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Direct-acting Antivirals Do Not Increase the Risk of Hepatocellular Carcinoma Recurrence after Local-Regional Therapy or Liver Transplant Waitlist Dropout

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Abstract

Whether direct-acting antivirals (DAA) increase the risk of hepatocellular carcinoma (HCC) recurrence after tumor-directed therapy is controversial. We sought to determine the impact of DAA therapy on HCC recurrence after local-regional therapy (LRT) and waitlist dropout among liver transplant (LT) candidates with HCC. We performed a retrospective cohort study of 149 LT candidates with HCV and HCC at a single center from 2014–2016. Cumulative incidence of HCC recurrence post-LRT and waitlist dropout was estimated by DAA group. Factors associated with each outcome were evaluated using competing risks regression. A propensity score stabilized inverse probability weighting approach was used to account for differences in baseline characteristics between groups. The no DAA group (n=87) had more severe cirrhosis and lower rates of complete radiologic tumor response after LRT than those treated with DAA (n=62), but had similar alpha-fetoprotein and tumor burden at listing. Cumulative incidence of HCC recurrence within 1-year of complete response after LRT was 47.0% in the DAA group and 49.8% in the no DAA group (p=0.93). In adjusted competing risk analysis using weighted propensity score modeling, risk of HCC recurrence was similar in the DAA group compared to those without DAA (HR 0.91, 95% CI 0.58–1.42, p=0.67). Patients treated with DAA had lower risk of waitlist dropout due to tumor progression or death compared to the no DAA group in adjusted weighted analysis (HR 0.30, 95% CI 0.13–0.69, p=0.005). **Conclusions**. In LT candidates with HCV and HCC with initial complete response to LRT, DAA use is not associated with increased risk of HCC recurrence, but rather is associated with reduced risk of waitlist dropout due to tumor progression or death.

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All authors provided final approval of the manuscript. Drs. Terrault, Mehta and Yao contributed to the conception of the work, the acquisition and interpretation of the data for the work, provided critical revisions to subsequent versions of the manuscript and approved the final submitted version. Dr. Huang contributed to the acquisition and interpretation of the data for the work, drafted the first version of manuscript, and approved the final submitted version. Ms. Dodge conducted the primary data analysis, contributed to the interpretation of the data, provided critical revisions to draft versions of the manuscript and approved the final version.

Keywords

HCV antiviral therapy; liver cancer; recurrence; mortality

INTRODUCTION

Direct-acting antivirals (DAA) have revolutionized the treatment of chronic hepatitis C (HCV), especially among patients with advanced disease. Safe and highly effective DAA therapies for patients with both compensated and decompensated cirrhosis allow patients previously ineligible for antiviral therapy to now be treated successfully. Benefits of achieving sustained virologic response (SVR) among patients with advanced liver disease include reversal of symptoms of decompensation (1), improvement in Model for End-Stage Liver Disease (MELD) and Child-Pugh (CP) scores (1–3), and reduced liver-related and all-cause mortality (4–7). In addition, HCV eradication with interferon (IFN)-based and DAA-based regimens have been associated with reduced rates of de novo hepatocellular carcinoma (HCC) (4,7–11). However, for patients with HCV and HCC, the benefits of DAA therapy have been challenged by recent studies suggesting an increased risk of HCC recurrence after tumor-directed therapy (12–14).

HCC is a known complication for patients with HCV-associated cirrhosis. The annual incidence of de novo HCC after inducing SVR with DAA treatment has been variably reported to be 3–5% (9,15), which is higher than that observed with IFN-based therapy (8,9) but likely reflects treatment in a patient population with higher baseline risk of HCC (16), as current cohorts of patients treated with DAA are typically older and have more advanced decompensation than previously treated IFN-based cohorts (9,17,18). More controversial is whether there is higher risk of tumor recurrence in patients with HCC with complete response after curative HCV treatment. There are multiple hypotheses, all speculative, to explain the biological mechanism of increased HCC severity and risk of HCC recurrence with curative DAA therapy. One theory is that DAA treatment, by inducing rapid eradication of HCV, alters immune cancer surveillance, such that the balance between neoplastic cell proliferation and immune-induced cell death is disrupted (9,12,13).

In recent uncontrolled studies of patients with HCC treated with curative therapies (resection, radiofrequency ablation, or liver transplantation), the rates of HCC recurrence were estimated to be nearly 30% after six months, which authors noted as an unexpectedly high rate (12–14). On the other hand, other studies, including one small study of patients on the liver transplant (LT) waitlist, have not demonstrated an increased risk of HCC recurrence in patients treated with DAA or IFN-free regimens (15,19,20). Ultimately, these findings have prompted significant commentary from the international community (17,21–23).

Given that patients with HCC in the DAA era are likely different from their predecessors in the IFN era, controlled studies of sufficient sample size are necessary to shed light on this controversial issue. Additionally, since withholding of DAA treatment in patients with advanced liver disease and HCC may have negative consequences, including a higher risk of decompensation and death, studies on DAA therapy must consider the competing risks of death due to HCC recurrence and decompensated cirrhosis. In this study, we focused on

patients on the LT waitlist with HCV and HCC, stratified by whether they received DAA therapy or not, and compared the rates of HCC recurrence after local-regional therapy (LRT) and waitlist dropout.

METHODS

Study Design and Patient Population

This is a retrospective cohort study of adult patients with HCV-associated cirrhosis and HCC who were listed for LT with MELD exception at the University of California, San Francisco (UCSF) from January 2014 to October 2016. Patients with tumor burden that exceeded Milan criteria, but met criteria for the UCSF down-staging protocol (24,25) were included once their tumor burden had been down-staged to within Milan criteria or had complete tumor response. Patients were grouped into two cohorts: those who were not treated with DAA therapy and those treated with DAA. All patients had history of HCC before starting DAA. The study was conducted at a time when there were no concerns regarding adverse consequences of DAA on HCC disease outcomes, so the decision to treat with DAA was based on non-HCC criteria, namely anticipated time to transplantation, severity of liver and renal disease, and access to DAA therapy, which improved over the study period as newer DAA agents became available. This study was approved by the UCSF Institutional Review Board.

Measurements

Specific DAA regimens and treatment duration was selected for each patient according to viral genotype, severity of cirrhosis, and availability of specific drugs. If the patient received multiple courses of DAA therapy, data on both initial and most recent DAA regimens were collected. DAA treatment response was determined by SVR12, defined as an undetectable HCV-RNA at week 12 after end of therapy. Other DAA treatment outcomes included completion of a full DAA regimen as prescribed, treatment up to the time of LT, or discontinuation of DAA therapy due to adverse events. CP class, MELD score, and alpha-fetoprotein (AFP) level within three months of initiation of DAA and three months after completion of DAA therapy were collected.

