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Recurrence of hepatocellular carcinoma after liver transplantation: Prognostic and predictive factors of survival in a Latin American cohort

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Abbreviations: AFP, alpha-fetoprotein; BSC, best supportive care; CI, confidence interval; CRF, case report form; CsA, cyclosporine A; CT, computerized tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; MVI, microvascular invasion; OS, overall survival; PEI, percutaneous ethanol injection; PRS, post-recurrence survival; RFA, radiofrequency ablation; RFS, recurrence free survival; Tac, acrolimus; TACE, trans-arterial chemoembolization; TTR, time to recurrence; UCSF-DS, University of California San Francisco – Down-Staging.

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Abstract

Background & Aim: Recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) has a poor prognosis, and the adjusted effect of different treatments on post-recurrence survival (PRS) has not been well defined. This study aims to evaluate prognostic and predictive variables associated with PRS.

Methods: This Latin American multicenter retrospective cohort study included HCC patients who underwent LT between the years 2005-2018. We evaluated the effect of baseline characteristics at time of HCC recurrence diagnosis and PRS (Cox regression analysis). Early recurrences were those occurring within 12 months of LT. To evaluate the adjusted treatment effect for HCC recurrence, a propensity score matching analysis was performed to assess the probability of having received any specific treatment for recurrence.

Results: From a total of 1085 transplanted HCC patients, the cumulative incidence of recurrence was 16.6% (CI 13.5-20.3), with median time to recurrence of 13.0 months (IQR 6.0-26.0). Factors independently associated with PRS were early recurrence (47.6%), treatment with sorafenib and surgery/trans-arterial chemoembolization (TACE). Patients who underwent any treatment presented "early recurrences" less frequently, and more extrahepatic metastasis. This unbalanced distribution was included in the propensity score matching, with correct calibration and discrimination (receiving operator curve of 0.81 [CI 0.72;0.88]). After matching, the adjusted effect on PRS for any treatment was HR of 0.2 (0.10;0.33); $P < .0001$, for sorafenib therapy HR of 0.4 (0.27;0.77); $P = .003$, and for surgery/TACE HR of 0.4 (0.18;0.78); $P = .009$.

Conclusion: Although early recurrence was associated with worse outcome, even in this population, systemic or locoregional treatments were associated with better PRS.

KEYWORDS
hepatocellular carcinoma, liver transplantation, prognosis, recurrence, treatment

1 | INTRODUCTION

Candidate selection for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) has evolved from Milan criteria to *composite* criteria, which include not only tumour burden but also serum alpha-fetoprotein levels (AFP).[1-3] However, even with appropriate candidate selection, HCC recurrence after LT still develops in 8% to 20% of cases,[4-7] with a median time to recurrence (TTR) of 14 months after LT and a post-recurrence median survival of 12.2 months.[8,9] Seventy per cent of recurrent cases are diagnosed within the first 2 years of follow-up and most of these (72.9%) are extrahepatic.[10-12]

Lay Summary

Hepatocellular carcinoma recurrence after liver transplantation in Latin America occurred in 16.6% of patients. Hepatocellular carcinoma recurrence until 1 year after liver transplantation, known as "Early recurrence", is associated with worse outcome. Treatment of hepatocellular carcinoma recurrence after liver transplantation, with any modality, even in early recurrence, is associated with better survival.

Hepatocellular carcinoma recurrence after LT is a dramatic event with dismal prognosis following diagnosis. Although consensus statements recommend surveillance for HCC recurrence after LT,[13,14] it is not clear whether early detection leads to better prognosis. Nevertheless, surveillance for HCC recurrence is recommended to underline candidate selection processes.[11]

Prognostic factors at time of recurrence associated with post-recurrence survival (PRS) have not previously been systematically analysed. Some studies have shown that TTR has been associated with worse prognosis,[5-7] and in other studies, malnutrition and specific site of recurrence, among others, have been shown to be associated with worse PRS.[6,7]

On the other hand, there is no effective or specific treatment for post-LT HCC recurrence. Heterogeneous data have been published so far, including curative and palliative approaches.[8,15] Some authors have proposed locoregional therapies and surgical resection, even in the setting of extrahepatic metastasis. However, it is still uncertain whether these therapies, alone or in combination with systemic treatment, are effective.[8,9,15] Supporting evidence comes from retrospective studies[16] in which the efficacy of specific therapies has not been appropriately adjusted for baseline prognostic factors at time of recurrence.[8,15] Despite the relevance of the subject, there are few published data from Latin America, a region where several health-related barriers have been described.[17] This study aimed to assess prognostic and predictive variables associated with PRS in a Latin American cohort.

2 | MATERIALS AND METHODS

This multicenter cohort included adult patients, over 18 years of age, with HCC who underwent LT between 1 January 2005 and 1 January 2018 in 22 different LT centres from Latin America. Study data were registered into a web-based electronic case report form (CRF), following STROBE guidelines, complying ethical standards from the revised Helsinki Declaration in 2008.[18] Study protocol was registered as part of an open public registry (NCT03775863; www.clinicaltrials.gov), maintaining a confidentiality agreement under each investigator.

