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Liver transplant for hepatocellular carcinoma in the United States: Evolving trends over the last three decades

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Hepatitis C virus 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 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 liver transplants 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; $P = .031$), but these differences disappeared in the DAA era. In addition, HCV patients had a significant improvement in survival when comparing the DAA era with IFN era ($P < .001$). 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.

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.

KEYWORDS
clinical research/practice, liver disease: infectious, liver disease: malignant, liver transplantation/hepatology

1 | 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), and other chronic liver diseases.[3] Curative treatment options are available for patients with local disease and include ablation, resection, and liver transplantation (LT).[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 dropout 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.[8] Treatment options of HCV have evolved tremendously in the recent years.[9] After November 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 settings 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]

Although HCV treatment options have evolved considerably,[13] the growing obesity epidemic in the United States 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 (a) the changing pattern of HCC-related LT etiologies over the past 30 years and (b) 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).

2 | MATERIALS AND METHODS

2.1 | 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 US Government. The SRTR data system includes data on all donor, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

2.2 | 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 United States. 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 (Table S1). 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.

2.3 | 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's exact test. Differences between quantitative variables were analyzed with a nonparametric 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 retransplant, 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 (Table S4). 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).

3 | RESULTS

3.1 | Study population

Between October 1987 and September 2017 there were a total of 132 731 adult DDLT recipients in the United States. 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 body mass index (BMI) (27.9 vs 32.3 kg/m^2), and lower MELD at transplant (12 vs 14) (all $P < .001$, Table S2). 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 $P < .001$) (Table S2).

TABLE 1 Baseline characteristics of the HCC recipients

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, %)	7521 (28.9)
Hypertension (yes, %)	5337 (28.2)
Ascites (n, %)	
None	10 195 (40)
Mild	11 767 (46.2)
Moderate	3503 (13.8)
Number of HCC lesions (n, %)	
1	15 173 (68)
2	5016 (22.5)
3	2024 (9.1)
>3	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	5824 (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)
Bilirubin (mg/dL)	1.8 (1-3.1)
INR	1.3 (1.2-1.6)

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; Bili, bilirubin; BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; M, male; MELD, model for end-stage liver disease.

The characteristics of the donors for the different etiologies of HCC-related LT are presented in Table S3.

3.2 | 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 ($P < .001$) (Figure 1). After 2002, the number and proportion of HCC-related LT

