Published in final edited form as:

Clin Gastroenterol Hepatol. 2017 May ; 15(5): 767–775.e3. doi:10.1016/j.cgh.2016.11.034.

Hepatocellular Carcinoma is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States

Ju Dong Yang[1], **Joseph J. Larson**[2], **Kymberly D. Watt**[1], **Alina M. Allen**[1], **Russell H. Wiesner**[1], **Gregory J. Gores**[1], **Lewis R. Roberts**[1], **Julie A. Heimbach**[3], and **Michael D. Leise**[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN

[2]Division of Biomedical Statistics and Informatics, Mayo Clinic College of Medicine, Rochester, MN

[3]Division of Transplant Surgery, Mayo Clinic College of Medicine, Rochester, MN

Abstract

Background & Aims—Management strategies for patients with hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC) have changed, along with liver allocation policies based on model for end-stage liver disease (MELD) score. We investigated etiologic-specific trends in liver transplantation in the United States (US) during different time periods.

Methods—We performed a retrospective study, using the United Network for Organ Sharing/ Organ Procurement and Transplantation Network registry data to identify all adult patients registered for liver transplantation in the US from January 1, 2004 through December 31, 2015. For subjects listed with multiple diagnoses, HCC was considered the primary listing diagnosis. To determine whether availability of direct-acting antiviral agents, which began in 2011, affected pre-transplant (death or dropout) and post-transplant outcomes for patients with HCV infection, we compared data from the time periods of 2004–2010 and 2011–2014. We used competing risk analysis to compare differences in endpoints between these periods. Differences between periods in pre- and post-transplantation outcomes were estimated using Kaplan-Maier analysis and compared using the log-rank test. Associations between year of listing and pre-liver transplant outcome, and year of liver transplant and survival following transplant, were examined using the

Corresponding Author: Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, Leise.Michael@mayo.edu; Phone: 507-284-3917.

Disclosure: The authors do not have conflict of interest related to this work.

Author Contributions:

Study concept, design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript: Ju Dong Yang
Confirmation of analysis, interpretation of data, critical revision of the manuscript: Joseph J. Larson
Study concept, interpretation of data and critical revision of the manuscript: Kymberly D. Watt, Alina M. Allen, Russell H. Wiesner, Gregory J. Gores, Lewis R. Roberts, Julie A. Heimbach Study concept, design, interpretation of data and critical revision and final approval of the manuscript: Michael D. Leise

log-rank test. Proportional hazard regression was used to evaluate the reliability of the time period effect with potential confounders.

Results—Among 109,018 registrants, 18.5% were registered for liver transplantation due to HCC. In 2015, HCC was the leading diagnosis among registrants (23.9% of registrations) and recipients (27.2% of recipients). Between 2004 and 2015, the ratio of registrants with vs without HCC increased 5.6-fold for patients with HCV infection, 1.9-fold for patients with HBV infection, 2.7-fold for patients with alcohol abuse, and 10.2-fold for patients with nonalcoholic steatohepatitis. After adjusting for covariates, we associated the period of 2011–2014 with a decreased probability that HCC registrants would undergo liver transplantation (hazard ratio [HR], 0.62; $P<.0001$). The period of 2011–2014 was also associated with decreased probability of dropout due to deterioration or death from HCV-induced (HR, 0.90; $P=.0003$), HBV-induced (HR, 0.71; $P=.002$), or alcohol-induced (HR, 0.90; $P=.01$) liver disease, and an increased probability of delisting due to clinical improvement in patients with HCV infection (HR, 3.4; $P<.0001$), HBV infection (HR, 2.3; $P=.004$, or alcohol abuse (HR, 2.2; $P<0.0001$). The period of 2011–2014 was associated with a decreased risk of graft loss or death, with the largest effect seen in HCV-infected recipients (HR, 0.76; $P<.0001$).

Conclusion—HCC was the leading indication for liver transplantation in the US in 2015. Despite this, the probability of liver transplantation decreased the most in registrants with HCC. Pre- and post-transplantation outcomes have improved, particularly in patients with HCV infection.

Keywords

UNOS/OPTN; database; liver cancer; LT

Introduction

Patients with hepatocellular carcinoma (HCC) within Milan criteria are eligible for the MELD exception score in the current UNOS (United Network for Organ Sharing) organ allocation system in the United States (US). There have been concerns raised that the current organ allocation system gives HCC patients an unfair advantage.[1] A recent study showed that HCC patients are more likely to be placed on LT waitlists than patients with decompensated cirrhosis.[2] In addition, increasing incidence rates of HCC further contributes to HCC becoming a major indication for LT in the US.[3, 4]

HCV, a major driver of the increasing incidence of HCC, has been the leading diagnosis in registrants and recipients for liver transplant (LT) over the past few years.[5, 6] With the introduction of highly potent direct antiviral agents (DAA), morbidity and mortality from HCV induced hepatic decompensation are expected to decrease.[7] Highly successful eradication of HCV infection has also been demonstrated in the post LT setting.[8] While robust data are lacking, successful treatment of HCV infection is expected to improve post-LT outcomes in patients with HCV.

A recent study showed that the burden of liver disease from nonalcoholic steatohepatitis (NASH) continues to increase.[95, 610] In parallel with the increasing trend of NASH as an

indication for LT among registrants, the number of LT recipients with alcoholic liver disease also continued to rise in the US between 2009 and 2013.[6]

The aim of the current study was to investigate recent etiology-specific epidemiologic trends in the LT registrants and recipients and the trend of pre- and post-LT outcomes in the US.

Methods

Database

United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) registry data was obtained to identify all adult patients aged 18 years and older who were registered for LT in the US between January 1 2004 and December 31 2015. The indication of LT was based on the primary or secondary listing diagnosis of individual registrants. Text fields were also screened to determine the listing diagnosis. Each registrant was assigned to a single listing indication in the following order: HCC > HCV > HBV > alcoholic liver disease > cholestatic liver disease > NASH > cryptogenic cirrhosis. Although UNOS provides a primary diagnosis code for NASH, a significant proportion of patients with cryptogenic cirrhosis may have unrecognized NASH as the underlying etiology of cirrhosis. Hence, we assigned registrants with cryptogenic cirrhosis and a body mass index (BMI) ≥30 to the NASH category, consistent with other recent high profile studies.[5, 6] The underlying etiology of HCC was determined based on either the primary or secondary listing diagnosis. Each registrant was represented once and those who were listed for re-transplant during the study period were not counted multiple times.

