Drop-out rate from the liver transplant waiting list due to HCC progression in HCV-infected patients treated with direct acting antivirals.

Title Drop-out rate from the liver transplant waiting list due to HCC progression in HCV-infected patients treated with direct acting antivirals

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Abbreviations: HCV = Hepatitis C virus; LT = liver transplantation; HCC = hepatocellular carcinoma; DAAs = direct antiviral agents; IFN = interferon; EASL = European Association for the Study of Liver; TTV = total tumor volume; FU = follow up; SVR = sustained viral response; CPT = Child-Turcotte-Pugh score; MELD = Model for End-Stage Liver Disease; AFP = alpha-fetoprotein; SOF = Sofosbuvir; RBV = Ribavirin; LDV = Ledipasvir; DCV = Daclatasvir; 24w = 24 weeks; 12w = 12 weeks.

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ABSTRACT

Background & Aim: concerns about an increased hepatocellular carcinoma (HCC) recurrence rate following directly acting antiviral (DAA) therapy in cirrhotic patients with a prior complete oncological response have been raised. Data regarding the impact of HCV-treatment with DAAs on waiting list drop-out rates in patients with active HCC and HCV-related cirrhosis awaiting liver transplantation (LT) are lacking.

Materials and Methods: HCV-HCC patients listed for LT between January 2015 and May 2016 at Padua Liver Transplant Centre were considered eligible for the study. After enrollment patients were divided into 2 groups, depending on whether they underwent DAAs treatment while awaiting LT or not. For each patient clinical, serological and virological data were collected. HCC characteristics were radiologically evaluated at baseline and during follow-up (FU). For transplanted patients, pathological assessment of the explants was performed and recurrence-rates were calculated.

Results: twenty-three patients treated with DAAs and 23 controls were enrolled. HCC characteristics at time of LT-listing were comparable between the 2 groups. Median FU was 10 and 7 months, respectively, during which 2/23 (8.7%) and 1/23 (4.3%) drop-out events due to HCC-progression were registered (p = 0.9). No significant differences in

terms of radiological progression were highlighted (p = 0.16). Nine out of 23 cases (39%) and 14/23 (61%) controls underwent LT, and histopathological analysis showed no differences in terms of median number and total tumor volume of HCC nodules, tumor differentiation or microvascular invasion. During post-LT FU, 1/8 DAAs treated patient (12,5%) and 1/12 control (8,3%) experienced HCC recurrence (p = 0.6).

Conclusions: Viral eradication does not seem to be associated with an increased risk of drop-out due to neoplastic progression in HCV-HCC patients awaiting LT.

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INTRODUCTION

Hepatitis C virus (HCV)-related end stage liver disease is still the main indication for liver transplantation (LT) worldwide (1). Cirrhotic patients experience a very high risk of hepatocellular carcinoma (HCC) development with a 5-year cumulative incidence of up to 30%, with the highest risk among those infected with HCV (2) as a result of the chronic inflammation associated with viral replication. This is corroborated by the fact that amongst HCV-infected patients with cirrhosis, HCC has been the main indication for listing (3).

The new era of direct antiviral agents (DAAs) has already changed the management approach to HCV infection in the transplant setting (4, 5). It is anticipated that the widespread application of DAAs therapy in the near future could lead to a significant reduction in HCV-related end stage liver disease and HCC (6) and the number of patients listed for liver transplantation will decrease markedly (7). However, DAA treatment rates are limited by the high cost in resource-limited environments and patients with HCV infection are not universally linked to care (8). It is therefore likely that HCV-related cirrhosis will continue to be a significant indication for LT in the coming decades (9).

Unlike the previous interferon (IFN)-based treatments (10, 11), most DAAs can be considered highly safe and well tolerated, even in cases of advanced liver disease (12-14). However, it is in this population that concerns about a high recurrence rate of HCC have been raised in patients who previously had a complete response to loco-regional HCC treatment and were subsequently treated with DAAs (15). After the first report by Reig and colleagues, several further studies have been published, exploring the potential role of DAAs based treatment in HCC occurrence and recurrence processes (16-25). To our knowledge, the impact of HCV eradication by DAAs on the progression of HCC in patients with active neoplastic disease has not been fully evaluated.

Belli and colleagues have shown that, through successful DAAs treatment, "delisting" is possible in almost one third of patients with non-oncological indications, reducing the need for LT in HCV positive patients and allowing organs to be allocated to others (26, 27). However, drop-out from the waiting list, due to tumor progression and the development of oncological contraindications to LT, represents a major challenge in the management of patients with HCC (28). Therefore, if were shown that HCV eradication by DAAs is related to the induction of HCC growth and progression in patients with active neoplastic disease, there would be major consequences in relation to the timing of DAAs therapy.