LRTs were used as bridge to LT and due to longer waiting times at our center, LRTs were given with intent to achieve complete response. LRTs used were trans-arterial chemoembolization (TACE), local ablation [radiofrequency ablation (RFA), cryotherapy, and ethanol injection], stereotactic body radiotherapy, and local surgical resection. The specific type of LRT performed for each patient was determined by a multidisciplinary tumor board, which consisted of transplant hepatologists and surgeons, oncologists, interventional radiologists, and diagnostic abdominal imaging radiologists. Repeated interventions were often performed to achieve complete necrosis of all tumor nodules. Response to LRT was made radiographically by either quadruple-phase computed tomography (CT) or magnetic resonance imaging (MRI) with gadolinium contrast. Complete tumor response to LRT was defined as the absence of residual tumor or complete necrosis according to modified response evaluation criteria in solid tumors (mRECIST) (26). HCC recurrence was diagnosed by arterial phase enhancement and washout during the

delayed images on either CT or MRI with gadolinium contrast, to meet criteria for the Liver Imaging and Reporting Data System (LI-RADS) categories four or five (27). Criteria for HCC recurrence were also met if a lesion demonstrated interval growth with the same imaging technique, or if clinical suspicion of tumor recurrence, as determined by the multidisciplinary tumor board, was high enough to recommend repeat LRT. Patients underwent abdominal CT or MRI at one month after each LRT, and at a minimum of once every three months while on the LT waitlist. All imaging studies were reviewed by the multidisciplinary tumor board.

Dropout from the LT waitlist could occur for any of the following reasons: HCC tumor progression beyond Milan criteria, death without LT, being too sick or medically unsuitable to undergo LT, non-compliance, patient decision not to undergo LT, or being lost to follow-up.

For patients who underwent LT, explant histopathologic characteristics were evaluated. These included the presence or absence of viable HCC on explant, histologic grade of differentiation based on the Edmondson and Steiner criteria (grade 1, well differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated) (28), the presence or absence of micro- or macrovascular invasion, and pathologic tumor stage, based on the United Network for Organ Sharing tumor-node-metastasis staging system (29).

Outcomes and Statistical Analysis

The primary outcomes of interest were probability of HCC recurrence after complete response and waitlist dropout secondary to tumor progression or liver-related death. Secondary endpoints included rates of LT and overall intention-to-treat survival. The exposure of interest was DAA therapy, with two groups compared: patients who were not treated with DAA therapy (no DAA group) and those treated with DAA (DAA group). Baseline patient, tumor, and explant characteristics were summarized by DAA exposure group using medians and interquartile ranges (IQR) for continuous variables and proportions for categorical variables. The Pearson chi-square and Wilcoxon rank sum tests were used to assess differences between groups and the Wilcoxon signed-rank test was used to assess differences in pre- versus post-DAA therapy lab values.

In observational studies, systematic differences in baseline characteristics of treatment groups may introduce confounding and limit direct comparison of treatment effects (30). Therefore, we applied propensity score methods to address selection bias and reduce related confounding (30). We estimated the propensity score for the probability of receiving DAA treatment using logistic regression. Baseline pre-treatment characteristics that were unbalanced between DAA treatment groups or expected to impact selection to DAA treatment (AFP, down-staging, complete response to LRT, CP class, and MELD) were included in the propensity score model. Inverse probability of treatment weights (IPTW) were calculated for each subject from the propensity score and stabilized to avoid extreme weights and reduce variance (31,32). Weighted, rather than matching, propensity score methods were used due to our relatively small sample with unequal treatment group sizes, allowing for inclusion of all study subjects in the analysis. To determine if adequate balance was achieved through propensity score weighting, we evaluated the standardized differences

(33) in baseline characteristics included in the propensity score for the unweighted and weighted DAA treatment groups.

Primary and secondary waitlist outcomes were evaluated using Fine and Gray competing risk regression (34). For HCC recurrence analyses, patient follow-up time was measured starting at the date of complete response with LRT to the date of HCC recurrence, other waitlist events (dropout due to tumor progression, liver-related death, or LT), or last follow-up. For waitlist dropout and LT analyses, patient follow-up time was measured from the date of HCC MELD exception listing to the date of the waitlist event (dropout due to tumor progression, liver-related death, or LT), or last follow-up. Waitlist outcomes other than the event of interest were treated as competing risks. For HCC recurrence, liver-related death and LT were modeled as competing events. For waitlist dropout, LT was modeled as a competing event. For LT, dropout due to tumor progression and liver-related death were modeled as competing events. Follow-up was censored at delisting for patients removed from the waitlist due to developing non-liver disease medical contraindication to LT, noncompliance with UCSF transplant policies, or were no longer interested in LT.

The cumulative incidence and 95% confidence intervals (CI) for HCC recurrence, waitlist dropout, and LT were estimated while accounting for competing risks and evaluated by DAA exposure. Using Fine and Gray competing risk regression (34), univariate subhazard ratios (HR) and 95% CIs for the association of explanatory variables for risk of HCC recurrence, waitlist dropout, and LT were calculated. Explanatory variables with a pre-specified statistical significance of p value <0.1 were included in the multivariable analysis. The final model was selected by backward elimination (p for removal >0.05), while retaining biologically plausible variables, as well as DAA treatment group as the primary variable of interest. Parallel analyses using unweighted and weighted (propensity score stabilized IPTW) methods were conducted.

Intention-to-treat survival and 95% CIs were estimated using the Kaplan-Meier method and applying the propensity score stabilized IPTW, both overall and stratified by DAA treatment group. Follow-up time was measured from the date of HCC diagnosis to the date of death (while on waitlist or post-LT) or last study follow-up. The modified log-rank test for weighted samples (30) was used to compare survival estimates by DAA group. Statistical analyses were performed using SAS v9.4 and Stata/IC 14.

RESULTS

Patient Characteristics

A total of 149 patients met inclusion criteria (Figure 1), with 87 patients who did not receive DAA (no DAA group) and 62 patients treated with DAA (DAA group). Baseline characteristics are shown in Table 1. Most patients were male (79.9%) with median age of 62 years (IQR 52–65) at listing. Prior heavy alcohol use was more common in the no DAA group (26.4%) than in the DAA group (11.3%, p=0.02). Patients who did not receive DAA were more likely to have CP class C disease (24.1%) compared to the DAA group (4.8%, p=0.006). At listing with MELD exception, median MELD score was 10 (IQR 8–13) for the

overall population. The no DAA group had higher median MELD score at listing (12, IQR 8–15) compared to those treated with DAA (9, IQR 7–11, p<0.001).

With regard to tumor characteristics at listing, median AFP (16.4 ng/mL, IQR 6.6–55.4) was similar between groups (p=0.92). There was also no difference in initial tumor burden, as characterized by size of largest lesion (p=0.36), number of HCC lesions (p=0.32), or the proportion of patients who were down-staged to Milan criteria (p=0.65). Overall, 144 of 149 patients (96.6%) received at least one LRT and 79 (53.0%) received ≥3 LRTs. There was a similar distribution of number of LRTs received among the two groups (p=0.14).

For the overall cohort, median follow-up time from HCC diagnosis to death or last follow-up was 27.3 months (IQR 17.6–35.1); overall median follow-up time from listing to death or last follow-up was 18.6 months (IQR 11.2–26.1). Compared to the no DAA group, patients treated with DAA had significantly longer median follow-up from both HCC diagnosis (31.4 months, IQR 23.3–39.9 vs. 21.9, IQR 14.7–31.0, p<0.001) and listing (22.9 months, IQR 17.3–28.0 vs. 16.1 months, IQR 6.3–22.0, p<0.001).

