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Abstract
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Reference

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The comprehensive outcomes of hepatitis C virus infection: A multi-faceted chronic disease

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Summary
Treatment of hepatitis C virus (HCV) infection has been revolutionized with the introduction of pangenotypic, interferon- and ribavirin-free regimens associated with high cure rates and a low side effect profile. Additionally, there is evidence that HCV cure reduces HCV complications, improves patient-reported outcomes and is cost-saving in most western countries in the long term. This is a review of the comprehensive burden of HCV and the value of eliminating HCV infection. With the introduction of the interferon-free all-oral, once a day pill treatment regimen for the cure of HCV, the potential to eliminate HCV by 2030 has become a possibility for some regions of the world. Nevertheless, there are barriers to screening, linkage to care, and treatment in many countries that must be overcome in order to reach this goal. In conclusion, globally, work must continue to ensure national policies are in place to support screening, linkage to care and affordable treatment in order to eliminate HCV.

KEYWORDS
clinical, economics, extrahepatic manifestations, patient-reported outcomes

Abbreviations: EHM, extrahepatic manifestations; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, health-related quality of life; LT, liver transplantation; MC, mixed cryoglobulinemia; NASH, non-alcoholic steatohepatitis; PROs, patient-reported outcomes; SF-36, Short Form-36.
1 | INTRODUCTION

Hepatitis C virus infection (HCV) affects 71.1 million persons globally which is equal to approximately 1.0% of the world population. Depending on the country, the prevalence of HCV infection may be concentrated in certain specific groups. In contrast, in other countries, the prevalence of HCV can be very high in the general population. Although the absolute number of HCV-infected individuals is high in Asia, the highest prevalence rates in the general population are reported from the Eastern Mediterranean and the European regions with prevalence rates of two·3% and 1.5%, respectively.

Hepatitis C virus infection is self-limiting in about 25% of patients whose HCV RNA in the serum becomes permanently undetectable after the initial infection. However, around 75% of the infected individuals do not clear the virus within 6 months after exposure, and develop chronic hepatitis which can then lead to end-stage liver disease. In fact, the risk of developing cirrhosis is between 10% and 30% within 20 years. Additionally, approximately 399 000 people die each year from hepatitis C, due mostly to cirrhosis and hepatocellular carcinoma (HCC).

Increasingly, chronic HCV infection is considered a systemic disease which negatively affects clinical, economic and patient-reported outcomes (PROs). Clinically, HCV-related cirrhosis can lead to several complications, including decompensated cirrhosis and HCC leading to increased mortality. Additionally, HCV infection impacts a number of organs outside the liver and is responsible for multiple extrahepatic manifestations. Finally, HCV infection can negatively impact PROs through the direct effects on the liver or by affecting extrahepatic organs. These hepatic and non-hepatic consequences of HCV infection are responsible for a tremendous burden on patients and the society. In this review, we provide the summary of a working group meeting which was sponsored by the Hepatitis B and C Public Policy Association held in Munich, Germany on 25 January 2018. The evidence gathered at this meeting was subsequently presented to the 2nd EU HCV Policy Summit “Securing sustainable funding for Hepatitis C Virus elimination plans” (http://www.hcvbrusselssummit.eu/) on 6 June 2018. Our aim is to emphasize the multifaceted nature of HCV infection, its impact on clinical, economic and PROs and the need for a multiprong approach to meet the goals of eliminating HCV by 2030.

2 | CLINICAL OUTCOMES OF HCV INFECTION—THE HEPATIC CONSEQUENCES

Hepatitis C virus infection is associated with chronic liver disease, cirrhosis, HCC and liver-related mortality. Among HCV-infected patients, 10%-30% will develop cirrhosis and 1%-5% will develop HCC over 20 years. However, the rate of progression of HCV-related liver disease can be influenced by many factors such as age at the time of infection, gender (male), ethnicity (African American), co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), and comorbid conditions such as alcohol abuse, immunosuppression, insulin resistance and superimposed non-alcoholic steatohepatitis (NASH), haemochromatosis or schistosomiasis.

