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Reduction in Liver Transplant Wait-Listing in the Era of Direct Acting Anti-Viral Therapy

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Abstract

Recent approval of direct-acting antiviral (DAA) therapy for patients with decompensated cirrhosis (DC) secondary to hepatitis C (HCV) is associated with improved hepatic function. We analyzed trends in liver transplant (LT) wait-listing (WL) to explore potential impact of effective medical therapy on WL registration. This is a cohort study using the Scientific Registry of Transplant Recipients database from 2003-2015. 47,591 adults wait-listed for LT from HCV, hepatitis B (HBV) and non-alcoholic steatohepatitis (NASH) were identified. LT indication was defined as DC if the model for end-stage liver disease (MELD) at WL was ≥ 15 or hepatocellular carcinoma (HCC). Era of listing was divided into “interferon” ([IFN] 2003-2010), “protease inhibitor” ([PI] 2011-2013), and “direct-acting antiviral” ([DAA] 2014-2015). Annual standardized incidence rates of WL were analyzed using Poisson regression. Adjusted incidences of LT WL for DC in HCV patients decreased by 5% in the PI era (P = 0.004) and 32% in the DAA era (P <.001) compared to the IFN era. Listing for DC in HBV also decreased in the PI (−17%, P = 0.002) and DAA eras (−24%, P <.001). Conversely, WL for DC in NASH increased by 41% in the PI era (P <.001) and 81% in the DAA era (P <.001). WL for HCC in both the HCV and NASH populations increased in both PI and DAA eras (P <.001 for all) while HCC WL in HBV remained stable (P > 0.05 for all). Conclusions: The rate of LT WL for HCV complicated by DC has decreased by over 30% in the era of DAA therapy. Further reductions in WL are anticipated with increased testing, linkage to care, and access to DAA therapy.

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Conflicts of Interest: JF: Instuitional grant support from Gilead and AbbVie. WRK: is a member of the Scientific Registry of Transplant Recipients (SRTR). He participates in advisory board for Gilead, Abbvie, and Merck. CB: Member of the Board of Directors, Tobira Therapeutics, Chair of the Scientific Advisory Board, ContraVir, consultant to Dynavax and Assembly; NT: Institutional grant support from Gilead, AbbVie, BMS. Advisory board for Merck.

Disclaimer: 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 author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

Keywords

non-alcoholic steatohepatitis; hepatocellular carcinoma; hepatitis C; hepatitis B; cirrhosis

Liver transplantation (LT) is a well-established therapy for patients with cirrhosis who have developed hepatic decompensation and small hepatocellular carcinoma (HCC). Viral hepatitis has long been the most common indication for LT in the United States (US) and Canada with over 30% of all LT wait-listed candidates having chronic hepatitis B (HBV) or hepatitis C (HCV) infections [1]. It has been estimated that the complications of decompensated cirrhosis (DC) and HCC from hepatitis C virus (HCV) infection will continue to rise into the next decade resulting in increased utilization of healthcare resources, including LT, for these populations [2,3]. It has been shown that effective anti-viral therapy resulting in either chronic viral suppression for those with HBV, or “cure” with a sustained virologic response (SVR) in those with HCV results in decreased rates of HCC, DC, and liver transplantation, as well as a decrease in overall mortality [4,5]. Our previous work spanning the years of 1994 to 2006 has shown that LT for DC and acute hepatic failure in patients with HBV were significantly lower from 2003-2006 compared to 1994-1997 in the US [6]. Although the observation was ecological without a direct demonstration of cause-effect relationship, the trend was attributed to the availability of FDA approved effective oral anti-viral therapy for HBV with an improved resistance profile, starting in 2002.

The availability of effective well-tolerated anti-viral therapies in the US has evolved differently for HBV as compared to HCV (supplemental figure 1), with an almost 15 year difference in access to all-oral treatment regimens for the two viruses. Potent and safe chronic antiviral therapies for patients with HBV, including those with cirrhosis, have been FDA approved and available for more than a decade [8]. In contrast, safe and highly effective direct acting anti-virals (DAAs) for HCV have only been available in the US since 2014 [9]. DAA therapy for HCV is curative and of a finite duration as opposed to chronic suppressive therapy in the majority of HBV cases. Current DAA combination therapy can achieve SVR in the majority of patients with HCV cirrhosis, both compensated and decompensated, and among those with decompensated cirrhosis and SVR, improvements in the model for end-stage liver disease (MELD) and Child-Turcotte-Pugh scores in months of completing treatment [10-13]. Further, achievement of SVR in patients with cirrhosis has been associated with significant reductions in liver-related complications, such as decompensation and HCC [4].

