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ORIGINAL ARTICLE

Performance of pre-transplant criteria in prediction of hepatocellular carcinoma progression and waitlist dropout

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Abstract

Background & aim: Liver transplantation (LT) selection models for hepatocellular carcinoma (HCC) have not been proposed to predict waitlist dropout because of tumour

Abbreviations: AFP, alpha-foetoprotein; CI, confidence interval; CT, computerized tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver; PD, progressive disease; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SHR, sub-hazard ratio; TACE, trans-arterial chemoembolization; WL, waiting list.

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progression. The aim of this study was to compare the alpha-foetoprotein (AFP) model and other pre-LT models in their prediction of HCC dropout.

Methods: A multicentre cohort study was conducted in 20 Latin American transplant centres, including 994 listed patients for LT with HCC from 2012 to 2018. Longitudinal tumour characteristics, and patterns of progression were recorded at time of listing, after treatments and at last follow-up over the waitlist period. Competing risk regression models were performed, and model's discrimination was compared estimating Harrell's adapted *c*-statistics.

Results: HCC dropout rate was significantly higher in patients beyond (24% [95% CI 16–28]) compared to those within Milan criteria (8% [95% IC 5%–12%]; $p < .0001$), with a SHR of 3.01 [95% CI 2.03–4.47]), adjusted for waiting list time and bridging therapies (*c*-index 0.63 [95% CI 0.57; 0.69). HCC dropout rates were higher in patients with AFP scores >2 (adjusted SHR of 3.17 [CI 2.13–4.71]), *c*-index of 0.71 (95% CI 0.65–0.77; $p = .09$ vs Milan). Similar discrimination power for HCC dropout was observed between the AFP score and the Metroticket 2.0 model. In patients within Milan, an AFP score >2 points discriminated two populations with a higher risk of HCC dropout (SHR 1.68 [95% CI 1.08–2.61]).

Conclusions: Pre-transplant selection models similarly predicted HCC dropout. However, the AFP model can discriminate a higher risk of dropout among patients within Milan criteria.

KEYWORDS
delisting, liver cancer, outcomes, radiological progression

1 | INTRODUCTION

Liver transplantation (LT) is a curative therapy for patients with hepatocellular carcinoma (HCC). Over the waiting list (WL) period, tumour progression may occur, precluding LT access among listed patients if surpassing transplant tumour limits. HCC progression not only depends on the tumour's baseline characteristics but also on the waitlist length of time.[1–4] It is expected that, among patients meeting Milan criteria,[5] HCC progression occurs in nine and 20% at 12 and 24 months of listing respectively.[1–4]

Several authors proposed that one of the best natural selectors for LT candidates is time on the WL, considered as a test of HCC progression. Time would theoretically select the best transplant candidates carrying the lowest risk of HCC recurrence and better overall survival after LT.[6–8] Nevertheless, there are tumour characteristics associated with a higher risk of progression over the waitlist period.[1–4]

A tumour diameter exceeding 3 cm, or the presence of multiple nodules,[1,7] high alpha-foetoprotein serum values (AFP)[2,4,9] and the absence of response to locoregional therapies[10,11] are risk factors for tumour progression and removal from the WL. Tumour treatment over the waitlist period can avoid tumour progression; however, liver function impairment precludes some specific bridging therapies, which may lead to a higher mortality risk because of liver decompensation.[3]

Lay summary/Key points

We compared the alpha-foetoprotein (AFP) model and other pre-liver transplantation (LT) models in their prediction of dropout from the waiting list because of HCC tumour progression. Although, pre-transplant selection models similarly predicted HCC dropout, the AFP model discriminated two risk populations of dropout among patients within Milan criteria.

During the last years, increasing focus in optimizing transplant selection models has been done. In this regard, composite models for HCC transplant candidate selection, including the French AFP model and the Metroticket 2.0,[12,13] have shown superior prediction of post-LT outcomes than Milan criteria. Nonetheless, these models have not been designed to predict HCC progression or waitlist dropout.[12,13]

More recently, a novel model including liver function scores and tumour burden has been recently proposed as another tool for candidate selection for granting model for end-stage liver disease (MELD) exception points in the United States of America.[14] Therefore, our objective was to evaluate predictors of HCC dropout and compare the AFP model with other transplant models in their

prediction of tumour progression and HCC waitlist dropout in a Latin American cohort.

2 | PATIENTS AND METHODS

2.1 | Study design, participating centres and eligibility criteria

A total of 20 Latin American liver transplant centres were invited to participate in this retrospective cohort study. The study protocol was provided to all the centres, and patients data registration was accomplished both in written and web-based case report forms. The study was part of an open-access public registry, incorporated to www.clinicaltrials.org (NCT03775863), following standards of observational studies (STROBE guides).[15] The study design and conduction fulfilled ethical requirements according to the Belmont report in 1979 and the revised version of the Helsinki declaration in 2008.

Study inclusion criteria were adult patients (>17 years) listed for LT because of HCC or patients listed for liver decompensation who develop HCC while on WL. HCC was diagnosed according to international and national guidelines from January 1, 2012 to December 31, 2018.[16–18] Patients evaluated but not enlisted for a liver transplant because of tumour extension (macrovascular invasion, extrahepatic disease or ganglionic metastasis) were excluded, as also those with incidental findings of HCC at the explant pathological examination.

2.2 | Exposure variables

The included exposure variables were demographic data, baseline aetiology of liver disease, liver function at listing and MELD exception points accreditation. As most of the countries had a MELD exception policy, we did not register baseline laboratory MELD score, and considered the Child Pugh score as the liver function categorization. Longitudinal tumour imaging characteristics as well as AFP values were recorded at time of HCC diagnosis, at time of listing, at waitlist reassessment and at last pre-LT evaluation. Pre-LT serum values were categorized according to the following stratum ≤100, 101–1000 and >1000 ng/ml.[12] Queries for missing values or discordant values were centrally requested and investigators who were accomplished with data registration were not involved in data analysis.

