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Trends in Waiting List Registration for Liver Transplantation for Viral Hepatitis in the United States

W. RAY KIM^{*}, NORAH A. TERRAULT[‡], RACHEL A. PEDERSEN[§], TERRY M. THERNEAU[§], ERICK EDWARDS^{||}, ANDREW A. HINDMAN[¶], and CAROL L. BROSGART[¶]

^{*} Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota

[‡] University of California-San Francisco, San Francisco, California

[§] Division of Biostatistics, Mayo Clinic College of Medicine, Rochester, Minnesota

^{||} United Network for Organ Sharing, Richmond, Virginia

[¶] Gilead Sciences, Inc, Foster City, California

Abstract

BACKGROUND & AIMS—In the last decade, significant progress has been made in the treatment of liver disease associated with chronic hepatitis, especially in patients infected with the hepatitis B virus (HBV). To investigate whether the population-wide application of antiviral therapies has impacted liver transplant waiting list registration, we analyzed longitudinal trends in waiting list registration for patients with hepatitis B and C and those with nonviral liver disease.

METHODS—This study represented a retrospective analysis of registry data containing all US liver transplant centers. All adult, primary liver transplantation candidates registered to the Organ Procurement and Transplantation Network between 1985 and 2006 were included in the analysis. Standardized incidence rates were calculated for waiting list registration for liver transplantation by underlying disease (HBV and HCV infection and other) and by indication for transplantation (fulminant liver disease, hepatocellular carcinoma [HCC], and end-stage liver disease [ESLD]).

RESULTS—Of 113,927 unique waiting list registrants, 4793 (4.2%) had HBV, and 40,923 (35.9%) had HCV infections; the remaining 68,211 (59.9%) had neither. The incidence of waiting list registration for ESLD and fulminant liver disease decreased, whereas that for HCC increased. The decrease in ESLD registration was most pronounced, and the increase in HCC was least dramatic among registrants with hepatitis B. The decrease in registration for ESLD secondary to HCV infection was also significantly larger than that for ESLD patients with non-viral etiologies.

CONCLUSIONS—The pattern of liver transplantation waiting list registration among patients with hepatitis B suggests that the widespread application of oral antiviral therapy for HBV contributed to the decreased incidence of decompensated liver disease.

Address requests for reprints to: W. Ray Kim, MD, Division of Gastroenterology and Hepatology (PL 6), 200 1st Street SW, Rochester, Minnesota 55905. kim.ray@mayo.edu; fax: (507) 538-3974.

Conflicts of interest

The authors disclose the following: W. Ray Kim received a grant from the Gilead Sciences, Inc, to conduct this study. He has served as a consultant for Roche, Bristol-Myers-Squibb, Idenix, Schering-Plough, and Gilead Sciences. Norah Terrault has received grants from Gilead Sciences, Cangene, NABI, and Roche and consulted Bristol-Myers-Squibb. Andrew Hindman was a former employee of Gilead Sciences, Inc, and Carol Brosgart was a former employee of Gilead Sciences. Terry Therneau, Rachel Pedersen, and Erick Edwards disclose no conflicts.

Chronic viral hepatitis resulting from chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) is an important cause of liver disease globally. In the United States, liver disease associated with chronic HBV and HCV infection constitutes major indications for liver transplantation (LTx) because chronic viral hepatitis not only causes liver failure associated with end-stage liver disease (ESLD) but also hepatocellular carcinoma (HCC).¹ The burden of chronic HBV infection in the United States is disproportionately among Americans that originate from other areas of the world, particularly Asians and Pacific Islanders, a rapidly increasing population group in the United States.² The prevalence of chronic HCV infection is the highest among middle-aged Americans (40 – 60 years of age).³ Given the long disease span of chronic HCV infection from its acquisition to the development of cirrhosis, it is feared that the burden of chronic HCV-related liver disease will continue to increase.⁴ An example of such a trend may be the increasing incidence, morbidity, and mortality associated with HCC, which is commonly associated with chronic viral hepatitis.^{5,6}

