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# Direct-Acting Antiviral Therapy in Liver Transplant Patients With Hepatocellular Carcinoma and Hepatitis C

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**Background:** Direct-acting antivirals (DAA) are highly effective for the treatment of hepatitis C (HCV), although there are limited data on the safety and efficacy of DAA therapy in hepatitis C-positive individuals awaiting liver transplantation for hepatocellular carcinoma (HCC). **Methods:** We conducted a retrospective cohort study of HCV-positive patients who underwent liver transplantation for HCC at 3 liver transplant centers across the United States from 2014 to 2017 with follow-up to July 2018. Transplant recipients who received DAA before transplant were compared with those who did not (DAA naive) for posttransplant HCC recurrence rate, sustained virological response (SVR), allograft failure, and death using Kaplan-Meier analysis and Cox proportional hazard models. **Results:** A total of 171 HCV-HCC transplant recipients (99 pretransplant DAA; 72 DAA naive controls) were included, with a median follow-up of 24 months. The overall posttransplant HCC recurrence rate was 9% (15/171). Pretransplant DAA was not associated with HCC recurrence (5% versus 14%;  $P=0.07$ ), graft failure (7% versus 3%;  $P=0.21$ ), or death (12% versus 19%;  $P=0.19$ ) as compared with DAA naive patients. SVR rates were significantly lower ( $P<0.01$ ) with pretransplant DAA (75%, 39/52) than posttransplant DAA (97%, 59/61) therapies. Those who received pretransplant DAA and those who did not were not statistically different in age, gender, alpha fetal protein levels, model for end-stage liver disease scores, or transplant wait time. **Conclusions:** Pretransplant DAA for HCV was not associated with an increased risk of posttransplant HCC recurrence, though pretransplant DAA had lower efficacy than posttransplant DAA in HCV-HCC transplant recipients.

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## INTRODUCTION

Liver transplantation (LT) for hepatocellular carcinoma (HCC) is increasing in the United States, and a significant proportion of these patients have underlying HCV.<sup>1</sup> The advent of highly effective and safe direct-acting antiviral (DAA) therapy for hepatitis C (HCV) has led to decreased registration for transplant, an increase in delisting due to improvement of clinical status, and a lower

rate of graft failure rates among patients undergoing transplant with HCV.<sup>1,2</sup> Despite the clinical success of pretransplant HCV treatment, there is current controversy as to whether patients with HCV-related HCC should undergo HCV treatment before or after transplant. A potential increased risk of HCC recurrence in DAA recipients was found in 2016 from a North American cohort<sup>3</sup> ( $n=81$ ) and subsequently in 3 European cohorts<sup>4-6</sup> (most recently

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from March 2020<sup>6</sup>). Second, 2 reports had demonstrated lower SVR12 rates among patients with HCV and HCC.<sup>7,8</sup> Finally, pretransplant HCV treatment may remove the patient from consideration of receiving an allograft from an HCV exposed donor. In the opioid epidemic, the availability of HCV-positive deceased donor is increased and some transplant programs opt to not treat HCV-HCC waitlisted patients for HCV.<sup>9</sup>

In a prior correspondence,<sup>3</sup> we reported on 81 patients (18 DAA, 64 DAA naive) who underwent LT for HCV-HCC between 2011 and 2015. All patients were within Milan criteria by imaging before transplant. The proportion beyond Milan on explant pathology was 39% in the DAA-treated group versus 28% in the control group ( $P=0.04$ ) even though patients with and without pretransplant DAA had received comparable pretransplant locoregional therapies. Those who received pretransplant DAA showed a trend toward a higher risk of posttransplant HCC recurrence (5/18, 27.8%) compared with untreated patients (6/63, 9.5%), but this did not reach statistical significance ( $P=0.06$ ). Of the DAA-treated patients with posttransplant HCC recurrence, 80% occurred within 6 months post LT.

Based on these reports of aggressive, early HCC recurrences in those undergoing locoregional therapy or resection, it was speculated that DAA treatments might affect the tumor surveillance system and allow for aggressive progression of unrecognized HCC or aggressive recurrence. It was recognized that larger studies would be needed to address these uncertainties. The current study aims to determine whether pretransplant DAA therapy is associated with posttransplant HCC recurrence, graft failure, and death, as well as the comparative efficacy of DAA therapy administered before and after transplant.

