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The impact of hepatitis C burden: an evidence-based approach

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SUMMARY

Background
Infection with the hepatitis C virus (HCV) has been considered a major cause of mortality, morbidity and resource utilisation in the US. In addition, HCV is the main cause of hepatocellular cancer (HCC) in the US. Recent developments in the diagnosis and treatment of HCV, including new recommendations pertaining to screening for HCV by the Centers for Disease Control and Prevention and newer treatment regimens with high efficacy, short duration and the potential for interferon-free therapies, have energised the health care practitioners regarding HCV management.

Aim
To assess the full impact of HCV burden on clinical, economic and patient-reported outcomes.

Methods
An expert panel was convened to assess the full impact of HCV burden on a number of important outcomes using an evidence-based approach predicated on Grading of Recommendations Assessment, Development and Evaluation methodology. The literature was summarised, graded using an evidence-based approach and presented during the workshop. Workshop presentations were intended to review recent, relevant evidence-based literature and provide graded summary statements pertaining to HCV burden on topics including the relationships between HCV and the development of important outcomes.

Results
The associations of HCV with cirrhosis, HCC, liver-related mortality, type 2 diabetes mellitus, rheumatological diseases and quality of life impairments are supported by strong evidence. Also, there is strong evidence that sustained viral eradication of HCV can improve important outcomes such as mortality and quality of life.

Conclusions
The current evidence suggests that HCV has been associated with tremendous clinical, economic and quality of life burden.

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INTRODUCTION

In the US, hepatitis C virus (HCV)-associated disease has been considered the leading indication for liver transplantation and the leading cause of hepatocellular cancer (HCC).[1–4] In addition to liver disease, HCV infection is suspected to be associated with a number of extrahepatic manifestations.[5] Chronic hepatitis C and its sequelae are associated with increased cause-specific and overall mortality.[6–13] A recent Centers for Disease Control and Prevention (CDC) review of death certificate data found that the hepatitis C mortality rate increased substantially during 1999–2007. The authors found that 73.4% of the HCV-related deaths occurred among persons aged 45–64 years, with a median age of death of 57 years, which is approximately 20 years less than the average lifespan of persons living in the US.[14] Finally, HCV infection has been shown to impose a high economic burden on US health care systems, individuals and society.[15] In fact, recent simulation studies have estimated that the clinical and economic burden of HCV will continue to increase over the next two decades.[16–18] Despite this tremendous burden, the vast majority of HCV-infected patients remain undiagnosed and therefore not appropriately managed.[19] Because persons aged 45–64 years are found to have a disproportionately higher prevalence of HCV infection and related disease, the CDC has recently augmented previous recommendations for risk-based HCV testing[20] and now recommends one-time testing without prior ascertainment of HCV risk for persons born during 1945–1965.[21] In addition, the US Preventative Services Task Force (USPSTF) recently supported the CDC's position and granted a B recommendation for birth cohort screening.[22] USPSTF recommends HCV screening in persons at increased risk and one-time screening in adults born between 1945 and 1965.

Despite the daunting statistics surrounding HCV-associated disease, better treatment regimens are rapidly becoming available. The addition of direct-acting antiviral agents to the therapeutic armamentarium has generated excitement among health care practitioners. Furthermore, the long sought after interferon-free HCV regimens for all HCV genotypes are in development and on the horizon.[23] Given the new developments in HCV screening and new anti-viral regimens, it is increasingly important to assess the full impact of HCV burden in an evidence-based manner. Our aim was to present the summary of a Workshop from an Expert Panel who recently examined the literatures evaluating the total impact of HCV in an evidence-based approach.

METHODS

Hepatologists from the spectrum of practice with an expertise in evidence assessment were invited to participate. Each participant was provided an area of focus. To ensure consistent search criteria for the presentations developed specifically for this workshop, presenters were given the following literature search guidelines: literature searches should be (i) conducted using PubMed; (ii) limited to peer reviewed articles; (iii) focused on studies involving human data only; (iv) published in English; and (v) published from the year 2000 onward (unless it was considered a critical piece of evidence for the section). The inclusion of review articles, scientific abstracts and book chapters was discouraged. Additional studies were added through review of the bibliographies of identified publications. Search terms and inclusion/exclusion criteria were specialised for each presentation.

Quality of evidence

Workshop participants were also asked to characterise the quality of evidence supporting recommendations using a Class (reflecting benefit vs. risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation consistent with development of Practice Guidelines.[24, 25] Recommendations received a strength grade of Strong (1; factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes and cost) or Weak (2; variability in preferences and values, or more uncertainty [recommendation is made with less certainty, higher cost or resource consumption]). In addition, recommendations were graded based on quality of evidence as either High (A; further research is unlikely to change confidence in the estimate of the clinical effect), Moderate (B; further research may change confidence in the estimate of the clinical effect) or Low (C; further research is very likely to impact confidence on the estimate of clinical effect). This grading system was applied to all recommendations with the exception of recommendations pertaining to the economic burden of HCV infection, as there are no interventional studies with economic end points.

