The Current Economic Burden of Cirrhosis

Guy W. Neff, MD, MBA, Christopher W. Duncan, MD, MPP,
and Eugene R. Schiff, MD, MACP, FRCP, MACG, AGAF

Dr. Neff is Chief of Hepatology at Tampa General Medical Group in Tampa, Florida. Dr. Duncan is affiliated with Highline Gastroenterology in Seattle, Washington. Dr. Schiff is a Professor of Medicine and Director of the Schiff Liver Institute and the Center for Liver Diseases at the University of Miami's Miller School of Medicine in Miami, Florida.

Address correspondence to:
Dr. Guy W. Neff
Chief of Hepatology
Tampa General Medical Group
409 Bayshore Blvd.
Tampa, FL 33606;
Tel: 813-844-8686;
E-mail: gneff@tgh.org

Abstract: Cirrhosis is a worldwide problem that is associated with a substantial economic burden. Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver disease are the main causes of cirrhosis, but cost-effective preventive strategies are only available for HBV infection. Treatment algorithms for HBV infection and HCV infection are numerous and may be economically advantageous, depending on the regimen utilized; however, effective treatment for alcoholic liver disease is lacking, with abstinence from alcohol consumption continuing to be the main treatment strategy. In addition, liver transplantation (the only cure for cirrhosis) continues to consume substantial economic resources despite a recent reduction in overall cost. More sensitive predictors of post–liver transplantation disability could reduce this cost by allowing interventions that would promote productivity and increase health-related quality of life after liver transplantation. This paper highlights recent publications that evaluate the cost-effectiveness of strategies that prevent or treat the main causes of cirrhosis as well as publications that assess the impact of quality of life on the overall cost burden of the disease.

Keywords
Cirrhosis, economic burden, hepatitis B virus, hepatitis C virus, cost, quality-adjusted life years

Cirrhosis is a chronic liver disorder caused by a variety of diseases, with the most common being hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcoholic liver disease.[1] These diseases attack the liver, leading to progressive liver damage and, ultimately, liver failure and death. For example, 1–46% of patients with chronic HCV infection will likely develop cirrhosis during a 30-year period.[2] Cirrhosis, the twelfth leading cause of death in the United States in 2007, represents a large economic burden, with the national cost for treatment in 2008 ranging from $14 million to $2 billion, depending on disease etiology.[3,4] This burden is expected to rise over the next 20 years, given that the percentage of patients with HCV-related cirrhosis is predicted to almost double.[5]

The overall cost of cirrhosis includes direct costs (drug and hospitalization costs) and indirect costs (due to loss of work pro-

ductivity and reduction in health-related quality of life [HRQOL]). In 2004, the direct costs of cirrhosis and chronic liver disease in the United States (excluding patients with HCV infection) were estimated to be $2.5 billion, whereas indirect costs were estimated to be $10.6 billion.[6] Because cirrhosis is a progressive disorder, preventing or arresting its causes may substantially reduce the monetary burden of the disease. Furthermore, effectively managing underlying diseases in order to slow the progression of cirrhosis to liver failure would be beneficial, assuming that such measures would not incur undue medical expenditures. However, even with management, cirrhosis may progress to liver failure, in which case liver transplantation will be required for the patient's survival.

Given that liver transplantation entails a large economic outlay for relatively few individuals, the cost-effectiveness of the procedure, particularly in terms of the allocation of available livers and patients' HRQOL post-transplantation, may be questionable. This paper examines the overall economic burden of cirrhosis, including the cost-effectiveness of preventive and therapeutic strategies, liver transplantation, and overall societal impact of cirrhosis.

Prevention of Cirrhosis

Hepatitis B Virus Infection

In the 1990s, the World Health Organization (WHO) recommended that all countries incorporate HBV vaccination into their national immunization programs. Many nations (such as the United States) heeded this advice and routinely require immunization (either 2 or 3 doses) for infants (at birth), children, adolescents (≤19 years of age), and adults (who have never previously been vaccinated).[7-9] Numerous studies have reported on the long-term efficacy of HBV vaccination, and various cost analyses support the economic efficacy of this practice (Table 1).[10-21] Nevertheless, several countries (such as Canada) delay immunization until adolescence, while other countries (such as the United Kingdom and Ireland) do not have universal vaccination programs, even though such programs may be economical.[19,21,22] In general, the most cost-effective vaccination strategy for a nation is determined by its level of HBV endemicity, the ease of implementing a widespread vaccination program, the duration of protection offered by vaccination, and the infection risk per age group.[23] The overall cost of a vaccination program also depends on the dosing regimen used (ie, 2 vs 3 doses) and whether it includes the administration of booster doses. Because 3-dose regimens and booster doses incur additional costs with uncertain efficacy, debate continues regarding the cost-effectiveness of these practices; further studies are necessary to determine the impact of these practices on the overall economic burden.[10-12,14,24,25] Regardless of the specific regimen used, the incidence of HBV infection significantly declined in several countries after the implementation of widespread vaccination, indicating that this practice is beneficial at least in terms of morbidity.[26-28]

Hepatitis C Virus Infection

Unlike HBV infection, there is currently no vaccine available for HCV, despite ongoing research. Thus, prevention of HCV infection focuses mainly on controlling nosocomial exposure (ie, blood screening, safe injection, and infection control) and reducing high-risk behaviors (ie, intravenous drug use).[29] Implementation of safe nosocomial practices may reduce HCV transmission, but these practices are often costly and exceed the economic ability of low-income countries.[29,30] In these cases, cooperation with and monetary subsidization by local and international agencies are essential.

