ORIGINAL ARTICLE

Multicenter validation of a score to predict prognosis after the development of HCC recurrence following liver transplantation

Nicolás Goldaracena[1], Neil Mehta[2], Irene Scalera[3], Carlo Sposito[4], Eshetu G. Atenafu[5], Francis Y. Yao[2], Paolo Muiesan[3], Vincenzo Mazzaferro[4] & Gonzalo Sapisochin[1]

[1]Multi-Organ Transplant, Division of General Surgery, Department of Surgery, University Health Network, University of Toronto, Canada, [2]Department of Gastroenterology, Division of Medicine, University of California San Francisco, USA, [3]Liver – University Hospital Birmingham NHS Foundation Trust, Birmingham, UK, [4]Department of Surgery, GI Surgery and Liver Transplantation, Instituto Nazionale dei Tumori, Milan, Italy, and [5]Biostatistics Department, University Health Network, University of Toronto, Canada

Abstract

Background: HCC recurrence after LT impacts negatively on survival. A recent study detected late recurrence (≥12 months), alpha-fetoprotein (AFP) <100 ng/mL at recurrence and being amenable for curative-intent treatments as good prognostic factors. With these variables a prognostic score was proposed. The objective of this study was to validate the prognostic score for hepatocellular carcinoma (HCC) recurrence following liver transplantation (LT).

Methods: Data from the University of California, San Francisco, the University Hospital of Birmingham and Instituto Nazionale dei Tumori, Milan including patients with HCC recurrence after LT were analyzed. The previous reported score was applied to this cohort.

Results: From June 2002–December 2014, 1328 patients had a confirmed HCC in their explanted liver. The study group comprised 130 patients (9.8%) diagnosed with HCC recurrence after LT. Overall median survival after HCC recurrence was 12.4 (95% CI 10.2–16.3) months. Application of the previously reported score showed a significantly superior survival for the good prognosis group compared to moderate and poor prognosis groups ($p < 0.0001$).

Conclusion: The score continues to identify a group of patients who would benefit from aggressive treatment and experience significant improved survival following recurrent HCC after LT.

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Correspondence

Gonzalo Sapisochin, Multi-Organ Transplant, Division of General Surgery, 585 University Avenue, 11PMB184, Toronto, M5G 2N2, ON, Canada. E-mail: gonzalo.sapisochin@uhn.ca

Introduction

Liver transplantation (LT) offers the best curative treatment option for patients with early stages of hepatocellular carcinoma (HCC) confined to the liver.[1] Its benefit derives from the principle that LT not only achieves a complete oncological resection but also corrects the underlying liver dysfunction. In addition, LT removes disease tissue that might predispose to future tumor development. Despite this, HCC recurs in approximately 15% of transplanted patients negatively affecting their long-term survival.[2,3]

Since the Milan criteria[4] became the "standard of care" for selecting patients with HCC for LT, many centers have expanded their patient selection by using less restrictive criteria.[5–7] However, although these more permissive criteria have shown to achieve excellent survival outcomes, the risk of post-transplant HCC recurrence has increased.[7] Therefore, there is a need to better understand the management of HCC recurrence after LT to offer patients the best chances of cure or palliation.

Unfortunately, the literature exploring the outcome of transplanted patients after HCC recurrence is scarce.[2,3,8] Moreover, the risk factors predicting survival after post-transplant tumor recurrence and the selection of patients who would benefit from treatment it is not well known. Recently, a multicentric study reported a ~50% 5-year survival post-recurrence in patients with good prognostic factors.[2] In this study, a multivariable analysis detected the following variables as good prognostic factors: late recurrence after transplant (≥12 months), an alpha-fetoprotein

(AFP) < 100 ng/mL at the time of recurrence and being amenable for a curative-intent treatment [i.e. surgery or radiofrequency ablation (RFA) of small liver lesions] at the time of recurrence. Using these variables a prognostic score was proposed and those patients who meet this criteria achieved an excellent survival (Table 1). This score could help clinicians for decision-making when facing HCC recurrence after LT. The main limitation of such study was that it did not have a validation cohort.

The present multicentric study was undertaken with the aim of validating the previous published score for predicting survival after the development of HCC recurrence following LT. Our hypothesis is that the previously developed score could be validated in a different set of patients.

