Direct-Acting Antivirals and Hepatocellular Carcinoma: No Evidence of Higher Wait-List Progression or Posttransplant Recurrence

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The association between direct-acting antivirals (DAAs) and hepatocellular carcinoma (HCC) wait-list progression or its recurrence following liver transplantation (LT) remains uncertain. We evaluated the impact of DAAs on HCC wait-list progression and post-LT recurrence. This Latin American multicenter retrospective cohort study included HCC patients listed for LT between 2012 and 2018. Patients were grouped according to etiology of liver disease: hepatitis C virus (HCV) negative, HCV+ never treated with DAAs, and HCV+ treated with DAAs either before or after transplantation. Multivariate competing risks models were conducted for both HCC wait-list progression adjusted by a propensity score matching (pre-LT DAA effect) and for post-LT HCC recurrence (pre- or post-LT DAA effect). From 994 included patients, 50.6% were HCV–, 32.9% were HCV+ never treated with DAAs, and 16.5% were HCV+ treated with DAAs either before (n = 66) or after LT (n = 98). Patients treated with DAAs before LT presented similar cumulative incidence of wait-list tumor progression when compared with those patients who were HCV+ without DAAs (26.2% versus 26.9%; $P = 0.47$) and a similar HCC-related dropout rate (12.1% [95% CI, 0.4%-8.1%] versus 12.9% [95% CI, 3.8%-27.2%]), adjusted for baseline tumor burden, alpha-fetoprotein values, HCC diagnosis after listing, bridging therapies, and by the probability of having received or not received DAAs through propensity score matching (subhazard ratio [SHR], 0.9; 95% CI, 0.6-1.6; $P = 0.95$). A lower incidence of posttransplant HCC recurrence among HCV+ patients who were treated with pre- or post-LT DAAs was observed (SHR, 0.7%; 95% CI, 0.2%-4.0%). However, this effect was confounded by the time to DAA initiation after LT. In conclusion, in this multicenter cohort, HCV treatment with DAAs did not appear to be associated with an increased wait-list tumor progression and HCC recurrence after LT.

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Hepatitis C virus (HCV)–induced cirrhosis and HCV-associated hepatocellular carcinoma (HCC) continue to be one of the leading indications for liver transplantation (LT) worldwide.[1] With the advent of direct-acting antivirals (DAAs) for HCV treatment, viral eradication has achieved extremely encouraging results even in patients with decompensated cirrhosis. The introduction of DAAs in Latin America was later than in Europe, Asia, and North America, but it achieved similar successful results in terms of viral eradication in real-life studies.[2-4]

Alarming figures of increased incidence of de novo HCC after viral eradication with DAAs were initially reported[5,6] and were later refuted by prospective studies.[7-10] Other authors described a higher incidence of tumor recurrence after curative therapies for HCC, particularly with more aggressive tumor patterns,[6,11] whereas other groups reported no association.[12-17] Consequently, whether rapid viral eradication with DAAs leads to an abrupt withdrawal of antineoplastic immunological surveillance is still under discussion.[18]

In this scenario, further clinical uncertainty has been established in patients listed for LT with HCC. The association between DAAs and tumor progression during the wait-list period or alternatively, HCC recurrence after transplantation, is currently controversial.[19] Two previous single-center retrospective cohort studies showed contrasting results.[20,21] Therefore, we sought to evaluate the association of treatment with DAAs and both wait-list HCC progression and post-LT recurrence in a large multicenter Latin American cohort.

Abbreviations: AFP, alpha-fetoprotein; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CRF, case report form; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MC, Milan criteria; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; PEG-IFN, peginterferon; PSC, primary sclerosing cholangitis; RECIST, Response Evaluation Criteria in Solid Tumors; R-HCC, hepatocellular carcinoma recurrence after LT; SD, standard deviation; SHR, subhazard ratio; SSC, secondary sclerosing cholangitis; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; SVR, sustained virological response.

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Patients and Methods

STUDY DESIGN, SETTING, PARTICIPATING CENTERS, AND ELIGIBILITY CRITERIA

This multicenter cohort study was conducted between 2012 and 2018 in 20 different LT centers from Latin America. Study data were registered into a Web-based electronic case report form (CRF) and included in an open public registry (www.clinicaltrials.gov, number NCT03775863), following STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[22] and complying with ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

Criteria for inclusion required (1) adult patients listed for LT because of HCC[23,24] or listed because of decompensated cirrhosis who developed HCC during the wait-list period and (2) treatment with DAAs following an HCC diagnosis in patients with HCV. Patients were excluded (1) if they were not listed for any reason or they were not candidates for LT because of tumor extension (extrahepatic or macrovascular tumor invasion at transplant evaluation) or (2) if HCC was discovered incidentally at explant pathology analysis.

