

## ORIGINAL ARTICLE

# Liver transplantation for hepatocellular carcinoma: impact of expansion criteria in a multicenter cohort study from a high waitlist mortality region

Federico Piñero<sup>1,2</sup> , Margarita Anders<sup>2,3</sup>, Ilka F. Boin<sup>4</sup>, Aline Chagas<sup>5</sup> , Emilio Quiñonez<sup>6</sup>, Sebastián Marciano<sup>7</sup>, Mario Vilatobá<sup>8</sup>, Luisa Santos<sup>9</sup>, Sergio Hoyos Duque<sup>10</sup>, Agnaldo Soares Lima<sup>11</sup>, Josemaría Menendez<sup>12</sup>, Martín Padilla<sup>13</sup>, Jaime Poniachik<sup>14</sup>, Rodrigo Zapata<sup>15</sup>, Alejandro Soza<sup>16</sup>, Martín Maraschio<sup>17</sup>, Ricardo Chong Menéndez<sup>18</sup>, Linda Muñoz<sup>19</sup>, Diego Arufe<sup>20</sup>, Rodrigo Figueroa<sup>21</sup>, Elaine Cristina de Ataíde<sup>4</sup>, Claudia Maccali<sup>5</sup>, Rodrigo Vergara Sandoval<sup>6</sup>, Carla Bermudez<sup>7</sup>, Luis G. Podesta<sup>1</sup>, Lucas McCormack<sup>3</sup>, Adriana Varón<sup>8</sup>, Adrián Gadano<sup>6</sup>, Juan Mattera<sup>5</sup>, Federico Villamil<sup>6,22</sup>, Fernando Rubinstein<sup>23</sup>, Flair Carrilho<sup>5</sup> & Marcelo Silva<sup>1,2</sup>

- 1 Hospital Universitario Austral, Buenos Aires, Argentina  
 2 Latin American Liver Research Educational and Awareness Network (LALREAN), Buenos Aires, Argentina  
 3 Hospital Alemán, Buenos Aires, Argentina  
 4 Hospital das Clínicas UNICAMP Campinas, Sao Paulo, Brazil  
 5 Hospital das Clínicas University of São Paulo School of Medicine, São Paulo, Brazil  
 6 Hospital El Cruce, Florencio Varela, Argentina  
 7 Hospital Italiano de Buenos Aires, Buenos Aires, Argentina  
 8 Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Tlalpan, México  
 9 Fundación Cardioinfantil, Bogotá, Colombia  
 10 Grupo de Gastrohepatología, Hospital Pablo Tobón Uribe, Universidad de Antioquia, Medellín, Colombia  
 11 Hospital das Clinicas da UFMG, Belo Horizonte, Brazil  
 12 Hospital de Clínicas, Montevideo, Uruguay  
 13 Hospital Guillermo Almenara, Lima, Perú  
 14 Hospital de la Universidad de Chile, Santiago, Chile  
 15 Clínica Alemana, Facultad de Medicina, Universidad del Desarrollo, Santiago, Chile

## SUMMARY

This study aimed to compare liver transplantation (LT) outcomes and evaluate the potential rise in numbers of LT candidates with hepatocellular carcinoma (HCC) of different allocation policies in a high waitlist mortality region. Three policies were applied in two Latin American cohorts (1085 HCC transplanted patients and 917 listed patients for HCC): (i) Milan criteria with expansion according to UCSF *downstaging* (UCSF-DS), (ii) the AFP score, and (iii) restrictive policy or Double Eligibility Criteria (DEC; within Milan + AFP score  $\leq 2$ ). Increase in HCC patient numbers was evaluated in an Argentinian prospective validation set (INCUCAI; NCT03775863). Expansion criteria in policy A showed that UCSF-DS [28.4% (CI 12.8–56.2)] or “all-comers” [32.9% (CI 11.9–71.3)] had higher 5-year recurrence rates compared to Milan, with 10.9% increase in HCC patients for LT. The policy B showed lower recurrence rates for AFP scores  $\leq 2$  points, even expanding beyond Milan criteria, with a 3.3% increase. Patients within DEC had lower 5-year recurrence rates compared with those beyond DEC [13.3% (CI 10.1–17.3) vs 24.2% (CI 17.4–33.1;  $P = 0.0006$ ), without significant HCC expansion. In conclusion, although the application of a stricter policy may optimize the selection process, this restrictive policy may lead to ethical concerns in organ allocation (NCT03775863).

*Transplant International* 2021; 34: 97–109

## Key words

allocation, hepatocellular carcinoma, liver transplantation, selection

Received: 4 August 2020; Revision requested: 25 August 2020; Accepted: 6 October 2020

## Correspondence

Federico Piñero MD, MSCE, Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Av. Presidente Perón 1500, (B1629HJ) Pilar, Buenos Aires, Argentina.  
 Tel.: +54 0230 448 2000;  
 fax: +54 0230 448 2236;  
 e-mail: fpinerof@cas.austral.edu.ar

- 16 Hospital Clínico, Universidad Católica de Chile, Santiago, Chile  
 17 Hospital Privado de Córdoba, Córdoba, Argentina  
 18 Hospital Carlos Andrade Marín, Quito, Ecuador  
 19 Hospital Universitario “Dr. José E. González”, Monterrey, Mexico  
 20 Sanatorio Sagrado Corazón, Buenos Aires, Argentina  
 21 Sanatorio Allende, Córdoba, Argentina  
 22 Hospital Británico, Buenos Aires, Argentina  
 23 Instituto de Efectividad Clínica y Sanitaria (IECS), Buenos Aires, Argentina

\*Shared first authors.

## Introduction

Liver transplantation (LT) is the treatment of choice for early-stage hepatocellular carcinoma (HCC). Although Milan criteria have been the standard selection model used around the world [1], other authors have suggested that these were too restrictive and have proposed *extended* criteria [2]. However, expansion models could increase the risk of HCC recurrence and decrease post-transplant survival [3]. Consequently, international guidelines [4,5] have underlined the need for *composite* models, including tumor burden and biological markers, to optimize transplant candidate selection [6–8]. Radiological response after bridging therapies should also be considered in this context [9].

Inaccurate HCC candidate selection for LT combined with additional prioritization could cause uneven organ distribution, lower transplant opportunities, and higher waitlist mortality for non-HCC patients [10–12]. The need to balance transplanting the sickest first, maximizing post-LT survival, and optimizing the use of a scarce resource is true for all countries, but differences in access to LT care vary significantly between them. Expansion beyond Milan criteria could also increase the number of HCC patients excessively, altering the balance in access to transplant against non-HCC patients [10–13] and resulting in unfair clinical patient selection, particularly in high waitlist mortality regions [12,13].

In Latin America, previous reports have shown lower donation rates per million population (pmp) compared with those reported in Europe and the United States of America (8.3 pmp vs. 15 pmp and 26 pmp, respectively) [13,14]. Moreover, within Milan criteria, HCC patients are granted transplant benefit, showing significantly lower waitlist mortality compared with non-HCC patients [12,15]. Consequences of adopting expansion criteria policies in regions with high waitlist mortality have not been previously reported. This study aimed to compare pre- and post-LT outcomes and evaluate the effects of an increase in the number of HCC patients

listed for LT based on three different allocation policies using a decision-tree analysis approach.

