ORIGINAL ARTICLE

Decreasing frequency and improved outcomes of hepatitis C-related liver transplantation in the era of direct-acting antivirals – a retrospective cohort study

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SUMMARY

Benefit of direct-acting antivirals (DAA) for hepatitis C virus (HCV) on clinical outcomes is unclear. We examined temporal trends in liver transplant (LT) listings, receipt of LT, re-LT, and survival between pre-DAA (2009–2012) and DAA era (2013–2016) using UNOS database. Of 32 319 first adult LT, 15 049 (47%) were performed for HCV. Trends on listing, first LT, and of re-LT for HCV showed 23%, 20%, and 21% decrease in DAA compared to pre-DAA era ($P < 0.0001$). One-year liver graft and patient survival among HCV LT improved in DAA era (90% vs. 86% and 92% vs. 88%, respectively, $P < 0.0001$). Non-HCV LT showed no improvement in survival (89% vs. 89% and 92% vs. 92.4%, P = NS). On cox regression, compared to non-HCV LTs in DAA era, LT for HCV in pre-DAA era had worse patient survival (HR 1.56 [1.04–2.35]). The outcome was similar when compared to LTs for HCV in DAA era and for non-HCV in pre-DAA era. Burden of HCV-related LT waitlist and LT is declining in DAA era, with improved post-transplant outcomes, more so in later than earlier DAA era. Our findings negate recent Cochrane meta-analysis on DAA therapy and encourage studies to examine HCV clinical outcomes outside LT setting.

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direct-acting antivirals, hepatitis C virus, survival, waitlist mortality

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Introduction

Chronic hepatitis C is a common cause of liver cirrhosis, with an estimated prevalence of about 1.0% in the US [1–3]. Recent evidence suggests that hepatitis C virus (HCV) incidence is increasing in the US [4–6]. HCV-related decompensated cirrhosis and/or hepatocellular carcinoma (HCC) is one of the most common indications for liver transplantation (LT) in the US [7,8]. Further, chronic HCV infection-related morbidity and mortality is high [9].

The epidemiology of the etiology of cirrhosis and LT in the US has been evolving. Alcohol and nonalcoholic steatohepatitis (NASH) are other common causes of cirrhosis and of LT [10]. While cirrhosis secondary to NASH is increasing in parallel with obesity, NASH has emerged as the second leading cause requiring LT in the US [11–13]. Further, patients with decompensated cirrhosis because of NASH or alcohol are less likely to be listed for LT HCV, and patients with HCC are 2–5 times more likely to be listed for LT [14].

Over last 5 years, the advent of interferon-free direct-acting antivirals (DAA) has revolutionized the treatment paradigm of HCV [15]. Highly effective DAA enable most chronic HCV patients to achieve sustained virologic response (SVR). Those who achieve SVR have reduced mortality, decompensated cirrhosis, and hepatocellular carcinoma compared to untreated patients or those who fail to achieve SVR [16–18]. Although there are little data on long-term outcomes, international guidelines by the American Association for the Study of Liver Disease and Infectious Diseases Society of America recommend that HCV patients with decompensated cirrhosis should be treated with DAA therapy, regardless of the eligibility for LT [19].

The improvement in the Model for End-Stage Liver Disease (MELD) scores and Child–Turcotte–Pugh scores among HCV patients with cirrhosis after treatment with the highly efficacious DAA suggests that these drugs may help reduce the proportion of chronic HCV as well as the need for LT. This is supported by the substantial decline in rate of LT waitlist registration for HCV by over 30% since the availability of oral HCV DAA [7,20–22]. Further, recent analyses of HCV prevalence data from National Health and Nutrition Examination Survey (NHANES) and the waitlist data from the transplant registries of US and Europe showed that the HCV disease burden as well as LT waitlist burden has decreased with the advent of DAA [11,23,24]. However, a recent Cochrane meta-analysis questioned efficacy of DAA in improving clinical outcomes for HCV despite their excellent safety and cure rates [25]. It remains unclear whether the new DAA therapies lead to survival improvement in setting of chronic HCV. Moreover, the exact temporal trends in LT for HCV, NASH, and other etiologies of cirrhosis and outcomes among transplanted patients in the current DAA era when compared to the pre-DAA era remain largely unknown. We performed this study using LT database in the US, with a central hypothesis that need for LT has decreased with improved post-transplant outcomes among HCV patients compared to HCV negative patients since the introduction of DAA in 2012.

Methods

Study design and source

This study was performed on a retrospective cohort, developed from the United Network for Organ Sharing (UNOS) registry on patients listed for and receiving LT for common etiologies of chronic liver disease. This database has clinical information on all LT recipients from the transplant centers across the US and includes recipient characteristics at the time of transplant listing, donor information, immunosuppression, and follow-up information on the recipient.

Study population

We included adults (≥18 years of age) on the LT list during 2009–2016 for end-stage liver disease secondary to seven common etiologies of cirrhosis: HCV (*UNOS code 4204 and 4216*), alcohol-related liver disease (*UNOS code 4215*), NASH (*UNOS code 4214*), chronic cholestatic liver disease (*UNOS code 4220, 4240, 4241, 4245*), and metabolic liver disease/autoimmune hepatitis (*UNOS code 4212, 4301, 4302*), hepatitis B virus (HBV) infection-related (*UNOS code 4202*), and cryptogenic cirrhosis (*UNOS code 4213*). To keep the study population homogeneous, those with concomitant HCC (*UNOS code 4400, 4401, 4402*) were excluded (Fig. 1). Patients with a dual diagnosis of HCV and alcohol-related etiologies were classified as HCV. LT registrants were excluded if they were <18 years of age, listed as status 1A or for acute liver failure, listed for indications other than six etiologies included in the analysis, or had history of prior LT.

