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REVIEW

Value of Treating All Stages of Chronic Hepatitis C: A Comprehensive Review of Clinical and Economic Evidence

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ABSTRACT

Introduction: The goal of chronic hepatitis C (CHC) treatment is to achieve a sustained virologic response (SVR). The new generation of direct-acting antivirals (DAAs) offers 90–100% SVR rates. However, access to these treatments is generally limited to patients with advanced liver disease. The aim of this review is to provide an overview of the clinical and economic benefits of achieving SVR and to better understand the full value of CHC treatment in all stages of liver disease.

Methods: A comprehensive literature review was performed using the PubMed, Embase, and Cochrane library databases to identify articles examining the clinical, economic, and quality of life benefits associated with SVR. Articles were limited to those published in English language from January 2006 through January 2016. Inclusion criteria were (1) patients with CHC, (2) retrospective and prospective studies, (3) reporting of mortality, liver morbidity, extrahepatic manifestations (EHMs), and economic outcomes and, (4) availability of an abstract or full-text publication.

Results: Overall this review identified 354 studies involving more than 500,000 CHC patients worldwide. Evidence from 38 studies ($n = 73,861$) shows a significant mortality benefit of achieving SVR in patients with all stages of fibrosis. Long-term studies with follow-up of 5–12 years suggest that, particularly among non-cirrhotic patients, there is a significant decrease in mortality in SVR versus non-SVR groups. Ninety-nine studies conducted in 235,891 CHC patients in all stages of fibrosis show that SVR reduces liver-related mortality, incidence of hepatocellular carcinoma (HCC), and decompensation. A total of 233 studies show that chronic HCV

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infection is associated with several serious EHMs, some of which can have high mortality. Evidence from four modeling studies shows that delaying treatment to CHC patient populations could significantly increase mortality, morbidity, and medical costs.

Conclusions: There is a robust body of evidence demonstrating diverse sources of value from achieving SVR in all stages of liver disease. While access to treatment is generally limited to late-stage patients, less restrictive treatment strategies that target HCV eradication have the potential to abate the burdens of mortality, liver morbidity and extrahepatic manifestations, and the associated healthcare costs.

Keywords: Clinical/economic burden; Extrahepatic manifestations; Hepatitis C virus; Liver mortality/morbidity; Sustained virologic response

INTRODUCTION

Hepatitis C virus (HCV) infection represents a significant public health burden, with at least 150 million individuals chronically infected worldwide [1]. The goal of chronic hepatitis C (CHC) treatment is to achieve a sustained virologic response (SVR), which represents HCV clearance to undetectable levels and is considered a "virologic cure" [2]. Until 2011 the only available treatment was based on the combination of pegylated interferon and ribavirin (PEG/RBV). However, in genotypes 1 and 4 the rates of SVR were less than 50%. In 2011 protease inhibitors in combination with PEG/RBV were approved for treatment of genotype 1. While the SVR rates improved to 75–80%, those treatments were associated with high toxicity and poor safety profile [3]. Novel, interferon (INF)-free direct-acting antiviral (DAA) therapies have demonstrated SVR rates of 90–100% and high tolerability in clinical trials [3, 4]. However, access to these agents is generally limited to patients with late-stage disease [5–7]. As such, it is important to offer a perspective on the consequences of this missed treatment opportunity in a broad range of patients.

This literature review was conducted with the objective of providing a comprehensive review of evidence demonstrating the value of achieving SVR at all stages of liver disease, focusing on four topics: (1) all-cause and liver-related mortality, (2) liver-related morbidity, (3) extrahepatic manifestations (EHMs), and (4) economic impact. The underlying hypothesis is that if HCV affects liver morbidity and EHMs, it should also impact liver-related and all-cause mortality and, ultimately, increase the economic burden of healthcare spending.

METHODS

The feasibility of conducting an original global systematic review was assessed using criteria from the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [8] for the last 10 years. Preliminary searches revealed more than 400 references that potentially met our inclusion criteria (described below). Within these publications, search was further limited to review articles and meta-analyses published between 2006 and January 2016 as well as updates since the last publication date of a review or meta-analysis. However, for the section on EHMs there were no systematic reviews that addressed a comprehensive list of EHMs. Hence, we pooled the references from two recent review articles [9, 10] and conducted additional searches for

any recent publications related to the EHMs associated with CHC treatment.