Collaboration between healthcare providers and patients at high risk for HCV infection (ie, intravenous drug users and incarcerated individuals) is also paramount.[29,31,32] Intravenous drug users contract the largest number of new HCV infections per year because of needle sharing.[32] Concerted efforts to educate this population and provide methods by which they can procure sterile injection equipment are indispensable and relatively economical, particularly in countries where prevention and support programs for substance abusers are already in place.[29,32] Screening populations at high risk for HCV infection may also reduce the overall economic burden of the disease by identifying patients with HCV infection and providing early treatment, thus potentially preventing progression to more serious and costly complications (eg, cirrhosis).[31-33]

Alcoholic Liver Disease

It is well established that alcohol consumption has a relationship with cirrhosis as well as with cirrhosis-related mortality, suggesting that policies and procedures intended to curtail alcohol intake and alcoholism may also reduce cirrhosis.[34-37] Such policies include school-based and public education campaigns on alcohol-associated disease, brief advice on alcohol consumption for individuals at risk for alcoholism, stringent alcohol purchase laws, government monopolies on alcohol, limitations on alcohol marketing campaigns, and taxes on alcohol.[38,39] A 2009 analysis by Anderson and associates on the economic benefit of each of these policies revealed that restriction of alcohol sales and a tax increase on retail alcohol purchases were generally cost-effective, whereas educational programs and counseling were not cost-effective.[38] Additionally, Alcoholics Anonymous intervention may impact the progression of liver disease and the overall outcome in patients with chronic alcoholism, although this find-

Table 1. Economic Evaluation of Universal Hepatitis B Virus (HBV) Vaccination in Various Countries

Study	Country	Conclusions
Bloom BS, Hillman AL, Fendrick AM, Schwartz JS[16]	United States	• Universal vaccination of infants is more cost-effective than only vaccinating infants who have a positive HBV screening result. • In adults, HBV screening before vaccination is more cost-effective than universal vaccination. • The cost per life year saved is lower for infant vaccination strategies (ie, vaccination of all infants [$3,066*] and screening plus vaccination of infants [$3,332*]) than adolescent vaccination strategies ($13,938*) or adult vaccination strategies ($54,524–59,101*).
Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA[20]	United States	• Routine infant HBV vaccination costs $6,110** per HBV infection prevented versus $12,744** per HBV infection prevented in an adolescent vaccination paradigm. • The cost per life year saved is $1,522** for an infant HBV vaccination program versus $3,730** for an adolescent vaccination program. • Both infant and adolescent vaccination programs are economically beneficial; however, delaying vaccination until adolescence does not prevent early childhood infections and, therefore, incurs additional cost.
Hung HF, Chen TH[17]	Taiwan	• Societal cost was reduced with vaccination ($7,539†) versus no vaccination ($62,740†). • Vaccination provided 70 QALYs versus 66 QALYs with no vaccination. • Universal vaccination is a cost-effective strategy in countries with a high prevalence of HBV infection.
Kim SY, Salomon JA, Goldie SJ[18]	Gambia	• Vaccination of infants would cost approximately $47‡ per DALY averted. • There is a 65% probability that the vaccination program would be affordable and cost-effective with a total budget expenditure of $207,000‡.
Krahn M, Guasparini R, Sherman M, Detsky AS[19]	Canada	• Universal vaccination of school-age children and adolescents reduced the cost of HBV infection by $75¶ per person versus no vaccination. • The cost per life year gained was $2,145¶. • Universal vaccination of school-age children significantly decreased the overall societal cost of HBV infection versus no vaccination.
Tilson L, Thornton L, O'Flanagan D, Johnson H, Barry M[21]	Ireland	• Universal HBV vaccination would prevent 316 cases of acute HBV infection, 95 cases of chronic HBV infection, 13 cases of cirrhosis, and 6 cases of hepatocellular carcinoma. • Universal infant vaccination is more cost-effective than selective vaccination.

DALY=disability-adjusted life year; QALY=quality-adjusted life year.

*Using 1989 values. **Using 1993 values. †Using 1984 values. ‡Using 2002 values. ¶Using 1994 values.

ing has not been statistically or experimentally verified.[40] Pharmacologic treatment of alcoholism may also prevent cirrhosis, but only one study has evaluated the cost of such interventions.[41] This investigation revealed that increased spending on alcoholism treatment correlated with reductions in cirrhosis-related death rates. It would be beneficial to conduct additional investigations regarding the cost advantages of different therapeutic treatments for alcoholism as they relate to cirrhosis.

Treatment of Underlying Causes of Cirrhosis

Hepatitis B Virus Infection

HBV infection is a global concern, requiring large expenditures for healthcare and prevention. Although guidelines for the prevention and treatment of HBV infection have been published by the WHO, adoption of and adherence to these recommendations vary among countries.[42,43] Therefore, it is difficult to compare healthcare costs and

the economic burden of HBV infection among countries, particularly given the diverse economic conditions worldwide. Nonetheless, progression of HBV infection to cirrhosis has been shown to increase healthcare costs in several countries, and economic analyses of standard treatment regimens in some of these nations indicate an economic benefit associated with stopping the progression of chronic HBV infection.[44-48] For example, the average yearly disease cost for an individual with chronic HBV infection without cirrhosis (€1,158–1,271) is lower than the average cost for patients with HBV infection and compensated cirrhosis (€1,254–1,512) or decompensated cirrhosis (€1,512–3,016), although the exact cost estimates may vary according to the treatment paradigms and drugs utilized.[49]

In the United States, 7 treatments are available for chronic HBV infection: interferon α-2b, peginterferon α-2a, lamivudine, adefovir (Hepsera, Gilead), entecavir (Baraclude, Bristol-Myers Squibb), telbivudine (Tyzeka, Novartis), and tenofovir (Viread, Gilead).[50] Recommended first-line therapies include entecavir, peginterferon α-2a, and tenofovir. These recommendations are based on efficacy, tolerability, and favorable resistance profiles in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients; however, these recommendations do not take cost-effectiveness into account. Numerous studies in several countries have evaluated the cost-effectiveness of HBV treatments, although these studies have varied in population data utilized, specific regimens compared, and overall data reported (ie, quality-adjusted life year [QALY] vs incremental cost-effectiveness ratio [ICER]).[49,51-58] In general, adefovir, entecavir, peginterferon α-2a, and tenofovir have been shown to be cost-effective, but there is little evidence supporting the cost-effectiveness of lamivudine (Table 2).

Hepatitis C Virus Infection

Treatment for chronic HCV infection focuses on viral suppression to an undetectable level, thereby deterring disease progression and preventing related complications such as cirrhosis and hepatic carcinoma.[59] The viral suppression is essential, as patients who do not achieve long-term viral suppression (ie, sustained virologic response) are more likely to have greater liver-related morbidity and mortality.[60] Five treatment options for HCV infection are available in the United States (interferon monotherapy, interferon plus ribavirin, peginterferon plus ribavirin, peginterferon plus ribavirin and telaprevir [Incivek, Vertex], and peginterferon plus ribavirin and boceprevir [Victrelis, Merck]). Published guidelines recommend the use of peginterferon combined with ribavirin plus 1 of the 2 direct-acting antiviral agents as first-line therapy in most chronic HCV genotype 1 infection patient populations. Treatment duration with peginterferon α plus ribavirin therapy varies with the patient's HCV genotype (ie, 24–48 weeks for HCV genotype 1 infection and 24 weeks for HCV genotypes 2 and 3 infection). Thus, genotype testing before treatment initiation is recommended in the United States.