Included patients were grouped according to main etiology of liver disease: HCV–, HCV+ never treated with DAAs, and HCV+ treated with DAAs either before or after transplantation. Cofactors or coetiologies were also registered. HCV– patients were included as a control group. The timing and scheme of the DAA regimen used were based on physician's criteria according to available regimens in each country following international guidelines.[25] We assessed

sustained virological response (SVR), defined as an undetectable HCV RNA (HCV viral load <15 IU/mL) at 12 weeks after completion of therapy.

OTHER EXPOSURE VARIABLES

Systematic recording of exposure variables on the CRF included patient demographics, liver function, HCV genotypes/subgenotypes, prior HCV treatments, and tumor characteristics at listing or at diagnosis if HCC developed after listing. Pretransplant tumor burden was categorized according to Milan criteria (MC)[26] and the alpha-fetoprotein (AFP) model.[27] Standard patient selection in all centers was limited to MC. Patients exceeding MC were also included according to each country's allocation policy. In addition, all locoregional or bridging HCC treatments during the wait-list period were recorded.

Explant pathology findings included the number of nodules, diameter of each nodule (cm), presence of microvascular invasion, degree of tumor differentiation according to Edmonson-Steiner grading system (dedifferentiated tumors considered when a nuclear grade >2 was observed in the specimen),[28] and the Up-to-7 tumor burden.[29]

STUDY ENDPOINTS

The primary event was HCC tumor progression during the wait-list period. For this analysis, HCV+ groups with or without DAAs before LT were compared with the HCV− cohort as the control group. Tumor progression was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1,[23,24] systematized through an automated calculator at each center and blindly confirmed comparing baseline (pre-DAA) and each imaging reassessment during the whole wait-list follow-up period with a minimum interval of once every 3 months. In patients receiving locoregional treatments, image re-evaluation was done 4-6 weeks after each procedure.[23,24] The study protocol considered RECIST 1.1 instead of modified RECIST[30] to avoid heterogeneous evaluation of hypervascular enhancement across centers. The type of tumor progression was further classified.[31]

Secondary endpoints were HCC-related dropout rates, post-LT HCC recurrence, and overall survival. For HCC recurrence, patients who underwent LT were grouped into HCV+ with DAAs (either before or after LT), HCV+ without DAAs, and HCV− cohorts. For the HCC recurrence analysis, we grouped all the patients treated with DAAs either before or after LT to evaluate the effect of this treatment on the natural history of HCC. Post-LT recurrence was determined by imaging criteria plus serum AFP or biopsy, as recommended by international consensus guidelines.[32] All patients were followed until death, dropout, or delisting from the waiting list or last pre- or post-LT outpatient visit.

STATISTICAL ANALYSIS

To avoid selection bias due to potential failure events and to evaluate the relationship of covariates to cause-specific failures, competing risks regression models were performed, with subhazard ratios (SHRs) and 95% confidence intervals (CIs) calculated using the Fine and Gray method.[33] For the outcome of wait-list tumor progression, non-HCC–related deaths while on the waiting list, non-HCC dropout, and transplantation were considered competing events, and a comparison was made between the HCV−, HCV+ without pre-LT DAAs, and HCV+ with pre-LT DAAs cohorts. Alternatively, competing events for post-LT HCC recurrence outcomes were non-HCC–related deaths after transplantations and a comparison was made between finally transplanted patients within each cohort, including HCV+ patients with pre- or post-LT DAAs.

Because pre-LT DAA treatment (the exposure of interest) was an intervention not randomly assigned, we used propensity score matching among HCV+ participants to adjust for group differences and reduce DAA indication bias. Therefore, we estimated the probability of being treated with DAAs in HCV+ patients from a multivariate logistic regression model with odds ratios (ORs) and 95% CIs. Calibration (Hosmer-Lemeshow test) and discrimination power (area under the receiver operating characteristic curve [AUROC]) were evaluated. Variables included in the propensity score matching were those we considered might be associated with the decision to treat or not treat with DAAs prior to LT:

1. Liver disease variables.
2. Tumor variables.
3. Confounding variables such as country and date of LT evaluation prior or after 2015, which was the date of full introduction of DAAs in Latin America.

We assessed the common support range and identified the optimal number of blocks from the propensity score and then evaluated the balancing property on each block. Data were analyzed with STATA, version 13.0 (StataCorp, College Station, TX).