Searches were conducted using the Embase, PubMed, and Cochrane library databases, as well as a review of conference abstracts and general web searches. Inclusion criteria were (1) patients with CHC (excluding special populations such as liver transplant recipients, HIV-HCV co-infected patients, and recurrent or acute HCV cases), (2) retrospective and prospective studies (excluding case report studies), (3) reporting of mortality, liver morbidity, EHM, and economic outcomes, and (4) availability of an abstract or full text from the study publication.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Our search results are summarized in Fig. 1. For the first topic we identified a 2015 meta-analysis on the survival benefit of SVR. This paper evaluated 31 studies published between 1990 and November 2014 [11]. We then conducted an additional search to include all articles published between December 2014 and January 2016. This identified seven new studies on the impact of SVR on survival or mortality (Table S1).

For the topic on liver morbidity, our search identified one systematic review from 2011 of 67 studies [12] and one meta-analysis from 2010 of 26 studies [13]. During our search for publications from 2010 to January 2016, we identified six new studies (Table S2).

Our literature search did not find systematic reviews or meta-analyses that addressed all major types of extrahepatic manifestations identified in the literature. However, we identified and summarized one meta-analysis on the prevalence of a few select EHMs [14], and located multiple commentary-style reviews, which collectively summarized between 150 and 250 studies. We also leveraged two recent reviews [9, 10] and pooled their references into one database, with a total of 350 references. This database was manually screened and prioritized for high-quality evidence based on study type (prospective versus retrospective) and size (Table S4). We identified seven epidemiological studies on several types of EHMs and 12 publications that studied the impact of SVR on EHMs (Table S5).

Lastly, on the topic of economic value, our search identified four studies on different strategies for treating HCV. We came across one systematic review on the methodology of cost-effectiveness analysis of antiviral therapy. We leveraged and updated that review to provide a summary of cost-effectiveness publications (Table S6). Overall, this review summarizes results from 354 studies conducted with more than 500,000 CHC patients worldwide. The studies in each section are summarized in a decreasing order of strength of evidence, meta-analysis followed by prospective and retrospective studies.

Survival Benefit of SVR

Our review shows that 38 studies with a total of 73,861 HCV patients have demonstrated significant improvement in long-term survival among patients who achieve an SVR versus those who do not. While this benefit is significant in all HCV patients, cirrhotic or non-cirrhotic, patients who achieve SVR at