The recent US Food and Drug Administration approval and inclusion of telaprevir and boceprevir combined with pegylated interferon and ribavirin as standard-of-care therapy in HCV genotype 1 infection patients will change the economic modeling for this disease. The increased sustained virologic response rates achieved with these new agents will require in-depth analysis involving cost analyses and treatment outcomes.

Overall cost evaluations of these therapies have been examined in a number of countries and suggest that interferon monotherapy is more cost-effective than no treatment, interferon plus ribavirin is more economically sound than interferon alone, and peginterferon plus ribavirin is more cost-effective than interferon plus ribavirin (Table 3).[61] Even in HCV patients who have a low risk of progression to cirrhosis, treatment with peginterferon combination therapy may be cost-effective because of the resulting improvement in quality of life. For example, in a 2003 cost-effectiveness analysis, peginterferon plus ribavirin therapy saved $15,000–55,000 per QALY, depending on HCV genotype, versus interferon monotherapy.[2] These savings were thought to be the result of improved HRQOL, as these patients were not likely to require substantial HCV-related healthcare costs during their lifetime.[2] Peginterferon plus ribavirin therapy may also be cost-beneficial in patients who are co-infected with HIV or who have chronic liver disease and persistently normal alanine aminotransferase levels.[62,63] In addition, compared to standard 24- and 48-week treatment regimens, it may be cost-effective to reduce the duration of treatment to 12 weeks in patients with HCV genotype 2 or 3 infection or to increase the duration of therapy to 72 weeks in HCV-infected patients who have a reduction in HCV RNA level of less than 2 $\log_{10}$ by Week 24 of therapy.[64,65]

Furthermore, although peginterferon α-2a plus ribavirin has been shown to be economically satisfactory when administered without regard to HCV genotype, adjusting treatment duration based on HCV genotype is cost-effective even in populations with a low prevalence of HCV genotype 2 or 3 infection, despite the additional cost of genotyping.[66,67] Cost analyses of the effect of adjusting peginterferon α-2a plus ribavirin treatment based on race and alanine aminotransferase level are not currently available but would be beneficial for determining the overall economic benefit of HCV therapies.

Table 2. Cost-Effectiveness of Various Hepatitis B Virus Treatment Regimens Worldwide

Treatment/Country	Incremental cost-effectiveness ratio		Quality-adjusted life year gained
	No treatment	Lamivudine	
Adefovir			
United States[52]*	$19,731**	NA	NA
United States[54]†	NA	NA	18.2
Spain[49]†‡	€954¶	NA	14.7
Singapore[53]†‡	SGD 6,078–9,993§	NA	0.3–0.5
Entecavir			
United States[52]*	$25,626**	NA	NA
United States[54]†	$27,184§	NA	18.7
United States[58]†	NA	$3,230£	0.7
Spain[49]†‡	NA	NA	15.2
Argentina[51]†‡	NA	NA	0.4–0.5
China[57]*	NA	RMB 13,330£	0.3
Lamivudine			
United States[52]*	NA	NA	NA
United States[54]†	NA	NA	18.4
United States[58]†	NA	NA	NA
Spain[49]†‡	€632–5,212§	NA	14.7
Singapore[53]†‡	SGD 3,393–7,053¶	NA	0.3–0.6
Taiwan[55]†	NA	NA	14.0
Taiwan[56]‡	NA	NA	10.1
China[57]*	NA	NA	NA
Interferon			
Singapore[53]†‡	SGD 61,940¶	NA	0.1
Pegylated interferon			
United States[54]†	NA	NA	18.6
Singapore[53]†‡	SGD 33,718–40,707¶	NA	0.5–0.6
Pegylated interferon α-2a			
Taiwan[55]†	NA	NTD 12,000**	14.5
Taiwan[56]‡	NA	NTD 346,868**	10.6
Telbivudine			
United States[54]†	NA	NA	18.6
Spain[49]†‡	NA	NA	15.0
Tenofovir			
Spain[49]†‡	NA	NA	15.4

NTD=New Taiwan dollar (year not provided); RMB=renminbi yuan; SGD=Singapore dollar.

*Population not specified. **Year not provided. †Hepatitis B e antigen–positive population. ‡Hepatitis B e antigen–negative population. ¶2005 value. §2008 value. £2006 value.

Table 3. Cost-Effectiveness of Various Hepatitis C Virus (HCV) Treatment Regimens Worldwide

Treatment/Study	Country	Therapy duration, weeks	Life year gained	Quality-adjusted life year gained
Interferon monotherapy				
Sagmeister M, Wong JB, Mullhaupt B, Renner EL[100]	Switzerland	48	0.71–2.43*	0.77–2.77*
Stein K, Rosenberg W, Wong J[101]	United Kingdom	24–48**	NA	1.90
Siebert U, Sroczynski G[102]	Germany	48†	1.27	1.32
Interferon plus ribavirin				
Wong JB, Koff RS[103]	United States	24–48**	1.60	2.40
Sagmeister M, Wong JB, Mullhaupt B, Renner EL[100]	Switzerland	24 48	1.47–5.36* 2.57–5.41*	1.61–6.21* 2.77–6.13*
Sennfält K, Reichard O, Hultkrantz R, Wong JB, Jonsson D[104]	Sweden	24 48	NA NA	1.10–4.10* NA–1.70*
Stein K, Rosenberg W, Wong J[101]	United Kingdom	24–28**	NA	4.82
Wong JB, Nevens F[105]	Belgium	24–28*	2.82	3.72
Siebert U, Sroczynski G, Rossol S, et al[106]	Germany	48†	3.60	3.80
Wong JB, Davis GL, McHutchison JG, Manns MP, Albrecht JK[107]	United States	12–48‡	3.10	4.00
Siebert U, Sroczynski G, Wasem J, et al[108]	Germany	24	2.84	2.97
Sroczynski G, Rafetseder O, Jonas S, Siebert U[109]	Austria	12–48‡	2.5	2.6
Brady B, Siebert U, Sroczynski G, et al[110]	Canada	12–48‡	2.91	2.11
Peginterferon plus ribavirin				
Wong JB, Nevens F[105]	Belgium	24–48	3.77	4.99
Siebert U, Sroczynski G, Rossol S, et al[106]	Germany	48†	4.20	4.30
Wong JB, Davis GL, McHutchison JG, Manns MP, Albrecht JK[107]	United States	12–48‡	3.60–4.00¶	4.60–5.20¶
Sroczynski G, Rafetseder O, Jonas S, Siebert U[109]	Austria	12–48‡	4.30	4.50
Brady B, Siebert U, Sroczynski G, et al[110]	Canada	12–48‡	3.90	2.80

*The range of values in patients with HCV genotype 1 infection and patients with other genotypes. **Depending on HCV genotype. †48 weeks of treatment for patients who responded to treatment at Week 24. ‡Depending on HCV genotype infection and early virologic response to treatment. ¶The range of values in patients with HCV genotype 1 infection and patients with HCV genotype 2 or 3 infection.