In the past decade, much progress has been made in the therapy of chronic viral hepatitis. For chronic HBV infection, the effectiveness of direct antiviral agents (ie, oral nucleos(t)ide analogues) has been shown in terms of sustained suppression of viral replication as well as biochemical and histologic improvement.^{7–13} Although permanent viral eradication is not expected because of the persistence of the intracellular replicative intermediary (so-called covalently closed circular DNA), long-term therapy is associated with significant clinical improvement, independent of the stage of liver disease. In particular, in patients with advanced fibrosis and cirrhosis, antivirals have been shown to prevent or reverse hepatic decompensation.^{14–16}

For chronic HCV infection, pegylated interferon α in combination with ribavirin has been the mainstay of therapy.^{17,18} Sustained virologic response, namely, undetectable viral HCV RNA 6 months after discontinuation of therapy, has been associated with cessation or reversal of fibrosis progression and improved survival.^{19,20} However, current antiviral therapy for chronic HCV infection has limited effectiveness, depending on the genotype, which is further reduced in patients with advanced fibrosis. Furthermore, it is poorly tolerated and generally contraindicated in patients with hepatic decompensation.²¹

Despite these advances in antiviral therapy against HBV and HCV, the population-wide effects of antiviral therapy have not been evaluated. Following a large increase in LTx activities for HBV-related liver disease in the 1990s when it became an accepted indication for LTx,²² anecdotal observations have been made by clinicians that liver transplantation for ESLD associated with chronic HBV infection has become less frequent. Accordingly, we hypothesized that waiting list registration for LTx related to chronic HBV infection has declined, whereas no such decrease would be found among patients with nonviral liver disease. The aims of this work included (1) to describe the longitudinal trend in LTx waiting list registration for viral and nonviral liver disease in the United States and (2) to explore possible reasons for the changes in the waiting list registrations.

Materials and Methods

Data Source and Elements

Data on all waiting list registrants in the United States were obtained from the Organ Procurement and Transplantation Network (OPTN; currently administered by the United Network for Organ Sharing), available as the Standard Transplant Analysis and Research file as of May 1, 2007. Of a wide array of information available in the database, elements necessary for the analysis included demographic information (age, sex, and race), diagnostic codes for underlying liver disease, presence of HCC, urgency status, and laboratory data

including viral serology and components of the Model for End-Stage Liver Disease system (MELD).

Subjects included in the analysis were all primary LTx candidates newly registered to OPTN between 1985 and 2006. Registration records in a given subject were linked together using a deidentified subject code, even if the subject was listed more than once at 1 or more listing centers. Thus, in a given subject, only the very first registration was identified and included in the analysis. Pediatric (<16 years of age) and repeat transplant candidates were excluded, although in the latter group, waiting list registration for their first LTx was included. Otherwise, candidates for multi-organ transplantation were included.

Liver disease diagnosis was determined primarily by the diagnostic codes (United Network for Organ Sharing codes 4102, 4106-7, 4202, 4206-7, and 4592 for HBV infection and 4103, 4104, 4106, 4204, 4206, 4216, and 4593 for HCV infection). However, it was not uncommon for diagnostic information to be written-in in the text fields available for supplemental comments. Text-based searches were conducted in those fields for specific diagnoses, allowing for typographical errors. Finally, results of serologic tests performed at the time of LTx were used to identify records with viral hepatitis, including hepatitis B surface antigen, hepatitis B e antigen, and immunoglobulin M (IgM) type antibodies against hepatitis B core or hepatitis B virus DNA for hepatitis B and antibodies against hepatitis C virus (anti-HCV) and hepatitis C RNA for hepatitis C.

Statistical Analysis

Based on the diagnostic information, patients were classified into 3 main diagnostic categories including HBV, HCV, and “Other” (non-HBV, non-HCV) groups. The rare patients with concomitant HBV and HCV infection were included in the HCV group. Within those groups, patients were further divided by the indication for LTx, including fulminant liver disease (FLD), HCC, and ESLD. FLD patients were identified by the status 1 designation. Patients who had an HCC diagnosis (United Network for Organ Sharing codes 4400, 4401) or an indication for HCC exception anytime prior to transplantation were included as HCC. Candidates with neither FLD nor HCC diagnosis were classified as ESLD.