Statistical analysis

We hypothesized that the introduction of DAA in 2011 resulted in significantly improved pre- and post-LT outcomes for HCV recipients. Therefore, year of listing or LT were dichotomized into two eras, 2004–2010 vs. 2011–2014. To avoid potential update bias and insufficient follow up, subjects who were listed or received LT in 2015 were not included in the outcome analysis.

Because there are multiple possible endpoints while on the waitlist, competing risk analysis was performed to assess differences in the endpoints between the study eras. The pre-transplant outcomes assessed included death or dropout due to clinical deterioration, transplant, or delisting due to clinical improvement. Differences in graft failure or graft failure combined with death between the two eras were assessed by Kaplan-Maier analysis. Associations between year of listing and pre-LT outcome, and year of LT and post-LT survival were examined using the log-rank test.

Proportional hazard regression was used to evaluate the reliability of the era effect with potential confounders including age, gender, MELD at listing, race/ethnicity, diabetes and BMI. As a sensitivity analysis, all pre-LT competing risk and post-LT Kaplan-Maier analyses were repeated, restricting to listings and LT through 2013 to allow all subjects the opportunity to have two full years of follow-up. All follow-up was censored at December 31, 2015. The study was exempt from Institutional Review Board of Mayo Clinic per institutional protocol. SAS version 9.4M3 (SAS Institute, Cary, NC) and R statistical

software, version 3.2.0 (R Foundation for Statistical Computing, Vienna) were used for statistical analysis.

Results

Clinical characteristics of registrants at the time of Listing

Clinical characteristics of LT registrants are summarized in Supplementary Table 1. A total of 109,018 registrants were listed for LT between January 1 2004 and December 25, 2015. The proportion of HCC registrants increased in the more recent era (15.1% in 2004–2010 vs. 22.9% in 2011–2015) while the proportion of HCV registrants decreased (35.4% in 2004–2010 vs. 25.2% in 2011–2015; P<0.0001). The mean biologic MELD score at listing (16.6 in 2004–2010 vs. 17.4 in 2011–2015) and BMI (28.5 in 2004–2010 vs. 28.8 in 2011–2015) both increased in the more recent era (both P<0.0001).

Etiology specific trends in the number of new registrants and recipients for liver transplant

The number of LT registrants with the indication of HCC increased 3-fold over the 12 year period of the study, from 775 in 2004 to 2,336 in 2015) (Figure 1A). HCV was the leading listing diagnosis between 2004 and 2014, but the number of HCV registrants (without HCC) dropped steeply after 2011, so that by 2015 it had become the third most common listing diagnosis after HCC and alcohol (Figure 1A).

The number of LT recipients with HCC increased progressively over the 12 year period, with HCC becoming the leading indication among LT recipients in 2015 (Figure 1B).

While the number of HCV recipients gradually declined over the study period, the number of recipients with alcohol and NASH increased progressively (Figure 1B). When HCC registrants were reclassified by the primary or secondary etiologic listing diagnosis, HCV was the leading indication for listing but the number of HCV registrants trended downwards after 2011 (Figure 1C). When HCC recipients were reclassified by primary or secondary etiologic listing diagnosis, HCV was the leading indication among LT recipients and the number of HCV recipients remained stable while the number of recipients with alcohol and NASH diagnosis continued to increase (Figure 1D).

Trends of Underlying Etiology in the HCC registrants

Figure 2 shows the trend of underlying etiology for LT registrants with HCC). In contrast to the rapid decline in the number of HCV registrants without HCC (Figure 1A), the number of HCV registrants with HCC continued to increase until 2014 and then plateaued (Figure 2A). The numbers of HCC registrants with alcohol or NASH etiology have steadily increased.

Between 2004 and 2015, the ratio of registrants with HCC versus without HCC for each etiology increased 5.6, 1.9, 2.7 and 10.2-fold for the HCV, HBV, alcohol and NASH etiologies, respectively (Figure 2B).

Etiology specific trends of pre transplant outcomes of LT registrants

We examined the recent trends in probability of receiving LT, drop out due to clinical deterioration or death and delisting due to clinical improvement (Figure 3). Given that a large proportion of HCC registrants had HCV, HCC registrants were divided in to two groups (HCC with HCV and HCC without HCV). Two year LT probability has minimally decreased in all etiology subgroups while the magnitude of reduction was most prominent in HCC with HCV registrants (81% to 74%, P<0.0001) and HCC without HCV registrants (70% to 64%, P<0.0001). Two year dropout probability due to clinical deterioration or death has slightly increased except in HBV registrants. Two year delisting probability due to clinical improvement has significantly increased in registrants with HCC with HCV, HCV, HBV and alcohol.

After adjusting for age, gender, race/ethnicity, MELD, diabetes and BMI, listing in the recent era was associated with a lower likelihood of receiving LT (Table 1). The magnitude of reduction in the probability of receiving LT in recent era was highest in HCC registrants with HCV (Hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.59–.0.64; P<0.0001) and HCC registrants without HCV (HR, 0.62; 95%CI, 0.58–0.66; P<0.0001). After adjusting for same covariates, listing in recent era (2011–2014) was associated with a lower probability of drop out due to clinical deterioration or death in registrants with HCV (HR, 0.90; 95%CI, 0.86–0.95; P=0.0003), HBV (HR, 0.71; 95%CI, 0.57–0.89 ; P=0.002) and alcohol (HR, 0.90; 95%CI, 0.84–0.97; P=0.01) and with a higher likelihood of delisting due to clinical improvement in registrants with HCV (HR, 3.42; 95%CI, 2.66–4.39; P<0.0001), HBV (HR, 2.25; 95%CI, 1.29–3.93; P=0.004) and alcohol (HR, 2.21; 95%CI, 1.75–2.80; P<0.0001) (Table 2). The result remained similar after excluding registrants listed after 2014 (Supplementary Table 2).

