Outcomes of Sorafenib for Recurrent Hepatocellular Carcinoma After Liver Transplantation in the Era of Combined and Sequential Treatments

OUTCOMES OF SORAFENIB FOR RECURRENT HEPATOCELLULAR CARCINOMA AFTER LIVER TRANSPLANTATION IN THE ERA OF COMBINED AND SEQUENTIAL TREATMENTS

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Abbreviations: HCC: hepatocellular carcinoma. LT: liver transplantation. OS: overall survival PFS: progression free survival. mTKI: multitarget tyrosine kinase inhibitors. HR: hazard ratio. CI: confidence interval.

ABSTRACT

Background. Sorafenib and other tyrosine kinase inhibitors are the current standard of care for hepatocellular carcinoma (HCC) recurring after liver transplantation (LT). Sorafenib is sometimes regarded as a scarcely effective treatment in this setting due to some studies showing a short overall survival (OS) indirectly compared to historical series of non-transplanted patients. Such comparisons are questionable due to the peculiar nature of post-LT recurrence.

Methods. Retrospective analyses of a large prospective dataset (n=632) of sorafenib-treated HCC patients to report the outcomes of LT recipients (n=81) and non-LT patients (n=551). The salient characteristics of LT patient are underlined and the feasability of a direct comparison trough a propensity score matching investigated.

Results. LT patients differed from controls in key prognostic baseline features (higher prevalence of metastatic disease, and lower prevalence of macrovascular invasion, alfafetoprotein>400 ng/ml, ALBI grade>1, performance status>0). The propensity score differed in a sensible way in LT and non-LT groups, confirming that the two categories are not directly comparable. With all of the limitation of indirect comparisons, LT patients were more likely to receive concurrent locoregional and post-progression systemic treatment, resulting in a median OS of 18.7 months.

Conclusions. Multimodal and sequential treatments are relatively frequent in post-LT HCC patients and contribute to a remarkable OS, together with more favourable baseline characteristics in comparison with non-LT patients. Despite the impossibility of a matching with non-LT patients, our results indirectly suggest that the metastatic nature of post—LT recurrence and concurrent anti-rejection regimens should not discourage systemic treatments as the prognosis of is not worse than in non-LT patients.

Keywords: transplantation, hepatocellular carcinoma, sorafenib, outcome, cirrhosis.

INTRODUCTION

Recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) is a serious event that tends to neglect the transplant benefit [1]. Systemic treatments for this condition are still primarily based on sorafenib and other multitarget tyrosine kinase inhibitors (mTKI), as immune checkpoint inhibitors have been associated with a non-negligible risk of graft rejection[2,3].

Sorafenib is the most explored frontline systemic drug in patients with post-LT HCC recurrence. Since LT recipients were excluded from the registrative SHARP and Asia-Pacific trials of sorafenib [4,5], current data derive from observational studies. Most of these studies are single-centre trials with no control arm, with sample size and patients' characteristics varying widely [6,7]. Two different meta-analyses reported significant heterogeneity in outcome measures, with median overall survival (OS) ranging from 5.0 to 23.5 months [6,7]. The few studies which compared the OS of sorafenib-treated LT recipients with that of historic transplanted patients who had received the best supportive care in the pre-sorafenib era reported a survival benefit of the systemic treatment [8–11]. Still, the short OS reported in some papers [12,13] led to suspicion that the immune suppression could hamper the anti-neoplastic benefits of sorafenib. The possible pharmaceutical interactions between sorafenib and anti-rejection drugs were also reported as a potential matter of concern [13–16].

Still, most of the remaining studies reported median OS values, which were grossly comparable with or even superior to those described in non-LT patients[6,7]. In a first meta-analysis [6], the pooled estimate of 1-year OS of LT patients who received sorafenib was 63.0% (95% CI 47-78), a slightly better figure of that reported in the pre-transplant setting[4,5,17]. A most recently published analysis, instead, estimated a median OS of 12.8 months (95% CI, 10.6-15.1) and a 1-year OS 56.8% (95% CI, 42.8-70.9)[7]. Both papers concluded that additional data from multicenter prospective studies were needed before drawing definite conclusions.

Establishing whether concurrent immune suppression actually leads to impaired survival is crucial in a therapeutic scenario in which immunotherapies are being increasingly explored[18]. Also, verifying whether LT patients are relatively resistant to sorafenib can be helpful to patient informing, especially in the light of the availability of second and third-line mTKIs, such as regorafenib and cabozantinib[19].