## MATERIALS AND METHODS

### Patients

Following Institutional Review Board approval from the Mayo Clinic (IRB no. 16-008127), we conducted a retrospective cohort study of HCV-positive patients who underwent liver transplant for HCC at the Mayo Clinic's 3 high-volume liver transplant centers in Rochester, MN, Jacksonville, FL, and Scottsdale, AZ, between January 1, 2014, and June 30, 2017, with follow-up till July 31, 2018. All study patients had detectable HCV viral load at the time of transplant listing. The study group consisted of patients who received DAA-containing therapy before transplant, and the control group consisted of those who did not (either naive patients or had persistent HCV viremia despite prior interferon-based therapies). HCV-directed therapies were administered at the discretion of the transplant hepatologist or the patient's primary/local gastroenterologist/hepatologist. Posttransplant, all transplant recipients received the same immunosuppression protocol: tacrolimus, mycophenolate mofetil, and prednisone initially, and then tapered to tacrolimus monotherapy. Post-LT HCC recurrence monitoring was described in a previous study,<sup>10</sup> which involves alpha-fetoprotein (AFP) laboratory testing and cross-sectional imaging at 4, 12, and 24 months after LT in addition to standard clinical follow-up, including abdominal ultrasound with dopplers at 4 and 12 months after LT, and then annually thereafter.

### Clinical Variables and Outcomes

Variables collected include patient demographics; HCV genotype, viral load, and treatments; HCC characteristics pretransplant and in the explanted liver; pretransplant HCC locoregional therapies; and posttransplant outcomes. The primary outcome is the posttransplant HCC recurrence rate, as determined by the 2010 American Association for the Study of Liver Diseases Guidelines<sup>11</sup> with dynamic radiographic imaging and biopsy. Secondary outcomes include the rate of sustained virological response (SVR) with pre- and posttransplant DAA therapy, liver allograft failure, and death.

### Statistical Analysis

Student *t*-test and chi-square ( $\chi^2$ ) tests were used to compare baseline variables. Kaplan-Meier analysis was performed to estimate the rate of HCC recurrence, and the Cox proportional hazard model was used to investigate the association between pretransplant DAA and the risk of HCC recurrence. For multivariate regression analysis, 1 predictor variable per 10 events (posttransplant HCC) was studied.<sup>12</sup> JMP (Version 14.0., SAS Institute Inc., Cary, NC) was used for statistical analysis.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patients

A total of 171 patients with HCV underwent liver transplant for HCC were included, of which 99 received DAA pretransplant and 72 did not (34 HCV treatment naive and 38 had persistent HCV viremia despite prior interferon-based therapies). Of those who received DAA pretransplant ( $n=87$  with 1 DAA regiment,  $n=9$  with 2 DAA regiments, and  $n=3$  with 3 DAA regiments), 40% received sofosbuvir and ledipasvir, 29% sofosbuvir and simeprevir, 26% sofosbuvir and ribavirin, 11% telaprevir with pegylated interferon and ribavirin, 1% paritaprevir and ritonavir and ombitasvir and dasabuvir, 1% sofosbuvir and daclatasvir, and 1% boceprevir with pegylated interferon and ribavirin.

At baseline, DAA-treated patients had higher levels of albumin (3.6 g/dL versus 3.2 g/dL;  $P < 0.01$ ) at the time of listing and fewer received transarterial chemoembolization (76% versus 89%;  $P=0.03$ ) compared with those without DAA; otherwise, both groups had similar rates for other bridging therapies (transarterial radioembolization and ablative therapies); AFP levels, model for end-stage liver disease scores; wait time on the transplant list, and histologic assessment of the explanted liver, including the size, number, and viability of the tumors, as well as the presence of lymphovascular invasion (Table 1). The median follow-up time was 24 months (interquartile range [IQR], 12–26).