Geographical location may also play a role in disease progression. In the United States (U.S.) and Europe, the rate of progression to cirrhosis ranges between 8% and 24% over a time span of 20-30 years, leading to an annual HCC development rate between 1% and 4%. However, in Japan, the rate of progression to cirrhosis is higher ranging between 30% and 46% with an annual rate of progression to HCC ranging between 5% and 7%.

Hepatitis C virus-related mortality is mainly attributed to HCC and complications of cirrhosis. In the United States, deaths associated with HCV are more likely to be caused from decompensated cirrhosis, while in Japan, the most common cause of HCV-related death is HCC.

It is important to note that development of gastro-esophageal varices and other decompensating events is associated with an additive increase in the risk for mortality. In fact, the cumulative probability of decompensation is 5% at year one, increasing to 30% at 10 years after diagnosing cirrhosis. Once decompensated cirrhosis occurs, 5-year survival of HCV patients is ≤50%. In contrast, 3, 5 and 10-year survival rates of compensated cirrhosis related to HCV are estimated to be 96%, 91% and 79%, respectively.

This high burden of HCV-liver disease globally has made HCV one of the leading indications for liver transplantation (LT). In one study from the United States, 52 540 or 41% of patients listed in 2010 was related to HCV-liver disease. Using birth cohorts, patients born in 1951-1955 accounted for the highest frequency of being listed for HCV. Additionally, there was a fourfold increase in new registrants with HCV and HCC which occurred between 2000 and 2010 in the 1941-1960 birth cohorts. It was concluded that there will be an increasing demand for LT as a result of HCV-HCC as these birth cohorts continue to age placing an increasing demand on a limited organ pool.

In addition, the presence or absence of viraemia affects mortality. Patients with detectable HCV antibodies and HCV RNA have almost eight times higher liver-related mortality rate than those with detectable antibodies and negative HCV RNA. Furthermore, all-cause mortality among HCV RNA-positive patients was more than double as compared to HCV RNA-negative cases, with mortality being higher for those who developed a non-liver-related disease in addition to being HCV RNA-positive.

These data suggest that HCV continues to pose a significant clinical burden related to cirrhosis, HCC, and as an indication for LT. These hepatic complications of HCV will continue to cause significant clinical burden in many countries in the next few decades.

3 | CLINICAL OUTCOMES OF HCV INFECTION—THE EXTRAHEPATIC CONSEQUENCES

There is strong evidence that HCV causes a number of important extrahepatic manifestations (EHM). A recent analysis found that the prevalence of auto-immune diseases in HCV-infected individuals.
included vasculitis (5%-15%), arthralgia-myalgia (25%) and sicca syndrome (10%-15%), while serum auto-antibodies were found in 10%-40%. In addition, about 15% of HCV-infected patients had symptomatic mixed cryoglobulinemia (MC) and 35% were at increased risk of developing lymphoma.21-22

In addition to these data, another systematic review and meta-analysis summarized the data on nine most common EHM-associated with HCV infection. These included MC, chronic kidney or end-stage renal disease, type 2 diabetes, B-cell lymphoma, lichen planus, Sjögren’s syndrome, porphyria cutanea tarda, rheumatoid-like arthritis and depression.23 Analysing 102 studies, the authors reported that type 2 diabetes (15%) and depression (25%) were the most common EHM of HCV. Furthermore, 4.9% of patients could develop symptomatic MC while 30% were found to have detectable cryoglobulinemia. In fact, HCV patients were at a 12-fold higher risk to develop MC than non-HCV patients. Also, HCV patients were found to have a 23% increased risk for developing a progressive kidney disease and/or end-stage kidney disease, a 23% increased risk for type 2 diabetes and a 60% increased risk for lymphoma. In addition to MC, HCV patients had a two times greater risk of developing lichen planus, Sjögren’s syndrome, rheumatoid-like arthritis and depression, while having eight times higher risk for developing porphyria cutanea tarda.23

Others have also quantified the impact of HCV infection on cardio- and cerebrovascular diseases. A recent meta-analysis determined that patients with HCV were 20% more likely to have cardiovascular disease and 35% more likely to have cerebrovascular disease when compared to those without HCV.24

In summary, both hepatic and extrahepatic consequences of HCV infection constitute important clinical outcomes that can affect patients’ mortality and morbidity.