It is estimated that over 100 million people in the US have non-alcoholic fatty liver disease and of those, 15-20 million will have non-alcoholic steatohepatitis (NASH) [14]. NASH is a recognized cause of cirrhosis and hepatocellular carcinoma and recent studies have shown that the rates of listing and receipt of LT for this indication have increased over the last decade [15,16]. In contrast to viral hepatitis, there are currently no FDA-approved therapies to decrease the risk of progression to DC or HCC or to reverse NASH-related liver fibrosis.

As wait-listing for LT is a reflection of the changing epidemiology of the underlying cirrhotic population in the US, the aims of this study were to evaluate the secular trends in

LT wait-listing registration for HCV, HBV and NASH based on the indication for LT (DC or HCC) to estimate how the availability of effective treatments influences LT listing rates.

Methods

Patients and Data Elements

This is a population-based cohort study of patients listed for LT from all 127 centers across the US. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted 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), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors [17].

Focusing on a post-MELD time period (January 1, 2003 – December 31, 2015), we identified all adult (≥ 18 years of age) waitlist registrants with an etiology of liver disease (based on primary or secondary SRTR diagnostic codes or manually entered text) of HBV, HCV, or NASH. Patients with a dual diagnosis of HCV and any other cause (ie. alcohol) were classified as HCV. Following the prior convention, patients listed with a diagnosis of cryptogenic cirrhosis with a body mass index (BMI) > 30, were classified as NASH [15,16]. Patients were excluded if they lacked a unique identifier, were listed for indications other than that in the inclusion criteria, listed as status 1, or had received a previous liver transplant. Those who had previous transplantation of other organs were included (0.7% of cohort).

Patients were classified as being wait-listed for the indication of DC if their MELD at LT listing was ≥ 15 to capture those with uniform indications for LT for decompensated liver disease. Though we recognize that patients with a MELD < 15 with complications of refractory ascites, hepatic hydrothorax, severe hepatic encephalopathy, or hepatopulmonary syndrome would be excluded, the SRTR data does not allow us to reliably capture this information. Patients were classified as being wait-listed for the indication of HCC if it was identified as the listing indication (based on SRTR codes or manually entered text) and/or they received an HCC MELD exception within the first 180 days of transplant wait-listing. If patients were listed with both HCC and a MELD score ≥ 15, they were classified as being listed with HCC. We divided the study period into three eras to reflect differences in availability of specific anti-viral therapies for HCV. Era 1 – “interferon era (IFN)” – was from 2003-2010, era 2 – “protease inhibitor (PI) era” was from 2011-2013, and “DAA era” – was from 2014-2015.

Demographic and clinical data were obtained from the SRTR at the time of listing for LT. The proportion of patients with LT wait-list death or drop-out was determined using SRTR codes. The proportion with WL death or de-listing due to worsening clinical status for LT by year of listing were calculated, including only those individuals listed from 2003 and 2014, to allow a minimum of 1 year of total follow-up. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki protocol and was approved by the Queen's University Health Sciences Research Ethics Board (DMED-1688-14).

Statistical Analyses

Demographics of the cohort are expressed as medians or percentages and compared using the Kruskall-Wallis or Chi-Squared tests respectively. To test for secular trends over time in median age, MELD score, and proportion of patients with death/drop-out or recovery on the WL, the non-parametric test for trend was used [18]. To calculate the age-standardized incidence rates (ASIR) for LT wait-listing, the number of patients listed annually by sex were tabulated into age categories using the entire annual US population estimates as the denominator (http://www.census.gov/cps) and standardized to the 2000 US population (http://seer.cancer.gov/popdata/index/htm) using the direct method. Differences between the annual rates of transplant wait-listing by indication were compared by calculating incidence rate ratios (IRR) using zero-weighted Poisson regression adjusting for age and sex after confirming this method was preferred over standard Poisson regression using the Vuong test [19]. All analyses were performed using STATA (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

Results

Baseline demographics of the cohort

A total of 47,591 wait-list registrants met inclusion and exclusion criteria for the study (Figure 1). The median age of the cohort was 56 years (IQR 51 – 61), 71% were male, and most patients were of Caucasian, non-Hispanic race-ethnicity (Table 1). The majority of patients were listed for DC (61%), with 39% being listed for HCC. Those with HCV and HBV had a higher proportion of individuals listed for HCC compared to those with NASH. Patients with NASH were older, more likely to have underlying diabetes, and a higher median BMI and biochemical MELD score at LT wait-listing. Those with HBV were more likely to be of Asian race compared to those with HCV or NASH.