### No association Between Pre-LT DAA Treatment and HCC Recurrence

The overall posttransplant HCC recurrence rate was 9% (15/171): 5% (5/99) with pretransplant DAA and 14% (10/72) in those who did not ( $P=0.07$ ). The median time from transplant to HCC recurrence was 14 months (IQR, 4–21), which was similar in those with and without pretransplant DAA (14 mo, IQR 5–20 mo; 14 mo, IQR, 3–24 mo;  $P=0.71$ ). Of the 15 patients with recurrent HCC, 9 had active HCV infection posttransplant (all were from the control group). There were only 5 study patients who did not receive DAA

**TABLE 1.****Baseline characteristics of patients with hepatitis C who underwent liver transplant for hepatocellular carcinoma (N = 171)**

Variable n (%) / median (IQR)		DAA (n = 99)	Controls (n = 72)	P
Male		78 (79%)	52 (72%)	0.32
White		82 (82%)	57 (79%)	0.92
Age at transplant, in y		61 (57, 64)	61 (57, 64)	0.65
Concomitant liver disease	NASH	8 (8%)	1 (1%)	0.08
	Alcoholic liver disease	36 (36%)	32 (44%)	0.28
	Hepatitis B	2 (2%)	2 (3%)	1.00
	Other	6 (6%)	7 (10%)	0.40
HIV		1 (1%)	1 (1%)	1.00
HCV viral load (IU/mL)	At transplant activation	93 800 (0, 2 222 500)	923 500 (229 750, 2 970 000)	0.96
	At liver transplant	0 (0, 0)	703 500 (240 500, 1 640 000)	0.23
HCV genotype	1	72 (73%)	54 (75%)	0.75
	2	3 (3%)	4 (6%)	
	3	14 (14%)	12 (17%)	
	4	1 (1%)	3 (4%)	
	Unknown	8 (8%)	1 (1%)	
Alpha fetal protein (ng/mL)	At transplant activation	13 (6, 29)	14 (7, 54)	0.15
	At liver transplant	7 (4, 19)	15 (8, 51)	0.90
Biological MELD-Na	At transplant listing	10 (8, 14)	11 (9, 15)	0.06
	At liver transplant	11 (8, 16)	12 (10, 19)	0.07
Exceptions MELD	At transplant listing	22 (17, 22)	22 (22, 22)	0.10
	At liver transplant	25 (22, 28)	28 (25, 28)	0.52
Months on LT waitlist		6 (3, 10)	6 (4, 10)	0.63
Liver donor	Deceased	97 (98%)	69 (96%)	0.65
	Living	2 (2%)	3 (4%)	
Months of follow-up		24 (12, 32)	26 (8, 43)	0.05
Hepatocellular carcinoma				
Tumor size at listing, in cm		2.5 (1.9, 3.0)	2.5 (1.9, 3.0)	0.81
Number of lesions at listing		2 (1, 3)	2 (1, 3)	0.23
Bridging therapy	Any	92 (93%)	69 (96%)	0.52
	TACE	75 (76%)	64 (89%)	0.03
	Ablative therapy	28 (28%)	16 (22%)	0.37
	RFA	18 (18%)	10 (14%)	0.45
	Microwave ablation	11 (11%)	7 (10%)	0.80
	TARE	5 (5%)	5 (7%)	0.74
	SBRT	1 (1%)	0	1.00
Liver explant pathology	Viable tumor identified	77 (78%)	58 (81%)	0.66
	Largest tumor, in cm	2.5 (1.9, 3)	2.5 (1.9, 3.2)	0.80
	Number of lesions	2 (1, 3)	2 (1, 3)	0.11
	Lymphovascular invasion	22 (22%)	22 (31%)	0.22
Inside Milan criteria <sup>a</sup>		77 (78%)	52 (72%)	0.40

<sup>a</sup>Milan's criteria: 1 lesion <5 cm or up to 3 lesions each <3 cm.

cm, centimeter; DAA, direct-acting antivirals; HCV, hepatitis C; IQR, interquartile range; LT, liver transplant; MELD-Na, model for end-stage liver disease-sodium; NASH, nonalcoholic steatohepatitis; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization; TARE, transarterial radioembolization.

throughout the entire study period (pretransplant to the last posttransplant follow-up). Details of the 15 study patients with recurrence of HCC post-LT are provided in Table 2.

