calculated and statistical significance determined. Heterogeneity between studies was evaluated using the I^2 statistic. Publication bias could not be assessed as there was an inadequate number of studies to examine a funnel plot accurately.

Results

Study selection

A total of 26 articles identified through the databases and hand-searches were ultimately included in this review (21 in the original SLR [17–37] and five in the update [38–42]). A PRISMA flowchart displaying the number of records identified or excluded at each stage of the search process is presented in Fig. 1. In the original 2016 SLR, a total of 209 systematic reviews, meta-analyses, HTAs and economic evaluations were identified through the database searches. Due to the large number of results, only the bibliographies of those deemed highly relevant were hand-searched ($n = 72$); however, no newly-identified studies fulfilled the inclusion criteria.

Study characteristics

Studies were conducted in a variety of countries with three in Germany [25, 26, 28], five in France [19, 20, 26, 27, 30], five in the USA [21, 27, 32, 33, 38], two in the UK [26, 37] and the remainder across multiple countries in Europe, South America, North America and Asia (Table 1) [17, 18, 22–24, 29, 32–36]. The sample sizes of the studies reported in the 26 publications were generally large with most studies reporting data on hundreds of participants (range 28 to 1092 participants; Table 1). The average age of participants across all studies varied between 35 and 63 years and, with the exception of one study, over half of all participants in each study were male (Table 1).

With respect to study setting, five publications reported data from the Adelphi Real World Hepatitis C Disease Specific Programme from a range of countries including France, Germany, the UK and the USA [19, 20, 25, 26, 37]. Additionally, two publications reported data from the same four clinical trials of sofosbuvir (SOF) treatment, namely POSITRON, FISSION, FUSION and NEUTRINO [32, 33]. In terms of specific patient populations, studies generally recruited a mixture of HCV genotypes with several studies exclusively recruiting genotype 1 populations. One study recruited HCV patients with opioid dependence, two studied blood donors and one study investigated patients with HCV and HIV coinfection (Table 1).

In all but one study (reported by two publications), HSUVs were measured using the EQ-5D questionnaire and a variety of valuation methods (Tables 1, 2, 3, 4, 5). In the one study that did not elicit utility measurements using this method, EQ-5D HSUVs were approximated by mapping data from the 36-Item Short Form Health Survey (SF-36) to the EQ-5D using a published mapping algorithm [32, 33].

HSUVs related to the majority of health states commonly used to model chronic hepatitis C infection in cost–utility analyses were identified (Fig. 2). The most commonly defined health states described various HCV-related liver conditions and treatment status [sustained virologic response (SVR) or no SVR]. Four publications specified health states according to METAVIR fibrosis score [17, 26, 30, 34], nine reported on patients diagnosed with cirrhosis [17–20, 23, 26, 34, 37, 41], three on patients with HCC [17, 23, 34] and four for liver transplantation

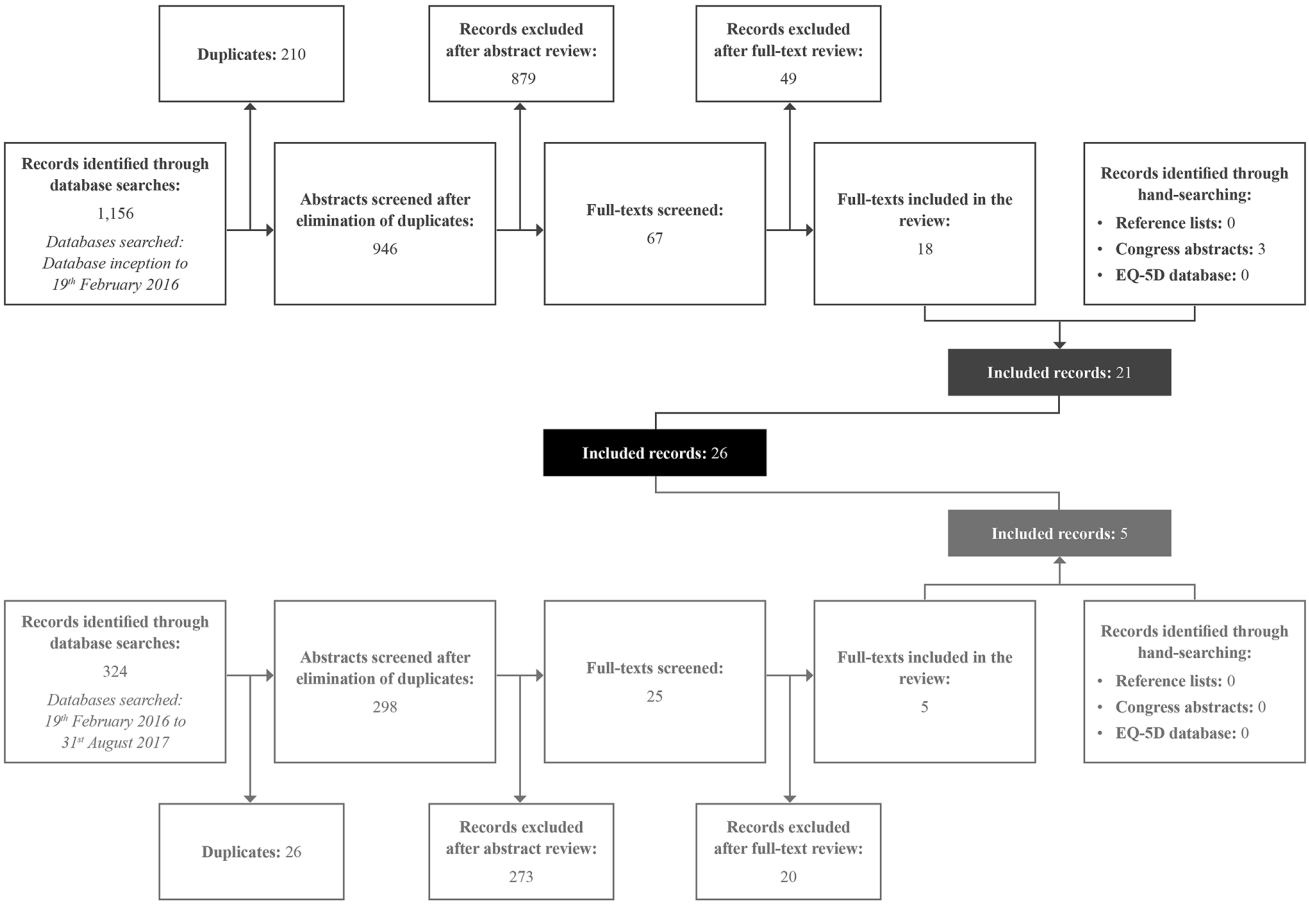

Fig. 1 PRISMA flowchart presenting study selection process from the SLR conducted in 2016 and update conducted in 2017. *EQ-5D* EuroQoL-5 dimensions, *SLR* systematic literature review

[17, 26, 34, 41]. Twenty publications specified health states relating to treatment status including patients receiving dual and triple therapies, or patients receiving treatment versus no treatment [17–20, 22, 25–28, 30–37, 39, 41, 42]. Some studies also reported EQ-5D scores for patients on specific treatment regimens [17–20, 22, 25–28, 30–37, 39, 41, 42]. The HSUVs for all included studies are reported in Tables 2, 3, 4 and 5.