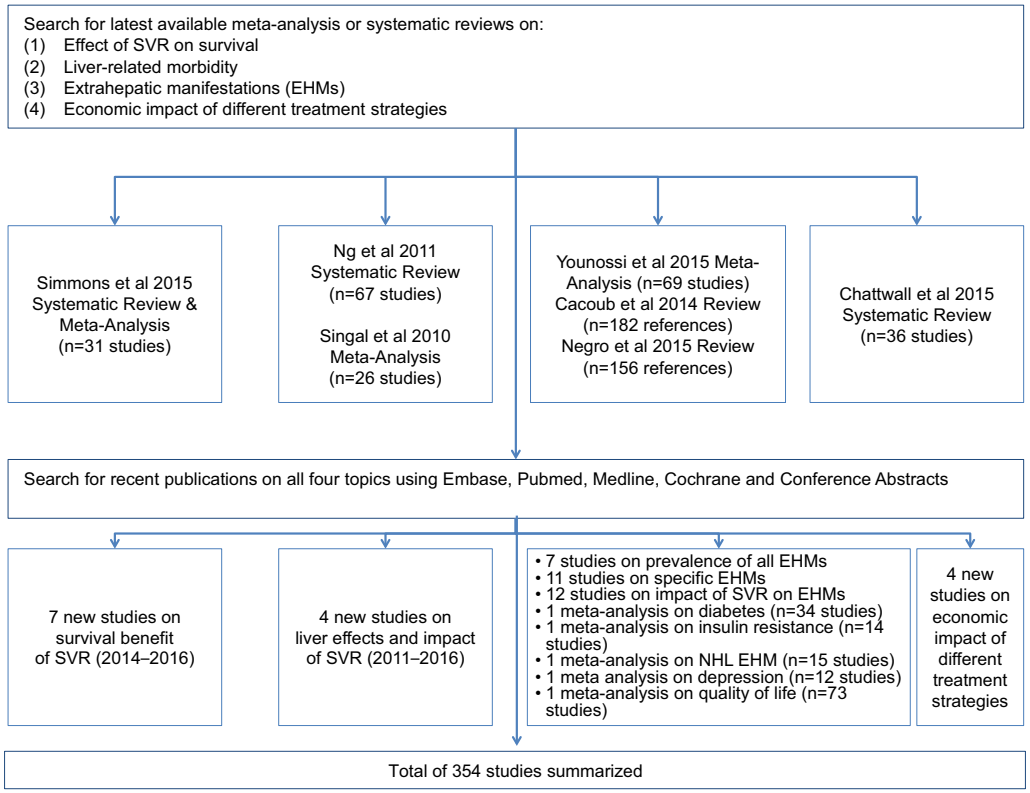

Fig. 1 Summary of search results

earlier disease stages have the lowest mortality risk.

A meta-analysis of 31 studies ($n = 33{,}360$ and median follow-up of 5.4 years) conducted between 2001 and 2014 found that there is a significant survival benefit of achieving an SVR compared with unsuccessful treatment in a broad range of populations infected with HCV. The general population group (monoinfected patients at all disease stages) included 17 studies ($n = 28{,}451$), with approximately 33% of the patients with F1 stage of liver fibrosis. The cirrhotic patient group included nine studies ($n = 2886$) with 100% of the patients in F3 stage or higher. In this meta-analysis, the adjusted hazard ratio (aHR) of all-cause mortality for HCV patients achieving SVR vs non-SVR was 0.50 (95% CI 0.37–0.67) in the general population and 0.26 (95% CI 0.18–0.74) in the cirrhotic group. The pooled 5-year mortality rates were significantly lower for patients achieving SVR compared with non-SVR in all three populations. The authors concluded that after adjusting for potential confounding factors, an SVR was associated with approximately a 50% and 74% decreased risk of all-cause mortality compared with not achieving an SVR in the general and cirrhotic populations, respectively [11].

A 12-year follow-up study was conducted with 24,968 HCV patients from the Kaiser Permanente integrated healthcare system in the USA. In this study, mortality was markedly higher in patients with cirrhosis who did not achieve SVR (23.7%) vs cirrhotics who did achieve SVR (8.1%), nearly a threefold increase ($p < 0.0001$). Among non-cirrhotics, there was a 2.5-fold increase in mortality in those who did

not achieve SVR (5.3%) compared to those who achieved SVR (2.1%). Importantly, patients who achieved SVR with cirrhosis had nearly four times higher mortality risk than patients who achieved SVR without cirrhosis [15].

Another large observational study with 9143 patients (moderate to advanced fibrosis) with a median follow-up of 6.4 years in four US health systems found that successful treatment leading to SVR significantly reduced mortality (aHR 0.40, 95% CI 0.28–0.56) compared to no treatment [16].

In France access to antiviral therapy is generally limited only to moderate-to-advanced fibrosis stage patients. To highlight the high incidence of mortality and morbidity in early Metavir fibrosis stage patients (F0 and F1) Jeźequel et al. conducted a follow-up study with 820 patients. After a median follow-up of 4.6 years, an increased fibrosis stage to F3 or F4 was observed in 15.3% of F0–F1 patients and 48% of F2 patients. In addition, 46.7% of F3 patients progressed to F4. After a median follow-up of 11.9 years, 248 patients died (16.7%), more frequently in fibrosis stages F2–F4 (24.4%) than in F0–F1 (11.5%) ($p < 0.05$). Median survival at 5, 10, and 15 years after the first liver biopsy was 97.4, 93.1, and 87% in F0–F1 patients and 93.2, 83.4, and 65.4% in F2–F4 patients. Survival was higher in treated patients with SVR than in untreated patients or treatment failures regardless of fibrosis stage ($p < 0.01$) [17, 18].

