LARGER PROSTATES REMAIN AT RISK FOR CLINICALLY SIGNIFICANT CANCER DESPITE LOW 4KSCORE

Yu Ozawa[1], Marcio Covas Moschovas[1], Rohan Sharma[1], Shady Saikali[1], Marco Sandri[2], Ahmed Gamal[1], Travis Rogers[1], Vipul Patel[1]

[1] AdventHealth Global Robotics Institute, Celebration, FL, USA

[2] Big and Open Data Innovation Laboratory (BODaI-Lab) and Data Methods and Systems Statistical, Brescia, Italy

Introduction

- The 4K score is a novel blood test that measures the probability of having Gleason ≥ 7 prostate cancer on a biopsy on a scale from 1% to 99%. Men with a 4Kscore <7.5% have a low long-term probability of developing metastasis or of prostate cancer mortality.*
- The 4K test combines four blood biomarkers (total PSA, free PSA, intact PSA, and human kallikrein 2 [hK2]), in addition to clinical factors, including age, digital rectal examination (DRE) results, and previous biopsy history. However, prostate volume is not included.
- We aimed to investigate the potential interaction between the 4Kscore and prostate volume in predicting the risk of Gleason ≥ 7 prostate cancer.

Method

- A total of 361 patients with a PSA level of ≥ 2 ng/mL underwent robot-assisted radical prostatectomy without hormonal therapy at our institute between 2017 and 2024.All patients had 4K score and underwent prostate MRI. Prostate volume (cc) was measured by a prostate MRI.
- Clinically significant prostate cancer (csPC) is defined as a Gleason score of ≥ 7 of the prostate specimen.
- We conducted a multivariate logistic regression analysis to evaluate the association between the 4K score (< 7.5%), prostate volume, PI-RADS score, and csPC. It included an interaction term between the 4K score and prostate volume to examine whether the effect of a 4K score < 7.5% on csPC varied by prostate volume.
- Predicted probabilities were calculated for each patient, and the differences between the two 4K score groups were compared across different prostate sizes.

Results

Study population

- 27 out of 361 patients had 4Kscore <7.5
- Patients with 4Kscore of <7.5 exhibited lower PSA value, PSA density, and D'Amico higher-risk prostate cancer.
- PI-RADS 4/5 lesions were observed less frequency in patients with 4Kscore of <7.5
- More patients with 4Kscore of <7.5 underwent multiple prostate biopsies.

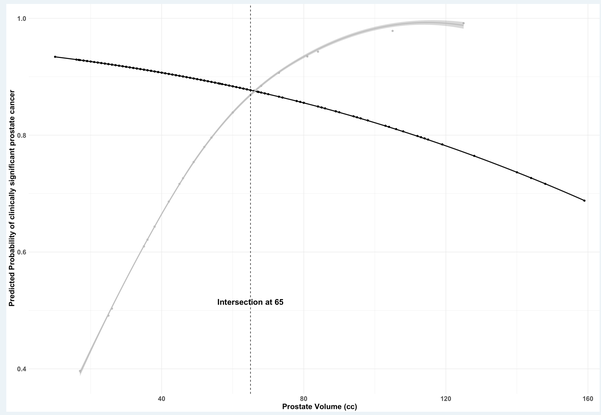
Table. Comparison of clinical and pathological characteristics between patients with 4Kscore ≥7.5% and <7.5%.

	Overall	4Kscore ≥7.5%	4Kscore <7.5%	p
Total number of patients, n (%)	361	334 (93%)	27 (7.4%)	
4Kscore (%), median (IQR)	31 [17, 53]	34 [19, 56]	5.0 [3.5, 6.7]	<0.001
< 7.5%, n(%)	27 (7.5%)	0	27 (100%)	<0.001
7.5%–20%, n(%)	89 (25%)	89 (27%)	0	
≥ 20%, n(%)	245 (68%)	245 (73%)	0	
Patient age (year), median (IQR)	65 [59, 69]	65.50 [59, 70]	65 [59.50, 68]	0.49
BMI (kg/m^2), median (IQR)	28 [25, 31]	28 [25, 31]	28 [26, 30]	0.97
PSA value (ng/mL), median (IQR)	6.2 [4.7, 8.8]	6.2 [4.7, 8.9]	5.3 [4.3, 6.4]	0.019
Prostate vlume, median (IQR)	42 [32, 60]	41.50 [31, 59]	49 [37, 67]	0.13
PSA density, median (IQR)	0.14 [0.10, 0.23]	0.15 [0.11, 0.24]	0.10 [0.07, 0.17]	0.002
PSA density <0.15, n (%)	187 (52%)	169 (51%)	18 (67%)	0.12
Biopsy grade group, n (%)				
Grade group 1	70 (19%)	60 (18%)	10(37%)	0.086
Grade group 2	176 (49%)	167 (50%)	9 (33%)	
Grade group 3	65 (18%)	60 (18%)	5 (19%)	
Grade group 4	35 (9.7%)	34 (10%)	1 (3.7%)	
Grade group 5	15 (4.2%)	13 (3.9%)	2 (7.4%)	
Clinical T stage, n (%)				
cT1	266 (74%)	244 (73%)	22 (82%)	0.57
cT2	93 (26%)	88 (26%)	5 (19%)	
cT3	2 (0.6%)	2 (0.6%)	0 (0.0)	
D'Amico risk stratification, n (%)				
Low risk	57 (16%)	47 (14%)	10 (37%)	0.014
Intermediate risk	244 (68%)	230 (69%)	14 (52%)	
High risk	60 (17%)	57 (17%)	3 (11%)	
Number of biopsy, n (%)				
1	287 (80%)	276 (83%)	11 (41%)	<0.001
2	54 (15%)	42 (13%)	12 (44%)	
≥ 3	20 (5.5%)	16 (4.8%)	4 (15%)	
PI-RADS category, n (%)				
PI-RADS 1–2	1 (0.4%)	1 (0.4%)	0	<0.001
PI-RADS 3	27 (11%)	18 (7.7%)	9 (41%)	
PI-RADS 4	144 (56%)	135 (57%)	9 (41%)	
PI-RADS 5	85 (33%)	81 (34%)	4 (18%)	