Health state utility value outcomes

HCV-positive health state

Table 2 presents EQ-5D scores for numerous HCV populations that are not defined as having a specific comorbidity, such as HCC, or receiving a specific treatment regimen. Populations include the 'typical' chronic hepatitis C-infected population, comprising patients with mild to moderate disease, for example, and other populations such as blood donors. EQ-5D scores ranged from 0.65 in chronic symptomatic patients to 0.94 in HCV-infected patients who were ineligible/intolerant to interferon ± ribavirin [19, 20, 22].

Compensated versus decompensated cirrhosis

Three studies specifically compared compensated cirrhosis patients to those with decompensated cirrhosis; in all three studies, patients with decompensated cirrhosis had lower EQ-5D scores than compensated cirrhosis patients (Fig. 3a) [17–20]. It was feasible to conduct a meta-analysis of these studies. SDs were not reported in the studies by Chong et al. and Samp et al. [17, 19, 20]. The 95% CIs for HSUVs reported by Chong et al. were therefore used to approximate the missing SDs [17]. SDs pooled from Chong et al. and Bjornsson et al. were used to estimate the SDs for the study by Samp et al. [18–20]. The results from the fixed-effect model showed that the overall mean difference in HSUVs was − 0.11 (95% CI − 0.19 to − 0.04) when comparing HSUVs in patients with decompensated to compensated cirrhosis (Fig. 4). The results of the analysis were statistically significant and the evidence suggests that patients with decompensated cirrhosis have lower HSUVs compared to patients with compensated cirrhosis, implying lower HRQoL. Only results from the fixed-effect model are

Table 1 Study characteristics, population characteristics and EQ-5D valuation methods

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Bjornsson et al. [18]	Sweden	472	Chronic hepatitis C infection	NR (62%)	46 (10)	Observational	EQ-5D-3L, but further details NR
			Compensated cirrhosis	NR (76%)	53 (10)		
			Decompensated cirrhosis	NR (71%)	55 (10)		
			SVR attainment	NR (56%)	49 (10)		
Chong et al. [17]	Canada	193	No liver biopsy	18 (51%)	Mean (SE) 47 (2.1)	Observational	EQ-5D-3L. The EQ-5D norms are based on a mail survey of 1518 Canadians living in Alberta, including those with comorbidities
			Compensated cirrhosis	17 (71%)[a]	57 (2.0)		
			Decompensated cirrhosis	6 (67%)	57 (3.9)		
			Mild/moderate chronic HCV	32 (73%)	44 (1.5)		
			HCC	14 (93%)	63 (2.7)		
			Liver transplant	21 (70%)	54 (1.7)		
			SVR attainment	23 (64%)	48 (1.3)		
			Percentages are calculated from the number of patients who responded to each question				
Custer et al. [abstract] [21]	USA	316	HCV-infected blood donors	NR	NR	Observational	NR
			Patients were blood donors infected with HCV ($n=316$). Controls were blood donors with false-positive screens for HCV, HIV, HBV or HTLV				
DeVecchis Wygant et al. [abstract] [22]	China (mainland), Korea and Taiwan	159	• HCV infection before treatment initiation • SVR attainment • Non-SVR attainment	NR	NR	Phase III study	NR
			Patients ($n=159$) had HCV GT1b and were receiving daclatasvir and asunaprevir. Patients were intolerant to IFN ± RBV				
Gschwantler et al. [abstract] [39]	Austria	151	• Completed questionnaire at baseline • Completed questionnaire at end of treatment	106 (70%)	n (%) 22 (15%) were older than 65 years of age	Prospective, observational	NR
			Patients with chronic HCV with GT1 and GT4 were recruited. Patients received OBV/PTV/r ± DSV ± RBV during the study				

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Huang et al. [abstract] [40]	China	997	Treatment naïve Treatment-naïve Han ethnic adults with recently confirmed HCV infection	NR (54.8%)	43.5 ± 12.8	Cross-sectional	NR
Kaishima et al. [abstract] [23]	Japan	212	• Chronic hepatitis C infection • Cirrhosis • HCC HCV patients receiving either IFN + RBV + SMV or SOF + LDV	NR	NR	Observational	NR
Kieran et al. [abstract] [41]	NR	270	• Total HCV population • Treatment naïve • Decompensated cirrhosis • Liver transplant • Treatment experienced • SVR attainment • Non-SVR attainment	NR	NR	Cross-sectional	NR
McDonald et al. [24]	Scotland	1092	• PWID HCV-positive • PWID HCV-positive (self-reported as having cleared HCV) Non-active PWID (those who had not injected in the past 6 months) were kept to a maximum of 25% of the sample	• PWID HCV-positive (aware they have HCV): 439 (75.2) • PWID HCV-positive (unaware they have HCV): 379 (74.6)	Median (IQR) • PWID HCV-positive (aware they have HCV): 37 (31 to 42) • PWID HCV-positive (unaware they have HCV): 34 (30 to 40)	Cross-sectional	EQ-5D-3L responses were valued using a UK general population sample (2997 respondents, 1993) with an established algorithm [43]
Nouvertne et al. [abstract] [25]	Germany	499	• Triple therapy • Dual therapy • Treatment naïve	NR (58%)	45 (NR)	Cross-sectional	NR

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Nwankwo et al. [poster] [27]	USA and France	34	• Untreated, no comorbidities • Untreated, ≥ 1 comorbidity • Treated, ≥ 1 comorbidity • Treated, ≥ 1 comorbidity, SVR attainment • Treated, ≥ 1 comorbidity, no SVR attainment	NR	• < 40 years = 25% • ≥ 40 years = 75%	Observational	EQ-5D-3L, but further details NR
Pol et al. [26]	France, Germany and the UK	831	• Fibrosis stage F0–F1 • Fibrosis stage F2 • Fibrosis stage F3–F4 • Decompensated cirrhosis/HCC • First year following liver transplant • Subsequent years following liver transplant Treated patients with SVR attainment • Fibrosis stage F0–F1 • Fibrosis stage F2–F3–F4	NR (58.8%)	47.1 (14.1)	Cross-sectional	The French value set was used to derive utilities

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Samp et al. [20], Samp et al. [abstract] [19]	France	297	Disease stage • Chronic, asymptomatic • Chronic, symptomatic • Compensated cirrhosis • Decompensated cirrhosis Treatment status • Never treated • Treatment completed • Treatment ongoing SVR status • SVR attainment • SVR non-attainment	190 (63.97%)	50.4 (NR)	Cross-sectional	EQ-5D-3L. Dimension scores were converted into single EQ-5D index summary scores using French tariffs
Scalone et al. [29]	Italy	346	Chronic HCV	NR (54.6%)	Median (min to max) 60.1 (20.2 to 83.1)	Cost-of-illness	EQ-5D-3L and EQ-5D-5L were utilised. The UK standard social tariffs were used to convert the EQ-5D-3L scores into utilities. Utilities for the EQ-5D-5L were obtained using the tariffs from the available value set created by mapping the 5 level to the 3 level existing set [44]
Schafer et al. [28]	Germany	1614	• Treated with IFN-α • Not treated with IFN-α Patients were currently in agonist maintenance therapy for opioid dependence with either buprenorphine or methadone, irrespective of prior duration of treatment	1076 (66.7%)	36.3 (7.9)	Prospective, observational	NR