Severity of liver disease at the time of waiting list registration was assessed by laboratory components of the MELD score, namely, serum concentrations of total bilirubin and creatinine as well as international normalized ratio (INR) for prothrombin time. OPTN began collecting MELD score data in 2001. MELD score was calculated according to the standard formula of $11.2 \log_e(\text{INR}) + 9.57 \log_e(\text{creatinine}) + 3.78 \log_e(\text{bilirubin}) + 6.43$; with a lower limit of 1 for all variables, creatinine capped at 4, and creatinine set to 4 in patients receiving renal replacement therapy. The MELD score (rounded to the nearest integer) had a possible range of 6 to 40.

The main analysis included comparison of the longitudinal trend in waiting list registration for HBV, HCV, and Other liver disease. The number of registrants in the 3 diagnostic groups was enumerated for each calendar year. The result was further divided into 3 indication categories, namely FLD, HCC, and ESLD. We then computed the incidence of waiting list registration in those categories, taking the entire adult US population as the denominator population at risk. The incidence was adjusted according to the age and sex distribution of the US census data. In estimating the variability of the data, it was assumed that, given a fixed number of person-years, the number of cases follows a Poisson distribution. This allowed the estimation of standard errors and the calculation of 95% confidence intervals (95% CI) for the incidence rates.

Temporal changes in waiting list registration were evaluated using the generalized linear model assuming a Poisson error structure. Based on the visually appreciable trends in waiting list registration, the Poisson model considered 3 eras (1994–1997, 1998–2001, and 2003–2006) as the main independent variable. Data prior to 1994 were not included in the analysis because of lack of consistent diagnosis and documentation for HCV. Year 2002 was omitted in the model because of the artificial reduction in the waiting list registration associated with the implementation of MELD-based allocation. Covariates considered in the Poisson model included the era, age (10-year intervals), sex, and race (white, African American [AA], and other). Temporal trends in the disease severity at the time of waiting list registration were examined by using linear regression to model MELD with listing year and diagnosis group.

Results

Between 1985 and 2006, there were 113,927 unique individuals registered to the OPTN waiting list for liver transplantation. Of those, 4.2% ($n = 4793$) met the criteria for HBV, whereas 35.9% ($n = 40,923$) were classified to have HCV. The remaining 59.9% ($n = 68,211$) did not have either hepatitis diagnosis and were grouped under “Other” diagnosis. The characteristics of these candidates are summarized in Table 1. The 3 groups were similar in age, whereas male sex predominated among patients with viral hepatitis, especially those with HBV. With regard to racial distribution, the proportion of non-white, non-AA subjects was much higher among those with HBV than the other 2 categories. As expected, the proportion of HCC was higher with viral hepatitis, particularly HBV, whereas status 1 registration for FLD was least common with HCV. Among patients with ESLD, the median MELD score was 16 for HBV, 14 for HCV, and 15 for Other ($P < .01$).

In Figure 1, the bars represent the total number of waiting list registrants by diagnosis between 1985 and 2006. There was a linear increase in the number of waiting list registrants in the 1980s and 1990s. The increase was seen in all 3 diagnosis groups, although HCV was not diagnosed prior to the introduction of anti-HCV testing in 1991. The number peaked at 8382 in 1999, followed by a substantial drop in 2002 ($n = 7319$), coincident with the implementation of MELD-based organ allocation. Since then, the number of registrants increased steadily to 8673 in 2006. The curve in Figure 1 depicts the age- and sex-adjusted incidence rates for waiting list registration, which showed a trend similar to the number of registrants. The incidence of waiting list registration peaked in 1999, dipped in 2002, and then showed a plateau at approximately 3.5 per 100,000 persons.

Figure 2 describes the incidence of waiting list registration for the 3 diagnosis groups. Figure 2A shows the incidence rate of waiting list registration for ESLD, FLD, and HCC with HBV. The most noticeable trend is the decline in waiting list registrations with ESLD since 1999—a 47% decrease over the ensuing 7 years. In contrast, those with HCC increased by 72% during the same period. Registrations with FLD decreased steadily after the initial uptake in the mid-1990s. In Figure 2B, registrations for ESLD and HCV, which increased rapidly during the 1990s, decreased since 1999, although the magnitude of decrease (30%) was smaller than that in HBV. In contrast, those with HCC increased by as much as 163% between 1999 and 2006. Finally, Figure 2C shows that registrations for ESLD for nonviral liver disease also reached a peak in 1999. It was followed by a small decrease and a plateau, such that the reduction between 1999 and 2006 was only 14%. Registrations for HCC in this category increased by 227% between 1999 and 2006.

