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# A Novel Prognostic Index in Patients With Hepatocellular Cancer Waiting for Liver Transplantation

## Time–Radiological-response–Alpha-fetoprotein–INflammation (TRAIN) Score

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**Objective:** A novel and easy prognostic score based on the combination of pre-operatively available variables in patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) has been developed from a long waiting time (WT) training set and then validated in a short-WT set.

**Summary of Background Data:** The role of radiological response to loco-regional therapies, alpha-fetoprotein modification, inflammatory markers, and length of WT has been recently shown to be important selection criteria for the risk of intention-to-treat (ITT)-death and recurrence.

**Methods:** The training set consisted of 179 HCC patients listed for LT during the period January 2000 to December 2012 from the UCL Brussels Transplant Centre; the validation set consisted of 110 patients listed during the period January 2005 to December 2014 from the Ancona Liver Centre.

**Results:** The proposed Time–Radiological-response–Alpha-fetoprotein–INflammation (TRAIN) score was the best predictor of microvascular invasion. A TRAIN score  $\geq 1.0$  excellently stratified both the investigated populations in terms of ITT and recurrence survivals. When compared with Milan criteria, the proposed score allowed obtaining an increase of potentially transplantable patients (+8.9% in training set and 24.6% in validation set) without additive recurrence risks.

**Conclusions:** The proposed TRAIN score is an easy selection tool based on variables available before LT. This score enables the selection process to be refined in the 2 different scenarios of long and short WT. In case of longer WT, the score is better at predicting risk of death during the WT; in case of short WT, the score is better at identifying risk of post-LT recurrence.

**Keywords:** alpha-fetoprotein slope, drop out, fast-track approach, hepatocellular cancer, liver transplantation, mRECIST, neutrophil-to-lymphocyte ratio, recurrence, waiting time

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Authorship: QL and JL designed the research; QL, DN, MIN, SI, and AA collected the data; QL, MV, and JL wrote the paper; QL and DN performed the statistical analysis; PG and AG gave final approval of the article to be published.

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Milan criteria (MC) remain the cornerstone in the selection process of hepatocellular cancer (HCC) patients waiting for liver transplantation (LT). Despite implementation in 1996, these criteria still dominate the process of wait-list registration worldwide.<sup>1</sup> Many attempts to widen MC have been reported, none of them being recognized as a valid substitute.<sup>2,3</sup> This is explained by the fact that most extended criteria are based on morphologic (number-diameter) tumor characteristics. Recently, biological parameters have been added, the most important being alpha-fetoprotein (AFP) levels,<sup>4–6</sup> radiological response to loco-regional treatments (LRT),<sup>6,7</sup> inflammatory markers,<sup>8</sup> and length of waiting-time (WT).<sup>9,10</sup>

This study aims to develop a prognostic score combining these variables able to predict intention-to-treat (ITT)-survival and recurrence rates. This "Time–Radiological-response–Alpha-fetoprotein–INflammation" (TRAIN) score has been developed using data of a training set (TS) with a long WT and an independent validation set (VS) with a short WT.

## METHODS

A retrospective analysis of prospectively collected data from 2 European centers was performed after approval by their local Ethics Committees. One hundred seventy-nine HCC patients listed for LT during the period January 2000 to December 2012 in the UCL-Brussels center were analyzed to produce a TS of data. Their median follow-up was 3.4 years [interquartile range (IQR) = 1.0 to 7.1]. We evaluated the significance of the obtained TS results using an independent VS consisting of 110 patients listed for LT during the period January 2005 to December 2014 in the Ancona center. Their median follow-up was 2.3 years (IQR = 0.7 to 4.9). According to the median WT of the 2 centers, TS was defined as having a long WT, VS as having a short WT. No specific WT cut-offs were used for this discrimination.

HCC diagnosis was made before LT according to proposed international guidelines; a biopsy was performed only in case of uncertain diagnosis.<sup>11,12</sup>

Both centers handled similar listing criteria: MC-IN patients were immediately considered for wait-list registration; MC-OUT patients first underwent downstaging. After downstaging, the accepted upper limit of tumor burden for registration corresponded to the University of California San Francisco criteria.