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Schwarzinger et al. [abstract] [30]	France	357	Sex • Female • Male Genotype • GT1 • GT2/3 • GT4/5/6 Fibrosis stage • F0–F2 • F3–F4 Prior treatment • Treatment naïve • Treatment experienced	182 (51%)	54.0 (9.6)	Cross-sectional	EQ-5D-3L, but further details NR
Scott et al. [31]	15 and 14 countries approved the study protocols for the PILLAR and ASPIRE studies, respectively (no further details reported)	• PILLAR: 386 • ASPIRE: 462	PILLAR Randomised to SMV Randomised to PR ASPIRE Randomised to SMV Randomised to PR	 174 (56.3%) 39 (50.6%) 269 (67.9%) 42 (63.6%)	Median (range) 47.0 (18 to 69) 45.0 (21 to 67) 50.0 (20 to 69) 50.5 (22 to 66)	Phase IIb RCT	UK tariffs were used to determine utility scores and were based upon the general public's preferences and determined using TTO

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Stepanova et al. [32], Younossi et al. [abstract] [33]	NR in publications. ClinicalTrials.gov lists the following locations for each trial POSITRON: USA, Australia, Canada, New Zealand, Puerto Rico [45] FISSION: USA, Australia, Canada, Italy, Netherlands, New Zealand, Puerto Rico, Sweden [46] FUSION: USA, Canada, New Zealand, Puerto Rico [47] NEUTRINO: USA, Puerto Rico [48]	• POSITRON: 262 • FISSION: 215 • FUSION: 201 • NEUTRINO: 326	POSITRON Randomised to SOF + RBV Randomised to placebo FISSION Randomised to SOF + RBV Randomised to IFN + RBV FUSION Randomised to SOF + RBV (16 weeks) Randomised to SOF + RBV (12 weeks) NEUTRINO SOF + RBV + PEG-IFN	NR	NR	Blinded, placebo-controlled RCT, open-label active-control Blinded, active-control Open-label uncontrolled	SF-36v2 questionnaire was administered at each study time point to all subjects in their native language (English, Swedish, Dutch and Italian). A published algorithm was then used to approximate EQ-5D values from the SF-36/SF-6D information [49–52]
			Patients were excluded if they had evidence or prior history of HCC, decompensated liver disease, other chronic liver disease, coinfection with HIV or HBV or other clinically significant abnormalities			Observational	
Vahidnia et al. [38]	USA	315	HCV patients	185 (58.7%)	44.7 (12.5)	Observational	EQ-5D health state was summarised applying weights that were generated based on a representative general USA population sample assessed using the TTO method [53]
			Population of blood donors recruited into The US Donor Risk Factor Study (US DRFS, 2010 to 2013) confirmed to have HCV infection following blood donation				

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Vargas et al. [34]	Chile	28	• Fibrosis stage F0–F3 • Fibrosis stage F4 • Decompensated cirrhosis: 2 • HCC • First year following liver transplant • Subsequent years following liver transplant • SVR attainment fibrosis stage F0–F1 • SVR attainment fibrosis stage F2–F3 • SVR attainment fibrosis stage F4	NR	NR	Cost-effectiveness	The results of the EQ-5D questionnaire were validated using the Chilean tariff which used the TTO valuation methodology [54]
Vera-Llonch et al. [35]	Sites from multiple countries participated in the ADVANCE study with approximately 60% of patients recruited from North America	722	Patients had HCV GT1b and were treatment naïve			Phase III RCT	USA-specific valuation weights were applied to EQ-5D-3L scores to derive utility values [55]
			Treatment arm				
			TVR 12 weeks, PR 24 weeks	128 (61%)	45.9 (10.4)		
			TVR 12 weeks, PR 48 weeks	86 (56%)	47.3 (11.2)		
			PR 48 weeks	211 (59%)	48.8 (10.0)		
			SVR status				
			SVR attainment 72 weeks	NR	NR		
			No SVR attainment 72 weeks	NR	NR		

Table 1 (continued)

Study	Country	Total sample size	Disease health states	Sex: male n (%)	Age Mean (SD)	Study design	HSUV methods of valuation (Using EQ-5D scores)
Wright et al. [37]	UK	• RCT: 196 • Observational Study: 302	RCT			RCT	UK-specific valuation weights were applied to EQ-5D-3L scores to derive utility values. Weights were derived using the TTO technique [56]
			Randomised to treatment (3 excluded ITT analysis for not completing the questionnaire)	63 (NR)	40.68 (8.82)		
			Randomised to no treatment (11 excluded ITT analysis for not completing the questionnaire)	56 (NR)	40.71 (8.29)		
			Observational study			Observational	
			Mild HCV	97 (52%)	39.8 (8.1)		
			Moderate HCV	42 (59%)	43.8 (10.4)		
			Cirrhosis	29 (73%)	47.0 (8.40)		
			Utilities were also presented from a previously published DoH-funded liver transplant study (post-transplantation patients) [57], for which the primary publication was not available online				
Wygant et al. [abstract] [42]	Asia (Subgroup of patients assessed for EQ-5D scores were from mainland China)	159	• Patients who were recruited into the study from Mainland China • Overall population (analysed in the study) • SVR attainment • Non-SVR attainment	Female 82 (65%)	Median (range) 54 (20 to 70)	Phase III study	NR
			HCV GT1b-infected Asian patients IFN/RBV intolerant/ineligible. Patients from mainland China were analysed in the study. Baseline characteristics of patients from mainland China ($n = 127$)				
Yeung et al. [36]	Canada	223	SVR attainment	Female 15 (17%)	Median (IQR) 46 (39 to 51)	Prospective, cohort	EQ-5D responses were converted into utilities using a Canadian-based algorithm [58]
			Non-SVR attainment	11 (16%)	48 (44 to 52)		
			Patients were treated with IFN-based therapy and in some cases this was combined with direct-acting antivirals				

[a]The article reports that 7/24 (71%) patients with compensated cirrhosis were male. Based on the proportion of male patients in other groups (51 to 93%) it is likely that this should read 17/24 (71%)

Table 1 (continued)

DoH Department of Health, *DSV* dasabuvir, *EQ-5D* EuroQol 5-dimensions, *EQ-5D-3L* EuroQol 5-dimensions 3 levels, *EQ-5D-5L* EuroQol 5-dimensions 5 levels, *GT1* genotype 1, *GT4* genotype 4, *HBV* hepatitis B, *HCC* hepatocellular carcinoma, *HCV* hepatitis C, *HIV* human immunodeficiency virus, *HTLV* human T-lymphotropic virus, *IFN* interferon, *IQR* interquartile range, *ITT* intention to treat, *LDV* ledipasvir, *NR* not reported, *OBV* ombitasvir, *PEG-IFN* pegylated interferon, *PR* peginterferon/ribavirin, *PTV* paritaprevir, *PWID* people who inject drugs, *r* ritonavir, *RBV* ribavirin, *RCT* randomised controlled trial, *SD* standard deviation, *SE* standard error, *SF-36* 36-Item Short Form Health Survey, *SF6D* Short Form 6D, *SMV* simeprevir, *SOF* sofosbuvir, *SVR* sustained virologic response, *TTO* time trade-off, *TVR* telaprevir

presented, as the I^2 statistic was 0%, indicating there was little evidence of heterogeneity across the studies.

