EVALUATING THE PREDICTIVE ACCURACY AND THE CLINICAL BENEFIT OF A NOMOGRAM AIMED TO PREDICT 68GA-LABELED PROSTATE-SPECIFIC MEMBRANE ANTIGEN-LIGAND POSITRON-EMISSION TOMOGRAPHY/COMPUTER TOMOGRAPHY POSITIVITY IN PATIENTS WITH BIOCHEMICAL RECURRENT PROSTATE CANCER AFTER RADICAL PROSTATECTOMY: EXTERNAL VALIDATION ON A SINGLE INSTITUTION DATABASE

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Introduction and objective

To assess the **predictive accuracy**, the **best cut-off value** and the **clinical impact** of a **recent published nomogram**[1] aimed to **predict the positivity of PSMA-PET/CT** in patients with **Biochemical Recurrent Prostate Cancer After Radical Prostatectomy**, through an **external validation**.

Material and methods

- **413 Prostate Cancer (PCa) patients** with evidence of **BCR after RP** and **PSA value between 0.2 and 1 ng/ml** were investigated at single tertiary center with PSMA PET/CT.
- **Multivariate logistic regression** were performed to assess the predictors of positive PSMA PET/CT results in patients-based analysis.
- **External validation** was performed using regression coefficients of the compact model of the previously published nomogram.
- The performance characteristics of the model were assessed by quantifying **PA**
- Moreover, **specificity, sensitivity, PPV, NPV** for each nomogram's derived probability cut off were systematically analyzed and Yuden's index was used to find the best nomogram's cut off.
- Finally, **DCA** was implemented, in order to quantify the nomogram's clinical value in routine practice

Results

Table 1. Patient characteristics and descriptive statistics of original nomogram population and current cohort of patients.

	ORIGINAL NOMOGRAM POPULATION	ACTUAL STUDY POPULATION
Variable	Overall	Overall
No. of patients (%)	272	413
Age		
Median	67	68
IQR	62-72	62-72
Pathologic stage (%)		
≤pT2c	97 (35.7)	161 (39)
≥pT3a	161 (59.2)	252 (61)
Unknown	14 (5.1)	0 (0)
Pathologic ISUP grade		
≤3	171 (62.9)	250 (60.5)
≥4	89 (32.7)	163 (39.5)
Unknown	12 (0.4)	0 (0)
Pathologic N stage		
pNx	-	85 (20.6)
pN0	180 (66.2)	256 (62)
pN1	60 (22)	72 (17.4)
Unknown	32 (11.8)	0 (0)
Additional treatment after RP		
ADT	26 (9.5)	55 (13.3)
Radiation therapy	94 (34.6)	93 (22.5)
PSA value prior to PSMA PET/CT		
0.2 - 0.5	134 (49.3)	249 (60.3)
0.51 - 1.0	138 (50.7)	164 (39.7)
^{68}Ga-PSMA-11 PET/CT detection rate, n (%)		
Overall	176 (64.7)	182 (44.1)
PSA 0.2 - 0.5 ng/ml	74 (55.2)	83 (35.8)
PSA 0.51 - 1.0 ng/ml	102 (73.9)	99 (54.7)

Table 2 Uni and multivariate logistic regression to predict positive findings at PSMA PET/CT (n=413)

	UNIVARIATE		MULTIVARIATE	
Variables	OR (95% C.I.)	P value	OR (95% C.I.)	P value
PSA at PSMA PET/CT (ng/ml) continuous variable	6.66 (2.80-15.86)	<0.001	7.06 (2.89-17.29)	<0.001
Pathologic ISUP group				
≤3	1 (Ref)		1 (Ref)	
≥4	1.46 (0.98-2.17)	0.06	1.23 (0.791.92)	0.4
Pathologic stage				
≤pT2c	1 (Ref)		1 (Ref)	
≥pT3a	1.39 (0.93-2.08)	0.1	1.01 (0.63-1.62)	0.9
Pathologic N stage				
pN0/pNx	1 (Ref)		1 (Ref)	
pN1	1.58 (0.95-2.63)	0.08	1.11 (0.63-1.98)	0.7
Radiotherapy after RP				
No	1 (Ref)		1 (Ref)	
Yes	1.57 (0.99-2.49)	0.06	1.36 (0.81-2.27)	0.24
ADT at time of 68Ga-PSMA PET				
No	1 (Ref)		1 (Ref)	
Yes	2.43 (1.31-4.50)	0.005	2.07 (1.07-3.99)	0.03
Time interval from RP to 68Ga-PSMA PET (years)	0.97 (0.92-1.02)	0.2	0.95 (0.90-1.01)	0.07

Table 3. Performance characteristics of various nomogram's cut-offs for discriminating between patients with and without positive PSMA PET/CT and the quantified number of avoidable PSMA PET/CT versus the number of potentially missed patients with positive PSMA PET/CT findings.

