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Liver Transplant for Hepatocellular Carcinoma in the United States: Evolving Trends over the Last Three Decades

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Abstract

HCV infection has been the most common etiology in HCC-related liver transplantation (LT). Since 2014, direct-acting antivirals (DAAs) have dramatically improved HCV cure. We aimed to

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Author Contributions

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Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Douglas Dieterich: Gilead, Merck, AbbVie. Josep Llovet: Prof. Josep M. Llovet is receiving research support from Bayer HealthCare Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb and Ipsen, and consulting fees from Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Eisai Inc, Celsion Corporation, Eli Lilly, Exelixis, Merck, Ipsen, Glycotest, Navigant, Leerink Swann LLC, Midatech Ltd, Fortress Biotech, Sprink Pharmaceuticals, Nucleix and CatFite. The other authors have no conflicts of interest to disclose.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

study the changing pattern of etiologies and impact in outcome in HCC-related LT according to HCV treatment-era through retrospective analysis of the Scientific Registry of Transplant Recipients (SRTR) database (1987–2017).

A total of 27,855 HCC-related LT were performed (median age 59 years, 77% male). In the DAA-era (2014–2017) there has been a 14.6% decrease in LT for HCV-related HCC; however, HCV remains the most common etiology in 50% of cases. In the same era, there has been a 50% increase in LT for NAFLD-related HCC. Overall survival was significantly worse for HCV-related HCC compared to NAFLD-related HCC during pre-DAA era (2002–2013; p=0.031), but these differences disappeared in the DDA era. In addition, HCV patients had a significant improvement in survival when comparing DAA-era with IFN-era (p<0.001). Independent predictors of survival were significantly different in the pre-DAA era (HCV, AFP, diabetes) than in the DAA-era (tumor size).

HCV-related HCC continues to be the main indication for LT in the DAA-era, but patients' survival has significantly improved and is comparable to that of NAFLD-related HCC.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer, and the fourth leading cause of cancer-related mortality worldwide (1, 2). At risk populations are well defined and include patients with cirrhosis due to alcoholic liver disease (ALD), hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD), as well as other chronic liver diseases (3). Curative treatment options are available for patients with local disease and include ablation, resection and liver transplantation (3). Particularly, patients with early stage HCC with cirrhosis, who are not eligible for surgical resection, represent ideal candidates for LT when the tumor burden is within Milan criteria (4, 5).

After the implementation of the model for end-stage liver disease (MELD) score in 2002, HCC patients were granted MELD exception points with the intent to balance the risk of tumor progression and subsequent drop-out from the waiting list with death compared to non-HCC patients (6). However, based on recent data demonstrating that the system advantaged HCC recipients compared to patients without HCC, the policy was modified in 2015 in order to decrease the priority awarded to HCC patients (6). Overall, the organ allocation policies for HCC have evolved over the recent years to deprioritize HCC relative to other indications (7).

Among the underlying etiologies of liver disease, HCV has been the most common indication for LT among HCC patients in the United States (US) (8). Treatment options of HCV have evolved tremendously in the recent years (9). After November of 2013, with the availability of interferon (IFN) free direct-acting antivirals (DAAs), sustained virologic response (SVR) rates of > 90% in both pre- and post-LT setting and in patients with impaired liver function is achievable (10, 11). Prior to 2011, IFN and ribavirin (RBV) were the only available treatment for HCV that were associated with low SVR rates of only 20–40% and significant side effects (12). In 2011, the first generation of protease inhibitors was

approved that improved the SVR rates to 50–60%; however, they were still associated with side effects because they were combined with IFN/RBV (13).

While HCV treatment options have evolved considerably(13), the growing obesity epidemic in the US has led to an increased prevalence of NAFLD(14). Current estimates indicate that 68% of US adults are overweight or obese, and between 75–100 million individuals likely have NAFLD (15). Herein, it has been speculated that due to the DAAs, the relative burden of HCC arising from HCV will diminish and NAFLD eventually will become the leading indication for HCC-related LT (16).

Patterns of underlying liver diseases giving rise to HCC and ultimately leading to LT are likely going to shift in the coming years, warranting a closer look at the etiologies. The recent changes in the MELD exception policies, the availability of DAAs to treat HCV, and the rise in the prevalence of obesity and fatty liver disease prompted us to study: 1) the changing pattern of HCC-related LT etiologies over the past 30 years and 2) the impact of etiology in HCC-related LT outcomes, focusing on HCV treatment changes. In order to reflect both the changing patterns in etiology and the outcomes as treatment for HCV has advanced we defined four time intervals: the pre-MELD era (1987–2001), the IFN-only era (2002–2010), early IFN-DAA era (2011–2013) and the DAA-only era (2014–2017).

Materials and Methods

Data Source

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study Population

Our study retrospectively evaluated adult patients who received a deceased donor LT (DDLT) in the SRTR database from 1987 to September 2017 in the US. LT recipients with HCC were identified using the primary or secondary coding for the diagnosis of HCC at the time of listing or at the time of transplant in the SRTR database. In addition to the aforementioned coding, we included recipients whose providers had sought HCC MELD exception points and were approved, even if the diagnosis of HCC had not been entered. Data regarding incidental HCCs among patients transplanted for their native MELD were not available within the database. Overall patients below age 18, living donor recipients, or any patient with prior history of organ transplant (except kidney transplant), or other primary or secondary liver malignancies were excluded (Supplementary Table 1). In line with this analysis and using additional available coding, the underlying etiologies of liver disease at

the time of listing were determined. Patients were categorized in the following groups: HCV, ALD, HBV, ALD/HCV, NAFLD, and cryptogenic. Patients who did not have any codes for these diagnoses or had codes under unknown etiology were included in the “unknown” category. Patients who had codes for autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), Budd-Chiari syndrome (BCS), hemochromatosis, alpha-1 antitrypsin deficiency, acute hepatic necrosis (AHN) or other diagnoses were included in the “other” category. Patients with ALD/HCV were considered separately and not included in the calculations for HCV or ALD patients. Patients with combination codes for NAFLD and HCV (n=89) or NAFLD and ALD (n=50) were not included in the HCV, NAFLD, and ALD groups.

Statistical analysis

Categorical variables are reported by percentages, and continuous variables are reported as medians with interquartile ranges (IQR). Differences between qualitative variables were assessed with the Fisher exact test. Differences between quantitative variables were analyzed with a non-parametric test (Mann-Whitney or Kruskal-Wallis for independent samples).

Survival was calculated for each patient between the date of transplantation relevant to the date of death or re-transplant, date of the last follow-up, or the end of the study period in September 2017. Univariate and multivariate Cox regression models were constructed to estimate mortality hazard ratios (HR) and 95% confidence intervals (CI) for baseline clinical and analytical parameters. We constructed two different models for the pre-DAA era (2002–2013) and the DAA era (2014–2017). The model obtained for the pre-DAA era was also applied to the DAA era. All the models were adjusted for known baseline factors related to survival, which were used as covariates (Supplementary Table 4). Survival curves by HCC etiology following LT were obtained from Kaplan–Meier estimates of mortality probabilities. Differences between survival curves were tested using the log-rank test. Statistical analyses were performed using the SPSS software package (version 24.0; SPSS Inc, Chicago, IL).

