Lower Likelihood of Post-transplant Graft Failure, Death, and Retransplantation in the Era of Direct-Acting Antivirals

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Background: Direct-acting antivirals (DAAs) are expected to improve outcomes for patients with hepatitis C virus (HCV) infection after liver transplantation (LT). We aim to evaluate trends in post-LT outcomes with availability of DAAs. **Methods:** We retrospectively evaluated US adults transplanted from January 1, 2002, to March 31, 2018, using the United Network for Organ Sharing Registry, stratified by pre-DAA (January 1, 2002– to December 31, 2013) vs. post-DAA (January 1, 2014–, to March 31, 2018) eras. Adjusted multivariate Cox regression analyses and competing risk models evaluated likelihood of graft failure, death, and retransplantation (re-LT). **Results:** Among 97,147 patients, 30.2% had HCV infection and 19.4% had hepatocellular carcinoma (HCC). Of all patients, 31.9% experienced graft failure, 27.1% died after LT, and 4.7% underwent re-LT. The post-DAA era experienced lower likelihood of graft failure (hazard ratio [HR] = 0.69, $p < 0.001$). Although patients with HCV infection (HR = 1.18, $p < 0.001$) and HCC (HR = 1.11, $p < 0.001$) had higher likelihood of graft failure in the pre-DAA era, no differences were seen in the post-DAA era. Although patients with HCV infection (HR = 1.20, $p < 0.001$) and HCC (HR = 1.17, $p < 0.001$) had higher likelihood of death after LT in the pre-DAA era, no differences were seen in the post-DAA era. The post-DAA era had lower likelihood of post-LT death when stratified by non-HCC (HR = 0.70, $p < 0.001$) and HCC cohorts (HR = 0.67, $p < 0.001$) or by non-HCV (HR = 0.73, $p < 0.001$) and HCV (HR = 0.58, $p < 0.001$) cohorts. **Conclusion:** Although patients with HCV infection and HCC had higher risk of post-LT graft failure and death in the pre-DAA era, the disparity disappeared in the post-DAA era independently of each other. This likely reflects impact of DAAs on improving post-LT outcomes among patients with HCV infection and improved selection of patients with HCC for LT after 2014. (J CLIN EXP HEPATOL 2020;10:581–589)

Hepatitis C virus (HCV)-related cirrhosis and hepatocellular carcinoma (HCC) are the leading causes for mortality and liver transplantation (LT) in the US.^{1–3} During the era of interferon and ribavirin therapies, sustained virologic response (SVR) rates were only 30–34% in patients with genotype 1 and 70–90% for patients with genotype 2 and 3.⁴ Furthermore, poor tolerance of interferon limited treatment compliance and thus effectiveness of the available therapies. Post-transplant survival for patients with decompensated liver disease due to HCV was low due to recurrent HCV infection, exacerbated by immu-

nosuppression, leading to more rapid fibrosis and graft failure.

Sofosbuvir, a second-generation direct-acting antiviral (DAA), was approved by the Food and Drug Administration in December 2013 and marked the change in the landscape of HCV treatment to better tolerated treatments with SVR rates in the 90th percentile even in the setting of decompensated cirrhosis.^{4–6} Achieving SVR is associated with decreased HCV-related liver failure, HCC, mortality, and need for LT and has been demonstrated with both interferon therapy and DAAs.^{7,8} Recently, studies have demonstrated the ability for DAAs to also achieve SVR in post-transplant patients without cirrhosis and in those with decompensated cirrhosis or even fibrosing cholestatic hepatitis.^{9–11} With the advent of these newer therapies, we thus aimed to evaluate the trends in post-transplantation outcomes for patients with HCV infection after the availability of the current DAAs.

METHODS

Patient Population

This retrospective cohort study consisted of all adult patients (age ≥ 18 years) in the United Network for Organ

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Abbreviations: CI: confidence interval; DAA: direct-acting antivirals; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HR: hazard ratio; LT: liver transplantation

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Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) registry who underwent LT for any reason between January 1, 2002, and March 31, 2018, with follow-up until June 8, 2018. The chronic HCV cohort was identified as patients who had HCV infection listed as a primary or secondary diagnosis in UNOS and includes patients who had concomitant nonalcoholic steatohepatitis (NASH), alcoholic cirrhosis, and hepatitis B virus infection listed as a diagnosis. Patients listed with acute hepatitis or acute liver failure (e.g., status 1) were excluded from the HCV cohort, but were included in the study.

Time periods were defined based on approval of sofosbuvir in December 2013. The pre-DAA era was defined as the period when patients were transplanted between January 1, 2002, and December 31, 2013, and the post-DAA era was defined as the period when patients were transplanted between January 1, 2014–, and March 31, 2018. Follow-up information was obtained until June 8, 2018. Demographic and clinical data were extracted from the UNOS database. Presence of HCC was determined based on diagnoses listed in the UNOS registry. Graft failure, death, and retransplantation (re-LT) status was determined from UNOS coding.