## Materials and methods

### Main policies and clinical decision-making analysis

Three LT candidate selection policies for HCC patients based on the most relevant transplant criteria from Eastern and Western regions around the world were compared. These are the Milan criteria [1], the AFP French model [8], and the University of California San Francisco *downstaging* protocol (UCSF-DS) [16,17].

#### Policy A

Milan criteria and AFP values below 1000 ng/ml [18]. Within this policy, expansion criteria in patients initially exceeding Milan included (i) within the UCSF-DS protocol (1 lesion >5 cm and ≤8 cm or 2–3 lesions at least one >3 and ≤5 cm with a total tumor diameter ≤8 cm, or 4–5 lesions each ≤3 cm with a total tumor diameter ≤8 cm) [16,17] and (ii) those patients beyond UCSF-DS (“all-comers”; Fig. 1a) [17].

#### Policy B

The AFP score (0–9 points) [8]. This score is calculated based on the largest tumor diameter, the number of HCC nodules, and AFP levels ng/ml [8]. The AFP model has been implemented in France since 2013 (Fig. 1b) [19]. It can expand eligibility beyond Milan criteria in patients with an AFP score less than or equal to two points.

#### Policy C

Double Eligibility Criteria approach (DEC): To explore a combination of LT models, another policy was proposed. It was not designed to be a new model, but

evaluated a combination of previously published models [8,20,21] and tumor changes following bridging therapies to make it more applicable in real-world scenarios [22,23]. For this study, we considered Milan criteria as the standard for selection but *optimized* results based on the AFP score and response to locoregional bridging therapies. DEC policy included patients within Milan and AFP scores  $\leq 2$  points at the last tumor reassessment before LT. Ultimately, the purpose of DEC was to apply a stricter longitudinal selection process avoiding excessive increase in the number of HCC transplant candidates, by taking into account tumor changes occurring while on the waiting list (Fig. 1c).

At listing, four categories were defined and compared. The first group of patients were those within the DEC; the second group were those within Milan criteria with AFP scores  $> 2$  points; the third group were patients beyond Milan criteria with AFP scores  $\leq 2$ ; and the fourth group were those beyond Milan criteria with AFP scores  $> 2$ . Final clinical selection or cutoff for DEC corresponded to patients within Milan criteria with AFP scores  $\leq 2$  at last pre-LT assessment. Thus, patients were considered to be within final DEC if they were at time of listing, remained stable while on the waitlist, or *downstaged* within Milan criteria with AFP scores  $\leq 2$  points at final pre-LT assessment.

### Potential expansion analysis

Based on population probabilities reported on previously published data [8,17], we analyzed application of each policy conducting a decision-tree analysis using TreeAge software (TreeAge Software, Inc, Williamstown, MA, USA). Population distribution probabilities of within/beyond each model were applied (Fig. 1a–c) [8,17,21]. We further evaluated the potential increase in the number of HCC patients who would have been transplanted according to each of the three Policies applying a decision-modeling approach in a set of patients who underwent LT in Argentina between January 1, 2009, and July 1, 2019. Data prospectively collected from the Argentine National Agency for Organ Sharing and Transplantation (INCUCAI) were analyzed ([www.sintra.incucai.gov.ar](http://www.sintra.incucai.gov.ar)). In this Argentinian National Data, numbers of LT are prospectively registered in an open and public registry. Patients with HCC within Milan criteria are registered and granted additional MELD points for LT. We specifically focused on data regarding the number of listed and transplanted patients per year, and the proportion of HCC candidates awarded with

supplementary MELD points. From this National Data ( $n = 7532$  of total LT patients,  $n = 684$  HCC patients with extra MELD points), we estimated the potential increase in the number of HCC patients from 2009 to 2019 for each policy.

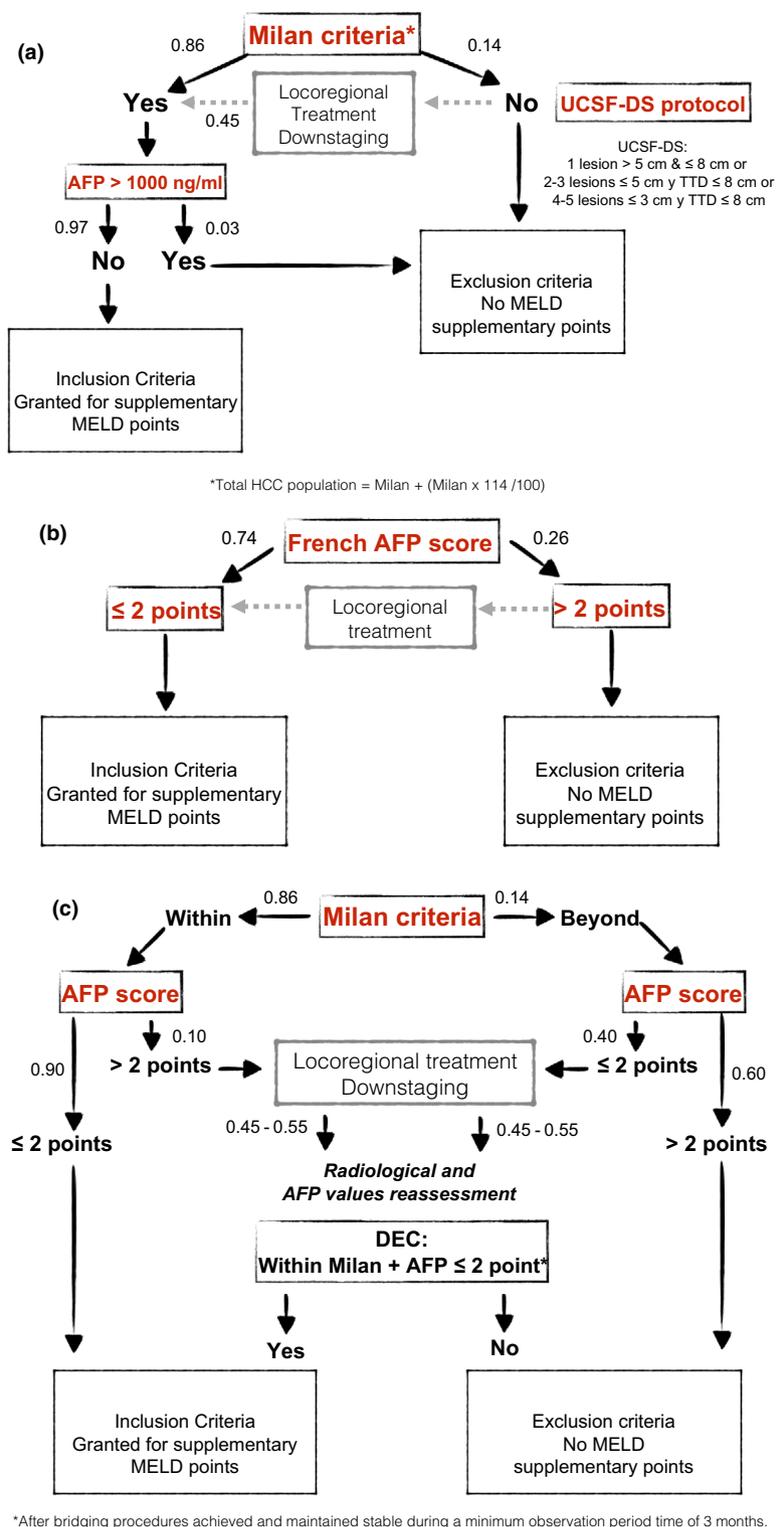
### Study cohorts

Probability of post-LT survival and HCC recurrence based on the three policies was compared in a large Latin American cohort. This retrospective cohort included adult patients (over 18 years of age) with HCC, from 22 different regional centers who underwent LT between January 1, 2005, and January 1, 2018 ( $n = 1085$ ). In order to evaluate pre-LT outcomes, including waitlist mortality and HCC dropout rate because of HCC progression, a second cohort including all listed patients with HCC from 2011 to 2018 was evaluated ( $n = 917$ ).