Materials and methods

Study design

This study was performed with the intention of validating the previous reported prognostic score (Table 1). For this, three prospectively collected databases from the University of California at San Francisco (UCSF), the University Hospital of Birmingham and the Instituto Nazionale dei Tumori in Milan including all patients with HCC recurrence after LT were retrospectively analyzed. Variables that negatively impact survival were identified. The previous reported score was then applied to the new cohort. Consequently, patient survival stratified by the prognostic score was analyzed.[2]

Patients included in this study were those that were transplanted with either a known HCC or an incidental HCC confirmed on explant pathologic examination and that presented HCC recurrence after LT. Patients without tumor recurrence were not included in the current study. Survival was analyzed from the time of HCC recurrence after LT.

Centers transplant eligibility criteria for HCC patients

Listing criteria for HCC patients and their prioritization for organ allocation differed among all three centers. In the study period, at the University Hospital of Birmingham HCC patients were included in the waiting list (WL) when they either fulfilled the Milan criteria or when patients with greater tumor burden (total tumor burden between 5 and 7 cm) were down-staged and had stable disease for at least 6 months after bridging therapy. Of note, in the United Kingdom HCC LT candidates do not obtain exception points in the WL. Similarly, at the Instituto Nazionale dei Tumori in Milan, listing criteria for HCC consists on patients' fulfilling the Milan criteria either at diagnosis or after down-staging. Finally, at UCSF the listing and prioritization for HCC patients followed the UNOS based allocation system for the study period.[9] Briefly, between 2001 and 2005 both T1 and T2 patients received exception points. However, beyond the year 2005 only patients with T2 tumors were prioritized on the WL. To clarify, at UCSF patients that exceeded Milan criteria and were successfully down-staged to within Milan were observed for at least 3 months to ensure adequate tumor biology and thereafter considered for LT.

Table 1 Previously reported prognostic score for HCC recurrence after LT[2]

Poor prognostic factors		
-Not amenable for curative-intent treatments		
-Early recurrence (<12 months) after LT		
-AFP ≥ 100 ng/mL		
Prognostic score		
0 points	No variables present	Good prognosis
1 point	1 variable present	Moderate prognosis
2 points	2 variable present	
3 points	All 3 variables present	Poor prognosis

hepatocellular carcinoma, HCC; liver transplantation, LT; alpha feto protein, AFP.

Bridging therapy on waiting list

In all three centers, all patients with an expected WL time >6 months underwent bridging therapy with transarterial chemoembolization (TACE), RFA or percutaneuos ethanol injection (PEI). In those patients that had a previous liver resection as intended definitive treatment, LT was performed for recurrence after resection.

Immunosuppression protocols

Patients' immunosuppression was managed according to their institutions protocols. Baseline immunosuppression regimens in all three centers were based either on tacrolimus or cyclosporine. In addition, steroids were given preoperatively and then tapered over the first 3 months post transplant. In the three participating institutions, treatment with mTOR inhibitors (mTORi) changed over the study period but it was not routinely used in HCC patients. Following recurrence of HCC, addition of, or switch to an mTORi was not routine and used predominantly in the palliative setting.

Postoperative HCC recurrence surveillance and diagnosis

At the Instituto Nazionale dei Tumori in Milan and at the University Hospital of Birmingham, post transplant monitoring for HCC recurrence was performed in every patient transplanted for HCC or that incidentally was found to have an HCC in the explant pathology. It consisted on an ultrasound and/or thoracoabdominal computed tomography (CT) every 6 months for the first three years after LT. AFP was also performed every 6 months. Thereafter, CT was performed annually or if symptoms occurred. Diagnosis of tumor recurrence was based on imaging. A biopsy was performed only if the image was non-conclusive. At UCSF the surveillance protocol was only performed in higher risk patients. Therefore, patients with tumors outside Milan criteria or evidence of vascular invasion in explant pathology, patients with

pre-transplant AFP > 300 ng/mL, patients whose tumors were biopsied or had radiofrequency ablation before transplant and those patients who were initially beyond Milan criteria and were down-staged would be follow-up every 6 months for the first 2 years with AFP and CT chest/abdomen.