4 | PATIENT-REPORTED OUTCOMES OF HCV INFECTION

Patient-reported outcomes are considered the surrogates for understanding the impact of a disease and its intervention on patients’ experience. Accordingly, health-related quality of life (HRQL), which is a type of PRO, is defined as “a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. HRQL goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life.”25

There is evidence that HCV patients have a diminished HRQL even before reaching advanced stages of liver disease. In fact, using a generic HRQL instrument (the Short Form-36 or SF-36), the decrement in HRQL scores of HCV-infected patients (compared to healthy controls) can range between -7% and -15-8% (Figure 1).26 These differences in HRQL scores are not only statistically significant but also clinically meaningful. It is important to note that the most important drivers of PRO and HRQL impairment in HCV are depression and other neuropsychiatric disorders.27

In addition to depression and neuropsychiatric disorders, fatigue is highly prevalent in HCV and has been assessed by fatigue-specific PRO measures.30,31 In one study that assessed predictors of depression in patients with different chronic liver diseases, fatigue was found to be a major predictor of depression in HCV-infected patients but not in those diagnosed with chronic hepatitis B or non-alcoholic liver disease.27 Another study reported that 61% of HCV-infected patients complained of overwhelming fatigue with fatigue having the strongest negative impact on patients’ HRQL.30 In addition to HRQL, work and activity impairments in HCV patients have been assessed using a self-administered questionnaire. Studies of HCV patients have suggested impairment in work productivity is found primarily in the presenteeism aspect of work productivity. In studies from the United States, absenteeism does not seem to be negatively impacted by HCV possibly since patients’ inability to work can mean the loss of associated health insurance and other benefits provided by their employer.28,29

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In addition to fatigue, other variables associated with impairment of PROs in HCV-infected patients are related to HCV viraemia, liver disease severity and the presence of co-morbidities. In this context, PRO impairment has been found to be associated with the presence of cirrhosis, type 2 diabetes mellitus, anxiety, depression, fatigue and co-infection with HIV.33-36 In fact, presence of clinically overt fatigue can cause 4.8%-12.8% decrease in HRQL scores, while depression can decrease HRQL by 7.0%-13.4%.28-32 On the other hand, when HCV is compared to other liver diseases, regardless of the aetiology of the liver disease, cirrhosis seems to have the greatest impact on PROs.33-36
However, HCV cure is associated with significant improvement in PROs. Following the development of new all-oral interferon-free direct acting antiviral regimens with high HCV cure rates, improvements in PROs after eradication of HCV were reported. 29,37-48,49 These findings were consistent across subgroup of HCV patients such as those on opioid substitution therapy, those who were co-infected with HIV, and across different regions of the world.50-52 Nevertheless, there are limited data from real world practices reporting PRO data outside clinical trials.53 Yet, as more HCV patients are treated and cured, further studies should be published using real world data to highlight the positive effects of the new all-oral interferon-free direct antiviral agents.

5 | HEALTH ECONOMICS OF HCV INFECTION

Health economics of HCV can provide different assessments related to the economic burden, cost-effectiveness, and budgetary impact of HCV infection and its treatment.54-62

The majority of studies on the HCV economic burden estimated the direct cost of liver disease [inpatient care, outpatient visits, prescription drugs, medical devices, rehabilitation costs and long-term nursing care] accounted for ~1/3 of the total economic burden of HCV, with the remaining 2/3rds attributable to indirect costs.55,56 In 2011 within the United States, the estimated average lifetime cost of HCV-related liver disease was $64 490 ($46 780-$73 190) per patient, yielding a total estimated cost of $6.5 billion (2011) projected to peak at $9.1 billion in 2024.57 Similar costs of HCV-liver disease in Europe have been reported.58 (Figure 2)

In addition to cost of HCV-liver disease, costs of EHM could add economic burden. The estimated total annual direct cost of the EHM of HCV infection in the United States (2014) was $1.505 billion (Figure 3).23 Another group reported the total annual costs associated with EHM of HCV infection. Investigators used rates from an international systematic literature review and meta-analysis applied to EU country-specific healthcare costs to report on the total costs of five EHM (type 2 diabetes mellitus, MC, myocardial infarction, ESRD and stroke) per country. The highest total costs were for Italy at €145 133 371 and the lowest were for the UK at €22 913 784 (Figure 4).63 In addition, the incremental annual non-healthcare costs of HCV in untreated patients compared with non-HCV patients were €4209 and ranged from €280 (UK) to €659 (France) in Europe.23,63,64