The aim of this study was therefore to investigate whether patients listed for HCC and treated with DAAs have an increased rate of tumor progression and consequent drop-out from the waiting list for LT at Padua Liver Transplant Centre.

MATERIALS AND METHODS

Patients

We retrospectively evaluated all consecutive patients listed for LT at Padua Liver Transplant Centre between January 2015 and May 2016. Patients, whose indication for LT was HCC with HCV-related cirrhosis and detectable viremia at time of listing for LT, were included in the study. They were subsequently divided into two groups, depending on whether they underwent DAAs treatment while awaiting LT or not. Eligibility for DAAs treatment was assessed following the criteria established by the national registry of the Italian Medicines Agency Committee (AIFA). At that time, there was not a single center protocol regarding the management of antiviral therapy in patients awaiting liver transplant.

Thus, the decision to start antiviral treatment before LT was at the discretion of the different hepatologists and it was mainly based on the probability of being transplanted (in patients with a high probability of getting liver transplanted in a short while, antiviral therapy was post-poned after the transplant).

Exclusion criteria were as follows: age < 18 years, patients listed for other co-etiologies in addition to HCV-related cirrhosis, HBV co-infections, re-transplantations. The inclusion criteria flow chart is shown in Figure 1.

Demographic, clinical and virological data were collected. Virological response to treatment was assessed by quantitative HCV-RNA detection, using real time PCR with a limit of detection of 12 IU/ml.

The study was approved by Padua University Hospital Ethical Committee.

Hepatocellular carcinoma

Diagnosis of HCC was based on the European Association for the Study of Liver (EASL) guidelines (29). As previously published, our policy for listing is based on the exclusion of HCC with aggressive features such as poor differentiation (G3 according to Edmondson's score), presence of vascular invasion and/or extra-hepatic spread, alpha-fetoprotein (AFP) levels higher than 400 ng/ml, irreversible radiological progression after down-staging treatments. On the other hand, size and number of nodules are not considered as absolute selection criteria (30-32). At time of listing for LT and at the end of FU, morphological HCC characteristics were collected through CT-scan or MRI, performed quarterly according to follow-up routine schedules. Radiological progression was defined according to mRECIST criteria (33). Vital tumor volume was quantified according to the following equation: "Tumor volume cm^3 = 4/3 x 3.14 x (radius of the tumor nodule in $cm)^3$".

Total tumor volume (TTV) was calculated as the sum of the tumor volume of each nodule (34, 35).

The radiological response was assessed by one expert radiologist who was unaware from both clinical and DAAs treatment.

Down-staging treatments on the waiting list (radiofrequency or microwave ablation, liver resection and transarterial chemoembolization), performed according to Padua Liver Transplant Centre policy (30) were recorded.

Follow-up and drop-out

The follow up period (FU) was defined as the total time spent on the LT waiting list, beginning at listing time and stopping at transplantation or, alternatively, at drop-out due to tumor progression or death on the waiting list. For patients that did not reach the established end of FU (i.e. patients still awaiting LT at the end of the study period) we collected the most recent data available.

In our centre, during waiting-list permanence, all HCC patients are treated with an aggressive multimodal adjuvant protocol to contain tumor progression prior to LT (36-39). During the FU, bridge treatments (radiofrequency or microwave ablation, liver resection and transarterial chemoembolization), were recorded. Vital tumor active burden was re-evaluated through the above-mentioned radiological techniques one month after each bridge treatment, according to clinical practice guidelines (29).

Patients were excluded from the LT waiting list during FU if there was evidence of: neoplastic vascular macro invasion, extra-hepatic metastases, AFP levels rising over 400 ng/ml irreversible radiological progression after bridging treatment or poor tumor differentiation if a tumor biopsy was performed (G3 HCC) (30-32, 40, 41).

Patients were also followed-up after LT for HCC recurrence, through CT-scan or MRI, every 3 months during the first year and every 6 months thereafter, according to European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer clinical practice guidelines (29). Post-LT HCC recurrence rate was calculated using the most recent radiological data available at the end of the study.

Objectives

The primary objective was the rate of exclusion from the LT waiting list, due to neoplastic progression in both cohorts; secondary objectives were rates of radiological progression and transplantation, histopathological HCC characteristics and the post-LT HCC recurrence rate.

For transplanted patients explant pathology evaluation was performed (number and TTV of HCC nodules, tumor differentiation and presence of microvascular invasion) by one expert pathologist who was unaware of DAAs treatments.

Statistical analysis

Qualitative data were described by frequency and percentage. Quantitative data were described by median (range). In the comparison between different subgroups, quantitative variables were compared using Student's *t* or Wilcoxon Rank Sums tests, as appropriate. Categorical variables were compared using χ^2 or Fisher's exact tests, as appropriate.