Overall, 120 of 149 patients (80.5%) achieved complete tumor response after LRT. In these 120 patients, the median number of LRTs required to achieve complete response was one (IQR 1–2). Those without DAA therapy were less likely to achieve complete tumor response after LRT (67.8%) compared to the DAA group (98.4%, p<0.001). Overall, TACE was the most common LRT used to achieve complete response, including when used alone (63.3%) or in combination with RFA (20.0%). There was no difference in either the number (p=0.73) or type of LRT (p=0.54) required to achieve complete response between the groups (Table 1).

Most patients had HCV genotype 1 infection (66.9%). Patients who did not receive DAA therapy were more likely to have HCV genotype 3 (32.5%) compared to those treated with DAA (14.5%, p=0.02). The specific DAA regimens used and associated baseline characteristics are shown in Supplementary Table 1. Thirteen percent of patients received more than one course of DAA therapy. The median time between HCC diagnosis and DAA therapy was 11.9 months (IQR 6.9–19.6). The median duration of latest DAA therapy received was 3.1 months (IQR 2.8–5.6). Of patients who received DAA therapy, 77.4% (48/62) achieved SVR12. Overall, 21.3% (13/61) of patients received DAA up to the time of LT.

With DAA treatment, median AFP decreased from 21.0 ng/mL (IQR 9.1–55.4) before receiving DAA (measured within three months prior to DAA initiation) to 8.1 ng/mL (IQR 4.6–18.5) after receiving DAA (measured within three months after completion of DAA therapy) (p=0.01). Median MELD scores were similar pre-DAA therapy (9, IQR 7–10) compared to post-DAA therapy (9, IQR 8–11, p=0.09). There was no difference in median CP score before (6, IQR 5–7) compared to after receiving DAA therapy (6, IQR 5–7, p=0.39).

Variables that were imbalanced between DAA treatment groups or expected to impact selection to DAA treatment were AFP, down-staging, complete response to LRT, CP class, and MELD, which were included in the propensity score model (Supplementary Table 2).

After applying propensity score stabilized IPTW techniques, the standard differences in covariate means were less than 10%, improved substantially from unweighted standard differences.

HCC Recurrence after Complete Response to Local-Regional Therapy

Of 120 patients who achieved complete response to LRT, 73 experienced HCC recurrence after a median of 6.0 months (IQR 3.5–11.7). The median time from complete response to HCC recurrence in the no DAA group was 5.5 months (IQR 3.1–7.6) compared to 8.2 months (IQR 3.7–12.8) in the DAA group (p=0.09).

The overall cumulative 6-month and 1-year incidence of HCC recurrence after complete response with LRT was 31.6% (95% CI 23.4–40.0) and 48.7% (95% CI 39.3–57.5) (Figure 2a). No statistically significant difference was detected in cumulative probability of HCC recurrence within one year between the two groups: 47.0% (95% CI 32.4–60.3) for the DAA group and 49.8% (95% CI 37.4–61.1) for the no DAA group (p=0.93).

Unweighted univariate and multivariate analyses for HCC recurrence after complete response are shown in Supplementary Table 3. In unweighted univariate competing risk models, the DAA group had similar risk of HCC recurrence compared to patients without DAA therapy (HR 0.96, 95% CI 0.61–1.51, p=0.86). In unweighted multivariable analysis, adjusted for number of LRT and initial tumor burden (number of HCC lesions at listing), risk of HCC recurrence remained similar for the DAA group compared to patients without DAA (HR 0.91, 95% CI 0.56–1.45, p=0.68).

Propensity score weighted analysis in both univariate and multivariate models (Table 2) demonstrated similar findings as unweighted analysis. Covariates included in the propensity score (AFP, down-staging, complete response to LRT, CP class, and MELD) were not assessed in weighted modeling. The weighted multivariate model was adjusted for number of LRT received. The DAA group had similar risk of HCC recurrence as the no DAA group in weighted univariate competing risk analysis (HR 1.02, 95% CI 0.65–1.60, p=0.93), as well as in weighted multivariate competing risk analysis (HR 0.91, 95% CI 0.58–1.42, p=0.67). Lower number of LRT received was also associated with decreased risk of HCC recurrence in both weighted univariate (HR 0.20, 95% CI 0.08–0.53, p=0.001) and multivariate models (HR 0.20, 95% CI 0.08–0.52, p=0.001).

Waitlist dropout

Overall, 20 out of 149 patients experienced dropout due to tumor progression and an additional 16 patients died while on the waitlist. The median time from listing with MELD exception to waitlist dropout due to tumor progression or liver-related death was 7.2 months (IQR 5.1–12.4).

The overall cumulative probability of waitlist dropout related to tumor progression or death after listing with MELD exception was 7.9% within six months (95% CI 4.2–13.1) and 16.1% within one year (95% CI 10.6–22.7) (Figure 2b). The 1-year cumulative incidence of dropout was significantly lower for the DAA group (5.9%, 95% CI 1.8–13.7), compared to 24.0% (95% CI 15.2–33.9) in the no DAA group (p=0.005). Patients in the DAA group were

required to survive until time of DAA therapy, potentially resulting in biased dropout estimates. For this reason, we also estimated dropout in this group with observation time starting at time of DAA treatment initiation, with a similar estimate of 1-year cumulative incidence of waitlist dropout (4.2%, 95% CI 0.0.9–11.5). In an alternative analysis to adjust for this survival bias, the median time from listing to DAA initiation (5.1 months) was added to dropout times in the no DAA group, which resulted in a slightly lower 1-year cumulative incidence of dropout in the no DAA group (19.7%, 95% CI 11.9–29.0). However, the DAA group still had significantly lower 1-year cumulative incidence of dropout compared to the no DAA group in this adjusted analysis (p=0.001).

In unweighted univariate competing risk models, those in the DAA group had a significantly decreased risk of dropout compared to those who did not receive DAA (HR 0.20, 95% CI 0.09–0.48, p<0.001) (Supplementary Table 4). In unweighted multivariable analysis, adjusted for CP class, patients who received DAA had decreased risk of waitlist dropout (HR 0.24, 95% CI 0.10–0.59, p=0.002), and those with CP class C (vs. A) at listing had significantly increased risk of dropout (HR 2.62, 95% CI 1.03–6.69, p=0.04).

Propensity score weighted analysis in both univariate and multivariate models (Table 3) demonstrated similar findings as unweighted analysis. DAA treatment group was the only variable included in the weighted multivariate model, as all other covariates, as seen in Table 3, were removed by backward elimination or were not eligible for evaluation in the multivariate model (univariate p>0.1). Patients treated with DAA had decreased risk of waitlist dropout compared to the no DAA group in weighted univariate competing risk analysis (HR 0.30, 95% CI 0.13–0.69, p=0.005), with no additional covariates that were statistically significant in the multivariate model.

Liver transplantation

Of the 149 patients, 76 underwent LT a median of 15.7 months (IQR 8.6–19.0) after listing with MELD exception. The overall cumulative incidence of LT was 18.1% (95% CI 12.2–25.0) within one year and 71.2% (95% CI 62.0–78.6) within two years (Figure 2c). The cumulative incidence of LT within one year was 14.2% (95% CI 6.9–24.2) for the DAA group and 21.0% (95% CI 12.8–30.6) in the no DAA group (p=0.42).