Liver transplant

Two publications demonstrated that patients who had received a liver transplant in the past year had considerably lower mean EQ-5D scores compared to those who had received a transplant more than 1 year ago (Fig. 3b) [26, 34]. The scores imply that patients experience greater HRQoL in the years following a liver transplant compared to the initial year in which transplantation occurs. It should be noted that in the study conducted by Vargas et al., only one and two patients had a liver transplant less than and more than 1 year ago, respectively [34]. Due to very small cohort sizes, no meta-analysis was performed for studies that examined HSUVs in patients who had received a liver transplant, either more than or less than 1 year ago.

METAVIR staging and sustained virologic response

A total of four publications specified health states according to METAVIR fibrosis score, covering the full range of fibrosis scores in the METAVIR scoring system of 0–4 (Fig. 3c) [17, 26, 30, 34]. Patients with higher METAVIR scores, and thus more severe fibrosis or cirrhosis, tended to have lower mean EQ-5D scores, implying lower HRQoL. However, EQ-5D scores were measured for different METAVIR fibrosis stages, or different ranges of fibrosis stages (e.g. 0–2 vs. 0–3), across studies. Also, the mean EQ-5D values for reported ranges may have been influenced by the proportion of patients with each individual fibrosis staging in the group. Direct inter-study comparative analysis of EQ-5D values presented for each METAVIR stage, or stages, is therefore difficult. A meta-analysis was not performed as there was substantial inter-study heterogeneity relating to fibrosis stages, or range of fibrosis stages that were grouped together, when comparing HSUVs (Fig. 3c, d).

Upon examining patients with varying METAVIR scores who had attained SVR, there was a similar trend; patients with higher METAVIR scores (more severe fibrosis or cirrhosis) reported lower mean EQ-5D scores (Fig. 3d). Additionally, patients who attained SVR tended to have higher EQ-5D scores compared to those patients who did not attain SVR. Scores for patients without SVR ranged from 0.67 to 0.82 and for those with SVR from 0.8 to 1.0 (Fig. 3c, d) [17, 18, 23, 26, 34, 37]. Patients who attained SVR with more severe fibrosis or cirrhosis demonstrated similar mean EQ-5D scores compared to patients who did not attain SVR but had less severe fibrosis. These results reflect the positive impact of SVR attainment on HSUVs, even in patients with severe fibrosis.

Table 2 EQ-5D HSUVs presented for different HCV populations across the included studies

Study	Sub population	Mean	SD	95% CI	*p* value
Bjornsson et al. [18]	Chronic HCV without cirrhosis ($n=158$)	0.811	0.230	NR	
Chong et al. [17]	No liver biopsy ($n=35$)	0.73	NR	0.62 to 0.83	$p<0.001$
	Canadian population norms ($n=1518$)	0.76		0.68 to 0.83	$p<0.05$
	HCV-infected blood donors ($n=316$)	0.821		0.810 to 0.832	NR
Custer et al. [abstract] [21]	HCV-infected patients at baseline ($n=159$)	0.83	0.20	NR	$p<0.001$ vs. controls
DeVecchis Wygant et al. [abstract] [22]	HCV-infected patients at baseline ($n=151$)	0.94	NR		
Gschwantler et al. [abstract] [39]	Treatment-naïve Han ethnic adults with recently confirmed chronic hepatitis C infection ($n=997$)	0.827	0.177	NR	
Huang et al. [abstract] [40]	Chronic HCV ($n=$NR)	0.780	0.083^		
Kaishima et al. [abstract] [23]	Chronic HCV without cirrhosis ($n=158$)	0.871	NR		
Kieran et al. [abstract] [41]	Total HCV population ($n=270$)	0.70	0.24	NR	
	Treatment naïve ($n=$NR)	0.67	NR		$p=0.04$ vs. treatment experienced
McDonald et al. [24]	PWID HCV-positive, all ($n=1092$)	0.69*	NR		
	PWID HCV-positive, self-reported as having cleared HCV ($n=$NR)	0.73*			
Nouvertné et al. [abstract] [25]	Treatment naïve ($n=172$)	0.87	NR		
Nwankwo et al. [poster] [27]	Untreated, no comorbidities ($n=33$)	0.89	0.14	NR	$p=0.001$ comorbidities vs. no comorbidities
	Untreated, ≥ 1 comorbidity ($n=87$)	0.77	0.21		
Samp et al. 2015,[20], Samp et al. [abstract] [19]	All HCV patients ($n=297$)	0.764	0.283	NR	$p<0.0001$ across disease stages, including asymptomatic/symptomatic compensated/decompensated cirrhosis
	Never treated ($n=82$)	0.769	NR		
	Chronic, asymptomatic ($n=180$)	0.833			
	Chronic, symptomatic ($n=53$)	0.651			
Scalone et al. [29]	Chronic HCV, EQ-5D-3L ($n=346$)	0.823	0.205	NR	NR
		Median: 0.848 Range: − 0.239 to 1	NR		
	Chronic HCV, EQ-5D-5L ($n=346$)	0.840	0.178	NR	NR
		Median: 0.879 Range: − 0.060 to 1	NR		
Schafer et al. [28]	All HCV patients at baseline ($n=1614$)	0.71	NR		$p=0.003$ vs. HCV-negative
	All HCV patients at 1 year follow-up ($n=$NR)	0.71			$p<0.001$ vs. HCV-negative
	HCV patients not on IFN-α at baseline ($n=$NR)	0.71	NR		
	HCV patients not on IFN-α at follow-up ($n=$NR)	0.71			

Table 2 (continued)

Study	Sub population	Mean	SD	95% CI	*p* value
Schwarzinger et al. [abstract] [30]	Treatment naïve ($n=174$)	0.81	NR		
	Female ($n=175$)	0.78			
	Male ($n=182$)	0.83			
	GT1 ($n=238$)	0.82			
	GT2/3 ($n=66$)	0.76			
	GT4/5/6 ($n=53$)	0.80			
Scott et al. [31]	PILLAR SMV arm ($n=309$)	0.9	0.01†	NR	
	PILLAR PR arm ($n=77$)	0.9	0.03†		
	ASPIRE SMV arm ($n=396$)	0.9	0.01†		
	ASPIRE PR arm ($n=66$)	0.9	0.02†		
Stepanova et al. [32], Younossi et al. [abstract] [33]	POSITRON all patients ($n=262$)	0.706	0.218	NR	
	FISSION all patients [n=215]	0.755	0.234		
	FUSION all patients ($n=201$)	0.749	0.221		
	NEUTRINO all patients ($n=326$)	0.793	0.219		
Vahidnia et al. [38]	HCV patients ($n=315$)	0.83	0.19	NR	
Wright et al. [37]	Mild HCV ($n=185$)	0.77	0.22	NR	
	Moderate HCV ($n=71$)	0.66	0.25		
Wygant et al. [abstract] [42]	HCV-infected patients at baseline ($n=126$)	Median: 1.00 IQR: 0.87 to 1.00	NR		
	Overall population CFB Wk 24	0.01	0.01†	NR	
		Median: 0.00 IQR: 0.00 to 0.00	NR		$p=0.65$ vs. baseline

CFB change from baseline, *CI* confidence interval, *EQ-5D* EuroQoL-5 dimensions, *GT1* genotype 1, *GT2/3* genotype 2/3, *GT4/5/6* genotype 4/5/6, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HTLV* human T-lymphotropic virus, *IFN* interferon, *IQR* interquartile range, *NR* not reported, *PR* peginterferon/ribavirin, *PWID* people who inject drugs, *SD* standard deviation, *SMV* simeprevir, *Wk* week

*Represents median

^Reported in the abstract as ±0.083 and assumed to be SD here

†Represents standard error (SE)

Hepatocellular carcinoma

Mean EQ-5D scores for patients with HCC varied considerably amongst the three publications that presented them; the scores were 0.65 [17], 0.78 [23] and 0.95 [34]. Additionally, one publication reported a EQ-5D score of 0.51 for a mixed group of patients with decompensated cirrhosis and/or HCC [26].