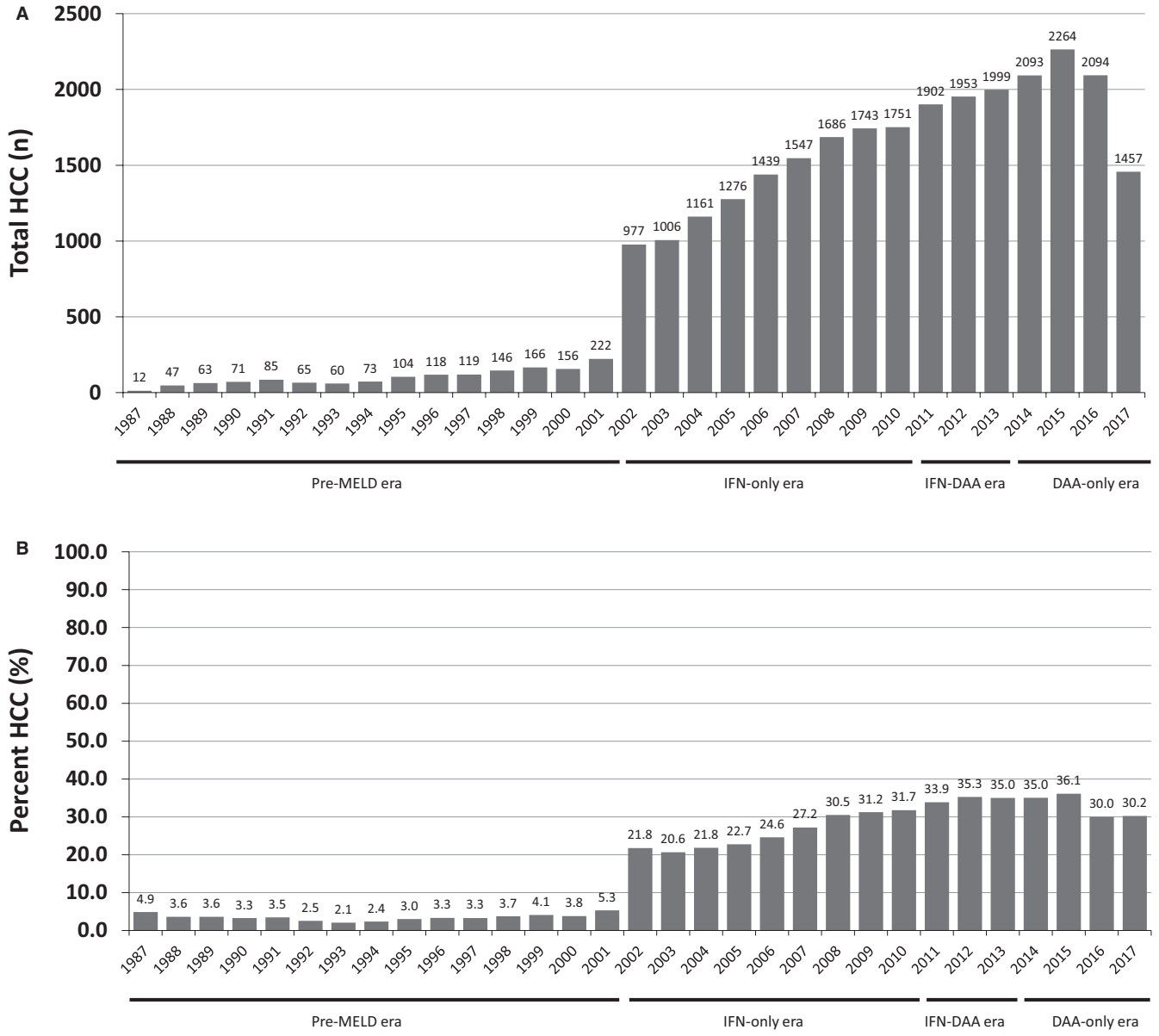

FIGURE 1 The trend of HCC-related liver transplants in the United States based on SRTR data. A, total number (n); B, percentage

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 ($P < .001$) (Figure 1). Although 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 ($P < .001$). 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 NAFLD/HCV 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%) (Figure S1). 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%) (Figures 2 and S1). 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 towards the ALD-only group (9%), then ALD will be the second leading cause of HCC-related LT (18%) (Figure S1E).