Inclusion criteria required patients with HCC based on imaging or histological diagnosis, be transplanted for HCC (first cohort) or listed for LT with HCC (second cohort). Patients were excluded if (i) tumors other than HCC were confirmed at explant pathology analysis, (ii) incidental HCC was diagnosed at explant analysis, but not observed on pre-LT imaging, (iii) extrahepatic or macrovascular tumor invasion was found during pre-transplant evaluation, and (iv) they had received a prior LT. Study data were registered on a Web-based electronic case report form (CRF), following STROBE guidelines [24], Helsinki Declaration ethical standards revised in 2008, and the study protocol registered as part of an open public registry (NCT03775863; [www.clinicaltrials.gov](http://www.clinicaltrials.gov)), under confidentiality agreement with each investigator.

Longitudinal tumor burden and AFP values were evaluated at listing and last pre-LT reassessment in all patients. Tumor burden was categorized according to Milan [1] and UCSF criteria [2], and the AFP score [8]. Standard patient selection in all centers was limited to Milan criteria. However, patients exceeding Milan criteria were also included according to local allocation policies. All patients were classified applying the aforementioned models based on radiological findings, size and number of lesions detected on computerized tomography (CT) or magnetic resonance images (MRI), and serum AFP values. Lung CT and bone scintigraphy were performed in all patients to rule out metastatic disease.

Tumor treatment prior to transplantation was determined by each transplant center, including trans-arterial



**Figure 1** Decision-tree analysis for Milan–UCSF-DS protocol (a), AFP score (b), and the DEC (c). Note. Flowchart and corresponding population probabilities for each decision-tree analysis. (a) Total HCC population (100%), 0.86 within Milan and 0.14 beyond Milan including those within UCSF-DS (0.11) and “all-comers” (0.03). Exclusion of AFP values above 1000 ng/ml 0.03 and adding the efficacy of *downstaging* reported to be 0.45–0.55 [17,21]. Policy B. AFP score, of which 74% and 24% presented with AFP score ≤2 or >2 points [8], and policy C (within Milan 0.86 of total HCC population; within Milan and AFP score ≤2 points 0.90 and within Milan and >2 points 0.10; beyond Milan 0.14 of total HCC population, of which 40% had an AFP score ≤2 points and 60% >2 points, adding the efficacy of *downstaging* in patients beyond Milan of 0.45–0.55) [8,21].

chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and liver resection. In patients receiving bridging therapies while on the waiting list, most recent radiologic tumor staging and AFP values following procedures were registered. In patients exceeding Milan criteria, *downstaging* protocols were evaluated following the UCSF-DS proposal [17].

Tumor shrinkage was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) at each center [4,5]. Imaging reassessment was performed in all patients either with CT or MRI at least once every 3 months. In patients receiving locoregional treatment, image re-evaluation was carried out 4–6 weeks after each procedure [4,5]. The study protocol considered RECIST 1.1 instead of modified RECIST criteria (mRECIST) [25] to avoid misinterpretation of necrotic areas or heterogeneous evaluation of hyper vascular enhancement across centers.

### Statistical analysis

The primary outcome chosen was post-LT HCC recurrence because it represents the most important event specifically affecting post-LT survival. Secondary outcomes were removal from the waitlist, because of HCC progression (HCC dropout rate), and overall survival after LT. For post-LT outcomes, all transplanted patients from the two cohorts were analyzed, whereas for pre-LT outcomes, only the second Latin American cohort was evaluated.

Post-transplant HCC recurrence monitoring consisted of CT or MRI and serum AFP assay (minimum interval 6 months). Recurrence was determined based on imaging criteria plus serum AFP or by biopsy. Competing risk regression models were performed for HCC recurrence (failure event), with sub-hazard ratios (SHR) and 95% confidence intervals (CI) calculated (Fine and Gray method) [26]. For HCC recurrence outcome, any cause of death preceding HCC recurrence was considered a competing event. For the outcome of HCC dropout during the waiting list, competing risk regression models were performed, considering non-HCC-related deaths while on the waiting list, non-HCC dropout and transplantation as competing events. All patients were followed until death or most recent outpatient visit. The Kaplan–Meier survival curves were compared using the log-rank test (Mantel–Cox). For survival analysis, multivariable Cox regression models with hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated to evaluate size of effect of each LT criterion on overall cohort survival. Proportional hazard assumption

was evaluated using graphics and Schoenfeld residual test. Data collected were analyzed using STATA 13.0 (StataCorp, College Station, TX, USA).

### Results

The first cohort included 1085 HCC patients who were transplanted in 22 transplant centers from Brazil ( $n = 377$ ), Argentina ( $n = 324$ ), Colombia ( $n = 157$ ), Chile ( $n = 90$ ), Mexico ( $n = 63$ ), Uruguay ( $n = 35$ ), Peru ( $n = 26$ ), and Ecuador ( $n = 13$ ; Table 1). The second Latin American multicenter cohort included 917 patients with HCC listed for LT, in whom pre-LT outcomes were evaluated.

### Performance of each LT criterion on post-LT outcomes

Baseline patient and HCC data at time of listing, as well as LT outcomes stratified by country of transplanted patients, are shown in Table S1. The median time on the waiting list was 4.9 months (IQR 1.7–10.1 months), with a median time from the last tumor reassessment to LT of 2.3 months (IQR 1.0–4.6 months). Five-year post-LT survival rate was 64.2% (CI 60.5–67.6), whereas the corresponding HCC recurrence rate was 16.6% (CI 13.5–20.3).

At listing, 84.4% of the cohort was within Milan criteria, with 5-year survival rate of 64.0% (CI 59.9–67.8), and 52.5% (CI 41.3–62.7) for those beyond Milan criteria. Corresponding 5-year recurrence rates for patients within or exceeding Milan criteria were 13.7% (CI 10.5–17.8) and 34.2% (CI 24.5–46.4) [SHR 0.35 (CI 0.23; 0.52;  $P < 0.0001$ )], respectively. For patients exceeding Milan but within UCSF ( $n = 72$ ), 5-year recurrence and survival rates were 23.1% (CI 12.3–40.8) and 59.2% (CI 43.2–72.1).