Treatment regimen-related health states

A number of publications reported mean and/or median EQ-5D scores for specific treatment regimens, including interferon-based regimens and DAAs (Table 5). For treatment-naïve patients, three publications reported mean EQ-5D scores of 0.87 [25], 0.81 [30] and 0.77 [19, 20], respectively. One publication also reported mean EQ-5D scores of 0.79 and 0.76 for treatment-naïve control patients at baseline and at the end of 24/48 weeks of follow-up, respectively [37]. Nouvertne et al. reported that mean EQ-5D values were similar between patients receiving dual and triple therapy (0.90 vs. 0.91, respectively) [25]. Patients who completed treatment had mean EQ-5D scores of 0.75 [19, 20], 0.79 [30], 0.89 [39] and 0.90 [35]. No meta-analysis could be performed because there was evidence of heterogeneity in terms of study design and treatment regimens.

Table 5 summarises the EQ-5D scores of patients treated with interferon and non-interferon-based regimens over different time periods. Mean EQ-5D scores were variable within and between treatment regimens ranging from 0.65 to 0.84.

Eight studies examined the change in HSUVs at baseline and following treatment initiation [22, 28, 31–33, 35, 37, 39, 42]. Results were mixed with only modest, if any, improvement in HSUV following 24 and 48 weeks of follow-up. Patients in DAA treatment groups also experienced a greater increase, or smaller decrease in utility values, compared to patients on non-DAA regimens, indicating these regimens may also improve HRQoL [28, 35].

Table 3 EQ-5D HSUVs presented for cirrhosis populations across the included studies

Study	Cirrhosis	
	Compensated cirrhosis	Decompensated cirrhosis
Bjornsson et al. [18]	Mean (SD) ($n=76$) 0.749 (0.212)	Mean (SD) ($n=53$) 0.656 (0.266)
Chong et al. [17]	Mean (95% CI); (p vs. population norms) ($n=24$) 0.74 (0.66 to 0.83) ($p<0.05$)	Mean (95% CI); (p vs. population norms) ($n=9$) 0.66 (0.46 to 0.86) ($p<0.05$)
Kaishima et al. [abstract] [23]	Mean ($n=$NR) 0.774	
Kieran et al. [abstract] [41]	NR	Mean ($n=$NR) 0.46
Pol et al. [26]	NR	Mean (SE) ($n=$NR) 0.51 (0.07)
Samp et al. [20], Samp et al. [abstract] [19]	Mean ($n=18$) 0.622	Mean ($n=11$) 0.405
Vargas et al. [34]	NR	Mean (SE) ($n=2$) 0.536 (±30%)
Wright et al. [37]	Mean (SD) ($n=40$) 0.55 (0.34)	

CI confidence interval, *NR* not reported, *SD* standard deviation, *SE* standard error

Table 4 EQ-5D HSUVs presented for fibrosis, HCC and liver transplant populations across the included studies

Study	By METAVIR score	HCC	Liver transplant recipients
Chong et al. [17]	Mild or moderate chronic HCV (METAVIR score 0–3) ($n=44$): Mean (95% CI); (p vs. population norms) 0.76 (0.68 to 0.83) ($p<0.05$)	Mean (95% CI); (p vs. population norms) ($n=15$) 0.65 (0.44 to 0.86) ($p<0.001$)	Liver transplant: Mean (95% CI); (p vs. population norms) ($n=30$) 0.69 (0.62 to 0.77) ($p<0.001$)
Kaishima et al. [abstract] [23]	NR	Mean ($n=$NR) 0.780	NR
Kieran et al. [abstract] [41]	NR	NR	Mean ($n=$NR) 0.57
Pol et al. [26]	Mean (SE) F0–F1 ($n=239$): 0.82 (0.02) F2 ($n=246$): 0.78 (0.02) F3–F4 ($n=101$): 0.67 (0.03) SVR, F0–F1 ($n=35$): 0.95 (0.01) SVR, F2–F4 ($n=36$): 0.85 (0.02)	Mean (SE) ($n=25$) 0.51 (0.07)	Mean (SE) First year ($n=5$): 0.46 (0.10) Subsequent years ($n=10$): 0.80 (0.08)
Schwarzinger et al. [abstract] [30]	Mean F0–F2 ($n=240$): 0.82 F3–F4 ($n=117$): 0.76	NR	NR
Vargas et al. [34]	Mean (SE) F0–F3 ($n=2$): 0.686 (±30%) F4 ($n=9$): 0.682 (0.285) F0–F1 with SVR ($n=5$): 1 (0) F2–F3 with SVR ($n=2$): 1 (0) F4 with SVR ($n=4$): 0.798 (±30%)	Mean (SE) ($n=4$) 0.952 (0.096)	Mean (SE) LT first year ($n=1$): 0.572 (±30%) LT subsequent years ($n=2$): 0.904 (±30%)

CI confidence interval, *HCC* hepatocellular carcinoma, *HCV* hepatitis C, *LT* liver transplant, *NR* not reported, *SE* standard error, *SVR* sustained virologic response

Vera-Llonch et al. reported the effects of treatment on HSUVs over a 72-week period [35]. HSUVs initially decreased in all three treatment groups up to week 12, then began to steadily and consistently increase over weeks 24, 36, 48 and 72, indicating HRQoL may improve following an initial decrease in HSUVs upon treatment initiation.