RESULTS

HCV and the development of cirrhosis

Several parameters may influence the development of cirrhosis among patients with chronic hepatitis C infection,

and the overall prevalence of cirrhotic disease remains uncertain. Because a confident diagnosis of cirrhosis requires invasive liver biopsy, there is the potential for an underestimation of the actual proportion of HCV patients with more advanced fibrosis. Factors that promote development of more advanced fibrosis have been carefully studied over the past two decades.

Using advanced computer software technology to construct a multicohort natural history model to project the future prevalence of chronic HCV, Davis *et al.*[16] showed that the prevalence of cirrhosis in HCV patients will steadily increase throughout the next decade, mostly affecting those >60 years of age, and that overall severity of fibrosis in the population with chronic HCV infection is shifting towards more severe grades. Similarly, in a study that calculated the annual prevalence of cirrhosis, decompensated cirrhosis and HCC among US veterans diagnosed with HCV, cirrhosis prevalence between 1996 and 2006 increased from 9% to 18.5%, decompensated cirrhosis prevalence doubled from 5% to 11%, and HCC prevalence increased approximately 20-fold from 0.07% to 1.3%.[26] A recent analysis of a large US private insurance database stratified by liver disease severity was defined by the International Classification of Diseases, 9th Revision, Clinical Modification codes and found that 78%, 7% and 15% of evaluable patients with chronic HCV (n = 53 796) had noncirrhotic liver disease, compensated cirrhosis and end-stage liver disease respectively.[18]

A 2008 systematic review attempted to provide increased precision in estimating fibrosis progression in chronic HCV. This meta-analysis and meta-regression study estimated stage-specific fibrosis progression rates in 33 121 individuals with chronic HCV, and detected a nonlinear course of disease progression. For all studies, the estimated prevalence of cirrhosis at 20 years after the infection was 16%, with cirrhosis prevalence varying according to study design. Duration of infection strongly and most consistently estimated disease progression. Factors including older age at infection, male gender, heavy alcohol use, human immunodeficiency virus (HIV) co-infection, study design factors, mode of acquisition and HCV G1 were found to be associated with fibrosis progression in the meta-regression.[27] HCV has been implicated in the induction of insulin resistance in a genotype-specific [HCV genotype 3 (HCV G3)] manner.[28] Insulin resistance, hyperinsulinaemia, diabetes and non-alcoholic fatty liver disease all contribute to fibrotic progression in patients with chronic HCV, irrespective of genotype.[29, 30] HCV G3 was associated with more rapid fibrosis progression in single-biopsy studies,[31] and additional data are needed to determine whether G3 disease progresses more rapidly than other genotypes.

Summary statements and grades of evidence

(i) The prevalence of HCV cirrhosis in the US population has increased over the past decade and will continue to increase over the next decade (1A).

(ii) Duration of infection and the metabolic syndrome are strongly correlated with HCV cirrhosis (1A).

(iii) Heavy alcohol use, HIV co-infection, male gender and age at/mode of acquisition correlate with development of HCV cirrhosis (2B).

HCV and hepatocellular carcinoma

The association between HCV and HCC will be summarised in three estimates: prevalence of HCV in HCC, relative risk and absolute risk. The prevalence rates of HCV in HCC range from 44% to 66% in Italy, 27% to 58% in France, 60% to 75% in Spain, 80% to 90% in Japan and 30% to 75% in the US.[30] The temporal changes in risk factors among patients with HCC have been documented and indicate that the proportion of HCV-related HCC increased from 11% between January 1993 and June 1996 to 21% between July 1996 and December 1999, whereas hepatitis B virus (HBV)-related HCC increased from 6% to 11% in those same time periods.[31] Risk factors for HCC in US patients have also been associated with ethnicity, such that anti-HCV positivity was the most frequent risk factor in both blacks and whites, and hepatitis B surface antigen positivity was the most frequent aetiological factor in Asians.[32]

Several studies have investigated the relative risk of HCC in patients with HCV. A meta-analysis of data from case–control studies published up to June 1997 indicated that anti-HCV antibodies or HCV RNA were associated with 8–34-fold increase in the odds ratio (OR) depending on the type of pooled analysis. In addition, a synergism was found between HBV and HCV infections, such that the OR (as high as 165) for co-infection was greater than the sum and lower than the product of those for each infection alone.[33] For example, results of a case–control study including data on 823 patients with HCC and 3459 cancer-free controls derived from the computerised database of the US Department of Veterans Affairs detected an increase in the adjusted OR for HCV of 17.27 and HBV of 9.22 after adjusting for the younger age of HCV- and HBV-infected cases and also revealed that the

combined presence of HCV and alcoholic cirrhosis further increased risk with an adjusted OR of 79.21.[34] Similar findings were obtained by a more recent meta-analysis of case–control studies conducted in China.[35]