Also, all patients experiencing HCC recurrence after transplantation were classified accordingly if they had or not impaired liver function. Impaired liver function was defined as Child score B/C or a model for end stage liver disease (MELD) ≥10 or presence of portal hypertension.

HCC recurrence treatment after transplantation

Treatment modalities for each patient were chosen depending on tumor burden recurrence, extension of the disease, liver function and performance status. All treatments were discussed at multidisciplinary meetings.

Curative-intent treatments

Treatment with curative-intent was defined as any surgical resection or ablation intended to achieve "no evidence of disease". This approach was considered in patients with recurrence at any site (hepatic or extra heaptic). When possible, surgical resection was the first treatment option. When surgical resection was not feasible an ablative technique was the treatment of choice. Of note, ablation therapy was only considered in patients with up to three liver recurrences (≤3 cm).

Palliative treatments

Patients' not eligible for either surgical resection or ablation were considered for palliative treatments. Among these, Sorafenib was offered to patients with advance HCC recurrence with good performance status and adequate liver function tests (Child A or B).[10] In some patients systemic chemotherapy was applied within study protocols. Radiotherapy was used in patients with symptomatic bone recurrence and selected patients with limited intra-abdominal disease were curative-intent treatments could not be applied.[11] In all those patients in whom no therapy could be offered, palliative care specialists offered best supportive care.

Statistical analysis

Data were expressed as means and standard deviation or median and interquartile range (IQR) when normality assumption was not appropriate. Students' t-test was used to compare continuous variables within binary factors. A nonparametric test (Mann–Whitney U) was used when a normality assumption failed. Chi-square test or Fisher's exact test as appropriate was employed for assessing association of categorical variables. Patient survival rates were estimated using the Kaplan–Meier product-limit method and compared with the log-rank test. Time to event was calculated from the time of HCC recurrence to the end of follow-up or death. Univariate analysis was performed only on variables with clinical significance. These variables with clinical importance were also used to obtain the score that define the prognostic model. A p value ≤ 0.05 was considered as evidence of independent statistical significance. Statistical analyses were performed with SPSS 23.0 (SPSS, Inc., Chicago, IL) and SAS version 9.4 of the SAS System for Windows, Copyright © 2002–2012 SAS Institute, Inc., Cary, NC, and the open source statistical software R version 3.0 (The R Foundation for Statistical Computing, Vienna, Austria, 2013).

Validation of prognostic model

First, the previous published score shown in Table 1 was applied to the new cohort. Briefly, patients were given 0 points if none of the variables was found and 1 point for each present variable. Herein, patients were divided into 3 groups based on the cumulative presence of the three independent variables predicting poor survival (good prognosis = 0 points; moderate prognosis = 1 or 2 points; poor prognosis = 3 points). Survival after HCC recurrence after LT was compared among all three groups.

Following the validation of the prognostic score, a C-statistic as well as sensitivity and specificity of the score was performed for the prediction of six months, one and two years event rates. Predicted probability (using prognostic score as covariate) with a threshold of 0.50 was used to calculate sensitivity and specificity. Of note, patients who were alive but did not have sufficient follow-up (one year when calculating one year rate, two years for two years rate and three years for three years rate) were excluded in that particular analysis. Moreover, Harrel's concordance index statistic was used to assess the predictive power of the prognostic score on survival using all the available data.

Results

From June 2002 to December 2014, 1328 patients in all three centers had a confirmed HCC in their explanted liver. Among these, 130 patients (9.8%) suffered HCC recurrence after LT and constitute the study group. Median follow-up time for the study group after LT was 30.8 (17.1–54.6) months for the entire cohort.

Study group characteristics

Patient's characteristics are shown in Table 2. At the time of diagnosis 88 patients (67%) were within the Milan criteria. From the entire cohort, 91 patients (70%) underwent bridging therapy while on the WL. The median number of treatments as a bridge to transplant was 2(1–3). For the different centers the median WL time expressed in months was as follows: UCSF 10.1 (6.6–14.2) months; Instituto Nazionale dei Tumori in Milan 2 (1–4.7) months; and at the University Hospital of Birmingham 1.3 (0.4–2.42) months.