Etiology specific trends of post transplant outcome of LT recipients

The number of post LT graft failures has rapidly decreased in the recent years for both HCV (alone) and HCC with HCV recipients (Supplementary Figure 1). Two year probability of graft failure decreased in recipients with HCC with HCV, HCC without HCV, HCV, alcohol and NASH (Figure 4). After adjusting for covariates, LT in the recent era was associated with a decreased risk of graft loss in recipients with HCC with HCV (HR, 0.70; 95%CI, 0.63–0.79; P<0.0001), HCC without HCV (HR, 0.74; 95%CI, 0.61–0.89; P=0.002), HCV (HR, 0.69; 95%CI, 0.64–0.75; P<0.0001), alcohol (HR, 0.70; 95%CI, 0.60–0.80; P<0.0001) and NASH (HR, 0.74; 95%CI, 0.63–0.86; P<0.0001) (Table 2).

Similar trends were noted for overall or graft survival in LT recipients (Supplementary Figure 2). Two year post LT overall or graft survival has improved significantly in recent years in recipients with HCC with HCV, HCC without HCV, HCV and alcohol. After adjusting for other covariates, LT in the recent era was associated with better overall or graft survival in recipients with HCC with HCV (HR, 0.82; 95%CI, 0.74–0.90; P<0.0001), HCC without HCV (HR,0.83; 95%CI, 0.71–0.98; P=0.03), HCV (HR, 0.76; 95%CI, 0.71–0.82; P<0.0001), alcohol (HR, 0.82; 95%CI, 0.72–0.93; P=0.002) and NASH (HR, 0.83; 95%CI, 0.72–0.95; P=0.01) (Table 2). The results remained stable after excluding LT recipients after 2014 (Supplementary Table 3).

Discussion

We conducted a study to investigate the recent indication and etiology specific trends in the number of LT registrants and recipients and the pre- and post-LT outcome in the US with special emphasis on HCC and HCV. Registrants and recipients with HCC continue to increase throughout the analysis period, making HCC the leading indication among both LT registrants and recipients in 2015. The number of HCV registrants without HCC declined rapidly between 2011 and 2015, resulting in a 48% overall reduction between 2004 and 2015. Compared to the previous era, being listed in the recent era was associated with a 38% decreased probability of LT among HCC registrants. Listing in the recent era was also associated with a decreased probability of dropout due to deterioration or death in HCV, HBV and alcohol and increased probability of delisting due to clinical improvement in HCV, HBV and alcohol after adjusting for covariates. While improvement in pre and post LT outcome was pervasive in most etiologies, the magnitude of improvement was highest in HCV registrants, possibly reflecting the impact of improved treatment of HCV using DAAs treatment in the recent era.

The Share 35 policy was adopted in June 2013. The policy generally results in HCC registrants with A or O blood type needing to accrue 35 exception points in most regions before receiving LT.[11–13] Despite this change and the decreased probability of receiving LT among HCC registrants, the absolute number of HCC recipients continues to increase due to the rapidly increasing number of HCC registrants. Thus, the ratio of HCC versus non HCC registrants increased in all underlying etiologies, suggesting that the increasing burden of HCC is pervasive among registrants with different etiologies of liver disease. The ratio of HCC versus non HCC was higher in registrants with viral hepatitis than in registrants with NASH or alcohol etiology. The decreased likelihood of death from hepatic decompensation and increasing number of older registrants with controlled hepatitis B or cured hepatitis C and stable cirrhosis may have resulted in higher ratios of HCC versus non HCC in registrants with viral hepatitis.[14] This ratio may continue to increase with better management of viral hepatitis and the complications of end stage liver disease particularly in patients with viral hepatitis.[7, 15]

There was a substantial reduction in the number of HCV registrants without HCC, particularly after 2011 when DAA’s became available for HCV. DAA use can result in the improvement of advanced liver disease from HCV and the availability of DAA may contribute to decreased frequency of hepatic decompensation, thus decreasing the number of registrants for LT among HCV patients.[16, 17] While successful treatment of HCV with DAA will likely continue to result in a decrease the number of HCV patients with decompensated liver disease, these patients need to be monitored on a regular basis after HCV treatment and be considered for LT if they develop HCC. Another potential explanation for the decreasing trend of HCV registrants is the aging of the birth cohort of HCV patients in the US general population, who may no longer qualify for LT listing due to advanced age or other medical comorbidities.

A multicenter European study of 103 HCV patients listed for LT receiving DAA treatment showed that 19% were delisted within 60 weeks due to clinical improvement.[17] While a

much smaller proportion of HCV registrants were delisted in the current study, it is encouraging that listing in the recent era was associated with a 3.4 fold increased probability of delisting due to clinical improvement among HCV registrants (HR, 3.4; P<0.0001). It is still controversial as to whether HCV registrants should be treated with DAA or not prior to versus post LT, as DAA treatment can potentially decrease the MELD scores without affecting portal hypertensive complications, leaving patients in 'MELD purgatory'.[1819, 20] Although information regarding HCV treatment of HCV registrants is not available in the OPTN registry, our data, together with the multicenter European study result, suggest that availability of DAA and pre-LT use may further increase the probability of delisting due to clinical improvement among LT registrants. While recent other studies showed an association between DAA and early recurrence of HCC post LT, recent era was not associated with adverse pre and post LT outcome in the current study.[21, 22]

High rates of HCV cure after LT has been shown in previous studies.[19, 23] The rapidly decreasing numbers of graft failure among HCV recipients and HCC recipients with HCV within the recent era appears to be a true reflection of the effectiveness of DAA in the prevention of graft failure in the post LT setting, thus post LT outcome may be expected to improve further in the near term.