Time trends and periods

We divided the study period into two eras to reflect differences in the modality of available HCV therapy:

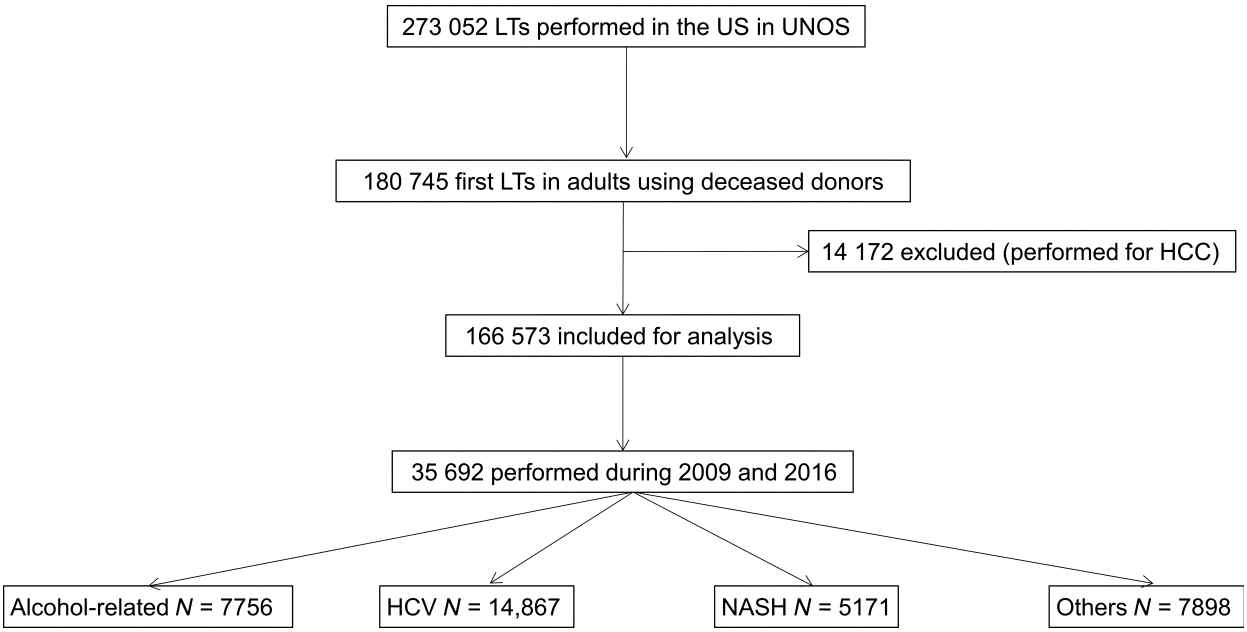

Figure 1 Study population and cohort selection.

pre-DAA era (2009–2012) and DAA era (2013–2016). Secular trend over time during the 6-year study period for LT listing, first LT and re-LT were examined.

Data collection

We extracted recipient data from the UNOS database on: (i) demographics: age, gender, race, BMI; (ii) pre-LT clinical parameters: liver disease etiology, MELD score at the time of LT listing, MELD score at the time of LT, diabetes, dialysis use, LT listing status, reason for removal from LT list including receipt of LT or pre-LT mortality; (iii) post-LT variables: status of and time to graft survival, status of and time to patient survival. Our study protocol was approved by the Institutional Review Board at the University of Alabama at Birmingham.

Exposure

The study population was stratified based on etiology of liver disease into HCV and non-HCV or LT for indications other than HCV.

Outcomes

We examined the HCV versus non-HCV patients on LT list to compare pre-DAA versus DAA era on (i) LT listings: frequency and trends, and waitlist mortality (WLM); (ii) recipients of first LT: frequency and trends, and post-transplant outcomes on graft and patient survival at 1 year from the date of LT; and (iii) re-transplantation: frequency and trends. For time to patient or graft survival, data were censored at the last follow-up date, if these outcomes did not occur through the study period.

Data and statistical analyses

Baseline characteristics were compared for liver disease etiology. Categorical and continuous variables were analyzed using chi-square and *t*-tests, respectively. To examine trends (DAA versus pre-DAA era) on LT listings and WLM, receipt of and outcomes after first LT, and on re-transplants over time in LT listing, the Armitage trend test was used [26].

Cumulative incidence rates and curves for WLM were generated comparing patients listed for HCV with those listed for non-HCV indications. As the WLM is dependent upon receipt of LT, deteriorating condition of the registrant because of any cause, and improvement in the liver disease, competing risk analysis was performed on WLM. Gray's test was used for these analyses. Fine and Gray regression model was built to determine independent effect of time period (pre-DAA and DAA era) and the indication of listing (HCV or non-HCV) after accounting for competing events and controlling for variables, which could have confounded the outcomes. Effect size on Fine and Gray regression analyses is reported as hazard ratio (HR) with 95% confidence interval (CI).

Kaplan–Meier survival curves were built comparing HCV and non-HCV LT recipients in the pre-DAA and

Table 1. Frequency and trends on LT listings, first LT, and re-transplants based on liver disease etiology comparing era before the availability of direct-acting antiviral (DAA) drugs (2009–2012) and the DAA era (2013–2016).