In unweighted univariate competing risk models, there was no statistically significant difference in the probability of LT in the DAA group compared to those not treated with DAA (HR 1.27, 95% CI 0.82–1.96, p=0.28) (Supplementary Table 5). By unweighted multivariate competing risk analysis, adjusted for blood type, number of LRT, and initial tumor burden (multiple HCC lesions at listing), there was also no statistically significant difference in rate of LT in the DAA group compared to patients not treated with DAA therapy (HR 1.39, 95% CI 0.85–2.28, p=0.19).

Propensity score weighted analysis in both univariate and multivariate models (Supplementary Table 6) demonstrated similar findings as unweighted analysis. There was no difference in probability of LT in the DAA group compared to those who did not receive DAA in weighted univariate analysis (HR 1.19, 95% CI 0.78–1.80, p=0.42) and in weighted

multivariate analysis (HR 1.21, 95% CI 0.76–1.92, p=0.42), which was adjusted for number of LRT and initial tumor burden.

Explant histopathologic characteristics for LT recipients are summarized in Supplementary Table 7. Complete necrosis with no residual viable tumor as a result of LRT was seen in 24.0% of explants (18/75). Viable tumors were within Milan criteria in 52.0% of explants (39/75), and microvascular invasion was present in 8.0% of explants (6/75). Among patients with viable tumors in the explant, 32.1% (18/56) had well differentiated HCC and 57.1% (32/56) had moderately differentiated HCC. Compared to the no DAA group, a higher proportion of patients treated with DAA had poorly differentiated HCC (13.2% vs. 2.8%, p=0.26) and vascular invasion (15.4% vs. 2.8%, p=0.15), though these differences were not statistically significant. Overall, AFP at LT (p=0.29) and presence of viable tumor on explant (p=0.67) were similar among those who received DAA and those who did not.

Intention-to-treat survival

Overall, patients were followed for a median of 27.3 months (IQR 17.6–35.1) from HCC diagnosis to death or last study follow-up, including the post-LT period. On an intention-to-treat analysis, survival for the entire study population was 92.1% (95% CI 83.4–96.4) at one year and 89.6% (95% CI 80.1–94.7) at two years from HCC diagnosis (Figure 3). When stratified by DAA group, overall weighted survival was similar in the DAA group compared to those who did not receive DAA therapy (p=0.08).

DISCUSSION

With the advent of effective and safe antiviral therapies for patients with advanced cirrhosis, most patients on the LT waitlist can be offered a chance at HCV cure, but the decision to treat is complex, such that potential benefits as well as harms must be taken into account. Current guidelines recommend treating patients with HCC with DAA therapy while on the waiting list (35), though this practice is controversial. Uncontrolled studies among patients with HCC with complete response to LRT reported higher than expected HCC recurrence rates in the setting of subsequent DAA therapy (12,13). Our study uniquely focuses on the waitlisted patient population and utilizes a contemporaneous untreated control group to better assess the benefits versus harms of DAA therapy. Additionally, recognizing that differences in severity of cirrhosis and other key baseline characteristics may influence outcomes on the waiting list, we used a propensity weighted approach. We found no negative association between DAA therapy and HCC recurrence among waitlisted patients. For this reason, our results lend strong support to the use of DAA therapy in waitlisted patients with HCC who have achieved complete response with LRT.

The controversy on use of DAA therapy in patients with HCV and HCC is partially fueled by early studies that suffered from limitations of study design and sample size (12–14). Most important among the limitations was the lack of controls or the use of IFN-treated controls. Differences in baseline characteristics between DAA and IFN-treated patients make comparisons with historical treated controls suboptimal (12,13). Several recent publications in HCV-infected patients with HCC have highlighted that DAA-treated cohorts are older and have more advanced cirrhosis, leading to higher baseline rates of HCC and likely also

influencing HCC recurrence rates after LRT (9,17). In more recent studies using contemporaneous controls, as was done in our study, no increased risk of de novo HCC or recurrent HCC after curative therapy was seen (15,18,19). Our study focuses on the waitlisted patient population, and while these patients are likely to have more advanced liver disease compared to other studies, our findings align with these recent cohort studies that found no association between DAA therapy and higher risk of HCC recurrence after curative LRT.

Due to long waiting times for patients with HCC at our center, our study of waitlisted patients presents a unique opportunity to evaluate potential benefits versus harms of DAA therapy in patients with cirrhosis and HCC, including those with decompensation. Among our patients listed with HCC exception status, approximately half had CP B or C cirrhosis, with significant risk of death due to worsening decompensation that may be modified by HCV eradication. Thus, understanding the contributions of DAA therapy to both HCC and cirrhosis outcomes is critical in guiding DAA use in the HCC population. In weighted propensity score modeling to adjust for differences in baseline characteristics, we found that DAA therapy was associated with a 70% reduction in waitlist dropout due to tumor progression or liver-related death. We speculate that patients who received DAA therapy benefited by stabilization of liver function and reduced risk of decompensating events. These findings align with previous literature showing that DAA therapy is associated with improvement in MELD and CP scores within 12 to 24 weeks of treatment (1–3,15) as well as lower rates of decompensation (1,15). Thus, when assessing the use of DAA therapy in patients with HCC, these additional benefits must be considered.

HCC management in the transplant setting was evaluated in another single center study from Italian investigators, with 23 DAA treated patients compared to 23 untreated contemporaneous controls (20). Though the sample size was smaller, similar trends were seen as in our study, with no significant differences in rate of waitlist dropout due to HCC progression, in addition to similar explant pathology as measured by number of HCC nodules and total tumor volume, stage of differentiation, and presence of microvascular invasion between treated and untreated patients. In addition, there was no difference in post-LT HCC recurrence (12.5%, 1/8 patients in DAA group) compared to 8.3% (1/12 in untreated group) (20). These results contrast those of a Mayo Clinic study that reported a greater proportion of explants outside Milan criteria and a trend towards higher post-LT HCC recurrence rates in patients treated with DAA versus those not treated (5/18 versus 6/63 patients), although differences in waiting time and post-LT follow-up limit interpretation of these results (14). We did not evaluate post-transplant outcomes in our study due to the limited duration of follow-up time available post-LT, but this is an important future area of investigation.

Patients received a wide range of bridging LRTs, but TACE was the predominant therapy used in our program. This highlights an important difference between the present study and previously published literature analyzing HCC recurrence risk after complete response to either surgical resection or ablation followed by DAA. TACE is the most commonly used treatment modality on the LT waitlist, typically employed when the expected wait time is at least six months (36). While TACE is not thought to be curative, it is applicable across a

broader spectrum of waitlisted patients than other LRTs such as RFA, and high rates of complete response were seen in the present study. There were no differences observed in either number or type of LRT required to achieve complete response in the two groups. Overall, 80% of our patient population achieved initial complete response after LRT with worse rates observed in those without DAA therapy, potentially explained by worse liver function in this group, leading to less aggressive LRT. The overall cumulative incidence of HCC recurrence after complete response with LRT was 32% within six months and 49% within one year. These results compare favorably with an Italian study involving 148 patients with a single nodule treated only with TACE, in which nearly 2/3 of patients had tumor recurrence at a median of 9 months after initial complete response (37).