Patients were excluded if (a) tumours other than HCC were confirmed in the explanted liver, (b) incidental HCC was identified (patients with tumours discovered on final pathology without a preceding imaging diagnosis), (c) extrahepatic or macrovascular tumour invasion was observed during pre-transplant evaluation and (d) there was a history of previous liver transplant. In all LT patients, exposure variables included pre-LT, explant-based and post-LT data. Pre-transplant patient demographics, aetiology of liver disease as well as longitudinal tumour burden and AFP values were evaluated at listing and at last pre-LT reassessment in all patients. The last image evaluation pre-LT was conducted with CT or MRI. All patients were classified according to pre-LT models or criteria (Milan and the AFP model) based on radiological reports, and serum AFP values.[1,2] Tumour treatment before transplantation was decided in each transplant centre and included transarterial chemoembolization (TACE), radiofrequency ablation, percutaneous ethanol injection and liver resection. In patients exceeding Milan criteria, *downstaging* protocols were evaluated following the University of California San Francisco – Down-Staging (UCSF-DS) proposal.[17]

At explant, aetiology of liver disease was recorded, macroscopic and microscopic evaluation including number and diameter (cm) of each nodule, presence of microvascular invasion (MVI) and degree of tumour differentiation according to Edmonson-Steiner grading system. Necrotic nodules were also measured including necrotic and viable tumour diameter. Finally, the up-to 7 criteria were also applied to the explanted liver specimen.[19]

Maintenance immunosuppression regimen during the first year after transplant was recorded, including Tacrolimus (Tac), cyclosporine A (CsA) or mammalian target of Rapamycin (mTOR) inhibitors (sirolimus or everolimus) with or without mycophenolate sodium/mofetil (MMF). Acute cellular rejection episode during the first 3 months after LT, histologically confirmed, was also registered.

2.1 | Selection criteria: patients with recurrent HCC after LT

From this large cohort, we included patients with HCC who presented recurrence after LT. Post-LT HCC recurrence monitoring consisted of CT or MRI and serum AFP assay with a maximum interval of once every 6 months, as recommended by international consensus.[20] Recurrence was determined based on imaging criteria showing typical hallmarks for HCC for intrahepatic recurrences or by tumour biopsy for extrahepatic sites.[13,14] Exposure variables registered at HCC recurrence diagnosis included site of tumour involvement, including liver, extrahepatic site or both, AFP value at recurrence, liver function, and performance status. Recurrences occurring during the first year after LT were defined as "early recurrence", whereas those occurring after the first year of transplant were defined as "late recurrence".[21]

Additionally, type and treatment initiation following recurrence diagnosis was also registered. As there is no specific international consensus for the treatment of post-LT HCC recurrence, each treatment was decided in each transplant centre on a case-by-case basis following feasibility and available options. As a general rule, for single intrahepatic or extrahepatic sites, resection was done either as a diagnostic or therapeutic approach for tumour recurrence. Systemic therapy included those available from 2005 to 2018 in Latin America. Sorafenib was the only agent approved in this region since 2008.[22] Thus, this time cut-off was additionally included. However, other systemic options were registered including chemotherapeutic agents. Data regarding sorafenib included: starting dose, maximum dose, dose reduction, main adverse events and grade III adverse events leading to sorafenib interruption or discontinuation. During this period, only sorafenib was available for systemic therapy because data on trials and approval of other systemic treatments were afterwards. Data for other recently approved systemic options, such

as lenvatinib, regorafenib, cabozantinib and ramucirumab, or even for immune check-point inhibitors were not registered because these were not available during the study period.[23] Patients not receiving any specific tumour treatment were assigned to best supportive therapy (BSC).

2.2 | Outcomes and statistical analysis

All patients were followed until death or last outpatient visit. Primary outcome analysed was death following recurrence. PRS was defined as the time elapse from recurrence diagnosis to death or last follow-up visit. Secondary outcomes were TTR, which was the time elapsed from LT to diagnosis of recurrence, and recurrence-free survival (RFS), which was the time elapsed from LT to either recurrence or death, whichever occurred first. Overall survival (OS) following LT was also a secondary outcome.

Kaplan-Meier survival curves were compared using the log-rank test (Mantel-Cox) for the primary and secondary outcomes. For the effect of each therapy, time 0 was considered from the date of each therapy. We performed and assessed correlation (*r*) between overall survival since LT and TTR. A multivariate Cox regression model with hazard ratios (HR) and 95% confidence intervals (95% CI) was done to evaluate the effect of exposure variables on mortality following HCC recurrence. Proportional hazard assumption was evaluated through graphic and Schoenfeld residual test.

Second, since treatment for HCC recurrence (the exposure of interest) was not a randomly assigned intervention among participants, propensity score matching was also used to adjust for group differences and reduce confounding bias in patients who underwent any kind of treatment and those who received best supportive care only. Therefore, we estimated the probability of being treated from a multivariate logistic regression model with odds ratio and 95% CI, including the variables that may have been considered for the decision to treat or not (age, country of origin, year of recurrence diagnosis, early recurrence and site of recurrence) and used that score as a single matching covariate. Variables included in the model were those included in the final logistic regression model. In each step, we assessed potential confounding effect. Variables with a $P < .1$ after the univariate analysis were included in the multivariate model, generated by stepwise forward selection and comparing each model's performance with Likelihood ratio test in order to prioritize a parsimonious model. In order to avoid overfitting, one variable per at least 10 events was included in all multivariable models. Calibration (Hosmer-Lemeshow test) and discrimination power (area under the receiving operator curve – AUROC) were evaluated. For the propensity score, we assessed the common support range, identified the optimal number of blocks from the propensity score and evaluated the balancing property in each block. We estimated the adjusted treatment effect of this intervention in the context of an observational study, as a strategy for causal inference. Collected data were analysed with STATA 13.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

This study cohort consisted of 1085 HCC patients who underwent LT in 22 transplant centres from Brazil (n = 377), Argentina (n = 324), Colombia (n = 157), Chile (n = 90), Mexico (n = 63), Uruguay (n = 35), Peru (n = 26) and Ecuador (n = 13). Most of the patients were transplanted during the period of 2012 to 2018 (64.1%; n = 695). Only three patients received a living donor liver transplant during this period. The median time on the waiting list was 4.9 months (IQR 1.7-10.1 months). During the first period of time (2005-2011; n = 435), imaging modality at HCC diagnosis was as follows: CT alone 57.8% (n = 251), MRI alone 27.0% (n = 118) and both methods in 15.2% (n = 66). During the last period (2012-2018: n = 650), imaging modality used for HCC diagnosis was CT in 49.4% of the patients (n = 321), 45.7% with MRI (n = 297), both methods in 2.6% (n = 17) and tumour biopsy in 2.3% (n = 15).