Tumour baseline extension was categorized at time of listing, at waitlist reassessment or following locoregional therapies and at last pre-LT evaluation according to Milan criteria,[5] the AFP model[12] and the Metroticket 2.0[13] at time of listing or at time of HCC diagnosis for those in whom tumour was diagnosed over the waitlist period. The AFP score (0–9 points) was calculated depending on the largest tumour diameter (≤3 cm = 0 points, 3–6 cm = 1 point, >6 cm = 4 points), number of HCC nodules (1–3 nodules = 0 points, ≥4 nodules = 2 points) and AFP levels ng/ml (≤100 = 0 points, 101–1000 = 2 points and > 1000 = 3 points).[12] The Metroticket 2.0 included the sum of the largest nodule diameter with the total number of HCC nodules, and the log10 AFP values; and three thresholds were included as a cut-off for LT selection, as proposed.[13] AFP response was defined as a reduction of at least 20% between listing and last reassessment over the waitlist period.[19] AFP slope was estimated using AFP values between listing and last reassessment over the waitlist period as proposed by Lai Q, et al.[20]

In all centres, transplant candidate's selection was based on the Milan criteria, but following each country's national allocation policy, patients exceeding Milan criteria were also included. Tumour treatment and type of bridging therapies before transplantation were decided at each transplant centre on a case-by-case basis, for example trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) or liver resection. Following these procedures, imaging and AFP values were registered at re-evaluation. Consequently, longitudinal changes in tumour burden over the WL period were registered.

2.3 | Study end-points and statistical analysis

The primary end-point analysis was dropout from the WL because of HCC tumour progression ('HCC dropout'). In all centres, macrovascular invasion or extrahepatic spread were a clear dropout indication. In cases of progression beyond Milan criteria, waitlist dropout was decided on a case-by-case basis, following each centre and country policy. This decision was based on uncertainty regarding the effect of any progression according to RECIST 1.1 criteria,[16,17] or the type of progression,[23] leading to a significant increased risk of recurrence after transplantation. Other causes of dropout were also registered, including death or other severe diseases.

In order to avoid selection bias and over estimation of risks because of potential failure/censoring events in Cox models, and evaluate the relationship of covariates to cause-specific failures, competing risk regression models were performed.[21] Sub distribution hazard ratios (SHR) and 95% confidence intervals (CI) were estimated according to the Fine and Grey method.[22] For the outcome of HCC dropout, non-HCC-related deaths while on the WL, non-HCC dropouts and transplantation were considered competing events. Each pre-transplant model's performance was compared including calibration (observed and predicted risk curves) and discrimination with Harrell's adapted *c*-statistics.[23]

Secondary events of interest were HCC progressive disease (PD) according to RECIST 1.1 criteria (even in the absence of waitlist dropout), overall survival since listing and post-transplant outcomes including tumour recurrence and survival. Patients were followed until death or last follow-up visit. Time-to-events were considered from the date of listing in patients listed for HCC or from the date of HCC diagnosis in the group of patients with tumour diagnosis over the waitlist period to the date of each event. Competing risk analysis was also applied for the outcome of HCC recurrence, considering death without recurrence after LT as competing event.

As some tumour progressions may have been within or beyond transplant criteria, we assess the effect of tumour progression using

objective radiological criteria for PD, using the Response Evaluation Criteria In Solid Tumours (RECIST 1.1).[16,17] For this objective, we focused on tumour diameters and number, avoiding misinterpretation or heterogenous assessment based on tumour residual enhancement across centres (avoiding differential misclassification). We shared a systematic RECIST 1.1 automatized calculator, assessed in each centre and centrally confirmed on a blinded manner. For tumour response we focused on objective response rate (ORR), as complete disappearance of tumour lesions according to RECIST 1.1 criteria is rather uncommon, in comparison to mRECIST criteria. Also, patterns of progression were also registered to evaluate delisting decisions across centres.[24] Time to PD, was registered from the date of waitlist enrolment or from HCC diagnosis to either the date of radiological progression, or last imaging reassessment while on the WL. Radiological re-evaluation was performed as recommended,[25] at least within a minimum 3-month period. We used RECIST 1.1 instead of the modified RECIST criteria (mRECIST)[26] in order to avoid any information bias because of heterogeneity in interpretation of necrotic areas and vascular enhancement across centres.

Finally, Kaplan Meier survival curves were compared using the log-rank test (Mantel–Cox), from the date of listing or from the date of HCC diagnosis in the group of patients with tumour diagnosis after listing to the last date of follow-up or death over the waitlist period. In order to evaluate comparisons across countries, we selected Argentina as the reference country for these analyses. Data were analysed with STATA 17.0 (StataBE).

3 | RESULTS

During the study period, 1117 patients were evaluated as potential candidates for LT because of HCC. Of these, 123 patients were not listed because of advanced HCC (n = 89), patient's refusal to LT (n = 5) and other medical contraindications (*n* = 29). From this initial cohort, 944 patients with HCC were listed and included in this study (Table 1). Median time on WL was of 6.1 months (IQR 2.4–10.4); longer in patients in whom HCC diagnosis was made over the waitlist period compared to those listed because of HCC (14.8 months [IQR 7.6–28.5] vs 6.7 months [IQR 2.9–11.9]).

At time of listing or HCC diagnosis (group with HCC diagnosis over the waitlist period), 81.9% (*n* = 814) were within Milan criteria, of which all of them were within the three Metroticket 2.0 thresholds, and 8.4% (*n* = 68) had an AFP score >2 points. On the contrary, 87.2% (*n* = 157) and 50.3% (*n* = 90) of patients exceeding Milan were within the Metroticket 2.0 and AFP scores ≤2 points respectively. Locoregional bridging therapies were performed in 67.0% of the cohort (*n* = 666); this group presented a longer median WL time than those not receiving any treatment (9.8 months [IQR 5.7–16.8] vs 3.9 months [CI 1.4–8.6]; $p < .0001$). The median time from last radiological evaluation to transplant was of 2.2 months (IQR 1.0–4.1), similar between those who did and did not receive a bridging therapy (2.1 months [IQR 0.9–3.8] vs 2.4 months [CI 1.1–4.3]; $p = .09$).