	AC (*N* = 16 033)	HCV (*N* = 27 456)	NASH (*N* = 9604)	Others (*N* = 8271)
LT Listings (%) 2009–2012 (*N* = 29 365)	23	51	13	14
LT listings (%) 2013–2016 (*N* = 31 399)	29	39	20	13
First LT (%) 2009–2012 (*N* = 14 607)	20	52	13	15
First LT (%) 2013–2016 (*N* = 17 712)	26	42	18	14
Re-transplants (%) 2009–2012 (*N* = 438)	19	52	8	20
Re-transplants (%) 2013–2016 (*N* = 522)	18	41	16	25

AC, alcohol-related cirrhosis; HCV, Hepatitis C virus; LT, liver transplant; NASH, Nonalcoholic steatohepatitis.

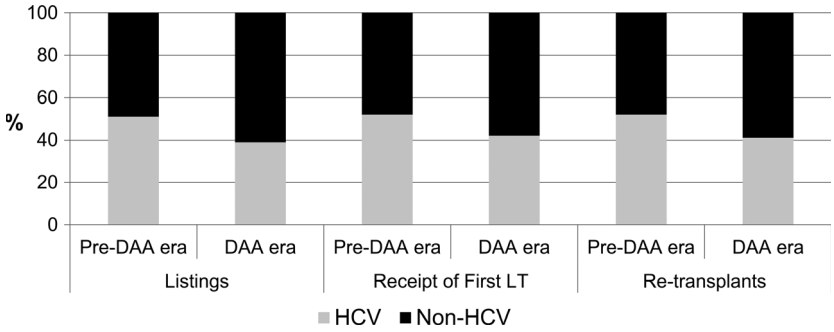

Figure 2 Etiology-based trends in liver transplantation (LT) listing, first LT, and re-LT for hepatitis C virus (HCV) and non-HCV etiologies of liver disease. The data show that HCV-related LT listing, need for LT, and for re-transplant has decreased in the era of availability of direct-acting antiviral (DAA) drugs.

DAA era for graft and patient survival at 1 year after LT. Log rank test was used to determine statistical significance. Cox proportional hazard regression analysis models were built to examine independent effect of HCV versus non-HCV etiology and DAA era versus pre-DAA era on the outcomes including 1-year post-LT graft and patient survival. Variables different at baseline or those with clinical relevance for the specific outcome were entered in the model. *P*-values < 0.05 were considered significant. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

Results

Liver transplant listings

Frequency and trends of LT listing based on liver disease etiology

A total of 70 691 cirrhosis patients were on the LT waitlist between 2009 and 2016, 33 816 in the pre-DAA, and 36 875 in the DAA era. Of all the LT listed patients, 61 364 patients (29 365 in the pre-DAA era) listed for seven etiologies of cirrhosis were analyzed in this study. Of these, 27 179 (45%) were listed for HCV cirrhosis, 15 845 (26%) for alcohol-related cirrhosis, 9604 (16%) for NASH cirrhosis, and 8271 (13%) for other four etiologies of cirrhosis. The proportions of LT listed for HCV decreased from 51% in pre-DAA to 39% in the DAA era. In contrast, proportions of LT listed for alcohol-related and for NASH increased from 23% to 29% and from 12% to 19%, respectively. Transplant listings for other etiologies remained stable at 14% in the pre-DAA era and at 13% in the DAA era (Table 1). Frequency and proportion of LT listings comparing HCV and non-HCV etiologies in the pre-DAA era were 14 837 (51%) vs. 14 528 (49%). Similar figures in the DAA era were 12 342 (39%) and 19 657 (61%), respectively, Armitage trend test, $P < 0.0001$ (Fig. 2).

Extended analyses on LT listings. Etiology-based proportion of LT listings was extended to available data on 12 798 LT listings until June 30, 2018 (8500 listed during 2017). The trend for decreasing proportion listed for HCV continued with 25% and 21% during 2017 and 2018, respectively. Similar figures were 36% and 39% for alcohol, 25% and 26% for NASH, and 14% and 13% for other etiologies (Fig. S1).

Frequency and trends of WLM based on liver disease etiology

Of 61 364 listed patients during 2009 and 2016 for seven indications analyzed in this study, 5005 died while waiting for LT, higher in the pre-DAA era (2551 of 29 365, 8.7%)

compared to DAA era (2454 of 31 999, 7.7%), $P < 0.0001$. Specifically within the DAA era the WLM was lower in 2015–2016 compared to 2013–2014 time period (6.6% vs. 7.9%, $P < 0.0001$). Of 2551 deaths in the pre-DAA era, the WLM was similar comparing patients listed for HCV (1303 of 14 837, 8.8%) vs. non-HCV (1248 of 14 528, 8.6%) indication, $P = 0.56$. In contrast, of the 2454 deaths in the DAA era, the WLM was lower among patients listed for HCV (896 of 12 342, 7.3%) compared to patients listed for non-HCV (1558 of 19 657, 7.9%) indication, $P = 0.029$. Similarly within the DAA era, WLM comparing HCV versus non-HCV in 2013–2014 was similar (8% vs. 8.6%, $P = 0.14$) and was lower in HCV patients in 2015–2016 (6.3% vs. 7.4%, $P = 0.012$).