Results

Overall, 994 patients listed for LT were included in this study, of whom 88.2% were listed because of HCC and 11.8% were listed because of decompensated cirrhosis and developed HCC in a median time from LT evaluation of 10.8 months (interquartile range [IQR], 3.5-10.8 months; Table 1). Median wait-list time was 6.1 months (2.4-10.4 months) for the entire cohort, though it was longer for those patients with HCC diagnosed after listing than those listed due to HCC (14.8 months [7.6-28.5 months] versus 6.7 months [2.9-11.9 months]). According to the etiology of liver disease, 50.6% were HCV– (n = 503), 32.9% were HCV+ never treated with DAAs (n = 327), and 16.5% (n = 164) were HCV+ treated with DAAs either before (n = 66) or after transplantation (n = 98; Fig. 1; Supporting Table 1).

Overall, 81.9% (n = 814) of the entire cohort were within MC, which included 81.3% of patients listed due to HCC and 86.3% of those with HCC diagnosed after listing. Bridging therapies were performed in 54.8% of the cohort (n = 545; Table 2). This group of patients had a longer median time on the waiting list than those without locoregional treatment (9.8 months [IQR, 5.7-16.8 months] versus 3.9 months [1.4-8.6 months]; $P < 0.01$). Median time from last imaging reassessment to LT in the overall cohort was 2.2 months (IQR, 1.0-4.1 months), and it was similar between patients receiving or not receiving bridging therapies (2.1 months [IQR, 0.9-3.8 months] versus 2.4 months [1.1-4.3 months]; $P = 0.09$).

Among patients treated with DAAs either before or after LT (n = 164), 43.1% had HCV genotype 1b, followed by genotype 1a (26.6%), genotype 3 (23.7%), genotype 2 (5.9%), and genotype 4 (0.7%). Patients with genotype 3 were more frequently treated after LT. The most commonly used DAA regimen was sofosbuvir/daclatasvir in 68.3% (n = 112), followed by paritaprevir/ritonavir/ombitasvir/dasabuvir in 12.2% of the patients (n = 20) and sofosbuvir/ledipasvir in 6.7% (n = 11). The overall SVR rate was 89.8% (95% CI, 81.0%-97.1%), which was not statistically different between patients treated before (90.6%; 95% CI, 83.9%-94.1%) or after transplantation (89.2%; 95% CI, 80.4%-94.9%). Most of the patients received a 12-week regimen duration with an overall ribavirin use of 34.8% (n = 57).

TABLE 1. Patients' Baseline Characteristics

Variable	Values (n = 994)
Age, years	59 ± 8
Sex, male	737 (74.1)
Diabetes mellitus	274 (27.6)
Time on waiting list, months	6.1 (2.4-10.4)
Cirrhosis	986 (99.2)
Child-Pugh score	
A	521 (52.4)
B	370 (37.2)
C	103 (10.4)
HCC diagnosis after listing	117 (11.8)
Etiology of liver disease	
Viral (HCV or HBV)	546 (54.9)
Alcohol	169 (17.0)
Cholestatic (PBC, SSC, and PSC)	20 (2.0)
NAFLD	115 (11.6)
Cryptogenic	96 (10.0)
Others (autoimmune, hemochromatosis, and miscellaneous)	39 (3.9)
HCV	491 (49.4)
Prior PEG-IFN–based treatment	177 (36.0)
Prior boceprevir/telaprevir–based treatment	12 (2.4)
HCV and chronic alcohol consumption	75 (7.5)
HBV	58 (5.8)
HCV-HBV coinfection	7 (0.7)
HIV	1 (0.1)
Within MC at listing	814 (81.9)
AFP model at listing	
≤2 points	830 (84.1)
>2 points	157 (15.9)
AFP	
Median (IQR), ng/mL	10.9 (4.5-58.7)
≤100 ng/mL	788 (79.8)
101-1000 ng/mL	157 (15.9)
>1000 ng/mL	42 (4.3)
Received exception MELD points	799 (80.4)

NOTE: Data are given as n (%), median (IQR), and median ± SD.

DAAS AND TUMOR PROGRESSION WHILE ON THE WAITING LIST

Cumulative incidence of HCC progression according to RECIST was 24.2% (95% CI, 21.2%-26.9%;