Table 2 summarizes the results of multivariable Poisson regression model to make formal comparisons for the trends seen in Figure 2. Compared with era 2 (1998–2001), waiting list registration during era 1 (1994–1997) was significantly lower except for HBV registrants

with FLD, confirming the substantial increase in overall registration during the 1990s. Between eras 2 and 3, for all 3 diagnosis groups, registrations for ESLD and FLD decreased, whereas those for HCC increased. When the slopes of these changes were compared across diagnosis, the reduction in ESLD registration for HBV was significantly steeper than that for HCV ($P < .01$), which, in turn, was significantly steeper than that for Other ($P < .01$). The rise in registration for HCC was significantly lower for HBV ($P < .01$), compared with HCV or Other, whereas the slopes in the latter 2 groups were comparable ($P = .15$). The reduction in FLD with HCV was steeper than that with HBV ($P = .02$) or Other ($P < .01$), whereas the slopes for the latter 2 were not significantly different from each other ($P = .15$).

Figure 3 compares the mean MELD scores of patients with ESLD at waiting list registration among the 3 diagnosis groups since MELD data started to be routinely collected during 2001. There was a gradual increase in MELD scores in all 3 groups. Consistent with data in Table 1, the MELD score among HBV registrants was significantly higher than those with Other diagnosis, which, in turn, was higher than that for HCV. However, the 3 curves moved parallel to each other over time (P for difference in slope = .67).

Discussion

In this work, we clearly demonstrate that, recently, there has been a significant decrease in waiting list registration for ESLD secondary to chronic viral hepatitis, particularly HBV. This reduction was partly attributable to a general trend in ESLD registration since implementation of the minimal listing criteria in 1998 and MELD-based organ allocation in 2002.^{23,24} However, the trend in HBV was much more pronounced and statistically significantly different compared with that in the HCV and nonviral categories. In contrast, against the backdrop of a general rise in the registration for HCC, the rate of increase was significantly lower among HBV registrants compared with HCV and Other diagnoses.

A decline in transplant waiting list registration for a particular diagnosis may stem from a true reduction in the suitable candidates with the condition and/or represent an artifact related to the changes in the listing practice. The latter possibility may include (1) reclassification of patients from ESLD to HCC, in light of the recent organ allocation system that has given preferential priority to patients with HCC or (2) difference in the timing of referral and waiting list registration in a subgroup of patients. Although the OPTN data may not completely address these possibilities, the following consideration suggests that neither of them is likely the main reason for the trends being reported.

First, with regard to the possibility of reclassification of registrants, it is likely that capture of the diagnosis of HCC in the OPTN data was more complete in the recent era than previously. The change in liver allocation system in 2002 ultimately had the impact of systematically increasing priority given to patients with HCC.²⁵ The diligence with which HCC is looked for and reported to OPTN in an LTx candidate has consequently become much greater and likely contributed to the trend of increased number of LTx candidates with HCC at the expense of reduction in those with ESLD. However, importantly, such reclassification should have affected all disease categories and, thus, would not explain the larger decline in waiting list registration seen in viral hepatitis. Furthermore, in the case of HBV, the increase in the registration with HCC was slower than the other categories, making it still less likely that reclassification from ESLD to HCC is the main reason for the decline in ESLD registration.

Second, it may be possible that changes in waiting list registration resulted from variability in the timing of referral or listing. For example, because viral hepatitis tends to be more prevalent in minority groups, an increasing delay in referral for LTx in those patients may

lead to some patient being too ill to be considered for LTx, resulting in a decrease in waiting list registration. If this was the case, one would expect to see higher MELD scores in those patients. In Figure 3, HBV patients were listed with significantly higher MELD scores than the others, which does indicate that HBV patients were indeed listed late. However, an important point is that the listing MELD scores in HBV patients changed in parallel to those in other patients while their registration was decreasing. If there was a bias unique to HBV registrants, their listing MELD scores would have increased at a greater rate than those of other groups.