Several longitudinal 'cohort' studies have examined the absolute risk of developing HCC in individuals with HCV and HCV-related cirrhosis. The results of a systematic review of 21 cohort studies revealed that the time to HCC in patients with HCV ranged between 17 and 31 years, the 30 year risk ranged between 0% and 3%, and the mode of acquisition associated with the highest risk was recipients of blood (1 per 1000).[36] In a review of longitudinal studies published in 2003, the HCC incidences per 1000 HCV patients were 0, 0.3 and 1.8 in one European study, one study from Taiwan and six Japanese studies respectively.[37]

Data from several countries including the US[38] indicate that most cases of HCC are associated with cirrhosis related to chronic HCV infection. As for the absolute risk of HCC in HCV-related cirrhosis, the results of a systematic review of 13 studies with data relating to 2386 patients estimated the annual rates of death/transplantation, decompensation and HCC in patients with compensated HCV cirrhosis to be 4.58%, 6.37% and 3.36% respectively.[39] Studies including patients who were treated for HCV reported significantly lower mean annual rates of HCC (2.52%) when compared with studies of untreated patients (4.79%).[39] In a review of longitudinal studies of absolute risk of HCC in HCV-related cirrhosis, the HCC incidences per 1000 HCV patients were 3.7 and 7.1 in 13 European and US studies and 7 Japanese studies respectively.[37]

In addition to the risk factors described above, the ORs of HCC are higher in subgroups such as men, the elderly, those with heavy alcohol consumption, diabetes and coinfection with HIV. Tobacco smoking may increase the risk further; a meta-analysis of 16 publications that evaluated the epidemiological interactions between HCV infection (and HBV) and HCC risk revealed more than multiplicative interaction between HCV infection and cigarette smoking,[40] whereas coffee may reduce the risk of HCC in HCV with or without cirrhosis.[41]

Summary statements and grades of evidence

(i) The prevalence of HCV infection in patients diagnosed with HCC ranges from 20% to 90% (1B).

(ii) The relative risk of HCC in HCV-infected individuals compared with uninfected controls is approximately 25-fold (1B).

(iii) The absolute risk of HCC in HCV-infected individuals is approximately 1 per 100 at 30 years (2A).

(iv) The absolute risk of HCC in HCV-related cirrhosis is approximately 3.5% per year [range 1–7%] (1B).

Liver-related mortality in individuals with HCV

Our review found nine cohort studies that compared liver-related (LR) mortality in patients with HCV with LR mortality in control groups.[6, 8–10, 42–46] In four studies, the control groups included patients who were exposed to HCV (anti-HCV+) but did not have chronic infection (HCV RNA−),[6, 8–10, 42] whereas remaining studies used subjects without HCV exposure as their controls. We also included three additional studies in our review that compared LR mortality of HCV subjects with the expected LR mortality in the reference population by calculating standardised mortality rates (SMR).[47–49] Most of the included studies used vital status (death certificate) data to ascertain LR mortality.

The magnitude of difference in LR mortality between HCV cases and controls varied based on the selection of the control groups in these studies; the differences were smaller for studies that used individuals who were exposed to but had recovered from HCV (i.e. anti-HCV positive but HCV RNA negative) as their control groups. Specifically, in a study by McMahon et.al, the age standardised mortality rates for HCV RNA-positive and -negative subjects were 7.14 and 5.33 per 1000 persons respectively. This difference was not statistically significant [hazard ratio (HR) = 1.42, 95% CI-0.71–3.11].[42] El-Kamary *et al.* found similar results in subjects who were enrolled in the NHANES III study.[10] LR mortality rates were 4.4/1000 person-year (95% CI: 1.5–12.9/1000 py) for those who were chronically infected (HCV RNA+) vs. 3.8/1000 person-year (95% CI: 1.5–9.7/1000 person-year) for those who were exposed (anti HCV+) but not chronically infected. However, in both studies, the rates of LR mortality in HCV-positive (HCV RNA+) subjects were substantially higher than LR mortality in the unexposed population [SMR = 16.68 (95% CI = 11.02–25.23) in the study by McMohan[42] and adjusted HR = 26.5, 95% CI = 8.00–87.5 in the report by El-Kamary].[10] In the two additional studies that compared LR mortality in individuals with chronic HCV vs. those who had recovered from HCV, LR was significantly higher in subjects with chronic HCV infection compared with those who cleared the virus.[6, 8]

Liver-related mortality was higher in cases than in controls in the studies that used subjects without HCV

exposure as their control groups. Based on the duration of follow-up, the LR mortality rates ranged from 6.1% to 9.7% in HCV subjects compared to 0.06% to 1.3% in controls. In studies that reported adjusted results,[6, 9, 42] the risk of LR mortality was consistently higher in patients with HCV as compared with controls (adjusted HR ranged from 10.0 to 16.6).