Adapted from Sroczynski G, et al.[61]

Given these data, treatment of patients with HCV infection is economically advantageous compared to do-nothing strategies. Using a multicohort, natural history model, treatment of 25% of patients with HCV infection reduces the incidence of cirrhosis by 1%.[5] In comparison, if 50% or 100% of HCV-infected patients received therapy, the expected reduction in the incidence of cirrhosis would be 8% or 16%, respectively. Overall, data involving direct-acting antiviral agents reveal impressive response rates, and these drugs have changed the management of

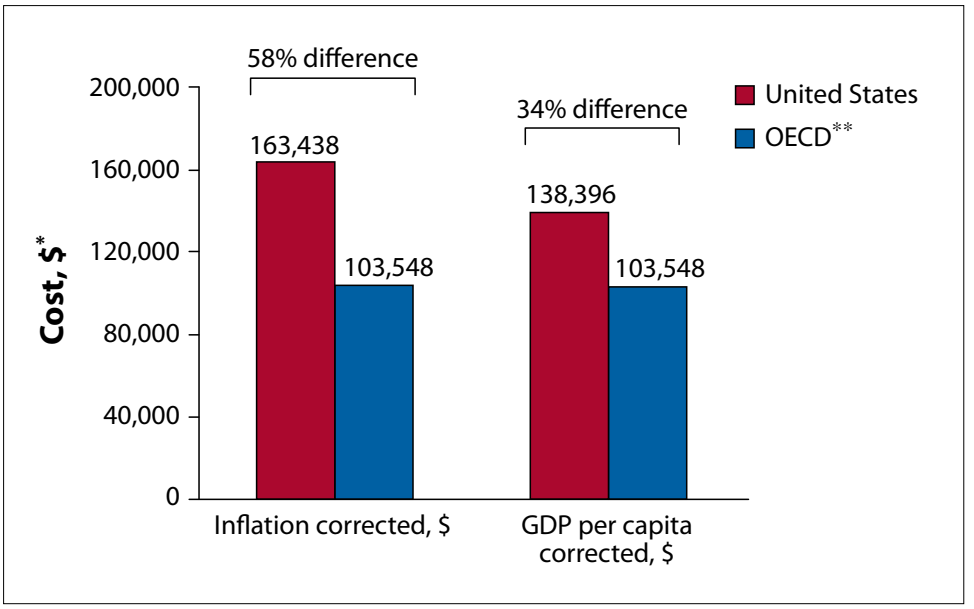

Figure 1. Overall, the cost of liver transplantation is higher in the United States than in other countries in the Organization for Economic Cooperation and Development (OECD), even when taking countries' gross domestic product (GDP) into consideration.

*2005 value. **OECD countries include Japan, Germany, the Netherlands, Italy, the United Kingdom, France, Switzerland, and Canada.

Data from van der Hilst CS, et al.[73]

chronic HCV infection. However, the therapeutic cost of these alterations requires further investigation.

Alcoholic Liver Disease

Alcoholic liver disease can present in several stages, including fatty liver disease, alcoholic hepatitis, and chronic hepatitis with cirrhosis.[68] Although these stages may overlap, therapeutic strategies to reverse and prevent progression of this disease to cirrhosis would likely be cost-effective, given that end-stage liver disease caused by this disorder can only be treated with liver transplantation. Reversal of fatty liver disease is possible within weeks of abstaining from alcohol; thus, the primary treatment recommendation is abstinence from alcohol. However, many patients continue to consume alcohol. Therapeutic agents to aid alcoholic abstinence are generally ineffective, although naltrexone or acamprosate (Campral, Forest Laboratories) may be used to reduce the likelihood of relapse in patients who abstain from alcohol. A cost-effectiveness analysis examined the use of acamprosate for 48 weeks in patients with fatty liver disease, cirrhosis, pancreatitis, or alcoholic cardiomyopathy and found that acamprosate was cost-effective compared to no treatment and resulted in a life-year gain of 1.2 years.[69] Although the cost of acamprosate (2,177 German marks in 1996) was greater than no treatment, this acquisition cost was insignificant compared to the cost of liver complications resulting from continued abuse of alcohol. Other treatment options, such as prednisolone and pentoxifylline, are also available for patients with alcoholic hepatitis, and although published cost-effectiveness analyses are not yet available, these interventions are likely cost-effective given their efficacy for deterring progression to liver failure.[68]

Liver Transplantation

Liver transplantation is the only effective treatment for the end-stage liver disease caused by chronic liver damage, and this procedure is associated with excellent survival rates.[70,71] Although both deceased and living donor transplantations are performed in the United States, an overall higher cost has been reported with living donor transplantations.[70,72] Despite the excellent survival rates associated with liver transplantation, its high expense and benefit to only a small number of individuals have brought its cost-effectiveness into question.[73] Indeed, the cost of liver transplantation in the United States is approximately 34% higher than in other countries in the Organization for Economic Cooperation and Development (OECD), although survival rates among these countries are similar (Figure 1). The higher cost of liver transplantation in the United States compared to other OECD countries is due to several factors, including a higher daily price of hospital stays (despite a

reduction in their duration), administrative complexity, and malpractice litigation. Differences in the allocation procedures for liver transplantation may also contribute to these cost differences.

In 2006, the United States began using Model for End-Stage Liver Disease (MELD) scores to allocate organs for liver transplantation, whereas other countries in the OECD have yet to adopt the MELD system.[73] There is substantial debate about whether MELD scores represent the most reliable evaluation of liver disease to designate hierarchy for liver transplantation and how the use of MELD scores may impact cost.[74-80] Patients with high MELD scores receive priority for liver transplantation over patients with low MELD scores, in an attempt to reduce mortality and healthcare utilization by these patients.[81] However, this policy results in increased waiting time for patients with mild liver dysfunction. This increase in waiting time may incur additional hospital costs for patients with minimal liver dysfunction as the disease progresses to a decompensated state. Furthermore, patients with higher MELD scores (ie, 28–40) incur significantly higher pretransplantation and total costs versus patients with lower MELD scores (ie, 6–27).[82] In addition, patients with better overall health are more likely to survive surgery than patients with comorbidities. Given these observations, it is possible that liver transplantation in patients with less severe liver function may be cost-effective because of these patients' decreased use of additional healthcare resources. Further studies examining the relationships among MELD score designation, cost, and successful liver transplantation are necessary to examine this possibility.