### Policy A. Milan criteria with AFP <1000 ng/ml restriction and expansion through UCSF-DS protocol ( $n = 1042$ )

Excluding patients with AFP serum values above 1000 ng/ml ( $n = 39$ ) at listing, 87.5% were within Milan criteria ( $n = 912$ ), 8.0% within UCSF-DS ( $n = 83$ ), and 4.5% were “all-comers” ( $n = 47$ ). At most recent tumor reassessment, 79.4% were within Milan criteria ( $n = 827$ ), 96% of which remained within Milan from listing through last evaluation ( $n = 794/827$ ). The rest were appropriately *downstaged* to Milan criteria from UCSF-DS ( $n = 25/83$ ) and “all-comers” ( $n = 8/47$ ). Consequently, effective *downstaging* to Milan

**Table 1.** Baseline patient characteristics at time of listing and at last tumor reassessment.

Variable	Values
Age, years ( $\pm$ SD)	58 $\pm$ 8
Gender, male, <i>n</i> (%)	844 (77.8)
Median time on waiting list, (IQR), months	4.9 (1.7–10.1)
Cirrhosis, <i>n</i> (%)	
Yes	1077 (99.3)
No	8 (0.7)
Child–Pugh A/B/C, <i>n</i> (%)	499 (46)/420 (39)/166 (15)
Etiology of liver disease, <i>n</i> (%)	
Viral	610 (56.4)
Alcohol	183 (16.9)
Cholestasis (PBC, SSC, PSC)	27 (2.0)
NAFLD	108 (10.0)
Cryptogenic	98 (9.1)
Autoimmune	18 (1.7)
Iron metabolism	21 (1.9)
Other	19 (1.7)
HCV, <i>n</i> (%)	463 (42.7)
HBV, <i>n</i> (%)	151 (13.9)
Supplementary MELD points, <i>n</i> (%)	875 (80.6)
Tumor data at listing	
Median AFP at listing, ng/ml (IQR)	11.0 (4.5–52.3)
$\leq$ 100 ng/ml, <i>n</i> (%)	876 (81.0)
101–1000 ng/ml, <i>n</i> (%)	166 (15.4)
$>$ 1000 ng/ml, <i>n</i> (%)	39 (3.6)
Within Milan, <i>n</i> (%)	938 (86.4)
AFP score $\leq$ 2 points	867 (92.5)
AFP score $>$ 2 points	71 (7.5)
Beyond Milan, <i>n</i> (%)	147 (13.5)
AFP score $\leq$ 2 points	78 (52.7)
AFP score $>$ 2 points	69 (47.3)
Within UCSF, <i>n</i> (%)	1010 (93.1)
Beyond Milan, within UCSF	72 (6.6)
Beyond UCSF	75 (6.9)
Milan + AFP $<$ 1000 ng/ml, <i>n</i> (%)	912 (87.5)
UCSF-DS, <i>n</i> (%)	83 (8.0)
All-comers, <i>n</i> (%)	47 (4.5)
Locoregional treatment, <i>n</i> (%)	601 (55.4)
Tumor data at last reassessment	
Median AFP at last reassessment, ng/ml (IQR)	10.3 (4.4–44.2)
$\leq$ 100 ng/ml, <i>n</i> (%)	892 (82.7)
101–1000 ng/ml, <i>n</i> (%)	148 (13.7)
$>$ 1000 ng/ml, <i>n</i> (%)	39 (3.6)
Within Milan, <i>n</i> (%)	859 (79.2)
AFP score $\leq$ 2 points	771 (89.8)
AFP score $>$ 2 points	88 (10.2)
Beyond Milan, <i>n</i> (%)	226 (20.8)
AFP score $\leq$ 2 points	166 (73.7)
AFP score $>$ 2 points	60 (26.3)
Milan + AFP $<$ 1000 ng/ml, <i>n</i> (%)	827 (79.4)
Remaining within Milan + AFP $<$ 1000 ng/ml, <i>n</i> (%)	794 (96.0)

**Table 1. Continued.**

Variable	Values
Downstaged from UCSF-DS to Milan, <i>n</i> (%)	25 (3.0)
Downstaged from “all-comers” to Milan, <i>n</i> (%)	8 (1.0)

AFP, alpha-fetoprotein; IQR, interquartile range; MELD, Model for End-stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis.

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.” Cumulative recurrence after LT was significantly higher both in patients in the UCSF-DS group [SHR 2.81 (CI 1.12–7.06)] and in “all-comers” [SHR 2.79 (CI 0.74–10.5)] compared to patients within and remaining on Milan criteria throughout their time on the waitlist (Table 2; Fig. 2a).

#### Policy B. Selection criteria according to the AFP score

At listing, 86.4% of the patients had an AFP score  $\leq$ 2 points ( $n = 936$ ; Table 1). Longitudinal changes during the waitlist period in the AFP model showed 92.3% of patients with AFP scores  $\leq$ 2 at listing remained within 2 points at final evaluation before LT. On the other hand, 30.1% of patients with AFP scores  $>$ 2 at time of listing showed a fall in AFP scores to  $\leq$ 2 points, at last tumor reassessment.

Five-year recurrence rates were higher in patients with AFP scores  $>$ 2 compared to those with AFP scores  $\leq$ 2 points [SHR 3.64 (CI 2.44–5.43);  $P < 0.0001$ ] (Table 2). Survival and recurrence rates were similar in patients within or beyond Milan criteria if AFP scores were  $\leq$ 2, but different compared to patients within or beyond Milan criteria when AFP scores were  $>$ 2 points (Fig. 2b).

#### Policy C

As proposed, DEC aimed to optimize selection toward patients within Milan criteria with AFP scores  $\leq$ 2, using longitudinal tumor assessment including response to locoregional therapies or tumor progression while on the waitlist (Table 3).

Patients initially within Milan with AFP scores  $\leq$ 2 (DEC) maintained this level of tumor burden in 84.9%

**Table 2.** Performance of each LT policy applied in the multicenter Latin American cohort at last tumor reassessment with 95% confidence intervals (CI).

	% 5-year HCC recurrence rate (95% CI)	% 5-year post-LT survival rate (95% CI)
Policy A*		
Within Milan ( <i>n</i> = 794)	13.1 (9.9–17.2)	66.0 (61.8–70.0)
UCSF-DS ( <i>n</i> = 25)	28.4 (11.5–60.1)	51.0 (26.6–71.1)
“All-comers” ( <i>n</i> = 8)	32.9 (11.9–71.3)	58.6 (26.7–80.5)
Policy B		
AFP score ≤2 points ( <i>n</i> = 908)	12.2 (CI 9.4–15.9)	67.4 (63.4–70.9)
AFP score >2 points ( <i>n</i> = 175)	37.3 (CI 27.7–50.0)	49.4 (39.5–58.5)
Policy C		
Within DEC ( <i>n</i> = 789)	13.3 (10.1–17.3)	67.0 (63.0–70.7)
Beyond DEC ( <i>n</i> = 294)	24.2 (17.4–33.1)	56.2 (48.0–65.9)

AFP, alpha-fetoprotein; DEC, Double Eligibility Criteria; UCSF-DS, University of California San Francisco *downstaging* protocol.

