Recurrence Risk Reassessment (R3) score based on explant features improves prediction of HCC recurrence compared with existing models

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INTRODUCTION

Patients with hepatocellular carcinoma (HCC) are selected for liver transplantation (LT) based on pre-LT imaging ± AFP level* but discrepancies between imaging and explant findings are frequent

Explant features remain the gold standard to reassess risk of HCC recurrence after LT in order to drive post LT screening strategies and adjustment of immunosuppressive regimen

Previously published explant-based models** of recurrence have intrinsic limitations precluding use generalization in routine practice

*Mazzaferro et al. N Engl J Med 1996   **Mazzaferro et al. Lancet Oncol. 2009
*Duvoux et al. Gastroenterology 2012   **Costentin et al. Liver Intern 2017
*Mazzaferro et al. Gastroenterology 2019   **Metha JAMA Oncol 2016

AIM

Design a explant-based user-friendly Recurrence Risk Reassessment score to refine the prediction of recurrence after LT for HCC

METHOD

Multicenter multinational cohort study of adult patients transplanted for HCC in 47 centers between 2000 and 2018.
- European training cohort (TC, n=1359) from France, Italy and Belgium.
- Latin American validation cohort (VC, n=1085) from Argentina, Uruguay, Chile, Brazil, Ecuador, Colombia and Mexico

Pathological tumor features collected across all sites from pathological reports
- Presence of microvascular invasion (MVI)
- Number and size of each nodule
- Tumor differentiation according to Edmondson and Steiner criteria

Endpoints:
- Primary: 5-year HCC recurrence after LT
- Secondary: 5-year survival

Design of the Recurrence Risk Reassessment (R3) score in the Training European cohort
- Univariate and multivariable Cox model with hazard ratios to evaluate explant features independently associated with HCC recurrence after LT
- Points assigned in the final model dividing each HR with the lowest HR observed
- Model performance assessed using Harrells-c and Somer's D estimations and compared to those of other scores graded on explants
  Milan (within/Beyond)
  Metroticket: Up to seven and no MVI vs all other combination
  RETREAT: ≤2 OR>2

Validation in the Latin American cohort

RESULTS

Patients and tumor characteristics

	Training cohort (n=1359)	Validation cohort (n=1085)	P
Age, years (± SD)	58 ± 8	58 ± 8	0.99
Male gender, n (%)	1124 (82.7)	844 (77.8)	0.002
Etiology of liver disease, n (%)			
Viral	786 (57.8)	610 (56.2)	
HBV	94 (6.9)	149 (13.7)	
HCV	696 (51.2)	466 (42.9)	
Alcohol	426 (31.3)	183 (16.9)	
Other	147 (10.8)	292 (26.9)	<.0001
Data at listing			
Within Milan criteria, n (%)	1039 (76.4)	939 (86.5)	<.0001
AFP score ≤2 points, n (%)	1221 (89.9)	942 (87.1)	0.66
Bridging therapy before LT, n (%)	931 (68.5)	782 (72.1)	0.055
Median time on waiting list, months (IQR)	6.1 (3.0-11.0)	4.9 (1.7-10.0)	<.0001
Median time frame between last tumor evaluation and LT, months (IQR)	2.2 (1.0-4.0)	2.3 (0.9-5.3)	
Number of HCC nodules			
1-3 nodules	1005 (73.9)	911 (84.0)	
≥4 nodules	354 (26.0)	174 (16.0)	<.0001
Largest nodule diameter			
≤3 cm	849 (67.1)	633 (59.2)	
3-6 cm	361 (28.6)	398 (37.3)	
>6 cm	54 (4.3)	38 (3.5)	<.0001
Complete major nodule necrosis, n (%)	94 (6.9)	11 (1.0)	<.0001
Presence microvascular invasion, n (%)	369 (27.1)	249 (22.9)	0.017
Tumor differentiation, n (%)			
Nuclear grade I-II	1003 (85.3)	753 (73.0)	
Nuclear grade >II	173 (14.7)	279 (27.0)	<.0001