A methodology comparing LT patients with controls matched for the main prognosticators is necessary to address these questions correctly. Until now, a single experience in the Asian population adopted such method. The results seemingly contradicted the fears of an impaired efficacy of sorafenib[20]. Still, the extreme

differences seen in the baseline characteristics of LT patients and controls leaves doubt regarding the actual validity, reliability and generalisability of such comparisons. Also, experiences outside of the Asia region are missing.

In this study we aimed to: 1) compare the baseline characteristics clinical management and outcome of LT and non-LT patients in a large multicenter cohort of patients treated with sorafenib in centers which are expert both in the management of systemic treatments for HCC and in liver transplantology (reporting unadjusted comparisons); 2) verify the feasibility of a direct comparison using propensity score matching technique.

METHODS

Design of the study

This study was performed using medical records from the Archives of Patients with hEpatocellular carcinoma treated with Sorafenib (ARPES) database. This prospective database was created in 2010 to collect data acquired in a real-life scenario of patients treated with sorafenib to identify clinical, laboratory, and imaging predictors of response to the drug. This database includes consecutive patients treated with sorafenib in 5 different Italian Centers (Bologna, Naples, Bergamo, Pisa, and Milan). Data were entered every 3–6 months starting from January 2010 into electronic data files by co-investigators from each centre and were checked at the data management centre for internal consistency. For this study, we considered patients who were prescribed sorafenib from January 2010 to December 2019. The starting date coincided with the creation of the database and, therefore, with the possibility of obtaining prospective data from all the study centres. The closing date was chosen to allow an adequate follow-up of patients. The closing time for the last follow-up was January 31, 2021. Patients in the LT group were not subject to exclusion criteria. For patients who had developed HCC on the native liver, chronic exposure to immune suppressant drugs (including corticosteroids > 5mg/day of prednisolone or equivalent, methotrexate, leflunomide, cyclosporine or other calcineurin inhibitors, mammalian target of rapamycin inhibitors, cyclophosphamide, anti-tumour necrosis factors antibodies, Janus kinase inhibitors, anti-CD20 monoclonal antibodies) was considered as an exclusion criterion. Classical contraindication to LT (such as very advanced age, non-hepatic active malignancies, significant comorbidities) were not considered exclusion criteria for the non-LT group since LT patients could develop these medical conditions after LT but before HCC recurrence.

Baseline evaluation

Parameters entailing the residual liver function according to the Child-Pugh score and ALBI grade [21], tumour staging according to the BCLC classification, baseline α-fetoprotein (AFP) value, performance status according to the Eastern Cooperative Group Performance Status (ECOG-PS) were available for all patients. Information about concurrent medical conditions and medications were also available. For this study, we analysed data about aspirin use (which has been recently reported as a possible factor related to a better outcome)[22,23] and immune suppressant agents.

Management of sorafenib

Sorafenib was started at an usual dosage of 400 mg twice a day. Dose modifications (including dose reductions and discontinuation) were performed in cases of intolerable adverse effects. Sorafenib was continued until: (i) radiological and clinical progression (for patients eligible for second-line clinical trials or licensed drugs, radiological progression alone was considered sufficient for discontinuation); (ii) unacceptable toxicity; (iii) clinically significant deterioration of liver function .The reason for the permanent discontinuation of sorafenib was categorised as previously proposed. [24]

Ethics

The study protocol was reviewed and approved by the local Ethics Committees. All patients gave their written informed consent for their data to be included in the prospective observational registry. The study was conducted according to the ethical guidelines of the latest Declaration of Helsinki.

Statistical analysis

Continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are expressed as frequencies. Group comparisons were performed with the Mann-Whitney test. Categorical variables were evaluated using the 2-tailed Fisher test. OS was measured from the starting date of sorafenib until the date of death or the last visit. Survival curves were estimated using the product-limit method of Kaplan-Meier. The role of stratification factors was analysed with log-rank tests. To define the predictors of OS, we used a time-dependent covariates survival approach including statistically significant clinical variables ($p<0.05$) from the univariate Cox analysis. Propensity scores were calculated in two different models, by including: 1) all of the baseline variables who were differently expressed in LT and non-LT groups

to obtain the best possible match (first model); 2) only variables which were independent predictors of OS in the multivariable model including the whole study population (second model). After calculating the propensity scores, analyses were performed according the two techniques: matching and inverse probability of treatment weighting (IPTW). For matching, the propensity scores were used to perform a 1:1 match between patients with similar scores (tolerance 0.02). For IPTW, treatment weights were calculated as 1/propensity score for LT patients and 1/(1 − propensity score) for controls. Statistical analysis was performed using SPSS Statistics for Windows (version 24.0; IBM) and STATA/SE 14.1 (StataCorp).