Cumulative incidence of WLM was analyzed using competing risk analysis controlling for candidate factors such as demographics (age at listing, gender, race, and height), ABO blood group, MELD score at listing, UNOS region, and removal from the list for any cause other than WLM including receipt of LT. Analysis of patients with available data on all these variables showed that the WLM in the pre-DAA era was similar comparing patients listed for HCV (1302 of 14 827, 8.8%) versus patients listed for non-HCV (1244 of 14 368, 8.7%) indications, Fine Gray $P = 0.84$ (Fig. 3a). In the DAA era, the WLM was lower for patients listed for HCV (896 of 12 337, 7.3%) compared to those listed for non-HCV (1556 of 19 532, 8%), Fine Gray $P = 0.018$ (Fig. 3b). In the Final and Gray regression model analysis, compared to patients listed for non-HCV indications in the DAA era, the WLM was 25% higher among patients listed for HCV in the pre-DAA era, 14% higher for patients listed for non-HCV indication in the pre-DAA era and similar to HCV listed patients in the DAA era (Table 2). Other predictors of WLM were age at listing, shorter candidate's height, Caucasian race, diabetes status, lower serum albumin at listing, listing MELD score, and UNOS region 1, 5, or 9 (Table 2). Specifically within the DAA era, the WLM was lower in HCV listings compared to non-HCV indications, the difference was much larger in 2015–2016 (6.3% vs. 7.4%, $P < 0.0001$) than in 2013–2014 (8% vs. 8.6%, $P = 0.02$).

Receipt of first liver transplants

A total of 273 052 adult LTs were performed in the US as available in the database. Of these, 35 692 first LT performed in adults using deceased donors between 2009 and 2016 were analyzed (Fig. 1), with 16 062 in the pre-DAA and 19 630 in the DAA era.

Baseline characteristics based on liver disease etiology

LT recipients for NASH were relatively older females with higher proportion of diabetes and obesity. Further, NASH recipients received liver graft with highest donor risk index (DRI) (Table 2). In contrast, LT recipients for HCV cirrhosis were less likely to be on dialysis and be on ventilator. MELD score at LT listing and at transplant were higher for alcohol-related cirrhosis (Table 3).

Frequency and trends based on etiology of liver disease

Of 35 692 first LT recipients, 14 867 (46%) received for HCV cirrhosis, 7756 (24%) for alcohol-related cirrhosis, 5171 (16%) for NASH, and 7898 (14%) for other liver disease etiologies including chronic cholestatic liver disease (CCLD), metabolic and autoimmune liver disease, HBV, and cryptogenic cirrhosis. The proportions of LT performed for HCV decreased from 52% in pre-DAA to 42% in the DAA era. Specifically within the DAA era, the proportion of LT decreased linearly from 49% in 2013 to 48%, 41%, and 33% in 2014, 2015, and 2016, respectively. In contrast, proportions of LT listed for alcohol-related and for NASH increased from 20% to 26% and from 13% to 18%, respectively. Transplant listings for other etiologies remained stable at 15% in the pre-DAA era and at 14% in the DAA era (Table 1). Frequency and proportion of LT recipients comparing HCV and on-HCV etiologies in the pre-DAA era were 8352 (52%) vs. 7710 (48%). Similar figures in the DAA era were 8244 (42%) and 11 386 (58%), respectively, Armitage trend test, $P < 0.0001$ (Fig. 2).

Extended analyses on receipt of first LT. Etiology-based proportion on receipt of first LT was extended to available data on 7702 LT until June 30, 2018 (5124 during 2017). The trend for decreasing proportion on receipt of first LT for HCV continued with 28% and 24% during 2017 and 2018, respectively. Similar figures were 34% and 38% for alcohol, 24% and 25% for NASH, and 15% and 13% for other etiologies (Fig. S2).

Post-transplant outcomes with trends comparing liver disease etiology

Graft survival at 1 year after LT. A total of 3995 grafts were lost over 1-year period. Graft survival was better in the DAA era compared to pre-DAA era among LT recipients for HCV cirrhosis (90.3% vs. 85.7%, log rank $P = <0.0001$, Fig. 4a). Although statistically significant, this difference was much lower among recipients of LT