Results

Study population

Between October 1987 and September 2017 there were a total of 132,731 adult DDLT recipients in the US. Of these 27,855 (21%) underwent an initial DDLT for an HCC-related indication. Overall, 22,280 (80%) of the HCC-related LT recipients had been granted HCC MELD exception points. Baseline characteristics of the study population are summarized in Table 1. The median age of LT recipients was 59 years, and 77% of the patients were males. Overall, 69.5% of patients had T2 TNM stage tumor. Median lab MELD of the cohort at the time of transplantation was 12 (9–17).

The most common underlying etiology was HCV (48.9%) followed by HCV/ALD (10.6%), ALD alone (8.1%), NAFLD (6.1%), HBV (5.8%), and cryptogenic (3%). HCV patients, compared to NAFLD, were younger (58.4 vs. 63.9 years), mostly male (76.9% vs. 65.2%), with lower BMI (27.9 vs. 32.3 kg/m^2), and lower MELD at transplant (12 vs. 14) (all

p<0.001, Supplementary Table 2). Proportion of diabetes (70.4% vs 23.9%) and hypertension (47.9% vs 28.2%) were significantly higher among NAFLD patients compared to HCV (both p<0.001) (Supplementary Table 2).

The characteristics of the donors for the different etiologies of HCC-related LT are presented in Supplementary Table 3.

Etiology trends of HCC-related LT

There was a remarkable increase in HCC-related LT from 222 (5.3%) in 2001 to 977 (21.8%) in 2002, following the implementation of the MELD system and MELD exceptions for HCC recipients (p<0.001) (Figure 1). After 2002, the number and proportion of HCC-related LT continued to increase steadily until 2015 (30.5% in 2008, 36.1% in 2015). Following the MELD policy change in 2015 that would deprioritize HCC patients, the rate of HCC as an indication for DDLT declined from 36.1% in 2015 to 30% in 2016 (p<0.001) (Figure 1). While the first patient undergoing LT for HCV-related HCC was reported in 1991, the first LT for NAFLD-related HCC was not until 2003. In the entire pre MELD era (1987–2001) the most frequent underlying liver disease for patients with HCC undergoing LT was HCV (31%) followed by an unknown etiology (23.8%). In the MELD era, patients with unknown liver disease only accounted for 3.8% of all patients with HCC related LT (p<0.001). The proportion of HCV-related HCC peaked at 55.5% in 2010 and slightly decreased in 2016 and 2017 (46.3% and 45.7%, respectively). On the other hand, there has been a steady increase in the number and proportion of NAFLD patients from 2003 (n=4, 0.4%) to 2016 (n=276, 13.2%). In parallel, the HCV/NAFLD ratio has decreased from 1/145 in 2003 (one NAFLD-related transplant for every 145 HCV-related transplants) to 1/12 in 2010 and 1/4 in 2017.

Considering the different HCV treatment eras, the proportion of HCV-related LT kept an increasing trend in the IFN-only era (48.2%) and the early IFN-DAA era (53%) but started to decrease in 2015 coinciding with the IFN-free DAA era (50.3%) (Supplementary Figure 1). Conversely, NAFLD-related LT rose constantly from the IFN-only era (3.1%) to the early IFN-DAA era (7%) and the DAA era (11.3%), with the highest proportion in 2016–2017 (13.3%) (Supplementary Figure 1 **and** Figure 2). Consequently, NAFLD is now the second leading cause of HCC-related LT in the IFN-free DAA era, after HCV. However, it is important to note that 9% of patients have concomitant HCV and ALD diagnosis. Hypothetically, if the recipients with HCV/ALD (9%) are counted toward ALD only group (9%), then ALD will be the 2nd leading cause of HCC-related LT (18%) (Supplementary Figure 1E).

Outcomes and survival in HCC patients

The causes of death were different according to etiology. HCV patients had a higher rate of graft-related death compared to NAFLD patients (12.4% vs. 4.8%, p<0.001). On the contrary, NAFLD individuals showed a higher rate of cardiovascular-related death (13.3% vs. 7.8%, p<0.001) (Table 2).

The main determinants of death (HR, 95% CI, p value) in the IFN era (2002–2013) as determined through Cox regression multivariate analysis were HCV etiology (1.155, 1.0179–1.237, p<0.001), AFP (1.288, 1.200–1.382, p<0.001), and diabetes (1.188, 1.102–1.280, p<0.001) (Figure 3A **and** Supplementary Table 4A). Remarkably, in the DAA era, etiology was not related to survival neither in the univariate (0.963, 0.836–1.110, p=0.603) nor in the multivariate analysis (1.115, 0.892–1.394, p=0.338) (Figure 3B **and** Supplementary Table 4B). Only tumor size (1.189, 1.079–1.311, p=0.001) was related to an impaired survival in the DAA era.

Overall, HBV patients had the best survival among the different etiologies (Log Rank <0.001) (Supplementary Figure 2). This difference in outcome was maintained when only patients transplanted in the MELD era were taken into consideration (Figure 4A). In the same period, HCV patients had lower survival compared to NAFLD patients (Log Rank=0.030) (Figure 4B). This impaired survival was conveyed through a markedly worse outcomes during the IFN-only era, and the early IFN-DAA era (Log Rank=0.031) as no significant difference was observed in the IFN-free DAA era (Log Rank=0.321) (Figure 4C). When evaluating the survival changes according to the HCV treatment era, HCV-related LT showed a significant improvement, comparing the IFN-only to the early IFN-DAA era (Log-Rank <0.001) and the early IFN-DAA era to the DAA era (Log-Rank=0.002) (Figure 4D). In contrast, NAFLD patients only showed improved survival when comparing the IFN-only era to the early IFN-DAA era (Log-Rank=0.001), but no difference compared to the DAA era (Log-Rank=ns).

Discussion

In this study, we retrospectively evaluated the evolving trends of HCC and the underlying diagnosis of liver disease in deceased donor LT recipients over the last three decades (1987 to September 2017) using the SRTR database. In addition to including patients with the diagnosis of HCC, we included recipients whose providers had sought HCC MELD exception points and were approved, even if the diagnosis of HCC had not been entered. This allowed us to identify cases with HCC as an indication for LT more broadly. Therefore, our reported HCC cases/per year are higher than those noted in previous publications (17). Our study shows a trend towards a decrease of HCV-related LT and a parallel increase in NAFLD-related LT following the implementation of DAAs in clinical practice. Moreover, we show a significant improvement in HCV patients' survival in the DAA era, being now comparable to NAFLD patients, whereas survival for the latter group remains unchanged.

Our study shows an increase in HCC-related LT, particularly in the MELD era. The trends and peaks of HCC over time are reflective of changes in the way patients with HCC are prioritized for LT. Following the implementation of MELD exception points in 2002, HCC has grown as an indication for LT and accounts for 21% of the total number of deceased donor LTs over a thirty-year period. As a result of a series of analyses indicating that the MELD exception scores advantaged HCC patients, the system was modified in 2003, 2004, and 2005 to reduce the priority accorded to these patients (6, 18, 19). Despite these modifications, we show that the rate of LT for HCC continued to rise.