TABLE 1 Patients' baseline characteristics (*n* = 994)

Variable	Values
Age, years (±SD)	59 ± 8
Gender, Male, *n* (%)	737 (74.1)
Diabetes mellitus, *n* (%)	274 (27.6)
Country of origin, *n* (%)	
Argentina	377 (37.9)
Brazil	337 (33.9)
Colombia	98 (9.9)
Mexico	65 (6.5)
Chile	47 (4.7)
Uruguay	32 (3.2)
Peru	25 (2.5)
Ecuador	13 (1.3)
Median time on waiting list, (IQR), months	6.1 (2.4–10.4)
Cirrhosis, *n* (%)	986 (99.2)
Child Pugh, *n* (%)	
A	521 (52.4)
B	370 (37.2)
C	103 (10.4)
HCC diagnosis after listing, *n* (%)	117 (11.8)
Aetiology of liver disease, *n* (%)	
Hepatitis C virus	491 (49.4)
Hepatitis B virus	58 (5.8)
Alcohol	169 (17.0)
Cholestatic (PBC, SSC, PSC)	20 (2.0)
NAFLD	115 (11.6)
Cryptogenic	96 (10.0)
Others (Autoimmune, Hemochromatosis, miscellaneous)	39 (3.9)
HCV-HBV co-infection, *n* (%)	7 (0.7)
HIV, *n* (%)	1 (0.1)
Supplementary MELD points, *n* (%)	799 (80.4)

At time of listing or HCC diagnosis in the group of patients in which HCC was diagnosed over the waitlist period.

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; PBC, primary biliary cholangitis; SSC, secondary sclerosing cholangitis; PSC, primary sclerosing cholangitis.

3.1 | Cumulative incidence of tumour progression and HCC dropout

At the end of the study period, 65% received a liver transplant (*n* = 650), 10% were still on the waitlist (*n* = 91) and 25.3% (95% CI 22.7–28.2) were delisted or dropped out (*n* = 253) (Figure 1). Causes of delisting were HCC progression in 43.9% (*n* = 111), death during the waitlist period 29.6% (*n* = 75) and liver decompensation or other medical conditions that precluded transplantation 26.5% (*n* = 67). There were no losses of follow-up over the waitlist period. Cumulative incidence of PD according to RECIST 1.1 criteria at last

tumour reassessment was observed in 24.2% (95% CI 21.2–26.9), 28.7% (n = 285) presented ORR and 49% (n = 487) stable disease (Figure S1). On the other hand, among patients presenting PD over the waitlist period, 33.8% (n = 75) were transplanted, and 60.0% (n = 133) were delisted. Among patients presenting PD, extrahepatic pattern of progression was observed in 6.3% (n = 14), macro vascular invasion in 8.6% (n = 19), diffuse infiltrative HCC in 16.7% (n = 37), new intrahepatic lesion in 61.3% (n = 136) and increase diameter of intrahepatic lesion in 7.2% (n = 16).

The overall incidence rate of HCC dropout was 2.4 dropouts per 100 persons months, with a cumulative incidence of 11.2% (95% CI 9.7–13.8), and a median time to dropout of 14.9 months (IQR 7.3–26.7). Corresponding HCC dropout rates at 1 and 2 years were 7.1% (95% CI 5.3–9.2) and 20.2% (95% CI 15.2–25.9) (Figure 2A). Cumulative survival since listing was significantly lower in patients who dropped out because of HCC progression (Figure S2). Table 2 shows a comparative analysis between patients with and without HCC dropout. The patterns of PD were associated with different cumulative hazard of HCC dropout (Figure 2B), and overall survival since listing (Figure S3). All the patients who had PD showing extrahepatic (n = 14) or vascular invasion (n = 19) were dropped out. The HCC dropout rate according to other patterns of PD was 70.3% for intrahepatic infiltrative pattern (n = 26/37), 30.9% for new intrahepatic progression (n = 42/136) and 25.0% for those with increase diameter of intrahepatic lesion (n = 4/16) (p < .0001). Locoregional therapies among the group of patients who developed HCC dropout were more frequently observed (78.4% vs 65.5% in those who did not dropout; p = .007) (Table S1). Cumulative HCC dropout rates were different across countries, depending on the proportion of patients exceeding Milan criteria and total number of patients included in each country (Table S2).

3.2 | Predictors of HCC dropout using competing risks

Independent variables associated HCC dropout from a multivariable competing risk regression analysis were WL time (months) (SHR 1.03 [95% CI 1.02; 1.04]; p < .0001), number of HCC nodules (SHR 1.10 [95% CI 1.07; 1.35]; p = .002), major nodule diameter (cm) (SHR 1.11 [95% CI 1.01; 1.22]; p = .03) and AFP values (reference ≤100 ng/mL) 101–1000 ng/ml (SHR 2.69 [95% CI 1.78–4.08]; p < .0001), >1000 ng/mL (SHR 3.60 [CI 1.73–7.49]; p = .001), adjusted for locoregional bridging therapy (Table 3). The c-index for this model to predict HCC dropout was 0.70 (95% CI 0.63, 0.76). We further explore predictors of HCC dropout only in patients granted with MELD additional points for LT (n = 799), of which 86.5% were within Milan criteria. Median time on the waitlist period was shorter in patients granted compared to those without this supplementary MELD points (7.0 months [IQR 3.0–12.4] vs 8.2 months [IQR 3.5–16.7]; p = .03). In this group of patients, independent variables associated with HCC dropout were WL time (months), number of HCC nodules and AFP values (Table S3).