\*All patients with AFP < 1000 ng/ml. Cumulative 5-year recurrence rates for patients within or beyond Milan (without AFP restriction policy) were 13.7% (CI 10.5–17.8) and 34.2% (CI 24.5–46.4), respectively. For patients beyond Milan but meeting UCSF, cumulative 5-year recurrence was 23.1% (CI 12.3–40.8).

of cases (*n* = 736 out of 867). Patients within Milan with AFP scores >2 remained within Milan and dropped AFP score to less or equal to 2 in 32.9% of cases (*n* = 23/70). Patients beyond Milan with AFP scores ≤2 were appropriately *downstaged* to DEC in 24.6% of cases (*n* = 17/69). Finally, the group of patients beyond Milan with AFP scores >2 were *downstaged* to DEC in only 17.1% of cases (*n* = 13/77).

A proportion of patients in each group beyond DEC at last pre-LT evaluation after this longitudinal assessment for each group are shown in Table 4. Overall, from policy A, the DEC resulted in an exclusion rate of 18.0% (CI 15.5–20.6), 73.5% (CI 62.7–82.7), and 83.3% (CI 69.8–92.5) for patients with AFP values below 1000 ng/ml and within Milan, UCSF-DS, and “all-comers”, respectively. For patients with AFP scores ≤2 and >2 points, exclusion rates using DEC were 19.1% (CI 16.6–21.2) and 75.3% (CI 67.5–82.1), respectively.

Recurrence rates were lower in all groups within DEC, except in patients *downstaged* from beyond Milan with AFP scores >2 (Table 4). In summary, patients within DEC at final pre-LT evaluation presented lower recurrence rates compared with patients beyond DEC [SHR 0.50 (CI 0.34; 0.74); *P* = 0.001] (Fig. 2c).

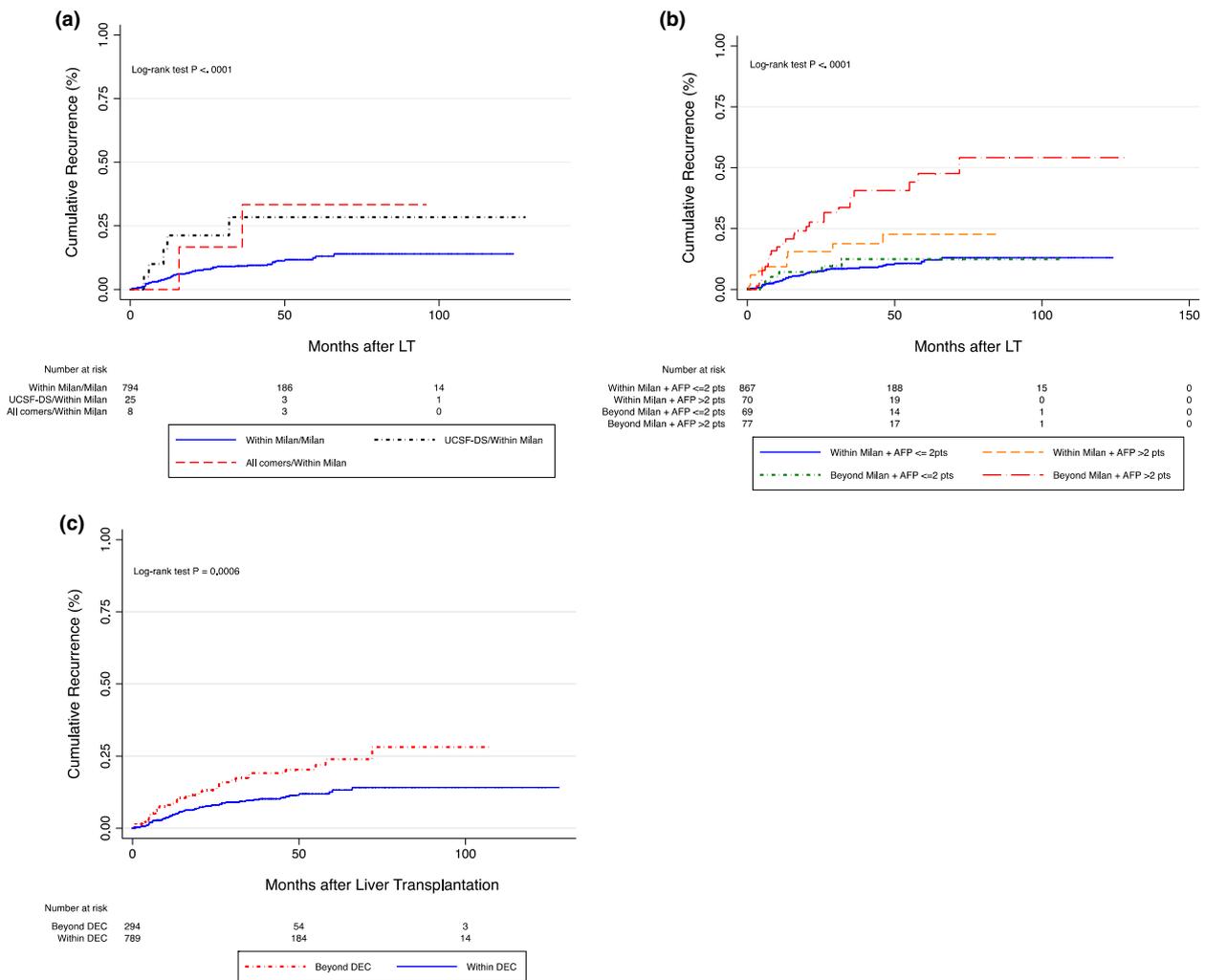
#### Performance of each LT criterion on pre-LT outcomes: HCC dropout rate

In the second Latin American cohort (*n* = 917), including all listed patients for HCC (Table S2), overall dropout rates due to HCC progression at 1 and 2 years of

listing were 7.1% (CI 5.3–9.2%) and 20.2% (CI 15.2–25.9%). HCC dropout rates increased from within Milan 8.1% (CI 6.2–10.3%) to within UCSF-DS 23.9% (CI 15.8–33.7%) and AC 27.3% (CI 16.1–41.0%) in policy A (*P* < 0.0001). Patients with an AFP score >2, either within [24.6% (CI 14.5–37.3)] or beyond Milan criteria at listing [25.9% (CI 17.0–36.5)], had significantly higher HCC dropout rates compared to patients with AFP scores ≤2 either within [7.1% (CI 5.3–9.3)] or beyond Milan criteria [23.7% (CI 15.0–33.9)]. Lower HCC dropout rate was observed among patients within DEC [7–1% (CI 5.3–9.3%)] compared to those exceeding DEC at listing [24.8% (CI 19.2–31.0%); *P* < 0.0001] (Table S3).

#### Potential expansion in the number of HCC patients for LT

We further explore expansion of absolute and relative number of HCC patients who could have undergone LT between 2009 and 2019 applying each policy (Milan/UCSF-DS, AFP score, and DEC) based on a prospective evaluation of the INCUCAI database ([www.sintra.incuca.gov.ar](http://www.sintra.incuca.gov.ar)). The Milan–UCSF-DS policy could have resulted in a potential 10.9% expansion in number of HCC patients and 2.1% increase in total LTs performed. The AFP model expanded the number of HCC transplanted patients by 3.3% and 0.6% increase in total LTs. DEC alone resulted in *optimization* of transplant selection without increasing the number of HCC LT patients (Fig. 3a–c).