Propensity score analysis of 2743 Japanese patients followed for more than 10 years (range 10.5–14.2 years) showed that the eradication of HCV (defined as achieving SVR) significantly reduced all-cause mortality (HR 0.265; 95% CI 0.06–0.38), including non-liver-related mortality (HR 0.439; 95% CI 0.23–0.83), compared to no treatment [19]. Another Japanese study of 1125 elderly HCV patients used propensity-score-adjusted Cox proportional analysis to show that achieving an SVR significantly reduced total mortality risk (HR 0.077, CI 0.011–0.550; $p = 0.011$), compared to no SVR or no treatment [20].

A retrospective analysis of 427 French HCV patients with advanced liver disease found that the risk of death or liver transplantation was significantly lower in SVR than in non-SVR patients and in non-SVR than in untreated patients (hazard ratios, 0.35 and 0.51, respectively; $p < 0.05$), suggesting that even unsuccessful treatment may convey survival benefits [21]. In a long-term retrospective study of 714 Austrian HCV patients with advanced liver disease, the 5- and 10-year mortality rates were 1.8% and 2.7% in the SVR group and 8.6% and 19.1% among non-SVR patients, respectively ($p < 0.001$) [22].

Liver-Related Morbidity

According to the National Institute of Health Consensus, the most important sequelae of chronic HCV infection are progressive liver fibrosis leading to cirrhosis (compensated-CC or decompensated-DCC), end-stage liver disease, and hepatocellular carcinoma (HCC) [23]. In our review we found one systematic review of 67 studies, one meta-analysis of 26 studies, and six recent studies showing strong evidence for high burden of liver-related complications in CHC patients in all stages of fibrosis. These publications cumulatively provide long-term follow-up evidence from 235,891 CHC patients.

A systematic review of 67 studies ($n = 17{,}025$) published during 1991 and 2011 worldwide found that SVR reduced liver-related mortality among patients with CHC (3.3- to 25-fold), the incidence of HCC (1.7- to 4.2-fold), and hepatic decompensation (2.7- to 17.4-fold). The authors concluded that the benefits were

seen in patients with all stages of liver fibrosis, and the effects were significant even in advanced fibrosis stages [12].

A meta-analysis of 26 studies ($n = 15,621$) published during 1990 and 2008 found high rates of liver-related mortality (2.73% per year; 95% CI 1.38–4.080), HCC (3.22% per year, 95% CI 2.02–4.42), and hepatic decompensation (2.92% per year; 95% CI 1.61–4.22) among patients with advanced fibrosis who failed treatment. Patients with SVR are significantly less likely than patients who experienced treatment failure to develop liver-related mortality (relative risk [RR] 0.23; 95% CI 0.10–0.52), HCC (RR 0.21; 95% CI 0.16–0.27), or hepatic decompensation (RR 0.16; 95% CI 0.04–0.59). Among studies of patients with varying levels of fibrosis, the annual rates of decompensated cirrhosis, HCC, and/or liver-related mortality vary from 0.56 to 1.39%. This meta-analysis included 20 studies with patients all stages of fibrosis and five studies with patients in F3 or F4 fibrosis [13].

In a French prospective cohort study of 1323 HCV patients with compensated cirrhosis treated with DAAs, there was a three- to five-fold reduction in critical events, liver-related or not, among patients achieving SVR, which led to improved overall and liver-related survival. Furthermore, SVR was an independent factor associated with a decreased incidence of HCC (5 years cumulative incidence: 3.3% vs. 21.8%, HR 0.21 [0.13–0.36], $p < 0.001$) and hepatic decompensation (5 years cumulative incidence: 4.2% vs. 24.0%, HR 0.17 [0.10–0.27], $p < 0.001$) [24].

In a long-term prospective study of up to 23 years with 194 cirrhotic Italian HCV patients, the rate of HCC was higher in patients without SVR compared to those with SVR: 2.7/100 person-years (95% CI 2.1–3.5) and 1.4/100 person-years (95% CI 0.7–2.7), respectively [$p = 0.02$, HR (95% CI) 0.42 (0.20–0.89)]. Using multivariate analysis the authors also found that SVR was not associated with risk reduction of HCC development if cirrhosis has already occurred. On the basis of these results, the authors of this study suggested that effective antiviral treatment should be recommended at early disease stages [25].