6 | INDIRECT COSTS RELATED TO PRODUCTIVITY LOSS DUE TO HCV INFECTION

In addition to the costs of clinical manifestation of HCV, the indirect economic burden due to worker productivity losses is important. The majority of HCV-infected persons of working age who are working have some degree of work impairment. However, the
employment rates among HCV-infected persons (U.S.) are low (54% vs 62% at the national level), but when employed, HCV-infected patients are more likely to incur increased rates of absenteeism (lost hours of work) and presenteeism (decreased productivity while at work). As a result, the estimated annual costs due to work productivity impairment as a result of HCV have been estimated to be $7.1 billion in the United States.\(^6\) In Europe, the annual cost of lost work has been projected to be 2.6 billion €, \(^23\)\(^30\) Lost work productivity costs have also been reported for Taiwan, South Korea, Hong Kong and Singapore to be $0.5 billion.\(^6\)

### 7 | THE VALUE OF ACHIEVING SUSTAINED VIROLOGIC RESPONSE AFTER TREATMENT OF HCV INFECTION

Since the approval of the new direct acting antiviral agents, the cost of these regimens has been debated despite the data showing high cure rates and excellent side effect profile.\(^6\)\(^7\)\(^9\) In order to fully appreciate the benefit of the new antiviral regimens for HCV, one must expand the debate beyond the “cost of the regimen” to include the “value of HCV cure.” The value of cure places the clinical and quality outcomes of HCV treatment in the context of the costs associated with delivering these outcomes. To address the value of HCV cure, a recent study used a model that combined clinical outcomes with quality of life and costs of treating HCV genotype (GT)-1 patients in the United States. In fact, the study concluded that treating these patients could potentially result in a “value” worth $111 billion. These cost savings were especially evident for the HCV GT1 patients with cirrhosis.\(^6\)

Others have also investigated the value of cure from different angles related to additional clinically relevant issues. Using a conservative model with 90% SVR-12 rates, treating patients without any fibrosis rather than waiting for fibrosis to progress was cost effective.\(^70\) In addition, a significant reduction in non-liver-related mortality can be observed in patients without fibrosis.\(^72\) Others have compared the new regimens to the older interferon-based regimens and documented significant economic gains by treating all HCV patients with the new regimens.\(^71\)\(^73\)

In addition to assessing the improvement in cost per quality-adjusted life (QALY) saved, it is also appropriate to assess the cost savings that could potentially be associated with HCV cure by assessing the reductions in complications such as HCC and decompensated liver disease. A recent study looked at the economic gains obtained when treatment leads to a reduction in cases of HCC and decompensated cirrhosis in Japan.\(^74\) Using a decision analytic Markov state-transition model, a hypothetical cohort of HCV GT 1b Japanese patients was treated with approved all-oral DAAAs. QALYs gained were also monetized using a willingness to pay threshold of 4-6 million Japanese Yen.\(^74\) The study documented significant cost savings related to avoidance of HCC and decompensated cirrhosis.\(^74\)

Another aspect of the comprehensive benefits of HCV cure must address the gains associated with the reduction in EHM and improvement in HRQL and work productivity loss due to HCV infection. In this context, achieving SVR with antiviral therapy has been shown to lead to a 61% reduction in the risk of stroke in HCV patients.\(^83\) Additionally, after 5 years of follow-up post-treatment, HCV patients who were cured experienced four times lower rates of cardiovascular events as compared to those who were not cured (3.5% vs 12.3%).\(^84\) Furthermore, there has been additional evidence supporting the positive impact of HCV cure in reducing chronic kidney disease and its associated costs.\(^85\) Similarly, there has been evidence supporting the benefits of HCV cure leading to better glycemic control in HCV-infected patients.\(^19\)\(^86\) These and other data suggest that treatment of HCV to achieve high SVR rates not only leads to improvement in clinical outcomes (cirrhosis and mortality) but also to substantial cost savings related to a reduction in both hepatic and extrahepatic complications of HCV infection.