**Figure 2** Cumulative recurrence rates according to decision-tree analysis for Milan-UCSF-DS protocol (a), the AFP model (b), and the DEC policy (within Milan + AFP score  $\leq 2$  points) (c). Note: a—Cumulative recurrence after LT was significantly higher in patients in the UCSF-DS group SHR 2.81 (CI 1.12–7.06) or “all-comers” SHR 2.79 (CI 0.74–10.5) compared with those patients initially and subsequently remaining within Milan criteria along the waiting list period. b—Corresponding recurrence rates for patients within or beyond Milan criteria with an AFP score  $\leq 2$  points and  $> 2$  points were 12.2% (CI 9.2–16.1), 12.6% (CI 5.7–26.4), 22.7% (CI 12.6–38.8), and 47.7% (CI 34.2–63.4;  $P < 0.0001$ ), respectively. Five-year survival rates for patients within [67.3% (CI 63.4–71.0)] or beyond Milan criteria [67.9% (CI 52.4–79.3)] with an AFP score  $\leq 2$  points were higher than those patients within [52.3% (CI 37.3–65.4)] or beyond Milan criteria [47.8% (CI 34.7–59.7)] with an AFP score  $> 2$  points. c—Corresponding 5-year recurrence rates were 13.3% (CI 10.1–17.3) and 24.2% (CI 17.4–33.1;  $P = 0.0006$ ) for those patients within and beyond the DEC at last tumor reassessment. Five-year survival rates were 67.0% (CI 63.0–70.7) and 56.2% (CI 48.0–63.6);  $P = 0.14$ ], respectively.

## Discussion

Using real-world data from a large Latin American cohort, a region with high waitlist mortality, we compared potential expansion applying three different policies and observed that post-LT recurrence was higher in patients who were *downstaged* applying either UCSF-DS or in all-comers, compared with Milan criteria. As for implementation of policy B, patients with AFP scores  $> 2$  also presented higher risk of HCC recurrence. Regarding

the call for *composite* models, we evaluated DEC policy based on a decision-tree analysis including Milan criteria and AFP scores, and compared this new approach to policies adopted in France [8,19] and the United States [17]. Potential expansion in the number of HCC patients for LT may unbalance transplant opportunities unless stricter selection of HCC candidates is implemented using these policies. Conversely, no expansion occurred with DEC, which optimized selection and generated comparable survival and recurrence rates.

**Table 3.** Patient characteristics and longitudinal changes during the waiting list according to DEC at listing.

	DEC at listing				P
	DEC <i>n</i> = 867 (80.1%)	Within Milan + AFP score >2 pts <i>n</i> = 71 (6.5%)	Beyond Milan + AFP score ≤2 pts <i>n</i> = 69 (6.4%)	Beyond Milan + AFP score >2 pts <i>n</i> = 78 (7.1%)	
Data at last listing					
Age, years (±SD)	58 ± 8	55 ± 11	58 ± 7	57 ± 11	0.02
Gender, male, <i>n</i> (%)	667 (76.9)	54 (77.1)	60 (87.0)	61 (79.2)	0.28
Supplementary MELD, <i>n</i> (%)	722 (83.3)	54 (77.1)	53 (76.8)	44 (57.1)	<0.0001
Median AFP, ng/ml (IQR)*	9 (4–29)	668 (221–1254)	11 (4–38.9)	102 (7–631)	<0.0001
≤100 ng/ml, <i>n</i> (%)	770 (88.8)	–	68 (98.5)	7 (49.3)	<0.0001
101–1000 ng/ml, <i>n</i> (%)	97 (11.2)	45 (64.3)	1 (1.4)	24 (32.0)	
>1000 ng/ml, <i>n</i> (%)	–	25 (35.7)	–	14 (18.7)	
Within Milan criteria, <i>n</i> (%)*	867 (100)	70 (100)	0	0	<0.0001
AFP model, <i>n</i> (%)*					
≤2 points	867 (100)	–	69 (100)	77 (100)	
>2 points	–	70 (100)	–	–	
WL time, median (IQR)	5.0 (2.0–10.1)	4.0 (1.7–8.4)	3.8 (1.1–8.5)	3.9 (1.0–11.2)	0.12
Locoregional treatment, <i>n</i> (%)	445 (51.3)	44 (62.9)	51 (73.9)	60 (77.9)	<0.0001
Data at last reassessment					
Median AFP, ng/ml (IQR)*	8 (4–23)	342 (124–1000)	13 (4–40)	47 (7–800)	<0.0001
≤100 ng/ml, <i>n</i> (%)	773 (89.3)	14 (20.3)	64 (92.7)	41 (54.7)	<0.0001
101–1000 ng/ml, <i>n</i> (%)	87 (10.0)	38 (55.1)	4 (5.8)	19 (25.3)	
>1000 ng/ml, <i>n</i> (%)	6 (0.7)	17 (24.6)	1 (1.4)	15 (20.0)	
Milan criteria, <i>n</i> (%)*					
Within	753 (86.8)	65 (92.9)	18 (26.1)	23 (29.9)	<0.0001
Beyond	114 (13.1)	5 (7.1)	51 (73.9)	54 (70.1)	
AFP model, <i>n</i> (%)*					
≤2 points	801 (92.4)	23 (32.9)	63 (91.3)	21 (27.3)	<0.0001
>2 points	66 (7.6)	47 (67.1)	6 (8.7)	55 (72.4)	
Milan + AFP model, <i>n</i> (%)*					
Within Milan/≤2 pts	736 (84.9)	23 (32.9)	17 (24.6)	13 (17.1)	<0.0001
Within Milan/>2 pts	17 (2.0)	42 (60.0)	1 (1.4)	9 (11.8)	
Beyond Milan/≤2 pts	65 (7.5)	0	46 (66.7)	8 (10.5)	
Beyond Milan/>2 pts	49 (5.6)	5 (7.1)	5 (7.3)	46 (60.5)	

DEC, Double Eligibility Criteria; Pts, points.

\*At last tumor reassessment or evaluation during the waitlist period.

In most Latin American countries, Milan criteria are applied to HCC patient selection and extra MELD points granted as a result. According to the prospectively registered Argentinian national data, the overall 1-year waitlist mortality rate for 2019 was 17% (<https://le.incucai.gov.ar/public/Modulo2.do>) [27]. Waitlist mortality in non-HCC patients has been reported to be higher than that of HCC patients granted with extra MELD points (28% vs. 7%) [12]. Patients with HCC on the other hand had lower dropout rates (3.8% vs. 6.7%) and higher transplant access (83% vs. 57%) [12]. Similar results have been reported in Brazil [15,28]. We evaluated potential effects of adopting any of the policies described above to organ allocation in the

Argentine National Registry and found that Milan–UCSF-DS policy would have increased number of HCC transplanted patients by 10.9% and the AFP score would have increased the number by 3.3%. The increase in total number of patients transplanted would have been 2.1% and 0.6%, respectively. DEC would have resulted in an optimization of selection but no further expansion.