RESULTS

Study population

This study included 632 patients selected according to inclusion and exclusion criteria. In particular, amongst the 641 patients included in the database,9 in the non-LT groups were excluded for taking concomitant immune suppressive medications (medical reasons: rheumatoid arthritis n=3; Sjogren syndrome, myasthenia gravis, pemphigoid, sarcoidosis, cryoglobulinemic syndrome, and polymyalgia rheumatic n=1 for each condition). The median age was 68 years (IQR 59-74), most patients (85.9%) were males. The median follow-up was 10.6 months (IQR 5.5-22.5). The median progression-free survival (PFS) and OS were 4.3 (95% CI 3.8-4.7) and 10.9 (95% CI 9.9-11.9) months, respectively.

Baseline characteristics of LT patients

Post-LT patients with a recurrent HCC were 81 (12.8%). Most patients (96.3%) had received at least one pre-LT treatment, which included: liver resection (n=13), percutaneous ablation (n=49), transarterial chemoembolization (n=45), selective internal radiation therapy (n=1). The median time from LT to the first HCC recurrence was 19.2 months (IQR 11.7-47.1). Six patients developed HCC after more than 5 years (i.e. 60 months). Amongst them, 4 patients were not cirrhotic at the time of recurrence. The remaining two patients had sign of chronic graft disease but had a extrahepatic-only recurrence. Consequently, the risk of misclassifying these patients as de novo HCC on cirrhotic graft was estimated as low. The median time from the first recurrence to the start of sorafenib was 4.0 months (IQR 1.7-11.1). Following the first recurrence and prior to the start of sorafenib, 51 patients (63.0%) received at least one non-systemic treatment, including: surgical resection (n=34), percutaneous ablation (n=17), transarterial chemoembolization (n=6), external beam radiation therapy (n=4). Also, three patients who had received calcineurin inhibitors at the time of

transplant had been switched to mTOR inhibitors at the first recurrence (always before starting sorafenib). At the time of sorafenib start, 56 patients were receiving calcineurin inhibitors and 28 patients mammalian target of rapamycin inhibitors (with five patients receiving a combination of both classes and two patients treated with other drugs). A detailed description of anti-rejection regimens is reported in Table 1.

Patients with recurrence after LT differed from patients with HCC on native liver under many factors (Table 2). They were significantly younger and had a higher prevalence of well-preserved liver function, metastatic disease, and low-dose aspirin use (usually adopted to reduce the risk of anastomotic hepatic artery thrombosis). Instead, they were less likely to have macrovascular invasion, high AFP, or compromised performance status.

Attempts at creating a propensity score matching

We first attempted to create a model which included all of the baseline variables who were differently expressed in LT and non-LT groups. These variables included: age (tolerance 5 years), etiology (viral vs nonviral), prior treatments (yes vs no), ALBI grade (1 vs 2-3), AFP (<400 or ≥400 ng/ml), ECOG-PS (0 vs 1-2), intrahepatic burden (massive vs non-massive HCC), extrahepatic burden (absent vs single organ vs multiple organs), macrovascular invasion (yes vs no), aspirin treatment (yes vs no).

In this model, the two groups had extremely different scores: 0.873 (IQR 0.567-0.943) in LT patients vs 0.004 (IQR 0.001-0.027) in controls. The matching identified only 4 possible couples of patients. The maximum weight for the inverse probability of treatment weight analysis was 264.98.

Secondly, we attempted to match LT and non-LT patients only for variables which were independent predictors of survival in the whole study cohort. The multivariable Cox regression identified the following predictors, which were used for creating the propensity score for this second model: AFP (<400 vs ≥400 ng/ml), ECOG-PS (0 vs 1-2), intrahepatic burden (massive vs non-massive HCC), extrahepatic burden (yes vs no), macrovascular invasion (yes vs no), aspirin treatment (yes vs no) (Table 3).