In 2013 “Share 35” policy was implemented with the goal of allowing an increased proportion of patients with a MELD > 35 to undergo LT and thus decreasing death on the waiting list. A study evaluating the effect of “Share 35” on patients who underwent LT for HCC demonstrated no change in the proportion of LT performed or overall waiting time. However, a higher rate of death/de-listing was observed (20). Similarly, in our study, we did not observe any significant change in the rate of LT for HCC in the Share 35 era, although our study did not specifically evaluate UNOS regional differences. Only after the most recent modification in 2015 in which HCC patients received no priority for six months and the MELD exception score was capped at 34 points (6, 7) has the rate of LT for HCC and proportion of HCC candidates undergoing LT declined (Figure 1). The most recent MELD policy change awards exception points equal to median MELD score of a DSA (donation service area) region minus 3 using a calculation based on a 250 nautical mile (NM) circle around each donor hospital that is recalculated every 180 days (21). Although this policy only was recently implemented, it is speculated that it may decrease the rate of LT and increase the dropout rate for HCC candidates.

Our study confirms that HCV has been the leading etiology for HCC as an indication for LT over the last 30 years, accounting for almost half of the cases. Even during the current IFN-free DAA era in which HCV is routinely cured, HCV remains the predominant etiology of liver disease in HCC patients, although there is a downward trend. It is worth noting that the SRTR database cannot distinguish active from cured-HCV in the LT candidates or recipients. Model-based simulation studies have predicted that HCC will continue to increase over the next decade (22). In addition, in some liver transplant centers patients with HCV and HCC are treated with DAA after LT to increase their chance of receiving a HCV positive organ and decreasing the waiting-list-time (10). Although achieving SVR decreases the risk of all-cause and liver-related mortality, the risk of developing HCC persists, more so in those with cirrhosis, in which the annual incidence of HCC in post-SVR patients is 1.82/100 person per year in patients with cirrhosis compared to 0.34/100 person per year in those without cirrhosis (23). While early reports suggested that DAA treatment may lead to increased risk of cancer occurrence/recurrence, that concern has proven unfounded (24, 25). From a public health perspective, it will be several years before there will be a decline in the rates of HCC secondary to HCV (26).

Based on the analysis herein presented, NAFLD-related HCC, which was first reported as a diagnosis in the SRTR database in 2003, is shown to be the most rising etiology of liver disease in HCC patients undergoing LT (27). It is estimated that the incidence of HCC secondary to NAFLD will increase by 137% by 2030 (28). Unlike other groups analyzing the SRTR database, we did not include patients with cryptogenic cirrhosis or unknown diagnosis with DM or elevated BMI > 30 in the NAFLD group (17, 29). This is of critical importance, as our analysis shows that up to fifty percent of HCC-related LT patients have underlying ascites, which falsely raises the BMI. Of note, cryptogenic cirrhosis accounted for less than three percent of cases.

As no patients with NAFLD codification were transplanted until 2003, we performed our survival analysis in the MELD era (2002–2017). In our study, HCV was a main determinant of death in the pre-DAA era (2002–2013) but was no associated with decreased survival in

the DAA era (2014–2017), confirming that HCV widespread cure has significantly improved the prognosis of HCV patients undergoing LT for HCC (30). During the 2002–2013 period, HBV patients showed the best survival, and HCV patients had an impaired survival compared to NAFLD patients. Even though diabetes was far more prevalent in the NAFLD population, and having diabetes was a strong predictor of mortality, survival was significantly worse for HCV-infected patients. However, this strong effect of HCV infection on survival disappeared in 2014, in concert with the rise of DAAs, and no differences in survival have been noted between HCV and NAFLD patients since then. Even though the follow-up is still short and median survivals are not reached, our study is, to the best of our knowledge, the first to show the changing trends on etiology and their impact on survival in HCC-related LT in the US. Of note, the causes of death were different among HCV and NAFLD patients, and as expected, more related to cardiovascular events in the latter. The higher rate of graft-related death among HCV patients may be explained by differences in recipient and donor characteristics or, plausibly, be related to post-LT HCV recurrence and related graft failure before the DAA era. Remarkably, graft-related deaths were comparable in patients with HBV and HCV.

There are several limitations to our study. Due to the nature of the database, the determination of the underlying etiology of chronic liver disease, by the primary and secondary diagnoses, is based on how the diagnosis codes were entered into the database. Therefore, the HCC cases could be under or over-reported. Data regarding HCV-RNA are not available in the database. Therefore it is unclear whether HCV recipients were post-SVR or had active HCV.Furthermore, a detailed history regarding the amount of alcohol use is not available. Besides, there are missing data, specifically prior to 2002, and cases with unknown etiology within the database. Patients with HCC with unknown etiology were noted to have the highest mortality compared to other groups. However, in recent years, these cases only accounted for five percent of the total.

In summary, changes in the MELD exception policy have overtime led to a decrease in the proportion of LT for HCC candidates after an initial significant increase with the adoption of the MELD score for organ allocation. While HCV remains the most common etiology of HCC-related LT, the availability of DAA is decreasing its burden. Conversely, there is in the same timeframe a steady increase in patients undergoing LT with NAFLD-related HCC. Whereas in the pre DAA era HCV-infection was one of the strongest determinants of death in the HCC-related LT population, NAFLD and HCV patients have similar survival in the DAA era, and HCV is no longer an independent predictor of an adverse outcome. The rate of death for cardiovascular disease is higher in NAFLD patients, while the rate of graft-related death is higher among HCV individuals. Further studies in the next years will be of high importance in order to confirm these changing trends.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AHN	Acute hepatic necrosis
ALD	alcoholic liver disease
AIH	autoimmune hepatitis
BCS	Budd-Chiari syndrome
CI	confidence intervals
DDLT	deceased donor LT
DAAs	direct-acting antivirals
DSA	donation service area
HR	hazard ratios
HRSA	Health Resources and Services Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HCC	Hepatocellular carcinoma
IFN	interferon
IQR	interquartile ranges
LT	liver transplantation
MMRF	Minneapolis Medical Research Foundation
MELD	model for end-stage liver disease
NM	nautical mile
NAFLD	nonalcoholic fatty liver disease
OPTN	Organ Procurement and Transplantation Network
PBC	primary biliary cholangitis
PSC	primary sclerosing cholangitis

RBV	ribavirin
SRTR	Scientific Registry of Transplant Recipients
SVR	sustained virologic response
US	United States