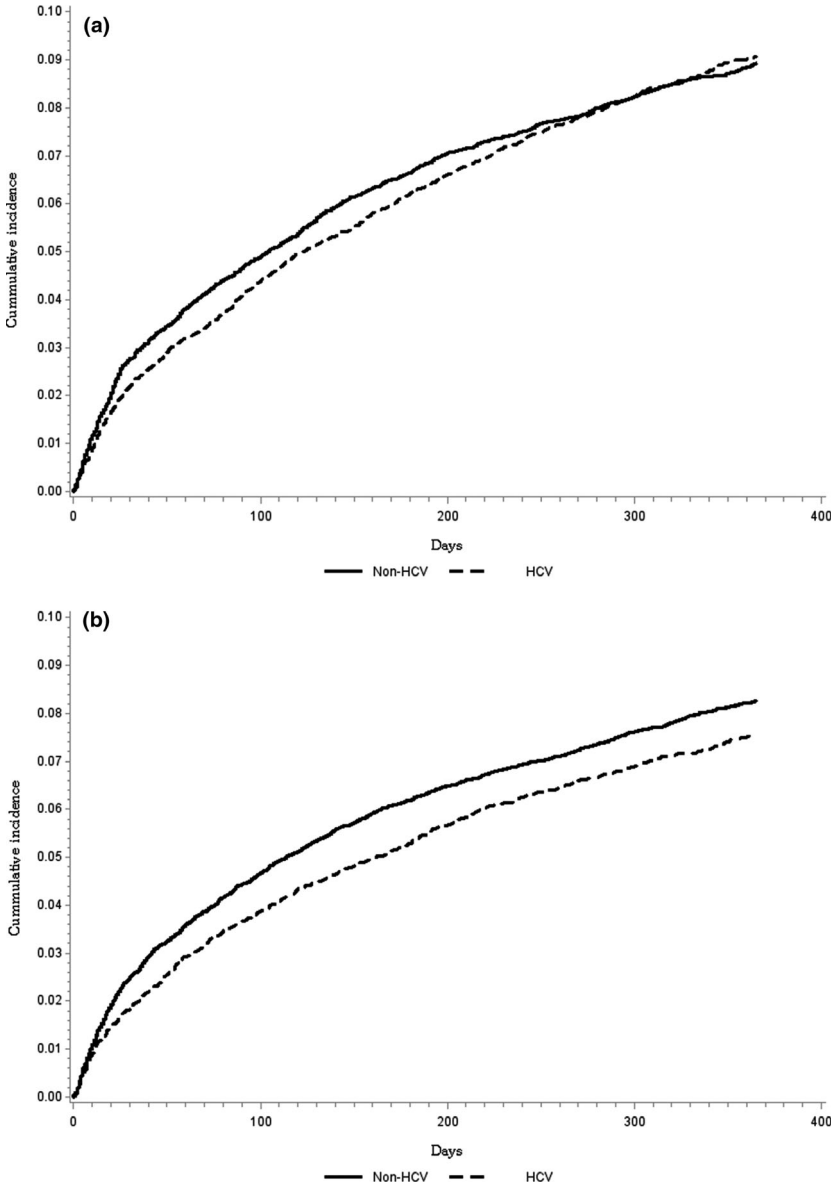

Figure 3 Cumulative probability of wait-list mortality (WLM) comparing candidates listed for hepatitis C virus (HCV)-related liver disease (dashed line) versus candidates listed for non-HCV indications (solid line) in the era before the availability of direct-acting antiviral (DAA) drugs (a) and in the DAA era (b). The results show decreasing WLM among HCV-related listed patients in the DAA era.

for indications other than HCV (89.1% vs. 88.9%, log rank $P < 0.0001$, Fig. 4a). Specifically within the DAA era, the graft survival at 1 year was better in the HCV group compared to other indications in 2015–2016 (91.7% vs. 90.5%) than in 2013–2014 (89.6% vs. 89.1%), $P < 0.0001$.

Patient survival at 1 year after LT. A total of 3052 patients died within 1 year after LT. Similarly, patient survival at 1 year was better in the DAA era compared to pre-DAA era among LT recipients for HCV cirrhosis (92% vs. 88.4%, log rank $P = <0.0001$, Fig. 4b). Although statistically significant, this difference was much lower among recipients of LT for indications other than HCV (92.1% vs. 91.6%, Log rank $P < 0.0001$, Fig. 4b). Specifically within the DAA era, the patient survival at 1 year tended to be better in the HCV group compared to other indications in 2015–2016 (93.1% vs. 92.7%) than in 2013–2014 (91.9% vs. 91.1%), $P = 0.11$.

Cox regression model for patient survival. Compared to non-HCV transplants in post-DAA era, LTs for

Table 2. Fine and Gray regression model for predictors of wait-list mortality.

	HR	95% CI	*P*
HCV pre-DAA versus non-HCV DAA	1.25	1.16–1.35	<0.0001
Non-HCV pre-DAA versus non-HCV DAA	1.14	1.05–1.23	<0.0001
HCV DAA versus non-HCV DAA	1.05	0.97–1.15	0.34
Age at listing in years	1.02	1.02–1.03	<0.0001
Female versus Male gender	1.05	0.97–1.14	0.22
Black versus White race	0.84	0.75–0.93	0.001
Hispanic versus White race	0.62	0.57–0.67	<0.0001
Height in cm. at listing	0.99	0.98–0.99	<0.0001
Diabetes versus no diabetes	1.08	1.01–1.15	0.018
Blood group B or AB versus A or O	0.74	0.60–0.90	0.003
MELD score at listing	1.05	1.05–1.06	<0.0001
Other UNOS regions versus 5	0.69	0.58–0.81	<0.0001

CI, confidence interval; DAA, direct-acting antivirals; HR, hazard ratio; HCV, hepatitis C virus; MELD, Model for end-stage liver disease; UNOS, United Network for Organ Sharing.

Table 3. Baseline characteristics of first liver transplant recipients based on liver disease etiology.

	AC (*N* = 7756)	HCV (*N* = 14 867)	NASH (*N* = 5171)	CCLD + MLD + AIH (*N* = 7898)	*P*
Age	55	57	61	52	<0.0001
Males %	76	74	55	42	<0.0001
Caucasians	70	61	77	65	<0.0001
Ventilator %	4.2	1.6	2.2	2.4	<0.0001
Diabetes %	21	24	58	16	<0.0001
Dialysis %	20	13	18	12	<0.0001
Obesity %	34	35	61	25	<0.0001
List MELD	21	13	17	15	<0.0001
MELD at Transplant	24	18	22	21	<0.0001
DRI	1.52	1.47	1.59	1.28	<0.0001

AC, alcohol-related cirrhosis; ALD, alcohol-related liver disease; AIH, autoimmune hepatitis; CCLD, chronic cholestatic liver disease; DRI, donor risk index; HCV, hepatitis C virus; MELD, Model for end-stage liver disease; MLD, metabolic liver disease; NASH, Nonalcoholic steatohepatitis.