Table 5 EQ-5D HSUVs presented for treatment regimens across the included studies

Study	Treated patients	
	SVR attainment	Non-SVR attainment
Bjornsson et al. [18]	Mean (SD) SVR after IFN ± RBV ($n = 52$): 0.792 (0.209)	NR
Chong et al. [17]	Mean (95% CI) SVR after previous IFN monotherapy or IFN + RBV treatment ($n = 36$): 0.83 (0.77 to 0.90)	NR
DeVecchis Wygant et al. [abstract] [22]	Mean (SE) SVR 12 wks daclatasvir/ asunaprevir ($n = 143$): CFB + 0.02 (0.01)	Mean (SE) No SVR 12 wks daclatasvir/ asunaprevir ($n = 143$): CFB − 0.12 (0.082)
Gschwantler et al. [abstract] [39]	Mean (SD) OBV/PTV/r ± DSV ± RBV 12 Wks ($n = 48$): 0.885 (0.121); CFB Wk 12 ($n = 143$): 0.006 (0.135)	
Kieran et al. [abstract] [41]	Mean Treatment experienced ($n = 48$): 0.74	
	Mean SVR attainment ($n = 48$): 0.81	Mean Non-SVR attainment ($n = 48$): 0.68 $p < 0.001$
Nouvertné et al. [abstract] [25]	Mean Triple therapy (PEG-IFN + RBV + PI) ($n = 123$): 0.91 Dual therapy (PEG-IFN + RBV) ($n = 187$): 0.90	
Nwankwo et al. [poster] [27]	Mean (SD) Treated, ≥ 1 comorbidity, SVR ($n =$ NR): 0.84 (0.13) ($p = 0.008$ vs. no SVR)	Mean (SD) Treated, ≥ 1 comorbidity, no SVR ($n =$ NR): 0.67 (0.29) ($p = 0.008$ vs. SVR)
Pol et al. [26]	Mean (SE) SVR, F0–F1 ($n = 35$): 0.95 (0.01) SVR, F2–F4 ($n = 36$): 0.85 (0.02)	NR
Samp et al. 2015 [20], Samp et al. [abstract] [19]	Mean Treatment completed ($n = 85$): 0.747 Treatment ongoing ($n = 95$): 0.782	
	Mean Treatment completed, SVR attained ($n = 36$): 0.873 ($p = 0.0035$ vs. no SVR)	Mean Treatment completed, SVR not attained ($n = 44$): 0.660 ($p = 0.0035$ vs. SVR)
Schafer et al. [28]	Mean HCV patients on IFN-α ($n = 122$): baseline: 0.72; follow-up: 0.72	
Schwarzinger et al. [abstract] [30]	Mean Treatment experienced ($n = 183$): 0.79	
Scott et al. [31]	Mean (SE) PILLAR SMV arm ($n = 309$): baseline: 0.9 (0.01); CFB Wk 24: − 0.14; CFB Wk 48: − 0.067 (95% CI − 0.111 to − 0.024) PILLAR PR arm ($n = 77$): baseline: 0.9 (0.03); CFB Wk 24: − 0.13; CFB Wk 48: − 0.119 (95% CI − 0.164 to − 0.075) Difference between HSUVs in treatment arms at week 48: 0.052 (95% CI − 0.011 to 0.114) ASPIRE SMV arm ($n = 396$): baseline: 0.9 (0.01); CFB Wk 24: − 0.13; CFB Wk 48: − 0.135 (95% CI − 0.187 to − 0.082) ASPIRE PR arm ($n = 66$): baseline 0.9 (0.02); CFB Wk 24: − 0.14; CFB Wk 48: − 0.155 (95% CI − 0.215 to − 0.095)	

Table 5 (continued)

Study	Treated patients	
	SVR attainment	Non-SVR attainment
Stepanova et al. [32], Younossi et al. [abstract] [33]	Mean (SD) POSITRON SOF + RBV arm ($n = 196$): baseline: 0.717 (0.214); end of treatment: 0.664 (0.212) POSITRON PBO arm ($n = 66$): baseline: 0.673 (0.227); end of treatment: 0.671 (0.238) FISSION SOF + RBV arm ($n = 105$): baseline: 0.740 (0.232); end of treatment: 0.737 (0.251) FISSION PEG-IFN + RBV arm ($n = 110$): baseline: 0.771 (0.236); end of treatment: 0.650 (0.224) FUSION SOF + RBV 16 wks arm ($n = 98$): baseline: 0.745 (0.211); end of treatment: 0.724 (0.225) FUSION SOF + RBV 12 wks arm ($n = 103$): baseline: 0.753 (0.231); end of treatment: 0.685 (0.225) NEUTRINO SOF + PEG-IFN + RBV ($n = 326$): baseline: 0.793 (0.219); end of treatment: 0.645 (0.213)	
Vargas et al. [34]	Mean (SE) SVR F0–F1 ($n = 5$): 1 (0) SVR F2–F3 ($n = 2$): 1 (0) SVR F4 ($n = 1$): 0.798 (± 30%)	NR
Vera-Llonch et al. [35]	Mean (95% CI) TVR 12 wks, PR 24 wks: baseline ($n = 203$): 0.92 (0.91 to 0.94); Wk4 ($n = 198$): 0.82 (0.80 to 0.84); Wk 12 ($n = 194$) 0.80 (0.77 to 0.82); Wk 24 ($n = 189$): 0.83 (0.81 to 0.85); Wk 36 ($n = 179$): 0.91 (0.89 to 0.93); Wk 48 ($n = 175$): 0.93 (0.92 to 0.95); Wk72 ($n = 171$): 0.94 (0.92 to 0.95) TVR 12 wks, PR 48 wks: baseline ($n = 144$): 0.90 (0.88 to 0.93); Wk 4 ($n = 122$): 0.81 (0.79 to 0.84); Wk 12 ($n = 115$): 0.78 (0.75 to 0.82); Wk 24 ($n = 109$): 0.81 (0.78 to 0.85); Wk 36 ($n = 112$): 0.85 (0.82 to 0.88); Wk 48 ($n = 114$): 0.83 (0.79 to 0.86); Wk72 ($n = 116$): 0.90 (0.88 to 0.93) PR 48 wks: baseline ($n = 346$): 0.91 (0.90 to 0.92); Wk 4 ($n = 334$) 0.84 (0.82 to 0.85); Wk 12 ($n = 328$): 0.82 (0.81 to 0.84); Wk 24 ($n = 313$): 0.80 (0.78 to 0.82); Wk 36 ($n = 296$): 0.83 (0.81 to 0.85); Wk 48 ($n = 278$): 0.84 (0.82 to 0.86); Wk 72 ($n = 296$): 0.89 (0.88 to 0.91)	
	Mean (95% CI) SVR 72 wks: 0.90 (0.88 to 0.92)	Mean (95% CI) No SVR 72 wks: 0.86 (0.83 to 0.88)
Wright et al. [37]	Mean (SD) IFN + RBV: baseline: 0.76 (0.19); end of follow-up: 0.77 (0.30) No treatment: baseline: 0.79 (0.19) ($p = 0.53$ vs. treatment group); end of follow-up: 0.76 (0.22) ($p = 0.73$ vs. treatment group)	
	Mean (SD) Treatment group with SVR: baseline: 0.80 (0.22); end of follow-up: 0.82 (0.21)	Mean (SD) Treatment group with no SVR: baseline: 0.75 (0.30); end of follow-up: 0.75 (0.34)
Wygant et al. [abstract] [42]	DCV + ASV SVR: Median (IQR) CFB Wk24 0.00 (0.00 to 0.00) $p = 0.38$ DCV + ASV SVR: Mean (SE) CFB Wk24 0.02 (0.01)	DCV + ASV no SVR: Median (IQR) CFB Wk24 0.00 (− 0.13 to 0.00) $p = 0.13$ DCV + ASV no SVR: Mean (SE) CFB Wk24 − 0.05 (0.03)
Yeung et al. [36]	Mean SVR (HCV/HIV co-infected patients): 0.88	Mean No SVR (HCV/HIV co-infected patients): 0.78

ASV asunaprevir, *CFB* change from baseline, *CI* confidence interval, *DCV* daclatasvir, *DSV* dasabuvir, *HCV* hepatitis C, *HIV* human immunodeficiency virus, *HSUV* health state utility values, *IFN* interferon, *IQR* interquartile range, *NR* not reported, *OBV* ombitasvir, *PBO* placebo, *PEG-IFN* pegylated interferon, *PI* protease inhibitor, *PR* peginterferon/ribavirin, *PTV* paritaprevir, *RBV* ribavirin, *SD* standard deviation, *SE* standard error, *SMV* simeprevir, *SOF* sofosbuvir, *SVR* sustained virologic response, *TVR* telaprevir, *Wk* week