Similarly, in the three studies that only reported the SMR data, the rates of LR mortality rates were significantly higher than the expected mortality in the reference population (SMR ranged from 16.8 to 64.5).[47–49] However, subjects in these studies were relatively young (mean age 32–34 years at the onset of study follow-up). After an average follow-up of 5.3, 7 and 6.3 years, the rate of liver-related mortality was 0.6%, 1.4% and 2.5% respectively.

LR mortality was associated with patient age and duration of follow-up. Specifically, when LR mortality was stratified by mean age at notification, studies that included patients who were 35 years or younger had lower LR mortality rates (1–2.5%)[46–48] than studies including patients ≥35 years old (~8%).[6, 9, 10, 45] Furthermore, the risk of LR death in young patients remained relatively low and stable when viewed as a function of years of follow-up duration as compared with those including older patients. One of the reviewed studies showed that among patients with HCV, ~ 58% of deaths from all causes (i.e. overall mortality) were attributable to HCV, and almost all (96.2%) LR deaths were attributable to HCV.[10]

Summary statements and grades of evidence

(i) LR mortality is significantly higher in HCV-infected population than in the general population (1A).

(ii) LR mortality among persons infected with HCV at a young age is low (~2%) (1A).

(iii) LR mortality increases as the infected population ages (1A).

(iv) In chronically infected individuals, more than half of total deaths may be attributable to HCV infection (2B).

Extrahepatic manifestations of HCV: type 2 diabetes mellitus, rheumatic disorders and lymphoma

Data available prior to the year 2000 and therefore outside of the scope of this literature review established a strong association between having chronic HCV and type 2 diabetes mellitus (T2DM), non-Hodgkin's lymphoma and various extrahepatic rheumatological manifestations, including, but not limited to mixed cryoglobulinaemia, membrano-proliferative glomerulonephritis, arthralgias and fatigue. Several more recent studies have continued to examine the relationship between HCV infection and T2DM, rheumatic disorders and lymphoma. The results of a study of Taiwanese patients with HCV demonstrated a moderate level of association between HCV infection and T2DM, which was strongest among patients aged 35–49 years and increased with the severity of their liver condition.[50] In a US-based study, the prevalence of T2DM in patients with HCV (14.5%) was found to be significantly higher than in the general population (7.8%) or in a control population with cholestatic liver disease (7.3%).[51] In addition, glucose abnormalities (DM/impaired fasting glucose) were found to be significantly associated with advanced fibrosis.[51] The association between HCV and T2DM was also found to have a racial component, as one study found that although the prevalence of DM was similar in whites with or without HCV (13.2% and 11.9%, respectively), 33.3% of blacks with HCV had DM compared with 6.3% of blacks without HCV.[52] Another study detected an association between HCV, T2DM and risk for developing HCC, such that T2DM in HCV patients significantly increased the risk of developing HCC and that the risk of developing HCC decreased significantly when T2DM patients had better glucose control.[53] The effects of HCV treatment on glucose abnormalities have also been examined and the results of one study indicated that the incidence of glucose abnormalities was not significantly different between patients with a long-term virological response and nonresponders, suggesting that HCV clearance does not significantly reduce the risk of glucose intolerance.[54] The results of two treatment-based studies indicated that a sustained virological response resulted in reductions in the risk of T2DM development[55, 56]; however, results from one of these studies also indicated that altered glucose metabolism impaired sustained response to viral treatment.[55]

Regarding extrahepatic rheumatological findings, the results of two studies revealed increased ORs for developing extrahepatic rheumatological manifestations[57] or a high prevalence of extrahepatic rheumatological manifestations in patients with chronic HCV infection.[58] In one study, most of the extrahepatic rheumatological manifestations were associated with impaired lymphoproliferation and cryoglobulin production, and long-standing infection and extensive liver fibrosis were found to be significant risk factors.[58]

The data regarding the relationship between HCV and lymphoma are limited and inconsistent. One study found no increased risk of developing Hodgkin's lymphoma or Non-Hodgkin's lymphoma as a consequence of having HCV.[57] An additional study failed to find a clear association between anti-HCV antibody positivity and the risk of Non-Hodgkin's lymphoma or Hodgkin's lymphoma.[59] Two studies that examined B-cell Non-Hodgkin's lymphoma presented conflicting results, such that one study found a statistically significant association of HCV RNA with B-cell Non-Hodgkin's lymphoma,[60] and the other found no evidence of HCV RNA in serum samples of patients with Non-Hodgkin's lymphoma that later developed B-cell malignancy.[61]

Summary statements and grades of evidence

(i) Patients that are chronically infected with HCV are at higher risk of developing T2DM; as the patient gets older, this risk is blunted by other factors (1A).

(ii) Patients that have HCV and liver cirrhosis are at higher risk of developing T2DM (1B).

(iii) Patients that have HCV, diabetes and cirrhosis are at higher risk for liver cirrhosis outcomes, but do not have an increased risk for diabetes outcomes (1B).