Even in this case, the difference in scores remained relevant: 0.813 (0.284-0.813) in LT patients vs 0.015 (0.004-0.826) in controls, maximum weight 15.85 (Figure 1)

Unadjusted outcomes

Once established that no models of propensity score matching could provide reliable results, we proceeded with unmatched comparisons.

Dermatological adverse events (including skin rash and hand-foot syndrome) occurred in 42 LT and 286 non-LT patients (51.9 vs 51.9%, p=1.000). Similarly, a permanent dose reduction to 400 mg daily was required in a similar proportion in the study groups (61.7 vs 54.2%, p=0.226). Instead, treatment duration was longer in the LT group (8.4 vs 4.7 months, p=0.005). Combined treatments with surgical/locoregional procedures were frequent amongst LT patients than in controls (12.3 vs 1.5%, p<0.001). These treatments included: tumour resections (n=5), percutaneous ablation techniques (n=3), transarterial chemoembolization (n=3). External beam radiation therapy (n=3). Six patients received more than one concurrent treatment. Grade ≥3 bleeding events were similar in the groups (3.7 vs 3.6%, p= 1.000).

A total of 76 and 544 (93.8 and 98.7%) patients in the LT and native liver groups, respectively, permanently discontinued sorafenib. Amongst them, discontinuation due to liver failure was less prevalent in LT than in non-LT patients (progressive disease: 72.4 vs 62.7%, p=0.126; adverse events 23.7 vs 22.1%, p=0.789, liver failure 3.9 vs 15.3%, p=0.004). After the permanent discontinuation of sorafenib, patients in the LT group were more likely to be prescribed second-line systemic drugs (34.2 vs 20.8%, p=0.039). The most frequently prescribed post-sorafenib regimens in the LT group were: regorafenib (n=8), cabozantinib (n=5), metronomic capecitabine (n=10), and conventional chemotherapy (n=3).

LT recipients had a slightly longer PFS (6.7 vs 4.3 months, p=0.013) and a superior OS (18.7 vs 10.3 months, p=0.001) compared to the patients with native liver (Figure 2). Instead, the disease control rate was similar (58.0 vs 50.5%, p=0.234).

Predictors of survival in the LT cohort

The cohort of 81 LT patients was examined to find predictors of OS in this peculiar setting. A separate analysis from the whole study population was deemed appropriate as the propensity score analysis previously demonstrated that this population had deeply different characteristics for the remaining patients.

The univariate analyses showed that ECOG-PS>0 and presence of liver lesions were associated with a worse survival, while dermatological adverse events had a protective role. The multivariable Cox regression confirmed ECOG-PS>0 and presence of liver lesions as independent prognosticators of survival (Table 4)

DISCUSSION

We explored two different aspects of sorafenib in LT patients. First, we described sorafenib efficacy and safety profile in a sizeable multicenter cohort of HCC patients with post-LT recurrence, answering the calls for large populations with prospectively collected data [6,25,26]. Second, we compared these data with patients which had received sorafenib in the same centers but with an HCC arisen on the native liver (by the means of unadjusted comparison and verifying the unfeasibility of matched comparisons).

Regarding the first part of our study, we found that the LT patients reached a median OS of about 19 months. This similar to the data provided in LT patients by some Authors [14,27–30], yet profoundly different from other reports [12,13,31–34]. As the available meta-analyses mention, the baseline characteristics of LT patients and the centres' policies are critical in understanding and interpreting the raw survival data [6,7].

In our study, the OS of the control group (patients treated with sorafenib for HCC in native liver) was extremely similar to that previously reported in multicenter clinical trials and real-life experiences[4,35,36]. Since LT patients enrolled in this study were managed by the same centers who enrolled the controls, and considering the multicenter nature of this study, it can assumed that the survival data of our LT population are reliable and representative of a broad reality.

In our study, the remarkable OS of transplanted patients depended on multiple factors. First, LT patients had more favourable baseline characteristics. Indeed, the metastatic nature of the post-LT recurrence led to a very high rate of extrahepatic spread. However, this factor was counterbalanced by a lower degree of liver dysfunction (due to the absence of liver cirrhosis) and lower rates of symptomatic disease, massive liver neoplastic occupation, macrovascular invasion, and high AFP (due to an early diagnosis favoured by strict controls with panoramic imaging during the first 1-2 years after LT[37]. Chronic use of low-dose aspirin has been recently advocated as a positive predictive factor in sorafenib-treated patients [22,23]. Its extensive use in LT patients to prevent the occlusion of the hepatic artery anastomosis [37] could be another factor contributing to higher OS values. Second, the preserved liver function and good performance status allowed a more frequent use of combined locoregional treatments during and after sorafenib. Also, more LT patients than controls were eligible for second-line systemic treatments after sorafenib discontinuation. This information is of particular interest as second and third-line mTKIs has become available over time. An observational multicenter retrospective study of regorafenib in LT patients [38] described outcomes similar to that reported in