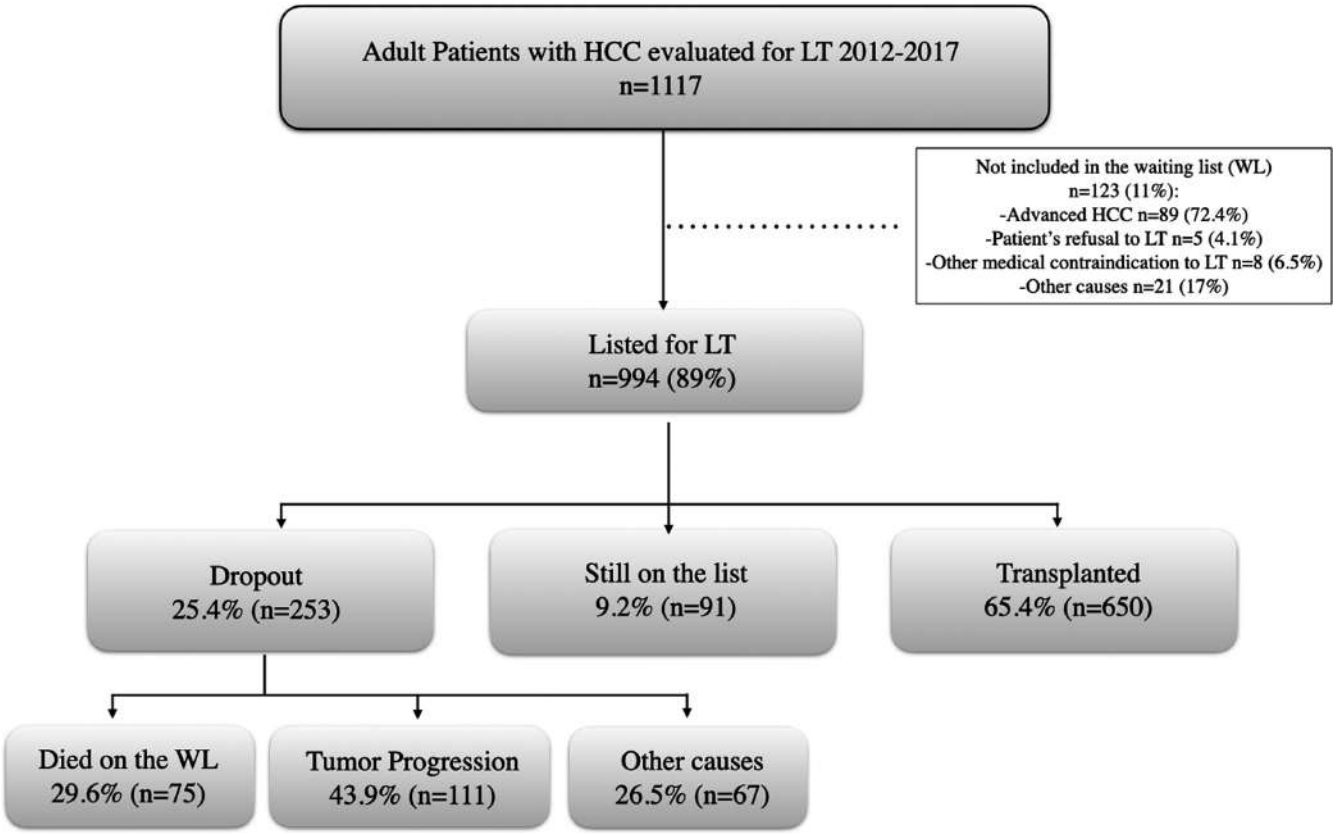

FIGURE 1 Flow chart of study population

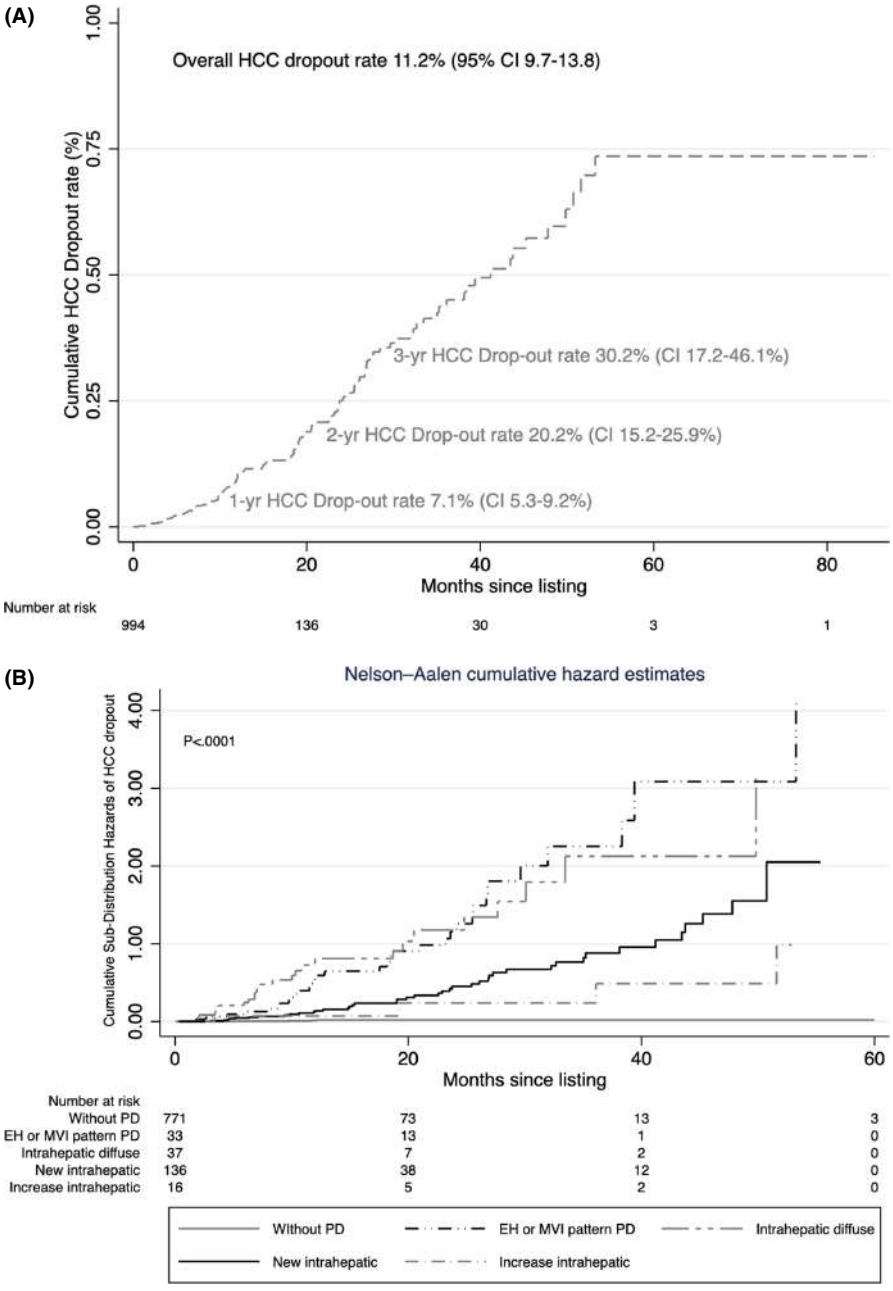

FIGURE 2 (A) Cumulative incidence of HCC dropout over the waitlist period in the entire cohort. (B) Cumulative Sub-Distribution Hazards of HCC dropout according to the pattern of radiological progression over the waitlist period

3.3 | HCC dropout rates according to pre-transplant selection criteria

The cumulative incidence of HCC dropout was significantly higher in patients beyond (24% [95% CI 16–28]) compared to those within Milan criteria (8% [95% IC 5%–12%]; $p < .0001$) with a SHR of 3.01 [95% CI 2.03–4.47]), adjusted for time on the WL and locoregional bridging therapies (Figure 3A). The *c*-index of Milan criteria to predict HCC dropout was 0.63 (95% CI 0.57; 0.69). Among patients within Milan, 24.3% ($n = 198$) progressed beyond Milan and 21.7% ($n = 39$) were *downstaged* from exceeding to within this transplant criterion over the waitlist period of time. In patients within Milan, AFP values stratified three different groups of HCC dropout risk over the waitlist period of time (Figure 3B). As all the patients within Milan criteria were within any of the three Metroticket 2.0 thresholds, we could not perform a stratified analysis.

In patients with AFP scores ≤2 points at listing, 16.6% ($n = 130/782$) increased to >2 points over the waitlist period, whereas decreasing AFP values from >2 to ≤2 points were observed in 21.1% ($n = 33/156$). HCC dropout rates were higher in patients with AFP scores >2 than those with ≤2 points with a SHR of 3.17 (CI 2.13–4.71; $p < .0001$), adjusted for time on the WL and bridging therapies (Figure 4) and a *c*-index of 0.71 (95% CI 0.65–0.77). In patients within Milan, the AFP model discriminated two populations with a higher risk of tumour progression (AFP >2 points SHR 1.68 [95% CI 1.08–2.61]), adjusted for locoregional treatment over the waitlist period. This discrimination was not reached in patients exceeding Milan criteria. Table 4 shows the comparison of *c*-index for prediction of HCC dropout according to the Milan, AFP and Metroticket 2.0 models.