On univariate analysis, pretransplant DAA therapy had a trend toward decreased risk of post LT HCC recurrence (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.13-1.11;  $P=0.07$ ) (Figure 1; Table 3). The presence of lymphovascular invasion (HR, 10.1; 95% CI, 3.2-31.7;  $P<0.01$ ) and tumors outside of Milan criteria identified on the explanted liver (HR = 11.0; 95% CI, 3.0-70.7;  $P<0.01$ ) were associated with an increased risk of post-LT HCC recurrence (Figure 2; Table 3). Similarly, on multivariate analysis, pretransplant DAA had a trend toward decreased HCC recurrence (HR,

0.38; 95% CI, 0.13-1.13;  $P=0.07$ ), whereas lymphovascular invasion (HR, 10.0; 95% CI, 3.2-31.6;  $P<0.01$ ) was associated with an increased risk of HCC recurrence.

### Pre-LT DAA Treatment and Other Secondary Outcomes

Of those who completed DAA with at least 12 weeks of follow-up, the SVR rate was significantly lower in those who received DAA pretransplant ( $n=52$ ) as compared with those who received DAA posttransplant ( $n=61$ ) (75% versus 97%;  $P<0.01$ ). In a subgroup analysis, the pretransplant SVR rate was similarly lower (77%, 23/30) for those who were treated with the newer, more potent DAA therapies (ie, sofosbuvir

**TABLE 2.****Patients with recurrent hepatocellular carcinoma postliver transplant (n = 15)**

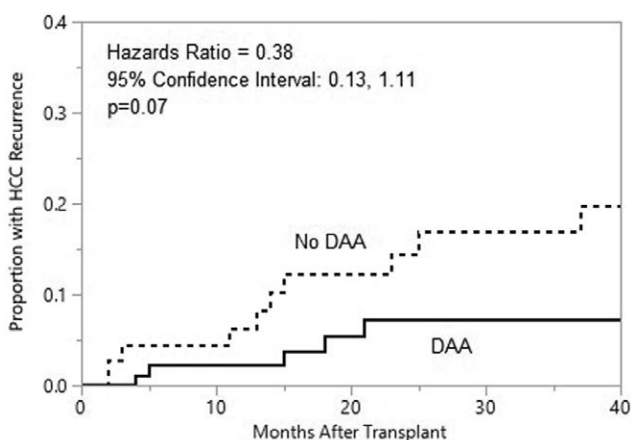
Pt <sup>a</sup> Age/ sex	HCV Rx pre-LT <sup>b</sup>	Mo on waitlist	HCC bridging therapy	Liver donor	HCV genotype	AFP HCV VL, at LT	Liver explant lymphovascular invasion/viable tumor	Post-LT and recurrent HCC course
57M	DAA <sup>c</sup> initiated 11 mo before LT listing	5	TACE, RFA	DCD	1a	64 ng/mL 0	Y/Y	Alive with recurrent HCC 21 mo post-LT
64M	DAA-INF	1	TACE	DCD	2	16 ng/mL 0	Y/Y	Diseased 15 mo post-LT with metastatic HCC
64M	DAA <sup>c</sup> initiated same month as LT listing	3	RFA	DCD	1a	29 ng/mL 0	Y/Y	Diseased 8 mo post-LT with metastatic HCC (dx 4 mo post-LT)
59M	DAA initiated 21 mo after LT listing (incomplete at LT)	20	TACE	DCD	3	125 ng/mL 0	N/Y	Diseased 19 mo post-LT with HCC (dx 18 mo post-LT)
44M	DAA initiated 20 mo after LT listing	22	RFA	Living	1	6.7 ng/mL 0	N/Y	Diseased 20 mo post-LT with metastatic HCC (dx 5 mo post-LT)
56 W	INF-based	12	TACE, MWA	DCD	3	41 ng/mL 870 000	Y/Y	Alive 25 mo post-LT with recurrent HCC dx 23 mo post-LT
61M	INF-based	4	TACE, MWA	DCD	1b	18 ng/mL 1 240 000	Y/Y	recurrent HCC 14 mo post-LT
55 W	Naive	4	TACE	DCD	1a	191 ng/mL 120 000	Y/N	Diseased 17 mo post-LT with metastatic HCC (dx 13 mo post-LT)
60M	Naive	8	TACE, TARE	DCD	1a	12 ng/L 3 690 000	Y/Y	Diseased 3 mo post-LT with metastatic mixed hepatocellular cholangiocarcinoma (dx 3 mo post-LT)
59 W	Naive	9	TACE	DCD	3	241 ng/mL 716 000	Y/Y	Diseased 22 mo post-LT with metastatic HCC (dx 2 mo post-LT)
57M	Naive	2	TACE	DCD	1a	357 ng/mL 7 760 000	Y/Y	Diseased 33 mo post-LT with metastatic HCC (dx 25 mo post-LT)
53M	INF-based	6	TACE, RFA	DCD	1a	7.5 ng/mL 726 000	Y/N	Diseased 34 mo post-LT with recurrent HCC (dx 15 mo post-LT)
54M	Naive	4	TARE	DCD	1a	16.7 ng/mL 87 500	Y/Y	Diseased 29 mo post-LT with metastatic cholangiocarcinoma (dx 2 mo post-LT)
63 W	INF-based	4	TACE	DCD	1a	42.6 g/mL 1 900 000	N/N	Alive 43 mo post-LT with recurrent HCC dx 37 mo post-LT