the registrative RESORCE trial[39], which did not enrol transplant recipients. Notably, The median OS calculated from sorafenib start was 28.8 months[38]. A Phase 2 trial of cabozantinib in patients with recurring HCC after LT has been designed (NCT04204850), but no definite data are still available. Of note, a recent real-life study of cabozantinib in HCC patients included 10 LT recipients amongst a total of 96 patients; the median survival from the start of a frontline systemic therapy to death was 36 months in patients who received the sorafenib-regorafenib-cabozantinib sequence [40]. Under normal conditions, only a minority of patients can receive more than one therapeutic line, as general conditions and liver function worsen at the time of progression [41]. However, since LT patients are more likely to receive post-sorafenib treatments, they might also be one of the populations which will benefit more from sequential strategies. The possible post-sorafenib treatments include both regorafenib and cabozantinib. Also, lenvatinib has become an alternative frontline treatment. Currrently, sorafenib is the only available per-label second-line drug in lenvatinib pre-treated patients. Third-line treatments will eventually include cabozantinib and regorafenib (the latter only in countries not limiting the possibility of prescription to the second-line setting).

The second purpose of our study was to try and match LT patients with controls with similar baseline characteristics. The aim was to understand whether LT and anti-rejection therapies could negatively affect the outcome of the patients. Unfortunately, the overt differences in the baseline characteristics of the patients did not allow such matches despite the numerosity of both cases and controls. Differently from the previous point, there are not much data in the literature which can be used to compare our findings. In the only study which explored the feasibility of matching, Lee et al. [20] examined f 832 consecutive HCC patients treated with sorafenib (790 in the non-LT group and 42 in the LT group) between 2008 and 2019 at the liver unit of a Korean centre. The enrolled population had similar characteristics to our study, except for a slightly higher prevalence of viral aetiology of liver disease and Child-Pugh B patients[20]. The Authors reported higher median OS (16.8 vs 7.1 months, $p<0.001$) and time-to-progression in LT compared to non-LT patients in the entire study population [20]. They also managed to match 42 pairs of patients using propensity scores, finding no significant survival differences in the matched population (18.2 vs 16.8 months). Differently from our study, performance status was not considered as a prognosticator nor as a matching factor. Also, liver function was categorized according to the Child-Pugh score, which is not entirely appropriate for non-cirrhotic patients such as most LT recipients at the time of HCC recurrence (resulting in easier match as both populations has an overwhelming majority of Child-Pugh A patients). These discrepancies were likely

responsible for the transition from a difficult match in Lee study[20] (the liver lesions of the matched population had a median diameter of 8 mm, suggesting a reduced generalizability) to an impossible one in our study.

Finally, we investigated to predictors of survival in the population of patients with post-LT recurrence of HCC who received sorafenib. The results of this analysis should be taken with caution as our sample size is one of largest in literature, but still suboptimal for multivariable regressions with a high number of covariates. With this limitation in mind, LT outside of the Milan criteria or concurrent therapy with calcineurin inhibitors were not associated with worse outcomes once sorafenib was started. This finding can be easily explained by the hypothesis that excessive pre-LT tumour burden or high level of exposure to calcineurin inhibitors might affect the time to recurrence[42], but not the response to sorafenib. Instead, we found that the presence of liver lesionswas associated with a worse outcome. This finding can not be justified bythe risk of liver failure due to the neoplastic occupation of the liver, as most patients had non-cirrhotic grafts when they started sorafenib (and were therefore unlikely to experience liver failure before very late stages). Instead, it could be hypothesized that hepatic and extrahepatic lesions have different pathogenic significance in the specific setting of post-LT recurrence. While extrahepatic lesions can theoretically derive from circulating tumour cells or represent a growth of pre-existing metastasis unde[22,43]cted by imaging, neoplastic lesions of the graft are metastatic in nature (either from circulating cells or from extrahepatic sites) and therefore with a greater potential of biological aggressiveness). Clearly, this hypothesis in mainly academical and will need dedicated studies.