TABLE 2 Comparative analysis between patients with or without HCC dropout

Variable	HCC dropout ($n = 111$)	Without HCC dropout ($n = 883$)	p
Age, years (±SD)	59 ± 7	58 ± 8	.46
Male gender, *n* (%)	75 (67.6)	662 (75.0)	.09
Diabetes mellitus, *n* (%)	27 (24.3)	247 (28.0)	.41
Child Pugh A/B/C, *n* (%)	67 (60)/38 (34)/6 (6)	454 (51)/332 (38)/97 (11)	.09
HCV, *n* (%)	63 (56.8)	428 (48.5)	.10
HBV, *n* (%)	10 (9.0)	48 (5.4)	.13
Months on the waiting list, median (IQR)	15.0 (7.3–26.7)	6.7 (2.8–11.9)	<.0001
Tumour characteristics at listing[a]			
Supplementary MELD points, *n* (%)	70 (63.1)	729 (82.6)	<.0001
Mean HCC nodules (±SD)	1.9 ± 1.2	1.5 ± 0.9	.0001
Mean major nodule diameter, cm (±SD)	3.9 ± 2.6	3.1 ± 1.5	<.0001
Median AFP, ng/ml (IQR)	58.7 (8–311.7)	9.4 (4.3–47)	<.0001
≤100 ng/ml, *n* (%)	65 (58.6)	723 (82.3)	<.0001
101–1000 ng/ml, *n* (%)	34 (31.2)	123 (14.1)	
>1000 ng/ml, *n* (%)	10 (9.2)	32 (3.6)	
Within Milan criteria, *n* (%)	67 (60.4)	747 (84.6)	<.0001
AFP model ≤ 2 points, *n* (%)	72 (66.1)	758 (86.3)	<.0001
Within Metroticket 2.0, *n* (%)	104 (93.7)	867 (98.2)	.003
Locoregional treatment, *n* (%)[b]	87 (78.4)	579 (65.6)	.007
Tumour characteristics at last evaluation[b]			
Patterns of PD, *n* (%)	111 (100)	117 (20.5)	<.0001
Uninodular intrahepatic	4 (3.8)	12 (10.3)	<.0001
Multinodular intrahepatic	42 (40.0)	94 (80.3)	
Diffuse intrahepatic pattern	26 (24.8)	11 (9.4)	
Vascular invasion	19 (18.1)	0	
Extrahepatic disease	14 (13.3)	0	
Within to beyond Milan criteria, *n* (%)	44 (65.7)	154 (20.6)	<.0001
AFP model ≤ 2 to >2 points, *n* (%)	35 (50.0)	95 (13.3)	<.0001
Within to beyond Metroticket 2.0, *n* (%)	20 (19.2)	124 (14.3)	.18

Abbreviations: HCC, hepatocellular carcinoma; PD, progressive disease by RECIST 1.1 criteria; WL, waiting list.

[a]At time of listing or HCC diagnosis in the group of patients in which HCC was diagnosed over the waitlist period.

[b]Over the waitlist period of time.