Median waiting time on the waiting list was expressed as median (range). Drop-out and LT probabilities were calculated from the day of waiting list inclusion until dropout from

any cause during the waiting list, LT, or latest follow-up. Dropout was defined as removal from the waiting list due to disease progression or patient death before LT. To construct and compare dropout and LT probability curves in the study and control groups, we used the competing risk method described by Fine and Gray (42). This method allows for all patients to be placed into a category; transplanted, dropped-out or still waiting.

In all analyses, a two-tailed P-value < 0.05 was considered statistically significant. All analyses were performed in JMP® 9.0.1 package (1989–2010 SAS Institute Inc.), and R.app GUI 1.51 (S. Urbanek & H.-J. Bibiko, © R Foundation for Statistical Computing, 2012).

RESULTS

Patients

Out of 244 patients listed for LT at Padua Liver Transplant Centre, 198 did not meet inclusion criteria (13 were under-age, 11 were listed for re-transplantation, 141 either for non HCV-related cirrhosis or had a previous virological response, 33 HCV-related cirrhosis had no evidence of HCC). Forty-six patients with HCC and HCV-related cirrhosis with detectable viremia at time of listing for LT, were included in the study.

Twenty-three of them underwent antiviral treatment with DAAs during the FU. Treatment regimens were as follows: 13 patients were treated with the association of Ledipasvir and Sofosbuvir (57%), 4 with Daclatasvir and Sofosbuvir (17%), 3 with Simeprevir and Sofosbuvir (13%) and 3 with Sofosbuvir alone (13%), in most cases the antiviral treatment was held for 12 weeks, starting within 1 month since listing time.

Ribavirin was added to treatment schedule in 13 cases (57%). All treated patients achieved SVR (23/23, 100 %).

A second group of 23 cirrhotic patients remained untreated while listed and thus maintained detectable viremia for the entire FU. Age, sex and virological characteristics resulted comparable in the two groups.

Compared to the controls, DAAs treated patients median MELD score was lower [10 (range: 7-17) vs 11 (range: 6-28), p = 0.09] as was the percentage of more advanced patients according to Child-Turcotte-Pugh Score [CPT A/B/C: 15/8/0 vs 13/3/7, p = 0.09]; however, these differences were not statistically significant.

Table 1 shows the patients' baseline characteristics.

Table 2 shows the reasons for not treating patients in the control group.

Hepatocellular carcinoma

At baseline the two groups were comparable in terms of the median number of HCC nodules [2 (range: 1-4) vs 2 (range: 1-6), p = 0.83], TTV [96 cm^3 (range: 42-272) vs 92 cm^3 (range: 34-222), p = 0.97] and AFP levels [6 ng/ml (range: 2-300) vs 12 ng/ml (range: 2-238), p = 0.68] in the DAA and control groups respectively. Both groups of patients underwent downstaging treatments before being listed (87% of treated patients and 96% of controls, p = 0.9).

Follow-up and drop-out

Median FU was similar for the two groups [10 months (range: 6-19) vs 7 months (range: 5-19), p = 0.42], during which both groups of patients underwent bridge treatments (61% of treated patients and 26% of controls, p = 0.003).

Comparing radiological images at the beginning and at end of FU, no significant differences in terms of radiological progression were highlighted, even though there was a positive trend in treated patients group; 35% of treated patients had radiological progression vs 17% of controls (p = 0.16), (Figure 2). Further, this slight positive trend was not supported by a parallel raise of AFP levels (AFP slope > 15 ng/ml/month in 2 patients among controls vs 0 DAAs treated patients, p = 0.2).

During the FU we registered 3 drop-outs in treated patients group (13%), due to patient death for intra-cerebral hemorrhage in one case, and HCC progression in the other 2 cases (neoplastic portal vein thrombosis in one, and subcutaneous metastases evidence in the other), and 3 drop-outs in controls group (13%) due to patient deaths for sepsis related multi organ failure in two cases, and HCC nodule's number and size progression after bridge treatment in the other case.

In terms of comparison between crude frequencies, we did not find significant differences in the drop-out rate due to HCC progression between groups (p = 0.9), even when we considered all radiological progressions as potential drop-outs (p = 0.8).

The characteristics of patients excluded from the LT waiting list due to HCC progression are summarized in Table 3.

Competing risk curves showed no significant differences in terms of dropout probabilities between groups (Figure 3, p = 0.8). Conversely, we found a significantly lower probability to be transplanted in treated patients when compared to controls (p = 0.04).

Three patients died for non-neoplastic related causes during the FU. One patient belonged to DAAs treated group and died from intracerebral hemorrhage, and two controls died both from multi organ failure due to sepsis.