At listing, 86.4% of patients were within Milan criteria (n = 938), of which 7.5% had AFP scores >2 points. In the beyond Milan criteria group at listing, 47.3% had AFP scores ≤2 points. Median AFP value at listing was 11.0 ng/mL (IQR 4.5-52.3 ng/mL); 3.6% of the cohort presented AFP value >1000 ng/mL (Table S1). Locoregional bridging therapies were performed in 55.4% of the study cohort (n = 601). Regarding downstaging, excluding patients with AFP serum values above 1000 ng/mL (n = 39) at listing, 87.5% were within Milan criteria (n = 912). Among patients beyond Milan criteria, 8.0% were within UCSF-DS protocol (n = 83) and 4.5% were exceeding the UCSF-DS protocol, defined as "all-comers" (n = 47). Effective downstaging to Milan criteria occurred in 30.1% (CI 20.5-41.7) of those within the UCSF-DS protocol and 17.0% (CI 7.6-30.8) of "all-comers".

At explant pathology analysis 22.9% of the patients presented MVI, 25.7% had poorly differentiated tumours and 10.3% were beyond the up-to 7 criteria. Complete necrosis of target lesion was observed in 2.8% of patients who underwent bridging therapies. Overall 5-year post-LT survival rate was 64.2% (CI 60.5-67.6), whereas corresponding HCC recurrence rate was 16.6% (CI 13.5-20.3) (Figure 1A).

3.1 | Patients with recurrent HCC after LT

A total of 105 patients presented HCC recurrence after LT, with a cumulative recurrence rate at 1, 3 and 5 years after LT of 5.8% (CI 4.4-7.6), 12.5% (CI 10.2-15.1) and 16.6% (CI 13.5-20.3) respectively (Figure 1A). Overall median RFS was 25.0 months (IQR 7.0-47.5) (Figure 1B) with a median TTR of 13.0 months (IQR 6.0-26.0). TTR significantly correlated with post-LT overall survival ($r = .82$; $P < .0001$) (Figure S1).

At listing, 68.6% of the patients with HCC recurrence were within Milan criteria, and median AFP values at listing were 41.6 ng/mL. In patients presenting recurrence, after excluding 10 patients with AFP values above 1000 ng/mL (according to the UCSF-DS protocol), 70.5% were within Milan criteria (n = 67), 19.0% were within UCSF-DS protocol (n = 18) and 10.5% (n = 10) were "all-comers". Effective downstaging to Milan criteria from listing to last tumour reassessment