Our paper has some limitations deserving discussion. First, our analyses were retrospective in nature; however, the prospective collection of consecutive cases and the availability of all the requested information for every patient significantly reduced the possibility of selection biases. Second, a certain degree of inter-center variability in the management of both sorafenib and post-transplant therapies should be considered; still, we considered only centers which manage both patients with HCC and a native liver as well as a LT graft. Consequently, possible confounders derived by individual choices (such as the clinicians' propensity to enroll cases with borderline eligibility and managing sorafenib toxicities (39)) should be equally distributed between the two studies groups. Third, the number of enrolled LT patients is the highest in the relevant literature but still not sufficiently high to compare the outcomes according to the concurrent anti-rejection treatment. The heterogeneity of the antirejection regimens partly depended on the evolving news cumulating during the enrolment. For instance, switching to mTOR inhibitors at the first HCC recurrence became less popular after the failure of the EVOLVE-1 trial for advanced HCC.[44]

In conclusion, we reported critical pieces of information. First, multimodal and sequential treatments are relatively frequent in patients with HCC recurring after LT. This factor, paired with a preserved liver function and more favourable tumour characteristics, contributed to achieving considerable OS values in LT patients, compared to those of an unmatched population with HCC and a native liver. This finding underlines the potentialities of both concurrent local treatments and mTKIs sequences in the LT population. Second, even with the important limitations deriving from comparing inherently different populations, we did not find inferior OS and PFS in LT patients compared with patients with native livers. This finding suggest that anti-rejection regimens do not automatically result in an impaired survival. Clearly, an accurate and methodologically correct evaluation of the actual prognostic impact of anti-rejection drugs would require matched populations and homogeneous anti-rejection regimens. Still, our results crudely suggest that even potential detrimental effects on survival (if existent) do not seem to translate into an overtly impaired OS or response to sorafenib. Also, we did not find new signals of adverse events. This information can be used in clinical practice to inform and reassure patients about their outcomes. Equally important, the apparent lack of relevant deleterious effects derived from the inhibition of specific immune pathways might provide indirect yet valuable information in the era of checkpoint inhibitors.

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TABLE 1: Breakthrough of the immune-suppressive therapies amongst the 81 patients with hepatocellular carcinoma recurrence after liver transplant at the time of sorafenib start.

Immune suppressive regimen	N (%)
Everolimus	13 (16.0)
Sirolimus	8 (9.9)
Cyclosporine	14 (17.3)
Tacrolimus	35 (43.2)
Mycophenolate	2 (2.5)
Corticosteroids	1 (1.2)
Everolimus+mycophenolate	1 (1.2)
Tacrolimus+everolimus	5 (6.2)
Tacrolimus+corticosteroids	1 (1.2)
Everolimus+tacrolimus+corticosteroids	1 (1.2)
TOTAL exposed to mTORi	28 (34.6)
TOTAL exposed to CNI	56 (69.1)

mTORi: mammalian target of rapamycin inhibitors; CNI: calcineurin inhibitors.

TABLE 2: Comparison of the characteristics of patients with and without liver transplant at the start of sorafenib.

	Native liver (n=551)	LT recipients (n=81)	p
Age (years)	69 (61-75)	57 (52-62)	<0.001
Sex (male)	471 (85.5)	72 (88.9)	0.495
Liver disease aetiology			
- HBV	126 (22.9)	19 (23.5)	
- HCV	277 (50.3)	49 (60.5)	0.080
- Nonviral	148 (26.9)	13 (16.0)	
ALBI grade 1	35 (6.4)	29 (35.8)	<0.001
AFP≥400 ng/ml	179 (32.5)	13 (16.0)	0.003
ECOG-PS>0	143 (26.0)	9 (11.1)	0.003
Tumour >50% liver volume or main trunk PVT	27 (4.9)	0	0.038
Macrovascular invasion	236 (42.8)	10 (12.3)	<0.001
Extrahepatic spread			
- No lesions	374 (67.9)	14 (17.3)	
- One organ	91 (16.5)	10 (12.3)	<0.001
- Multiple organs	86 (15.6)	57 (70.4)	
Aspirin treatment	72 (13.1)	66 (81.5)	<0.001
Metformin treatment	70 (12.7)	11 (13.5)	0.859

LT: liver transplant; HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alfa fetoprotein; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; PVT: portal vein thrombosis.