The increasing prevalence of obesity and metabolic syndrome in the US has placed NASH as the one of the most rapidly increasing indication for LT registration.[6, 24, 25] A previous study anticipated that, NASH will become the most common indication for LT in the US within the next 10 to 20 years should the recent trends continue.[5] While the increasing number of registrants with NASH has been well recognized and anticipated, increasing number of registrants with alcohol etiology has not been expected.[5, 6] In spite of the stringent criteria involved in selecting reformed patients with alcohol induced liver disease for LT, the number of registrants has steadily increased since 2009, tracking more steeply upward between 2014 and 2015, making it the leading indication for LT registrations among non HCC registrants, surpassing HCV in 2015. Our data are consistent with recent report showing that alcohol was a more common indication for LT than NALFD in 2014.[26] When the listing indication of HCC registrants were replaced by the diagnosis of underlying etiology of liver disease (Figure 1C), alcohol induced liver disease was still the second leading cause among LT registrants after HCV, but exhibits a trajectory of becoming the leading underlying etiology for LT listing, surpassing HCV in the next few years. Excessive alcohol consumption is a major public health concern and it is the third leading cause of preventable death in the United States, accounting for almost 90,000 deaths including 18,000 deaths from alcoholic liver disease per year.[27]

As with other previous studies utilizing the UNOS/OPTN database, we acknowledge several limitations of the current study. The listing diagnosis was based on the diagnosis code entered by transplant center coordinators, not based on a study specific definition of the liver disease. Thus, there could be misclassification of listing diagnosis. HCV therapies are not available for analysis in UNOS database, Hence the current study is unable to prove that era effect in the HCV cohort is due to DAA treatment. Lastly, DAA treatment has been available just over the past several years and longer periods of observation might be needed to clearly

demonstrate changes related to DAA treatment in HCV registrants and recipients of LT in the U.S.

In conclusion, LT registrants and recipients with HCC have continued to increase over the past 12 years, making HCC the leading indication among both LT registrants and recipients in 2015. The number of HCV registrants without HCC declined rapidly in recent years possibly due to wide availability and effectiveness of DAA in prevention of hepatic decompensation. On the other hand, LT registrants with NASH and alcohol etiology continued to increase and alcohol is the most common listing diagnosis among non HCC registrants in 2015. Despite the institution of the Share 35 policy and the consequent decreased probability of receiving LT in HCC registrants, the number of HCC recipients continues to increase due to the more rapid increase in the number of registrants. It is very encouraging that the number of graft failures among HCV recipients and HCC recipients with HCV has decreased substantially, likely reflecting increased utilization and effectiveness of anti-HCV therapies in the post LT setting as well as overall improvements in patient selection and post LT clinical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: This publication was supported by Grant Number T32 DK07198 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (to JY). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH

This publication was supported by a 2016 American Liver Foundation Postdoctoral Research Fellowship (to JY).

Abbreviations

ALD	alcoholic liver disease
BMI	body mass index
CI	confidence interval
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
LT	liver transplantation
MELD	Model for End Stage Liver Disease
NASH	nonalcoholic steatohepatitis
OPTN	Organ Procurement and Transplantation Network

OR	odds ratio
UNOS	United Network for Organ Sharing

Reference

1. Ghabril M, Charlton M. Lack of Survival Benefit Following Liver Transplantation With MELD Exception Points for Hepatocellular Carcinoma: Beyond the Unblinding of Lady Justice. Gastroenterology. 2015; 149:531–534. [PubMed: 26226568]
2. Goldberg D, French B, Newcomb C, et al. Patients with Hepatocellular Carcinoma Have Highest Rates of Wait-listing for Liver Transplantation Among Patients With End-stage Liver Disease. Clin Gastroenterol Hepatol. 2016
3. Yang JD, Kim B, Sanderson SO, et al. Hepatocellular carcinoma in olmsted county, Minnesota, 1976–2008. Mayo Clinic proceedings. 2012; 87:9–16. [PubMed: 22212963]
4. Yang JD, Roberts LR. Hepatocellular carcinoma: A global view. Nature reviews. Gastroenterology & hepatology. 2010; 7:448–458. [PubMed: 20628345]
5. Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011; 141:1249–1253. [PubMed: 21726509]
6. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015; 148:547–555. [PubMed: 25461851]
7. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308:2584–2593. [PubMed: 23268517]
8. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology. 2015; 61:1880–1886. [PubMed: 25722203]
9. Siddiqui MS, Charlton M. Liver Transplantation for Alcoholic and Nonalcoholic Fatty Liver Disease: Pretransplant Selection and Posttransplant Management. Gastroenterology. 2016; 150:1849–1862. [PubMed: 26971826]
10. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014; 59:2188–2195. [PubMed: 24375711]
11. Wedd JP, Nordstrom E, Nydam T, et al. Hepatocellular carcinoma in patients listed for liver transplantation: Current and future allocation policy and management strategies for the individual patient. Liver Transpl. 2015; 21:1543–1552. [PubMed: 26457885]
12. Alver SK, Lorenz DJ, Marvin MR, et al. Projected outcomes of six-month delay in exception points vs. an equivalent MELD score for HCC liver transplant candidates. Liver Transpl. 2016
13. Heimbach JK, Hirose R, Stock PG, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. Hepatology. 2015; 61:1643–1650. [PubMed: 25644186]
14. Kim WR, Terrault NA, Pedersen RA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology. 2009; 137:1680–1686. [PubMed: 19632234]
15. Jang JW, Choi JY, Kim YS, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology. 2015; 61:1809–1820. [PubMed: 25627342]
16. Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016; 64:1224–1231. [PubMed: 26829205]
17. Belli LS, Berenguer M, Cortesi PA, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol. 2016