(iv) Patients cured from chronic HCV are less likely to develop *de novo* T2DM than those who fail or do not receive therapy (1B).

(v) Patients with chronic HCV who also have T2DM respond less well to anti-HCV therapy with pegylated interferon and ribavirin (1A).

(vi) Data published from the year 2000 onwards confirm the increased prevalence of rheumatological extrahepatic manifestations in patients with chronic HCV (1A).

(vii) The association of chronic HCV infection and B-cell malignancies, specifically Non-Hodgkin's B-cell lymphoma, is marginal and heavily influenced by multiple factors (2C).

HCV-related cardiac disease and cardiac mortality

In the early 1970s, a theory referred to as the monoclonal hypothesis was proposed and asserted that infective agents could induce pro-inflammatory effects that played a crucial role in atherothrombosis. The hypothesis proposed that a virus-induced mutation triggered or a viral agent initiated events able to transform a single smooth muscle cell into a proliferative clone resulting in the formation of a plaque. Although limited data pertaining to the relationship between HCV infection and atherosclerosis were available to support the hypothesis, one study demonstrated that seropositivity for HCV was positively associated with carotid artery plaque and carotid intima–media thickening, independent from other risk factors for atherosclerosis.[62]

Over the past decade, a few additional studies have examined HCV-related cardiac disease and cardiac mortality. In a study that evaluated whether seropositivity for HCV was associated with the occurrence of coronary artery disease (CAD), HCV seropositivity was detected in 2% of control subjects and 6.3% of those with CAD with percentages increasing as a function of the number of vessels affected (4.5% for one vessel disease, 6.6% for two vessel disease and 8.4% for three vessel disease).[63] Furthermore, HCV seropositivity was found to be associated with the presence of CAD with an OR of 3.2 in a univariate logistic regression analysis and found to represent an independent predictor for CAD with an OR of 4.2 in a multivariate logistic regression analysis.[63] Another study assessed the prevalence of atherosclerosis and the role of HCV, cardio-metabolic risk factors and hepatic histology in liver biopsy-proven treatment naive patients with chronic HCV and age- and gender-matched controls, including healthy subjects without steatosis and with non-alcoholic fatty liver disease.[64] HCV infection was found to be a risk factor for earlier and facilitated occurrence of carotid atherosclerosis via viral load and steatosis and that these factors in turn modulated atherogenic factors such as inflammation and a dysmetabolic milieu.[64] A study designed to investigate the association of HCV infection with insulin resistance and atherosclerosis at the population level in an HCV hyperendaemic area classified inhabitants into three groups according to HCV infection status: uninfected, transiently infected and chronically infected.[65] Study results suggested that chronic HCV infection was associated with severe insulin resistance and with mild atherosclerosis.[65] Another study assessed the association of chronic HCV with risk factors for cardiovascular diseases using US population data and demonstrated that chronic HCV was independently associated with the presence of insulin resistance, DM and hypertension and independently associated with the congestive heart failure subtype of cardiovascular diseases, but not ischaemic heart disease and stroke in multivariate analyses.[12] An additional study evaluated the risk of HCV infection on hepatic and extrahepatic deaths and found that the cumulative risk of cerebrovascular deaths was lower (1.0%) for those seronegative for anti-HCV antibodies than for those who were seropositive (2.7%).[66]

Study findings also indicated that the HR of cerebrovascular death was 2.18 and that the multivariate-adjusted HRs were 1.40, 2.36 and 2.82 for anti-HCV-seropositive participants with undetectable, low and high serum levels of HCV RNA respectively.[66] In a more recent report from the same study sample, patients that were anti-HCV seropositive were found to have higher mortality from both hepatic and extrahepatic diseases, such that the multivariate-adjusted HR was 1.89 for all causes of death and 1.50 for cardiovascular diseases.[9] To examine whether HCV conferred additional CAD risk among HIV-infected individuals, a study was conducted using data collected on HIV and HCV status, risk factors for and the incidence of CAD, and mortality from January 2000 to July 2007 from participants enrolled in the Veterans Aging Cohort Study Virtual Cohort who participated in the 1999 Large Health Study of Veteran Enrollees.[67] Study results indicated that HIV+HCV+ participants had an increased risk of CAD compared with HIV+HCV− and HIV−HCV− participants.[67]

Based on the aforementioned studies indicating that HCV infection has been linked to an increased risk of insulin resistance and carotid atherosclerosis, one recent study investigated the association between HCV infection and stroke, and the effect of interferon-based therapy (IBT) on stroke risk in patients with chronic HCV.[67] Study results demonstrated that use of IBT significantly reduced stroke risk in patients with HCV (adjusted HR = 0.39) after adjusting for known prognostic factors.[68] In summary, the limited data presented above need to be replicated in larger studies. Therefore, the relationship between HCV and CAD remains unclear. In addition, further studies are needed to clearly define the association between HCV and cardiovascular disease. It is not clear at this time whether cardiovascular disease is associated with hepatic steatosis and insulin resistance that accompanies HCV infection or HCV infection *per se*.