In a long-term prospective study with 351 HCV patients in Sweden (most patients were treated with PEG/RBV), the incidences of HCC, any liver complication, liver-related death, and overall death per 100 person-years were significantly lower in the time lived with SVR (1.0, 0.9, 0.7, and 1.9), compared to the time lived treated but without SVR (2.3, 3.2, 3.0, and 4.1) and the time lived without treatment (4.0, 4.9, 4.5, and 5.1) [26]. This supports the notion that CHC treatment mitigates the risk of liver morbidity, even when it is unsuccessful.

Tada et al.'s Japanese study ($n = 2743$) showed that the eradication of HCV (defined as achieving SVR) reduced the incidence of HCC (HR 0.275; 95% CI 0.156–0.448) [19]. Another Japanese study by Kobayashi et al. ($n = 1125$) showed that achieving an SVR significantly reduced HCC risk (HR 0.118, CI 0.029–0.476; $p = 0.003$), compared to no SVR or no treatment [20].

A large retrospective database study of US Veteran Affairs patients ($n = 187,860$) showed that initiating treatment before Fibrosis-4 score (FIB4) >1.00 reduced morbidity by 41% and death by 36% [27]. Similar results were observed in an insurance database study in Turkey showing that mortality (2.27% vs. 5.31%; $p < 0.001$) and HCC rates (0.69% vs. 1.96%; $p < 0.001$) were lower for treated patients compared to untreated patients [28].

Extrahepatic Manifestations (EHMs)

In addition to liver-related morbidity, chronic HCV infection is associated with changes in organ systems outside the liver, including metabolic, cardiovascular, and neurological systems, and with autoimmune and immune-mediated conditions such as mixed cryoglobulinemia (MC), thyroid disease, and glomerulonephritis. According to a recent review up to 74% of CHC patients suffer from EHMs [10]. There is a significant amount of evidence on prevalence and burden of EHMs in CHC. Recent reviews have included summaries from 150 to 250 studies. In this review we provide an overall summary from 233 studies on the epidemiology and value of SVR for reducing the risk of EHMs.

Studies Estimating Broad Prevalence of EHMs

A recent meta-analysis of 69 studies estimated the overall burden of seven EHMs due to HCV (Table S3). In this analysis the pooled prevalence estimate of MC ($n = 14$ studies) was 32% in the HCV group (95% CI 21–43%) and 3% (95% CI 0–8%) in the non-HCV group ($n = 3$ studies). The pooled prevalence of diabetes mellitus (DM) ($n = 16$ studies) among HCV patients was 15% (95% CI 13–18%) compared to 10% (95% CI 4–15%) in the non-HCV population. The pooled odds ratio (OR) of developing chronic kidney disease/end-stage renal disease (CKD/ESRD) in patients with HCV compared to the non-HCV group ($n = 11$ studies) was 1.29 (95% CI 1.13–1.45). The risk of lymphoma was 64% higher (OR 1.64; 95% CI 1.18–2.11) in patients with HCV compared to the non-HCV population. The pooled prevalence estimate of lichen planus among HCV ($n = 11$ studies) was 2.1% (95% CI 1.1–3.1%) while the prevalence in non-HCV ($n = 3$ studies) was 1.4% (95% CI 0–3.4%). The pooled prevalence of Sjögren's syndrome ($n = 6$ studies) was 1.11% (95% CI 0.17–0.53%) compared to 0.11% (95% CI 0.09–0.13%) in the non-HCV group ($n = 1$ study). The pooled prevalence of porphyria cutanea tarda (PCT) among HCV patients ($n = 5$) was 0.7% (95% CI 0.2–1.1%) whereas the prevalence in the non-HCV group ($n = 1$ study) was 0.06% (95% CI 0.05–0.07) [14].

Globally, a relatively significant prevalence of EHMs has been found in CHC patients in five retrospective studies conducted in Italy ($n = 440$), Poland ($n = 340$), China ($n = 297$), Romania ($n = 162$), and Turkey ($n = 62$) [29–33].

Studies on Specific EHMs

Mixed Cryoglobulinemia (MC)

Cacoub et al. suggests that the overall 5-year survival rate after the diagnosis of vasculitis ranges from 90 to 50%, in case of renal involvement [10]. In our review we found five studies with a total of 810 CHC patients which also show that HCV-related MC can lead to high mortality in some patients [34–38]. A study from Spain ($n = 279$) found that HCV-related cryoglobulinemia may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, central nervous system involvement) life-threatening organ damage. During mean follow-up of 14 months the mortality rate from these manifestations in the study group was between 20% and 80% [37]. In a long-term efficacy study in France ($n = 72$), it was shown that an early virologic response (odds ratio 3.53, 95% confidence interval [CI] 1.18–10.59) was independently associated with a complete clinical response of MC [38].