In addition to the economic benefits related to the reduction in clinical complications of HCV infection, the monetary value of improvement of HRQL and work productivity after HCV cure are also substantial. Noted previously, HCV infection leads to impairment in work productivity.\(^87\)\(^88\) While older regimens containing interferon, temporarily reduced work productivity,\(^89\)\(^90\) regardless of treatment, achieving SVR led to improvement in work productivity.\(^91\)\(^92\) More recently, an analysis of a large cohort of HCV patients treated with new DAA regimens provided strong evidence that SVR was not only associated with improvement of HRQL but also substantial gains in the presenteeism aspect of work productivity, both potentially leading to economic gains.\(^92\)

In summary, it is clear that HCV is associated with high cost burden related to liver disease, EHM, quality of life impairment and worker productivity losses. In contrast, the cure of HCV can be associated with improvement of all these cost outcomes maximizing the value delivered by the new antiviral regimens.

### 8 | COMPARING COSTS ASSOCIATED WITH HCV TREATMENT WITH COSTS OF TREATING OTHER CHRONIC DISEASES

Investigators have also reported the cost of curing HCV in comparison with the costs of treating other chronic diseases. In 2013, the cost of cure for treating a patient with HCV GT1 was estimated to be between $82 000 and $91 000.\(^75\) This cost was substantially smaller than the per patient lifetime costs of treatment for type 2 diabetes mellitus ($109 000-$114 000), HIV ($268 000-$427 000), rheumatoid arthritis ($165 000-$187 000), breast cancer with metastases ($136 000) and relapsing/remitting multiple sclerosis ($433 000-$459 000).\(^75\) Since 2013, there have been significant reductions in the cost of HCV regimens due to market competition, discounts, use of generics and other contracting agreements which have made the cost of these regimens more favourable. Nevertheless, it is important to remember that the cost of treating HCV is upfront while the cost of other chronic diseases is spread overtime. This has important
budgetary impact for payers with short-term perspectives. However, the societal perspective with its long-term view must be adopted so national policies will support the initial investment for the long-term gains of reducing HCV-related complications and their associated costs.

9 ECONOMICS OF HCV SCREENING

If HCV cure is cost effective, then there must be a strategy to effectively screen for HCV and link the infected patients to care. Nevertheless, it is important to note that initiating a screening program is expensive and implementation can be complex. Several investigators have assessed the costs associated with effective screening programs for HCV. Although some have demonstrated that HCV screening the entire population (in comparison to screening the at-risk population) is cost effective, others have argued that the large-scale population-based screening can only be considered in the context of a national policy and registry. 76–82

10 CONCLUSIONS

Hepatitis C virus infection causes a “systemic disease” associated with adverse clinical, PRO and economic outcomes. Both the hepatic and EHM of HCV infection are costly and add substantially to the overall economic burden of HCV infection. Additionally, the economic burden of lost work productivity and impairment of HRQL can add an additional burden to the indirect and social costs of HCV infection. All these costs must be included to understand the comprehensive burden of HCV infection. 95,96

In the context of comprehensive burden of HCV, the value of antiviral regimens must not only consider the clinical improvement after SVR but also improvement in PROs and economic gains. Considering all these components, new antiviral regimens represent a good value to the society. Although cost of treatment regimens has important budgetary implications, long-term societal benefit of curing HCV is quite clear.

In the context of eliminating HCV by 2030, the most important challenges are to identify innovative and cost-effective approaches to optimize the continuum of care from screening and linkage to care. 95 This can be achieved by national, regional and global policies that will provide evidence about the comprehensive benefit of HCV cure, worldwide.

CONFLICT OF INTEREST

ZY, GP, PC, FN, HW and AH have all received research grants and or been consultants for Gilead Sciences; LH has no disclosures.

AUTHORS’ CONTRIBUTIONS

All authors contributed equally.

ETHICS COMMITTEE APPROVAL

This was a summary of published material and did not include any patient data so it is considered an exempt study under the Inova Health Care Systems IRB.

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