Explant features associated with HCC recurrence after LT

Training cohort (TC)	5-year recurrence rate (95% CI)	Unadjusted Hazard Ratio (95% CI)	P	Adjusted Hazard Ratio (95% CI)	P
Number of nodules		1.03 (1.01-1.04)	<.0001		
1-3 nodules (n=1005)	14.2 (11.7-17.1)	-			
≥4 nodules (n=354)	35.7 (29.4-42.9)	2.79 (2.12-3.69)	<.0001	1.77 (1.28-2.43)	<.0001
Major nodule diameter		1.37 (1.31-1.44)	<.0001		
≤3 cm (n=849)	13.8 (11.1-17.1)	-		-	-
3-6 cm (n=361)	30.4 (24.5.37.7)	2.38 (1.76-3.22)	<.0001	2.00 (1.42-2.82)	<.0001
>6 cm (n=54)	74.5 (58.7-87.9)	11.01 (7.33-16.55)	<.0001	6.89 (4.33-10.9)	<.0001
Complete necrosis					
Yes (n=94)	2.96 (0.7-11.7)	0.16 (0.05-0.50)	0.002	-	-
Microvascular invasion					
Yes (n=990)	39.6 (32.9-46.3)	4.07 (3.09-5.38)	<.0001	2.69 (1.94-3.71)	<.0001
Nuclear grade >II					
Yes (n=173)	28.2 (21.2-36.9)	1.45 (1.23-1.73)	<.0001	1.18 (0.99-1.41)	0.061

R3 score (based on Cox model in the TC)

	Adjusted HR (95% CI)	P	Points
Number of nodules			
1-3 nodules (n=1005)			0
≥4 nodules nodules (n=354)	1.77 (1.28-2.43)	<.0001	1
Major nodule diameter			
≤3 cm (n=849)	-	-	0
3-6 cm (n=361)	2.03 (1.50-2.77)	<.0001	1
>6 cm (n=54)	6.89 (4.33-10.9)		3
Microvascular invasion			
Yes (n=990)	2.69 (1.94-3.71)	<.0001	1
Absence (n=369)			0

R3 score was associated with an incremental hazard of recurrence for every additional point

Log-rank test P<.0001   Harrel-C 0.74 (95% IC: 0.71-0.79)
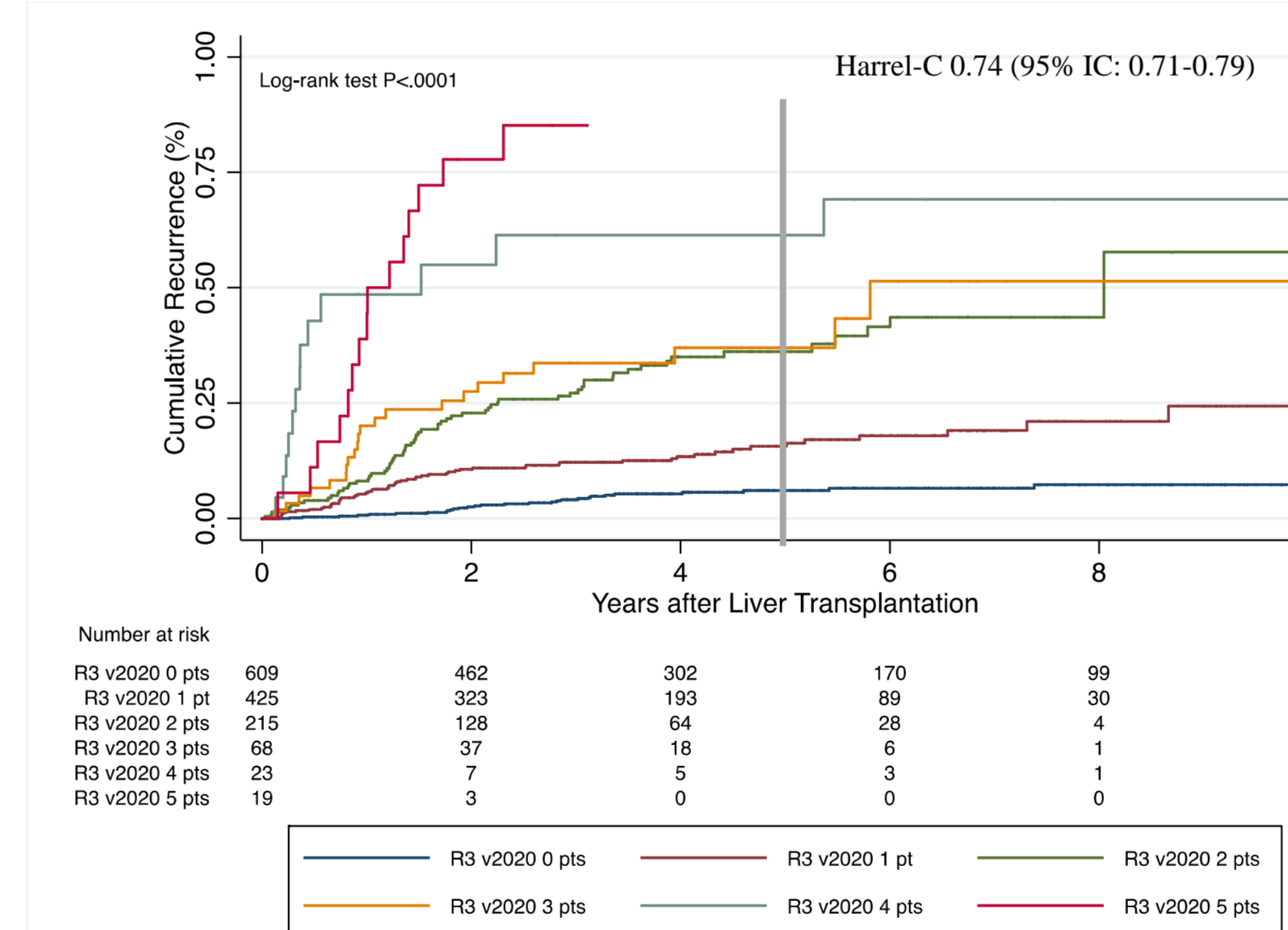
R3_score (points)	5-year recurrence rate % (95% CI)
0 (n=609)	6.6 (4.5-9.6)
1 (n=425)	17.7 (13.5-23.0)
2 (n=215)	41.7 (33.2-51.3)
3 (n=68)	48.1 (31.6-67.8)
4 (n=23)	70.5 (47.7-90.0)
5 (n=19)	87.6 (66.0-98.2)