These considerations point to a true reduction in the number of candidates with ESLD secondary to chronic viral hepatitis. This trend, in turn, may be a result of (1) a real change in disease epidemiology (ie, decreased incidence in ESLD in the population) or (2) reduction in the proportion of patients that are suitable candidates among patients developing ESLD. With regard to epidemiology of HBV, available data indicate that the prevalence of chronic HBV infection in the US population has been increasing as a result of influx of immigrants from regions of the world endemic with HBV.²⁶ Thus, there is a dichotomy between increasing prevalence of chronic HBV infection and decreasing incidence of ESLD associated with it. The most likely explanation for this dichotomy is widespread use of effective antivirals that have been shown to reduce the incidence of hepatic decompensation.¹⁴

The other plausible explanation may be that a decreasing proportion of patients remain suitable candidates for LTx without a true decrease in the number of patients who develop ESLD. We suspect that this scenario might turn out to be the case, at least in part, with ESLD secondary to HCV for which our data showed a decline in waiting list registration, while there is no other epidemiologic evidence for a reduction in the incidence of ESLD. Regardless of the incidence of ESLD secondary to HCV in the population, it is possible that fewer patients are registered for LTx because an increasing proportion of patients are unsuitable candidates. For example, as the average age of HCV patients increase, many may become too old or have unacceptable comorbid conditions such that LTx is no longer offered. In case of HBV, however, Everhart and Ruhl recently demonstrated a decreasing trend in mortality rate from HBV infection in the United States, essentially in parallel with the reduction in waiting list registration shown in this analysis.²⁷ These 2 corroborating analyses suggest that there has been true reduction in the incidence of ESLD attributable to HBV.

The last piece of circumstantial evidence for the causal role of HBV antivirals in the reduction in the incidence of ESLD is the temporal correlation and the rapidity with which the reduction occurred. Lamivudine became available (for human immunodeficiency virus patients) in 1995 and was approved by the US Food and Drug Administration for HBV in 1998. Adefovir dipivoxil was approved in 2002, entecavir in 2005, and telbivudine in 2006. In addition, tenofovir disoproxil fumarate, approved for HBV in 2008, had been used in clinical practice “off-label” since its introduction in 2001 for the human immunodeficiency virus indication.¹³ These medications rapidly and potently suppress HBV replication, which has been associated not only with reversal of fibrosis and, in some cases, of cirrhosis but also with prevention and reversal of hepatic decompensation among those with advanced fibrosis and cirrhosis.^{14,16,28} Although the impact of oral antivirals on the incidence of HCC is less well established, it is probably smaller and delayed compared with that on ESLD.¹⁴ One could hypothesize that the slower increase in HCC registration in the HBV category, compared with others, may also be related to the effect of antivirals.¹⁴

Whether antiviral therapy played any role in the reduction in HCV registration is much more difficult to assess. Population surveys have shown that, as the cohort of Americans infected

with HCV grows older, the number of individuals with long-standing HCV infection is increasing.^{3,29} On the other hand, recent nationwide statistics indicate that mortality related to chronic HCV infection may have reached a plateau.³⁰ The effect of anti-HCV therapy at the population level is likely to have a much longer lag period compared with that for HBV, because the regimens available to date are not uniformly effective, especially in patients with advanced fibrosis and contra-indicated, by and large, in those with decompensated liver disease.²¹ Thus, it is difficult to be confident that antiviral therapy has led to a decrease in ESLD waiting list registration secondary to HCV. As previously stated, the proportion of HCV patients with ESLD eligible for LTx may be decreasing, independent of the incidence of ESLD related to HCV.

Last, we found that waiting list registration for FLD (“status 1”) decreased over time in all 3 diagnosis groups. We believe there may be several reasons for the observation. First, for HBV, it is likely that the pool of susceptible individuals being exposed to the infection has decreased. There has been a precipitous drop in the incidence of new HBV infection in the United States since the mid-1990s as a result of a number of public health interventions such as increasing coverage of the population with HBV vaccine and widespread awareness of risks of parenteral transmission of human immunodeficiency virus and other infectious diseases.³¹ Second, we believe that there was a misclassification in the past of patients presenting with acute deterioration of underlying chronic liver disease as FLD. This very likely explains the trend seen in HCV registration. FLD presentation with acute HCV infection is extremely rare, and the patients registered as status 1 previously probably represent misclassification, which has decreased over time. Finally, acute non-viral liver disease showed the least amount of changes over time, consistent with lack of epidemiologic data to indicate meaningful changes in the incidence of FLD from nonviral etiologies in the United States.^{32,33}