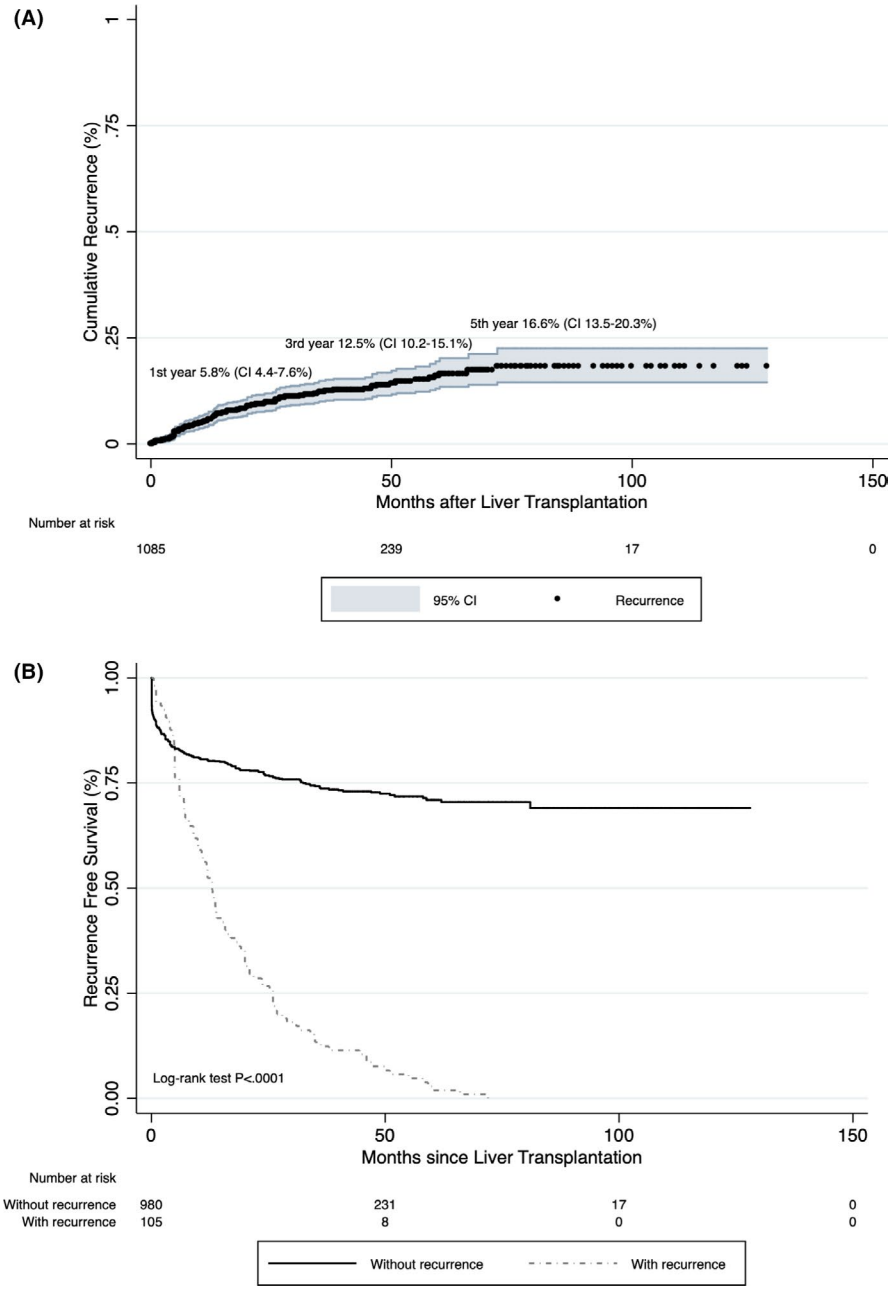

FIGURE 1 Kaplan-Meier cumulative recurrence curve for the overall cohort (Panel A). Recurrence-free survival in patients with or without recurrence (Panel B). *Note*. Median time to recurrence in patients with hepatocellular carcinoma recurrence after liver transplantation (LT) was 13.0 mo (IQR 6.0-26.0). Most of recurrences occurred during the first 2 y after LT; 47.6% presenting early recurrence (A). Recurrence free survival was significantly shorter for those patients presenting recurrence (B)

occurred in 27.8% (CI 9.7-53.4) of those within the UCSF-DS protocol and 30.0% (CI 6.7-65.2) of "all-comers". When analysing explant features, 34.3% were beyond the up-to 7 criteria, 52.4% presented MVI and 29.5% had a nuclear grade ≥II (Table 1). Recurrence diagnosis was conducted using imaging plus AFP values in 77.1% and tumour biopsy in 22.9%. Median AFP values at recurrence diagnosis were 400 ng/mL (IQR 8.0-3270 ng/mL). Extrahepatic sites of recurrence were more frequent than liver alone (76.2% vs 44.7%); most common extrahepatic sites were lungs (34.3%) and bones (31.4%).

The most used drugs for maintenance immunosuppression during the first year after LT in patients with recurrent HCC were Tac in 65.7%, MMF in 53.3% and steroids in 89.1%. Use of CsA with or without steroid or MMF was in 21.9%. The use of mTOR inhibitors, either alone or with MMF, was observed in 32.4% after the first year of transplant in patients presenting HCC recurrence. Acute cellular rejection was reported in 9.2% of these patients.

Early recurrence presented in 47.6% of patients (Table 2). Variables associated with "early recurrence" are shown in Table 3. Only the presence of poorly differentiated tumours at explant pathology was independently associated with "early recurrence" with an OR of 2.49 (CI 1.02;6.06), adjusted for the presence of MVI [OR 1.2 (CI 0.53;2.65)] and pre-LT AFP values [AFP >1000 ng/mL OR 1.9 (CI 0.48;7.70)].

3.2 | Variables associated with PRS

Median PRS was 6.2 months (IQR 2.3-14.4 months). Analysing prognostic factors assessed at recurrence diagnosis, "early recurrence"

TABLE 1 Baseline characteristic of patients with recurrent HCC (n = 105)

Variable	Value
Age, y (±SD)	57 ± 9
Gender, male, n (%)	83 (79.0)
Waiting list, mo, median (IQR)	4.6 (2.1-10.2)
Supplementary MELD points, n (%)	72 (68.6)
Year of transplant, n (%)	
2005-2011	62 (59.0)
2012-2018	43 (40.9)
Year of recurrence, n (%)	
Before 2008	16 (15.2)
After 2008	89 (84.8)
Pre-transplant images at listing	
Within Milan, n (%)	72 (68.6)
AFP, ng/L, median (IQR)	41.6 (8.5-350)
AFP ≤ 100 ng/mL, n (%)	66 (64.7)
AFP 100-1000 ng/mL, n (%)	26 (25.5)
AFP > 1000 ng/mL, n (%)	10 (9.8)
Locoregional treatment before LT, n (%)	63 (60.0)
Explanted liver features	
Within up-to 7, n (%)	69 (65.7)
MVI, n (%)	55 (52.4)
Nuclear grade > II, n (%)	31 (29.5)

Note: Normal values: alpha-fetoprotein 0.6-4.4 ng/mL.

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; MVI, microvascular invasion.

was associated with worse PRS (median PRS 3.9 vs 8.4 months, $P = .0003$) (Figure 2). Baseline prognostic variables associated with death after recurrence are shown in Table 3. "Early recurrence" [HR 2.1 (CI 1.37;3.38)], adjusted for pulmonary metastasis, was independently associated with death after recurrence. Type of immunosuppression regime at the first year of transplant was not associated with better PRS.

3.3 | Adjusted treatment effect after propensity score matching

Regarding post-LT HCC recurrence treatment, only 55.2% of the patients (n = 58) received any kind of treatment (curative or palliative) and 44.8% (n = 47) best supportive care. Among patients who underwent treatment for HCC recurrence, 10 were submitted to resection, 3 were treated with TACE, 5 received radiotherapy, 6 underwent systemic chemotherapy and 41 received sorafenib. The median sorafenib treatment duration was 9.3 months (IQR 3.3-22.6 months). Most frequent sorafenib starting dose was 800 mg/day in 58.3%, 77.8% of the patients achieved the maximum dose of 800 mg and 27.8% needed dose reduction during follow-up. The most frequent adverse events were hyporexia (n = 8) and diarrhoea (n = 7) and 30.6% required sorafenib interruption or discontinuation caused by grade III adverse events (anorexia and fatigue in 5 patients, abnormal liver function tests in 2 patients and hand-foot-skin reaction, gastrointestinal bleeding, congestive heart failure and encephalopathy in 1 patient each). Four patients received combined treatment including sorafenib: one with resection, one with resection and TACE and two with systemic chemotherapy and radiotherapy.