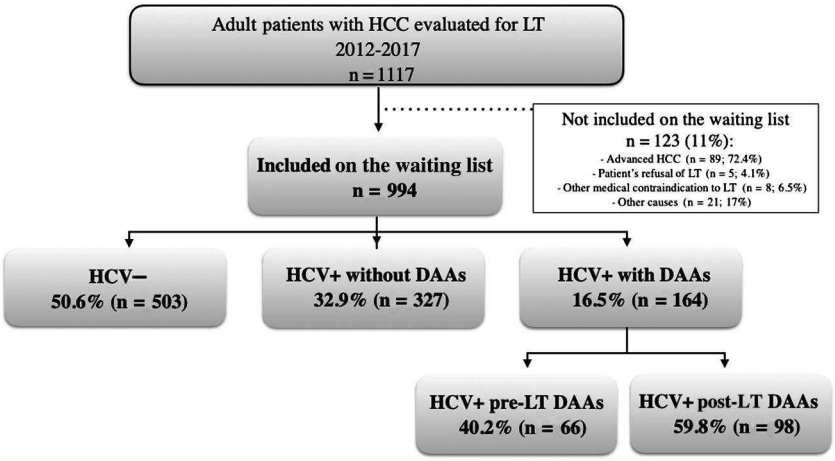

FIG. 1. Overall study cohort flowchart. Included patients were from Argentina, 37.9% (n = 377); Brazil, 33.9% (n = 337); Colombia, 9.9% (n = 98); Mexico, 6.5% (n = 65); Chile, 4.7% (n = 47); Uruguay, 3.2% (n = 32); Peru, 2.5% (n = 25); and Ecuador, 1.3% (n = 13).

n = 222). The type of tumor progression was extrahepatic in 6.3% (n = 14), vascular invasion in 8.6% (n = 19), infiltrative intrahepatic in 16.7% (n = 37), multinodular intrahepatic in 61.3% (n = 136), and uninodular intrahepatic growth in 7.2% (n = 16). Dropout rates due to HCC at 1 and 2 years of listing were 7.1% (95% CI, 5.3%-9.2%) and 20.2% (95% CI, 15.2%-25.9%), respectively.

While on the waiting list, 13.4% (n = 66) of HCV+ patients received DAA treatment and 86.6% (n = 425) did not. Median time on the waiting list was longer in patients with pre-LT DAAs (Table 2). Baseline differences between HCV+ groups are shown in Table 2. Median time from pre-LT DAA initiation to last imaging evaluation following DAAs was 3.9 months (IQR, 1.0-10.1 months). There was no statistically significant difference between groups regarding median time since last imaging evaluation to LT: 2.1 months (95% CI, 0.9-3.9 months) in HCV+ without DAAs and 2.1 months (95% CI, 1.4-2.9 months) in the pre-LT DAA group.

Although the HCV+ group without DAA treatment showed a higher incidence of tumor wait-list progression when comparing the 3 cohorts (Fig. 2A), this effect was not statistically significant after adjusting for confounding variables (Table 3). Patients treated with DAAs before LT presented similar cumulative incidence of tumor wait-list progression (26.2%; 95% CI, 15.8%-39.1%) when compared with the HCV+/DAA– group (26.9%; 95% CI, 22.5%-31.6%; $P = 0.47$) and a similar HCC-related dropout rate: 12.1% (95% CI, 0.4%-8.1%) versus 12.9% (95% CI, 3.8%-27.2%), respectively. A nonsignificant numerically higher proportion of patients with pre-LT DAAs presented extrahepatic progression or vascular invasion when compared with those without DAAs [4/66 (6.1%) versus 17/425 (4%); $P = 0.12$].

SHRs showed that DAAs were not associated with a higher incidence of wait-list tumor progression when compared with HCV- patients (SHR 1.1 (CI 0.7-1.8; $P = 0.63$) Table 3) and when compared with the HCV+ without DAA group adjusted for baseline tumor burden, AFP values, and bridging therapies (SHR, 0.7; 95% CI, 0.4-1.1; $P = 0.17$).

We then analyzed the effect of pre-LT DAAs on wait-list tumor progression adjusted for the propensity score matching to balance the probability of receiving pre-LT DAAs among HCV+ patients. The following variables were included: male sex, year of listing after 2015, Child-Pugh score (reference Child-Pugh A), HCC diagnosis after listing, tumor burden, bridging therapy, and country of origin (Supporting Table 2). This multivariate model showed an AUROC of 0.86 (95% CI, 0.82-0.89; Supporting Fig. 1). The mean propensity score and each of the included variables were balanced in each block from the final propensity score (Supporting Fig. 2).

Treatment with DAAs was not associated with HCC progression adjusted for the propensity score matching (SHR, 0.9; 95% CI, 0.6-1.6; $P = 0.95$; Fig. 2B). In a sensitivity analysis excluding patients in

TABLE 2. Comparative Analysis of HCV+ Patients With or Without Pre-LT Treatment With DAAs