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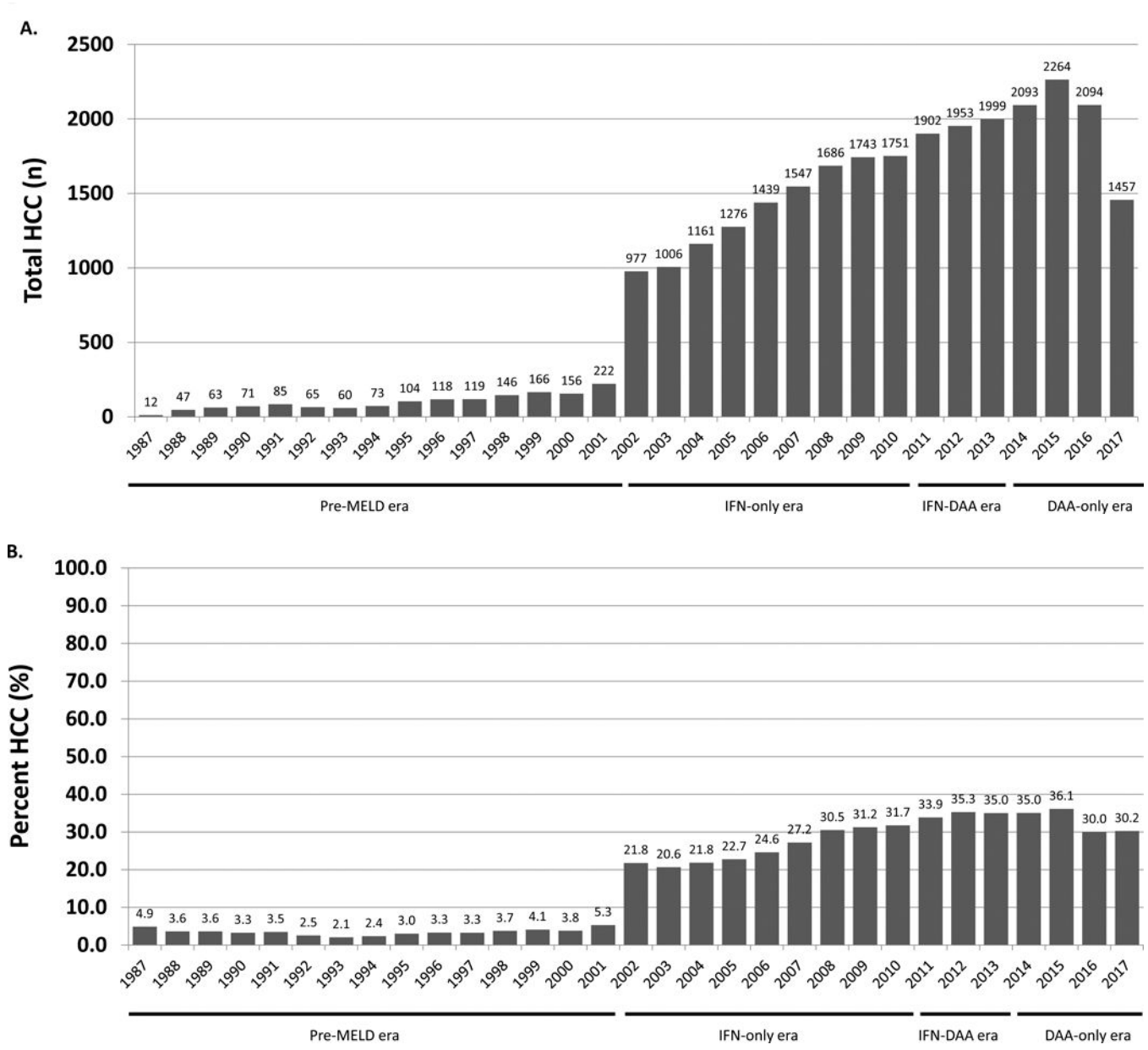


Figure 1.

The trend of HCC-related liver transplants in the United States based on SRTR data. A) total number (n); B) percentage.