In conclusion, since the mid-1990s, a number of trends in the waiting list registration have occurred, including an overall reduction in ESLD and FLD over time, along with persistent increase in HCC. Whereas some of these changes are attributable to the changes in the organ allocation system, the trend seen with hepatitis B-related liver disease, namely a more rapid decrease in ESLD and slower rise in HCC, was significantly more pronounced compared with that with hepatitis C-related and non-viral liver disease. The evidence to link this trend to antiviral therapy is indirect and circumstantial; however, there are few other plausible explanations for this trend other than a widespread application of antiviral therapy. The changes in ESLD in other categories in the last few years, downward in those with HCV infection and slightly upward in those with non-viral diseases, need to be followed in the future.

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Abbreviations in this paper

FLD	fulminant liver disease
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HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
LTx	liver transplantation
OPTN	Organ Procurement and Transplantation Network

References

1. Kim WR, Brown RS Jr, Terrault NA, et al. Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002;36:227–242. [PubMed: 12085369]
2. Kim WR, Benson JT, Therneau TM, et al. Changing epidemiology of hepatitis B in a US community. *Hepatology* 2004;39:811–816. [PubMed: 14999701]
3. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705–714. [PubMed: 16702586]
4. Davis G, Albright J, Cook S, et al. Projecting the future healthcare burden from hepatitis C in the United States (abstr). *Hepatology* 1998;28:390A.
5. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745–750. [PubMed: 10072408]
6. El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003;139:817–823. [PubMed: 14623619]
7. Dienstag J, Schiff E, Wright T, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256–1263. [PubMed: 10528035]
8. Marcellin J, Chang T-T, Lim S, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;384:808–816. [PubMed: 12606735]
9. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003;348:800–807. [PubMed: 12606734]
10. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354:1001–1010. [PubMed: 16525137]
11. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354:1011–1020. [PubMed: 16525138]
12. Lai C-L, Gane E, Liaw Y-F, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007;357:2576–2588. [PubMed: 18094378]
13. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442–2455. [PubMed: 19052126]
14. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–1531. [PubMed: 15470215]
15. Fontana RJ, Keeffe EB, Carey W, et al. Effect of lamivudine treatment on survival of 309 North American patients awaiting liver transplantation for chronic hepatitis B. *Liver Transplantation* 2002;8:433–439. [PubMed: 12004342]
16. Schiff ER, Lai C-L, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology* 2003;38:1419–1427. [PubMed: 14647053]
17. Manns M, McHutchison J, Gordon S, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958–965. [PubMed: 11583749]
18. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–982. [PubMed: 12324553]

19. Poynard T, McHutchison J, Davis GL, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000;32:1131–1137. [PubMed: 11050066]
20. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alfa is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007;45:579–587. [PubMed: 17326216]
21. Strader DB, Wright T, Thomas DL, et al. American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004;39:1147–1171. [PubMed: 15057920]
22. Kim WR, Poterucha JJ, Kremers WK, et al. Outcome of liver transplantation for hepatitis B in the United States. *Liver Transpl* 2004;10:968–974. [PubMed: 15390321]
23. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997;3:628–637. [PubMed: 9404965]
24. Kamath PS, Kim WR. Model for End-stage Liver Disease (MELD). *Hepatology* 2007;45:797–805. [PubMed: 17326206]
25. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004;127(5 Suppl 1):S261–S267. [PubMed: 15508092]
26. Welch S, Chiang B, Shadday P, et al. Estimated prevalence of chronic hepatitis B in foreign-born persons living in the United States by country/region of origin (abstr). *Hepatology* 2008;48:687A. [PubMed: 18666260]
27. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States, part III: liver, biliary tract, and pancreas. *Gastroenterology* 2009;136:1134–1144. [PubMed: 19245868]
28. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–117. [PubMed: 12512035]
29. Alter M, Moran-Kruszon D, Nainan O, et al. The prevalence of hepatitis C virus infection in the United States. *N Engl J Med* 1994;341:556–562. [PubMed: 10451460]
30. Wise M, Bialek S, Finelli L, et al. Changing trends in hepatitis C-related mortality in the United States, 1995–2004. *Hepatology* 2008;47:1128–1135. [PubMed: 18318441]
31. Hepatitis surveillance report 61. Atlanta, GA: Centers for Disease Control and Prevention; 2006.
32. Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. *Am J Gastroenterol* 2007;102:2459–2463. [PubMed: 17608778]
33. Lee WM, Squires RH Jr, Nyberg SL, et al. Acute liver failure: summary of a workshop. *Hepatology* 2008;47:1401–1415. [PubMed: 18318440]