Statistical Analysis

Patient demographic and clinical characteristics were stratified by the DAA era, with categorical variables presented as proportions (%) and continuous variables presented as means with standard deviations. Comparisons were made using chi-square analysis for categorical variables and Student's t-test for continuous variables.

Era-specific graft failure was evaluated using univariate Kaplan-Meier methods and multivariate Cox regression models. Era-specific death after transplantation and re-LT was evaluated using univariate Kaplan-Meier methods and multivariate competing risk models. Patients who were alive at the time of the study end period were used as controls. Multivariate models were adjusted for sex, age, ethnicity, biological model for end stage liver disease (MELD) at transplant, HCC status, and UNOS region.

RESULTS

Patient Population

A total of 97,147 patients were transplanted between January 1, 2002, and March 31, 2018. Of these patients, 67,845 (68.1%) were transplanted in the pre-DAA era and 29,302 (31.9%) were transplanted in the post-DAA era. A total of 29,295 (30.2%) patients transplanted had chronic HCV infection. The proportion of patients with chronic HCV infection transplanted in the pre-DAA era was 32.1% and decreased to 25.7% in the post-DAA era ($\chi^2 = 395.8$, $p < 0.001$) (Table 1). A total of 18,869 (19.4%) patients with HCC were transplanted over the study period,

decreasing from 32.09% in the pre-DAA era to 25.4% in the post-DAA era ($\chi^2 = 675.5$, $p < 0.001$) (Table 1).

The majority of patients in both treatment eras were men: 67.0% in the pre-DAA era and 65.9% in the post-DAA era ($\chi^2 = 9.96$, $p = 0.002$). The majority of patients in both treatment eras were whites: 72.6% in the pre-DAA era and 72.0% in the post-DAA era ($\chi^2 = 31.60$, $p < 0.001$) (Table 1). The proportion of patients with diabetes increased from 25.4% in the pre-DAA era to 28.7% in the post-DAA era ($\chi^2 = 239.1$, $p < 0.001$) (Table 1). The mean age at listing increased from 53 years in the pre-DAA era to 55 years in the post-DAA era ($p < 0.001$), while the mean BMI increased (pre-DAA = 28.4, post-DAA = 29.0; $p < 0.001$), and the mean biologic MELD at transplant also increased (pre-DAA = 21.7, post-DAA = 23.1; $p < 0.001$) (Table 1).

The proportion of patients who experienced graft failure decreased from 28.2% in the pre-DAA era to 24.7% in the post-DAA era ($\chi^2 = 7200$, $p < 0.001$) (Table 1). The proportion of patients who were retransplanted decreased from 5.8% in the pre-DAA era to 2.2% in the post-DAA era, and the proportion of patients who died after LT decreased from 34.3% in the pre-DAA era to 10.4% in the post-DAA era ($\chi^2 = 7178$, $p < 0.001$) (Table 1).

Graft Failure

On univariate KaplanMeier analysis, 1-year and 2-year graft survival was 84.6% (95% confidence interval [CI] = 84.3–84.9%) and 79.6% (95% CI = 79.3–79.9%) in the pre-DAA era and 89.6% (95% CI = 89.2–89.9%) and 85.7% (95% CI = 85.2–86.2%) in the post-DAA era, respectively (Table 2).

On multivariate Cox regression analysis, patients transplanted in the post-DAA era were significantly less likely to suffer from graft failure than those transplanted in the pre-DAA era (hazard ratio [HR] = 0.69, 95% CI = 0.66–0.71, $p < 0.001$) (Table 3). Patients transplanted in the post-DAA era still had a lower likelihood of graft failure even when stratified to either the non-HCV (HR = 0.73, 95% CI = 0.70–0.76, $p < 0.001$) or HCV cohort (HR = 0.59, 95% CI = 0.55–0.63, $p < 0.001$) (Supplemental Table 1). The magnitude of the effect is observed to be higher in the HCV cohort. We similarly observed a significantly lower likelihood of graft failure in the post-DAA era in both non-HCC (HR = 0.70, 95% CI = 0.67–0.73, $p < 0.001$) and HCC (HR = 0.68, 95% CI = 0.63–0.74, $p < 0.001$) stratified cohorts (Supplemental Table 1).

On univariate KaplanMeier analyses, 1- and 2-year graft survival was found to be 86.2% (95% CI = 85.9–86.4%) and 81.9% (95% CI = 81.6–82.2%) in the non-HCV cohort and 85.5% (95% CI = 85.1–85.9%) and 79.3% (95% CI = 78.9–79.8%) in the HCV cohort, respectively (Table 2). On multivariate analysis, the HCV population was significantly more likely to have graft failure

Table 1 Patients Who Underwent Liver Transplantation From January 1, 2002–to March 31, 2018, in the US.