The cost of liver transplantation includes postsurgical management of patients to prevent complications, which should be taken into account when determining patients' fitness and the cost-effectiveness of liver transplantation. For example, patients' MELD scores have been associated with post-transplantation peritonitis, pneumonia, and *Clostridium difficile* colitis, which increase total hospital costs by a median of $75,433, $50,572, and $29,031, respectively.[83] In addition, underlying diseases such as HBV infection and HCV infection must also be controlled to prevent the recurrence of cirrhosis. For patients with HBV infection, standard-of-care treatment involves post-transplantation prophylaxis with lamivudine and/or adefovir and hepatitis B immunoglobulin, which have been shown to be efficacious and cost-effective.[50,84] Post-transplantation HCV prevention is more difficult because of patients' intolerance to standard prophylactic antiviral regimens; however, these treatments have been shown to be cost-effective, resulting in an ICER of $29,100 per life year saved versus no prophylactic therapy.[85,86]

Societal Impact of Cirrhosis

As mentioned, the total cost of cirrhosis encompasses direct costs (medical costs) and indirect costs (due to reduced HRQOL and lost productivity). Because liver transplantation is the ultimate treatment for cirrhosis, substantial attention has been given to the HRQOL and productivity of liver transplantation recipients. Reduced HRQOL in patients before liver transplantation has been reported, but improvement of HRQOL after transplantation remains debatable, with several studies demonstrating improvement and other studies reporting continued impairment.[87-93] In studies that report continued reductions in post-transplantation HRQOL compared to the HRQOL of the general population, post-transplantation HRQOL correlated with employment, suggesting that employment may be reduced in patients even after transplantation compared to the general population.[91,93] Overall, 55% of patients report employment after transplantation, although the number of unemployed patients was greatly increased post-transplantation in one study (Figure 2).[90,94] The main causes of unemployment or reduction in employment were poor physical functioning and poor health, although some patients were reluctant to return to the workplace for fear of losing government-sponsored health insurance and disability income.[89,90,94,95] These observations suggest that liver transplantation may not fully restore HRQOL and workplace productivity to patients and, thus, may not alleviate monetary expenditures from government-sponsored programs such as Medicaid. Therefore, establishing effective indicators of reduced post-transplantation HRQOL and work productivity would be beneficial. The most intuitive indicator for such an assessment is MELD score; however, conflicting data make its use as an adequate predictor questionable.[87,96-99]

Summary

Prevention and treatment of chronic liver diseases (ie, HBV infection, HCV infection, and alcoholic liver disease) may lessen the economic impact of these diseases by reducing comorbidities associated with cirrhosis and the need for liver transplantation. The preventive measures for HBV infection that are currently available may be economically advantageous in some countries, but prevention of HCV infection and alcoholic liver disease remains challenging. There are several effective treatment strategies for reducing symptoms of HBV infection and HCV infection, and some of these strategies may be cost-effective compared to do-nothing strategies. In contrast, treatment of alcoholic liver disease remains difficult, with the primary therapy consisting of abstinence from

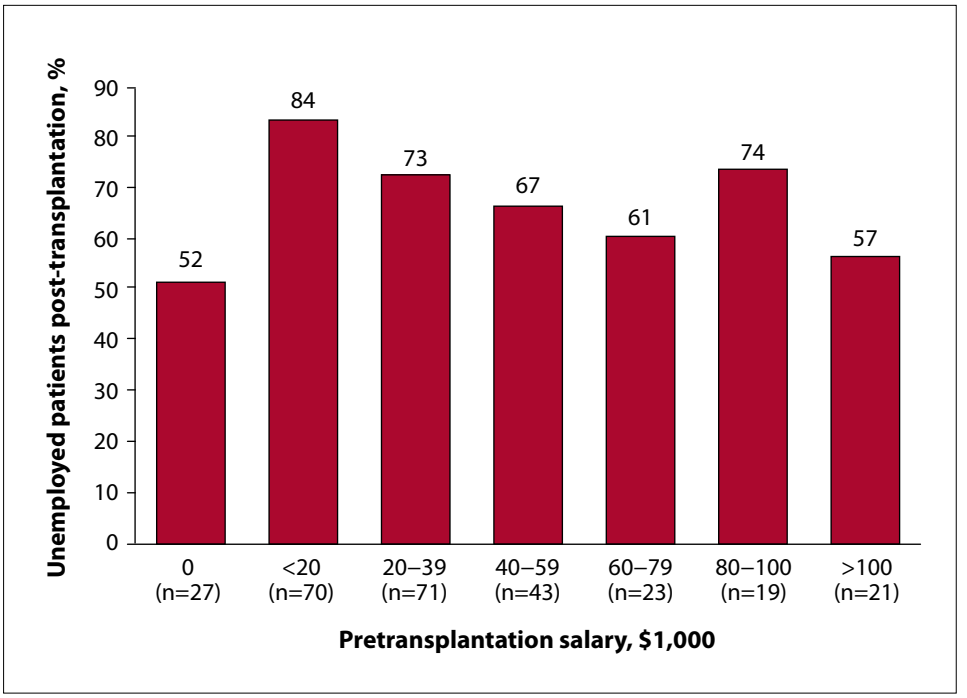

Figure 2. A greater percentage of patients were unemployed after liver transplantation than before the procedure. Data from Saab S, et al.[90]

alcohol. More effective therapies for maintaining alcoholic abstinence would be beneficial and could greatly reduce the need for liver transplantation and retransplantation. Liver transplantation costs have decreased in recent years; however, this procedure remains costly and has questionable economic benefit, given that patients who receive a liver transplant may not regain adequate HRQOL and/or rejoin the workforce. Additional cost-effective preventive and treatment strategies, along with more reliable pretransplantation predictors of post-transplantation work productivity, are essential before the economic burden of cirrhosis can be sufficiently reduced.

Dr. Neff was assisted by Medthink Communications in pulling references for review. The authors have no competing interests or financial support for research to declare.