HCV in pre-DAA era had worse patient survival at 1 year with HR (95% CI) of 1.56 (1.04–2.35). Non-HCV LT in the DAA era had similar patient survival to LT for HCV in the DAA era and to non-HCV LT in the pre-DAA era (Table 4). DRI was a strong predictor of outcomes, while other variables including MELD score at LT, diabetes, obesity, and dialysis did not predict patient survival after LT. Specifically within the DAA era, compared to non-HCV transplants in 2015–2016, LT for HCV in 2013–2014 had worse survival at 1 year with HR (95% CI) of 1.18 (1.02–1.37), $P = 0.025$. Non-HCV LT in 2015–2016 had similar patient survival to LT for HCV in 2015–2016 and to non-HCV LT in 2013–2014 with HR (95% CI) of 0.99 (0.84–1.17), $P = 0.89$ and 1.02 (0.89–1.18), $P = 0.78$, respectively.

Receipt of liver re-transplants

Frequency and trends of re-transplants of liver based on liver disease etiology

A total of 990 recipients of first LT received a subsequent re-transplantation of liver, 448 in the pre-DAA and 542 in the DAA era. Of all the re-transplants, liver disease etiology for index LT was HCV in 454 (46%), alcohol in 183 (18%), NASH in 127 (13%), and other etiology in 226 (23%) recipients. The proportions of re-LT performed for HCV decreased from 52% in pre-DAA to 41% in the DAA era. Specifically within the DAA era, proportions of re-LT performed for HCV decreased from 45% in 2013–2014 to 30% in 2015–2016. In contrast, proportions of re-transplants for alcohol as index etiology remained stable from 19% in the

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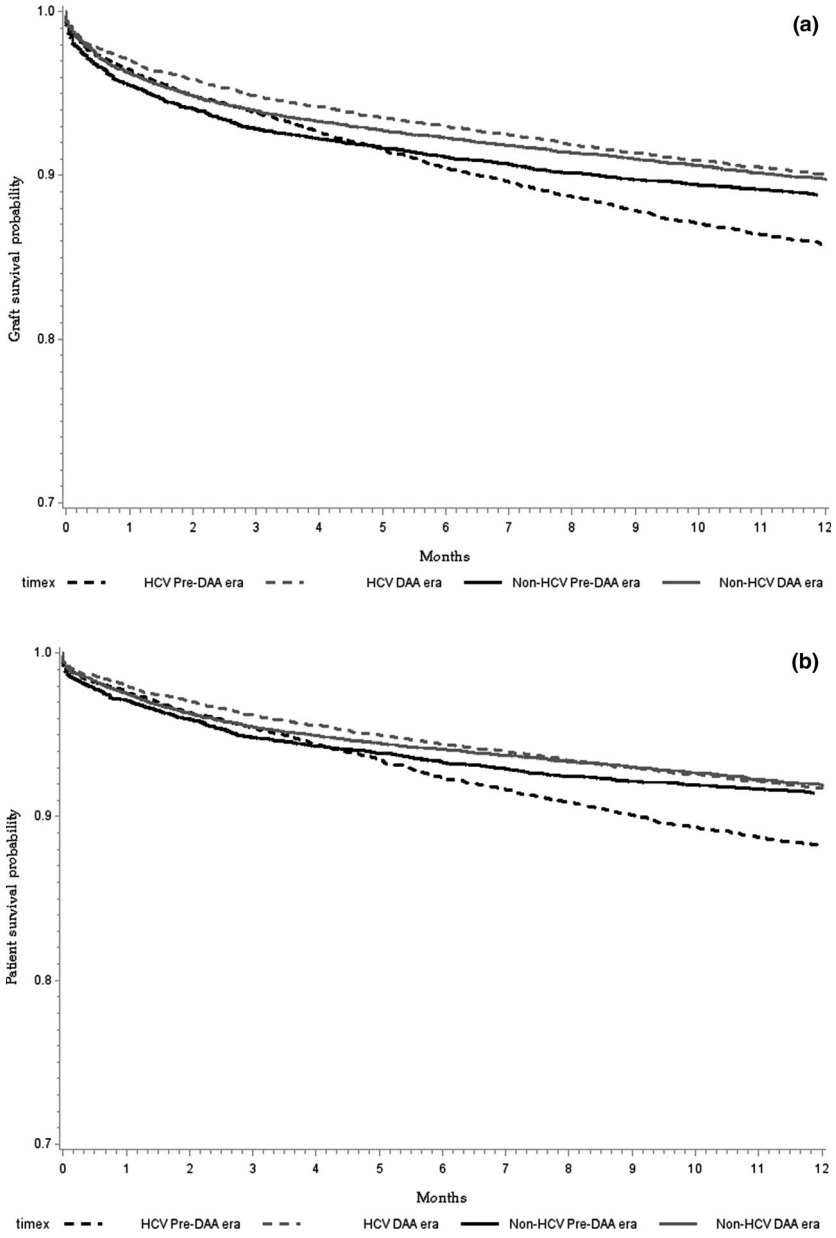

Figure 4 Kaplan–Meier curves comparing liver transplant (LT) recipients for liver disease because of hepatitis C virus (HCV) infection versus non-HCV-related LT for 1-year graft survival (a) and for patient survival (b). The results show improved liver graft and patient survival among LT recipients for HCV after the availability of direct-acting antiviral (DAA) drugs (dashed gray line). The outcomes are worse among HCV-related transplants before the DAA availability (dashed black line). Black and gray solid lines represent transplant recipients for non-HCV indications before and after the DAA availability.

pre-DAA to 18% in the DAA era. However, proportion of re-transplants for NASH and for other etiologies for index LT increased from 8% to 16% and from 20% to 25%, respectively (Table 1). Frequency and proportion of LT recipients comparing HCV and on-HCV etiologies in the pre-DAA era were 232 (52%) vs. 216 (48%). Similar figures in the DAA era were 222 (41%) and 320 (59%), respectively, Armitage trend test, $P < 0.0001$ (Fig. 2).