		Total population		Pre-DAA		Post-DAA	
		N	%	N	%	n	%
Sex	Male	64,757	66.66%	45,438	66.97%	19,319	65.93%
	Female	32,390	33.34%	22,407	33.03%	9983	34.07%
				χ^2	9.9618	P	0.002
Ethnicity	White	69,734	72.59%	48,911	72.82%	20,823	72.05%
	Black	9144	9.52%	6441	9.59%	2703	9.35%
	Hispanic	12,840	13.37%	8716	12.98%	4124	14.27%
	Asian	4346	4.52%	3095	4.61%	1251	4.33%
				χ^2	31.597	P	<0.001
HCV	No	67,834	69.84%	46,066	67.91%	21,768	74.30%
	Yes	29,295	30.16%	21,765	32.09%	7530	25.70%
				χ^2	395.78	P	<0.001
HCC	No	78,260	80.57%	56,125	72.06%	22,135	74.62%
	Yes	18,869	19.43%	21,765	27.94%	7530	25.38%
				χ^2	675.51	P	<0.001
Diabetes	No	71,382	74.56%	50,543	76.00%	20,839	71.28%
	Yes	24,355	25.44%	15,957	24.00%	8398	28.72%
				χ^2	239.13	P	<0.001
Era	Pre-DAA	66,174	68.12%				
	Post-DAA	30,973	31.88%				
		Mean		Mean		Mean	
Age at listing		53.34		52.95	<0.001	54.95	
				t-test			
BMI at transplant		28.6		28.42	<0.001	29.01	
				t-test			
Biological MELD at transplant		22.07		21.71	<0.001	23.09	
				t-test			
		Overall		Era 1		Era 2	
Graft failure	No	66,174	68.12%	40,557	71.76%	25,617	75.31%
	Yes	30,973	31.88%	15,957	28.24%	8398	24.69%
				χ^2	7200	P	<0.001
Patient status	Died	26,332	27.11%	23,268	34.31%	3044	10.39%
	Retransplanted	4559	4.69%	3926	5.79%	633	2.16%
	Alive at last known follow-up	66,256	68.20%	40,631	59.91%	25625	87.45%
				χ^2	7178.9	P	<0.001

DAA = direct-acting antiviral; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; BMI = body mass index.

than the non-HCV population (HR = 1.15, 95% CI = 1.12–1.18, $p < 0.001$) (Table 3). When stratified by eras, the HCV population in the pre-DAA era was significantly more likely to have graft failure than the non-HCV population (HR = 1.18, 95% CI = 1.15–1.21, $p < 0.001$). However, in the post-DAA era, no significant differences in graft failure was observed by HCV status (HR = 0.94, 95% CI = 0.87–1.02, $p = 0.14$) (Table 3).

On univariate KaplanMeier analysis, 1- and 2-year graft survival was 85.4% (95% CI = 85.1–85.7%) and 80.9% (95% CI = 80.6–81.2%) in the non-HCC population and was 88.3% (95% CI = 87.8–88.8%) and 82.0% (95% CI = 81.4–82.6%) in the HCC population, respectively (Table 2). The HCC population was significantly more likely to have graft failure than the non-HCC population during the entire study period (HR = 1.09, 95% CI = 1.06–1.13, p

Table 2 Univariate KaplanMeier Analyses Evaluating Median Cumulative 1-Year and 2-Year Rates of Graft Failure, Post-LT Death, and Retransplantation, Stratified by HCC, HCV, and Treatment Era.

		1 year			2 years		
		Median	95% CI		Median	95% CI	
Graft failure	Non-HCC	14.6%	14.3%	14.9%	19.1%	18.8%	19.4%
	HCC	11.7%	11.2%	12.2%	18.0%	17.4%	18.6%
	Non-HCV	13.8%	13.6%	14.1%	18.1%	17.8%	18.4%
	HCV	14.5%	14.1%	14.9%	20.7%	20.2%	21.1%
	Pre-DAA	15.4%	15.1%	15.7%	20.4%	20.1%	20.7%
	Post-DAA	10.4%	10.1%	10.8%	14.3%	13.8%	14.8%
		1 year Median	95% CI		2 years Median	95% CI	
Post-LT Death	Non-HCC	11.5%	11.3%	11.7%	15.6%	15.3%	15.8%
	HCC	9.3%	8.8%	9.7%	15.3%	14.8%	15.9%
	Non-HCV	10.8%	10.5%	11.0%	14.6%	14.3%	14.9%
	HCV	11.7%	11.3%	12.1%	17.5%	17.0%	18.0%
	Pre-DAA	12.0%	11.8%	12.3%	16.6%	16.3%	16.9%
	Post-DAA	8.5%	8.1%	8.8%	12.1%	11.7%	12.6%
		1 year Median	95% CI		2 years Median	95% CI	
Retransplantation	Non-HCC	3.4%	3.3%	3.6%	4.1%	4.0%	4.3%
	HCC	2.6%	2.4%	2.9%	3.2%	2.9%	3.4%
	Non-HCV	3.4%	3.2%	3.5%	4.0%	3.9%	4.2%
	HCV	3.1%	2.9%	3.3%	3.8%	3.6%	4.0%
	Pre-DAA	3.7%	3.6%	3.9%	4.5%	4.3%	4.6%
	Post-DAA	2.1%	1.9%	2.3%	2.5%	2.3%	2.7%
		1 year Median	95% CI		2 years Median	95% CI	

DAA = direct-acting antiviral; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; LT = liver transplantation; CI = confidence interval.