Our study has some limitations. This is a single center, observational study and assignment of DAA therapy was not randomized. Thus, untreated patients tended to have more severe baseline cirrhosis and were less likely to achieve complete tumor response with LRT. To address these differences, we performed weighted analysis with propensity scores. There is also potential bias in the DAA group, such that patients treated with DAA had to survive long enough to receive DAA therapy. We addressed this potential bias by analyzing cumulative incidence of waitlist dropout with observation time starting at time of DAA initiation, rather than at time of listing. In addition, overall median wait time from listing with MELD exception to LT was 16 months; the benefits of DAA therapy may be influenced by wait times, with longer wait times providing the opportunity to both complete DAA therapy and derive benefit from clinical improvement. There are multiple additional factors to take into account when deciding on the optimal timing of DAA initiation in a patient with HCC. Delaying DAA therapy until after complete response to LRT may increase SVR rates (38), but if a patient has advanced or worsening hepatic decompensation, DAA therapy may stabilize their liver disease allowing for additional LRT if needed and decreasing the risk of waitlist dropout due to liver-related death. Finally, the decision to treat with DAA should take into account regional availability and use of HCV-positive donors (39). Additional studies are needed but, as highlighted by our study, future studies need to consider both potential harms versus benefits of DAA therapy in patients with HCC.

In conclusion, we did not find an association between DAA use and increased risk of HCC recurrence after complete response to LRT in patients with HCV-associated cirrhosis and HCC on the LT waitlist. Our results argue against recent literature that suggests DAA therapy promotes HCC recurrence. Moreover, we show that DAA treatment is associated with reduced waitlist dropout due to tumor progression or death, and that DAA use is not associated with decreased probability of LT or overall survival. Ultimately, the decision to treat HCV in waitlisted patients needs to be individualized, but our study provides support for the use of DAA therapy in patients on the transplant waiting list with HCC who have achieved initial response to LRT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DAA	direct-acting antivirals
HCV	hepatitis C
SVR	sustained virologic response
MELD	Model for End-Stage Liver Disease
CP	Child-Pugh
HCC	hepatocellular carcinoma
IFN	interferon
LT	liver transplantation
LRT	local-regional therapy
UCSF	University of California, San Francisco
AFP	alpha-fetoprotein
TACE	trans-arterial chemoembolization
RFA	radiofrequency ablation
CT	computed tomography
MRI	magnetic resonance imaging
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
LI-RADS	Liver Imaging and Reporting Data System
IPTW	inverse probability of treatment weights
95% CI	95% confidence interval
HR	hazard ratio