3.4 | Recurrence rates according to pre-transplant criteria and tumour progression over the waitlist period

The post-transplant incidence rate of recurrence was 1.9 recurrences per 100 persons months of follow-up, with cumulative rates at 12 and 36 months of 3.8% (95% CI 2.5–5.9) and 9.9% (95% CI 7.4–13.5) respectively. Patients presenting PD at last tumour reassessment according to RECIST 1.1 were not associated with a significant instantaneous risk of recurrence (SHR 1.64 [95% CI 0.60–4.49]; $p = .33$). There was no significant increased risk of recurrence considering tumour progression regarding transplant criteria, including within-to-beyond

TABLE 3 Competing risk regression analysis of probability of HCC dropout in the entire cohort

Variable	HCC Dropout (%)	Unadjusted SHR (95% CI)	*P*	Adjusted SHR (95% CI)	*P*
Age (years)		1.01 (0.98; 1.03)	0.36		
Gender					
Male (*n* = 737)	10.2	0.70 (0.47; 1.04)	0.08		
Female (*n* = 257)	14.0				
Child Pugh					
A (*n* = 521)	12.9	–	–		
B (*n* = 370)	10.3	0.80 (0.54; 1.19)	0.27		
C (*n* = 103)	5.8	0.44 (0.19; 1.01)	0.05		
HCV					
Yes (*n* = 491)	12.8	1.40 (0.96; 2.03)	0.08		
No (*n* = 503)	9.5				
HBV					
Yes (*n* = 58)	17.2	1.53 (0.82; 2.86)	0.18		
No (*n* = 936)	10.8				
Model I including tumour characteristics at listing and waiting list time					
WL time (months)		1.03 (1.02; 1.04)	<.0001	1.03 (1.02; 1.04)	<.0001
Supplementary MELD points					
Yes (*n* = 799)	8.8	0.35 (0.24; 0.51)	<.0001		
No (*n* = 195)	21.0				
Number of HCC nodules					
1–3 HCC nodules (*n* = 954)	10.8				
≥4 HCC nodules (*n* = 39)	20.5	1.26 (1.14; 1.41)	<.0001	1.20 (1.07; 1.35)	0.002
Major nodule diameter (cm)		1.16 (1.07; 1.26)	<.0001	1.11 (1.01; 1.22)	0.03
≤3.0 cm (*n* = 578)	9.2	–	–		
3.1–6.0 cm (*n* = 383)	12.5	1.45 (0.99; 2.14)	0.06		
>6.0 cm (*n* = 33)	30.3	3.88 (1.98; 7.60)	<.0001		
Sum of nodules and major diameter		1.17 (1.09; 1.16)	<.0001		
AFP (ng/ml)		1.00 (0.99; 1.01)	0.11		
≤100 ng/ml (*n* = 788)	8.2	–	–	–	–
101–1000 ng/ml (*n* = 157)	21.7	2.90 (1.92; 4.38)	<.0001	2.69 (1.78; 4.08)	<.0001
>1000 ng/ml (n = 42)	23.8	3.55 (1.78; 7.06)	<.0001	3.60 (1.73; 7.49)	.001
Log10 AFP		1.28 (1.18; 1.39)	<.0001		
Model II including dynamic tumour changes over the waitlist period					
Bridging therapy					0.60
Yes (*n* = 545)	13.1	1.79 (1.13; 2.82)	0.012	1.14 (0.69; 1.87)	
No (*n* = 449)	7.3				
Increased number of HCC nodules					0.45
Yes (*n* = 190)	28.9	4.38 (3.02; 6.32)	<.0001	1.21 (0.73; 2.02)	
No (*n* = 804)	8.9				
Increased major nodule diameter (>1 cm)					0.21
Yes (*n* = 242)	21.5	2.98 (2.06; 4.33)	<.0001	1.34 (0.85; 2.10)	
No (*n* = 752)	13.2				
ORR after 1st treatment					0.65
Yes (*n* = 238)	4.6	0.17 (0.09; 0.32)	<.0001	0.82 (0.34; 1.98)	
No (*n* = 307)	12.2				

TABLE 3 (Continued)

Variable	HCC Dropout (%)	Unadjusted SHR (95% CI)	P	Adjusted SHR (95% CI)	P
PD at first reassessment					<.0001
Yes (n = 155)	53.5	20.34 (13.23; 31.26)	<.0001	10.3 (4.71; 22.6)	
No (n = 839)	3.2				
AFP response[a]					
Yes (n = 79)	6.3	0.53 (0.22; 1.27)	0.15	-	
No (n = 915)	12.7				
AFP slope >15 ng/ml/month[a]					0.004
Yes (n = 108)	33.3	4.45 (3.02; 6.57)	<.0001	1.98 (1.25; 3.13)	
No (n = 886)	8.3				

Note: Wolber's *c*-index for HCC dropout Model I was 0.70 (95% CI 0.63; 0.76). Model II includes probability of HCC dropout comparing tumour characteristics at listing and re-assessment over the waitlist period, except for ORR and PD, which were considering after first locoregional therapy for this model. Wolber's *c*-index for HCC dropout Model II was 0.77 (95% CI 0.73; 0.80).

Abbreviations: ORR, objective response rate; PD, progressive disease by RECIST 1.1; WL, waiting list.

[a]AFP response was defined as a reduction of at least 20% between listing and last reassessment over the waitlist period, as defined by Personeni et al.[19] AFP slope was estimated using AFP values between listing and last reassessment over the waitlist period as proposed by Lai et al.[20]

Milan, within-to-beyond Metroticket 2.0 and AFP values ≤2 to >2 points. The only pattern of progression over the waitlist period significantly associated with an increased risk of HCC recurrence was intrahepatic infiltrative pattern (SHR 4.33 [95% CI 2.42, 7.73]; $p < .0001$), adjusted for AFP slope >15 ng/ml/month, microvascular invasion and complete tumour necrosis at pathology specimen (Table S4).

4 | DISCUSSION

This study is the first one to address HCC dropout rates in a multicentre cohort from Latin America. Most of these studies had come from Europe and North America and consequently are novel not only from regional but also worldwide perspective. We observed that of the total number of listed patients for a liver transplant with HCC, two-thirds were able to achieve transplantation and almost one-third were delisted, primarily because of HCC progression. The vast majority of patients were within Milan criteria with AFP values below 100 ng/mL. More than half of the cohort were treated before transplantation, as a bridge to liver transplant, more frequently in those exceeding Milan criteria.