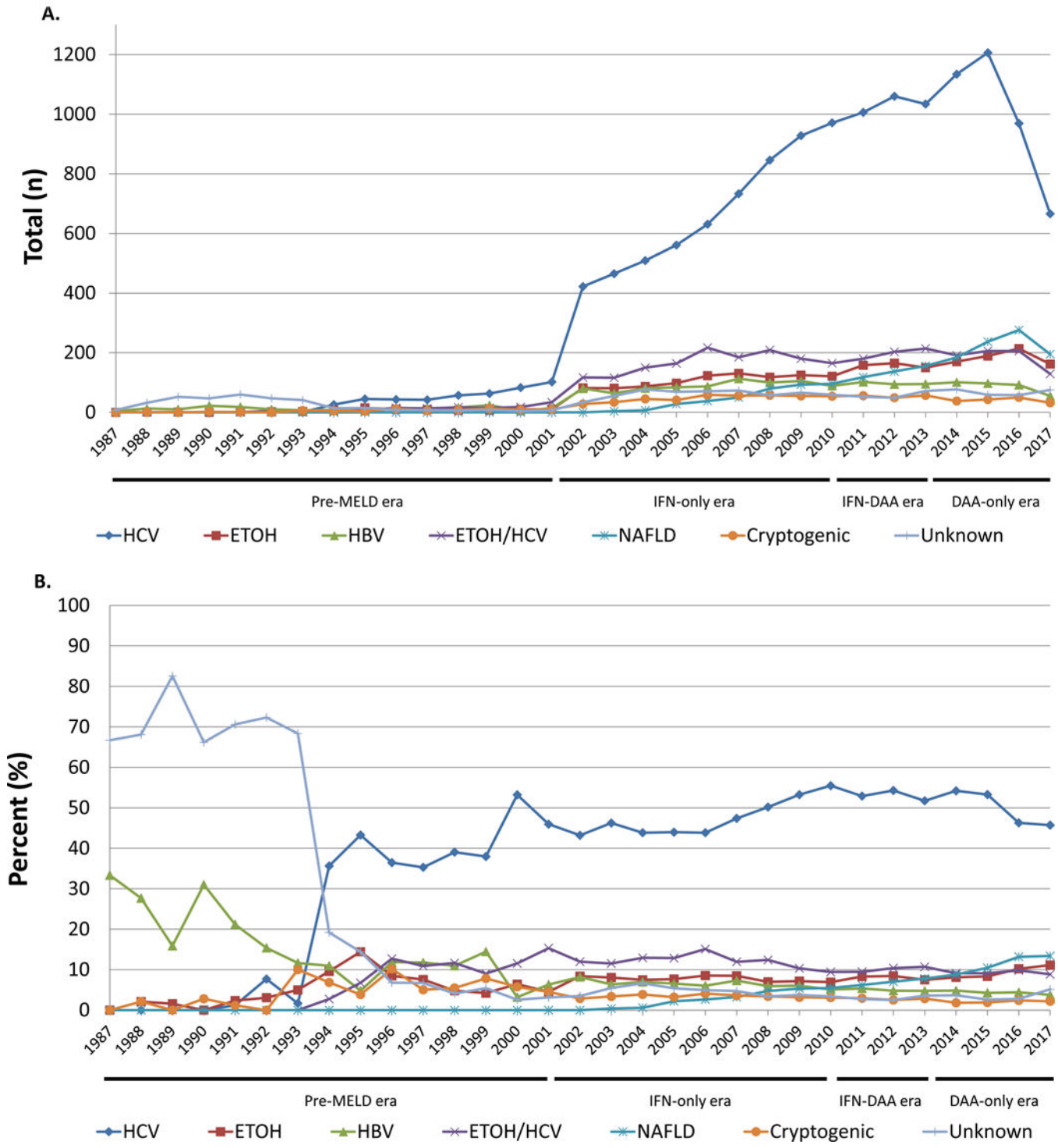
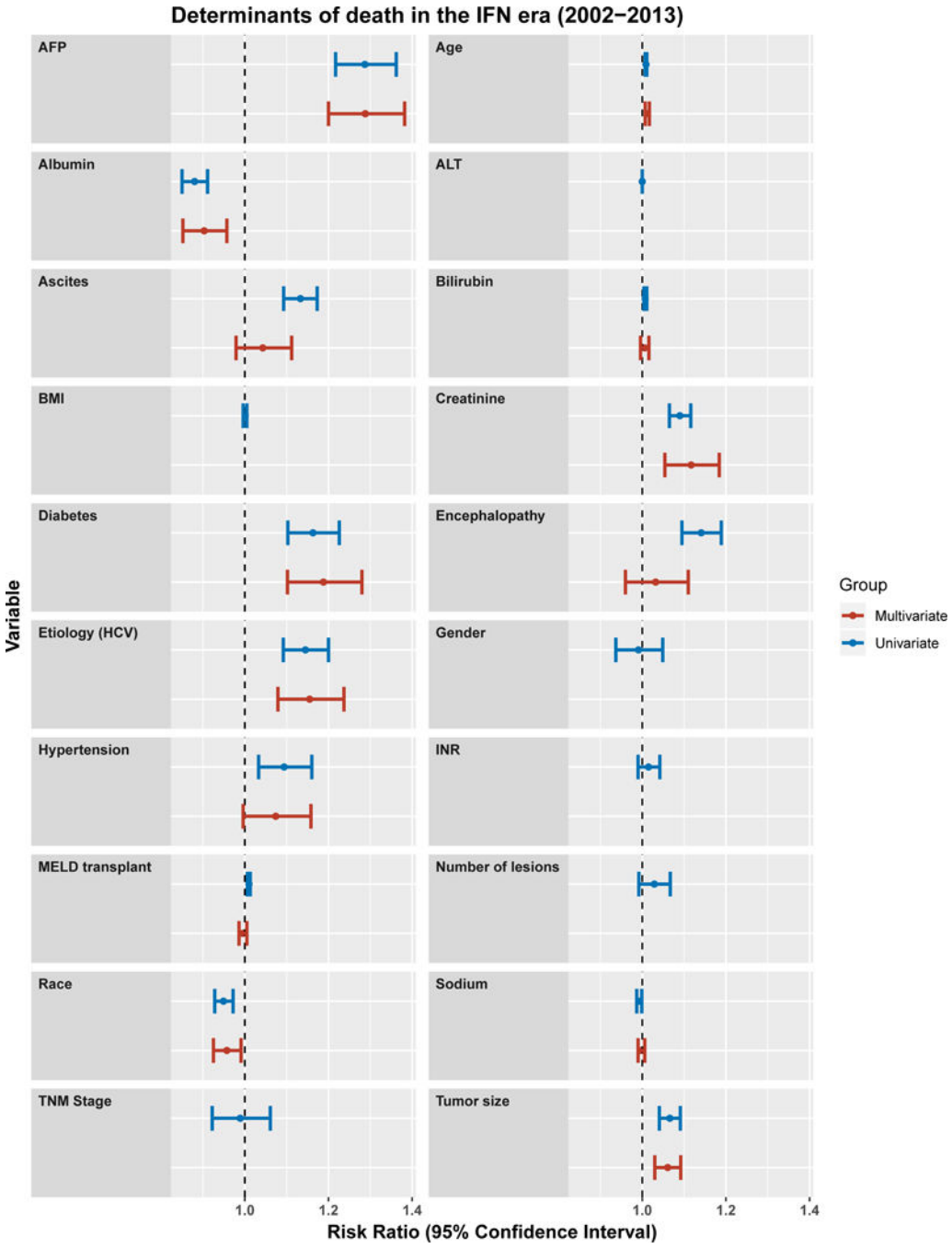


Figure 2.

Annual trend of etiologies of liver disease in LT recipients with HCC in the US. A) total number (n); B) percentage.