Quality assessment

The overall quality of included studies was variable. Publications reported a wide variety of health states of interest to the review, many encompassing HCV-related liver conditions ($n = 10$) [17–20, 23, 26, 30, 34, 37, 41] or treatment statuses ($n = 20$) [17–20, 22, 25–28, 30–37, 39, 41, 42]. As HCV is a chronic disease, capturing an assortment of health states provided a good representation of HSUVs for a large proportion of the chronic hepatitis C-infected population. The quality of a small number of studies was limited due to small patient sizes for health states [17, 19, 20, 22, 26, 34, 42]. Additionally, a number of the studies did not specify the valuation method used

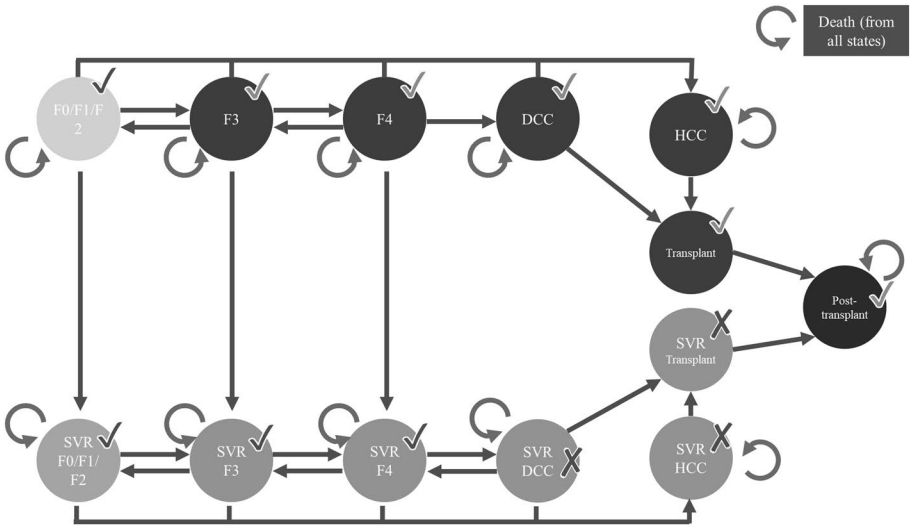

Fig. 2 Health states used in a typical HCV MARKOV model depicting the HCV patient pathway. Tick (✓) symbols represent health states for which HSUVs were identified in the review. Cross (✗) symbols represent health states for which no HSUVs were identified in the review. *DCC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *HCV* hepatitis C, *HSUV* health state utility value, *SVR* sustained virologic response

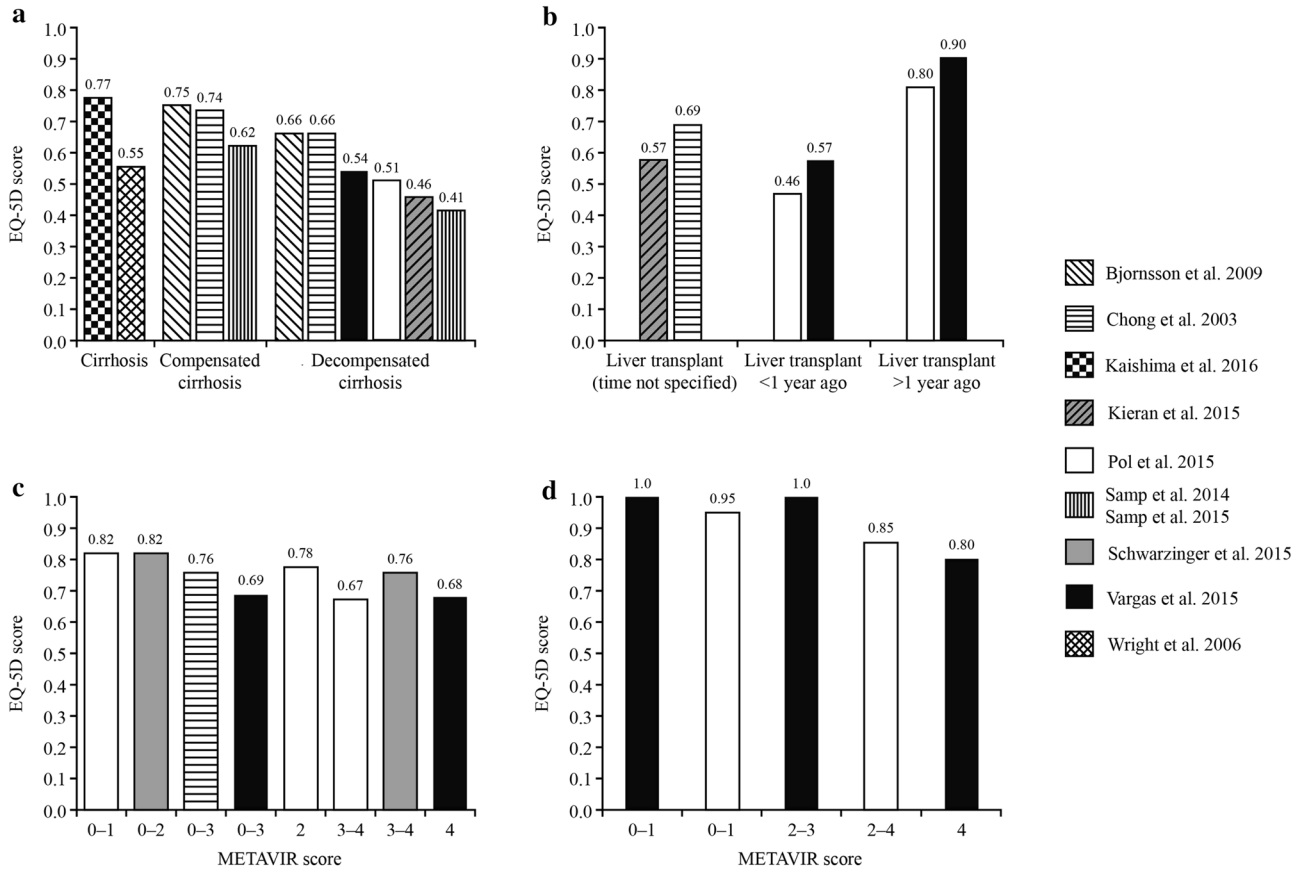

Fig. 3 EQ-5D scores reported for patients with **a** cirrhosis, **b** liver transplants, **c** fibrosis, **d** fibrosis with SVR. *EQ-5D* EuroQoL-5 dimensions, *SLR* systematic literature review

(e.g. time trade-off or standard gamble) to transform the generic EQ-5D responses to HSUVs [18, 21–23, 25, 27, 28, 30, 39–42]. Published literature suggests the choice of valuation method may impact the final HSUV [59]. Therefore, without this information it is difficult to consider the effects of the valuation method upon the resulting HSUVs.