Secular trends in wait-listing for LT based on indication and etiology of disease

The ASIR of LT wait-listing by listing indication (overall, DC and HCC) and the etiology of liver disease based on the total US population are listed in the supplementary table 1 and displayed in figure 2. Secular trends in wait-listing over the study period based on the underlying etiology of disease are shown in Figure 3. The ASIR rate for overall LT wait-listing, over the 10-year study period, increased in those with HCV and NASH while it decreased in those with HBV. For the indication of DC, the ASIR decreased in those with HCV in and HBV in both the PI and DAA eras, but increased over 3-fold in those with NASH. If we consider these rates in the context of individual patient numbers, it suggests that there were almost 700 fewer HCV patients in the US WL for DC in 2015 compared to 2003. Of importance, in 2015, the ASIR of LT WL for DC for NASH was similar to that for HCV (2.80/100,000 vs. 2.73/100,000 respectively). Wait-listing for the indication of HCC increased two-fold for HCV and over 10-fold in the NASH population while it remained stable in those with HBV.

Table 2 describes IRRs for the three eras for the different indication and etiology of underlying liver disease. For the HCV population the overall rate of LT wait-listing increased by 24% in the PI era but decreased by 8% during the DAA era when compared to

the IFN era. When focusing on WL for DC, the rate decreased by 5% during the PI era and 32% since FDA approval for DAA therapy when compared to 2003-2010. In contrast, listing for HCC in the HCV population increased by 62% in the PI era and 34% in the DAA era. In those with HBV, listing for DC decreased from both 2011-2013 and 2014-2015 while listing for HCC remained constant. For the NASH population, rates of LT WL increased overall and for both DC and HCC in both eras.

Secular trends in age at wait-listing, MELD score, and drop-out from the wait-list among patients listed with ESLD

Other factors that could explain the secular trends in LT wait-listing for DC were explored. First, to determine if the observed trends were secondary to the aging population and specifically, the “baby boomer” population of individuals with HCV, we calculated the median age at LT wait-listing (Table 3). Overall, the median age at the time of WL increased significantly over the study period for all groups ($p<.05$ for all etiologies). However, this increase in median age was most pronounced in the HCV population increasing from 53 years in 2003 to 57 years (IQR 52-61) in 2015. In contrast, the median age of the NASH population in 2015 was similar (59 years, IQR 53-65).

Second, we explored whether patients listed for LT for DC had more advanced liver failure in the recent eras reflecting a more advanced population of cirrhotics in the US with fewer surviving to be listed for LT. We did this in two ways: (i) evaluating the median biochemical MELD score at LT listing by etiology of liver disease and (ii) the proportion of candidates wait-listed who either died or dropped off the LT list for worsening clinical status. In general, those with HBV listed for DC had higher laboratory MELD scores at LT wait-listing than individuals with HCV or NASH. The proportion of individuals listed for DC with wait-list death/drop-out or hepatic recovery was unchanged over the eras ($P > 0.05$ for all).

Discussion

In this population-based study in the US, we show that since the approval of all oral HCV DAA regimens, there has been an over 30% decrease in the rate of LT WL registration for DC in patients with HCV in the US. These trends are similar to the trends we previously observed in the HBV population where effective anti-viral therapy for patients with DC has been available for over a decade. This is in contrast to the growing burden that the NASH population is putting on the healthcare system with rates of LT WL increasing dramatically over past 15 years and the number patients listed for DC with NASH is now at least comparable to, if not higher than that of HCV. This trend is almost guaranteed to continue into the next decade as testing, linkage to care, and access to DAA therapy improve for HCV while NASH is currently a disease without any FDA approved therapeutic agent(s) able to alter the natural history.