Variable	HCV+ Without DAAs (n = 425)	HCV+ With DAAs (n = 66)	*P* Value
Age, years	57 ± 7	58 ± 7	0.79
Sex, male	298 (70.1)	53 (80.3)	0.11
Diabetes mellitus	77 (18.1)	7 (10.6)	0.16
Waiting list time, months	6.8 (3.3-11.5)	8.9 (5.9-18.8)	<0.01
Prior PEG-IFN–based therapy	162 (38.1)	15 (22.7)	0.01
Chronic alcohol consumption	64 (15.1)	11 (16.7)	0.91
HCV-HBV coinfection	6 (1.4)	0	0.33
Child-Pugh score			0.29
A	247 (58)	33 (50)	
B	138 (32)	28 (42)	
C	40 (10)	5 (8)	
HCC diagnosis after listing	35 (8.2)	19 (28.8)	<0.01
AFP			
Median (IQR), ng/mL	24.4 (6.5-135.6)	14.3 (5.9-36.3)	
≤100 ng/mL	304 (72.9)	54 (83.1)	0.04
101-1000 ng/mL	91 (21.5)	10 (15.4)	0.13
>1000 ng/mL	28 (6.6)	1 (1.5)	
Mean HCC nodules	1.5 ± 1.0	1.4 ± 0.7	0.16
1-3 HCC nodules	408 (96.0)	64 (97.0)	0.69
≥4 HCC nodules	17 (4.0)	2 (3.0)	
Major nodule diameter, mm	31 ± 13	31 ± 12	
≤30 mm	247 (58.1)	42 (63.6)	0.84
31-60 mm	166 (39.1)	23 (34.8)	0.69
>60 mm	12 (2.8)	1 (1.5)	
Within MC*	341 (80.2)	56 (84.8)	0.50
HCC bridging therapy	234 (55.1)	48 (72.7)	<0.01

NOTE: Data are given as n (%), median (IQR), and mean ± SD.
*Data at listing or at diagnosis for patients in whom HCC was diagnosed before or after listing, respectively.

whom HCC was diagnosed after listing, the pre-LT DAA group was not associated with a higher cumulative incidence of HCC progression (SHR, 0.8; 95% CI, 0.5-1.5; $P = 0.57$; Fig. 2C; Supporting Fig. 3).

HCC RECURRENCE AND SURVIVAL AFTER TRANSPLANTATION

At the end of study follow-up, 65% of the cohort underwent LT (n = 650). Transplantation rates were 68.6% for the HCV– cohort (n = 345/503), 62.8% for HCV+ patients not treated with DAAs (n = 267/425), and 57.6% for the HCV+ cohort treated with DAAs before LT (n = 38/66; $P = 0.07$; Table 4). Overall cumulative incidence of HCC recurrence was 6.3% (95% CI, 1.5%-19.9%) with a median time to recurrence of 13.4 months (IQR, 6.1-21.9 months; Fig. 3A).

None of the patients treated with DAAs before LT presented HCC recurrence, and there was only 1 recurrence among patients who received DAAs after LT (n = 98). When considering the effect of DAAs on post-LT HCC recurrence, we observed that median time from LT to DAA initiation was 21.8 months (IQR, 7-34.5 months), which was longer than that observed for median time to recurrence. Thus, although a lower incidence of post-LT HCC recurrence was observed in the DAA group (0.7%; 95% CI, 0.2%-4.0%) when compared with the HCV+ without DAA group (11.2%; 95% CI, 6.9%-17.0%; Fig. 3B), this effect was confounded by a higher incidence of recurrence in the non-DAA group before the introduction of DAA treatment (Fig. 3A,B).

Overall median survival since listing was 22.7 months (IQR, 9.9-43.1 months), which was significantly higher among HCV+ patients treated with DAAs (32.3 months; 16.3-54.6 months) when compared with those untreated (15.2 months; 7.3-34.1 months) and with HCV– patients (24.4 months; 10.5-45.9 months). However, the effect of DAAs upon posttransplant survival showed a confounding effect considering time to DAA initiation as a covariate factor.

Discussion

This study is the first multicenter study from Latin America in which there is a detailed evaluation of the impact of DAAs on the natural history of HCC during the wait-list and posttransplant periods and the first study to include an HCV– cohort as a control group.[20,21,33] In this study, we divided the analysis in order to show the (1) association between DAAs and tumor progression while on the waiting list (including those HCV+ patients treated or not treated before LT), and then (2) the association between DAAs and tumor recurrence after LT, including all treated patients either before or after LT. Similar cumulative incidences of wait-list HCC progression among patients with or without DAAs before LT