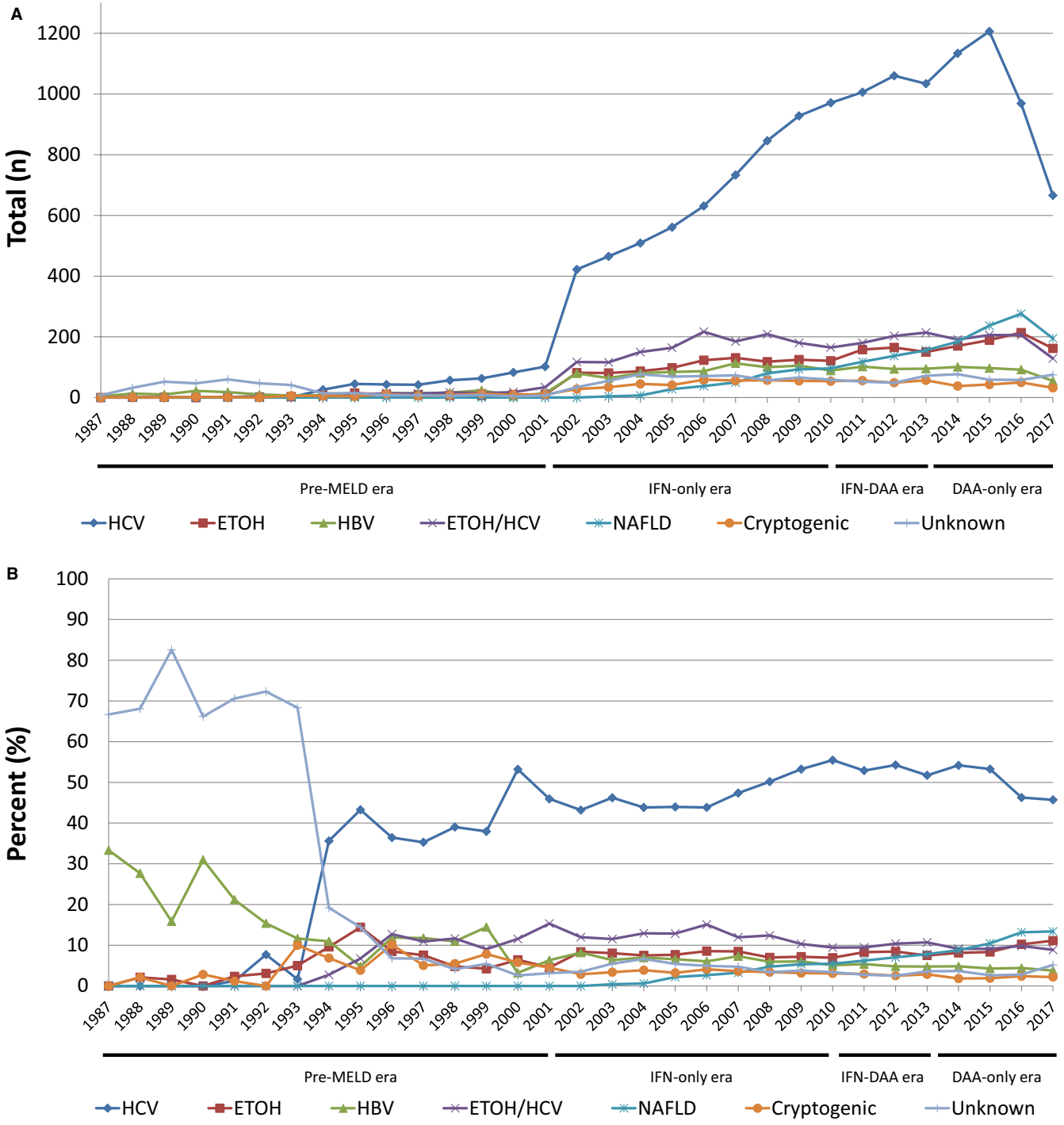

FIGURE 2 Annual trend of etiologies of liver disease in LT recipients with HCC in the United States. A, total number (n); B, percentage [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | 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%, $P < .001$). On the contrary, NAFLD individuals showed a higher rate of cardiovascular-related death (13.3% vs 7.8%, $P < .001$) (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, $P < .001$), alpha-fetoprotein (1.288, 1.200-1.382, $P < .001$), and diabetes (1.188, 1.102-1.280, $P < .001$) (Figure 3A and Table S4A). Remarkably, in the DAA era, etiology was not related to survival neither in the univariate (0.963, 0.836-1.110, $P = .603$) nor in the multivariate analysis (1.115, 0.892-1.394, $P = .338$) (Figure 3B and Table S4B). Only tumor size (1.189, 1.079-1.311, $P = .001$) 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) (Figure S2). This difference in outcome

TABLE 2 Comparison of causes of death based on liver disease etiology in HCC liver transplant recipients

	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, %)	8008 (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)
Retransplant (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)
Multiorgan 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)

ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

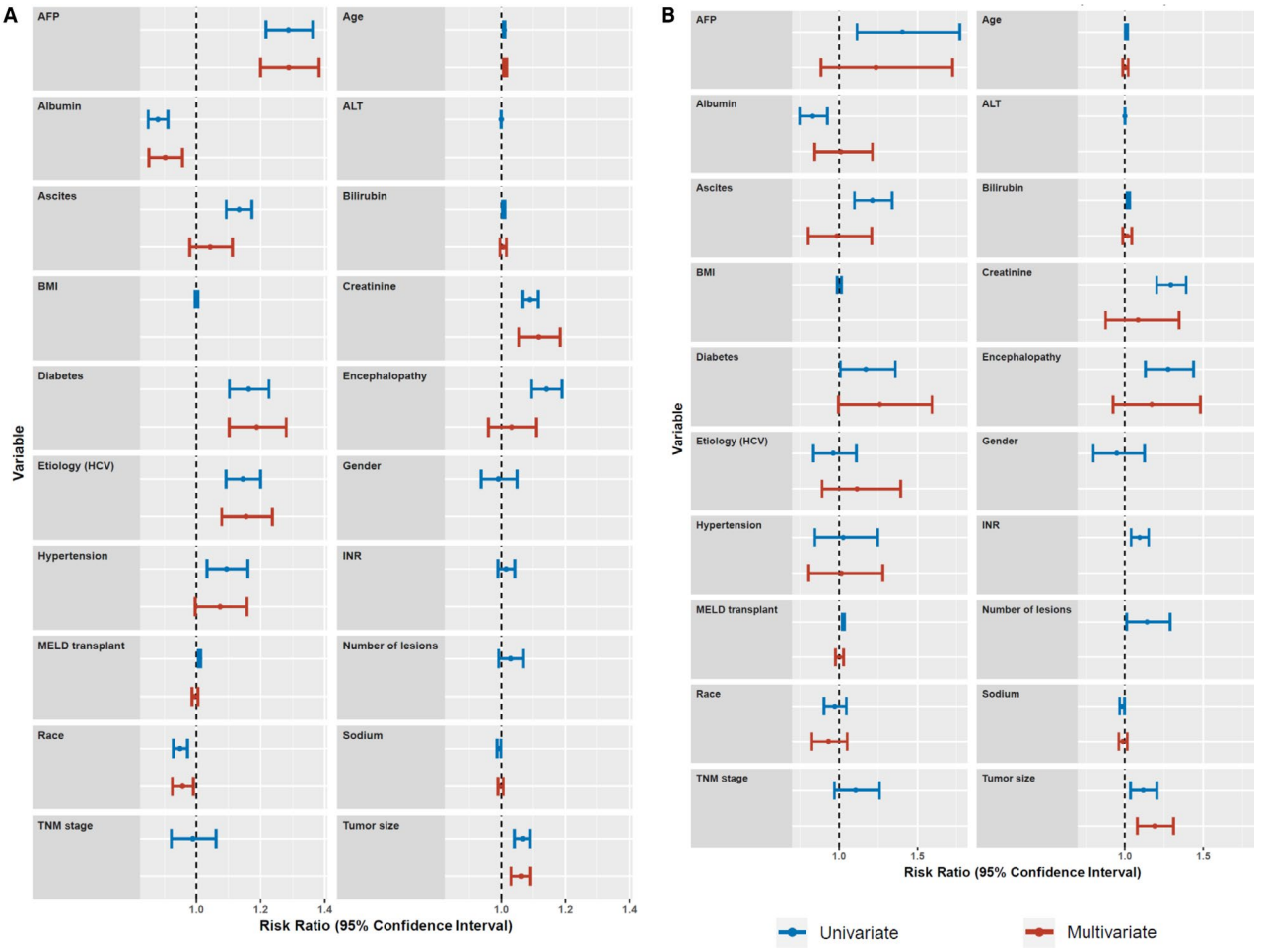

FIGURE 3 Determinants of death in HCC-related LT. A, IFN-era (2002-2013); B, DAA-era (2014-2017) [Color figure can be viewed at wileyonlinelibrary.com]

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 showed improved survival only 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).

4 | 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 toward a decrease in 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 30-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.