Patients who received treatment for HCC recurrence presented a longer median PRS compared to BSC {11.4 vs 3.2 months [HR 0.2 (CI 0.12;0.32); $P < .001$]} (Table 2). Median PRS was longer in patients receiving sorafenib or liver resection/TACE when compared to BSC [(11.3 vs 5.2 months, $P < .001$) and (16.8 vs 5.2 months, $P = .001$), respectively], even in patients with "early recurrence" (Figure 3). In Cox regression multivariate analysis, early recurrence [HR 1.9 (CI 1.22;3.03)], treatment with sorafenib [HR 0.4 (CI 0.22;0.59)] and surgery/TACE [HR 0.3 (CI 0.14;0.61)] were factors independently associated with mortality after recurrence (Table 4).

Patients who underwent treatment for HCC recurrence presented "early recurrences" less frequently, and a higher frequency of extrahepatic metastasis (Table 2). This unbalanced distribution of "early recurrence" between groups could have led to a treatment selection bias. Variables included in the propensity score matching evaluating the probability of having received treatment for HCC recurrence were as follows: year of recurrence before 2008 (OR 0.1 [CI 0.02;0.67]; $P = .01$), "early recurrence" (OR 0.2 [CI 0.08;0.57]; $P = .002$) and hepatic site at recurrence (OR 0.2 [CI 0.08;0.67]; $P = .007$), adjusted for country of origin (Table S2). Calibration of the model was correct (Hosmer-Lemeshow $P = .77$) and the AUROC was 0.81 (CI 0.72;0.88) (Figure 4). Five blocks of treatment probability were generated for the propensity score and all variables were balanced in each block. Standardized bias across covariates included in the propensity score before and after matching was not significant (Figure S2). The adjusted effect on PRS after the propensity score matching estimation showed that any kind of treatment [adjusted HR of 0.2 (0.10;0.33); $P < .0001$], sorafenib therapy [adjusted HR of 0.4 (0.27;0.77); $P = .003$] and surgery/TACE [adjusted HR of 0.4 (0.18;0.78); $P = .009$] were associated with better PRS.

4 | DISCUSSION

In this large Latin American multicenter study, the 5-year cumulative recurrence rate was 16.6%, similar to the latest published studies.[10,24] We evaluated prognostic factors at the time that recurrence was diagnosed, and the effect of specific therapies for recurrent HCC. Patients with early recurrence presented worse prognosis, and treatment of HCC recurrence impacted positively on survival. Adjusted for these prognostic factors, through propensity score matching, both sorafenib and locoregional therapy prolonged PRS.

Hepatocellular carcinoma recurrence has been associated with a dismal prognosis, it is one of the most significant causes of death

TABLE 2 Comparative analysis between patients receiving and not receiving treatment for HCC recurrence

Variable	With treatment n = 58 (55.2%)	Without treatment n = 47 (44.8%)	*P*
Age, y (±SD)	58 ± 9	57 ± 9	.79
Gender, male, n (%)	42 (72.4)	41 (87.2)	.09
Country, n (%)			
Argentina (n = 27)	15 (55.6)	12 (44.4)	.03
Uruguay (n = 6)	4 (66.7)	2 (33.3)	
Chile (n = 12)	5 (41.7)	7 (58.3)	
Brazil (n = 30)	12 (40.0)	18 (60.0)	
Mexico (n = 9)	9 (100)	0	
Peru (n = 1)	1 (100)	0	
Colombia (n = 20)	12 (60.0)	8 (40.0)	
Ecuador (n = 0)	0	0	
Data at recurrence diagnosis			
Year of recurrence, n (%)			
Before 2008	3 (5.2)	13 (27.7)	.002
After 2008	55 (94.8)	34 (72.3)	
Early recurrence, n (%)	17 (29.3)	33 (70.2)	<.0001
Hepatic site of recurrence, n (%)	20 (34.5)	27 (57.4)	.01
Extrahepatic site of recurrence, n (%)	48 (82.8)	32 (68.1)	.06
AFP at recurrence > 1000 ng/L, n (%)	7 (12.1)	7 (14.9)	.44

Note: Normal values: alpha-fetoprotein 0.6-4.4 ng/mL.

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; LT, liver transplantation.

after LT, with a median OS less than a year after the diagnosis.[14,25] Generally, post-LT HCC recurrence occurs in a multifocal state with a fast progression rate caused by immunosuppression.[15] In this study, the median TTR was 13 months and the median PRS was 6.2 months, similar to other series.[9,21,26] We observed that TTR was an important prognostic factor, half of patients presented recurrences within the first 12 months, and was an independently associated factor with poor survival, as previously reported.[18,23] Different from what was observed in other studies,[9,24] where AFP values impacted on survival of these patients, in our study AFP levels at recurrence had no impact on post-recurrence mortality. However, AFP values at recurrence diagnosis have not been robustly associated with worst outcomes after LT.

Early recurrence (<12 months) has been associated with a negative impact on survival, regardless of specific treatment.[9] These prompt tumour presentations may be related to a failure of pre-transplant staging, a high original cancer load with circulating tumour cells in other organs or an expression of a more aggressive tumour biology.[26,27] We observed an independent association between early recurrence and presence of poorly differentiated tumours which reinforce this hypothesis. Late recurrence has been associated with a better prognosis, in part owing to late engrafting of HCC cells that remained latent or neo-oncogenesis.[8,28]

Although the effect of therapy for HCC recurrence upon PRS has been evaluated in different previous publications, the adjusted treatment effect considering selection bias has not been conducted before. Indeed, as there are no prospective, randomized or controlled studies, most of these data came from retrospective publications. Consequently, the treatment strategy in this group is still controversial.[4,8]

In the present study, patients who underwent treatment presented a better PRS that was significantly higher compared to those receiving best supportive care, even after adjusting through propensity score matching for the probability of having received any treatment. In a Brazilian retrospective multicenter study, patients who were submitted to any kind of treatment after recurrence also presented better survival, and it was an independent factor associated with better prognosis.[24] However, the effect of treatment was not adjusted with a potential indication of selection bias,[8-10] showing better PRS in those patients who could only be treated owing to better unreported prognostic factors (nutrition status, performance status, site preferences, feasibility, among others).[4,15,29]