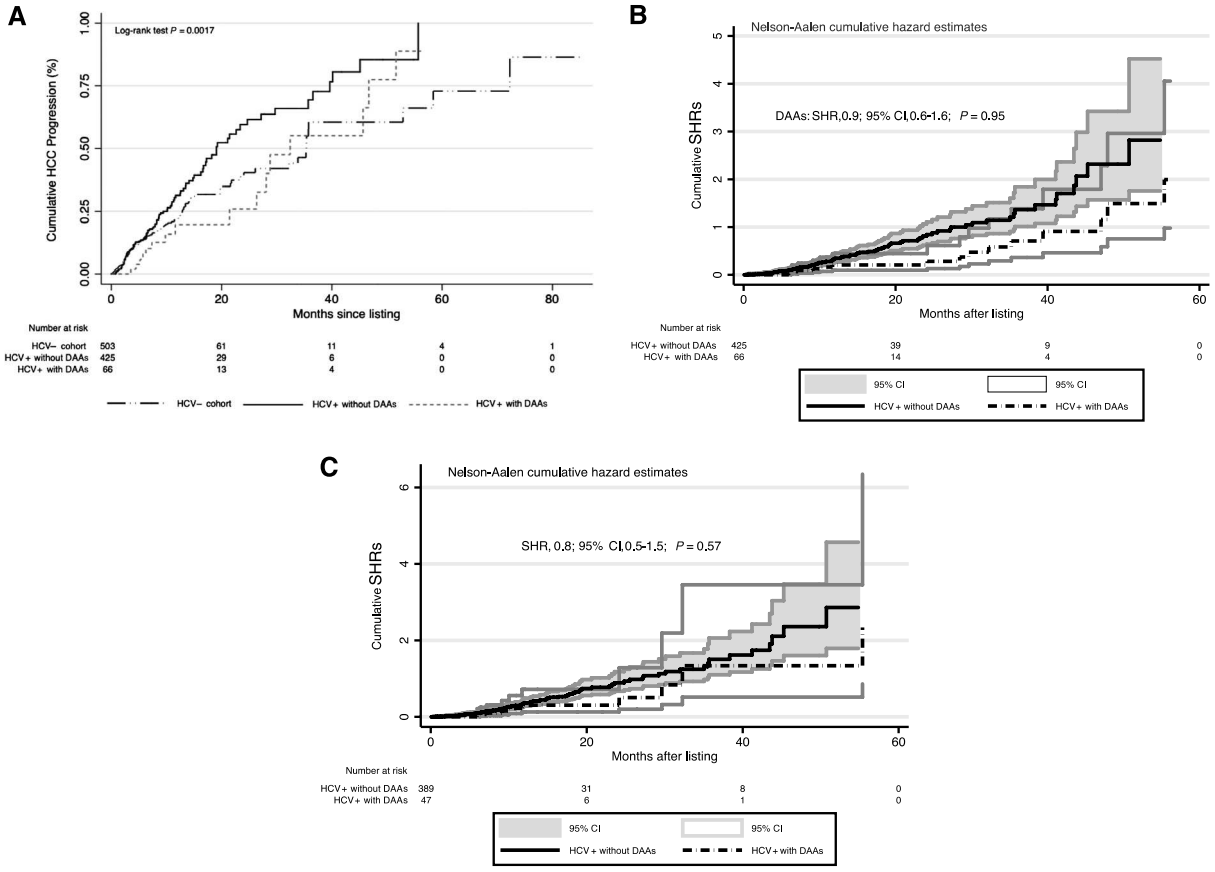

FIG. 2. (A) Cumulative tumor progression while on the waiting list comparing the 3 cohorts including patients with or without DAAs before LT and the HCV− cohort as reference. Note that the *P* value for the comparison describes the null hypothesis comparing the 3 cohorts (log-rank test hypothesis). (B) Cumulative SHRs of tumor progression between HCV+ patients treated and not treated with DAAs before LT. (C) Cumulative SHRs of tumor progression between HCV+ patients treated and not treated with DAAs before LT in those listed for LT due to HCC.

were observed, adjusted for tumor extension, bridging treatments, and the probability of having received DAAs through a propensity score matching analysis. Although a lower incidence of post-LT recurrence was associated with the use of DAAs, this effect was confounded by the time to DAA initiation after LT.

The effect of DAAs on tumor progression while on the waiting list has been studied recently.[25] Tumor progression beyond MC has been reported to be 4%-6% at 6 months and close to 20% at 12 months.[34,35] Three single-center retrospective cohort studies addressed the effect of DAAs and HCC wait-list progression and recurrence following transplantation.[20,21,36] Opposing results were previously reported. A nonsignificant higher rate of wait-list tumor progression and post-LT recurrence in patients treated with DAAs before transplantation was observed in an Italian study,[20] whereas a reduced risk of wait-list tumor progression was observed in a cohort from the University of California, San Francisco.[21]

Zanetto et al. reported in a small cohort (n = 46) that tumor progression according to RECIST was not significantly different between HCV+ DAA-treated and DAA-untreated groups (35% versus 17%, respectively), without differences regarding HCC dropout rates (13% versus 13%, respectively) and HCC recurrence after LT (12.5% versus 8.3%, respectively).[20] We performed a similar competing risks regression analysis to that published by the group from the University of California, San Francisco,[21] which included 62 patients who received DAAs before LT. In that study, the authors observed a lower dropout rate due to HCC tumor progression and a lower transplantation rate in patients with DAAs. We described similar