R3 score improves discrimination of HCC recurrence compared to other explant-based models

	Harrell's C (95% CI)	Somers' D (95% CI)	P
R3 score	0.75 (0.71-0.78)	0.54 (0.45-0.64)	-
Milan criteria	0.64 (0.61-0.68)	0.30 (0.23-0.37)	<.0001
Metroticket	0.70 (0.66-0.72)	0.41 (0.34-0.48)	0.005
RETREAT score	0.69 (0.67-0.72)	0.41 (0.35-0.48)	0.008

R3 score stratifies survival into 4 groups

External validation of the R3 score

Despite differences in patients and HCC characteristics in the VC compared to the TC, R3 score performed well in the VC, also identifying 4 level of risk for HCC recurrence and survival at 5 years
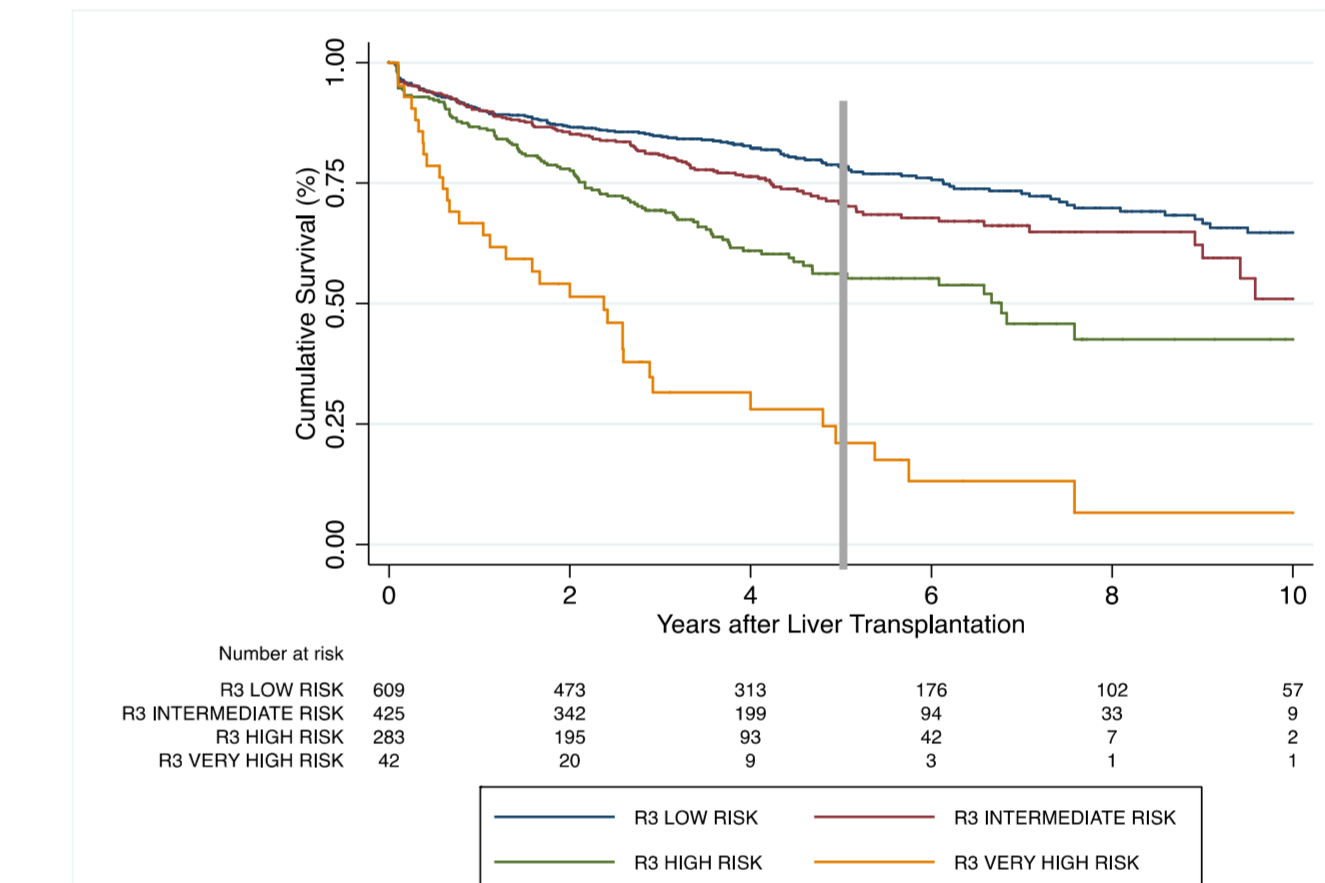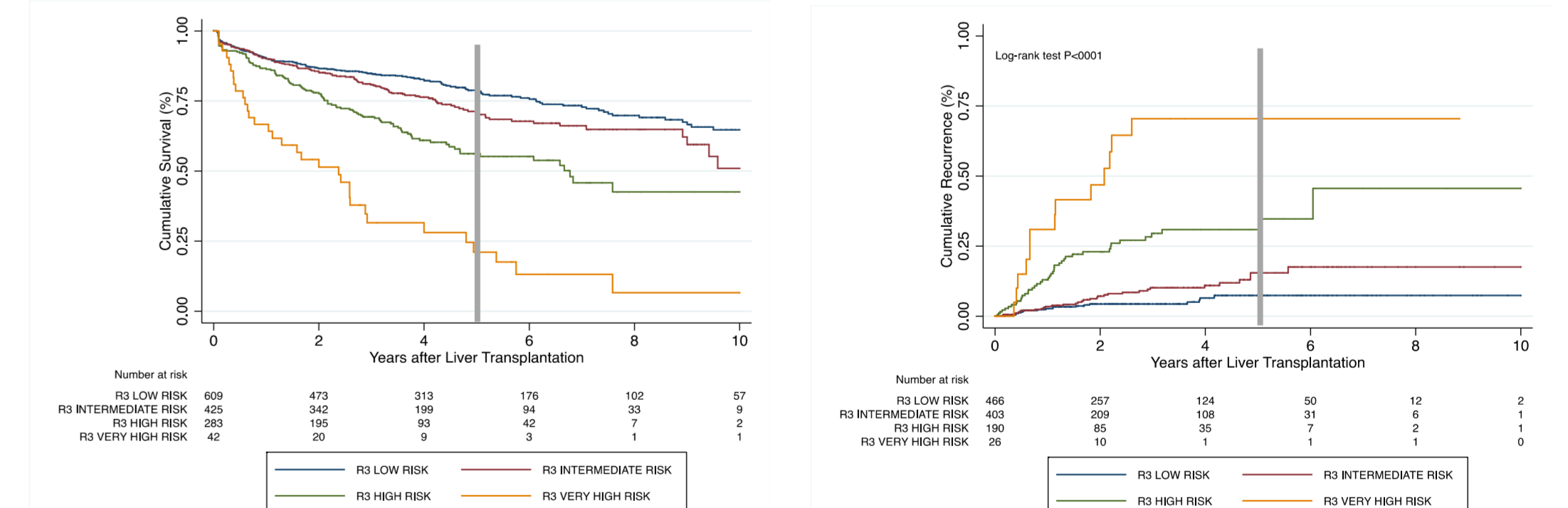

CONCLUSIONS

- Based on a multinational database, we designed and validated a simple and robust R3 score allowing stratification of recurrence risk after LT for HCC into 4 groups.

- The R3 score improves prediction of HCC recurrence compared with other explant-based models.

- The R3 score can easily be implemented in pathological reports and be proposed as a standardized predictive tool to adjust post-LT surveillance strategies, and as a framework of clinical trials design for adjuvant therapies.

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