<sup>a</sup>All Caucasian, none had concomitant HBV.

<sup>b</sup>All HCV therapies were completed before liver transplant with EOTR, defined as undetectable HCV viral load upon completion of DAA unless otherwise specified

<sup>c</sup>Newer DAA regimens: sofosbuvir/ledipasvir, sofosbuvir/simeprevir, paritaprevir/ritonavir/ombitasvir

AFP, alpha-fetoprotein; cm, centimeter; DAA, direct-acting antiviral; DCD, Donation after circulatory death; EOTR, end-of-treatment response; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; INF, interferon; LT, liver transplant; M, man; mo, months; MWA, microwave ablation; pt, patient; RFA, radiofrequency ablation; Rx, therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; VL, viral load; W, woman.



**FIGURE 1.** Inverse Kaplan-Meier curve for hepatocellular carcinoma recurrence post-liver transplant, by pretransplant DAA therapy. DAA-treated patients (solid line), DAA-naive patients (dash line). DAA, direct-acting antivirals; HCC, hepatocellular carcinoma.

and ledipasvir; sofosbuvir and simeprevir; or paritaprevir-ritonavir and ombitasvir and dasabuvir).

With regards to the timing of DAA therapy and the initial HCC development, 62% (62/99) were diagnosed with HCC then started on DAA pretransplant; of these, one-third (32%, 20/62) started DAA therapy before being listed for liver transplant, and two-thirds (68%, 42/62) started DAA during the pretransplant waitlist period. The remaining 38% (27/99) were treated with DAA before the initial diagnosis of HCC; of these, 63% (17/27) had achieved SVR12, 22% (6/27) did not achieve SVR12, and 15% (4/27) underwent liver transplant before completion of DAA therapy. Posttransplant recurrence rates among pretransplant DAA-treated patients were not different ( $P=0.76$ ) between those who received DAA before or after HCC diagnosis.

Liver transplant graft failure (7% versus 3%;  $P=0.21$ ) and death (12% versus 19%;  $P=0.19$ ) were not different among those who received DAA pretransplant and those who did not.

**TABLE 3.****Univariate analysis of factors associated with recurrence of postliver transplant hepatocellular carcinoma (N = 171)**