Over the past year, multiple studies have confirmed the safety and impact of achieving SVR with DAA therapy in those with decompensated HCV disease (10-13,20-21). Investigators from the United Kingdom have recently shown that the ability to reverse hepatic decompensation after SVR can occur in as little as 6 months [20] and therefore it is rational

to assume that the decrease in HCV WL registration for DC that we have shown is likely a result of the uptake of DAA therapy at the population level. Further, it had been common practice before the availability of DAA therapy for patients being considered for anti-viral therapy with decompensated HCV disease to be WL for LT due to the concern of further decompensation with IFN or PI containing regimens. In the presence of excellent safety of the DAA regimens, there may be more clinicians willing to treat patients with DC without LT WL prior to starting therapy. We did not find an increase in the proportion of HCV patients removed from the LT WL for hepatic recovery during the DAA era. However, this is likely due to the short follow-up time of the cohort post-DAA availability, as we looked only at those listed in 2014 to allow for one year of follow-up. We expect that this trend will become apparent as WL trends are observed into the future. Another potential reason for the secular decrease in LT WL that we observed may be the increasing age of the “baby boomers” who represent the age group with the greatest burden of advanced liver disease but who will be less eligible for LT wait-listing with aging. This interpretation is supported by the observations of higher median ages at LT wait-listing in the HCV patients over the study period. However if this were the only explanation for the decrease in WL then we would have expected that the rate of decline would be similar in both the PI and DAA eras. As we observed a more precipitous drop in WL for DC with the approval of DAAs, the decrease from 2014-2015 is likely a combination of both the aging HCV population and a higher proportion of HCV patients in receipt of anti-viral therapy.

We did not observe the same degree of decrease in LT WL registration for the indication of HCC. This is not unexpected as it has been shown that improvements in underlying hepatic dysfunction secondary to viral suppression occurs much more rapidly than does the decrease in the risk of HCC [22,23]. This is likely due to the fact that in those achieving viral suppression or cure, duration of disease, underlying cirrhosis and other non-modifiable risk factors known to be associated with the development of HCC in the cirrhotic population such as age, sex, and the presence of underlying diabetes persist [24,25]. Recent data from the Veterans Affairs system suggests that the incidence of HCC after achieving SVR in patients with cirrhosis was 1.4% per year and this risk was dependent on age and HCV genotype [26]. As more patients with HCV cirrhosis achieving cure after DAA therapy are observed into the future, the risk of HCC will be further quantified but the impact of DAA therapy on WL for HCC is not yet apparent. Similarly, we hypothesize that in addition to the impact on the LT wait list we have observed here, the use of DAA therapy in the HCV population will have other downstream effects in the future. This may include variations in the median biochemical MELD score at the time of transplant and improvements in post-transplant HCV graft survival due to the ability to treat post-LT with DAA regimens. However, this will require several years of observation before these trends will become apparent.

Our results on NASH are consistent with other recent studies indicating that the rates of wait-listing and receipt of LT for NASH is on the rise in the US [15,16]. The increase in obesity and metabolic syndrome-associated complications, including diabetes, in the US population, are likely responsible for this and NASH as an LT indication is projected to continue to increase in the years ahead [27]. However, unlike these previous studies, we looked specifically at the difference in the rates based on the listing indication. Importantly,

this study shows that in contrast to trends in the populations with HBV and HCV, the indications for listing in the NASH population is increasing for both HCC and DC. As opposed to chronic viral hepatitis, medical therapies that can decrease or reverse the progression of NASH are limited. Therapeutic investigational clinical trials of vitamin E, pioglitazone, metformin, obeticholic acid, and most recently cenicriviroc [28-30], suggest modest improvements in NASH histology with limited duration therapy. However, there is no current FDA approved therapy, for the NASH indication, that can prevent or reverse the development of DC or HCC-related to fatty liver, during the study period. Additionally, improvements in liver histology have been shown with bariatric surgery in select patient populations [31,32], but randomized clinical trials with prevention or reversal of cirrhosis as the treatment endpoint are lacking. Further, bariatric surgery is controversial in patients with cirrhosis outside of highly specialized centers and therefore not widely available in the US. While it has been expected for some time that NASH would surpass chronic viral hepatitis B and C as an indication for LT, this analysis shows that for the indication of DC, this has already occurred in 2015. Furthermore, our study likely underestimates the true burden of complications from NASH in the US population, as NASH patients have a higher burden of medical co-morbidities that may limit their eligibility for LT.