< 0.001) (Table 3). When stratified by treatment era, the HCC population had significantly higher likelihood of graft failure in the pre-DAA era (HR = 1.11, 95% CI = 1.07–1.15, $p < 0.001$) but was not significantly different than the non-HCC population in the post-DAA era (HR = 1.03, 95% CI = 0.94–1.13, $p = 0.46$) (Table 3).

Patients with diabetes had a significantly higher likelihood of graft failure overall (HR = 1.26, 95% CI = 1.23–1.29, $p < 0.001$) and in each stratified treatment era (pre-DAA era: HR = 1.27, 95% CI = 1.24–1.31, $p < 0.001$; post-DAA era: HR = 1.19, 95% CI = 1.11–1.28, $p < 0.001$) (Table 3).

Women had significantly lower likelihood of graft failure than men overall and in each stratified treatment era (Table 3). Compared with non-Hispanic whites, blacks were significantly more likely to have graft failure overall and in each stratified treatment era. Although Hispanics and Asians had lower likelihood of graft failure overall and in the stratified pre-DAA cohort, they did not have any significant difference when compared with non-Hispanic whites in the post-DAA era (Table 3).

Post-transplantation Death

On univariate KaplanMeier analysis, 1- and 2-year post-LT survival was 88.0% (95% CI = 87.7–88.2%) and 83.4% (95% CI = 83.1–83.7%) in the pre-DAA era and was 91.5% (95% CI = 91.2–91.9%) and 87.9% (95% CI = 87.4–88.3%) in the post-DAA era, respectively (Table 2).

Patients transplanted in the post-DAA era had a significantly lower likelihood of post-LT death than those transplanted in the pre-DAA era (HR = 0.68, 95% CI = 0.66–0.71, $p < 0.001$) (Table 4). Patients transplanted in the post-DAA era were also significantly less likely to die after LT even when stratified into the non-HCC cohort (HR = 0.70, 95% CI = 0.67–0.73, $p < 0.001$) and the HCC cohort (HR = 0.67, 95% CI = 0.61–0.72, $p < 0.001$) (Supplemental Table 2). The post-DAA era was also associated with lower likelihood of post-LT death when stratified into the non-HCV (HR = 0.73, 95% CI = 0.70–0.77, $p < 0.001$) and the HCV cohorts (HR = 0.58, 95% CI = 0.54–0.63, $p < 0.001$) (Supplemental Table 2). The effect is more notable in the HCV cohort than in the non-HCV cohort.

Table 3 Multivariate Regression Analyses Evaluating Predictors of Overall Graft Failure After Liver Transplantation.

						Pre-DAA				Post-DAA			
		HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Gender	Male	1				1				1			
	Female	0.95	0.93	0.98	0.0001	0.96	0.93	0.98	0.001	0.93	0.86	1.00	0.04
Ethnicity	White	1				1				1			
	Black	1.18	1.14	1.22	<0.001	1.19	1.14	1.23	<0.001	1.17	1.05	1.30	0.005
	Hispanic	0.90	0.86	0.93	<0.001	0.89	0.85	0.92	<0.001	0.96	0.87	1.06	0.44
	Asian	0.76	0.72	0.81	<0.001	0.74	0.69	0.79	<0.001	0.91	0.77	1.09	0.31
HCV	No	1				1				1			
	Yes	1.15	1.12	1.18	<0.001	1.18	1.15	1.21	<0.001	0.94	0.87	1.02	0.14
HCC	No	1				1				1			
	Yes	1.09	1.06	1.13	<0.001	1.11	1.07	1.15	<0.001	1.03	0.94	1.13	0.46
Diabetes	No	1				1				1			
	Yes	1.26	1.23	1.29	<0.001	1.27	1.24	1.31	<0.001	1.19	1.11	1.28	<0.001
Era	Pre-DAA	1											
	Post-DAA	0.69	0.66	0.71	<0.001								
Age at listing		1.01	1.01	1.01	<0.001	1.01	1.01	1.01	<0.001	1.01	1.00	1.01	0.002
BMI at transplant		0.99	0.99	0.99	<0.001	0.99	0.99	0.99	<0.001	0.99	0.99	1.00	0.02
Biologic MELD at transplant		1.01	1.01	1.01	<0.001	1.01	1.01	1.01	<0.001	1.01	1.01	1.02	<0.001

DAA = direct-acting antiviral; HR = hazard ratio; CI = confidence interval; BMI = body mass index; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; UNOS = United Network for Organ Sharing.