In both populations, all patients had at least 1 LRT before LT or drop-out (DO). Multimodal LRT was done in 60 of 179 (33.5%) TS patients and in 18 of 110 (16.4%) VS patients. Details on LRTs are reported in Table 1.

Demographic data, radiological and pathological tumor characteristics, clinical course, and blood tests, including albumin, C-reactive protein (CRP), AFP, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were collected.





**TABLE 3.** Prognostic Ability of Different Variables to Predict ITT-death (Entire Population: Training Set, n = 179 and Validation Set, n = 110), Microvascular Invasion and Post-LT Recurrence (Only LT Patients: Training Set, n = 145 and Validation Set, n = 95)

Variables	AUROC	95% CI	P	AUROC	95% CI	P
	Training Set (n = 179)			Validation Set (n = 110)		
ITT-death						
TRAIN score	71.9	64.1–79.7	□ 0.001	53.9	42.1–65.7	0.51
mRECIST PD	63.8	55.2–72.5	0.002	52.6	41.0–64.1	0.66
MC-OUT status	49.3	40.6–58.0	0.88	49.1	37.6–60.5	0.87
AFP slope ≥15.0 ng/mL	60.4	51.6–69.2	0.02	53.3	41.7–64.9	0.57
Training set (n = 145)      Validation set (n = 95)						
Microvascular invasion						
TRAIN score	68.2	59.9–75.8	0.005	76.6	65.2–88.0	0.004
mRECIST PD	65.3	56.9–73.1	0.02	72.2	54.9–89.6	0.02
MC-OUT status	55.4	46.8–63.8	0.8	60.6	41.5–79.7	0.3
AFP slope ≥15.0 ng/mL	54.1	45.5–62.5	0.5	57.1	38.0–76.1	0.4
Post-LT recurrence						
TRAIN score	58.2	37.2–79.1	0.35	58.8	36.9–80.6	0.32
mRECIST PD	65.2	46.9–83.5	0.08	64.8	47.0–82.6	0.10
MC-OUT status	50.1	33.0–67.2	0.99	62.3	45.2–79.4	0.16
AFP slope ≥15.0 ng/mL	58.4	40.0–76.8	0.34	65.2	46.7–83.7	0.09

### ITT-survival and Recurrence Rate

ITT-survival rates were extremely poor in TRAIN score  $\geq 1.0$  in both sets. Twenty-seven TS and 13 VS patients exceeding this cut-off had 5-year survivals of 23.5% (median value = 12.0, 95% CI = 9.6–14.4) and 20.7% (median value = 53.7, 95% CI = 0.0–141.2).

In TS, TRAIN score allowed to discriminate patients in relation to 5-year recurrence rate (30.0% vs 8.9% in patients with a score  $\geq$  or  $\square 1.0$ ; log-rank = 0.1). All VS patients exceeding the cut-off recurred within 3 years (5-year recurrence rates: 100.0% vs 13.8% in patients with a score  $\geq$  or  $\square 1.0$ , log-rank  $\square 0.001$ ) (Table 4, Fig. 1A).

In TS, 5-year ITT-survival rates were 67.5% and 61.1%, when meeting TRAIN score and MC-status; when exceeding them, survival rates were 23.5% and 62.6%, respectively. Similarly, 5-year recurrence rates were 8.9% and 10.4% in patients meeting TRAIN and MC-status; when exceeding the scores, recurrence rates were 30.0% and 10.4%, respectively.

In VS, 5-year ITT-survival rates were 66.7% and 61.5% in patients meeting TRAIN score and MC-status; when exceeding them, survival rates were 20.7% and 63.4%, respectively. Similarly, 5-year recurrence rates were 13.8% and 9.9% in patients meeting TRAIN score and MC-status; when exceeding the scores, recurrence rates were 100.0% and 34.1%, respectively.

These findings indicate that, when compared with the “gold-standard MC”, TRAIN score allowed, in both sets, to obtain higher survivals without increasing recurrence risk.

As the number of patients meeting the TRAIN score encompassed the number of MC-IN patients, these results indicate that the number of transplantable patients can be substantially raised (+8.9% in TS and 24.6% in VS) without raising the recurrence risk (Fig. 2).