Summary statements and grades of evidence

(i) Prospective studies have demonstrated that chronic HCV infection is associated with an increased mortality from cardiovascular disease. But, these data have not been consistently replicated (2B).

(ii) HCV has been associated with cerebrovascular death. However, these data need to be replicated (2B).

(iii) HCV may stimulate atherothrombosis by triggering a cascade of immune and inflammatory responses, either locally within vascular tissue or systematically through inflammatory mediators (2B).

HCV and liver transplantation

HCV is the leading diagnosis in patients undergoing liver transplantation.[69] In addition, recurrence of hepatitis is nearly 100% in patients who are viraemic at the time of transplantation.[70] Furthermore, fibrosing cholestatic hepatitis, which occurs in approximately 4% of patients following liver transplantation, is unique to patients who are immunosuppressed, and has been associated with rapid progression to cirrhosis and decompensation and uniformly poor outcomes.[71] In fact, several studies have demonstrated that fibrosis progression, median time to cirrhosis and the decompensation rate after development of cirrhosis in HCV-infected patients are accelerated following liver transplantation.[72–74] In addition, survival after decompensation and overall patient survival are reduced in HCV-infected patients following liver transplantation.[72, 75, 76] Although early single-centre studies with relatively short follow-up periods suggested that patients with HCV had similar outcomes to those without HCV, a review of the United Network for Organ Sharing (UNOS) Database from 1992 to 1998 revealed an increased rate of both graft loss and decreased patient survival in patients with HCV over a 5-year follow-up.[75] In a similar study, evaluation of the UNOS Database from 1991 to 2001 revealed decreased overall patient and graft survivals in patients with HCV despite an overall improvement in patient survivals in all patients from early to later periods.[77] In addition, unlike patients without HCV, graft and patient survivals for patients with HCV did not significantly improve over the time periods examined.[77] In fact, data from the Scientific Registry of Transplant Recipients for those patients transplanted in 2006 showed that overall graft survival was worse for HCV when compared with other diagnoses.[69] In a study utilising UNOS data during two time periods, 1992–1996 and 1997–2002, although graft survival appeared similar between the two periods, when grafts surviving >1 year were selected, findings showed a decrease in graft survival in the latter period.[78] Interestingly, when patients with HCV were isolated, graft survival was found to be significantly worse in later years as compared with the early time period, and even in patients with an alternate diagnosis but positive for HCV antibodies, outcomes were worse as compared with those without a diagnosis of HCV or positive testing.[78]

One of the most important factors that has been implicated in worse outcomes in patients with HCV includes donor age.[76, 79, 80] Likewise, several agents including bolus corticosteroids,[81] OKT3[82] and rapid tapering of steroids[83] have been correlated with worse outcomes. Although retransplantation is one means of treatment following recurrent disease and graft loss to HCV, outcomes with retransplantation due to recurrent HCV appear to be worse than for other diagnoses.[84, 85] However, one study found that outcomes were not significantly different for patients with HCV as compared with other patients undergoing retransplantation, although it should be noted that the study patients were highly selected and would have been considered low risk.[86] Several authors have confirmed that anti-viral treatment following liver transplantation for HCV results in both lower overall SVR rates and increased side effects as compared with treatment prior to transplantation.[87] It is also important to note that successful HCV treatment can improve survival in transplant patients with HCV reinfection. In one study of 61 treated patients, 28% achieved a sustained virological response and had a significantly lower mortality compared with patients with treatment failure.[88] In another study that compared 89 treated patients with 75 nontreated controls, patient survival at 7 years was higher in treated patients (74%) compared with controls (62%); 5-year survival was greater in treated patients that achieved a sustained virological response (93%) as compared with nonresponders (69%); and in patients without baseline cirrhosis, progression to cirrhosis occurred more frequently in nonresponders.[89]

Summary statements and grades of evidence

(i) HCV recurs following liver transplantation (1A).

(ii) Fibrosis progression in HCV-infected patients is accelerated following liver transplantation (1A).

(iii) Patient and graft survivals following liver transplantation in patients with HCV are inferior (1A).

(iv) Factors that contribute to more rapid progression include donor age and immunosuppression (1B).

(v) Active management of factors accelerating fibrosis may impact post-transplant outcomes (2B).

(vi) Successful HCV treatment response following liver transplantation improves survival (1B).