In our study, systemic therapy with sorafenib presented better PRS when compared to BSC, independently of TTR, and was well tolerated in the majority of patients. Systemic therapy is usually applied in patients who HCC relapse presents or become

TABLE 3 Prognostic variables associated with post-recurrence mortality. Cox regression analysis

Variable	Median post-recurrence survival, mo (IQR)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age, y		1.00 (0.98;1.03)	.68		
Milan criteria at listing[a]					
Within (n = 72)	5.0 (2.1-11.9)	–			
Exceeding (n = 33)	9.6 (5.3-18.5)	1.24 (0.78;1.96)	.36		
AFP level at listing, ng/mL					
≤100 (n = 66)	6.3 (3.1-16.4)	–	–		
101-1000 (n = 26)	4.9 (1.5-11.5)	1.16 (0.68;1.96)	.59		
>1000 (n = 10)	6.2 (2.0-14.4)	1.13 (0.54.2.39)	.74		
Up-to 7 criteria[a]					
Within (n = 69)	5.6 (2.3-14.1)	0.79 (0.51;1.25)	.32		
Exceeding (n = 36)	6.7 (3.2-16.0)	.			
Microvascular invasion[a]					
Presence (n = 55)	5.8 (3.1-16.8)	0.91 (0.58;1.41)	.67		
Absence (n = 50)	6.3 (2.2-14.4)	.			
Poorly differentiated tumours[a]					
Presence (n = 31)	6.3 (1.6-11.5)	1.21 (0.76;1.95)	.42		
Absence (n = 74)	6.2 (2.6-16.4)	.			
Immunosuppression at first year of LT					
Tac (n = 69)	5.8 (2.6-15.3)	0.67 (0.43;1.05)	.08		
MMF (n = 56)	4.7 (1.8-11.1)	1.20 (0.77;1.87)	.41		
CsA (n = 23)	8.1 (2.3-16.8)	1.28 (0.78;2.09)	.32		
mTORs (n = 34)	6.7 (3.1-6.7)	1.14 (0.72;1.81)	.57		
Early recurrence					
Yes (n = 50)	3.9 (1.5-11.3)	2.23 (1.43;3.49)	<.0001	2.15 (1.37;3.38)	.001
No (n = 55)	8.4 (5.0-19.0)	.			
Extrahepatic site					
Yes (n = 80)	6.3 (2.8-16.8)	0.71 (0.43;1.18)	.19		
No (n = 25)	5.0 (2.1-9.1)	.			
Pulmonary metastasis					
Yes (n = 36)	6.7 (2.2-22.0)	0.69 (0.43;1.11)	.13	0.80 (0.49;1.31)	.38
No (n = 69)	6.0 (2.6-11.8)	.			
Bony metastasis					
Yes (n = 33)	6.3 (3.1-11.5)	1.35 (0.84;2.17)	.22		
No (n = 72)	6.1 (2.4-18.8)	.			
Other sites metastasis					
Yes (n = 29)	6.2 (2.6-13.9)	1.13 (0.70;1.82)	.62		
No (n = 76)	6.1 (2.2-14.9)	.			
AFP at recurrence, ng/L		1.00 (0.99;1.01)	.77		

(Continues)

TABLE 3 (Continued)

Variable	Median post-recurrence survival, mo (IQR)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
≤1000 (n = 91)	6.2 (2.3-16.8)	–			
>1000 (n = 14)	4.5 (2.2-11.5)	1.59 (0.85;2.96)	.15	1.47 (0.78;2.77)	.23

Note: Normal values: alpha-fetoprotein 0.6-4.4 ng/mL.

Abbreviations: AFP, alpha-fetoprotein; CsA, cyclosporine A; HCC, hepatocellular carcinoma; HR, hazard ratio; MMF, mycophenolate mofetil; mTOR, mammalian target of Rapamycin; Tac, Tacrolimus; TACE, transarterial chemoembolization.

[a]At explant pathology analysis.

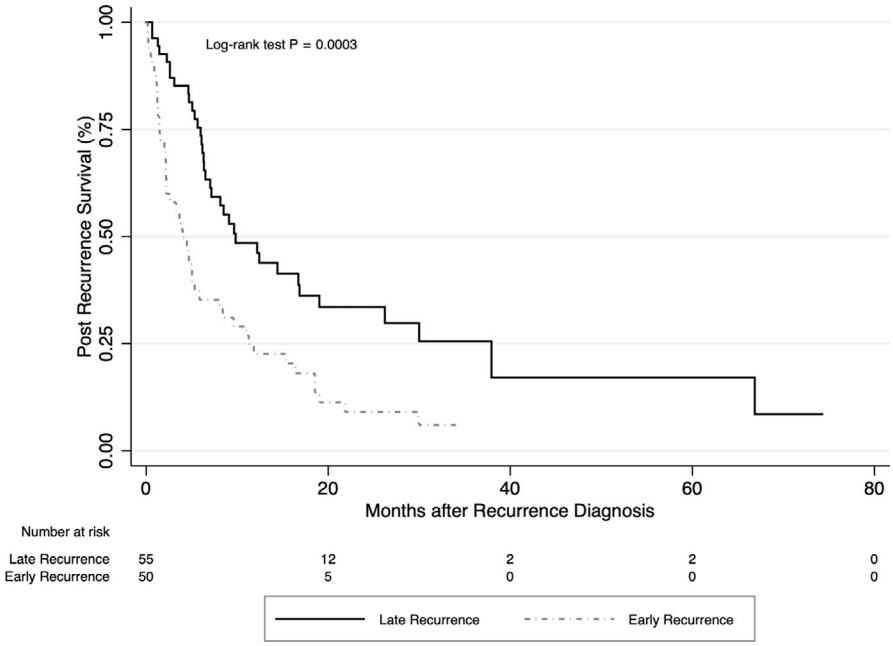

FIGURE 2 Post-recurrence survival in patients presenting "early" vs "late" recurrent hepatocellular carcinoma after liver transplantation

spread systemically.[29] In a meta-analysis, sorafenib improved PRS when compared to BSC and some studies of this review reported side effects with required dose reduction or discontinuation.[8] Nevertheless, the use of sorafenib appears to be well tolerated with few severe adverse events in the post-LT setting.[29-31] We did not evaluate the association of sorafenib and mTOR inhibitors. Some retrospective studies, not adjusting for some selection biases, have shown improved survival as a result of this association.[8] In this study the effect of treatment, including sorafenib, was adjusted for by conducting propensity score matching.