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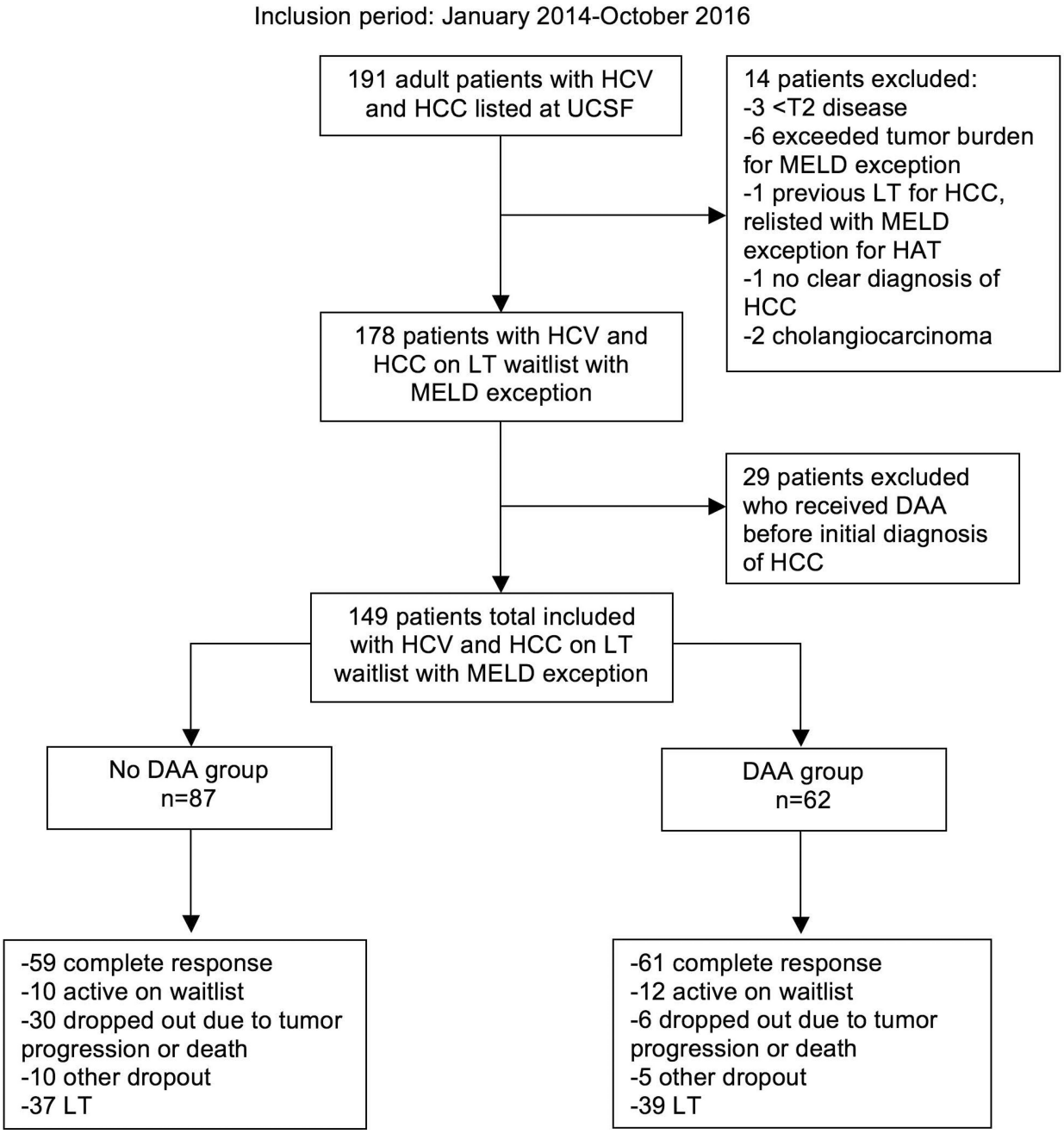
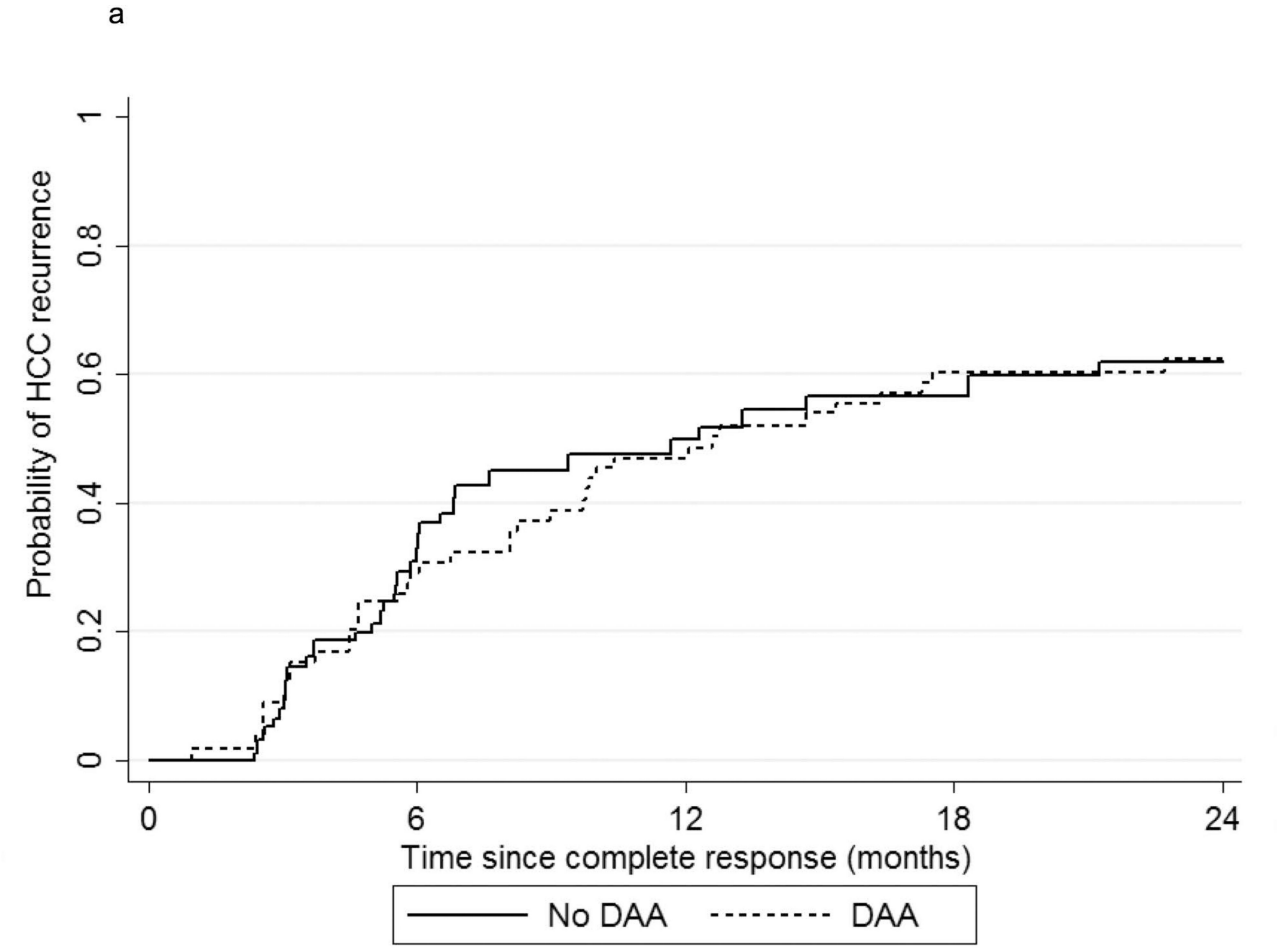
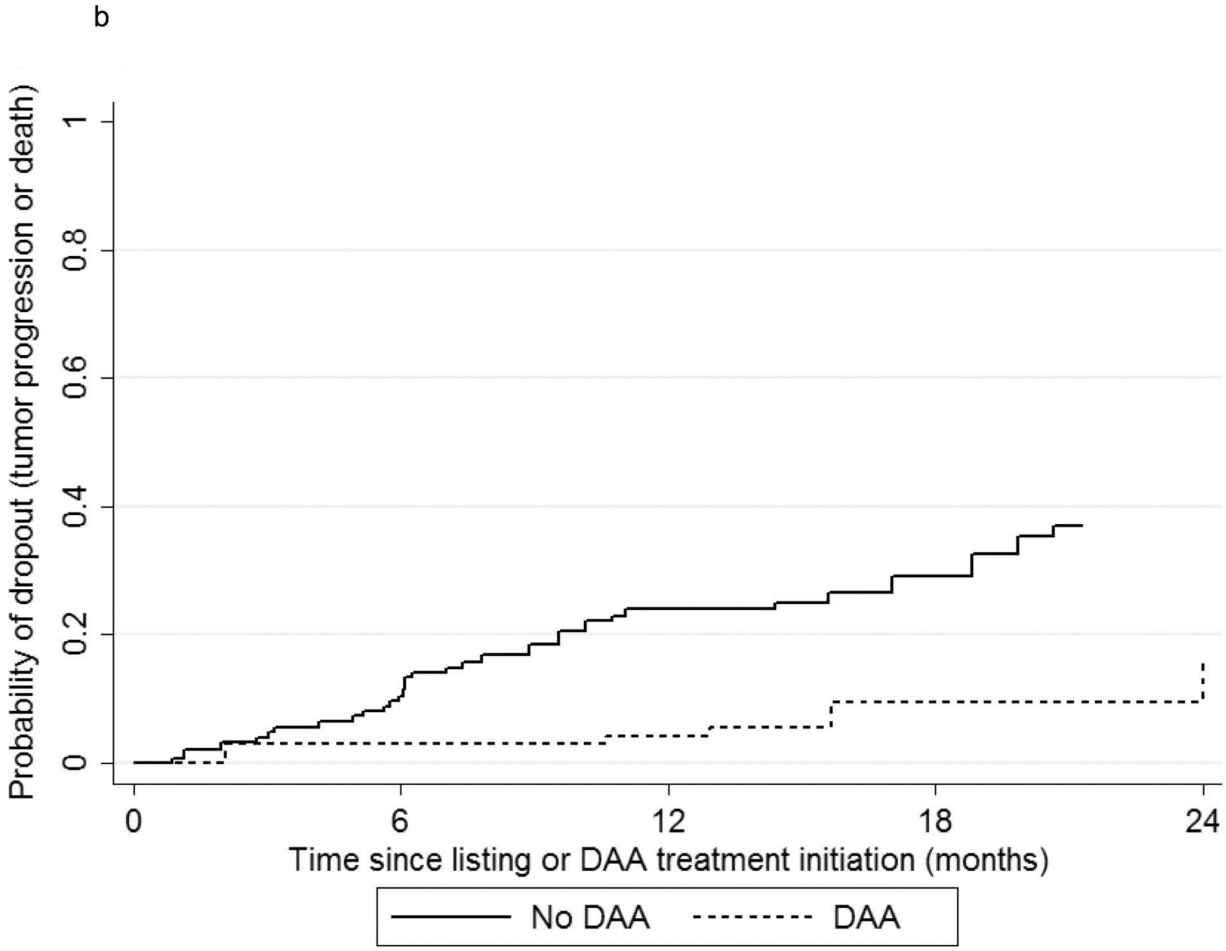