There is another group of patients who initially are beyond Milan criteria, but may revert to lower disease stages after locoregional therapies (*downstaging*), for whom the UCSF-DS protocol has been adopted in the United States [16,17,21,29]. However, national application of the UCSF-DS protocol in the United States has

**Table 4.** Exclusion, post-LT survival, and HCC recurrence rates according to the DEC at last tumor reassessment.\*

Observed results, % (95% CI)	DEC at listing				P
	DEC n = 867	Within Milan + AFP score >2 pts n = 71	Beyond Milan + AFP score ≤2 pts n = 69	Beyond Milan + AFP score >2 pts n = 78	
Exclusion rate <sup>†</sup>	15.1 (12.8–17.7)	67.1 (54.9–77.9)	75.4 (63.5–84.9)	82.9 (72.9–90.7)	<0.0001
Downstaged to DEC	–	32.9 (21.7–44.5)	24.6 (15.0–36.5)	17.1 (9.2–26.8)	<0.0001
5-year HCC recurrence					
Within final DEC	7.7 (3.7–15.7)	8.1 (2.7–23.9)	4.5 (0.6–28.1)	44.2 (18.8–80.6)	0.0006
Beyond final DEC	12.6 (9.4–16.9)	23.4 (8.1–56.7)	30.9 (17.1–52.0)	47.4 (32.4–65.5)	
5-year post-LT survival					
Within final DEC	67.2 (63.0–71.1)	69.7 (41.7–86.1)	72.2 (47.8–86.6)	45.1 (15.5–71.2)	0.14
Beyond final DEC	67.9 (57.0–77.0)	66.6 (42.3–80.3)	44.3 (26.9–60.5)	49.4 (34.8–62.3)	

DEC, Double Eligibility Criteria; Pts, points.

\*Longitudinal tumor changes during the waiting list from listing to last tumor reassessment in each group of patients, as proposed for the DEC. All the patients should have met the DEC at two time points, without tumor progression or have been downstaged to the DEC (final tumor burden before LT). At last tumor reassessment or evaluation during the waitlist period.

<sup>†</sup>Not granted for supplementary MELD or MELD-sodium points.

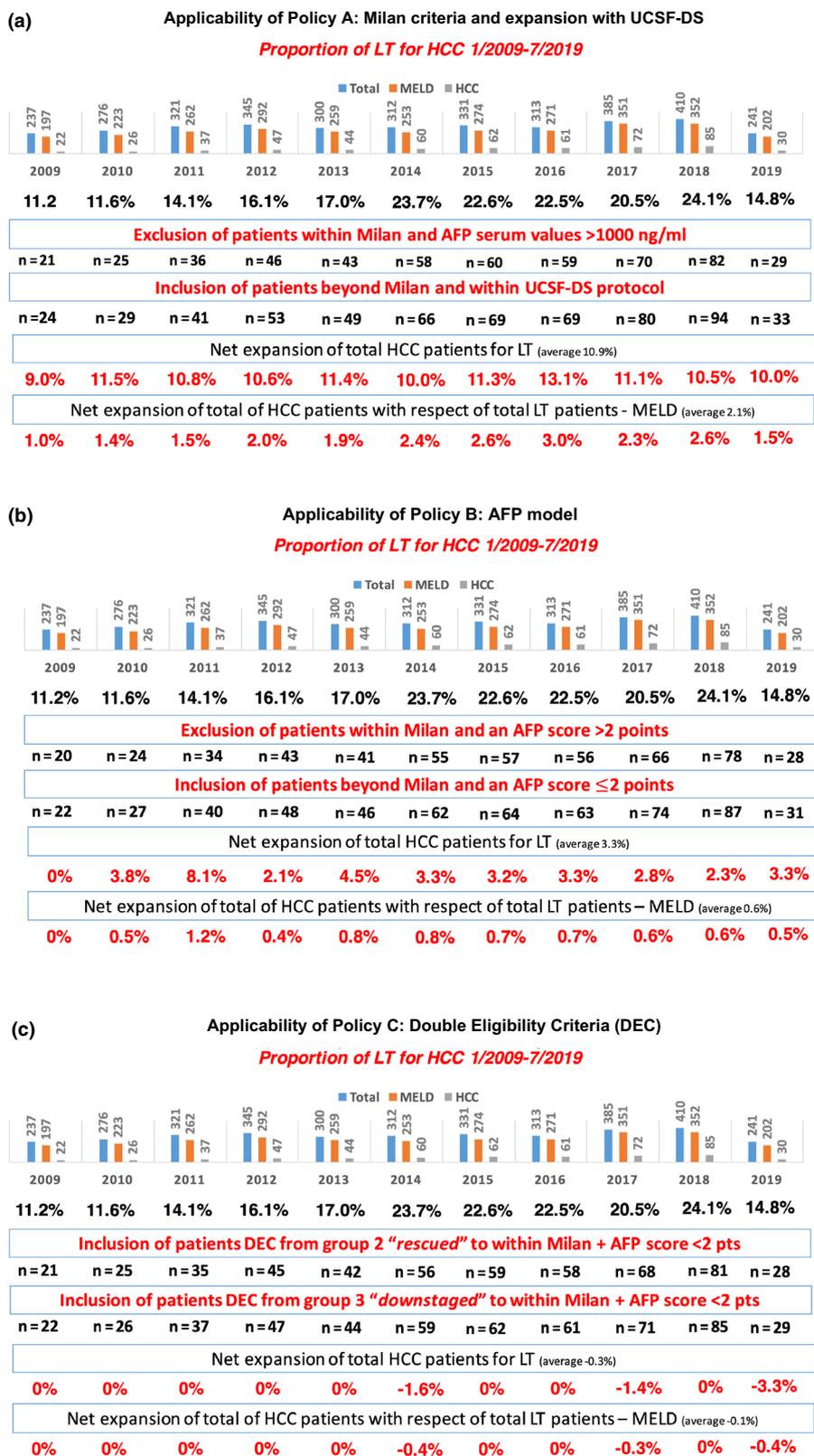
shown lower than expected results [17], with lower post-transplant survival and higher recurrence rates. The authors suggested including AFP values for better candidate selection for *downstaging* [17]. Our results were similar to those from the US national policy. Recently, Lai et al developed the WE-DS model aimed to select the best candidates for downstaging based on the tumor burden and AFP level at referral time [30]. The authors identified three risk categories including AFP below 200 ng/ml and up to ten, AFP between 200 and 500 ng/ml and up to seven, and AFP between 501 and 1000 ng/ml and up to five to identify an upper limit of tumor burden for downstaging. The Metroticket 2.0 [7], the AFP French model [8], and the HALTHCC [31] also had an excellent diagnostic performance, mainly revealed in the validation set of this study. Conversely, the UNOS-DS model performed worse. It is clear that in order to obtain the best outcomes after LT in downstaged HCC we should take into account both the tumor load and AFP levels on referral. In DEC, we suggested taking into account the relationship between tumor burden, the AFP level, and the treatment response.

Certain ethical dilemmas are worthy of mention. Is DEC too restrictive? Is it unethical to exclude patients with good expected outcomes from prioritization? On the one hand, we must first identify the most accurate model ensuring the best survival with the lowest recurrence rate following LT. On the other hand, we need to define the degree of prioritization to be implemented on the waiting list. Both issues are independent. However, whether HCC expansion and prioritization run parallel course remains a

matter of debate [10,11]. It may be unethical to exclude HCC patients with very good outcomes, but it may be equally unfair to non-HCC patients, particularly in high waitlist mortality regions [13].