### ITT-survival and Recurrence rate in the Subgroups of Initially MC-IN and MC-OUT Patients

When considering initially MC-IN patients only, TRAIN score allowed to discriminate both sets in terms of ITT-survival and recurrence rate. When considering TS, TRAIN score well discriminated initially MC-IN patients, with a more than 4-fold increased risk of 5-year recurrence in patients with a score  $\geq 1.0$  (35.7% vs 8.4%; log-rank = 0.04). In VS, half of the patients having a

TRAIN score  $\geq 1.0$  recurred, no patient surviving more than 21 months after LT (Table 4, Fig. 1B).

When considering initially MC-OUT patients only, TRAIN score  $\geq 1.0$  well selected TS patients in terms of 5-year ITT-survival (69.9% vs 21.4%;  $P = 0.009$ ); no conclusions could be made in terms of recurrence due to the small sample size. In VS, a good stratification was possible in relation to 5-year recurrence rate (26.7% vs 100%:  $P = 0.008$ ). Although better ITT-survivals were observed in patients meeting the TRAIN score, no statistical significance was observed in the specific subanalysis of MC-OUT patients (70.0% vs 41.7%;  $P = 0.28$ ) (Table 4, Fig. 1C).

## DISCUSSION

In HCC patients, WT and post-LT course may be considered as a “continuum,” in which HCC-related DO and post-LT recurrence represent different consequences of a higher tumor aggressiveness. Despite refined allocation strategies, up to one-fifth of patients still experience an unfavorable tumor-related course following waiting-list registration. Differences observed across centers in terms of DO or recurrence may relate to different WT lengths. In “long-WT centers,” tumor selection more commonly takes place during the wait-list period ( $\square$  DO), leading to a lower number of post-LT recurrences. Conversely, “short-WT centers” report less DO but more post-LT recurrences. This is demonstrated at its best in the living-donor LT scenario, in which there is theoretically no WT.<sup>15</sup> A UNOS survey, including 5002 HCC recipients, revealed higher post-LT 1-year recurrences in case of short-WT ( $\leq 120$  days) (3.9% vs 2.2%,  $P = 0.002$ ); long WT reduced recurrence risk by 40%.<sup>9</sup> Another US study, including 6160 HCC listed patients, showed a higher incidence of death on the waiting list (8.4% vs 1.6%,  $P \square 0.001$ ) but a better ITT recurrence-free survival ( $P \square 0.001$ ) in patients belonging to long WT regions.<sup>10</sup>

All these observations are in line with our findings: the long WT TS had more DO but less recurrences, the short WT VS revealed the contrary. In the TRAIN score, WT was a protective parameter; the longer the WT, the less the risk of ITT-death.

NLR, another TRAIN score component, has been reported to be a predictor of death and recurrence in HCC patients.<sup>10,16</sup> The importance of NLR may be linked to the tumor burden. A UK study

**TABLE 4.** ITT-Survival and Post-LT Recurrence Rate According to the Proposed TRAIN Score Cut-Off  $\leq$  or  $>$  1.0 in the Entire Population and in the Subgroups of Initially MC-IN and MC-OUT Patients

Variables	1 yr	3 yrs	5 yrs	1 yr	3 yrs	5 yrs
<b>Entire Population</b>						
ITT-survival						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 152)	83.5	73.0	67.5	$\leq 1.0$ (n = 97)	83.3	73.9
$> 1.0$ (n = 27)	45.2	23.5	23.5	$> 1.0$ (n = 13)	62.2	62.2
		Log-rank $P < 0.001$			Log-rank $P = 0.01$	
Post-LT recurrence*						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 133)	3.5	7.7	8.9	$\leq 1.0$ (n = 88)	2.8	11.3
$> 1.0$ (n = 12)	12.5	30.0	30.0	$> 1.0$ (n = 7)	0.0	100.0
		Log-rank $P = 0.1$			Log-rank $P < 0.001$	
<b>Initially MC-IN patients</b>						
ITT-survival						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 116)	82.7	70.6	66.8	$\leq 1.0$ (n = 64)	84.3	76.2
$> 1.0$ (n = 20)	52.9	31.8	23.8	$> 1.0$ (n = 6)	50.0	50.0
		Log-rank $P = 0.001$			Log-rank $P = 0.011$	
Post-LT recurrence*						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 99)	1.1	6.7	8.4	$\leq 1.0$ (n = 60)	1.9	6.9
$> 1.0$ (n = 10)	14.3	35.7	35.7	$> 1.0$ (n = 4)	0.0	50.0†
		Log-rank $P = 0.041$			Log-rank $P = 0.012$	
<b>Initially MC-OUT patients</b>						
ITT-survival						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 36)	86.0	80.0	69.9	$\leq 1.0$ (n = 33)	81.5	70.0
$> 1.0$ (n = 7)	21.4	21.4	21.4	$> 1.0$ (n = 7)	83.3	83.3
		Log-rank $P = 0.009$			Log-rank $P = 0.28$	
Post-LT recurrence*						
		Training set			Validation set	
TRAIN score				TRAIN score		
$\leq 1.0$ (n = 34)	10.9	10.9	10.9	$\leq 1.0$ (n = 33)	4.5	19.4
$> 1.0$ (n = 2)	0.0	0.0	0.0	$> 1.0$ (n = 7)	50.0	100.0‡
		Log-rank $P = 0.70$			Log-rank $P = 0.008$	