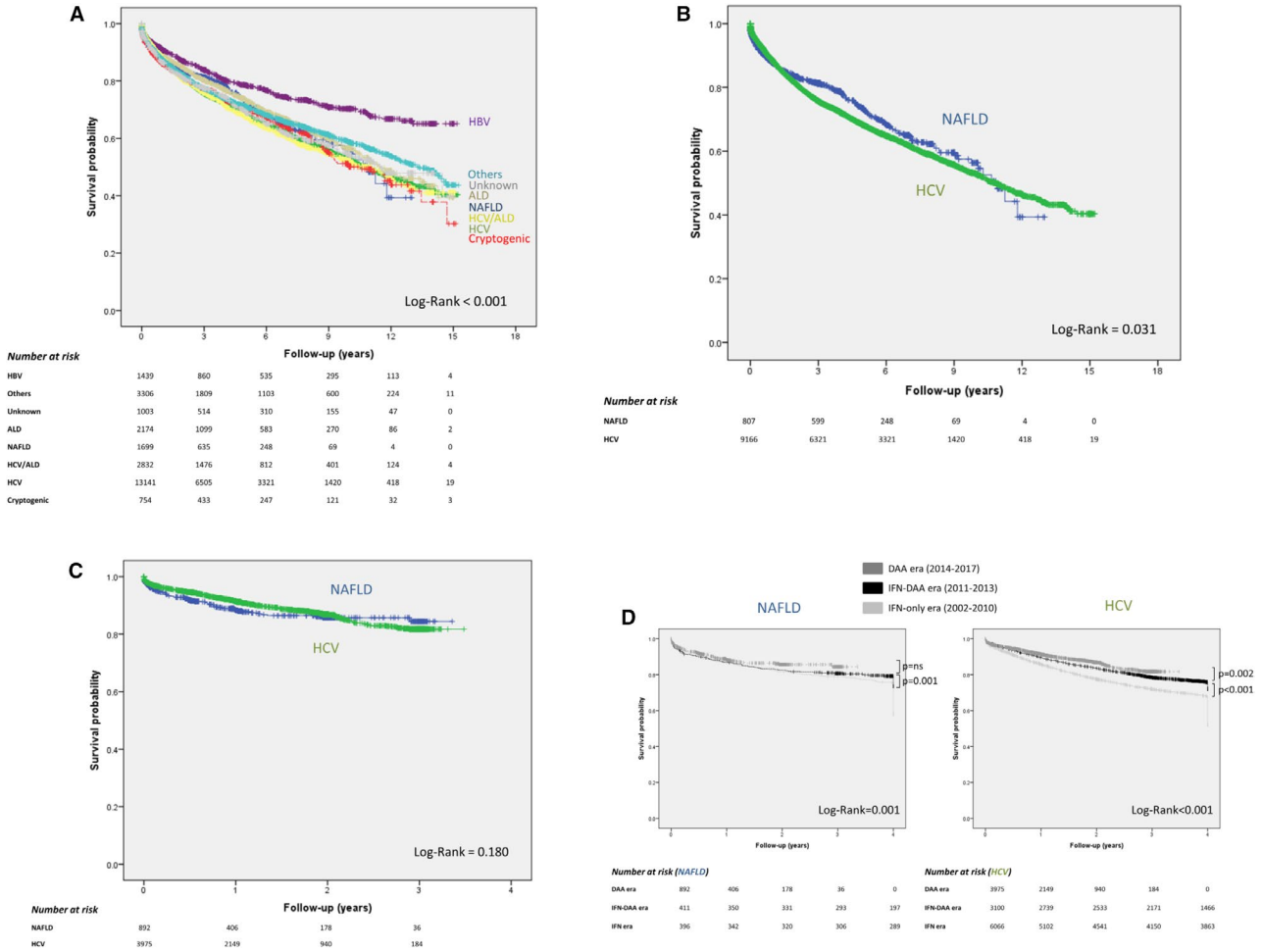

FIGURE 4 Kaplan–Meier estimates of survival based on etiology of liver disease in HCC liver transplant recipients. A, MELD era (2002-2017); B, IFN era (2002-2013); C, DAA era (2014-2017); D, survival according to HCV treatment era in HCV and NAFLD patients (2002-2017) [Color figure can be viewed at wileyonlinelibrary.com]

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/delisting 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 United Network for Organ Sharing regional differences. Only after the most recent modification in 2015 in which HCC patients received no priority for 6 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 25 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] Although 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 50% of HCC-related LT patients have underlying ascites, which falsely raises the BMI. Of note, cryptogenic cirrhosis accounted for less than 3% 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 not 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 have not been 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 United States in the recent years. 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 overreported. 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 accounted for only 5% of the total.

In summary, changes in the MELD exception policy have over time 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. Although 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, whereas 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.

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AUTHOR CONTRIBUTIONS

MP (study concept and design, analysis and interpretation of data, statistical analysis, drafting and critical revision of the manuscript); DH (study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript); PKH (study concept and design, analysis and interpretation of data, statistical analysis, drafting and critical revision of the manuscript); AD (study concept and design, analysis and interpretation of data, drafting of the manuscript); TDS (study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content); AA (study concept and design, analysis and interpretation of data, drafting of the manuscript); TK (analysis and interpretation of data, drafting of the manuscript); GK (analysis and interpretation of data, statistical analysis, drafting of the manuscript); PT (study concept and design, drafting of the manuscript); MS (study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content); AG (study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content); DD (study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content); PB (contribution to study design and analysis plan; critical review of the manuscript); SLF (study concept and design, analysis and interpretation of data,

drafting of the manuscript, critical revision of the manuscript for important intellectual content); JML (analysis and interpretation of data, critical revision of the manuscript for important intellectual content); and BS (study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision).

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.

DATA AVAILABILITY STATEMENT

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 US Government. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

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SUPPORTING INFORMATION

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

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