Explant pathology characteristics

The explant characteristics are summarized in Table 2. More than 50% of patients had tumor micro-vascular invasion in their explanted liver. Moderate differentiation was the most common (58.6%) type of tumor differentiation. Only 8% of patients had

Table 2 Characteristics of patients with HCC recurrence after LT

Preoperative Characteristics		**n = 130**
Median age at the time of LT (years)		58.4 (53.5–62.9)
Sex (M/F)		104 (80%)/26 (20%)
Cause of liver disease	HCV	72 (55.4%)
	HBV	28 (21.5%)
	Alcohol	16 (12.3%)
	NASH	6 (4.6%)
	Others	8 (6.2%)
Race	Caucasian	95 (73.1%)
	Asian	20 (15.4%)
	Afro-American	10 (7.7%)
	Hispanic	5 (3.8%)
Median MELD score at diagnosis		9 (7–12)
Median AFP at diagnosis (ng/mL)		25.6 (6–189)
Median number of tumors at diagnosis		1 (1–2.5)
Median size of the largest tumor at diagnosis (cm)		3 (2.3–4)
Median waiting list time (months)		3.4 (1–9.8)
Pathology findings at explant		
Median number of viable tumors		2 (1–3)
Median size of the largest viable tumor (cm)		4 (2.3–25)
Microvascular invasion		72 (55.4%)
Tumor differentiation	Well-differentiated	16 (12.5%)
	Moderately-differentiated	75 (58.6%)
	Poorly-differentiated	27 (21.1%)
	No viable tumor	10 (7.8%)
Patients within Milan criteria		60 (46%)

liver transplantation, LT; hepatitis C virus, HCV; hepatitis B Virus, HBV; non-alcoholic steatohepatitis, NASH.

no viable tumor and therefore were completely treated. Based on the surgical specimen, less than 50% of the patients fulfilled the Milan criteria.

Tumor recurrence characteristics

Median time to recurrence after LT was 17.8 (8.8–28.1) months. Most patients (63.8%) recurred after 1 year. Similarly, the majority of patients (62.3%) presented with extrahepatic recurrence alone. In 27.7% (36 patients) of the cohort the liver was the first site of recurrence. Instead, the lungs and bones were the most common site of extrahepatic recurrence (Table 3). While 75 patients (62%) had a preserved liver function at the time of recurrence, only 9.8% (12 patients) presented with clinically significant portal hypertension. Of note, almost 40% (45 patients) of the study group had a median AFP level >100 ng/mL at the time of recurrence.

Eleven (8%) patients with non-viable tumor on explant pathology still recurred. Median time to recurrence for this patient population was 18 (8–39) months. While the main site of recurrence was the lung (6 patients); 2 patients recurred in the spine; 1 patient recurred with lesions in the lung and ribs; one recurred at multiple sites (liver, adrenal gland and bones) and one only recurred in the liver. The majority of them (10/11, 91%) were within Milan criteria at diagnosis.

HCC recurrence treatment approach

Thirty-nine (31.2%) of the 130 patients experiencing HCC recurrence after LT received curative-intent treatment. Of those, 34 patients (87%) underwent surgical resection and in 5 patients (13%), tumors were treated by ablation. Treatment approach after HCC recurrence in the rest of the study cohort is summarized in Table 3. No patient was re-transplanted for HCC recurrence.

At the time of HCC recurrence 35 (34.7%) of 130 patients were treated with sorafenib either as a palliative treatment or in addition to other treatments.

Table 4 compares patients that received curative-intent treatments versus those that did not. These results show the favorable tumor characteristics and the significantly improved survival experienced by those patients who underwent curative intent treatments after HCC recurrence following LT.

Table 3 Tumor recurrence characteristics after LT

Tumor recurrence characteristics		n = 130
Median AFP at the time of recurrence (ng/mL)[a]		24 (4–338)
0–20 ng/mL		57 (49.6%)
21–100 ng/mL		13 (11.3%)
>100 ng/mL		45 (39.1%)
Time from transplant to recurrence	<12 months	47 (36.2%)
	≥12 months	83 (63.8%)
Location of first tumor recurrence	Hepatic	36 (27.7%)
	Extrahepatic	81 (62.3%)
	Hepatic + Extrahepatic	13 (10%)
Extrahepatic location of first tumor recurrence (n = 94)	Lung	40 (42.6%)
	Bone	23 (24.5%)
	Adrenals	6 (6.4%)
	Lymph nodes	4 (4.3%)
	Peritoneal	15 (16%)
Treatment of first tumor recurrence[b]	Curative-intent	39 (31.2%)
	Palliative treatment	62 (49.6%)
	Best supportive care	24 (19.2%)
Types of treatment (n = 101)	Surgical resection	34 (33.7%)
	Ablation	5 (5%)
	Chemotherapy	8 (7.9%)
	Radiotherapy	11 (10.9%)
	Sorafenib	35 (34.7%)
	TACE	8 (7.9%)
Median time from recurrence to death (months)		11.6 (4.9–22.5)