Transplanted patients

Histopathological analysis

Nine of twenty-three (39%) patients treated with DAAs and 14/23 (61%) controls underwent LT. Histopathological analysis of HCC performed on the explanted liver, showed no differences in terms of: median number [3 (range: 1-7) vs 3 (range: 1-8), p = 0.5], and TTV of HCC nodules [14.2 cm^3 (range: 5.4-78.5) vs 11 cm^3 (range: 6.3-39.8), p = 0.3], tumor differentiation (G3 HCC %: 12.5% vs 14.3%, p = 0.7) or microvascular invasion (cases %: 44% vs 29%, p = 0.4).

Post-LT HCC recurrence

Median post-LT FU was 9 (6-13) and 11 (3-18) months for DAAs treated patients and controls, respectively.

During post-LT FU 1/8 DAAs treated patient (12.5%) and 1/12 control (8.3%), experienced HCC recurrence (p = 0.6), respectively at 7 and 12 months after LT (characteristics showed in Table 4); 1 DAAs treated patient and 2 controls died soon after LT and it was not possible to evaluate the post-LT outcome. Ten out of twelve controls started antiviral treatment with DAAs within 2 months after LT, 6 of which reached SVR12, 3 are still in treatment and 1 is currently being evaluated for re-treatment after viral breakthrough.

DISCUSSION

The recent approval of highly effective, well-tolerated direct-acting antiviral regimens has revolutionized the management of HCV-infected patients (4, 5, 27). Nevertheless, some concerns, that wait to be more clearly evaluated, have been raised (8, 9, 15) and require further evaluation. One such concern is whether HCV clearance from the liver, together with the consequent impairment of the liver immunological microenvironment, can impact HCC biology (15, 18, 20). Currently, there are no data regarding the role that antiviral therapy with DAAs might play in terms of tumor progression and consequent drop-out from the waiting list, in patients awaiting LT for HCV-related cirrhosis and HCC.

Since HCV-HCC patients represent an important proportion of patients on LT waiting lists, it is crucial to understand any drug's hypothetical effect on oncological progression leading to exclusion or drop-out from the waiting list. In our opinion, this subpopulation of cirrhotic patients is an ideal model to answer the question of whether there is a contribution of DAAs treatment to neoplastic progression, as these patients have active cancer and are regularly studied on a quarterly basis with second level radiological techniques. These features allow us to investigate if there is any additional effect of DAAs therapy, on HCC progression in a short follow up period. Indeed, unlike cirrhotic patients who are screened for HCC occurrence or recurrence after curative treatments, for whom neoplastic progression timings are less easily identifiable, in our cohort the neoplastic process was already underway and was well defined at the start of DAAs treatment.

In our study, the two groups did not show any significant difference in terms of dropout rate, during a median FU of 10 and 7 months, this being our primary objective. Nevertheless, the small sample size as well as the potential bias due to the retrospective nature of the study does not allow to draw any definitive conclusions.

There was a slight positive trend in the DAAs treated patients for radiological tumor progression, which was not statistically significant and there was no concomitant AFP slope.

Interestingly enough, a significantly lower probability to be transplanted in treated patients when compared to controls was found. In this scenario, DAAs based antiviral therapy could be associated with an improvement of liver function, reducing the need of transplantation, as showed by Belli et al (26). However, again, the small sample size does not allow to draw any definitive assumptions.

During the FU a higher percentage of DAAs treated group underwent bridge treatments compared to controls. This finding can be explained by the higher prevalence of patients with more advanced liver disease in the control group (even not statistically significant), which limited the feasibility of HCC loco-regional treatments. We believe this could conceivably explain the same drop-out rate even in the presence of a slightly higher radiological progression.

Nearly a third of the newly detected liver cancers in the study by Reig and colleagues (15) occurred in the first months after the start of antiviral therapy, suggesting that the time frame of most interest is during treatment and immediately afterwards. Therefore, even though our FU is relatively short, it seems possible that HCV eradication by DAAs did not enhance HCC progression in our cohort, an effect that could be expected to be more rapid and more evident in patients with active tumors at start of therapy.

Even though LT is considered a curative treatment for HCC, its recurrence is still possible, mostly in period immediately after LT, so that radiological surveillance is mandatory (29). In deciding whether to treat HCV-patients with DAAs before or after LT, one must also take into account the potential role of DAAs in post-LT HCC recurrence. The French prospective multicenter study (22), included one cohort of HCC LT recipients, subsequently treated with DAAs (ARNS CO23 CUPLIT Cohort) in which HCC recurrence

was observed in 7/314 patients (2.2%). This recurrence rate appears to be lower in these post LT DAA recipients compared to that expected, which ranges from 8 to 20% within the first two years after LT (43). Conversely, Yang and colleagues found in their study a trend towards a higher risk of HCC recurrence in patients who received pre-LT DAAs (5/18, 27.8%) compared to the risk in untreated patients (6/63, 9.5%) (p=0.6). Interestingly enough, in patients who underwent DAA therapy a higher proportion of microvascular invasion in comparison to untreated controls was described (39% vs 28%; p=0.4) (24), similarly to what was found in our cohort (44% vs 29%, p = 0.4).