Nomogram calculated cutoff (%)	Patients in whom PSMA PET/CT would not be recommended according to the cutoff (below cutoff)	Patients below cutoff with negative PSMA PET/CT [1]	Patients below cutoff with positive PSMA PET/CT	Patients in whom PSMA PET/CT would be recommended according to the cutoff (above cutoff)	Patients above cutoff with negative PSMA PET/CT	Patients above cutoff with positive PSMA PET/CT [2]	NPV (%)	PPV (%)	Accuracy (%)
≥5	37 (9)	29 (12.6)	8 (4.4)	376 (91)	202 (87.4)	174 (95.6)	78.3%	46.3%	54.1%
≥10	72 (17.4)	54 (23.4)	18 (9.9)	341 (82.6)	177 (76.6)	164 (90.1)	75%	48.1%	56.7%
≥15	110 (26.6)	80 (34.6)	30 (16.5)	303 (73.4)	151 (65.4)	152 (83.5)	72.7%	50.2	59.1%
≥20	134 (32.4)	90 (39)	44 (24.2)	279 (67.6)	141 (61)	138 (75.8)	67.2%	49.5%	57.4%
≥25	153 (37)	100 (43.3)	53 (29.1)	260 (63)	131 (56.7)	129 (70.9)	65.4%	49.6%	57.1%
≥30	189 (45.8)	125 (54.1)	64 (35.2)	224 (54.2)	106 (45.9)	118 (64.8)	66.1%	52.7%	59.5%
≥35	225 (54.5)	148 (64.1)	77 (42.3)	188 (45.5)	83 (35.9)	105 (57.7)	65.7%	55.9%	60.9%
≥40	254 (61.5)	160 (69.3)	94 (51.6)	159 (38.5)	71 (30.7)	88 (48.4)	63%	55.3%	58.8%
≥45	281 (68)	178 (77.1)	103 (56.6)	132 (32)	53 (22.9)	79 (43.4)	63.3%	59.8%	60.2%
≥50	310	191 (82.7)	119 (65.4)	103 (25)	40 (17.3)	63 (34.6)	61.6%	61.2%	58.6%
≥55	327 (79.2)	196 (84.8)	131 (72)	86 (20.8)	35 (15.2)	51 (28)	59.9%	59.3%	56.4%
≥60	337 (81.6)	201 (87)	136 (74.7)	76 (18.4)	30 (13)	46 (25.3)	59.6	60.5%	56.1%

[1] Percentage indicative of specificity; [2] Percentage indicatives of sensitivity
RP: radical prostatectomy; NPV: negative predictive value; PPV: positive predictive value; CSM cancer specific mortality

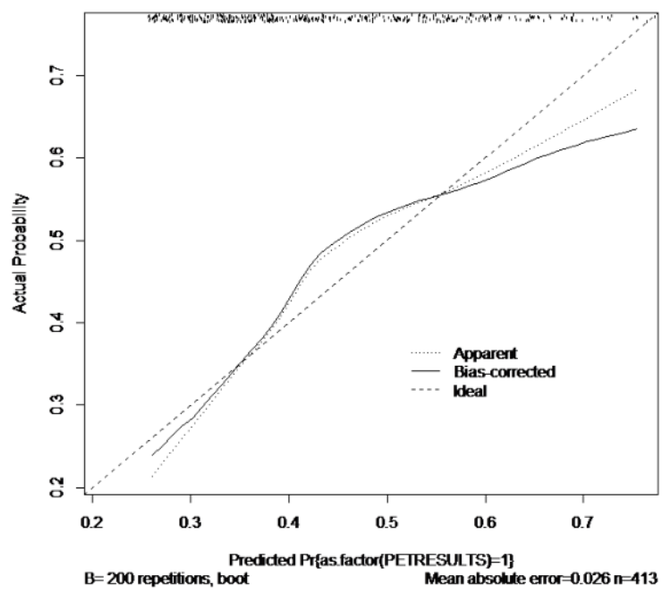

Figure 1. Calibration plot of the nomogram: the PA of nomogram in the external validation was comparable to that reported in the original model (64% vs. 67%, respectively)

Figure 2. Decision curve analysis: the nomogram revealed clinical net benefit when the threshold probabilities of positive 68Ga-PSMA-11-PET/CT is >35%
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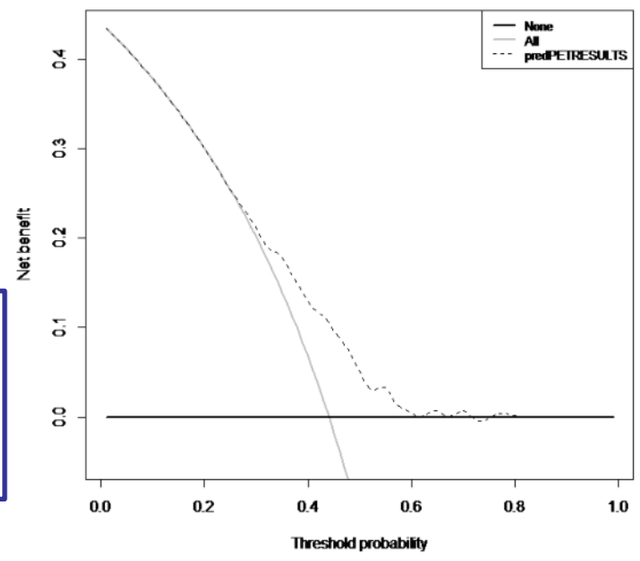

Using a **nomogram cut-off of 35**%, 225 of 413 patients (**54.5%) would be spared 68Ga-PSMA-11-PET/CT** and **positive 68Ga-PSMA-11-PET/CT would be missed in 77 patients (42.3**%).
The sensitivity, specificity and NPV associated with 35% as best cut-off were 64%, 58%, 65.7%, respectively.

Conclusion

In an **external setting**, the compact **nomogram** showed a **suboptimal PA** as referred to the original population.
Nomogram total points values of ≥35 emerged as the **best cut-off point** to **detect lesions indicative of PCa recurrence at PSMA-PET/CT**.
However, **DCA** showed a **clinical net benefit**, suggesting a clinical implication to correctly restage PCa patients.

1. Rauscher I, Duwel C, Haller B, et al. Efficacy, Predictive Factors, and Prediction Nomogram for 68Ga-labeled Prostate-specific Membrane Antigen–ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy. European Urology 73 (2018) 656– 661.