Figure 1. Total number of waiting list registrants (*bars*) and age-, gender-, and race-adjusted incidence rate of waiting list registration between 1985 and 2006.

Figure 2.
Incidence rates for waiting list registration: (A) for HBV, (B) HCV, and (C) other diagnosis.

Figure 3.
Mean MELD scores at the time of waiting list registration.

Table 1

Characteristics of Waiting List Registrants: 1985–2006

	HBV (n = 4793)	HCV (n = 40,923)	Other (n = 68,211)	P value
Age, y ^a	51 [43–58]	50 [45–55]	51 [42–59]	
Male, n (%)	3739 (78.0)	28,591 (69.9)	36,709 (53.8)	<.01
Race, n (%) ^b				<.01
AA	469 (9.8)	3379 (8.3)	4792 (7.0)	
Other	2064 (43.1)	7777 (19.0)	9563 (14.0)	
White	2260 (47.1)	29,765 (72.7)	53,695 (78.7)	
Indication, n (%)				<.01
Fulminant (status 1)	542 (11.3)	1246 (3.1)	8060 (11.8)	
HCC	913 (19.1)	4968 (12.1)	2901 (4.3)	
ESLD	3338 (69.6)	34,709 (84.8)	57,250 (83.9)	
Severity ^c				
Bilirubin	2.5 [1.3–6.0]	2.1 [1.3–3.5]	2.5 [1.4–5.2]	
Creatinine	1.0 [0.8–1.4]	0.9 [0.8–1.2]	1.0 [0.8–1.3]	
INR	1.5 [1.2–1.9]	1.4 [1.2–1.6]	1.3 [1.2–1.7]	
MELD	16 [11–23]	14 [11–18]	15 [11–20]	

AA, African American.

^aMedian [interquartile range].^bRace designation was missing in 161 (0.14%) patients including 2 in HCV and 159 in Other categories.^cAmong registrants with ESLD. Median [interquartile range].

Results of Multivariable Poisson Regression Analysis Evaluating the Effects of Era of Registration and Indication for Registration, Adjusting for Age, Gender, and Race: 1994–2006 Data, Excluding 2002

Table 2

Variable	Hepatitis B			Hepatitis C			Other		
	IRR (95% CI)	P value		IRR (95% CI)	P value		IRR (95% CI)	P value	
ESLD	n = 3003		n = 31,401			n = 40,925			
Era 1	0.91 (0.84–0.99)	.04	0.65 (0.63–0.67)	<.01	0.89 (0.87–0.91)	<.01			
Era 3	0.61 (0.56–0.67)	<.01	0.80 (0.78–0.83)	<.01	0.89 (0.87–0.92)	<.01			
HCC	n = 807		n = 4393			n = 2581			
Era 1	0.71 (0.55–0.91)	<.01	0.41 (0.36–0.46)	<.01	0.51 (0.44–0.59)	<.01			
Era 3	1.31 (1.13–1.54)	<.01	2.13 (1.99–2.29)	<.01	1.96 (1.79–2.15)	<.01			
FLD	n = 491		n = 1099			n = 4731			
Era 1	1.06 (0.86–1.30)	.58	1.34 (1.18–1.53)	<.01	1.21 (1.13–1.30)	<.01			
Era 3	0.75 (0.60–0.94)	.01	0.53 (0.45–0.63)	<.01	0.89 (0.83–0.95)	<.01			

IRR, incidence rate ratio.

NOTE. Era 1 (1994–1997) and era 3 (2003–2006) were compared with era 2 (1998–2001).