TABLE 3. Competing Risks Regression Analysis of Probability of HCC Progression While on the Waiting List in the Overall Cohort

Variable	Progression rate, % (95% CI)	Unadjusted SHR (95% CI)	Univariate *P* Value	Adjusted SHR (95% CI)	Mutivariable *P* Value
Age	—	1.0 (0.9-1.03)	0.18		
Sex					
Male	22.5 (19.4-25.9)	0.7 (0.6-0.9)	0.03	0.7 (0.5-0.9)	0.02
Female	29.0 (23.3-35.2)				
Diabetes mellitus					
Yes	23.1 (18.1-28.7)	1.0 (0.8-1.4)	0.76		
No	24.7 (21.4-28.1)				
Child-Pugh score					
A	25.5 (21.7-29.5)	—	—		
B	23.4 (19.0-28.2)	1.0 (0.7-1.3)	0.78		
C	20.4 (12.6-30.4)	0.8 (0.5-1.2)	0.29		
Cohorts					
HCV–	21.8 (18.1-25.8)	—	—	—	—
HCV+/DAA–	26.9 (22.5-31.6)	1.3 (1.0-1.8)	0.02	1.1 (0.9-1.5)	0.31
HCV+/DAA+	26.2 (15.8-39.1)	1.2 (0.7-1.8)	0.49	1.1 (0.7-1.8)	0.63
Time since DAA therapy		1.0 (0.9-1.04)	0.34		
Prior PEG-INF–based therapy					
Yes	41.0 (32.0-50.4)	1.28 (0.9-1.8)	0.17		
No	32.7 (26.5-39.4)				
Time on the waiting list		1.0 (0.9-1.01)	0.59		
HCC diagnosis after listing					
Yes	20.0 (12.8-28.9)	0.4 (0.3-0.7)	<0.01	0.5 (0.3-0.7)	<0.01
No	24.7 (21.8-27.9)				
MC					
Within	20.9 (18.1-24.0)				
Beyond	39.5 (31.9-47.5)	1.9 (1.4-2.5)	<0.01	1.6 (1.2-2.2)	<0.01
Median AFP					
≤100 ng/mL	21.5 (18.5-24.8)	—	—	—	—
101-1000 ng/mL	35.9 (28.0-44.5)	1.8 (1.3-2.4)	<0.01	1.3 (0.9-1.8)	0.08
>1000 ng/mL	39.5 (24.0-56.6)	2.2 (1.2-3.8)	<0.01	1.5 (1.1-3.1)	0.01
HCC bridging therapy					
Yes	29.7 (25.8-33.9)	1.7 (1.2-2.2)	<0.01	1.5 (1.1-2.0)	<0.01
No	17.0 (13.5-21.1)				
SVR at 12 weeks while on the waiting list					
Yes	31.1 (18.2-46.6)	0.8 (0.2-2.4)	0.67		
No	40.0 (5.3-85.3)				

NOTE: For this competing risks regression analysis, 77 patients without any imaging re-evaluation after listing were excluded.

findings in our cohort. First, tumor burden was similar between the DAA and non-DAA groups in those patients either listed due to HCC or for those in whom HCC was diagnosed after listed. Pre-LT treatment with DAAs was not associated with a higher incidence of HCC wait-list progression adjusted for tumor burden, AFP values, bridging therapies, and propensity score matching.

Finally, we found that treatment with DAAs did not increase the risk of post-LT HCC recurrence. Although other retrospective studies have addressed the association between DAAs in pre- and post-LT settings and HCC recurrence after transplantation,[12] a cautious analysis should be done considering DAA initiation as a time-dependent covariate. However, we did not observe a higher HCC recurrence, even in