[a] Missing information in 15 patients.
[b] Missing information in 5 patients.

Table 4 Comparison between patients with and without curative intent treatment

	No curative intent treatment (n = 91)	Curative intent treatment (n = 39)	p
Time to recurrence (months)	14 (6.63–26.64)	24 (17.80–42.34)	0.004
Recurrence within 1 year (%)	41 (45)	6 (15)	0.001
AFP at recurrence (ng/mL)	60 (4.7–609)	10 (3.17–129.10)	0.007
AFP ≥ 100 (ng/mL) (%)	37 (41)	9 (23)	0.038
Nº Tumors at recurrence	3 (1.75–5)	1 (1–1)	<0.0001
Size of largest tumor at recurrence (cm)	4 (3–7)	3 (3–4)	0.033
Recurrent lesion <5 cm	16 (18)	28 (72)	<0.0001
Recurrent lesion >5 cm/multiple lesions	71 (78)	9 (23)	
Single site of recurrence	66 (72)	37 (95)	0.007
Location of first tumor recurrence:			0.022
Hepatic	29 (32)	7 (18)	
Extrahepatic + Hepatic	12 (13)	1 (3)	
Extrahepatic	50 (55)	21 (54)	
Normal liver function at recurrence (Child A, Meld<10, No portal hypertension)	52 (57)	29 (74)	0.077
Survival after recurrence (months)	9 (3.94–15.70)	22 (8.57–42.74)	<0.0001

Alpha feto protein, AFP.

Patients' outcomes after HCC recurrence

Overall median survival after HCC recurrence for the entire cohort was 12.4 (95% CI 10.2–16.3) months. While the 1- year overall survival rate after HCC recurrence was 51% (95% CI 42.2%–59.5%), the 3- and 5-year overall survival was 20% (95% CI 13.4%–28.5%) and 12% (95% CI 5.6%–21.1%). All deaths were causally related to tumor recurrence.

Prognostic score validation

The previous reported score was applied to the current cohort of patients. Only 113 of 130 patients had information on all 3 prognostic variables. Therefore, the score was ultimately applied to 113 patients. Among them, while 23 patients fell into to the category of good prognosis (no risk factors for poor survival), 72 patients had 1 or 2 variables present (moderate prognosis) and 18 patients had all 3 variables present (poor prognosis) at the time of tumor recurrence. As hypothesized, Fig. 1 shows that the 1-(73% vs 55% vs. 17%), 3-(41% vs. 19% vs. 0%) and 5-year (34% vs. 6% vs. 0%) survival after HCC recurrence is significantly superior for the good prognosis group when compared to the other moderate and poor prognosis groups, respectively ($p < 0.0001$).

As shown in Table 5, for the 6 month, 1-year and 2-year event rate the C-statistic (~0.68) revealed the score to be a good model to predict survival after HCC recurrence. Harrel's concordance index was 0.72 (95% CI 0.65–0.79) showing a strong survival prediction. Fig. 2 shows the calibration plots for the 3 event rates (6 months, 1-year and 2-years).

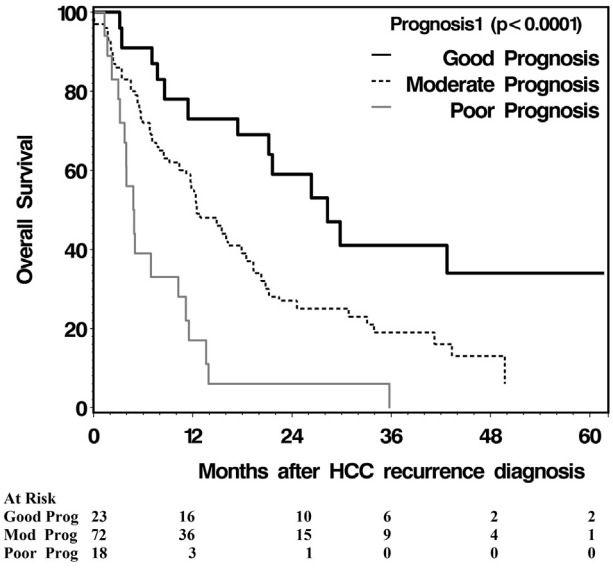

Figure 1 Patient survival after HCC recurrence following LT stratified by previous reported score