Non-Hodgkin's Lymphoma (NHL)

A large meta-analysis of 15 case–control studies and three prospective studies with a total number of 12,235 CHC patients estimated the pooled RR of NHL among HCV-positive individuals as 2.5 (95% CI 2.1–3.0) [39]. Another meta-analysis conducted primarily with Italian and Japanese studies including 4049 NHL patients and 1813,480 controls also found a strong positive association between anti-HCV seropositive test subjects and risk of NHL (OR for NHL was 5.70, 95% CI 4.09–7.96, $p < 0.001$) [40].

Type II Diabetes Mellitus (DM)

In a meta-analysis of 34 studies the pooled estimate indicated significant DM risk in HCV-infected cases in comparison to non-infected controls in both retrospective ($OR_{adjusted} = 1.68$, 95% CI 1.15–2.20) and prospective studies ($HR_{adjusted} = 1.67$, 95% CI 1.28–2.06) [41].

Insulin Resistance (IR)

In a retrospective study of the US National Health and Nutrition Examination Survey (NHANES) ($n = 173$) CHC was independently associated with the presence of IR [OR (95% CI) 2.06 (1.19–3.57)], DM [OR 2.31 (1.18–4.54)], and hypertension [OR 2.06 (1.30–3.24)] [42]. Recently, the evidence of IR in HCV patients was confirmed by a meta-analysis of 14 studies, involving 3659 patients. This analysis showed that the RR of IR among HCV subjects with advanced hepatic fibrosis (F3 and F4) was 1.63 [95% confidence interval (CI) 1.34–2.01], compared to patients with F0–F2 fibrosis [43].

In a recent review, Negro et al. suggested that the most compelling evidence that HCV causes IR is the observation that curing HCV with antiviral therapy results in reduced levels of IR, citing a Japanese study of 89 patients, which showed that clearance of HCV improves IR, beta-cell function, and hepatic IRS1/2 expression [9, 44].

Renal Insufficiency

In a retrospective study of patients in the US Veteran Affairs healthcare system ($n = 1928$ HCV antibody positive and $n = 23,854$ HCV antibody negative), after adjustment for age, race, gender, diabetes, and hypertension, HCV-positive veterans had a 40% higher odds for renal insufficiency (odds ratio 1.40; 95% CI 1.11–1.76) as compared with HCV-negative veterans [45].

A large-scale community study ($n = 54,966$) on the effect of viral hepatitis (HCV or HBV) on nephropathy in Taiwan found that HCV infection alone (OR 1.26; 95% CI 1.17–1.38) was an independent risk factor for CKD, but not HBV infection alone or HBV/HCV coinfection [46].

Cardiovascular Disorders

A meta-analysis of six studies showed a strong link between HCV and risk of stroke, with 22,171 HCV-infected individuals and 87,418 controls, and an estimated pooled OR of 1.58 (0.86, 2.30) [47]. Similarly, high risk of stroke was observed in a large retrospective database study in Taiwan ($n = 4084$ HCV and $n = 16,376$ controls), with a cumulative risk of stroke for people with and without HCV of 2.5% and 1.9%, respectively ($p < 0.0001$). Compared to people without HCV, the adjusted HR of stroke was 1.27 (95% CI 1.14–1.41) for people with HCV [48].

A strong link between HCV and coronary artery disease (CAD) was observed in a large database study of US Veteran Affairs patients ($n = 82,083$ HCV-infected and $n = 89,582$ HCV-uninfected). The study showed that HCV infection was associated with a higher risk of CAD (HR 1.25; 95% CI 1.20–1.30) [49].

Depression

A meta-analysis including 12 studies ($n = 130,039$ in 5 cross-sectional, 3 longitudinal, 3 prospective, and 1 retrospective chart review) estimated the pooled prevalence of depression among HCV patients at 24.5% (95% CI 14.1–34.9%) [50]. This rate of depression is almost 20% higher than the rate of depression in the general population.