In our cohort we found similar post-LT HCC recurrence rates in the two groups (12.5 % vs 8.3 %, p = 0.6), suggesting that there is no higher risk of tumor recurrence in patients treated with DAAs in the pre-LT treatment setting compared to post-LT treatment. Furthermore, we reported similar HCC patterns on liver explant histopathological analysis.

This study has some critical limitations. As previously reported, the most important one is certainly the small number of patients included. As a matter of fact, the number of HCC patients with radiological progression and micro-vascular invasion in the explant was higher among treated patients. Indeed, it is also possible that the difference was not statistically significant due to low number of patients in each group. Furthermore, the small sample size may mean that the study was underpowered to detect a true difference in our primary objective and tumor progression.

Certainly, these should be considered as preliminary findings. Indeed, they must be confirmed in different setting before considering the antiviral treatment with DAAs completely safe offered in this patient population. Moreover, waiting list drop-out rates depend on HCC management and waiting list inclusion/exclusion criteria, that vary across centers and these would need to be harmonized in a larger study.

Secondly, a longer FU (both pre- and post-LT) would better reveal differences in terms of HCC progression and post-LT recurrence, respectively. Finally and importantly,

the HCC tumor biology in our cohort might be unique in some way, but we are unable to describe this since we did not perform pre-LT HCC biopsies. Nevertheless, for patients that underwent LT during the study period, HCC histopathological analysis performed on explanted livers showed no differences in terms of tumor biology between pre-LT DAA treated and control groups.

In conclusion, viral eradication with DAAs does not seem to be associated with an increased risk of drop-out due to HCC progression in HCV patients awaiting LT even if, given the low number of patients included, prudence is clearly advised. The clinical implications of these findings deserve further and larger investigations. Additionally, it is true that the retrospective nature of the present study is not the appropriate way to define a firm causality between DAAs treatment and HCC drop-out or recurrence after transplant. Despite the important limitations mentioned above, to our knowledge this is the only study evaluating this very relevant and novel clinical question.

Deferring HCV treatment until after LT in order to guarantee access to the expanded pool of HCV+ donors has been proposed as the most cost-effective strategy for well-compensated HCV-infected cirrhotics listed for liver transplantation with HCC (44). However, this still depends on HCV epidemiology. Furthermore, HCV eradication in the pre-LT setting prevents recurrence of liver infection (45) and has been associated to higher survival in patients transplanted for HCC (46). Additionally, Martini et al. recently showed that reaching HCV-RNA undetectability in the pre- or peri-LT setting could lower the risk of early allograft dysfunction in HCV positive recipients (47). This finding, together with our results, should further encourage clinicians to treat HCV patients as early as possible, especially in HCC patients awaiting LT, who may be more likely to receive grafts from marginal donors, with the consequent higher risk of post-LT complications.

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Table 1: Patients baseline characteristics.

	DAAs treated patients (N = 23)	Controls (N = 23)	p value
Age, years	59 (49-69)	58 (46-70)	0.67
HCV Genotype (1a/1b/2/3/4)	5/9/1/5/3	6/8/2/6/1	0.81
Viral load, UI/ml	602,504 (7,484-7,650,000)	544,816 (12,244-5,785,675)	0.67
CPT score (A/B/C)	15/8/0	13/3/7	0.09
MELD score	10 (7-17)	11 (6-28)	0.09
HCC nodules number	2 (1-4)	2 (1-6)	0.83
TTV, cm^3	96 (42-272)	92 (34-222)	0.97
Patients exceeding Milan Criteria at listing, n (%)	12/23 (52%)	13/23 (56.5)	0.64
AFP, ng/ml	6 (2-300)	12 (2-238)	0.68
Downstaging treatments	20 (87%)	22 (96%)	0.90
FU, months	10 (6-19)	7 (5-19)	0.42

Legend: For each variable median and reference range were calculated; CPT = Child-Turcotte-Pugh score; MELD = Model for End-Stage Liver Disease; HCC = hepatocellular carcinoma; TTV = total tumor volume; AFP = alpha-fetoprotein; FU = follow-up.

Table 2. Reasons for no antiviral treatment in the control cohort.

	Patients: 23
Too advanced liver disease (Child B/C), n (%)	10 (43.5)
Hepatocellular carcinoma exceeding Milan Criteria*, n (%)	13 (56.5)

* At the time of the study was performed, in Italy, patients with hepatocellular carcinoma awaiting for liver transplantation could be treated only if HCC was within Milan criteria (according to the Italian Medicines Agency criteria).