Discussion

Cirrhosis secondary to chronic HCV remains a key indication for LT [3,7]. The availability of DAA for HCV has changed the landscape of HCV treatment since 2012, with excellent cure rates and eradication of HCV infection. However, whether these benefits of DAA translate into improved survival and reduction in disease burden remains unclear. Further, a recent

Table 4. Cox regression analysis model on 1-year patient survival.

	Patient survival		Graft survival	
	P	HR (95% CI)	*P*	HR (95% CI)
HCV Pre-DAA versus Non-HCV DAA era	<0.0001	1.63 (1.48–1.80)	<0.0001	1.54 (0.41–1.68)
HCV DAA versus Non-HCV DAA era	0.1	1.10 (0.98–1.23)	0.48	1.04 (0.94–1.15)
Non-HCV Pre-DAA versus Non-HCV DAA era	0.1	1.09 (0.98–1.22)	0.001	1.13 (1.03–1.24)
Age	<0.0001	1.03 (1.02–1.04)	<0.0001	1.02 (1.01–1.03)
Females	0.13	1.06 (0.98–1.15)	0.29	1.04 (0.97–1.12)
African American versus Caucasian	0.08	1.12 (0.98–1.28)	0.12	1.10 (0.98–1.23)
Hispanic versus Caucasian	0.84	1.01 (0.92–1.12)	0.66	1.02 (0.94–1.10)
Others versus Caucasian	0.42	0.91 (0.73–1.14)	0.61	0.95 (0.78–1.15)
DRI	<0.0001	1.49 (1.35–1.65)	<0.0001	1.75 (1.61–1.91)
Dialysis	<0.0001	1.44 (1.31–1.59)	<0.0001	1.39 (1.27–1.52)
Diabetes	<0.0001	1.24 (1.15–1.35)	0.0003	1.14 (1.06–1.23)
Obesity	0.56	0.98 (0.91–1.06)	0.87	1.01 (0.94–1.08)
MELD score at Transplantation	<0.0001	1.03 (1.02–1.04)	<0.0001	1.014 (1.01–1.02)

CI, confidence interval; DAA, direct-acting antivirals; DRI, donor risk index; HR, hazard ratio; HCV, hepatitis C virus; MELD, Model for end-stage liver disease.

Cochrane meta-analysis showed that while treatment with DAA has remarkably improved HCV clearance rates, there is insufficient evidence to decide if DAA are beneficial to HCV-related morbidity and mortality [25].

The main findings of our study demonstrate reducing disease burden among HCV-related patients with cirrhosis in the DAA era as compared to pre-DAA era, with decreasing (i) frequency of LT listing, (ii) WLM, (iii) frequency of receipt of LT, (iv) 1-year post-transplant graft loss and patient mortality, and (v) need for re-transplantation of liver. Specifically within the DAA era, the results on all the outcomes were more robust in later than the earlier period of the DAA era.

Telaprevir and boceprevir were the first DDA approved by the Food and Drug Administration for the treatment of HCV [27,28]. The year 2013 revolutionized the HCV treatment with the availability of many oral DAA effective against all HCV genotypes with excellent safety and cure rates exceeding 95%, compared to historic rates of 5% in 1991 with interferon and only 40–50% with pegylated interferon and ribavirin in the pre-DAA era [29–36]. Our findings of the decline in the number of HCV patients waitlisted and transplanted in the DAA era (2013–2016) also correlate with the Medicare data (Medicare beneficiaries with Part D prescription coverage), which reflected a substantial increase (five times) in the number of DAA prescriptions between 2013 and 2016 [14].

WLM for HCV patients in a recently reported study using the Scientific Registry of Transplant Recipients database was shown to be decreased by 32% in the DAA era as compared to the interferon era, similar to our study [20]. However, this study did not examine other important surrogate outcomes of disease-related morbidity and mortality including frequency of LT, and post-transplant graft and patient survival. Further, this study included registrants with liver disease secondary to HCV, HBV, and NASH and not the other etiologies as we included in our study. In another study using the NHANES, Health Core Integrated Research, and the UNOS (2003–2015) databases, proportion of patients with cirrhosis or liver failure, need for LT waitlist, and receipt of LT decreased for chronic HCV infection, while these outcomes increased for alcohol-related cirrhosis and for NASH [11]. However, the NHANES data have potential to underscore the true impact, as the data exclude veterans, homeless, and incarcerated, all populations in the US with high prevalence of HCV. Further, Health Core Integrated Research database includes only patients with commercial health insurance. Two other studies reported analysis from the European transplant registries showed similar findings with decrease in listing of patients from HCV with improvement of post-transplant survival in the DAA era [23,24].

Our study is unique in measuring outcomes including the temporal trends in LT wait listing, receipt of LT with post-transplant outcomes, and need for re-transplantation of liver. Large sample size, analysis using a homogeneous database, and inclusion of all the registrants on the transplant list irrespective of the insurance status are other strengths of our study. However, our study suffers from the limitations of any observational study on analysis using the database cohort. Our study

is further limited by inability to analyze the impact of DAA on patients who were not listed for LT or did not meet the LT eligibility because of comorbid illness or financial or psychosocial barriers.