The probability of having received each therapy included recurrences occurring prior to 2008 (sorafenib was available throughout the region from 2008), early recurrence[23,27] and hepatic site.[8,22] A surprising result in this study is the lower probability of treatment in patients with hepatic recurrence. As there are several factors that impact on the likelihood of treatment in these patients and were not addressed by this research; other studies should be conducted to elucidate this result.[8,15]

This study has a few noteworthy limitations. It is a retrospective study for treatment evaluation based on real-life reports from 7 countries. However, to avoid heterogeneous reporting of data, a specific CRF was conducted and centrally reviewed. Secondly, a centralized imaging or explant pathology review was not feasible. Most importantly, performance status or additional comorbidities at recurrence diagnosis, and site feasibility of each treatment were not available. For this reason, we adjusted the treatment effect including country in the propensity score.

In conclusion, in this large multicenter study, early recurrence (<12 months) was the most important factor associated with prognosis after recurrence. Systemic treatment with sorafenib was associated with better PRS, even in early recurrences. Surgical or locoregional therapies were also capable of prolonging PRS. We believe that HCC recurrence is a dismal event, which may be a consequence of unappropriated candidate selection, leading to the use of a graft that could have been used in other HCC or non-HCC patient. Whether early recurrence as a primary outcome, which is associated with worst outcomes, should lead to further refinement of candidate selection is still controversial. Whether new systemic treatment options, such as immunotherapy,[32] will be feasible in this setting is a matter of debate. Although sequential treatment with sorafenib-regorafenib has been recently published,[16] other options such as *checkpoint inhibitors* might increase the risk of graft rejection. This demonstrates the importance of

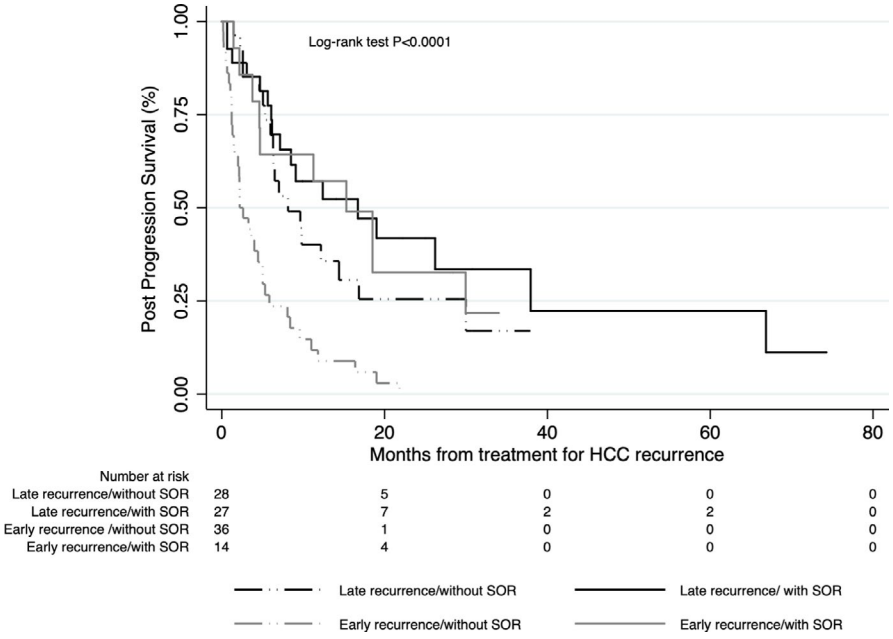

FIGURE 3 Stratified effect on post-recurrence survival according to "early" vs "late" recurrent hepatocellular carcinoma (HCC) after liver transplantation and treatment with or without sorafenib

TABLE 4 Effect of treatment on post-recurrence mortality adjusted for prognostic baseline variables at HCC recurrence diagnosis

Variable	Median post-recurrence survival, mo (IQR)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Early recurrence					
Yes (n = 50)	3.9 (1.5-11.3)	2.23 (1.43;3.49)	<.0001	1.92 (1.22;3.03)	.005
No (n = 55)	8.4 (5.0-19.0)	.			
Treatment of recurrence					
Yes (n = 58)	11.4 (5.6-22.2)	0.19 (0.12;0.32)	<.0001		
No (n = 47)	3.2 (1.3-6.0)	–			
Sorafenib					
Yes (n = 41)	11.3 (4.7-22.2)	0.42 (0.26;0.68)	<.0001	0.36 (0.22;0.59)	<.0001
No (n = 64)	5.0 (2.1-9.6)	–			
Surgery and TACE					
Yes (n = 17)	16.8 (8.4-30.7)	0.33 (0.16;0.67)	.002	0.29 (0.14;0.61)	.001
No (n = 88)	5.3 (2.2-11.4)	–			

Note: Normal values: alpha-fetoprotein 0.6-4.4 ng/mL.

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; TACE, transarterial chemoembolization.

carrying out prospective or even better, randomized controlled studies, comparing different types of treatments in patients with post-LT HCC recurrence, in order to define a treatment strategy for this group of patients.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by *Liver International*.