There are several limitations to our study. First, detailed information about medication use is not reported to the OPTN and therefore not included in the SRTR data. Thus, this work is unable to provide a direct link to WL registration and DAA therapy. Further, as we are looking at secular trends at the population-level, other factors associated with a decrease in LT wait-listing could be present that we are unable to account for. However, these would have to be unique to both the underlying liver disease and the indication for LT wait-listing to account for these trends which we feel is unlikely. Secondly, as we are examining trends in LT wait-listing and therefore looking solely at individuals who meet criteria for wait-listing, we are unable to comment on individuals with significant co-morbid illnesses or with financial or social barriers that limit eligibility for LT. Conversely however, those eligible for LT wait-listing would likely also have greater access to antiviral therapy, so our study is representative of the potential impact of new drug therapies on DC complications, and as we have previously seen following the release of safe and effective oral HBV therapies. One final limitation is that the time period studied represents a time during which NASH as a cause for cirrhosis was increasingly recognized. Thus the increase in wait-listing for NASH could be secondary to the increased recognition of this condition over the past decade which may have previously been classified as cryptogenic cirrhosis. To try and account for this, we included patients with cryptogenic cirrhosis and a BMI >30; however, while this has also been done by investigators in the past [33], it remains a limitation.

In conclusion, this population-based study shows a significant decrease in LT WL registration for the indication of decompensated HCV disease during the era of DAA therapy in the US. We expect that with further implementation and expansion of the Centers for Disease Control and Prevention recommended screening of the ‘baby-boomer’ population (born 1945-1965), linkage to care, and availability and utilization of available DAA regimens that this trend will continue into the future and will likely eliminate HCV as the leading cause for liver transplant in the US. In contrast, the rising rates of DC and HCC listings for NASH portend a major transplantation need today and in future. Although a large

number of investigational therapeutic agents for the treatment of NASH are in current clinical development, LT wait-listing for NASH is anticipated to rise in the immediate future until effective well tolerated therapy becomes available in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASIR	Age-standardized incidence rate
BMI	body mass index
CDC	Center for Disease Control and Prevention
DAAs	direct acting anti-virals
DC	decompensated cirrhosis
HCC	hepatocellular carcinoma
HBV	hepatitis B
HCV	hepatitis C
IRR	Incidence rate ratio
LT	liver transplant
MELD	model for end stage liver disease
NASH	non-alcoholic steatohepatitis
SRTR	Scientific Registry for Transplant Recipients
SVR	sustained virologic response
US	United States

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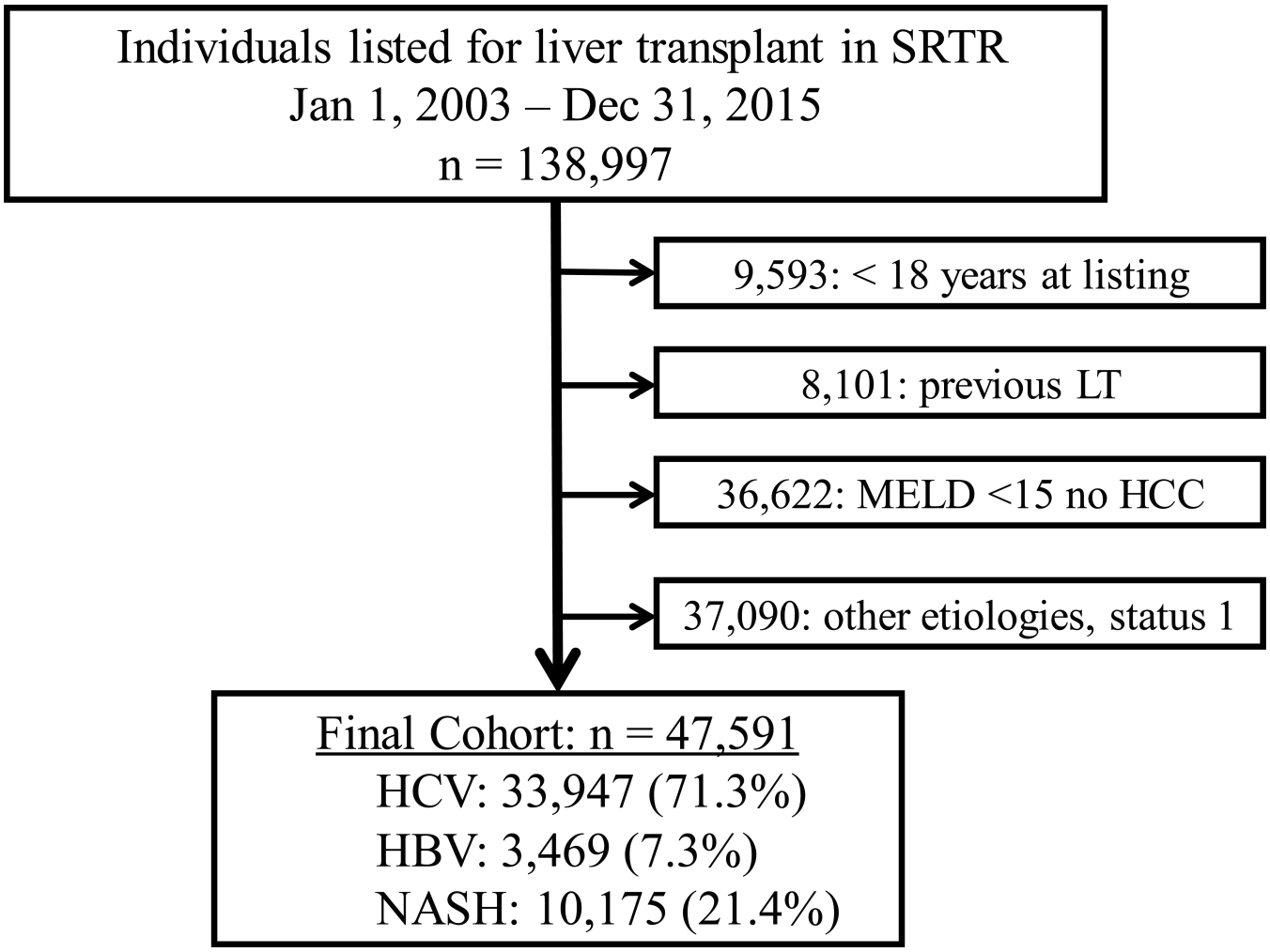