References

1. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician*. 2006;74:756-762.
2. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *JAMA*. 2003;290:228-237.
3. Miniño AM, Xu J, Kochanek KD, Tejada-Vera B. Death in the United States, 2007. *NCHS Data Brief*. 2009;1-8.
4. Agency for Healthcare Research and Quality. HCUPnet. http://hcupnet.ahrq.gov.
5. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010;138:513-521.
6. Ruhl CE, Sayer B, Byrd-Holt DE, Brown DM. Costs of digestive diseases. In: Everhart J, ed. *The Burden of Digestive Diseases in the United States*. Washington, DC: US Dept of Health and Human Services, Public Health Service, National Institutes of Health, and National Institute of Diabetes and Digestive and Kidney Diseases; 2008:137-143. NIH publication 09-6443.
7. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep*. 2005;54(RR-16):1-31.
8. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. *MMWR Recomm Rep*. 2006;55(RR-16):1-33.
9. Ni YH, Huang LM, Chang MH, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. *Gastroenterology*. 2007;132:1287-1293.
10. Alfaleh F, Alshehri S, Alansari S, et al. Long-term protection of hepatitis B vaccine 18 years after vaccination. *J Infect*. 2008;57:404-409.
11. Bialek SR, Bower WA, Novak R, et al. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth: a 15-year follow-up study. *Pediatr Infect Dis J*. 2008;27:881-885.
12. But DY, Lai CL, Lim WL, Fung J, Wong DK, Yuen MF. Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: final report. *Vaccine*. 2008;26:6587-6591.
13. McMahon BJ, Dentinger CM, Bruden D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. *J Infect Dis*. 2009;200:1390-1396.
14. Poorolajal J, Mahmoodi M, Majdzadeh R, Nasseri-Moghaddam S, Haghdoost A, Fotouhi A. Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine*. 2010;28:623-631.
15. Ramezani A, Eslamifar A, Banifazl M, et al. Efficacy and long-term immunogenicity of hepatitis B vaccine in haemodialysis patients. *Int J Clin Pract*. 2009;63:394-397.
16. Bloom BS, Hillman AL, Fendrick AM, Schwartz JS. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. *Ann Intern Med*. 1993;118:298-306.