Variable		Recurrent HCC (n = 15)	No recurrent HCC (n = 156)	P
n (%) / mean (IQR)				
Male		11 (73%)	119 (76%)	0.80
White		82 (82%)	57 (79%)	0.92
Age at transplant, in y		59 (55, 63)	61 (57, 64)	0.88
Concomitant liver disease	NASH	1 (7%)	8 (5%)	0.80
	Alcoholic liver disease	5 (33%)	63 (40%)	0.59
	Hepatitis B	2 (2%)	4 (3%)	0.53
	Other	0 (0%)	12 (8%)	0.40
HIV		0 (0%)	2 (1%)	1.00
HCV genotype	1	10 (67%)	116 (74%)	0.28
	2	2 (13%)	5 (3%)	
	3	3 (20%)	23 (15%)	
	4	0 (0%)	3 (2%)	
	Unknown	0 (0%)	9 (6%)	
Alpha fetal protein (ng/mL)	At transplant listing	20 (11, 138)	13 (6, 35)	0.64
	At liver transplant	41 (16, 125)	10 (5, 23)	0.22
HCV viral load (IU/mL)	At transplant listing	726 000 (0, 2 130 000)	511 000 (0, 2 560 000)	0.69
	At liver transplant	716 000 (0, 1 900 000)	3615 (0, 698 250)	0.23
Biological MELD-Na	At transplant listing	11 (9, 13)	11 (8, 15)	0.91
	At liver transplant	11 (7, 15)	12 (9, 17)	0.73
Exceptions MELD	At transplant listing	22 (22, 22)	22 (22, 22)	0.11
	At liver transplant	25 (22, 28)	28 (25, 28)	0.51
Months on LT waitlist		5 (4, 9)	6 (4, 10)	0.50
Liver donor	Deceased	14 (93%)	152 (97%)	0.37
	Living	1 (7%)	4 (3%)	
Months of follow-up		24 (12, 32)	26 (8, 43)	0.05
Pre-liver transplant HCV treatment				
Any		8 (53%)	129 (83%)	0.01
DAA		5 (33%)	94 (60%)	0.04
Non-DAA		3 (30%)	35 (56%)	0.12
Hepatocellular carcinoma				
Tumor size at listing, in cm, median (IQR)		2.1 (1.7, 2.7)	2.2 (1.4, 2.7)	0.93
Number of lesions at listing, median (IQR)		2 (1, 3)	2 (1, 2)	0.25
Bridging therapy	Any	15 (100%)	146 (94%)	0.31
	TACE	12 (80%)	127 (81%)	0.89
	Ablative therapy	6 (40%)	38 (24%)	0.18
	RFA	4 (27%)	24 (15%)	0.26
	Microwave ablation	2 (13%)	16 (10%)	0.71
	TARE	2 (13%)	8 (5%)	0.20
	SBRT	0 (0%)	1 (1%)	0.76
Liver explant pathology	Viable tumor identified	11 (73%)	124 (79%)	0.58
	Largest tumor, in cm, median (IQR)	2.5 (2.0, 3)	2.5 (1.9, 3.1)	0.85
	Number of lesions, median (IQR)	3 (2, 4)	2 (1, 3)	0.06
	Lymphovascular invasion	11 (73%)	33 (21%)	<0.01
	Inside Milan criteria <sup>a</sup>	9 (60%)	120 (77%)	0.15

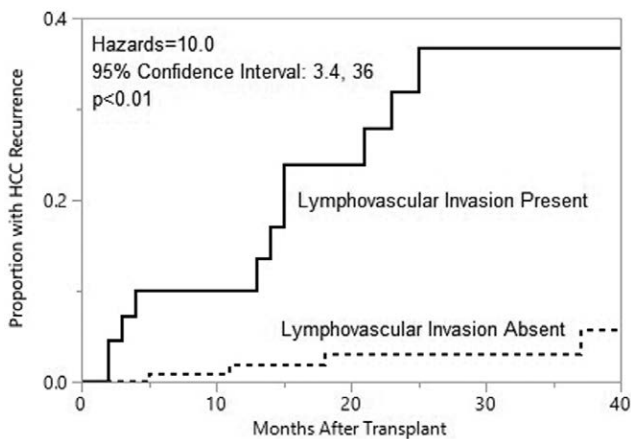
<sup>a</sup>Milan's criteria: 1 lesion <5 cm or up to 3 lesions each <3 cm  
 cm, centimeter; DAA, direct-acting antivirals; HCV, hepatitis C; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

## DISCUSSION

The introduction of second- and third-line DAA therapy for HCV has led to cure rates exceeding 95% with excellent tolerance.<sup>13</sup> Given the relative ease of use and the treatment success rates, the field of transplant hepatology has been tasked with determining how to best use these agents in patients awaiting LT. Three categories of waitlisted patients have to be taken into account when considering the question of when, and in whom, to recommend DAA therapy:

those with decompensated HCV cirrhosis, compensated HCV cirrhosis with HCC, and decompensated HCV cirrhosis with HCC. Although there have been some data to suggest a rational model for end-stage liver disease-sodium thresholds beyond which DAA therapy is not cost-effective for the decompensated cirrhotic patient,<sup>14,15</sup> there is still controversy in regards to the optimal timing of treatment (pre- versus posttransplant) in those with HCV-HCC.<sup>16,17</sup> Factors informing the decision making in HCV-HCC





**FIGURE 2.** Inverse Kaplan-Meier curve for hepatocellular carcinoma recurrence post-liver transplant, by lymphovascular invasion in explanted native liver. Lymphovascular invasion present on explanted liver (solid line), lymphovascular invasion absent on explanted liver (dash line). HCC, hepatocellular carcinoma.