18. Gallegos-Orozco JF, Charlton MR. Treatment of HCV prior to liver transplantation to prevent HCV recurrence - wise or wasteful? Liver Int. 2015; 35:9–11. [PubMed: 25412996]
19. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015; 149:649–659. [PubMed: 25985734]
20. Burr AT, Li Y, Tseng JF, et al. Survival after liver transplantation using hepatitis C virus-positive donor allografts: case-controlled analysis of the UNOS database. World J Surg. 2011; 35:1590–1595. [PubMed: 21384242]
21. Yang JD, Aqel BA, Pungpapong S, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. J Hepatol. 2016; 65:859–860. [PubMed: 27392425]
22. Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65:719–726. [PubMed: 27084592]
23. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology. 2015; 148:100.e1–107.e1. [PubMed: 25261839]
24. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. Jama. 2012; 307:491–497. [PubMed: 22253363]
25. Pham T, Dick TB, Charlton MR. Nonalcoholic Fatty Liver Disease and Liver Transplantation. Clin Liver Dis. 2016; 20:403–417. [PubMed: 27063277]
26. Gallegos-Orozco JF, Charlton MR. Alcoholic Liver Disease and Liver Transplantation. Clin Liver Dis. 2016; 20:521–534. [PubMed: 27373614]
27. Udompap P, Kim D, Kim WR. Current and Future Burden of Chronic Nonmalignant Liver Disease. Clin Gastroenterol Hepatol. 2015; 13:2031–2041. [PubMed: 26291665]

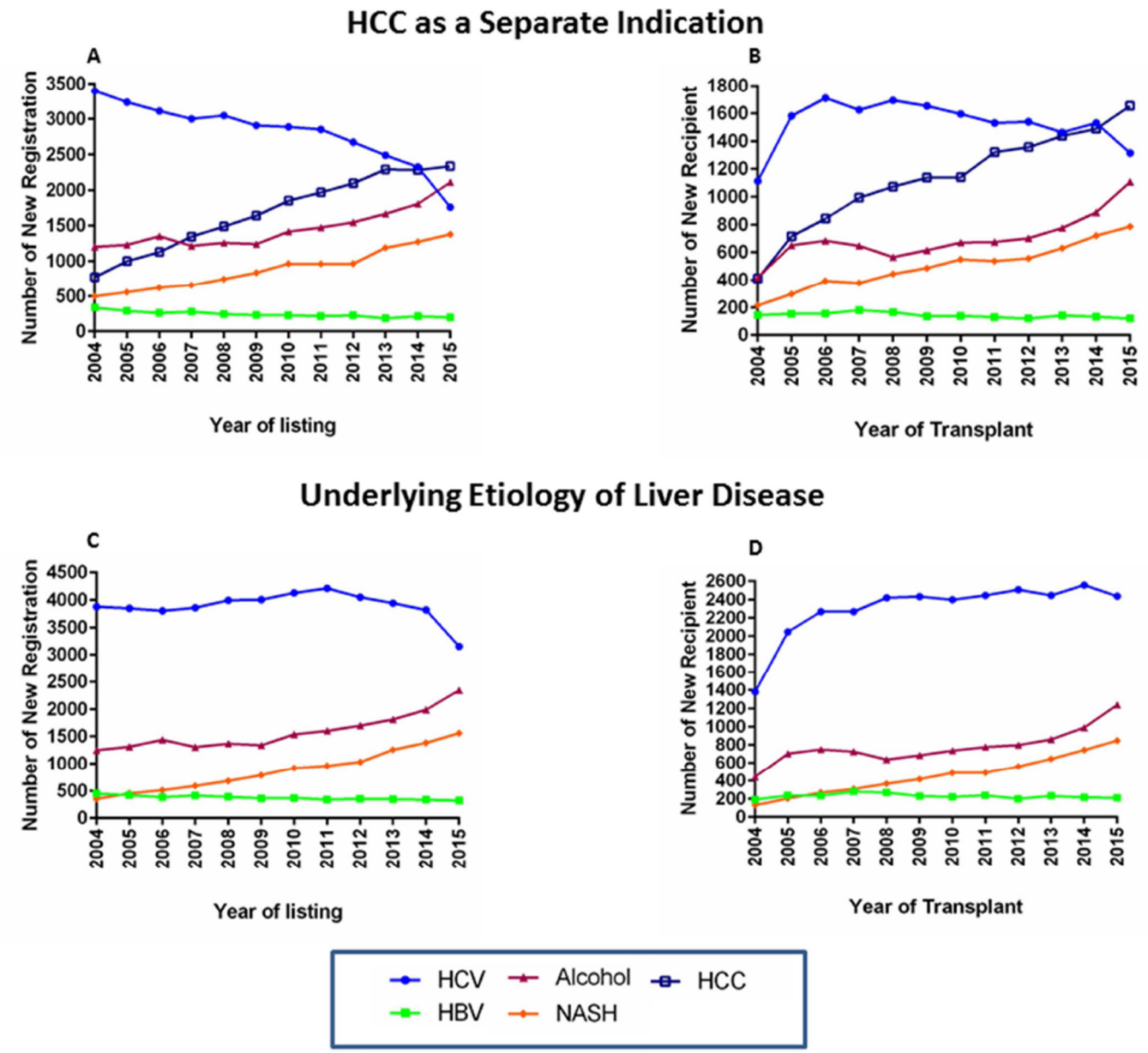


Figure 1.

Number of new liver transplant waitlist registrants and recipients in the United States, 2004–2015

A: Number of new registrants with HCC as a separate indication

B: Number of new recipients with HCC as a separate indication

C: Number of new registrants with classified by underlying liver disease diagnosis

D: Number of new recipients with classified by underlying liver disease diagnosis

In panel B and D, the number of LT recipients does not reflect all LT recipients in each index year as only recipients who were listed after 2004 were included (LT recipients who were registered before 2004 were not included in the current figure)