TABLE 3: Univariable and multivariable Cox regression analysis of factors associated with the overall survival in the whole study population.

UNIVARIABLE ANALYSIS				VARIABLE	MULTIVARIABLE ANALYSIS			
HR	95% CI		p		HR	95% CI		p
.999	.991	1.007	.774	Age (years)	-	-	-	-
.938	.744	1.182	.587	Male sex	-	-	-	-
				Aetiology (nonviral=reference)				
1.098	.870	1.386	.433	HBV	-	-	-	-
1.090	.895	1.326	.391	HCV	-	-	-	-
.705	.578	.861	.001	Aspirin treatment	.712	.521	.903	.029
0.888	0.652	1.232	.611	Metformin treatment	-	-	-	-
1.242	0.948	1.601	0.112	ALBI grade>1	-	-	-	-
2.699	1.938	3.998	<.001	Tumour >50% liver volume or main trunk PVT*	1.657	1.015	2.682	.042
1.508	1.278	1.780	<.001	Macrovascular invasion	1.476	1.240	1.757	<.001
1.290	.998	1.511	.097	Extrahepatic lesions (no=reference)**	1.562	1.199	1.987	.012
1.397	.996	1.569	.088	Single organ	-	-	-	-
1.080	.894	1.366	.193	Multiple organs	-	-	-	-
1.498	1.244	1.804	<.001	ECOG-PS>0	1.487	1.247	1.711	.002
1.482	1.244	1.765	<.001	AFP≥400 ng/ml	1.503	1.204	1.850	<.001
.655	.557	.771	<.001	Dermatological AEs***	.679	.540	.805	<.001

*In preliminary analyses, the survival was similar in patients with no liver lesions, uninodular, and multinodular disease<50% of liver volume.

** based on the results of he univariable analysis, extrahepatic lesions were categorized as yes vs no for the multivariable regression.

***evaluated with a time-dependent analysis.

HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alfa fetoprotein; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status, AEs: adverse events.

TABLE 4: Univariable and multivariable Cox regression analysis of factors associated with the overall survival in the cohort of patients who had received liver transplant

UNIVARIABLE ANALYSIS				VARIABLE	MULTIVARIABLE ANALYSIS			
HR	95% CI		p		HR	95% CI		p
0.990	.968	1.013	0.380	Age (years)	-	-	-	-
0.627	0.294	1.340	0.228	Male sex	-	-	-	-
				Aetiology (nonviral=reference)				
1.785	0.800	3.982	0.157	HBV	-	-	-	-
1.514	0.766	2.996	0.233	HCV	-	-	-	-
1.125	0.625	2.026	0.695	Milan out	-	-	-	-
1.155	0.625	2.134	0.646	Recurrence <12 months	-	-	-	-
0.840	0.427	1.654	0.615	mTORi treatment	-	-	-	-
1.043	0.568	1.916	0.892	Aspirin treatment	-	-	-	-
1.081	0.274	5.013	0.912	Metformin treatment	-	-	-	-
1.111	0.817	2.116	0.555	ALBI grade>1	-	-	-	-
1.803	1.122	2.897	0.015	Liver lesions (yes vs no)	1.710	1.058	2.761	0.028
1.167	0.593	2.298	0.655	Macrovascular invasion	-	-	-	-
				Extrahepatic lesions (no=reference)				
1.017	0.345	2.999	0.976	Single organ	-	-	-	-
0.928	0.333	2.588	0.887	Multiple organs	-	-	-	-
4.259	2.079	8.725	<.001	ECOG-PS>0	3.513	1.612	7.657	0.002
1.321	0.674	2.589	0.418	AFP≥400 ng/ml	-	-	-	-
.545	0.331	0.897	0.017	Dermatological AEs*	0.729	0.432	1.231	0.237

*evaluated with a time-dependent analysis.

HBV: hepatitis B virus; HCV: hepatitis C virus; mTORi: mTORi: mammalian target of rapamycin inhibitors, AFP: alfa fetoprotein; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status, AEs: adverse events.

FIGURE 1: Distribution of the propensity scores in the models with the best possible matching (A) and matching for prognostic variables only (B). In both models, the overlap between scores of patients with native liver and liver transplant is minimal and does not allow generalizable results.

FIGURE 2: Kaplan-Mayer curves of overall survival stratified according to the liver transplant (LT) status in the whole study population.