TABLE 4. Comparative Analysis Between HCV+ Cohorts Finally Transplanted

Variable	HCV+ Without DAAs (n = 169)	HCV+ With DAAs (n = 136)*	*P* Value
Age, years	58 ± 7	56 ± 7	<0.01
Sex, male	122 (72.2)	107 (78.7)	0.23
Diabetes mellitus	34 (20.1)	25 (18.4)	0.77
HCC diagnosis after listing	10 (5.9)	22 (16.2)	<0.01
Child-Pugh score			0.69
A	101 (60)	75 (55)	
B	51 (30)	47 (35)	
C	17 (10)	14 (10)	
Within MC	152 (89.9)	125 (91.9)	0.69
AFP			
Median (IQR)	24.8 (6.8-107.3)	14.2 (5.7-47.2)	
≤100 ng/mL	125 (74.4)	113 (83.1)	0.07
101-1000 ng/mL	37 (22.0)	20 (14.7)	0.19
>1000 ng/mL	6 (3.6)	3 (2.2)	
HCC treatment while on the waiting list, n (%)	82 (48.5)	73 (53.7)	0.42
HCC at last evaluation			
Within MC, n (%)	129 (76.3)	109 (80.1)	0.49
AFP			
Median (IQR)	16.8 (6.0-89.4)	10.9 (5.4-24.3)	
≤100 ng/mL	128 (76.6)	119 (87.5)	0.01
101-1000 ng/mL	31 (18.6)	15 (11.0)	0.04
>1000 ng/mL	8 (4.8)	2 (1.5)	
Explant pathology findings			
Microvascular invasion	45 (28.5)	29 (24.2)	0.49
Dedifferentiated tumors	55 (41.0)	39 (39.0)	0.79
Within Up-to-7 criteria	158 (93.5)	128 (94.1)	1.0

NOTE: Data are given as n (%), median (IQR), and mean ± SD.
*HCV+ transplanted patients (n = 136) who received DAA treatment before LT (n = 38) and after LT (n = 98).

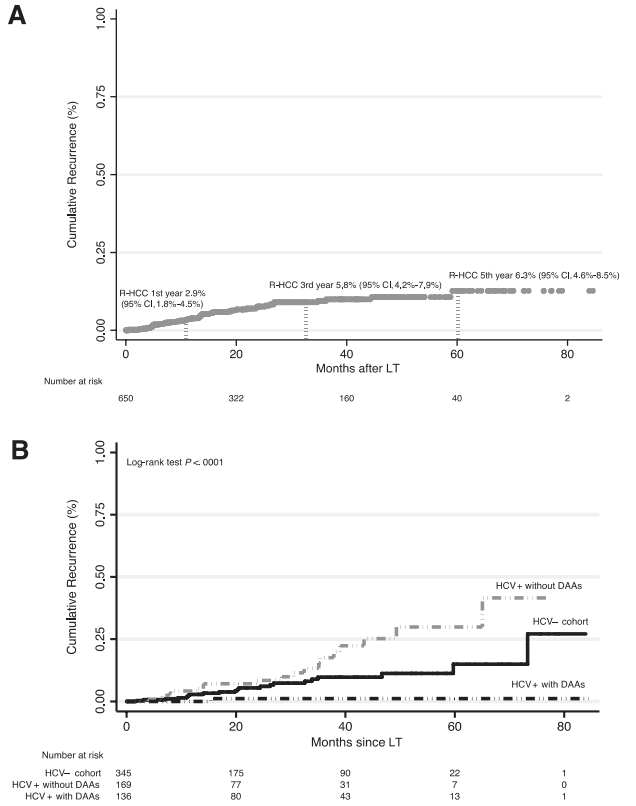

FIG. 3. Overall cumulative recurrence of HCC after LT (A) among the entire cohort and (B) between HCV+ patients treated with DAAs (either before or after LT), HCV+ never treated with DAAs, and the HCV– cohort.

patients treated with DAAs during the pre-LT setting. Similar findings were observed, including a landmark or time-varying exposure analysis in another retrospective cohort study.[37]

This study has limitations worthy of mention that are common in observational cohort studies. Although the main common selection criteria across countries were the MC, there might be heterogeneous selection criteria in patients beyond MC. In this regard, we adjusted for this confounding factor in both the propensity score matching and in the competing risks regression analysis. There was not a central revision of all images because this would have been unfeasible. Anticipating this potential bias, a common automatized RECIST 1.1 calculator was submitted to all centers and centrally re-evaluated. A time bias and the availability of DAAs in each country might have biased the results. Thus, this time-covariate variable was included in propensity score matching. Finally, a power limitation might have explained the nonstatistical association between DAAs and wait-list HCC progression in our cohort. As previously reported by Zanetto et al., HCC progression was 37% and 17% in the DAA and non-DAA groups, respectively.[20] Considering the published data of Zanetto et al. regarding HCC progression, a minimum sample size of 112 patients per group would have been included in order to reject the null hypothesis and to have a sample size calculation comparing cumulative incidence and hazard ratio (HR) curves with a desired power of 90%.

In conclusion, we observed that treatment with DAA did not appear to be associated with an increased cumulative incidence of HCC progression while on the waiting list. Moreover, we found that DAA treatment after LT might not increase the risk of HCC recurrence either. Whether this or prior observational studies support sufficient evidence or further demands an appropriate sample size is a question of time. However, we believe our results and those previously published[20,21] support the use of DAA therapy in patients with HCC either during the wait-list or posttransplant periods. The optimal time for treatment should be individualized on a case-by-case basis.

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