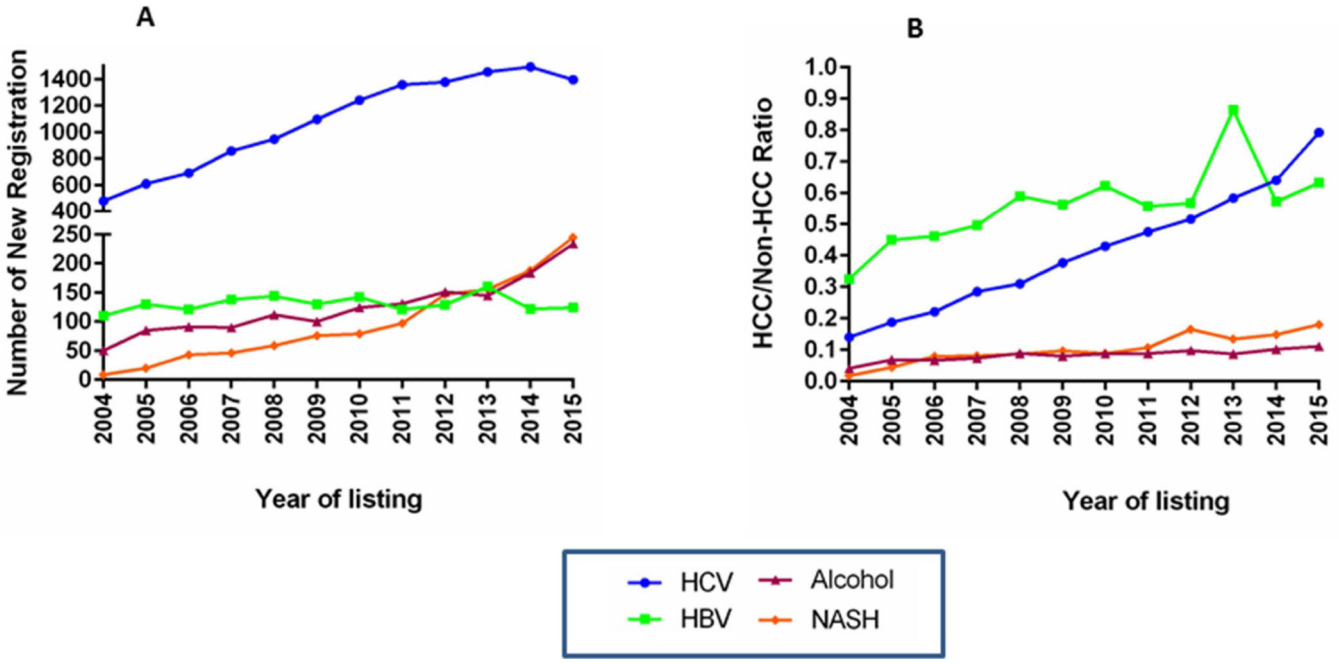


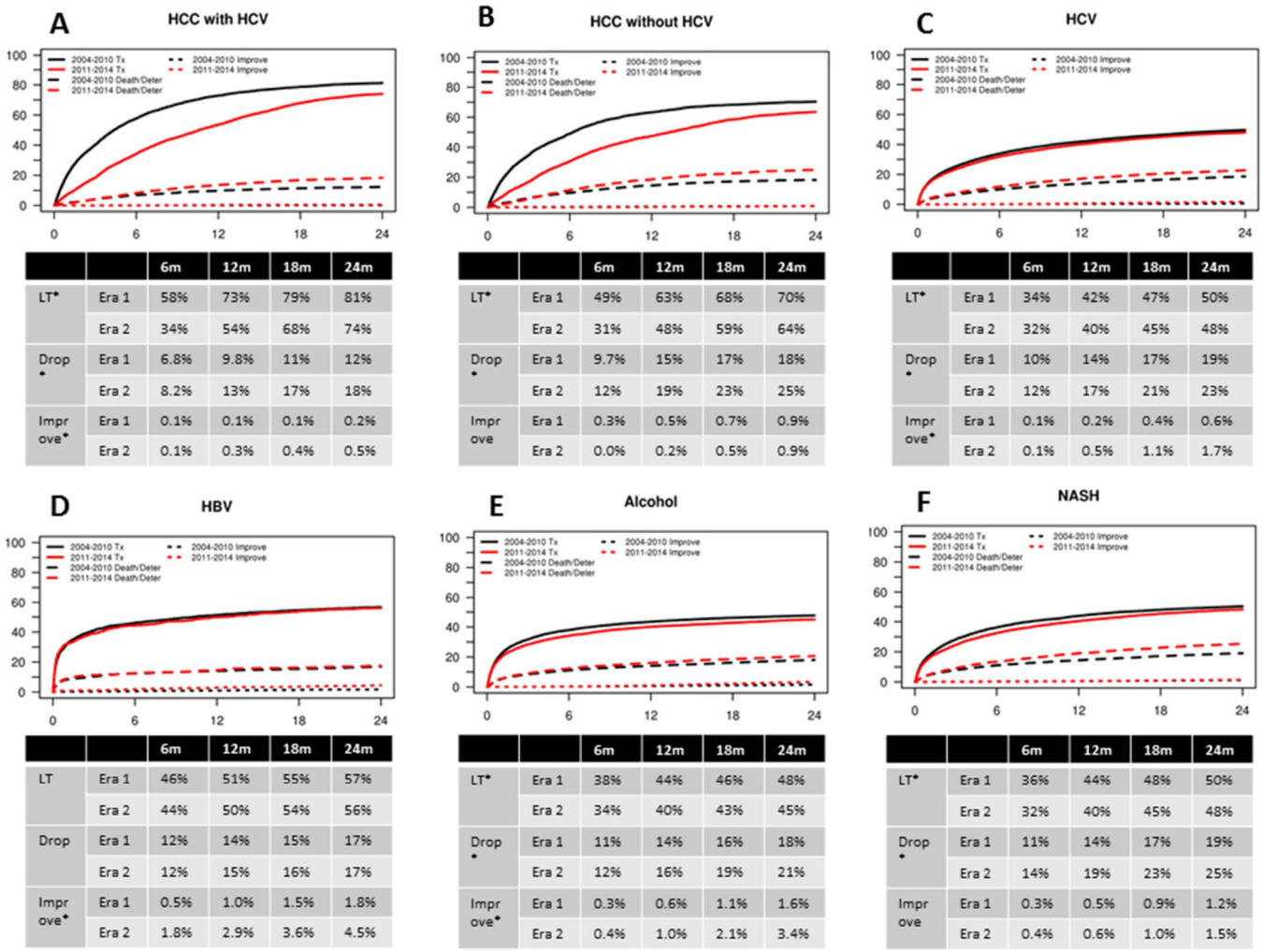
Figure 2.