Table 3: Characteristics of patients excluded from LT waiting list for HCC progression

	DAAs treated patients (N = 2)		**Controls (N = 1)**
Age, years	59	68	59
HCV Genotype	1b	1b	1a
Baseline viral load, UI/ml	1,316,828	135,233	64,493
CPT score	A	B	A
MELD score	8	16	14

Drop-out	Neoplastic portal vein thrombosis	Extra-hepatic metastases	HCC progression after bridge treatment
AFP, ng/ml Baseline Drop-out	4.5 16.5	28 24.7	2.9 4.8
FU, months	12	6	5
DAAs treatment	SOF+RBV 24w	LDV/SOF+RBV 12w	
IFN exp (NR)	Yes	Yes	Yes

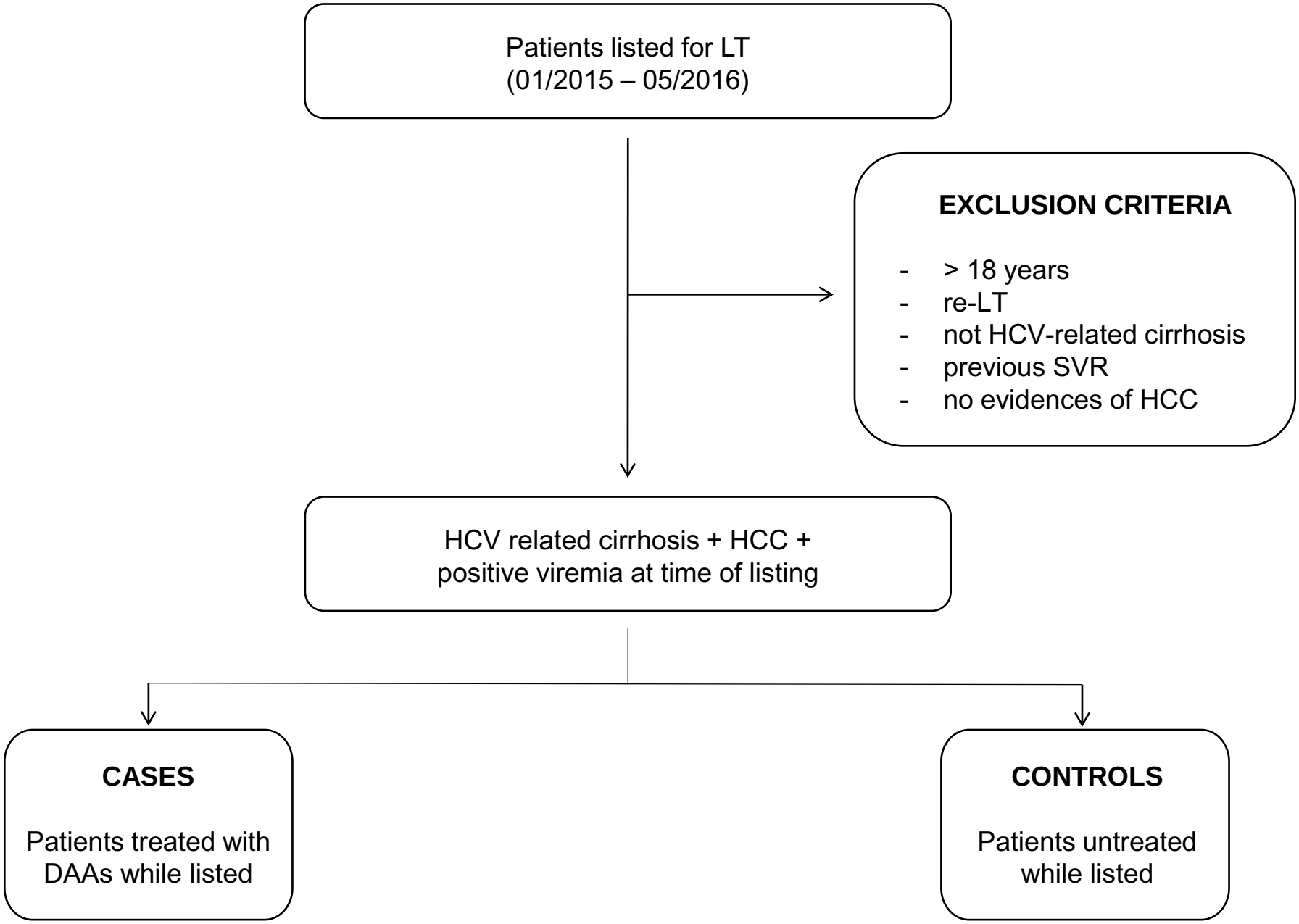
Legend: CPT = Child-Turcotte-Pugh score; MELD = Model for End-Stage Liver Disease; HCC = hepatocellular carcinoma; AFP = alpha-fetoprotein; FU = follow-up; SOF = Sofosbuvir; RBV = Ribavirin; LDV = Ledipasvir; 24w = 24 weeks; 12w = 12 weeks.