\*Post-LT recurrence analysis was performed only in transplanted patients.

†All the patients censored within 21 months after LT with a 50.0% of recurrence rate.

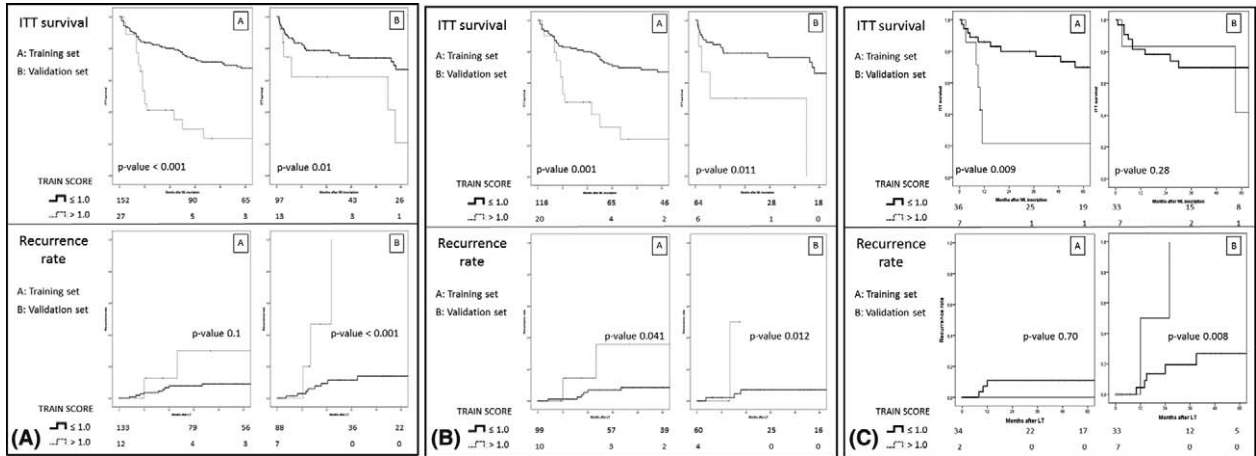
‡All the patients censored within 26 months after LT with a 100.0% of recurrence rate.

looking only at MC-IN patients inquired its prognostic value.<sup>17</sup> However, it has been shown that the impact of NLR increases with the growing percentage of initially MC-OUT patients.<sup>18</sup> In the present study, the initial radiological MC-OUT cases were 24% to 36%, explaining the inclusion of NLR in the equation.

In our study, the strongest predictor of ITT-death was, as already shown in previous reports, mRECIST-PD.<sup>6,7,19–21</sup> The Mainz group reported that any post transarterial chemo-embolization (T-ACE) progression overruled MC-status as a predictor for recurrence risk, with an AUC = 86.<sup>7</sup> A recent multicenter European study combining radiological and AFP progression corroborated these observations in both MC-IN and MC-OUT scenarios.<sup>6</sup> Similarly, the San Francisco group showed that effective downstaging allowed to obtain similar survivals independently from the initial MC-status, while LRT failure was associated with a higher number of DOs.<sup>20</sup> This group was also able to identify a subgroup of patients with a low risk of DO ( $< 2\%$  at 2 yrs) based on their post-LRT radiological and biological response.<sup>21</sup>