Number of HCC registrants (Panel A) and the ratio of HCC versus non HCC (panel B) among new liver transplant waitlist registrants with different underlying etiologies of liver disease

The Y-axis of panel A is split. The interval between tick marks is 50 in the lower Y-axis and 200 in the upper Y-axis

Panel A: Number of HCC registrants with underlying etiology of HCV, HBV, Alcohol or NASH

Panel B: The ratio of registrants with HCC versus non-HCC classified by underlying etiology of liver disease



		6m	12m	18m	24m
LT*	Era 1	58%	73%	79%	81%
	Era 2	34%	54%	68%	74%
Drop*	Era 1	6.8%	9.8%	11%	12%
	Era 2	8.2%	13%	17%	18%
Improve*	Era 1	0.1%	0.1%	0.1%	0.2%
	Era 2	0.1%	0.3%	0.4%	0.5%

		6m	12m	18m	24m
LT*	Era 1	49%	63%	68%	70%
	Era 2	31%	48%	59%	64%
Drop*	Era 1	9.7%	15%	17%	18%
	Era 2	12%	19%	23%	25%
Improve	Era 1	0.3%	0.5%	0.7%	0.9%
	Era 2	0.0%	0.2%	0.5%	0.9%

		6m	12m	18m	24m
LT*	Era 1	34%	42%	47%	50%
	Era 2	32%	40%	45%	48%
Drop*	Era 1	10%	14%	17%	19%
	Era 2	12%	17%	21%	23%
Improve*	Era 1	0.1%	0.2%	0.4%	0.6%
	Era 2	0.1%	0.5%	1.1%	1.7%

		6m	12m	18m	24m
LT	Era 1	46%	51%	55%	57%
	Era 2	44%	50%	54%	56%
Drop	Era 1	12%	14%	15%	17%
	Era 2	12%	15%	16%	17%
Improve*	Era 1	0.5%	1.0%	1.5%	1.8%
	Era 2	1.8%	2.9%	3.6%	4.5%

		6m	12m	18m	24m
LT*	Era 1	38%	44%	46%	48%
	Era 2	34%	40%	43%	45%
Drop*	Era 1	11%	14%	16%	18%
	Era 2	12%	16%	19%	21%
Improve*	Era 1	0.3%	0.6%	1.1%	1.6%
	Era 2	0.4%	1.0%	2.1%	3.4%

		6m	12m	18m	24m
LT*	Era 1	36%	44%	48%	50%
	Era 2	32%	40%	45%	48%
Drop*	Era 1	11%	14%	17%	19%
	Era 2	14%	19%	23%	25%
Improve	Era 1	0.3%	0.5%	0.9%	1.2%
	Era 2	0.4%	0.6%	1.0%	1.5%

Figure 3.

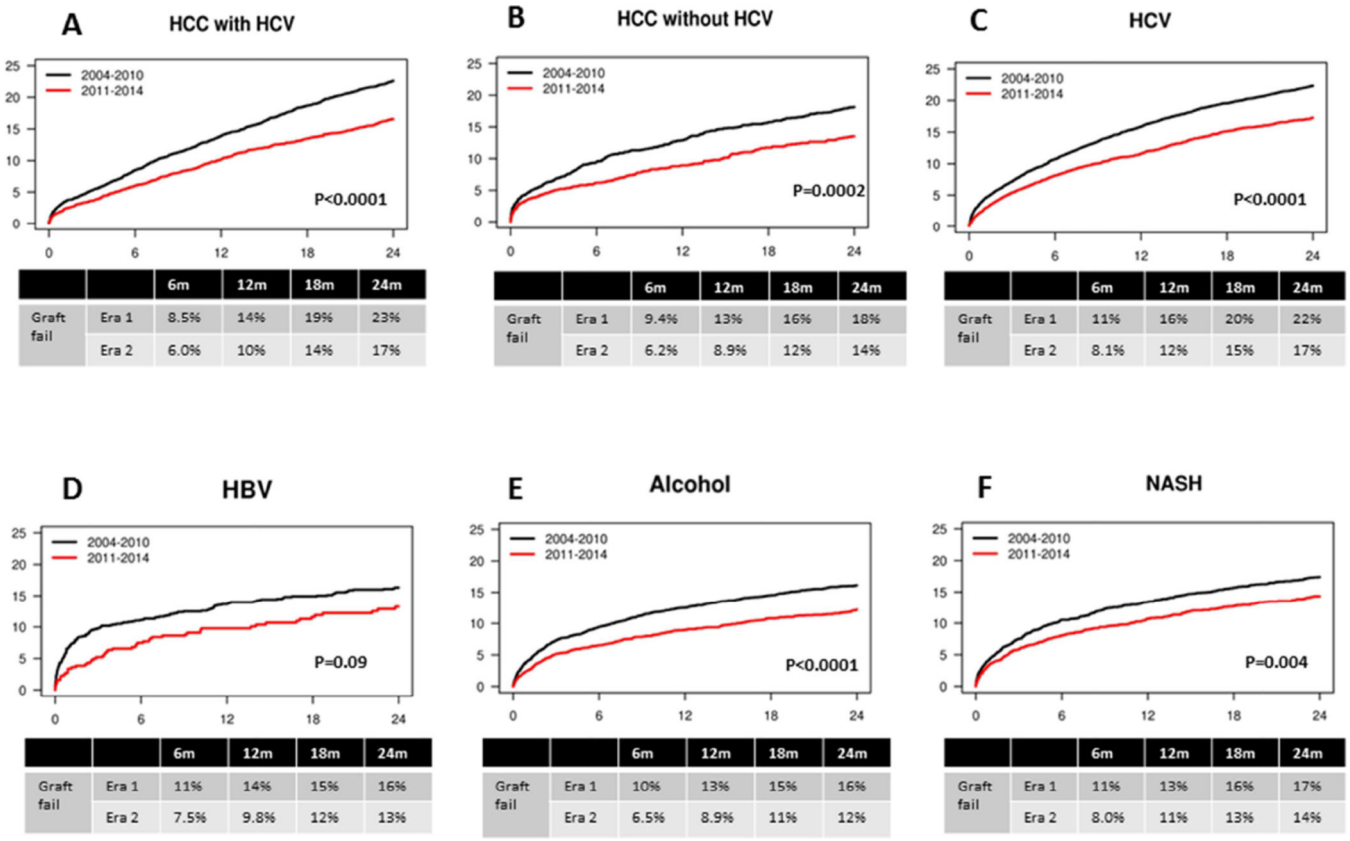
Trends in the probability of liver transplant, drop out due to death or deterioration, and delisting due to clinical improvement among new liver transplant waitlist registrants in the United States, 2004–2014