This study has limitations common to other observational studies. This extended duration of the study period may have included different imaging modalities (CT or MRI scans) across centers, and there was no centralized imaging review. This would have been unfeasible. Anticipating this potential bias, RECIST 1.1 rather than mRECIST was required in the study protocol to report tumor assessment after bridging therapies, to decrease heterogeneity. Additionally, “ablate and wait” policies were not unified across centers. It could be argued that patients with single HCC lesions with a diameter <3 cm and complete response following locoregional therapies should not be prioritized. We believe that the question of whether or not prioritize this group of patients depends not only on tumor burden, but also on liver function, treatment feasibility, and expected time on the waiting list.

In conclusion, we believe our findings are relevant from a public health perspective as optimization of organ allocation in patients with HCC, which is paramount in countries with organ shortage. These measures should be accompanied by others, to help improve access to liver transplantation for non-HCC patients whose MELD score does not reflect the severity of their liver disease. We propose using DEC for clinical decision in HCC patient selection for LT which ultimately will not increase HCC candidate numbers in



**Figure 3** Potential expansion of the number of HCC patients which might have been transplanted in Argentina if each policy had been applied between 2009 and 2019.

high waitlist mortality regions. However, ethical concerns suggesting DEC may be too restrictive still need to be addressed.

### Authorship

FP, MA and IFB: designed the research and wrote the paper. AC, SM, SHD, ASL, RZ, LGP, LM, AV, AG, FR, FC and MS: provided important contributions and collected data. FP and FR: analyzed data. MS and FV: critically revised the manuscript. CP: contributed to language and grammar of the manuscript. All the authors approved the final version of the manuscript.

### Funding

This research received no specific grant from any funding agency in the public, commercial, or nonprofit sectors.

### Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplant International*. Study protocol was registered as part of an open public registry (NCT03775863; www.clinicaltrials.gov), maintaining a confidentiality agreement under each investigator.

### Acknowledgements

We would like to thank all other the co-authors who participated in this study: Argentina: M Fauda, A Gonzalez Campaña, L G Podesta, M Balmer, O Gil, R Traverso, G Casares Diaz, A Alcaraz, M Barrabino, J Menna, and P Raffa; Brazil: S Reges Perales, L Zanaga, Raquel Stucchi. Uruguay: S Gerona, and P Vanerio; Chile: V Henriquez, A Iracheta, A Ginesta, M Rius. Peru: J Chaman Ortiz, C Rondon, and O Mantilla Cruzatti. Ecuador: X Armijos Salinas, C Garces Vizcarra, and J Rojas Macanchi; Colombia: O Beltrán, M Garzón, and Isabel Arenas Hoyos; and Mexico: Sara Hurtado Gomez, Ignacio García-Juarez, and Carlos Moctezuma-Velazquez. All the authors approved the final version of the manuscript. We also thank C Podesta, native English speaker, for her contribution.

### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Comparison of patients included per country.

**Table S2.** Second Latin American cohort ( $n = 917$ ).

**Table S3.** Performance of each LT policy applied in the second multicenter Latin American cohort.

### REFERENCES

- Mazzaferro VV, Regalia EE, Doci RR, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693.
- Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394.
- Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transpl* 2011; **17**: S44.
- Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182.
- Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358.
- Toso C, Andres A, Kneteman N, Hernandez-Alejandro R, Majno P. Alpha-fetoprotein: further evidence to add a biological marker to refine Milan criteria. *Liver Int* 2016; **36**: 1580.
- Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2018; **154**: 128.
- Duvoux C, Thoraval FR, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; **143**: 986.e3.
- Otto G, Herber S, Heise M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006; **12**: 1260.
- Goldberg David, Benjamin French P, Craig Newcomb MS, et al. Patients with hepatocellular carcinoma have highest rates of wait-listing for liver transplantation among patients with end-stage liver disease. *Clin Gastroenterol Hepatol* 2016; **14**: 1638.
- Goldberg D, French B, Abt P, Feng S, Cameron AM. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. *Liver Transpl* 2012; **18**: 434.
- Cejas NG, Villamil FG, Lendoire JC, et al. Improved waiting-list outcomes in argentina after the adoption of a model for end-stage liver disease-based liver allocation policy. *Liver Transpl* 2013; **19**: 711.
- Salvalaggio PR, Caicedo JC, de Albuquerque LC, et al. Liver transplantation in Latin America. *Transplantation* 2014; **98**: 241.
- Massie AB, Caffo B, Gentry SE, et al. MELD exceptions and rates of waiting

- list outcomes. *Am J Transplant* 2011; **11**: 2362.
15. Rodriguez S, Fleck ADM Jr, Mucenic M, Marroni C, Brandão A. Hepatocellular carcinoma patients are advantaged in the current Brazilian liver transplant allocation system. A competing risk analysis. *Arq Gastroenterol* 2020; **57**: 19.
  16. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl* 2005; **11**: 1505.
  17. Mehta N, Dodge JL, Grab JD, Yao FY. National experience on down-staging of hepatocellular carcinoma before liver transplant: influence of tumor burden, AFP, and wait time. *Hepatology* 2020; **71**: 943.
  18. Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level >1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl* 2014; **20**: 945.
  19. Durand F, Antoine C, Soubrane O. Liver transplantation in France. *Liver Transpl* 2019; **25**: 763.
  20. Piñero F, Tisi Baña M, de Ataíde EC, et al. Liver transplantation for hepatocellular carcinoma: evaluation of the AFP model in a multicenter cohort from Latin America. *Liver Int* 2016; **36**: 1657.
  21. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. *Liver Transpl* 2015; **21**: 1142.
  22. Firl DJ, Kimura S, McVey J, et al. Reframing the approach to patients with hepatocellular carcinoma: longitudinal assessment with hazard associated with liver transplantation for HCC (HALTHCC) improves ablate and wait strategy. *Hepatology* 2018; **68**: 1448.
  23. Samoylova ML, Dodge JL, Yao FY, Roberts JP. Time to transplantation as a predictor of hepatocellular carcinoma recurrence after liver transplantation. *Liver Transpl* 2014; **20**: 937.
  24. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453.
  25. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52.
  26. Dignam JJ, Zhang Q, Kocherginsky M. The use and interpretation of competing risks regression models. *Clin Cancer Res* 2012; **18**: 2301.
  27. McCormack L, Gadano A, Lendoire J, et al. Model for end-stage liver disease-based allocation system for liver transplantation in Argentina: does it work outside the United States? *HPB* 2010; **12**: 456.
  28. Salvalaggio PR, Felga G, Axelrod DA, Guardia Della B, Almeida MD, Rezende MB. List and liver transplant survival according to waiting time in patients with hepatocellular carcinoma. *Am J Transplant* 2015; **15**: 668.
  29. Sinha J, Mehta N, Dodge JL, Poltavskiy E, Roberts J, Yao F. Are there upper limits in tumor burden for down-staging of hepatocellular carcinoma to liver transplant? Analysis of the all-comers protocol. *Hepatology* 2019; **70**: 1185.
  30. Lai Q, Vitale A, Halazun K, et al. Identification of an upper limit of tumor burden for downstaging in candidates with hepatocellular cancer waiting for liver transplantation: a west-east collaborative effort. *Cancers* 2020; **12**: 452.
  31. Firl DJ, Sasaki K, Agopian VG, et al. Charting the path forward for risk prediction in liver transplant for hepatocellular carcinoma: international validation of HALTHCC among 4,089 patients. *Hepatology* 2019; **71**: 569.