Figure 1.

Development of the study cohort. SRTR: scientific registry of transplant recipients; LT: liver transplant; MELD: model for end stage liver disease; HCC: hepatocellular carcinoma; HCV: hepatitis C; HBV: hepatitis B; NASH: non-alcoholic steatohepatitis.

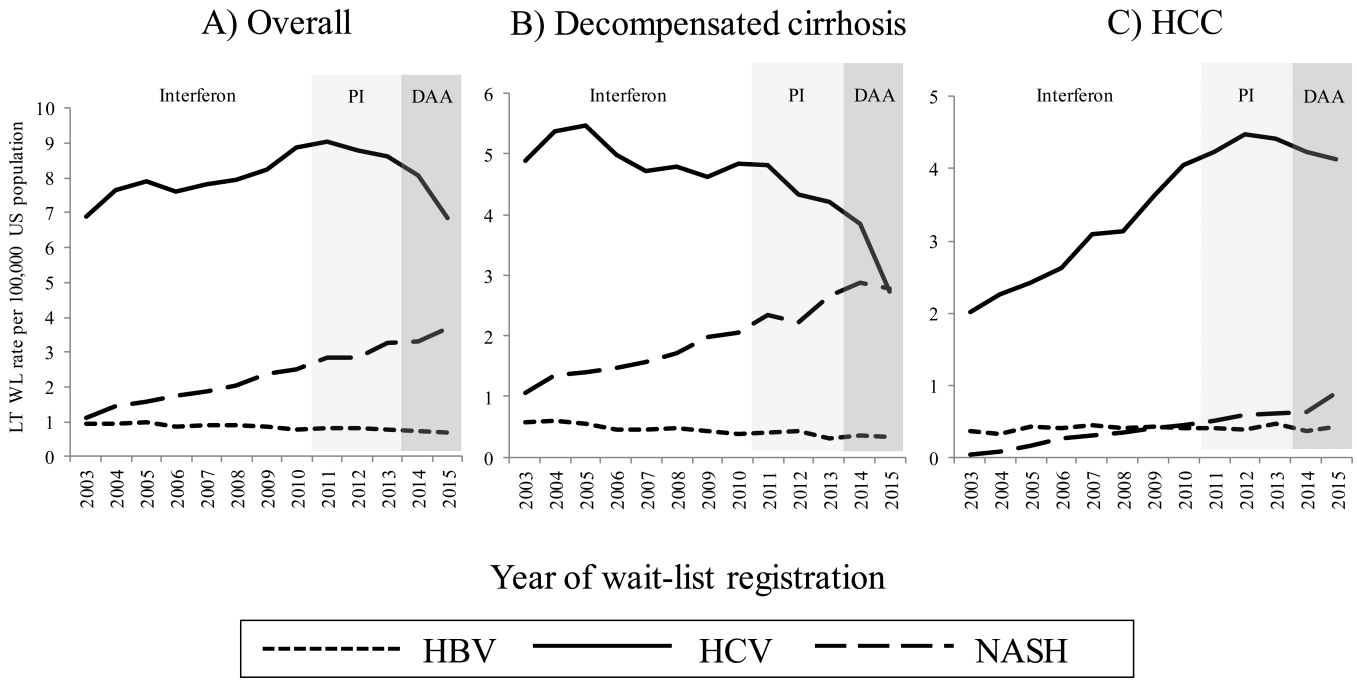

Figure 2.