Model adjusted for demographics, HCV status, HCC status, diabetes, treatment era, BMI, biologic MELD at transplant, age at listing, and UNOS region.

On univariate KaplanMeier analysis, 1- and 2-year post-LT survival was 89.2% (95% CI = 89.0–89.5%) and 85.4% (95% CI = 85.1–85.7%) for the non-HCV population and was 88.3% (95% CI = 87.9–88.7%) and 82.5% (95% CI = 82.0–83.0%) for the HCV population, respectively (Table 2).

On multivariate competing risk analysis, the HCV population was significantly more likely to die after LT than the non-HCV population overall (HR = 1.17, 95% CI = 1.14–1.21, $p < 0.001$) and when stratified in the pre-DAA era (HR = 1.20, 95% CI = 0.17–1.24, $p < 0.001$). The HCV population was also noted to have significantly higher likelihood of post-LT death when stratified to either the non-HCC (HR = 1.20, 95% CI = 1.16–1.23, $p < 0.001$) or HCC cohorts (HR = 1.11, 95% CI = 1.05–1.18, $p = 0.0005$) (Supplemental Table 2). However, when stratified to the post-DAA era, the HCV population and non-HCV population did not have significant difference with regard to post-LT death (HR = 0.97, 95% CI = 0.89–1.06, $p = 0.49$) (Table 4).

On multivariate competing risk analysis, the HCC population had significantly higher likelihood of post-LT death overall (HR = 1.15, 95% CI = 1.11–1.19, $p < 0.001$) and when in the stratified pre-DAA era (HR = 1.17, 95% CI = 1.13–1.22, $p < 0.001$) (Table 4). Similarly, HCC conveyed a higher likelihood of post-LT death in both the non-HCV cohort (HR = 1.16, 95% CI = 1.11–1.21, $p < 0.001$) and in the HCV cohort (HR = 1.17, 95% CI = 1.10–1.23, $p < 0.001$)

(Supplemental Table 2). However, when stratified in the post-DAA era, the HCC and non-HCC population had no significant difference with regard to post-LT death (HR = 1.07, 95% CI = 0.97–1.19, $p = 0.17$) (Table 4).

Patients with diabetes had a significant higher likelihood of post-LT death overall (HR = 1.32, 95% CI = 1.28–1.36, $p < 0.001$) and when stratified in the pre-DAA era (HR = 1.33, 95% CI = 1.29–1.37, $p < 0.001$) and the post-DAA era (HR = 1.26, 95% CI = 1.16–1.36, $p < 0.001$) (Table 4).

Women had slightly lower likelihood of post-LT death than men; however, this was statistically significant overall and in the post-DAA era, but not in the pre-DAA era (Table 4). Blacks were significantly more likely to have post-LT death than non-Hispanic whites overall and when stratified by both pre-DAA and post-DAA eras. Hispanics and Asians were less likely to have post-LT death than non-Hispanic whites overall and when stratified to the pre-DAA era; however, they were not significantly different in the post-DAA era (Table 4).

Retransplantation

On univariate KaplanMeier analysis, 1- and 2-year cumulative incidence of re-LT was 3.7% (95% CI = 3.63–3.9%) and 4.5% (95% CI = 4.3–4.6%) for the pre-DAA era and was 2.1% (95% CI = 1.9–2.3%) and 2.5% (95% CI = 2.3–2.7%) for the post-DAA era, respectively (Table 2).

Table 4 Multivariate Competing Risk Analyses Evaluating Predictors of Death After Liver Transplantation.

						Pre-DAA Era				Post-DAA Era			
		HR	95% CI		p	HR	95% CI		p	HR	95% CI		P
Gender	Male	1				1				1			
	Female	0.97	0.94	0.99	0.01	0.97	0.94	1.00	0.07	0.92	0.85	1.00	0.04
Ethnicity	White	1				1				1			
	Black	1.16	1.11	1.21	<0.001	1.16	1.11	1.22	<0.001	1.16	1.03	1.31	0.01
	Hispanic	0.88	0.84	0.92	<0.001	0.87	0.83	0.91	<0.001	0.96	0.86	1.08	0.53
	Asian	0.73	0.68	0.79	<0.001	0.72	0.66	0.77	<0.001	0.84	0.68	1.02	0.08
HCV	No	1				1				1			
	Yes	1.17	1.14	1.21	<0.001	1.20	1.17	1.24	<0.001	0.97	0.89	1.06	0.49
HCC	No	1				1				1			
	Yes	1.15	1.11	1.19	<0.001	1.17	1.13	1.22	<0.001	1.07	0.97	1.19	0.17
Diabetes	No	1				1				1			
	Yes	1.32	1.28	1.36	<0.001	1.33	1.29	1.37	<0.001	1.26	1.16	1.36	<0.001
Era	Pre-DAA	1											
	Post-DAA	0.68	0.66	0.71	<0.001								
Age at listing		1.02	1.02	1.02	<0.001	1.02	1.02	1.02	<0.001	1.01	1.01	1.02	<0.001
BMI at transplant		0.99	0.99	0.99	<0.001	0.99	0.99	0.99	<0.001	0.99	0.98	1.00	0.01
Biologic MELD at transplant		1.01	1.01	1.02	<0.001	1.01	1.01	1.01	<0.001	1.02	1.02	1.02	<0.001