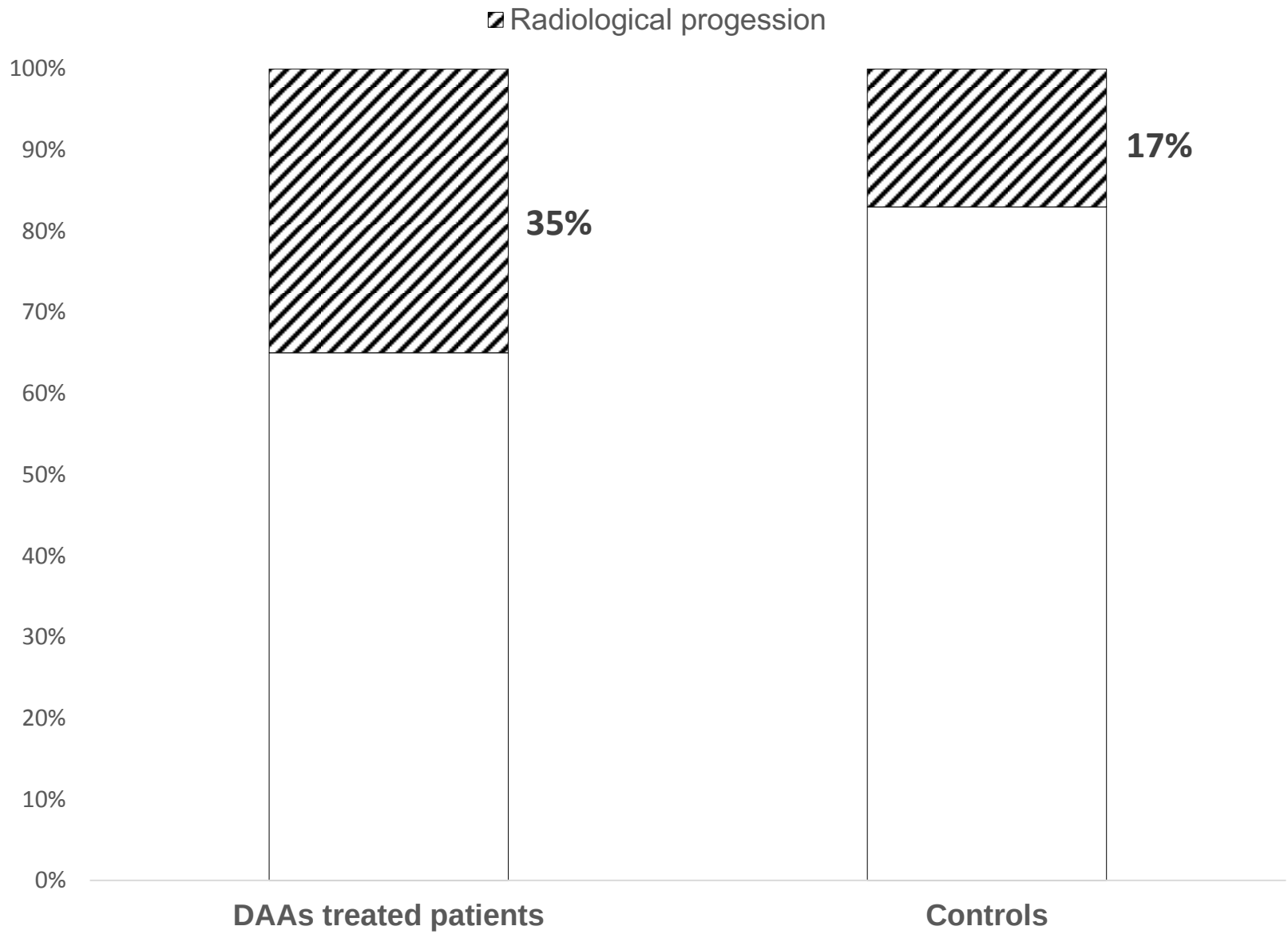
Table 4: Characteristics of patients with post-LT HCC recurrence

	DAAs treated patients (N = 1)	**Controls (N = 1)**
Age, years	54	59
HCV Genotype	3	1a
HCC nodules number Baseline LT*	2 2	2 3
TTV, cm^3 Baseline LT*	100.5 14.2	88 39.8

AFP, ng/ml Baseline LT	 3.2 2	 29.9 8
HCC differentiation	G2	G3
Microvascular invasion	No	Yes
Recurrence timing, months after LT	7	12
Downstaging treatments Bridging treatments	Yes Yes	Yes Yes
LT waiting time, months	6	5
DAAs treatment	DCV/SOF+RBV 24w	
IFN exp (NR)	Yes	No

Legend: HCC = hepatocellular carcinoma; LT = liver transplantation; DAAs = direct antiviral agents; IFN exp = Interferon experienced; TTV = total tumor volume; SOF = Sofosbuvir; RBV = Ribavirin; DCV = Daclatasvir; 24w = 24 weeks. * explant pathology.