Overall mortality from chronic hepatitis C

The results of five of the identified publications supported the conclusion that chronic HCV did not affect the overall mortality of the patient populations studied.[43, 44, 90–92] In a study by Seeff *et al.*,[43] the authors concluded that the results of their long-term follow-up study indicated no increase in mortality from all causes after transfusion-associated non-A, non-B hepatitis; however, they did find a small but statistically significant increase in the number of deaths related to liver disease. In a follow-up study, the same research team reached similar conclusions in that the overall mortality of patients did not seem to be affected by HCV infection, but they remarked that many of the patients may not have been infected with HCV and that the overall mortality rate was higher for patients as compared with the general population.[90] One of the studies that did not detect a difference in all-cause mortality between those with and without HCV did find that among injection drug users with chronic HCV infection that survived until 50 years of age, HCV infection was the main cause of death.[91]

Conversely, the results of eight other publications that tended to have larger sample sizes and better characterised cohorts than the five aforementioned publication, supported the conclusion that HCV did affect the overall mortality of the patient populations studied.[6–13] In general, the results of these studies suggested that LR complications were the primary cause of mortality.

Five additional publications focused on the impact of anti-viral treatment on overall mortality.[47, 93–96] In general, the results of these studies supported the conclusion that achieving a sustained viral response resulted in decreased mortality rates and improved clinical outcomes, mainly prevention of LR complications in patients with advanced liver disease from chronic HCV. In addition, duration of treatment was found to be associated with decreased mortality rates and improved outcomes.[95]

Summary statements and grades of evidence

(i) Chronic HCV may affect overall mortality (2B).

(ii) Differences are best demonstrated in studies with well-characterised cohorts and long-term follow-up (2B).

(iii) Competing causes of death are important in high-risk patients, which may mitigate the impact of HCV on mortality (1B).

(iv) Achieving a sustained viral response improves overall mortality in patients with advanced liver disease (1A).

(v) It is possible that much of the impact of chronic HCV on overall mortality is related to LR mortality in patients with advanced liver disease (1A).

Economic burden of hepatitis C virus infection

Individuals with HCV infection tend to be heavy users of health care. This is in part because of comorbidity associated with HCV. Some of the comorbid conditions may be causally related to HCV, examples of which are immune-mediated kidney or vascular disease and diabetes. Other comorbidities are associated with HCV infection to the extent that the prevalence of substance/alcohol abuse and related mental health disorders is high in individuals with HCV infection.[97] Assessing the economic burden solely attributable to HCV infection can be difficult because these co-existing conditions can account for a large proportion of health care resource utilisation in a given patient.

Recent data, however, do suggest that HCV infection independently and significantly increases health care costs. These studies, often utilising propensity scores to optimise comparison between individuals with and without HCV, have shown that adjusting for differences in relevant characteristics of individuals, patients with HCV infection had significantly more out-patient care, hospitalisation and emergency room utilisation.[98, 99] Furthermore, increasing evidence corroborates that health care costs increase as the severity of liver disease deepens.[18, 100] Although it is not surprising for hepatologists, advancing fibrosis and cirrhosis, particularly when hepatic decompensation is present, incur high health care costs. In a study by Gordon *et al.*,[18] after adjusting for demographics and comorbidity profile, the monthly cost was $691 per month for a patient without cirrhosis, which increased to $1277 for compensated cirrhosis and $3682 for decompensated cirrhosis per month respectively. Available data also indicate that indirect costs (lost wages and productivity as a result of morbidity and mortality) are also substantial.[98, 101]

In the light of the relatively high prevalence of HCV infection in the general US population, particularly of the baby boomer generation, in whom both the duration of infection and severity of liver disease are increasing, the aggregate economic impact of HCV infection is expected to be substantial.[16] However, for similar reasons as discussed above for individual patients, it is also not straightforward to estimate the nationwide expenditure for HCV.[15, 102] Health care cost estimates drawn from national surveys may underestimate the true economic burden of HCV, because of difficulty capturing all health care activities related to HCV (e.g. a record with a diagnosis of HCC may omit HCV as the underlying cause), or overestimate it because isolating health care costs attributable to HCV is not always feasible (e.g. a record with surgical complication precipitated by HCV cirrhosis).

Other investigators have used modelling approaches to estimate the economic impact of HCV. The typical approach is to create disease progression models, which include a number of disease states and costs associated with each state.[17] Based on a number of assumptions, the model may be utilised to estimate the current and future economic impact of HCV infection at the population level. The limitation of this approach is that their results are only as accurate as their assumptions and input data. For example, in the model by Pyenson *et al.*, cirrhosis was estimated to occur 0.6% to 2.3% annually depending on the duration of infection.[17] The models used in that and many other analysis do not account for the wide individual variability in the progression rate of hepatitis C – the incidence of cirrhosis is clearly dependent on the stage of fibrosis and a number of factors as outlined a preceding section. Even a small error in these estimates, when applied to the whole population, may magnify the inaccuracy of the estimates.

Thus, depending on the method of calculation, the estimates for the nationwide impact of HCV infection vary widely from a few hundred million dollars to more than 30 billion dollars a year. However, there is a broad consensus that the number of Americans with serious long-term complications of HCV will increase in the next decade, incurring increasing amount of health care costs, particularly in the public sector (i.e. Medicare).