DAA = direct-acting antiviral; HR = hazard ratio; CI = confidence interval; BMI = body mass index; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; UNOS = United Network for Organ Sharing.

Model adjusted for demographics, HCV status, HCC status, diabetes, treatment era, BMI, biologic MELD at transplant, age at listing, and UNOS region.

On multivariate competing risk analysis, patients transplanted in the post-DAA era had a significantly lower likelihood of re-LT than those transplanted in the pre-DAA era (HR = 0.65, 95% CI = 0.59–0.70, $p < 0.001$) (Table 5). This significant lower likelihood of re-LT in the post-DAA era was also seen in both the stratified non-HCC cohort (HR = 0.70, 95% CI = 0.57–0.85, $p = 0.0003$) and HCC cohort (HR = 0.62, 95% CI = 0.56–0.69, $p < 0.001$) (Supplemental Table 3), as well as in both the stratified non-HCV cohort (HR = 0.65, 95% CI = 0.59–0.72, $p < 0.001$) and the HCV cohort (HR = 0.63, 95% CI = 0.53–0.76, $p < 0.001$) (Supplemental Table 3).

On univariate KaplanMeier analysis, 1- and 2-year cumulative incidence for re-LT was 3.4% (95% CI = 3.2–3.5%) and 4.0% (95% CI = 3.9–4.2%) for the non-HCV population and was 3.1% (95% CI = 2.9–3.3%) and 3.8% (95% CI = 3.6–4.0%) for the HCV population, respectively (Table 2). On multivariate competing risk analysis, the HCV population was not significantly different from the non-HCV population with regard to re-LT when accounting for all transplanted patients between 2002 and 2018. However, there was a trend toward higher likelihood of re-LT for the HCV population in the pre-DAA era (HR = 1.08, 95% CI = 1.00–1.16, $p = 0.06$) and a trend for lower likelihood of re-LT for the HCV population in the post-DAA era (HR = 0.84, 95% CI = 0.69–1.03, $p = 0.10$) (Table 5). In the non-HCC stratified cohort, the HCV population tended to have higher likelihood of re-LT than the non-

HCV population (HR = 1.06, 95% CI = 0.99–1.15, $p = 0.10$) (Supplemental Table 3). However, in the HCC cohort, patients with HCC and HCV and those with HCC without HCV had no difference with regard to likelihood of re-LT.

On univariate KaplanMeier analysis, 1- and 2-year median cumulative incidence of re-LT was 3.4% (95% CI = 3.3–3.6%) and 4.1% (95% CI = 4.0–4.3%) for non-HCC patients and was 2.6% (95% CI = 2.4–2.9%) and 3.2% (95% CI = 2.9–3.4%) for HCC patients, respectively (Table 2). On multivariate competing risk analysis, patients with HCC had significantly lower likelihood of re-LT overall (HR = 0.82, 95% CI = 0.74–0.90, $p < 0.001$) and when stratified into the pre-DAA era (HR = 0.80, 95% CI = 0.72–0.89, $p < 0.0010$) (Table 5). However, in the post-DAA cohort, the HCC population had no significant difference compared with the non-HCC population in with regard to re-LT. When stratified by HCV status, the HCC population had lower likelihood of re-LT in both the non-HCV cohort (HR = 0.83, 95% CI = 0.73–0.95, $p = 0.005$) and HCV cohort (HR = 0.81, 95% CI = 0.70–0.94, $p = 0.01$) (Supplemental Table 3).

Patients with diabetes had a significantly lower likelihood of re-LT overall and in the pre-DAA era; however, they were not significantly different from patients without diabetes in the post-DAA era (Table 5).

Women had a significantly lower likelihood of re-LT than men overall and in the pre-DAA cohort; however, they were not significantly different from men in the

Table 5 Multivariate Competing Risk Analysis for Retransplantation.