The overall cumulative incidence of HCC progression over the WL period was similar to other published series.[1–4,14] Over the study period, 24% of the patients developed tumour progression according to objective imaging criteria (RECIST 1.1). Of these, two-thirds were delisted, considering the pattern of progression sufficiently and significantly relevant to be removed from the waitlist. The most frequent progression pattern among delisted patients was new intrahepatic lesions. All the patients progressing with macrovascular invasion or extrahepatic spread were removed from the transplant list. Also, we observed that, there is a specific pattern of tumour progression that should be identified with a higher risk of dropout and post-transplant recurrence (infiltrative diffuse pattern), and that should be included as a strict criteria of delisting apart from vascular invasion or extrahepatic spread. Patterns of progression have not been evaluated before among transplant candidates.[24]

We observed that the HCC dropout rate during the first year of listing was less than 10%, slightly higher than that previously reported from Argentina.[27] In other countries, some authors have reported an HCC dropout rate of 20% at 1 year of listing among patients exceeding Milan criteria.[4,28] Using a competing risk multivariable model, we observed a 3% increasing risk of HCC dropout for every month since listing; a 20% increasing risk for every additional nodule, 11% increasing risk for every increase in the major nodule diameter (cm) and a three- and fourfold higher risk of HCC dropout with AFP values above 100 and 1000 ng/ml respectively. These predictive variables were adjusted for bridging therapy before transplantation. C Toso and colleagues proposed a dropout score including the number and diameter of tumours, AFP values and the MELD score.[9] In other series, patients with single lesions <3 cm and AFP values below 20 ng/ml, presented a very low risk of progression during the waitlist period, underlined if a complete response after locoregional treatments were observed.[1] This observation led to a new policy of MELD-Sodium supplementary point assignment in the United States. Almost 18% of the patients presented a complete response in our cohort, and this group did not present HCC dropout.

Pre-transplant models were designed to select candidates with the lowest risk of tumour recurrence and better survival after transplantation. However, these models were not developed to predict pre-LT outcomes. Although tumour progression while on the waitlist period may carry a higher risk of tumour recurrence after transplantation, this is not always the case. It depends on what criteria to define PD is used. Patients still on transplant criteria can present PD according to RECIST 1.1. Also, it is likely that several additional factors such as length of waitlist timing, access to HCC treatments, and progression of underlying liver disease may affect the risk of

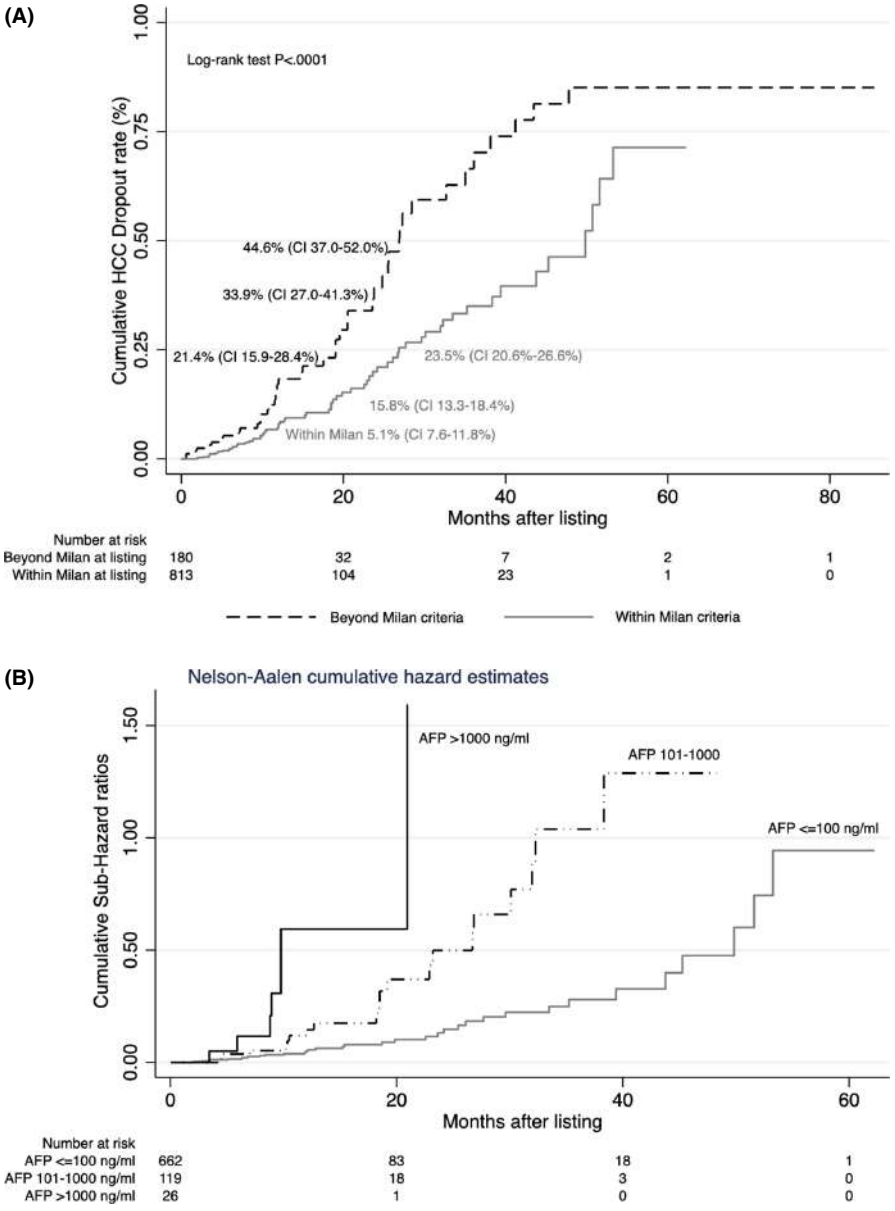

FIGURE 3 Cumulative incidence of HCC dropout according to Milan criteria (A), and according to AFP values in patients within Milan criteria (B)

drop-out during the waitlist period. HCC dropout because of HCC progression may have been because of baseline tumour burden, biological differences (AFP values) and length of time during the WL (meaning access to transplantation). We observed that dynamic tumour changes over the waitlist period are of independently associated with a higher risk of HCC dropout and should demand cautious clinical-decision-making processes.