AFP increase during the WT was another significant risk factor for ITT-death in our study, confirming recent findings looking at raising AFP values.<sup>22</sup> Multicenter studies from France and US showed that a pre-LT “static” AFP value  $> 1000$  ng/mL strongly correlated with recurrence risk in MC-IN patients.<sup>4,23</sup> Studies investigating “dynamic” AFP modifications also showed an excellent ability to predict ITT-death and recurrence.<sup>5,6,24</sup> Recently, scores integrating AFP have been developed with the intent to predict the risk of DO.<sup>25,26</sup>

The combination of these 4 variables, making up the TRAIN score, has been tested in the different scenarios of “short-” and “long-WT.” The TRAIN score revealed to best predict mvi, an established risk factor for post-LT recurrence, in both scenarios.<sup>27,28</sup> ITT-survival was poor in both TS and VS patients exceeding TRAIN score  $\geq 1.0$ , thereby confirming the efficacy of the model in predicting death during the entire period starting from first waiting-list registration. Also of note is that in the “long-WT” scenario, TRAIN score was partially able to discriminate patients in terms of



**FIGURE 1.** (A) Kaplan-Meier survival curves: ITT-survival and post-LT recurrence rate according to the proposed TRAIN score. (B) Kaplan-Meier survival curves: ITT-survival and post-LT recurrence rate according to the proposed TRAIN score in the subgroup of initially MC-IN patients. (C) Kaplan-Meier survival curves: ITT-survival and post-LT recurrence rate according to the proposed TRAIN score in the subgroup of initially MC-OUT patients.

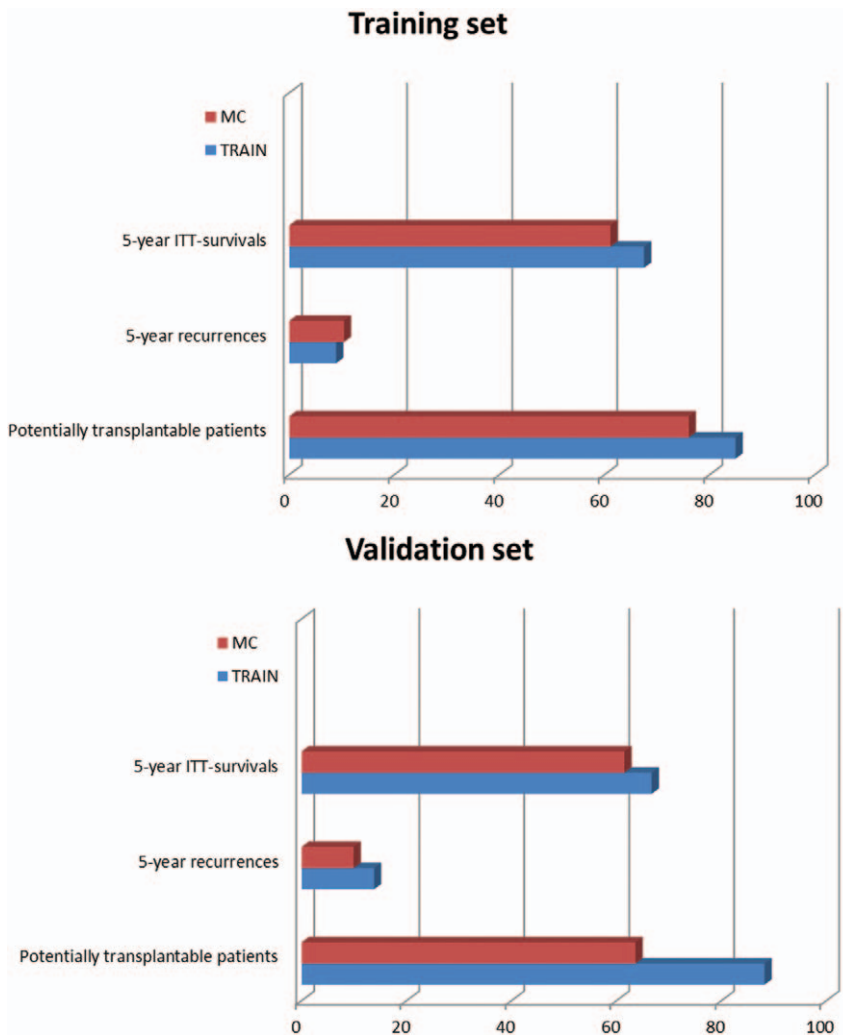


Figure 1 & Figure 2:  
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**FIGURE 2.** Comparison between TRAIN and MC scores in terms of ITT-survivals, recurrence rates, and number of potentially transplantable patients.