*indicates $p<0.05$

LT indicates liver transplant; Drop indicates drop out of list due to death or clinical deterioration; Improve indicates delisting due to clinical improvement

The X-axis indicates months after listing

The Y-axis indicates probability of LT, drop out due to drop out due to death or deterioration, and delisting due to clinical improvement



		6m	12m	18m	24m
Graft fail	Era 1	8.5%	14%	19%	23%
	Era 2	6.0%	10%	14%	17%

		6m	12m	18m	24m
Graft fail	Era 1	9.4%	13%	16%	18%
	Era 2	6.2%	8.9%	12%	14%

		6m	12m	18m	24m
Graft fail	Era 1	11%	16%	20%	22%
	Era 2	8.1%	12%	15%	17%

		6m	12m	18m	24m
Graft fail	Era 1	11%	14%	15%	16%
	Era 2	7.5%	9.8%	12%	13%

		6m	12m	18m	24m
Graft fail	Era 1	10%	13%	15%	16%
	Era 2	6.5%	8.9%	11%	12%

		6m	12m	18m	24m
Graft fail	Era 1	11%	13%	16%	17%
	Era 2	8.0%	11%	13%	14%

Figure 4.

Trends in post-transplant graft failure among liver transplant recipients, 2004–2014

The X-axis indicates months after Liver transplant

The Y-axis indicates probability of graft failure.

Table 1

Association between listing years (2011–2014 vs 2004–2010) and Pre-LT outcomes: Probabilities of LT, dropout due to clinical deterioration or death and delisting due to clinical improvement

	Liver Transplant		Dropout due to clinical deterioration or death		Delisting due to clinical improvement	
Subgroups	**HR [95%CI]**	**P**	**HR [95%CI]**	**P**	**HR [95%CI]**	**P**
HCC/HCV		<0.0001		0.64		0.26
2004–2010 (Ref)	-		-		-	
2011–2014	0.62 [0.59–0.64]		0.98 [0.88–1.08]		1.54 [0.72–3.28]	
HCC/No HCV		<0.0001		0.07		0.23
2004–2010 (Ref)	-		-		-	
2011–2014	0.62 [0.58–0.66]		0.90 [0.81–1.01]		0.69 [0.38–1.26]	
HCV		<0.0001		0.0003		<0.0001
2004–2010 (Ref)	-		-		-	
2011–2014	0.80 [0.78–0.83]		0.90 [0.86–0.95]		3.42 [2.66–4.39]	
HBV		<0.0001		0.002		0.004
2004–2010 (Ref)	-		-			
2011–2014	0.80 [0.71–0.89]		0.71 [0.57–0.89]		2.25 [1.29–3.93]	
Alcohol		<0.0001		0.01		<0.0001
2004–2010 (Ref)	-		-		-	
2011–2014	0.76 [0.73–0.80]		0.90 [0.84–0.97]		2.21 [1.75–2.80]	
NASH		<0.0001		0.74		0.19
2004–2010 (Ref)	-		-		-	
2011–2014	0.77 [0.73–0.81]		1.02 [0.93–1.10]		1.29 [0.88–1.87]	

Cox model adjusted age, gender, race/ethnicity, MELD, diabetes and BMI

CI, confidence interval; HCC, Hepatocellular carcinoma; HR, hazard ratio; NASH, nonalcoholic steatohepatitis

Patients listed in 2015 were not included in the model to avoid potential update bias and insufficient follow up duration

Table 2

Association between LT year eras (2011–2014 vs 2004–2010) and Post-LT outcomes: Probabilities of graft loss or death

	Graft loss only		Graft loss or Death	
Subgroups	**HR [95%CI]**	**P**	**HR [95%CI]**	**P**
HCC/HCV		<0.0001		<0.0001
2004–2010 (Ref)	-		-	
2011–2014	0.70 [0.63–0.79]		0.82 [0.74–0.90]	
HCC/No HCV		0.002		0.03
2004–2010 (Ref)	-		-	
2011–2014	0.74 [0.61–0.89]		0.83 [0.71–0.98]	
HCV		<0.0001		<0.0001
2004–2010 (Ref)	-		-	
2011–2014	0.69 [0.64–0.75]		0.76 [0.71–0.82]	
HBV		0.13		0.57
2004–2010 (Ref)	-		-	
2011–2014	0.76 [0.53–1.08]		0.91 [0.67–1.25]	
Alcohol		0.57		0.002
2004–2010 (Ref)	-		-	
2011–2014	0.70 [0.60–0.80]		0.82 [0.72–0.93]	
NASH		<0.0001		0.01
2004–2010 (Ref)	-		-	
2011–2014	0.74 [0.63–0.86]		0.83 [0.72–0.95]	

Cox model adjusted age, gender, race/ethnicity, MELD, diabetes and BMI

CI, confidence interval; HCC, Hepatocellular carcinoma; HR, hazard ratio; NASH, nonalcoholic steatohepatitis

Patients transplanted in 2015 were not included in the model to avoid potential update bias and insufficient follow up duration