We evaluated pre-LT models and their prediction of HCC dropout. Although there was not a statistically significant difference in the discrimination power between Milan criteria,[5] the AFP score[12] and the Metroticket 2.0 model,[13] we observed that using threshold models of Milan and the AFP score can identify two risk populations of HCC progression and dropout. The AFP model discriminated two risk populations among patients meeting the Milan criteria. On the other hand, patients reducing their initial AFP score from more than two to lower than two points reduced the risk of progression and HCC dropout. However, the AFP score could not discriminate risk of HCC dropout among patients exceeding Milan criteria, as initially described for post-LT outcomes.[12]

This study may present some limitations worthy of mention, typical in retrospective observational studies. First, it could be argued that heterogeneous primary outcome assessment may have been observed across different LT centres from several countries. However, in all the countries, Milan criteria were the transplant gold standard, and unequivocal HCC dropout was common across centres. Second, RECIST 1.1 criteria were used for PD definition and imaging reassessment, opposing most recent recommendations.[16,17] As aforementioned, we chose this criterion to deal with potential information bias across centres. Response to locoregional therapy might have been biased because of the fact that radiological assessment was not centrally reviewed. Although we submitted a common automatized RECIST 1.1 calculator to be done at each centre, there might have been information bias in this assessment. However, we considered this a non-differential misclassification towards the null

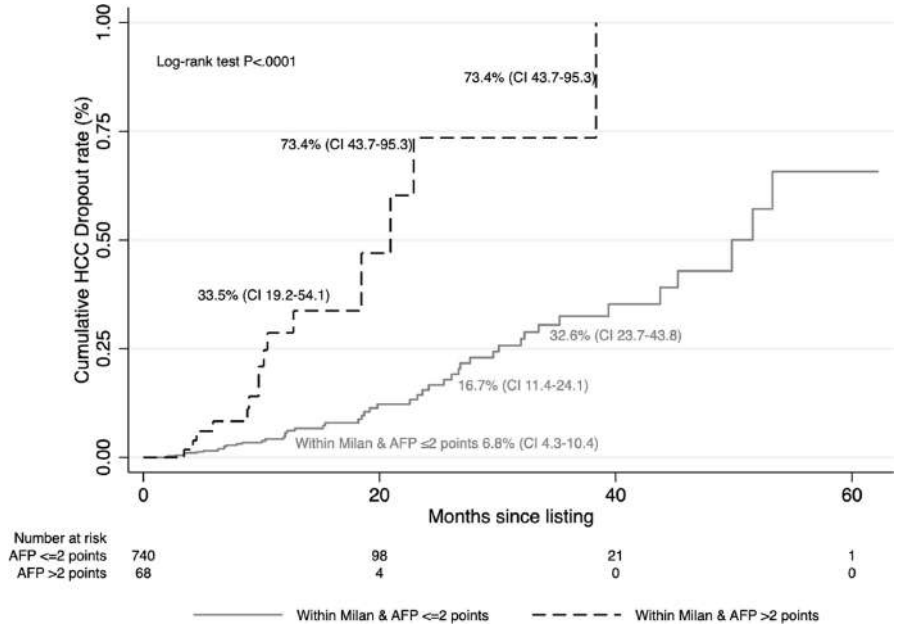

FIGURE 4 Cumulative incidence of HCC dropout according to the AF score in patients within Milan criteria

TABLE 4 Discrimination power regarding HCC dropout between Milan criteria, the AFP model and Metroticket v2.0 criteria

Models	Wolber´s *c*-index (95% CI)	*p* value vs Milan as reference	*p* value vs AFP model as reference
Milan criteria	0.63 (0.57–0.69)	—	
AFP score[a]	0.70 (0.64–0.77)	.09	—
Metroticket 2.0[b]	0.70 (0.63–0.77)	.12	.95

Note: All models assessed at listing.

[a]AFP as originally proposed by Duvoux et al.

[b]Metroticket 2.0 as originally reported by Mazzaferro et al.

hypothesis. For this reason, we chose RECIST 1.1 rather mRECIST (we expected to have much more misclassification with mRECIST than RECIST 1.1 criteria). Third, there might have been a low sample power to detect discrimination in the group of patients exceeding Milan criteria, when evaluating composite models. Finally, the SARS-Cov2 pandemic has challenged transplant access and healthcare systems in all over the world. Unfortunately, our results could not be explored in this pandemic situation, in which LT access and dropout rates have been negatively impacted as a consequence of longer waitlist times and HCC progression while on the waitlist period.[29]

The present study addressed whether transplant criteria, which were all design to predict post-transplant outcomes, could stratify the risk of tumour progression while on the WL. There might be different definitions for this end-point in the real-world practice (including RECIST 1.1, mRECIST or just progression beyond transplant criteria and the decision to delist the patient). This has been deepened in the discussion more recently.[30] In other words, we consider that patients with an expected baseline higher risk of HCC dropout are more likely at a higher risk of recurrence if transplanted. Particularly, dynamic tumour changes including PD based on RECIST 1.1 criteria after the first treatment and an AFP slope >15 ng/mL are independent risk factors for HCC dropout. This model had a high discrimination power.[20]

In conclusion, pre-transplant models appropriately discriminate HCC dropout over the waitlist period. We underline the independent value of serum AFP in predicting HCC progression and delisting. Although composite models, the AFP score and the Metroticket 2.0, designed to predict post-LT outcomes, they both can discriminate HCC dropout in a similar power. Consequently, this study showed that both models could further discriminate pre-LT events appropriately and be further choose as pre-transplant selection models. These results should be explored in prospective cohorts with a higher sample power for patients exceeding Milan criteria.

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CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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