Figure 1.
Flowchart of patient population



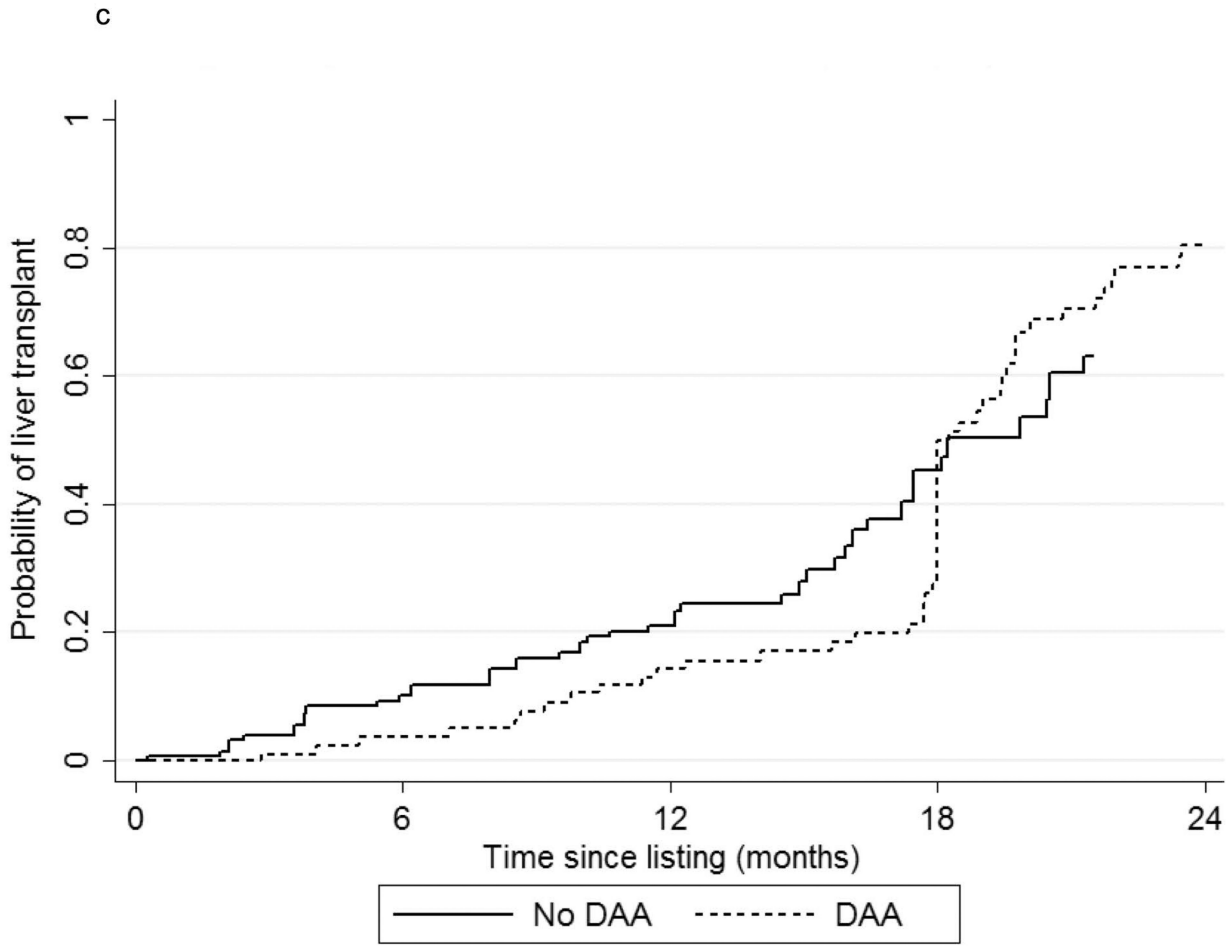
Number of patients at risk

Month	0	6	12	18	24
No DAA	59	30	13	3	1
DAA	61	38	23	6	3



Number of patients at risk

Month	0	6	12	18	24
No DAA	87	57	32	11	0
DAA	62	45	25	15	7



Number of patients at risk

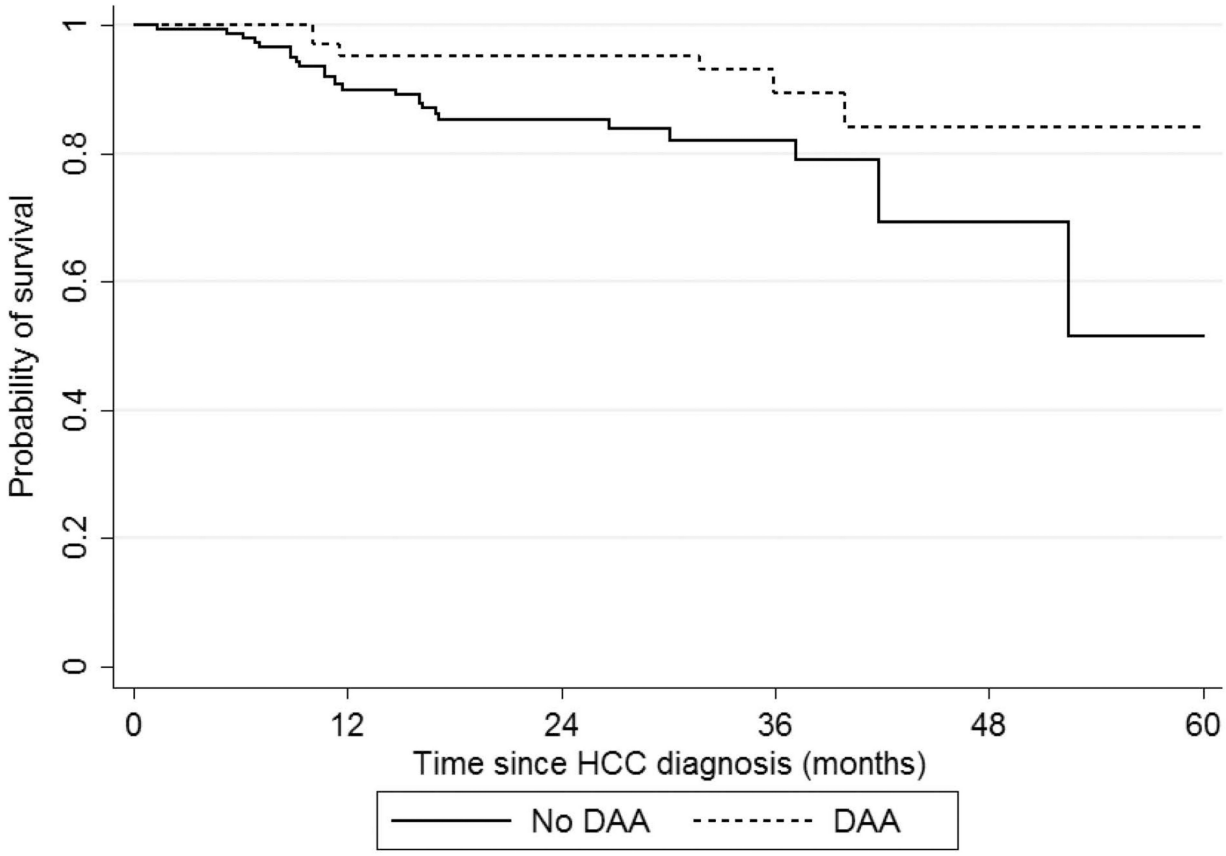
Month	0	6	12	18	24
No DAA	87	57	32	11	0
DAA	62	58	45	26	4

Figure 2.

a: Weighted cumulative incidence of HCC recurrence after complete response by direct-acting antiviral (DAA) group. Weighted using propensity score stabilized inverse probability of treatment weights.

b: Weighted cumulative incidence of waitlist dropout due to tumor progression or death by direct-acting antiviral (DAA) group. Weighted using propensity score stabilized inverse probability of treatment weights.

c: Weighted cumulative incidence of liver transplantation by direct-acting antiviral (DAA) group. Weighted using propensity score stabilized inverse probability of treatment weights.



Number of patients at risk

Month	0	12	24	36	48	60
No DAA	87	71	38	14	4	3
DAA	62	60	44	19	5	1

Figure 3.