17. Hung HF, Chen TH. Probabilistic cost-effectiveness analysis of the long-term effect of universal hepatitis B vaccination: an experience from Taiwan with high hepatitis B virus infection and hepatitis B e antigen positive prevalence. *Vaccine*. 2009;27:6770-6776.
18. Kim SY, Salomon JA, Goldie SJ. Economic evaluation of hepatitis B vaccination in low-income countries: using cost-effectiveness affordability curves. *Bull World Health Organ*. 2007;85:833-842.
19. Krahn M, Guasparini R, Sherman M, Detsky AS. Costs and cost-effectiveness of a universal, school-based hepatitis B vaccination program. *Am J Public Health*. 1998;88:1638-1644.
20. Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization: an economic analysis of current recommendations. *JAMA*. 1995;274:1201-1208.
21. Tilson L, Thornton L, O'Flanagan D, Johnson H, Barry M. Cost-effectiveness of hepatitis B vaccination strategies in Ireland: an economic evaluation. *Eur J Public Health*. 2008;18:275-282.
22. Edmunds WJ. Universal or selective immunisation against hepatitis B virus in the United Kingdom? A review of recent cost-effectiveness studies. *Commun Dis Public Health*. 1998;1:221-228.
23. Rots NY, Wijmenga-Monsuur AJ, Luytjes W, et al. Hepatitis B vaccination strategies tailored to different endemicity levels: some considerations. *Vaccine*. 2010;28:893-900.
24. Hammitt LL, Hennessy TW, Fiore AE, et al. Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years. *Vaccine*. 2007;25:6958-6964.
25. Williams JL, Christensen CJ, McMahon BJ, et al. Evaluation of the response to a booster dose of hepatitis B vaccine in previously immunized healthcare workers. *Vaccine*. 2001;19:4081-4085.
26. Loomba R, Liang TJ. Treatment of chronic hepatitis B. *Antivir Ther*. 2007;12(suppl 3):H33-H41.
27. Paat G, Uusküla A, Tefanova V, Tallo T, Priimägi L, Ahi K. The trends and risk factors for hepatitis B occurrence in Estonia. *Cent Eur J Public Health*. 2009;17:108-111.
28. Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298:2155-2163.
29. Van Herck K, Vorsters A, Van Damme P. Prevention of viral hepatitis (B and C) reassessed. *Best Pract Res Clin Gastroenterol.* 2008;22:1009-1029.
30. Schmunis GA, Rodriguez G, Coenen J, Bellorin EG, Gianella A. Prevention of blood-borne diseases in Bolivia, 1993-2002. *Am J Trop Med Hyg*. 2008;79:803-808.
31. NIH consensus statement on management of hepatitis C: 2002. *NIH Consens State Sci Statements.* 2002;19:1-46.
32. Edlin BR, Kresina TF, Raymond DB, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. *Clin Infect Dis*. 2005; 40(suppl 5):S276-S285.
33. McHutchison JG, Bacon BR, Owens GS. Making it happen: managed care considerations in vanquishing hepatitis C. *Am J Manag Care*. 2007;13(suppl 12): S327-S336.
34. Mann RE, Smart RG, Rush BR, Zalcman RF, Suurvali H. Cirrhosis mortality in Ontario: effects of alcohol consumption and Alcoholics Anonymous participation. *Addiction*. 2005;100:1669-1679.
35. Ramstedt M. Population drinking and liver cirrhosis mortality: is there a link in Eastern Europe? *Addiction*. 2007;102:1212-1223.
36. Smart RG, Mann RE, Suurvali H. Changes in liver cirrhosis death rates in different countries in relation to per capita alcohol consumption and Alcoholics Anonymous membership. *J Stud Alcohol*. 1998;59:245-249.
37. Norström T, Ramstedt M. Mortality and population drinking: a review of the literature. *Drug Alcohol Rev.* 2005;24:537-547.
38. Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. *Lancet*. 2009;373:2234-2246.
39. Toomey TL, Wagenaar AC. Policy options for prevention: the case of alcohol. *J Public Health Policy*. 1999;20:192-213.
40. Ferri M, Amato L, Davoli M. Alcoholics Anonymous and other 12-step programmes for alcohol dependence. *Cochrane Database Syst Rev.* 2006;3:CD005032.
41. Smart RG, Mann RE, Lee SL. Does increased spending on alcoholism treatment lead to lower cirrhosis death rates? *Alcohol Alcohol*. 1996;31:487-491.
42. Department of Vaccines and Biologicals, World Health Organization. Introduction of hepatitis B vaccine into childhood immunization services: management guidelines, including information for health workers and parents. http://whqlibdoc.who.int/hq/2001/WHO_V&B_01.31.pdf.
43. Department of Communicable Diseases Surveillance and Response, World Health Organization. Hepatitis B. http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf.
44. Hsieh CR, Kuo CW. Cost of chronic hepatitis B virus infection in Taiwan. *J Clin Gastroenterol*. 2004;38(10 suppl 3):S148-S152.
45. Lee TA, Veenstra DL, Iloeje UH, Sullivan SD. Cost of chronic hepatitis B infection in the United States. *J Clin Gastroenterol*. 2004;38(10 suppl 3):S144-S147.
46. Li SC, Ong SC, Lim SG, et al. A cost comparison of management of chronic hepatitis B and its associated complications in Hong Kong and Singapore. *J Clin Gastroenterol*. 2004;38(10 suppl 3):S136-S143.
47. Yang BM, Kim CH, Kim JY. Cost of chronic hepatitis B infection in South Korea. *J Clin Gastroenterol*. 2004;38(10 suppl 3):S153-S157.
48. Zhiqiang G, Zhaohui D, Qinhuan W, et al. Cost of chronic hepatitis B infection in China. *J Clin Gastroenterol*. 2004;38(10 suppl 3):S175-S178.
49. Buti M, Brosa M, Casado MA, Rueda M, Esteban R. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. *J Hepatol*. 2009;51:640-646.
50. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.
51. Calcagno JI, Augustovski F, Gadano A, Souto A, Yuan Y. Cost-effectiveness analysis of entecavir versus lamivudine in patients with chronic hepatitis B [in Spanish]. *Acta Gastroenterol Latinoam*. 2008;38:260-273.
52. Kanwal F, Farid M, Martin P, et al. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. *Am J Gastroenterol*. 2006;101:2076-2089.
53. Lacey LF, Gane E. The cost-effectiveness of long-term antiviral therapy in the management of HBeAg-positive and HBeAg-negative chronic hepatitis B in Singapore. *J Viral Hepat*. 2007;14:751-766.
54. Spackman DE, Veenstra DL. A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B. *Pharmacoeconomics*. 2008;26:937-949.
55. Sullivan SD, Veenstra DL, Chen PJ, et al. Cost-effectiveness of peginterferon alpha-2a compared to lamivudine treatment in patients with hepatitis B e antigen positive chronic hepatitis B in Taiwan. *J Gastroenterol Hepatol*. 2007;22:1494-1499.
56. Veenstra DL, Sullivan SD, Lai MY, Lee CM, Tsai CM, Patel KK. HBeAg-negative chronic hepatitis B: cost-effectiveness of peginterferon alfa-2a compared to lamivudine in Taiwan. *Value Health*. 2008;11:131-138.
57. Yuan Y, Iloeje U, Li H, Hay J, Yao GB. Economic implications of entecavir treatment in suppressing viral replication in chronic hepatitis B (CHB) patients in China from a perspective of the Chinese Social Security program. *Value Health*. 2008;11(suppl 1):S11-S22.
58. Yuan Y, Iloeje UH, Hay J, Saab S. Evaluation of the cost-effectiveness of entecavir versus lamivudine in hepatitis B e Ag-positive chronic hepatitis B patients. *J Manag Care Pharm*. 2008;14:21-33.
59. Department of Veterans Affairs Hepatitis C Resource Center; Yee HS, Currie SL, Darling JM, Wright TL. Management and treatment of hepatitis C viral infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center program and the National Hepatitis C Program office. *Am J Gastroenterol*. 2006;101:2360-2378.
60. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol*. 2010;8:280-288.
61. Sroczynski G, Esteban E, Conrads-Frank A, et al. Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. *J Viral Hepat*. 2010;17:34-50.
62. Campos NG, Salomon JA, Servoss JC, et al. Cost-effectiveness of treatment for hepatitis C in an urban cohort co-infected with HIV. *Am J Med.* 2007;120:272-279.
63. Gerkens S, Nechelput M, Annemans L, Peraux B, Beguin C, Horsmans Y. A health economic model to assess the cost-effectiveness of pegylated interferon alpha-2a and ribavirin in patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels. *Acta Gastroenterol Belg*. 2007;70:177-187.
64. De Compadri P, Koleva D, Mangia A, Motterlini Stat Sci N, Garattini L. Cost minimisation analysis of 12 or 24 weeks of peginterferon alfa-2b + ribavirin for hepatitis C virus. *J Med Econ*. 2008;11:151-163.
65. Nakamura J, Toyabe SI, Aoyagi Y, Akazawa K. Economic impact of extended treatment with peginterferon alpha-2a and ribavirin for slow hepatitis C virologic responders. *J Viral Hepat*. 2008;15:293-299.
66. Siebert U, Sroczynski G, Aidelsburger P, et al. Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines. *Pharmacoeconomics*. 2009;27:341-354.
67. Tahan V, Ozaras R, Karaca C, et al. Is HCV genotyping cost-effective even when the prevalences of genotypes 2 and 3 are low? *Hepatogastroenterology*. 2009;56:1425-1428.

68. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Am J Gastroenterol*. 2010;105:14-32.
69. Palmer AJ, Neeser K, Weiss C, Brandt A, Comte S, Fox M. The long-term cost-effectiveness of improving alcohol abstinence with adjuvant acamprosate. *Alcohol Alcohol*. 2000;35:478-492.
70. Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology*. 2005;41:1407-1432.
71. Scarborough JE, Pietrobon R, Marroquin CE, et al. Temporal trends in early clinical outcomes and health care resource utilization for liver transplantation in the United States. *J Gastrointest Surg*. 2007;11:82-88.
72. Northup PG, Abecassis MM, Englesbe MJ, et al; Adult-to-Adult Living Donor Liver Transplantation Cohort Study Group. Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost. *Liver Transpl*. 2009;15:148-162.
73. van der Hilst CS, Ijtsma AJ, Slooff MJ, Tenvergert EM. Cost of liver transplantation: a systematic review and meta-analysis comparing the United States with other OECD countries. *Med Care Res Rev*. 2009;66:3-22.
74. Cholongitas E, Marelli L, Shusang V, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl*. 2006;12:1049-1061.
75. Farnsworth N, Fagan SP, Berger DH, Awad SS. Child-Turcotte-Pugh versus MELD score as a predictor of outcome after elective and emergent surgery in cirrhotic patients. *Am J Surg*. 2004;188:580-583.
76. Hoteit MA, Ghazale AH, Bain AJ, et al. Model for end-stage liver disease score versus Child score in predicting the outcome of surgical procedures in patients with cirrhosis. *World J Gastroenterol*. 2008;14:1774-1780.
77. Wiesner R, Edwards E, Freeman R, et al; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124:91-96.
78. Axelrod DA, Koffron AJ, Baker T, et al. The economic impact of MELD on liver transplant centers. *Am J Transplant*. 2005;5:2297-2301.
79. Kogure T, Ueno Y, Kawagishi N, et al. The model for end-stage liver disease score is useful for predicting economic outcomes in adult cases of living donor liver transplantation. *J Gastroenterol*. 2006;41:1005-1010.
80. Washburn WK, Pollock BH, Nichols L, Speeg KV, Halff G. Impact of recipient MELD score on resource utilization. *Am J Transplant*. 2006;6:2449-2454.
81. Lopez PM, Martin P. Update on liver transplantation: indications, organ allocation, and long-term care. *Mt Sinai J Med*. 2006;73:1056-1066.
82. Buchanan P, Dzebisashvili N, Lentine KL, Axelrod DA, Schnitzler MA, Salvalaggio PR. Liver transplantation cost in the model for end-stage liver disease era: looking beyond the transplant admission. *Liver Transpl*. 2009;15:1270-1277.
83. Ammori JB, Pelletier SJ, Lynch R, et al. Incremental costs of post-liver transplantation complications. *J Am Coll Surg*. 2008;206:89-95.
84. Saab S, Ham MY, Stone MA, Holt C, Tong M. Decision analysis model for hepatitis B prophylaxis one year after liver transplantation. *Liver Transpl*. 2009;15:413-420.
85. Gee I, Alexander G. Liver transplantation for hepatitis C virus related liver disease. *Postgrad Med J*. 2005;81:765-771.
86. Saab S, Ly D, Han SB, et al. Is it cost-effective to treat recurrent hepatitis C infection in orthotopic liver transplantation patients? *Liver Transpl*. 2002;8:449-457.
87. Russell RT, Feurer ID, Wisawatapnimit P, Lillie ES, Castaldo ET, Pinson CW. Profile of health-related quality of life outcomes after liver transplantation: univariate effects and multivariate models. *HPB (Oxford)*. 2008;10:30-37.
88. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M; Cost-Effectiveness of Liver Transplantation Team. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl*. 2002;8:263-270.
89. Santos Junior R, Miyazaki MC, Domingos NA, Valério NI, Silva RF, Silva RC. Patients undergoing liver transplantation: psychosocial characteristics, depressive symptoms, and quality of life. *Transplant Proc*. 2008;40:802-804.
90. Saab S, Wiese C, Ibrahim AB, et al. Employment and quality of life in liver transplant recipients. *Liver Transpl*. 2007;13:1330-1338.
91. Kousoulas L, Neipp M, Barg-Hock H, et al. Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation. *Transpl Int*. 2008;21:1052-1058.
92. van Ginneken BT, van den Berg-Emons RJ, van der Windt A, et al. Persistent fatigue in liver transplant recipients: a two-year follow-up study. *Clin Transplant*. 2010;24:E10-E16.
93. Aberg F, Rissanen AM, Sintonen H, Roine RP, Höckerstedt K, Isoniemi H. Health-related quality of life and employment status of liver transplant patients. *Liver Transpl*. 2009;15:64-72.
94. Rongey C, Bambha K, Vanness D, et al. Employment and health insurance in long-term liver transplant recipients. *Am J Transplant*. 2005;5:1901-1908.
95. Thomas DJ. Returning to work after liver transplant: experiencing the roadblocks. *J Transpl Coord*. 1996;6:134-138.
96. Castaldo ET, Feurer ID, Russell RT, Pinson CW. Correlation of health-related quality of life after liver transplant with the model for end-stage liver disease score. *Arch Surg*. 2009;144:167-172.
97. Kanwal F, Gralnek IM, Hays RD, et al. Health-related quality of life predicts mortality in patients with advanced chronic liver disease. *Clin Gastroenterol Hepatol*. 2009;7:793-799.
98. Kanwal F, Hays RD, Kilbourne AM, Dulai GS, Gralnek IM. Are physician-derived disease severity indices associated with health-related quality of life in patients with end-stage liver disease? *Am J Gastroenterol*. 2004;99:1726-1732.
99. Saab S, Ibrahim AB, Shpaner A, et al. MELD fails to measure quality of life in liver transplant candidates. *Liver Transpl*. 2005;11:218-223.
100. Sagmeister M, Wong JB, Mullhaupt B, Renner EL. A pragmatic and cost-effective strategy of a combination therapy of interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 2001;13:483-488.
101. Stein K, Rosenberg W, Wong J. Cost effectiveness of combination therapy for hepatitis C: a decision analytic model. *Gut*. 2002;50:253-258.
102. Siebert U, Sroczynski G; German Hepatitis C Model GEHMO Group; HTA Expert Panel on Hepatitis C. Effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security. *Int J Technol Assess Health Care*. 2005;21:55-65.
103. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med*. 2000;133:665-675.
104. Sennfält K, Reichard O, Hultkrantz R, Wong JB, Jonsson D. Cost-effectiveness of interferon alfa-2b with and without ribavirin as therapy for chronic hepatitis C in Sweden. *Scand J Gastroenterol*. 2001;36:870-876.
105. Wong JB, Nevens F. Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium. *Acta Gastroenterol Belg*. 2002;65:110-111.
106. Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut*. 2003;52:425-432.
107. Wong JB, Davis GL, McHutchison JG, Manns MP, Albrecht JK; International Hepatitis Interventional Therapy Group. Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C. *Am J Gastroenterol*. 2003;98:2354-2362.
108. Siebert U, Sroczynski G, Wasem J, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. *Eur J Health Econ.* 2005;6:112-123.
109. Sroczynski G, Rafetseder O, Jonas S, Siebert U. *Antiviral Combination Therapy in Patients with Chronic Hepatitis C in Austria. Health Economic Evaluation of the Antiviral Combination Therapy with Interferon/Peginterferon Plus Ribavirin.* ITA project report vol B29. Vienna, Austria: ITA; 2006.
110. Brady B, Siebert U, Sroczynski G, et al. *Pegylated Interferon Combined with Ribavirin for Chronic Hepatitis C Virus Infection: An Economic Evaluation.* Technology report number 82. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2007.