Quality of Life

A systematic review of 73 studies ($n = 130,039$) concluded that HCV has a negative impact on health-related quality of life (HRQL, 61 studies), fatigue (20 studies), and work productivity (3 studies) [51].

Studies on Value of Antiviral Therapy in Patients with HCV-Related EHMs

In our review we found 15 studies ($n = 12,974$), which have demonstrated value of antiviral therapy in lowering the burden of EHMs in CHC patients (Table S4). A prospective study of 424 CHC patients in Italy showed that in the majority of patients (36 patients, 57%) all mixed cryoglobulinemia syndrome (MCS) symptoms persistently disappeared after achieving SVR [52]. In a retrospective study of Japanese patients ($n = 3209$) the HR of lymphomagenesis in 1048 patients with SVR was significantly lower than in patients with persistent infection (hazard ratio 0.13; $p < 0.05$), demonstrating that SVR protects against the development of malignant lymphoma in patients with chronic HCV [53]. Another Japanese study of 2842 patients showed that SVR caused a two-thirds reduction in the risk of type 2 DM development in HCV-positive patients treated with antiviral therapy [54]. In a US randomized study of 1121 CHC patients, SVR was associated with improvement at follow-up on all Short-Form Health Survey (SF-36) and Functional Systems Scores (FSS) components [55]. SF-36 is a validated and commonly used questionnaire for assessing HRQOL; it has 36 measures with 8 subscales including physical functioning and vitality.

Economic Value of Treatment

The cost-effectiveness of antiviral therapy (including DAAs) has been demonstrated in 35 published studies, which include 30 Markov models, 2 micro simulations, 1 discrete event simulation, and 1 hybrid model (Table S6). Fifteen of the 35 analyses were conducted in the USA, 5 in Italy, 4 in the UK, and 3 in Spain. Cost-effectiveness of treatment for naïve and non-cirrhotic patients was specifically analyzed in 11 and 4 analyses, respectively. We conducted additional search for any cost-effectiveness analyses, economic impact, or database studies examining the impact of delaying or deferring antiviral treatment. Overall, these modeling analyses show that newer-generation treatments (e.g., INF-free DAAs) are more cost-effective than older (e.g., INF-based) regimens, and early treatment is cost-effective compared to treatment at late CHC stages.

A US decision analytic model analyzed the cost-effectiveness of six novel DAAs at different stages of fibrosis. Their analysis shows that treatment with DAA as early as stage F1 is cost-effective (incremental cost-effectiveness ratios [ICERs] of US$50,000–150,000 per quality-adjusted life year [QALY] gained) and less than US$50,000 per QALY gained when treatment is initiated at stage F2 vs stage F3 [56].

A Markov modeling analysis in the USA showed that treatment with a DAA at F2 rather than F3–F4 is projected to have even greater efficacy, decreasing the average number

of cases of DCC by 63.3%, HCC by 89.0%, liver transplants by 83.3%, and HCV-related deaths by 84.5% [57]. Similar results were observed for a model in the Spanish setting, which demonstrated that, compared to delayed administration of therapy at F4, initiating DAA treatment at early disease stages (F2–F3) reduced the incidence of new cases of liver-disease complications and was associated with cost savings for the Spanish National Health System in previously untreated genotype 1 HCV patients [58].

A natural history Markov model showed that initiation of treatment with DAAs at later stages of fibrosis resulted in greater average annual lifetime post-treatment costs and fewer life years compared to treatment initiation at earlier fibrosis stages; in particular, treatment-naïve patients treated in F0 stage had average annual medical costs of US$314 (US$228 discounted), whereas patients treated in F4 stage had over 10-fold greater annual medical costs (US$3187) [59].

A disease progression model estimated the cost-effectiveness of using PEG/RBV and/or PEG/RBV with protease inhibitors in 16 countries and showed that treatments with higher efficacy and increased uptake are needed to control HCV burden [60]. Bruggmann et al. developed a follow-up model to assess the impact of delaying treatment scenarios in Switzerland. The model showed that a 2-year delay in treatment could reduce the impact of disease burden control efforts by 10%, while a 5-year delay could reduce the impact by 30% [61]. The authors concluded that a substantial reduction in disease burden could be achieved by means of both higher efficacy drugs and increased treatment uptake, underscoring the importance of comprehensive treatment with INF-free DAA therapies [62].