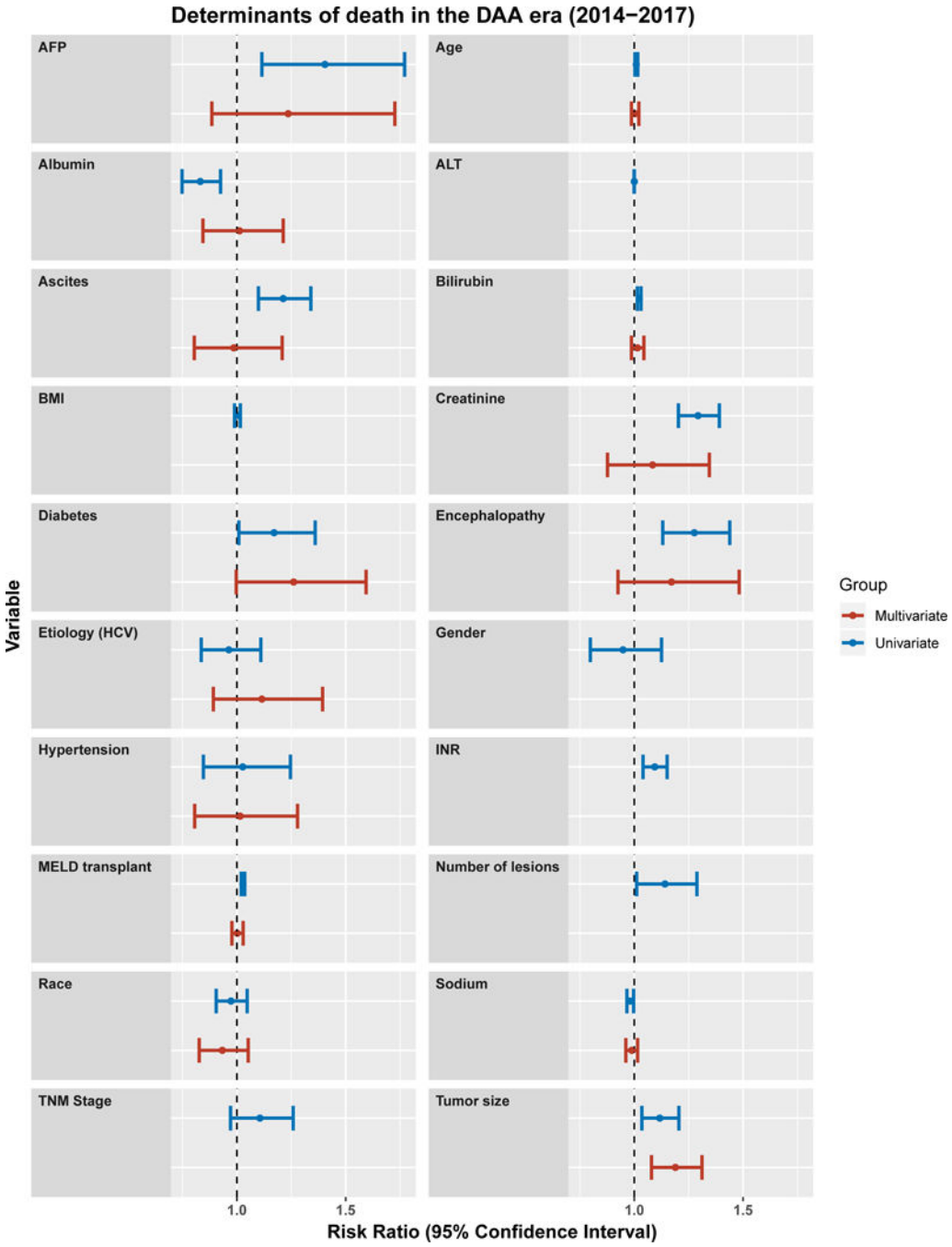
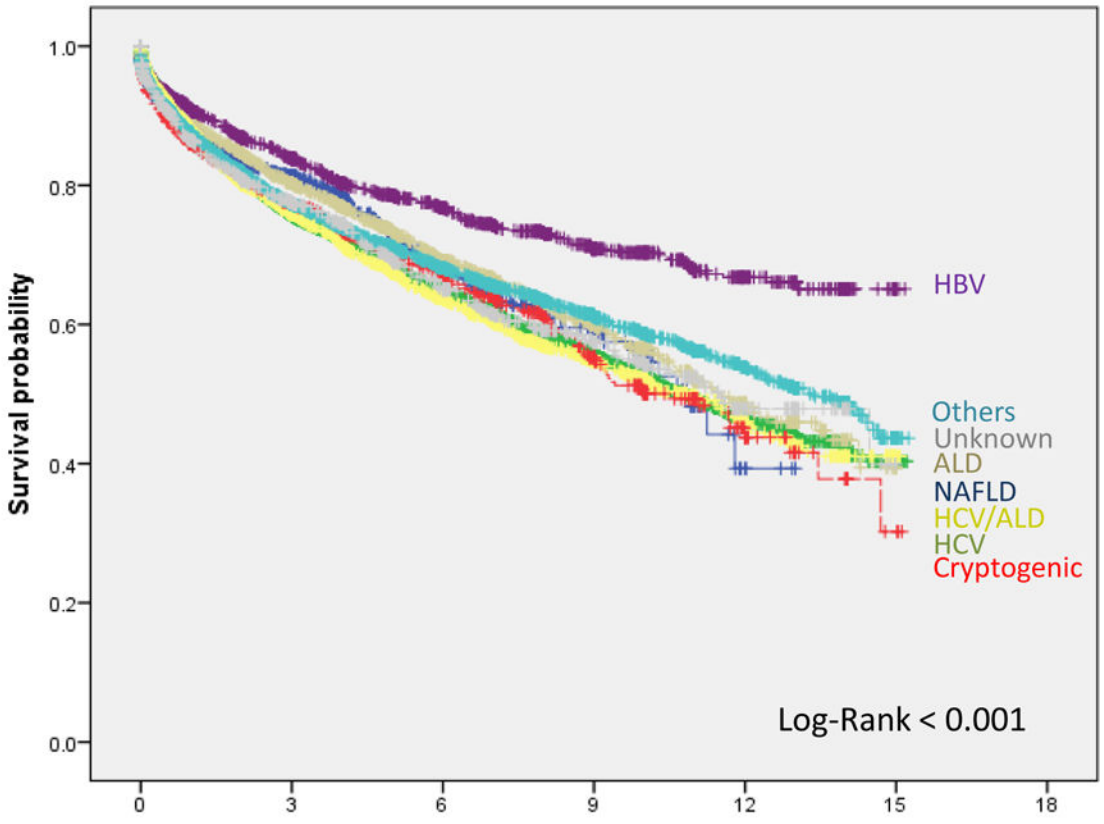


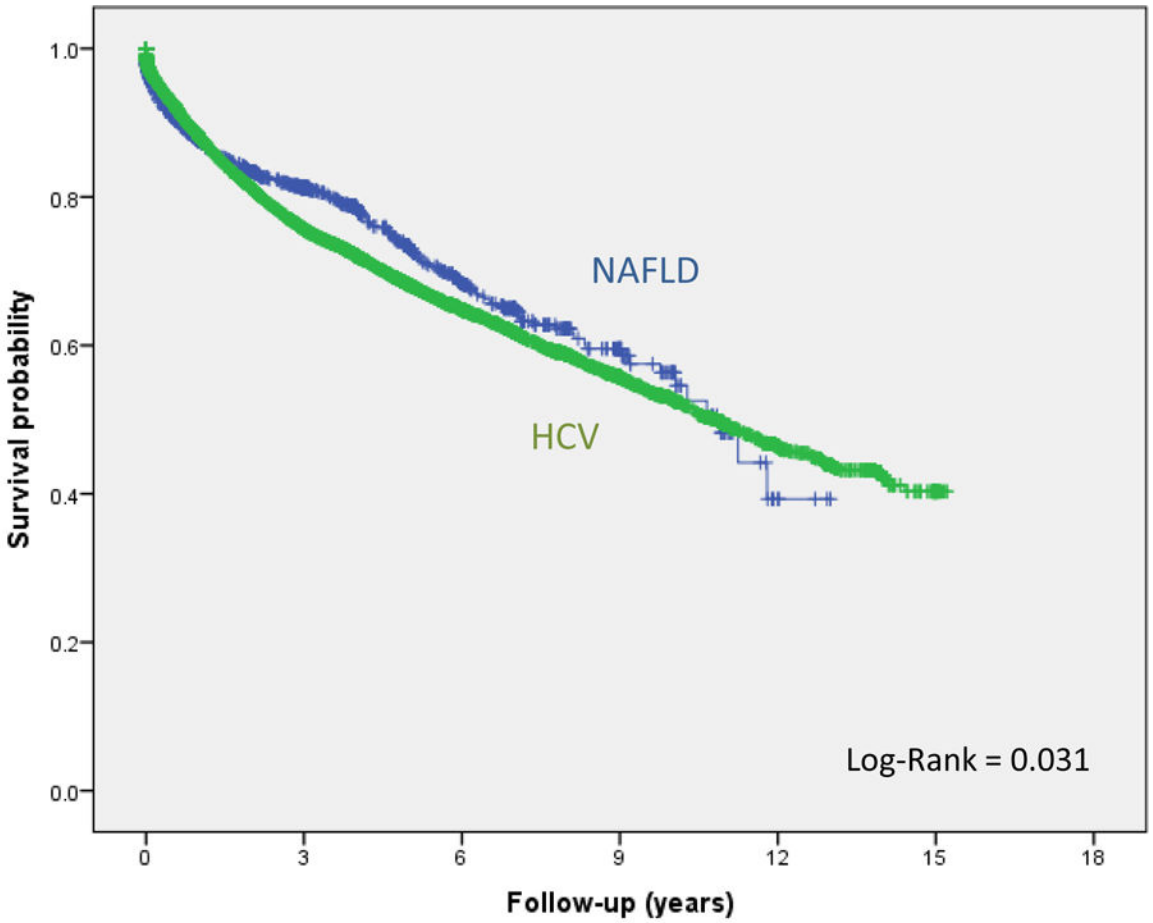
Figure 3.