All in all, health economic studies have reported significantly divergent data on the economic impact of HCV infection in the US and elsewhere. The sources of variability include the extent to which HCV-specific burden was separated from comorbidities associated with the infection and inaccuracies inherent in projection models. These limitations in data notwithstanding; these economic data point to substantial economic consequences associated with HCV infection, and they are useful in informing resource allocation decisions for future health care, public health and biomedical research.

Summary statements and grades of evidence

(i) Chronic HCV independently and significantly increases health care costs, including out-patient care, hospitalisation and emergency room utilisation (Quality A, multiple valid observational studies).

(ii) In patients with chronic HCV, health care costs escalate as the severity of liver disease increases (Quality A, multiple valid observational studies).

(iii) Chronic HCV increases indirect costs, such as lost wages and productivity as a result of morbidity and mortality (Quality B, a few observational studies).

(iv) The aggregate health care expenditure in the US related to chronic HCV is estimated to be large ranging from several hundred million to 30 billion dollars a year (Quality C, multiple valid observational studies).

(v) The number of Americans with serious long-term complications of HCV will increase in the next decade, incurring increasing amount of health care costs, particularly in the public sector (i.e. Medicare) (Quality A, multiple valid observational studies).

Evidence supporting the impact of chronic hepatitis C on health-related quality of life

Health-related quality of life (HRQoL) refers to the impact of both physical and mental health on a patient's well-being. Measuring HRQoL is important for assessing the full impact of chronic liver disease or its intervention on patients' well-being. In addition to its own importance, HRQoL can indirectly impact the efficacy of a treatment regimen via compliance to the regimen.[103] Because HRQoL cannot be directly observed, it is indirectly measured using fully validated HRQoL instruments. These instruments assess HRQoL through a series of items (questions) scored to derive domain scores and/or summary scores.[103, 104] Both generic and disease-specific HRQoL instruments have been used to assess HRQoL in patients with HCV and are considered to be complementary.

In reviewing the literature assessing the impact of HCV on HRQoL, a number of important studies were identified. One of the identified studies assessed HRQoL in patients with advanced fibrosis or cirrhosis in the relatively large ($N = 1144$) HALT-C Trial using a generic instrument, the 36-item Short Form Health Survey (SF-36),[105] and found that patients with chronic HCV had markedly reduced HRQoL in all eight scales of SF-36 compared with population norms.[106] In addition, patients with cirrhosis and depression had more HRQoL impairment.[106] Furthermore, psychological factors such as depression were found to be significantly associated with HRQoL impairment.[106] In another study that assessed HRQoL in patients with HCV, it was revealed that viral clearance was associated with improved HRQoL and that those with cirrhosis or HCC had lower HRQoL as compared with those with chronic HCV.[107] When comparing and contrasting HRQoL in patients with HCV or with other chronic liver diseases, a study using the SF-36 found that patients with HCV were not as impaired in physical component HRQoL scores as those with primary biliary cirrhosis, but that patients with HCV showed greater impairment in mental component HRQoL scores compared with those with other chronic liver diseases.[108]

In addition to HRQoL, health utilities measure patients' preferences for a state of health. In a study that assessed health utility in 140 patients with chronic liver diseases, patients with HBV were found to have the highest health utility status; however, after controlling for confounders, patients with HCV continued to have significantly poorer health utility scores than patients with HBV.[109] In another study that assessed health utility in patients with HCV, it was revealed that viral clearance was associated with improved health utility status and that those with cirrhosis or HCC had lower health utility scores as compared with those with chronic HCV.[107]

These examples of the application of HRQoL research for HCV patients provide evidence that HRQoL is profoundly impaired in chronic HCV patients. The impairment seems to be more severe for the mental health aspects of QoL and worsen with severity of liver disease. Finally, patients who are cured from HCV show improvement in their HRQoL and health utilities.

Summary statements and grades of evidence

(i) HRQoL of patients with HCV is lower than general population norms using generic, disease-specific, and utility assessments (1A).

(ii) Compared with other liver diseases, HCV has the lowest mental aspect of HRQoL (1B).

(iii) Severity of liver disease in patients with HCV worsens HRQoL (1B).

In summary, the significant burden of HCV infection with regard to morbidity, mortality, resource utilisation and economic burden in the US should represent a call to action for liver and infectious disease specialists. The outcome of this CLDF workshop, over 40 graded, evidence-based summary statements predicated on reviews of current, relevant literature, may serve as new guidance for health care providers managing patients with HCV. These data should encourage future research not only to better understand the virus and develop improved treatment regimens to eradicate HCV but also to clearly assess the long-term outcomes of HCV on patients' survival and extrahepatic diseases, as well as economic and

patient-related outcomes. It will only be through this multifaceted approach to HCV that we could fully appreciate and recognise the total impact of HCV burden on the patients and the society.

AUTHORSHIP

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