Discussion

In the recent Euro-American series analyzing the benefit of treating HCC recurrence after LT a score predicting survival of patients suffering HCC recurrence following LT was proposed.[2] In the current study, the previous reported score was applied and validated. In this manner, the previously identified risk factors for poor outcome (i.e. amenable to curative intent treatments, HCC recurrence <12 months after LT, AFP ≥ 100 ng/mL at time of diagnosis) probed to be a valuable tool to recognize patients with good prognosis after HCC recurrence following LT.

Neither the American Association for the Study of Liver Disease Guidelines,[12] nor the National Comprehensive Cancer Network[13] guidelines have specific recommendations for surveillance of HCC recurrence after LT. The present study emphasizes on the need of carefully following these patients after LT as treatment of HCC recurrence is feasible and should be offered in selected cases to prolong patients' survival. What is not clear yet though is for how long and by which means this surveillance needs to be done.[14] Certainly, as previously reported, treating these patients with curative means (if possible) impacts on survival.[3] As expected, our data supports that patients with better "tumor biology" (i.e. less tumor burden or serum AFP) are more likely to be treated with curative-intent therapies. Therefore, our data identifies patients who would potentially benefit from aggressive treatment once the recurrence is diagnosed and also, reinforces the importance of identifying these patients.

The developed prognostic score had to be validated with an external data source and therefore, we applied the score to this multicentric cohort. Patients that fulfilled the criteria for good prognosis had a significantly higher survival after HCC recurrence when compared to the moderate and poor prognosis groups. However, although the univariate analysis of the current study continued to identify not being amenable for curative-intent treatments and early recurrence after transplantation (<12 months) as strong predictors of poor outcome, AFP <100 ng/mL at the time of recurrence failed to have the same strength that in the previous study. The nature of this finding is unknown; one hypothesis could be that these results are related to a type II error due to the relative small sample size. Nevertheless, AFP has been identified in many studies as a risk factor for tumor recurrence after LT,[14,15] so it is possible that there is an

Table 5 Prognostic score C-statistic, sensitivity and specificity

	Number of event (sample size used)	C-Statistics	Sensitivity	Specificity
Six Month event rate	33 (111)	0.684	61.11	76.34
One year event rate	52 (107)	0.666	83.33	58.43
Two years event rate	74 (100)	0.685	80.25	52.63