Determinants of death in HCC-related LT. A) IFN-era (2002–2013); B) DAA-era (2014–2017).



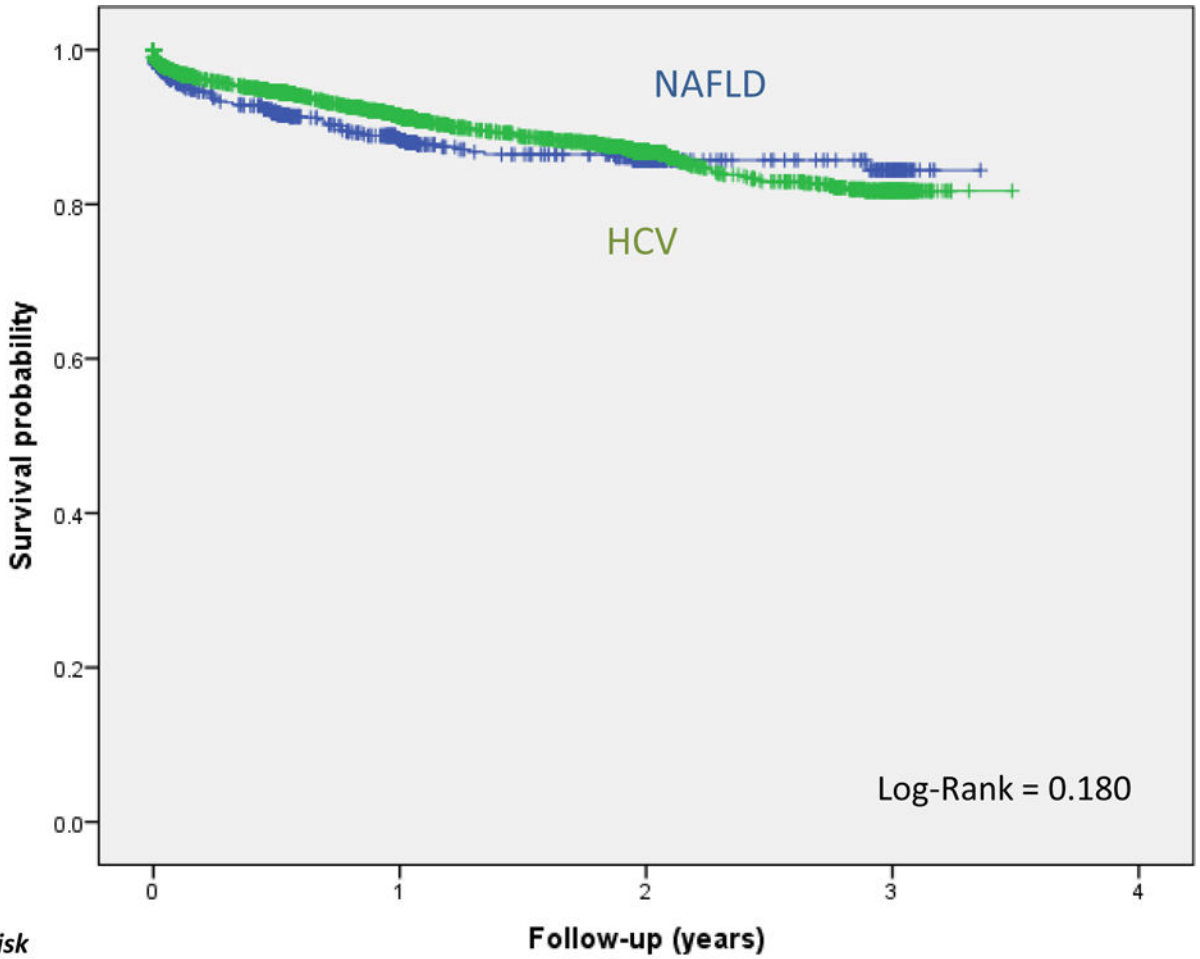
Number at risk

HBV	1439	860	535	295	113	4
Others	3306	1809	1103	600	224	11
Unknown	1003	514	310	155	47	0
ALD	2174	1099	583	270	86	2
NAFLD	1699	635	248	69	4	0
HCV/ALD	2832	1476	812	401	124	4
HCV	13141	6505	3321	1420	418	19
Cryptogenic	754	433	247	121	32	3

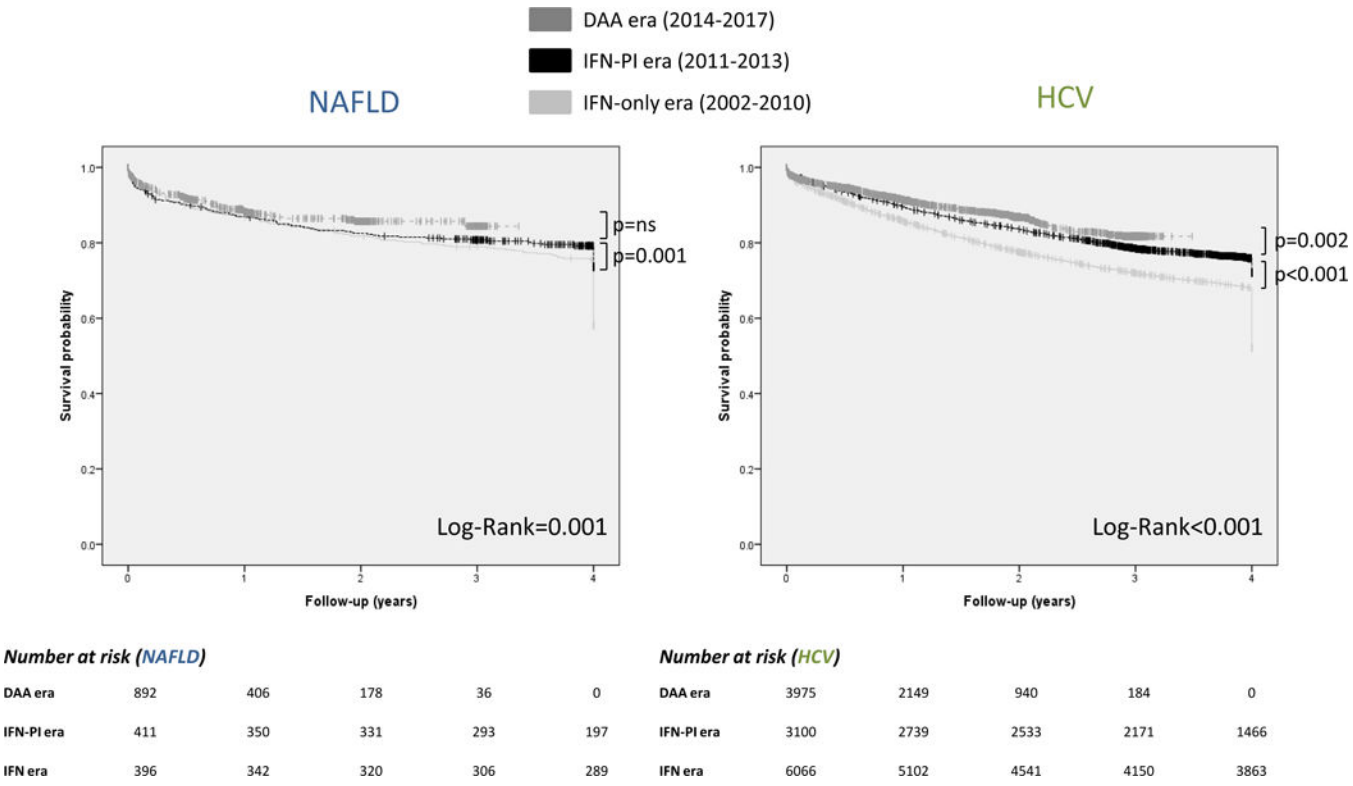


Number at risk

NAFLD	807	599	248	69	4	0
HCV	9166	6321	3321	1420	418	19



Number at risk				
NAFLD	892	406	178	36
HCV	3975	2149	940	184



Number at risk (NAFLD)