patients include perceived proximity to transplant (waitlist time) and the availability an HCV-positive organ; concerns about attenuated SVR rates in patients with HCV-HCC<sup>7,18</sup> and possible increased rates of HCC recurrence;<sup>3,5,19</sup> and the potential to improve or maintain native liver function for additional locoregional therapies to remain within Milan criteria for transplant.<sup>20</sup>

Prior studies have shown an increased risk for HCC recurrence with increased size/viability of HCC on the liver explant,<sup>21</sup> the presence of lymphovascular invasion,<sup>22,23</sup> and AFP levels.<sup>6,24</sup> In 2016, our group reported in abstract form and later, a communication, that posttransplant HCC recurrence appeared heightened (28%) in a small cohort of DAA-treated transplant patients with HCV-HCC.<sup>3</sup> Additionally, in 2016, Reig et al<sup>5</sup> reported early recurrence of HCC (also 28%) after DAA therapy in patients with prior history of HCC who had complete radiologic response after ablation, resection, or chemoembolization. Other reports from Conti et al in 2016 and Sangiovanni et al in 2020 demonstrated early and aggressive HCC recurrence (28.8% and 32%) after DAA therapy in those with prior resection or local ablation for HCC.<sup>4,6</sup> However, there were some limitations with these studies, including the small sample size, the variability of HCC treatment modalities, and immortal time bias.

Most recently, a multicenter study of 875 HCV-HCC who underwent liver transplant between 2005 and 2015, of which 121 (14%) received pre-LT DAA and 754 (86%) did not, found that pre-LT DAA was not associated with post-LT HCC recurrence (HR=0.44; 95% CI, 0.19-1.00).<sup>25</sup> Similarly, our current study of 171 HCV-HCC patients did not find an increased risk of pre-LT DAA with posttransplant HCC recurrence when the transplant occurred from 2014 to 2017 when the newer DAA approved by the FDA since 2014 were used.<sup>26</sup> In contrast, another recent study from Italy of showed an early peak (median of 7.7 mo) of HCC recurrence in 32% (40/124) of DAA-treated cirrhotic patients from 2015 to 2017 who had undergone curative therapy for HCC.<sup>6</sup>

Our study cohort demonstrated a trend toward a lower risk of HCC recurrence posttransplant HCC with pretransplant DAA therapy as compared to those without (5% versus 14%;  $P=0.07$ ), although this did not reach statistical significance.

Nonetheless, this finding is in congruence with large cohort studies that demonstrated a significantly lower risk of de novo development of HCC in HCV-positive cirrhotic patients who achieve SVR with DAA therapy or interferon, as compared to those who had failed treatment or were treatment naive.<sup>27</sup> The authors postulate that eradication of HCV might reduce the risk of HCC by “abrogating direct carcinogenic effects of the virus,”<sup>27</sup> although any relationships and mechanisms remain to be studied. Moreover, our findings are in line with other recent data from a multicenter North American cohort study from Singal et al<sup>19</sup> (793 patients; 304 DAA-treated and 489 untreated) that demonstrated no association between DAA and HCC recurrence (HR, 0.90; 95% CI, 0.70-1.16) after resection, local ablation, transarterial chemo- or radioembolization, or radiation therapy. In comparison, our study is novel in the respect that it studies HCV-HCC patients who underwent LT as a curative therapy for HCC.

Limitations of this study include its retrospective nature, which renders the results susceptible to residual confounding and type II error. However, conventional risk factors of lymphovascular invasion and tumors beyond Milan criteria had increased risk of HCC recurrence in our study cohort, which provides internal validation. Moreover, this study’s sample size limits the generalizability of the results; sample size calculations require at least 160 patients in each arm to perform an adequate evaluation (parameters: 80% power, 0.05 probability of type I error, and 20% HCC recurrence posttransplant<sup>27</sup>). Nonetheless, the patients in this study have a follow-up timeframe expected to capture the vast majority of recurrence HCC.<sup>3,27</sup>

In conclusion, this multicenter study of HCV-HCC liver transplant recipients did not find an association between pretransplant DAA therapy, including the new wave of DAA therapy approved by the FDA after 2014, and posttransplant HCC recurrence.

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