						Pre-DAA era				Post-DAA era			
		HR	95% CI		p	HR	95% CI		p	HR	95% CI		p
Gender	Male	1				1				1			
	Female	0.89	0.83	0.95	0.001	0.88	0.82	0.94	<0.001	0.95	0.80	1.12	0.53
Ethnicity	White	1				1				1			
	Black	1.20	1.09	1.32	<0.001	1.21	1.09	1.34	<0.001	1.14	0.87	1.48	0.34
	Hispanic	1.00	0.90	1.10	0.95	1.01	0.90	1.12	0.91	0.93	0.73	1.18	0.54
	Asian	0.95	0.81	1.12	0.54	0.90	0.75	1.09	0.28	1.19	0.83	1.70	0.35
HCV	No	1				1				1			
	Yes	1.05	0.98	1.13	0.20	1.08	1.00	1.16	0.06	0.84	0.69	1.03	0.10
HCC	No	1				1				1			
	Yes	0.82	0.74	0.90	<0.001	0.80	0.72	0.89	<0.001	0.89	0.71	1.12	0.33
Diabetes	No	1				1				1			
	Yes	0.90	0.83	0.98	0.01	0.90	0.82	0.98	0.02	0.91	0.75	1.09	0.31
Era	Pre-DAA	1											
	Post-DAA	0.65	0.59	0.70	<0.001								
Age at listing		0.96	0.96	0.97	<0.001	0.96	0.96	0.97	<0.001	0.97	0.97	0.98	<0.001
BMI at transplant		1.01	1.00	1.01	0.02	1.01	1.00	1.01	0.04	1.01	1.00	1.02	0.15
Biologic MELD at transplant		0.99	0.98	0.99	<0.001	0.99	0.98	0.99	<0.001	0.98	0.97	0.99	<0.001

DAA = direct-acting antiviral; HR = hazard ratio; CI = confidence interval; BMI = body mass index; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; UNOS = United Network for Organ Sharing.

Model adjusted for demographics, HCV status, HCC status, diabetes, treatment era, BMI, biologic MELD at transplant, age at listing, and UNOS region.

post-DAA era. Blacks had a significantly higher likelihood of re-LT overall and in the pre-DAA era; however, they were not significantly different in the post-DAA era. Hispanics and Asians had no significant difference in likelihood of re-LT compared with whites (Table 5).

DISCUSSION

In this comprehensive assessment of adults undergoing LT in the US, this study observed that patients with chronic HCV infection are experiencing improved post-LT outcomes after availability of DAAs. Specifically, we observed a transition from higher likelihood of graft failure and post-transplant mortality in patients with HCV than in those without HCV before 2014 to having no significant difference in post-LT outcomes after 2014. Previous US studies have noted improved waitlist mortality and lower risk of disease progression on the waitlist for patients with HCV infection in the era of current DAAs.^{12–17} Therefore, it is expected that patients with HCV infection after transplant would also experience improved post-LT outcomes. A retrospective study based in Catalonia similarly observed that among 1483 patients with HCV infection transplanted between January 2008 and December 2016, the 3-year post-LT survival improved from 76% among the pre-2014 cohort to 91% in the post-2014 cohort ($p = 0.001$).¹⁸ Improved post-LT survival in the Catalonia population was attributed to the advent of DAA therapies

as the investigators did not observe any similar improvement in mortality in the non-HCV cohort (88% vs. 91%, $p = 0.359$). A European Liver Transplant Registry database study similarly reported improvement in post-LT outcomes after 2014 for the population of patients with HCV infection. Among the 60,527 patients transplanted between January 2007 and June 2017, investigators noted an improved 3-year post-LT survival in patients with HCV infection and without HCC from 65.1% in the interferon era (2007–2010) to 76.9% during the DAA era (2014–2017) ($p < 0.0001$). They also noted that there was a significant decrease of HCV recurrence as a cause of death or re-LT in the era of DAAs (1.27%) compared with the era of interferon (6.37%, $p < 0.0001$).¹⁹

The advent of DAAs most likely contributed to the improved post-LT outcomes in the HCV population owing to the known increased SVR rates with DAA therapy and the known correlation between SVR and improved mortality for patients with chronic HCV infection.^{7,8} However, in our US study, we also observed improved post-LT outcomes in the overall population between the treatment eras, even when stratified by HCV status and HCC status. Thus, the advent of DAAs cannot completely account for the improved outcomes our study concurrently observed in the non-HCV population.

The improved post-LT outcomes after 2014 therefore may also be attributable to improved patient selection for transplant or new UNOS policies in liver allocations.

Share 35 was enacted in June 2013 to address inequity in liver allocation to patients with severe hepatic decompensation and cirrhosis. An analysis of the UNOS database between January 2010 to March 2016 found that patients with MELD ≥ 35 transplanted after implementation of Share 35 had improved one-year post-transplant mortality (83.9–88.4%, HR = 0.69 in multivariate Cox regression analyses), whereas there was no significant impact on survival of patients with MELD < 35 .²⁰ While patients with MELD ≥ 35 make up only a small proportion of the transplanted population, Share 35 has led to improved post-transplant outcomes for the sickest patients.