In summary, our study shows that HCV-related disease burden is decreasing in the DAA era with decreasing need for LT listing, WLM, need for LT, and post-transplant morality. These findings call into question the conclusions of the Cochrane meta-analysis [25]. Further data are needed to examine similar benefits of DAA therapy on HCV-related morbidity and mortality outside the transplant setting.

Authorship

SA and AKS: conceptualized the study hypothesis, design, and methodology. SA, PA, ZA, and AS: involved in data extraction, drafting, and review of the manuscript. AKS and Y-FK: performed the statistical analysis. AKS, Y-FK, SS, and RW: contributed to critical revision of the manuscript for important intellectual content and expert opinion. All authors approved the final draft submitted. Ashwani Singal is the author guarantor.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

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

Figure S1. Etiology-specific proportion of liver transplant listings from January 1, 2009 until June 30, 2018.

Figure S2. Etiology-specific proportion of receipt of first liver transplant from January 1, 2009 until June 30, 2018.

REFERENCES

1. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology* 2015; **62**: 1353.
2. Ditah I, Ditah F, Devaki P, *et al.* The changing epidemiology of hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2001 through 2010. *J Hepatol* 2014; **60**: 691.
3. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705.
4. Udompap P, Mannalithara A, Heo NY, Kim D, Kim WR. Increasing prevalence of cirrhosis among U.S. adults aware or unaware of their chronic hepatitis C virus infection. *J Hepatol* 2016; **64**: 1027.
5. Smith MR, Rye K, Haldane TR, Gunson B, Bramhall S, Mutimer DJ. Combined liver and kidney transplantation: a single centre experience. *Hepatology* 2011; **54**: 660.
6. Razavi H, Elkhoury AC, Elbasha E, *et al.* Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; **57**: 2164.
7. Dultz G, Graubard BI, Martin P, *et al.* Liver transplantation for chronic hepatitis C virus infection in the United States 2002–2014: an analysis of the UNOS/OPTN registry. *PLoS ONE* 2017; **12**: e0186898.
8. Wolfe RA, Roys EC, Merion RM. Trends in organ donation and transplantation in the United States, 1999-2008. *Am J Transplant* 2010; **10**(4 Pt 2): 961.
9. Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. *Clin Infect Dis* 2016; **62**: 1287.
10. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: the multiethnic cohort. *Hepatology* 2016; **64**: 1969.
11. Goldberg D, Ditah IC, Saeian K, *et al.* Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology* 2017; **152**: 1090 e1.
12. Wong RJ, Aguilar M, Cheung R, *et al.* Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; **148**: 547.
13. Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001–2013. *Gastroenterology* 2015; **149**: 1471 e5; quiz e17–8.
14. Goldberg D, French B, Newcomb C, *et al.* Patients with hepatocellular carcinoma have highest rates of waitlisting for liver transplantation among patients with end-stage liver disease. *Clin Gastroenterol Hepatol* 2016; **14**: 1638 e2.
15. Chhatwal J, Wang X, Ayer T, *et al.* Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology* 2016; **64**: 1442.
16. Foster GR, Irving WL, Cheung MC, *et al.* Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **64**: 1224.
17. Cheung MCM, Walker AJ, Hudson BE, *et al.* Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **65**: 741.

18. van der Meer AJ, Veldt BJ, Feld JJ, *et al.* Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584.
19. D'Amico G, Di Benedetto F, Tarantino G, *et al.* Liver or combined liver-kidney transplantation for autosomal dominant polycystic kidney disease. *Liver Transpl* 2011; **17**: S282.
20. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology* 2017; **65**: 804.
21. Belli LS, Berenguer M, Cortesi PA, *et al.* Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. *J Hepatol* 2016; **65**: 524.
22. Kim WR, Terrault NA, Pedersen RA, *et al.* Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. *Gastroenterology* 2009; **137**: 1680.
23. Crespo G, Trota N, Londono MC, *et al.* The efficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition. *J Hepatol* 2018; **69**: 11.
24. Belli LS, Perricone G, Adam R, *et al.* Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol* 2018; **69**: 810.
25. Jakobsen JC, Nielsen EE, Feinberg J, *et al.* Direct-acting antivirals for chronic hepatitis C. *Cochrane Database Syst Rev* 2017; **9**: CD012143.
26. Buonaccorsi JP, Laake P, Veierod MB. On the power of the Cochran-Armitage test for trend in the presence of misclassification. *Stat Methods Med Res* 2014; **23**: 218.
27. Poordad F, McCone J Jr, Bacon BR, *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195.
28. Jacobson IM, McHutchison JG, Dusheiko G, *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405.
29. Feld JJ, Jacobson IM, Hezode C, *et al.* Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med* 2015; **373**: 2599.
30. Yau AH, Yoshida EM. Hepatitis C drugs: the end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: a concise review. *Can J Gastroenterol Hepatol* 2014; **28**: 445.
31. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. *Liver Int* 2014; **34**(Suppl 1): 69.
32. Manns M, Marcellin P, Poordad F, *et al.* Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; **384**: 414.
33. Afdhal N, Zeuzem S, Kwo P, *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889.
34. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med* 2013; **368**: 1907.
35. Lawitz E, Mangia A, Wyles D, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878.
36. Fried MW, Buti M, Dore GJ, *et al.* Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013; **58**: 1918.