Annual standardized incidence rates (ASIR) of LT wait-listing per 100,000 US population by etiology of liver disease and indication for wait-listing. X-axis is the year of LT wait-listing registration. PI: protease inhibitor; DAA: direct acting antiviral

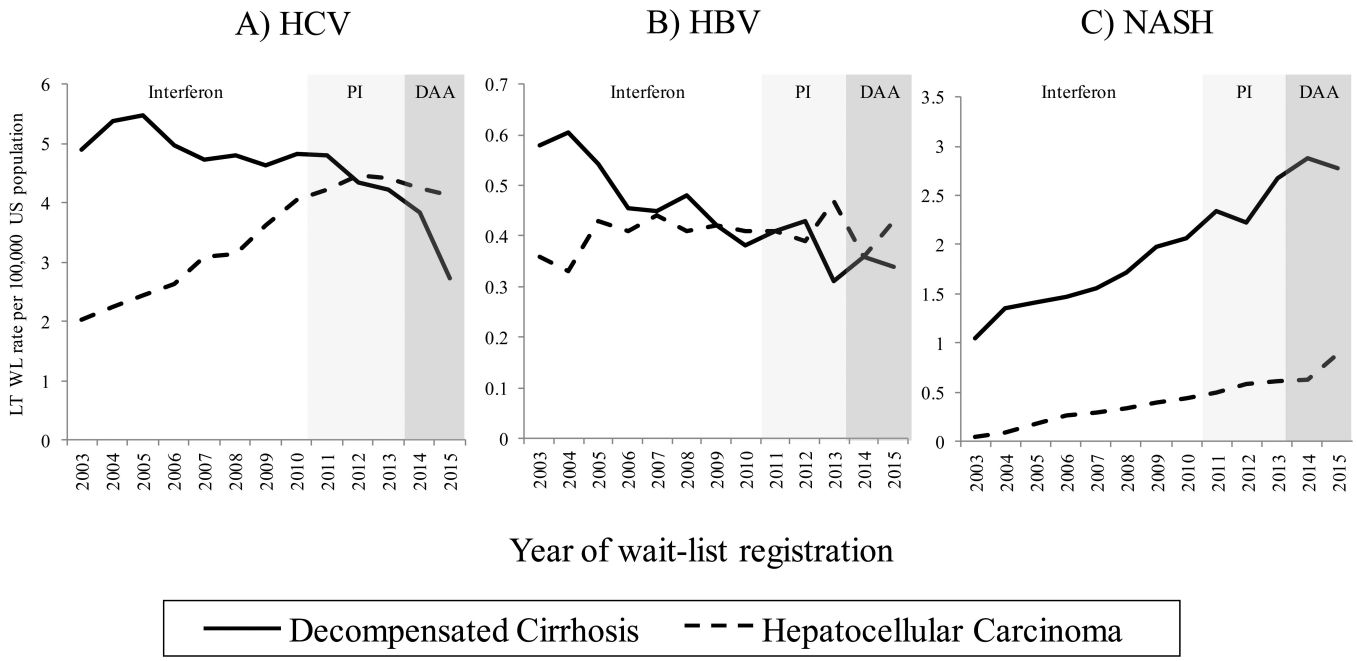

Figure 3.

Annual standardized incidence rates (ASIR) of LT wait-listing per 100,000 US population by etiology of liver disease and indication for wait-listing. X-axis is the year of LT wait-listing registration. PI: protease inhibitor; DAA: direct acting antiviral

Table 1

Baseline characteristics of patients listed for liver transplantation for HCV, HBV or NASH in the United States 2003-2015.