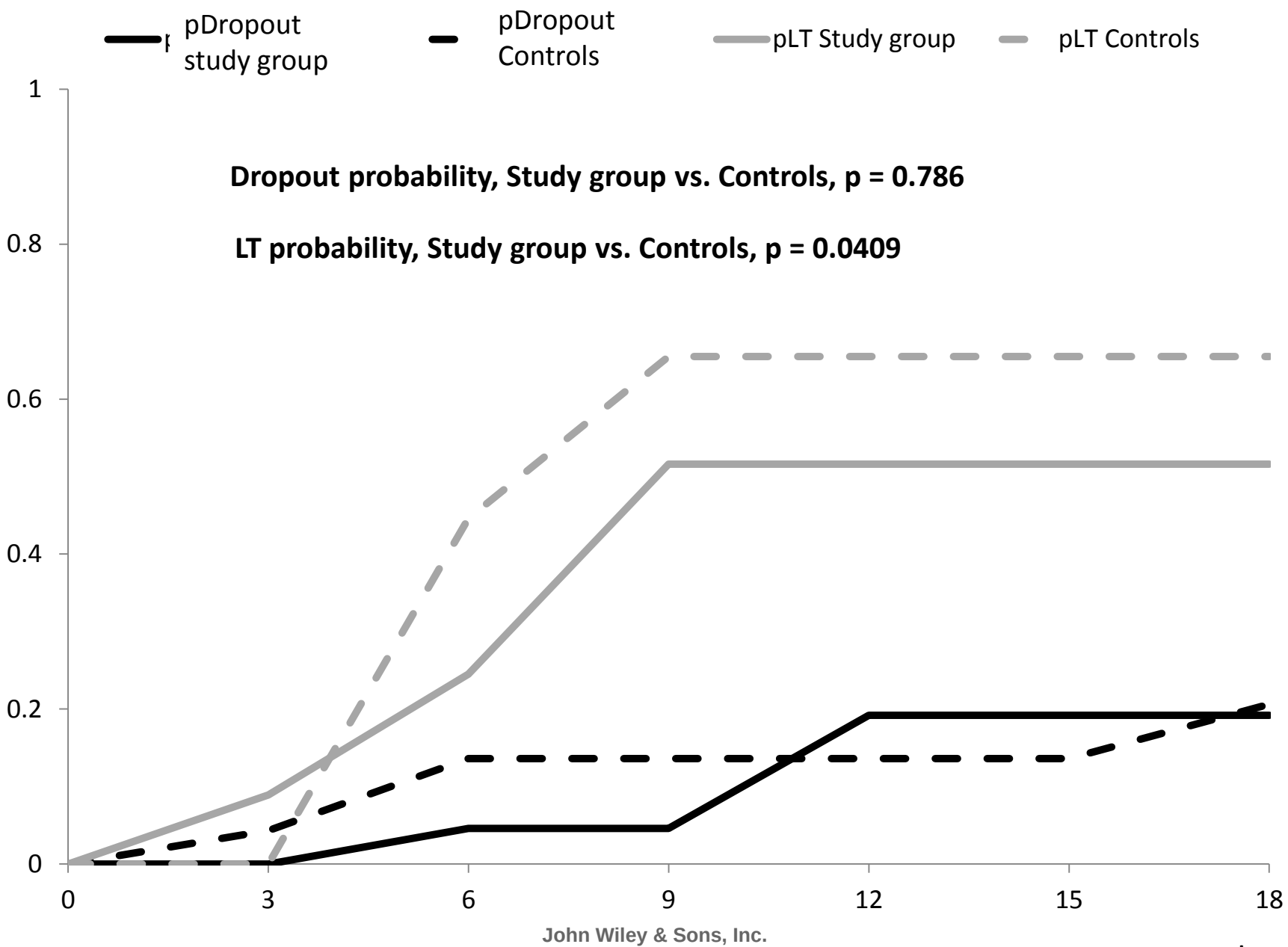


Fig. 1. Patients inclusion criteria flow chart. LT = liver transplantation; SVR = sustained viral response; HCC = hepatocellular carcinoma; DAAs = direct antiviral agents.

Fig. 2. Radiological HCC progression. Radiological progression was present in 35% of DAAs treated patients and 17% of controls, at the end of follow-up (p = .157).

Fig. 3. Drop-out free survival during the waiting list. During the FU period we registered 2 drop outs in treated patients group (8.7 %), respectively after 4 and 12 months from listing, and 1 drop out in controls group (4.3 %) after 4 months (p = .897).