AUTHOR CONTRIBUTIONS

Research design: Federico Piñero, Claudia Maccali, Aline Chagas. Contribution with important reagents and data collection: all other co-authors including those in acknowledgements. Analysed data: Federico Piñero, Fernando Rubinstein. Wrote the article: Claudia

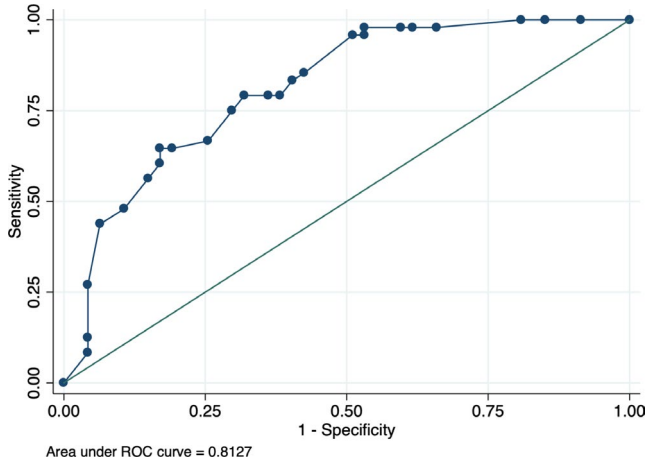

FIGURE 4 Receiving operator curve for the propensity score matching covariate analysis, assessing the probability of having received treatment for hepatocellular carcinoma recurrence

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REFERENCES

1. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693-699.
2. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan Criteria. *Gastroenterol*. 2012;143:986-994.
3. Mazzafero V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterol*. 2018;154:128-139.
4. Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat Rev Gastroenterol Hepatol*. 2017;14:203-217.
5. Roberts JP. Tumor surveillance-what can and should be done? Screening for recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transpl*. 2005;11:S45-46.
6. Schwartz M, Roayaie S, Llovet J. How should patients with hepatocellular carcinoma recurrence after liver transplantation be treated? *J Hepatol*. 2005;43:584-589.
7. Zimmerman MA, Ghobrial M, Tong MJ, et al. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. *Arch Surg*. 2008;143:182-188.
8. De'Angelis N, Landi F, Carra MC, Azoulay D Managements of recurrent hepatocellular carcinoma after liver transplantation: a systematic review. *World J Gastroenterol*. 2015;21:11185-11198.
9. Sapisochin G, Goldaracena N, Astete S, et al. Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large Euro-American Series. *Ann Surg Oncol*. 2015;22:2286-2294.
10. Fernandez-Sevilla E, Allard MA, Selten J, et al. Recurrence of hepatocellular carcinoma after liver transplantation: is there a place for resection? *Liver Transpl*. 2017;23:440-447.
11. Sotiropoulos GC, Molmenti EP, Losch C, Beckebaum S, Broelsch CE, Lang H. Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. *Eur J Med Res*. 2007;12:527-534.
12. Shetty K, Timmins K, Brensinger C, et al. Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. *Liver Transpl*. 2004;10:911-918.
13. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67:358-380.
14. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182-236.
15. Hollebecque A, Decaens T, Boleslawski E, et al. Natural history and therapeutic management of recurrent hepatocellular carcinoma after liver transplantation. *Gastroenterol Clin Biol*. 2009;33:361-369.
16. Iavarone M, Invernizzi F, Czauderna C, et al. Preliminary experience on safety of Regorafenib after Sorafenib failure in recurrent hepatocellular carcinoma after liver transplantation. *Am J Transplant*. 2019;19:3176-3184.
17. Piñero F, Marciano S, Fernández N, et al. Intermediate-advanced hepatocellular carcinoma in Argentina: treatment and survival analysis. *World J Gastroenterol*. 2019;25:3607-3618.
18. Elm EV, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495-1499.
19. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35-43.
20. Kneteman N, Livraghi T, Madoff D, Santibañez E, Kew M. Tools for monitoring patients with hepatocellular carcinoma on the waiting list and after liver transplantation. *Liver Transpl*. 2011;17:117-127.
21. Toso C, Cader S, Mentha-Dugerdil A, et al. Factors predicting survival after post-transplant hepatocellular carcinoma recurrence. *J Hepatobiliary Pancreat Sci*. 2013;20:342-347.
22. Llovet JM, Ricci S, Mazzafero V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;329:378-390.
23. Rimassa L, Pressiani T, Merle P. Systemic treatment options in hepatocellular carcinoma. *Liver Cancer*. 2019;8:427-446.
24. Chagas AL, Felga GEG, Diniz MA, et al. Hepatocellular carcinoma recurrence after liver transplantation in a Brazilian multicenter study: clinical profile and prognostic factors of survival. *Eur J Gastroenterol Hepatol*. 2019;31:1148-1156.
25. Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol*. 2012;57:675-688.
26. Bodzin AS, Lunsford KE, Markovic D, Harlander-Locke MP, Busuttil RW, Agopian VG. Predicting mortality in patients developing recurrent hepatocellular carcinoma after liver transplantation: impact of treatment modality and recurrence characteristics. *Ann Surg*. 2017;266:118-125.
27. Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: risk fator, screening and clinical presentation. *World J Hepatol*. 2019;11:261-272.

28. Taketomi A, Fukuhara T, Morita K, et al. Improved results of a surgical resection for the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Ann Surg Oncol*. 2010;17:2283-2289.
29. Sposito C, Mariani L, Germini A, et al. Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: a case control study. *J Hepatol*. 2013;59:50-66.
30. Piñero F, Marciano S, Anders M, et al. sorafenib for recurrent hepatocellular carcinoma after liver transplantation: a South American experience. *Acta Gastroenterol Latinoam*. 2016;46:300-309.
31. Kang SH, Cho H, Cho EJ, et al. Efficacy of sorafenib for the treatment of post-transplant hepatocellular carcinoma recurrence. *J Korean Med Sci*. 2018;33:e283.
32. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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