recurrence rates. This could be explained by the fact that the patients were highly selected before LT by the “time-factor,” so that finally all transplanted patients were effectively at low risk for recurrence. However, when looking at MC-IN patients only, TRAIN score allowed to discriminate for recurrence risk also in the “long-WT” group. This can be due to the fact that a small but non-negligible group of MC-IN patients are at a high risk for post-LT recurrence. Indeed, although MC-IN patients are commonly considered as a homogeneous “low-risk” group, it has been recently shown that this is not fully true, showing that biologic markers are able to predict worse outcomes even in the favorable MC-IN setting.<sup>6,21</sup>

Several criticisms can be addressed to this study. First, TRAIN score variables are not available when entering the ITT analysis because at least 1 LRT is required before doing so. It should be reminded that such practice corresponds to the typical “today’s” management of, even MC-IN, HCC patients waiting for LT (“bridging” approach). On the basis of our results, we propose to consider patients with TRAIN score  $\geq 1.0$  as at “high-risk” for DO and recurrence, therefore managing them similarly to MC-OUT patients by applying more frequent pre-LT LRT and respecting a “mandatory” pre-LT minimal WT.<sup>29</sup>

Second, TRAIN score did not entirely give satisfactory AUCs in relation to diagnosis of mvi and incidence of post-LT recurrence. This can be explained by the fact that the score does not fully capture the complex reality of HCC patients waiting for LT: however, this fact is even more true for other scores such as MC. It is likely that the few number of events and small sample sizes reported in some subanalyses explain some “unsatisfactory” results.

Third, the presence of a “time-dependent” variable in the TRAIN score, namely the length of WT, might represent a problem in the specific subcohort of HCC patients presenting advanced liver disease (Child-Turcotte-Pugh-C, MELD  $\square 15$ ). In fact, the first objective of TRAIN score, namely selecting “high-risk” HCC population in order to avoid organ “wasting” (concept of “utility”), is overruled by the concept of “transplant benefit” (“the sickest first”) in case of advanced liver disease. So, the advantage of longer WT, aiming at achieving lower recurrence rates, is counteracted by the higher risk of tumor-unrelated DO. Consequently, in such (fortunately uncommon) condition, a balancing between these 2 concepts should be considered for minimizing the risk to remove too many patients from LT opportunity.

Fourth, this study includes relatively small patient cohorts belonging to 2 geographical distant centers adhering also to some, albeit small, clinical management differences. Apart from a very limited number of (heterogeneous) multicenter studies,<sup>3,4,6</sup> almost all studies reported in this field include smaller numbers. Moreover, a major benefit of our study was the confirmation of a mathematical model in a VS. We feel that the differences between the studied groups rather represent a benefit, allowing to test and validate a score in 2 very different scenarios.

Finally, it is important to emphasize that the arbitrary decision to select the TRAIN score cut-off at 1.0 resulted from the intention to obtain a high specificity of the test (avoiding thereby false positives). Despite the fact that such decision hampers the possibility of completely eliminating the risk of post-LT HCC recurrence, we feel that the main objective of a good selection tool in the “oncological transplant scenario” should be to look simultaneously at minimizing both risks of recurrence and exclusion from potentially curative treatments. For this reason, a “high” cut-off value representing the 85th percentile of the TS population was chosen. Such strategy has been already adopted by other authors focusing on the detection of cut-off values for selective scores of HCC patients waiting for LT.<sup>4,23</sup>

## CONCLUSIONS

The proposed TRAIN score combining radiological progression, increase of AFP and inflammatory marker NLR, and short WT is a promising tool allowing to predict, on an ITT base, the risks of death and post-LT recurrence both in long- and short WT scenarios. The availability of all components of this score in all HCC transplant candidates will allow its implementation and validation in daily clinical practice.

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