Although not yet a common practice in all transplant centers, the addition of HCV antibody+/nucleic acid amplification testing (Ab+/NAT) – livers into the donor pool may also soon be affecting overall trends in LT by increasing likelihood of transplantation without increasing the risk of graft function or loss in the era of current DAAs. Patients who may have waited longer in the pre-DAA era, with progression of deconditioning or progression of their liver disease, by accepting a HCV Ab+ donor liver in the post-DAA era may be posed to have higher success in the post-transplant setting, driven by the lower waiting time for a donor. Lockett et al²¹ showed that in 55 candidates with HCV infection and without viremia who accepted HCV+/NAT– donor livers, only 5 (9%) transplanted patients developed HCV viremia and 4 of them were successfully treated with DAAs to achieve SVR. The one patient who developed viremia and who was not treated had died owing to unrelated causes.²¹

Interestingly, our study saw that the proportion of patients with HCC transplanted decreased from 27.9% in the pre-DAA era to 25.4% in the post-DAA era. This is in contrast to other studies that have reported a rise in HCC listings for LT since 2014 in the setting of decreasing HCV listings.^{22–24} A possible explanation for this is that although a higher proportion of patients with HCC are listed, a larger proportion of them are not being transplanted in the most recent era. Reasons for potential delisting could include possible clinical improvement with locoregional therapy or progression of their disease to beyond transplant criteria.

Although our study showed that patients with HCC had a worse graft survival and post-LT survival before 2014, there were no significant differences in post-LT outcomes between the HCC and non-HCC population after 2014. This effect was similarly seen even when the patient population was stratified by HCV status, suggesting that the observed improvements in post-LT outcomes for patients with HCC are not just driven by the HCV population. Yang et al²⁴ who had reported an increase in the proportion of patients with HCC listed for transplant across all liver diseases between 2004 and 2014 also observed improved graft survival in both patients with HCC and HCV infection

(HR = 0.70, 95% CI = 0.63–0.79, $p < 0.001$) and those with HCC and without HCV infection (HR = 0.74, 95% CI = 0.61–0.89, $p = 0.002$) from the preprotease inhibitor era (2004–2010) to the protease inhibitor era (2011–2014).²⁴

A possible explanation for the improved post-LT outcomes in the HCC population could be due to better HCC characterization and selection for transplant. Patients with HCC in the current era may have favorable tumor characteristics, whereas in prior eras, higher risk patients with HCC in the past reached transplantation and were thus prone to worse post-LT survival. Although this study did not explore reasons for delisting, it is possible that in the current era, closer monitoring with improved imaging techniques and the new 6-month deferment of HCC exception points are leading to high-risk patients with HCC being delisted owing to disease progression. Although Croome et al²⁵ found no difference in 2-year graft survival or 2-year post-transplant survival for patients with HCC in the pre- or post-Share 35 eras, they did observe that patients with HCC in the post-Share 35 era were more likely to be delisted owing to sickness or disease progression.

Although this study captures the US population on the LT list and is thus powered to observe the effects of treatment and policy changes, it is limited by the nature of database studies. We used diagnosis coding to define liver disease etiologies, and thus, these populations are subject to potential misclassification biases. Although treatment eras were defined based on the timing of sofosbuvir approval, our study was unable to determine if and which HCV therapy was prescribed to patients with HCV infection on the waitlist. Along the same lines, more granular detail on HCV treatment, including timing of treatment, the specific antiviral regimen used, and whether sustained virologic response was achieved, was not available in the current UNOS/OPTN database for incorporation into our study. Similarly, we could not account for SVR status between the two eras or between HCC and non-HCC populations. Our study is also limited to the patients who were transplanted, and our findings may not apply to patients with HCV infection who were not listed. Finally, although our study period was specifically designed to evaluate the impact of DAA availability on post-LT outcomes, it is likely that improvements in post-LT outcomes are multifactorial and should not be attributed to DAA therapy alone. Although short-term improvements in liver synthetic function may be associated with highly effective DAA therapies, it is also important to note that many of the benefits of DAA therapy are also observed in the long term (e.g., reduced risk of HCV-related HCC). Thus, short-term improvements in post-LT outcomes also likely reflect improvements in surgical techniques, immunosuppression, and overall post-LT care.

In summary, in the era after the introduction of DAAs, US patients who have undergone LT have experienced

lower likelihood of graft failure, post-LT death, and re-LT. Although the direct impact of DAAs cannot be refuted in the HCV population, the resulting improved post-LT outcomes observed in the non-HCV population may be secondary to nationwide allocation policy changes or clinical practice shifts.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Kellie Young: Supervision. **Robert J. Wong:** Conceptualization, Methodology, Writing - review & editing, Supervision.

CONFLICTS OF INTEREST

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jceh.2020.02.003>.