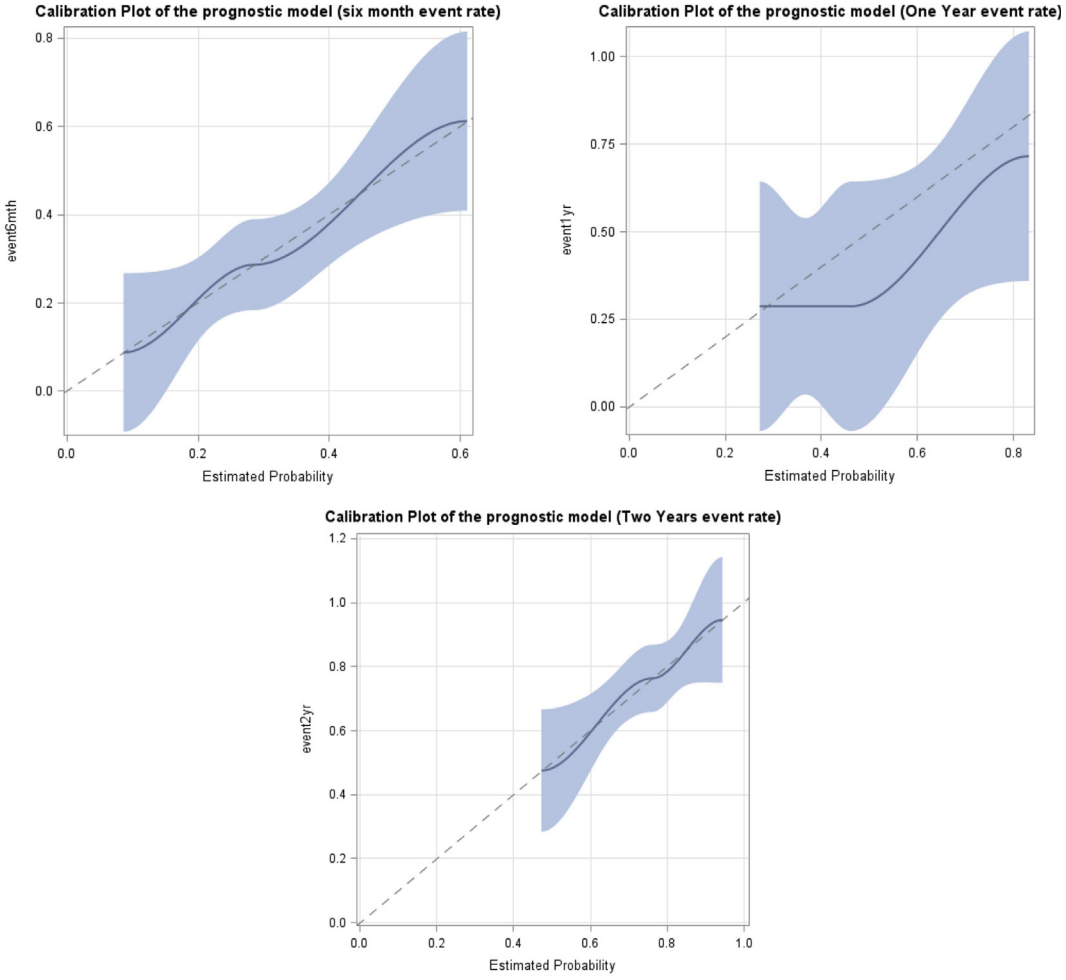

Figure 2 Prognostic model calibration plots. Calibration plot graphs with using a true probability (event rate) vs. predicted probability using the classifier (model). A diagonal on the graph represents a perfectly calibrated classifier and the graphs above show predicted probabilities (in particular six month and 2 year) with solid lines very close to diagonal lines and dotted lines. Therefore, a very good calibration is demonstrated

impact in this setting too. No additional variables predicting poor outcome were identified in the current cohort.

Our score, in contrast to what has been previously reported, has failed to find any predictive value in the number and size of the lesions at the time of recurrence. Nevertheless, likely "being able to treat" is a surrogate of smaller tumor burden. Recently, the UCLA group reported a series of 108 patients with HCC recurrence following LT.[16] Another complex prognostic score was proposed. In their study, as in ours, early recurrence was found to be one of the most important variables predicting survival. Indeed, tumor biology likely plays a role as early recurrence probably is related to the growth of occult metastases.[17] Unfortunately, being amenable for curative treatment, which was the strongest predictor of good outcome in our study, was not included in their score. On the contrary, we believe that from a practical point of view the possibility of curative treatment after HCC recurrence following LT should be the first step in the algorithm to manage this patient population making our score more applicable. From a clinical perspective this score can aid clinicians in discussing with the patients and families the goals of care after recurrence has occurred given that it can predict the outcomes after recurrence.

This study has several limitations. Firstly, because of the retrospective nature of this study, many of the procedures and follow-ups were not standardized among centers. In this regard, one of the centers did not strictly follow-up low risk patients, generating a potential bias since recurrence in this set of patients might have been missed. Also, this study did not randomly assign patients with recurrence to a "curative-intent" arm or a "non-curative intent" arm, therefore, unknown confounders may be affecting our analysis. In addition, this study describes a 12-year period, during which there has been a shift towards a more 'aggressive' management of recurrent HCC after LT, which has the potential to impact results. Prospective validation of this score is encouraged.

In conclusion, the previous reported prognostic score for HCC patients experiencing recurrence after LT was successfully validated in the current cohort of patients.

Source of funding

None declared.

Conflict of interest

None declared.

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