	Entire Cohort n = 47,591	HCV n = 33,947	HBV n = 3,469	NASH n = 10,175	p value *
Listing indication %					
- ESLD	60.8	55.5	50.7	81.9	<.001
- HCC	39.2	44.5	49.3	18.2	
Age at listing, Median (IQR)	56 (51-61)	56 (51 – 60)	55 (47 – 61)	60 (53 – 65)	<.001
Male sex, %	70.9	75.1	80.1	54.0	<.001
Race-Ethnicity %					
- Caucasian	66.4	66.4	31.5	78.4	<.001
- Hispanic/Latino	15.0	15.8	5.6	15.4	
- Black	11.0	13.2	12.1	3.1	
- Asian	6.5	3.5	49.4	1.9	
- Other	0.8	0.8	1.5	0.9	
- Missing	0.4	0.4	0.2	0.3	
MELD at listing †, Median (IQR)	17 (12 – 22)	16 (11 – 21)	16 (9 – 28)	19 (16 – 25)	<.001
Body mass index, Median (IQR)	29 (25 – 33)	28 (25 – 32)	26 (23 – 29)	33 (30 – 37)	<.001
Diabetes present, %	24.7	19.2	18.8	45.2	<.001

HCV: hepatitis C; HBV: hepatitis B; NASH: non-alcoholic steatohepatitis; ESLD: end-stage liver disease; HCC: hepatocellular carcinoma; IQR: interquartile range; MELD: model for end-stage liver disease.

* p value compares HCV vs. HBV vs. NASH

† Laboratory MELD score

Table 2

Average percent change of the rate of LT wait-listing based on era from 2003-2015 in the United States.

	Hepatitis C		Hepatitis B		NASH	
	IRR (95% CI)	**P value**	**IRR (95% CI)**	**P value**	**IRR (95% CI)**	**P value**
Overall						
- IFN era	Ref		Ref		Ref	
- PI era	+23.6% (20.6-26.6)	<.001	+0.0% (−7.4 – 8.9)	0.923	+48.7% (42.0-55.7)	<.001
- DAA era	−7.8% (−10.7 - −4.9)	<.001	−14.0% (−21.8 - −5.4)	0.002	+90.7% (81.7-100.0)	<.001
HCC						
- IFN era	Ref		Ref		Ref	
- PI era	+62.2% (56.4-68.2)	<.001	+11.4% (−0.1 – 24.7)	0.062	+79.5% (60.6-100.0)	<.001
- DAA era	+34.1% (28.5-40.0)	<.001	−8.5% (−19.6 – 4.2)	0.181	+147.2% (121.0-176.5)	<.001
DC						
- IFN era	Ref		Ref		Ref	
- PI era	−4.8% (−7.9- −1.5)	0.004	−17.0% (−26.3 - −6.7)	0.002	+41.2% (34.3-48.6)	<.001
- DAA era	−31.9% (−35.1 - −28.6)	<.001	−24.1% (−34.1 - −12.6)	<.001	+80.8% (71.2-90.8)	<.001

LT: liver transplant; HCC: hepatocellular carcinoma, IRR: incidence rate ratio; CI: confidence interval; DC: decompensated cirrhosis

Table 3

Secular trends in the demographic characteristics of LT candidates wait-listed for decompensated cirrhosis based on etiology of liver disease.

	HCV (n=18,846)	p value‡	HBV (n=1,759)	p value‡	NASH (n=8,328)	p value‡
Median age LT WL, (IQR)						
- IFN era	53 (48-57)	<.001	51 (43-58)	0.008	58 (52-63)	<.001
- PI era	56 (52-60)		51 (44-59)		59 (53-64)	
- DAA era	57 (52-61)		51 (43-58)		59 (53-65)	
Median MELD LT WL, (IQR)						
- IFN era	19 (16-25)	<.001	26 (19-36)	0.005	20 (17-27)	0.08
- PI era	21 (17-27)		27 (20-38)		21 (17-27)	
- DAA era	21 (17-29)		30 (20-38)		21 (17-28)	
Drop-out/death on WL#, %						
- IFN era	26.4	0.204	22.9	0.671	24.9	0.883
- PI era	29.7		22.9		28.5	
- DAA era	21.6		20.8		25.7	
Recovery on WL#, %						
- IFN era	0.9	0.200	4.1	0.464	2.0	0.666
- PI era	1.3		4.4		1.6	
- DAA era	0.7		7.5		1.7	

LT: liver transplant; HCV: hepatitis C; HBV: hepatitis B; NASH: non-alcoholic steatohepatitis; WL: waitlisting; IQR: Interquartile range; IFN: interferon; PI: protease inhibitor; DAA: direct acting antivirals.

‡P-value for trend is reported for all.

#those listed from 2003-2014 only