	Decompensated cirrhosis			Compensated cirrhosis					
Study	Total	Mean	SD	Total	Mean	SD	MD	95% CI	Weight
Bjornsson 2009	53	0.656	0.2660000	76	0.749	0.2120000	-0.09	-0.18 to -0.01	71.8%
Chong 2003	9	0.660	0.3061224	24	0.740	0.2124557	-0.08	-0.30 to 0.14	11.3%
Samp 2015	11	0.405	0.2365089	18	0.622	0.2365089	-0.22	-0.39 to -0.04	16.9%
Fixed-effect model	**73**			**118**			**-0.11**	**-0.19 to -0.04**	**100.0%**
Heterogeneity: I^2=0%, T^2=0, p=0.45									

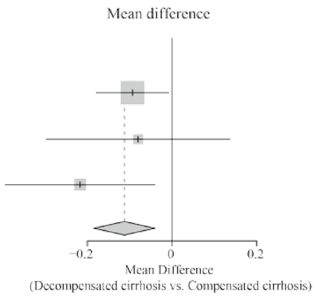

Fig. 4 Results of the meta-analysis assessing the mean difference in HSUVs comparing decompensated cirrhosis patients to compensated cirrhosis patients. Measures of variability (e.g. SE or SE) are presented alongside all EQ-5D results in Table 2. *CI* confidence interval, *EQ-5D* EuroQoL-5 dimensions, *HSUV* health state utility value, *MD* mean difference, *SD* standard deviation, *SE* standard error

Discussion

This SLR provides a comprehensive overview of the published literature investigating HSUVs, using the EQ-5D questionnaire, in chronic hepatitis C infection. Twenty-six publications and abstracts were identified, presenting a variety of health states encompassing chronic hepatitis C infection-related liver conditions and treatment status. The identified data demonstrate that patients with more severe liver conditions and those who did not achieve SVR tended to have lower HSUVs, implying poorer HRQoL. Whether different treatments have different impacts on HSUVs is unclear; there were no clear trends on the effects of different treatments on EQ-5D values across studies.

The results generally demonstrated that patient subgroups with more severe liver conditions, such as decompensated cirrhosis, advanced fibrosis or cirrhosis and patients who had not attained SVR, tended to have the lowest EQ-5D scores, thus implying poorer HRQoL. Achieving SVR was commonly associated with an improvement, irrespective of the fibrosis severity; patients attaining SVR generally had higher EQ-5D scores than those patients with similar fibrosis staging but who did not attain SVR. However, the comparisons between SVR and non-SVR at different METAVIR stages are limited due to the lack of data at comparable METAVIR stages. Therefore, these data must be interpreted carefully, taking into account the potential for bias.

The meta-analysis showed that patients with decompensated cirrhosis have statistically significantly lower HSUVs compared to patients with compensated cirrhosis. All studies utilised the same HRQoL questionnaire, the EQ-5D-3L. Since HRQoL questionnaires can consist of different questions and use alternative scoring systems, no bias attributable to choice of questionnaire was introduced. The low I^2 statistic suggested that there was little heterogeneity across studies. In addition, the baseline characteristics were generally similar and all three studies were conducted in developed countries, so there was no apparent heterogeneity in reported patient demographics. Finally, SDs for two of the three studies were approximated from CIs or pooled SDs. These approximated values may not be an accurate representation of the true SDs for each study, which could lead to poor estimation of the population variance.

When assessing the change in HSUVs from baseline until the end of treatment follow-up, Vera-Llonch et al. showed that whilst HSUVs initially decreased in three different DAA- and interferon-based treatment groups, after week 12 HSUVs began to steadily and consistently increase until the end of follow-up (week 72) [35]. This suggests that the effects of treatment on HRQoL should be assessed over longer time periods, rather than the commonly used 24- or 48-week follow-up. Extended follow-up periods could allow a more accurate assessment of the long-term benefits or, alternatively, adverse effects of different treatment regimens.

There was no clear trend in HSUVs when comparing interferon- to DAA-containing regimens. This lack of trend may be attributable to inter-study variability, such as patient demographics, treatment history, years since disease onset and presence of comorbidities, as well as sample size and length of follow-up. The time at which the studies were conducted may also be a factor; the older studies identified tended to report on interferon-based regimens, and the use of interferon-based regimens was limited to patients who were more likely to complete a full treatment course, such as those who were mentally stable or had fewer comorbidities, and could tolerate the side effects. Further evidence is required to distinguish how DAAs and interferon-containing regimens affect HSUVs differently.

The range of health states identified enables distinction between HSUVs reported for different patient groups and will therefore be useful for future studies that aim to improve HRQoL in specific patient subgroups. This will be of particular importance for patient subgroups deemed to experience the lowest HRQoL, such as those with advanced liver

conditions like decompensated cirrhosis. The range of health states will also be useful for those developing cost–utility analyses; HSUVs were identified for most health states commonly included in a typical cost–utility model (Fig. 2) and are therefore extremely relevant to any HTAs or economic evaluations in the area of chronic hepatitis C infection, due to the chronic and progressive nature of the disease. Obtaining HSUVs for a variety of DAA treatment regimens is likely to be of importance for future HTAs in which DAAs are expected to be comparators.

The strengths of this review include the size of the evidence base, consisting of 26 studies that were identified using rigorous methodology such as formal database searches, hand-searching the reference lists of all highly relevant systematic reviews, meta-analyses, economic evaluations and HTAs, and additional hand-searches of congress abstract books and the EQ-5D online database. This stringent search method ensured the literature was thoroughly and reliably searched.

It is important that the limitations of this SLR are also considered. Articles that were not published in the English language were excluded, so any relevant data reported in non-English language articles will not have been captured in this review. Secondly, HRQoL outcomes are often included as secondary endpoints in clinical trials. Therefore, relevant articles may not have been identified in the searches or may have been excluded during the abstract review if HRQoL outcomes were omitted from the abstract. However, full-text articles were always reviewed when there was uncertainty about the abstract reporting HRQoL outcomes to ensure relevant articles were captured. Additionally, inter-study variability existed between studies reporting the same or similar health states. The EQ-5D valuation method was not specified by all studies and, when reported, different valuation methods were used by the included studies, such as country-specific tariffs (Table 1). Therefore, the choice of HSUVs for health states included in cost–utility analyses should be carefully considered and kept in mind during the interpretation and comparison of EQ-5D values across studies. Finally, whilst the EQ-5D is often used to elicit HSUVs, other measurement scales, such as the Short Form 6D (SF-6D), do exist and may capture aspects of patients' emotional, social and physical wellbeing that the EQ-5D does not. The EQ-5D is not disease specific and may lack sensitivity to capture some important aspects of hepatitis C, such as the impact of side effects following treatment.

The cross-sectional nature or relatively short follow-up periods of many studies may not accurately reflect the real-life burden of chronic hepatitis C infection on patients. Although the studies in this review generally report large cohort sizes, patient subgroups were small for a number of specific health states and this may have affected the accuracy and generalisability of these results. Furthermore, there was uncertainty about the size of the cohorts versus the size of the population that responded to the EQ-5D questionnaire, which may also have affected the accuracy and generalisability of the reported results of some studies.

This SLR synthesises EQ-5D HSUVs for patients with chronic hepatitis C infection at various points of disease progression and treatment. Future studies should consider using a larger number of patients within particular subgroups of interest and measuring HSUVs for a range of health states. Additionally, studies should assess HRQoL for treatments over longer follow-up periods in order to determine the long-term effects of chronic hepatitis C infection and treatment, particularly due to the recent advancements in novel DAAs. This is important for studies aiming to investigate whether HRQoL can be improved in the long-term, after treatment with novel DAA regimens.

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Compliance with ethical standards

Conflict of interest ABH, KH, BL and LE are employees of Costello Medical Consulting Ltd. David Slater was an employee at Costello Medical Consulting Ltd. at the time the SLR was conducted. MB has received research grants from Gilead, Merck Sharp & Dohme and AbbVie. MW has received speaker honoraria and participated in advisory boards for Gilead, AbbVie and Merck Sharp & Dohme.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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