* **Variables are presented as the median with the interquartile range (IQR) or as the number of patients with the percentage.**

† **p-values were calculated using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.**

Figure. Interaction effect between prostate volume and 4Kscore of < 7.5% on clinically significant prostate cancer.



Below the 65cc threshold, there was an increasing relationship between the probability of 4Kscore <7.5% and csPC, whereas above 68 cc, this relationship decreased (a clear shift in the trend).

Table. Multivariable logistic regression analyses to evaluate the association between 4Kscore, prostate size, PI-RADS score, and clinically significant cancer.

	4Kscore <7.5%		4Kscore ≥7.5%	
Variables	OR	95% CI	OR	95% CI
Prostate size (increase per 5cc)	1.23	1.01–1.62	0.92	0.87–0.97
PI-RADS 4 or 5 lesion	0.97	0.17–5.38	2.95	1.65–5.33

Large vs Small Prostate (≥ 65 cc vs < 65 cc)

Patients with large prostate were

- 4 yeas older
- 1.3-fold higher PSA value but 0.5-fold lower PSA density
- Multiple times of biopsies
- 3-fold lower tumor involvement rate of specimen

⇒ 4Kscores were significantly lower in patients with large prostate. (median 26% [IQR: 13–45]) vs. 32% [IQR: 18–57])

Table. Comparison of clinical and pathological characteristics between patients with small and larger prostate.

Variables	Small (< 65 cc)	Large (≥ 65 cc)	p valu
Total number of patients, n (%)	297	64	
Prostate volume, median (IQR)	38 [30, 47]	83 [69, 103]	<0.001
4Kscore (%), median (IQR)	32 [18, 57]	26 [13, 45]	0.01
< 7.5%, n(%)	19 (6.4%)	8 (12.5)	0.145
7.5%–20%, n(%)	207 (70%)	38 (59.4)	
≥ 20%, n(%)	71 (24%)	18 (28)	
Patient age (year), median (IQR)	64 [59, 69]	68 [63, 71]	0.006
BMI (kg/m^2), median (IQR)	28 [25, 31]	29 [26, 32]	0.105
PSA value (ng/mL), median (IQR)	6.0 [4.6, 8.2]	7.5 [5.0, 10.6]	0.013
PSA density, median (IQR)	0.17 [0.12, 0.24]	0.08 [0.06, 0.12]	<0.001
PSA density <0.15, n (%)	132 (44%)	55 (86%)	<0.001
Number of biopsy, n (%)	0.17 [0.12, 0.24]	0.08 [0.06, 0.12]	<0.001
1	244 (82%)	43 (67%)	0.001
2	43 (15%)	11 (17%)	
≥ 3	10 (3.4%)	10 (16%)	
Biopsy grade group, n (%)			
Grade group 1	50 (17%)	20 (31%)	0.019
Grade group 2	154 (52%)	22 (34%)	
Grade group 3	53 (18&)	12 (19%)	
Grade group 4	30 (10%)	5 (7.8%)	
Grade group 5	10 (3.4%)	5 (7.8%)	
Clinical T stage, n (%)			
cT1	217 (73%)	49 (77%)	0.263
cT2	79 (27%)	14 (22%)	
cT3	1 (0.3%)	1 (1.6%)	
D'Amico risk stratification, n (%)			
Low risk	42 (14%)	15 (23%)	0.118
Intermediate risk	207 (70%)	37 (58%)	
High risk	48 (16%)	12 (19%)	
PI-RADS category, n (%)			
PI-RADS 1–2	1 (0.5%)	0	0.772
PI-RADS 3	21 (10%)	6 (13%)	
PI-RADS 4	120 (57%)	24 (52%)	
PI-RADS 5	69 (33%)	16 (35%)	
Prostate specimen weight (g), median (IQR)	52 [45, 63]	91 [82, 111]	<0.001
Tumor involvment rate of specimen (%), median (IQR)	15 [8, 25]	5 [5, 15]	<0.001
Pathological Gleason Score ≥7	265 (89%)	54 (84%)	0.284

* **Variables are presented as the median with the interquartile range (IQR) or as the number of patients with the percentage.**

† **p-values were calculated using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables.**

Limitation

- 4Kscore is designed for patients undergoing prostate biopsy and associated with biopsy csPC. 4Kscore test is recommended for young patients without biopsy history. Our cohort is different from ideal cohort.
- The 4K score acts as an effect modifier on the association between prostate volume and csPC, altering its direction. However, this reversal was observed in a small subset of patients (27/289).
- The detected interaction may be 'fragile' with respect to small changes in the 7.5% threshold.

Conclusion

- Our data demonstrated that 4K score < 7.5% was not predictive of csPC in larger prostates (≥ 65 cc).
- Future prospective studies involving patients undergoing prostate biopsy are needed to investigate the predictive value of 4K in large prostate.