Weighted intention-to-treat Kaplan-Meier survival by direct-acting antiviral (DAA) group. Weighted using propensity score stabilized inverse probability of treatment weights.

Table 1

Baseline and waitlist characteristics of liver transplant candidates at listing (n=149)

Variable	Overall (n=149)	No DAA (n=87)	DAA (n=62)	p-value
Median age (IQR)	62 (52–65)	62 (56–65)	63 (60–66)	0.13
Male sex (%)	119 (79.9)	73 (83.9)	46 (74.2)	0.15
Race/ethnicity (%)				0.56
Caucasian	82 (55.0)	49 (56.3)	33 (53.2)	
Asian	8 (5.4)	5 (5.7)	3 (4.8)	
Hispanic	38 (25.5)	22 (25.3)	16 (25.8)	
Black	13 (8.7)	5 (5.7)	8 (12.9)	
Other	8 (5.4)	6 (6.9)	2 (3.2)	
Blood type (%)				0.96
A/O	130 (87.2)	76 (87.4)	54 (87.1)	
B/AB	19 (12.8)	11 (12.6)	8 (12.9)	
Etiology of liver disease (%)				**0.02**
HCV alone	**119 (79.9)**	**64 (73.6)**	**55 (88.7)**	
HCV + alcohol	**30 (20.1)**	**23 (26.4)**	**7 (11.3)**	
HCV genotype (%) *				**0.04**
1	**97 (66.9)**	**51 (61.4)**	**46 (74.2)**	
2	**10 (6.9)**	**5 (6.0)**	**5 (8.1)**	
3	**36 (24.8)**	**27 (32.5)**	**9 (14.5)**	
4/6	**2 (1.4)**	**0 (0.0)**	**2 (3.2)**	
Child-Pugh class (%)				**0.006**
A	**84 (56.4)**	**43 (49.4)**	**41 (66.1)**	
B	**41 (27.5)**	**23 (26.4)**	**18 (29.0)**	
C	**24 (16.1)**	**21 (24.1)**	**3 (4.8)**	
Median MELD score (IQR)	**10 (8–13)**	**12 (8–15)**	**9 (7–11)**	**<0.001**
Median AFP, ng/mL (IQR)	16.4 (6.6–55.4)	16.4 (6.6–50.3)	16.4 (6.6–57.4)	0.92
Size of largest lesion, cm (IQR)	2.8 (2.2–3.5)	2.9 (2.3–3.7)	2.7 (2.2–3.5)	0.36
Number of HCC lesions (%)				0.32
1	105 (70.5)	60 (69.0)	45 (72.6)	
2	29 (19.5)	15 (17.2)	14 (22.6)	
≥3	15 (10.1)	12 (13.8)	3 (4.8)	
Down-staged to Milan criteria (%)	24 (16.1)	13 (14.9)	11 (17.7)	0.65
Total Number LRT (%)				0.14

Variable	Overall (n=149)	No DAA (n=87)	DAA (n=62)	p-value
0	5 (3.4)	5 (5.7)	0 (0.0)	
1	27 (18.1)	18 (20.7)	9 (14.5)	
2	38 (25.5)	19 (21.8)	19 (30.6)	
≥3	79 (53.0)	45 (51.7)	34 (54.8)	
Achieved complete response (%) †	**120 (80.5)**	**59 (67.8)**	**61 (98.4)**	**<0.001**
Total Number LRT required to achieve complete response (%)‡				0.73
1	66 (55.0)	32 (54.2)	34 (55.7)	
2	27 (22.5)	12 (20.3)	15 (24.6)	
≥3	27 (22.5)	15 (25.4)	12 (19.7)	
Type of LRT required to achieve complete response (%)‡				0.54
TACE alone	76 (63.3)	35 (59.3)	41 (67.2)	
RFA alone	6 (5.0)	3 (4.9)	3 (4.9)	
TACE+RFA	24 (20.0)	15 (25.4)	9 (14.8)	
Other	14 (11.7)	6 (10.2)	8 (13.1)	

* n=145 (missing in 4 patients)

† n= 143 (not applicable in 6 patients)

‡ n=120 achieved complete response

Table 2

Weighted univariate and multivariate analyses of predictors of HCC recurrence after complete response by competing risk regression (n=120)*

	Univariate		Multivariate†	
Predictor	**Weighted HR (95% CI)**	**p-value**	**Weighted HR (95% CI)**	**p-value**
DAA (vs. no DAA)	**1.02 (0.65–1.60)**	**0.93**	**0.91 (0.58–1.42)**	**0.67**
1 LRT (vs. ≥2)	**0.20 (0.08–0.53)**	**0.001**	**0.20 (0.08–0.52)**	**0.001**
Multiple HCC lesions at listing	1.30 (0.78–2.16)	0.31		
Number of HCC lesions at listing				
2 (vs. 1)	1.05 (0.59–1.86)	0.88		
3 (vs. 1)	2.38 (0.87–6.54)	0.09		
4 (vs. 1)	1.46 (0.23–9.36)	0.69		
Age at HCC diagnosis (per year)	0.98 (0.94–1.01)	0.20		
Female gender	1.15 (0.65–2.05)	0.63		
Blood type B/AB (vs. A/O)	0.51 (0.21–1.22)	0.13		
HCV + alcohol etiology (vs. HCV alone)	0.94 (0.51–1.74)	0.85		
HCV genotype 3 (vs. other)‡	1.41 (0.86–2.34)	0.18		

*Weighted using propensity score stabilized inverse probability of treatment weights. Covariates included in the propensity score were not assessed in the weighted modeling.

†Weighted multivariate model adjusted for DAA group and number of LRT

‡n=117 (missing in 3 patients)

Table 3

Weighted univariate and multivariate analyses of predictors of waitlist dropout by competing risk regression (n=148)[*†]

	Univariate		Multivariate[‡]	
Predictor	**Weighted HR (95% CI)**	**p-value**	**Weighted HR (95% CI)**	**p-value**
DAA (vs. no DAA)	**0.30 (0.13–0.69)**	**0.005**	**0.30 (0.13–0.69)**	**0.005**
≥2 LRT (vs. 0–1)	0.78 (0.32–1.90)	0.58		
Multiple HCC lesions at listing	0.70 (0.32–1.50)	0.36		
Number of HCC lesions at listing				
2 (vs. 1)	0.41 (0.15–1.13)	0.08		
3 (vs. 1)	2.28 (0.70–7.38)	0.17		
4 (vs. 1)	1.25 (0.22–7.16)	0.80		
Age at HCC diagnosis (per year)	0.98 (0.94–1.03)	0.53		
Female gender	1.10 (0.44–2.75)	0.84		
Blood type B/AB (vs. A/O)	1.24 (0.43–3.60)	0.69		
HCV + alcohol etiology (vs. HCV alone)	0.92 (0.40–2.11)	0.85		
HCV genotype 3 (vs. other)[§]	1.51 (0.73–3.12)	0.27		

[*] One patient excluded from analysis with unknown complete response

[†] Weighted using propensity score stabilized inverse probability of treatment weights. Covariates included in the propensity score were not assessed in the weighted modeling.

[‡] Weighted multivariate model included DAA group only. All other variables removed by backward elimination.

[§] n=144 (missing in 4 patients)