DISCUSSION

In our review of the literature we found a large body of evidence demonstrating diverse sources of value for CHC patients achieving SVR in all stages of liver disease. Overall, this review summarizes results from 354 studies conducted in more than 500,000 patients. The summarized evidence confirms our hypothesis that HCV affects liver morbidity and EHMs, which leads to increased liver-related and all-cause mortality and high economic burden. The evidence also strongly demonstrates that achievement of SVR can increase survival, reduce liver and extrahepatic morbidity, and lower long-term costs. Even unsuccessful CHC treatment appears to have a protective effect against mortality and liver morbidity. Furthermore, treatment with newer-generation regimens (e.g., INF-free DAAs) is generally cost-effective compared to older (e.g., INF-based) regimens. Similarly, treatment in early fibrosis stages is cost-effective relative to late treatment.

Most notable is the evidence from 38 studies showing ($n = 73,861$) significant mortality benefit of SVR in patients with all stages of fibrosis. Ninety-nine studies conducted in 235,891 CHC patients in all stages of fibrosis have shown that SVR reduces liver-related mortality (3.3- to 25-fold), incidence of HCC (1.7- to 4.2-fold), and hepatic decompensation (2.7- to 17.4-fold) [12, 13]. Evidence from modeling studies confirms these results by showing that delaying treatment could significantly increase mortality, morbidity, and medical costs. Additionally, there are more than 200 studies which have shown that chronic HCV infection is associated with several serious EHMs, some of which can have high mortality [9, 10].

Despite a compelling and robust body of clinical and economic evidence, current access to DAAs has been limited largely to patients with advanced liver disease. This restriction on access is either due to a perception that patients in early stages of fibrosis can wait and/or due to the short-term costs of treating patients in all fibrosis stages. However, as this review shows, there is compelling clinical and economic evidence that treatment for patients in early and all stages of fibrosis improves survival, reduces liver-related and extrahepatic morbidity, and is cost-effective.

In spite of numerous challenges, some countries or regions have implemented comprehensive treatment strategies for CHC. In 2013, when INF-free DAAs were licensed, Georgia engaged partners to develop a national HCV prevention and control plan targeting the elimination of HCV transmission and disease [63]. Similarly, the Hepatitis Prevention, Control, and Elimination (HPCE) Program was officially launched in September 2014 to radically change the current state of viral hepatitis in Mongolia and significantly reduce the disproportionate and sustained burden of liver cirrhosis, liver cancer, and mortality [64]. In Egypt, the government has launched a comprehensive HCV treatment program with a goal to treat 300,000 people a year (WHO 2015). In these exemplary cases, a strong healthcare infrastructure and political will are crucial to battle HCV by implementing effective screening and treatment programs [65]. In Australia, the federal government has announced that it will subsidize new breakthrough HCV treatments to cure all patients [66]. The implementation and outcomes of these programs should be closely monitored as they could provide valuable real-world policy lessons for other regions. Recently, the French government announced plans to provide universal access to new HCV medications [67].

The demonstrated value of achieving SVR underscores the importance of comprehensive treatment strategies targeting all stages of liver disease and based on the most effective and tolerable class of DAA regimens. It should be further noted that the majority of the studies summarized here were conducted with INF-based antivirals which had relatively low cure rates and high toxicity. The new generation of DAAs offer 90–100% cure rates and have a significantly better safety profile, making the case even stronger to offer these treatment options to patients in all stages of liver disease [3].

There are some limitations of our review. As a result of the broad scope of the topic and robust body of evidence it was not possible to conduct a full systematic review. However, to provide a summary on relevant topics we leveraged the highest-quality evidence such as meta-analyses and systematic reviews. Additionally, our review focused only on the treatment for HCV. There are other areas such as disease awareness, diagnosis, and monitoring which also need policy interventions for developing successful and comprehensive HCV eradication plans.

Though this review demonstrates the need and value of treatment for all HCV patients, expansion of access should be considered within comprehensive plans aimed at the prevention, control, and eradication of HCV, taking into account the budgetary impact and health system infrastructure of each country. The design and implementation of healthcare solutions for effective CHC control remains a crucial topic of analysis in order to capture the full value of effective and comprehensive treatment opportunities.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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