DAA era	892	406	178	36	0
IFN-PI era	411	350	331	293	197
IFN era	396	342	320	306	289

Number at risk (HCV)

DAA era	3975	2149	940	184	0
IFN-PI era	3100	2739	2533	2171	1466
IFN era	6066	5102	4541	4150	3863

Figure 4.

Kaplan Meier estimates of survival based on etiology of liver disease in HCC liver transplant recipients. A) MELD era (2002–2017); B) IFN era (2002–2013); C) DAA era (2014–2017); D) Survival according to HCV treatment era in HCV and NAFLD patients (2002–2017).

Table 1.

Baseline clinical characteristics of the HCC recipients. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; Bili, bilirubin; BMI, body mass index; F, female; HCC, hepatocellular carcinoma; HTN, hypertension; INR, international normalized ratio; M, male; MELD, model for end-stage liver disease.

	All patients N= 27,855
Age (years)	58.8 (53.4–63.8)
Gender (male, %)	21,515 (77.2)
Etiology (n, %)	
HCV	13,609 (48.9)
NAFLD	1699 (6.1)
BMI (Kg/m^2)	28 (24.9–31.7)
Diabetes (yes, %)	7,521 (28.9)
Hypertension (yes, %)	5,337 (28.2)
Ascites (n, %)	
None	10,195 (40)
Mild	11,767 (46.2)
Moderate	3,503 (13.8)
Number of HCC lesions (n, %)	
One	15,173 (68)
Two	5,016 (22.5)
Three	2,2024 (9.1)
> Three	94 (0.4)
Size of HCC lesions (cm)	2.5 (2.1–3.2)
TNM Stage (n, %)	
T1	477 (2.1)
T2	16,079 (69.5)
Outside criteria	5,824 (25.2)
Others	744 (3.2)
AFP (ng/mL)	12 (5–49)
MELD transplant	12 (9–17)
Sodium (mmol/L)	138 (135–140)
Creatinine (mg/dl)	0.9 (0.8–1.2)
Albumin (g/dl)	3.2 (2.7–3.7)
ALT (IU/L)	51 (32–85)

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	All patients N= 27,855
Bilirubin (mg/dl)	1.8 (1–3.1)
INR	1.3 (1.2–1.6)

Table 2.

Comparison of outcome and causes of death based on liver disease etiology in HCC recipients. ALD, alcoholic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease.

	All patients N=27,855	HCV n=13,609 (48.9%)	ALD n=2258 (8.1%)	NAFLD n=1699 (6.1%)	HBV n=1623 (5.8%)	Cryptogenic n=831 (3%)	ALD/HCV n=2953 (10.6%)	Others n=3521 (12.6%)	Unknown n=1361 (4.9%)
Overall outcome									
Died (n, %)	8,008 (28.8)	3864 (28.4)	599 (26.5)	330 (19.4)	389 (24)	291 (35)	921 (31.2)	1047 (29.7)	567 (41.7)
Alive (n, %)	16,732 (60.1)	8238 (60.5)	1417 (62.8)	1271 (74.8)	1024 (63.1)	450 (54)	1681 (56.9)	2057 (58.4)	602 (44.2)
Re-transplant (n, %)	1021 (3.7)	511 (3.8)	54 (2.4)	29 (1.7)	61 (3.8)	29 (3.5)	118 (4.0)	156 (4.4)	64 (4.7)
Lost to follow up (n, %)	1297 (4.7)	609 (4.5)	115 (5.1)	18 (1.1)	103 (6.3)	41 (4.9)	154 (5.2)	176 (5.0)	87 (6.4)
No show (n, %)	561 (2.0)	288 (2.1)	45 (2.0)	21 (1.2)	36 (2.2)	20 (2.4)	65 (2.2)	71 (2.0)	15 (1.1)
Unknown (n, %)	236 (0.8)	98 (0.7)	28 (1.2)	30 (1.8)	10 (0.6)	0 (0.0)	14 (0.4)	14 (0.5)	26 (1.9)
Cause of death (COD)									
Graft related (n, %)	880 (11)	480 (12.4)	39 (6.5)	16 (4.8)	53 (13.6)	18 (6.2)	110 (11.9)	102 (9.7)	62 (10.9)
Infections (n, %)	771 (9.6)	352 (9.1)	85 (14.2)	38 (11.5)	29 (7.5)	20 (6.9)	81 (8.8)	105 (10.0)	61 (10.8)
Cardiovascular (n, %)	668 (8.6)	303 (7.8)	61 (10.2)	44 (13.3)	19 (4.9)	39 (13.4)	72 (7.8)	98 (9.4)	49 (8.6)
Multi-organ failure (MOF) (n, %)	578 (7.2)	314 (8.1)	35 (5.8)	25 (7.6)	20 (5.1)	20 (6.9)	72 (7.8)	64 (6.1)	28 (4.9)
Cerebrovascular (n, %)	155 (1.9)	71 (1.8)	10 (1.7)	8 (2.4)	8 (2.1)	7 (2.4)	20 (2.2)	14 (1.3)	13 (2.3)
Bleeding (n, %)	143(1.8)	76 (2.0)	9 (1.5)	6 (1.8)	6 (1.5)	4 (1.4)	18 (2.0)	22 (2.1)	6 (1.1)
Malignancy: primary (n, %)	368 (4.6)	167 (4.3)	28 (4.7)	10 (3.0)	21 (5.4)	12 (4.1)	43 (4.7)	34 (3.3)	53 (9.3)
Malignancy: metastasis (n, %)	1289 (16.1)	596 (15.4)	103 (17.2)	50 (15.2)	94 (24.2)	45 (15.5)	134 (14.5)	158 (15.1)	109 (19.2)
Malignancy: other (n, %)	617 (7.7)	280 (7.2)	51 (8.5)	31 (9.4)	27 (6.9)	23 (7.9)	70 (7.6)	86 (8.2)	38 (6.7)
Other (n, %)	1275 (15.9)	604 (15.6)	88 (14.7)	61 (18.5)	55 (14.1)	62 (21.3)	148 (16.1)	256 (24.4)	79 (13.9)
Unknown (n, %)	1244 (15.5)	621 (16.1)	90 (15.0)	41 (12.4)	57 (14.7)	41 (14.1)	153 (16.6)	105 (10.3)	69 (12.2)