Original Article

Challenges in magnetic resonance imaging-based detection of clinically significant prostate cancer in young patients: two alternative approaches

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Background: Addition of magnetic resonance imaging (MRI) in prostate cancer screening remains controversial issue. Despite the increased utilization of MRI, several studies have revealed its potential suboptimal diagnostic efficacy in young patients. This study aimed to further substantiate the limited diagnostic efficiency of MRI positivity [defined as Prostate Imaging Reporting and Data System (PI-RADS) scores ≥3] among young individuals aged ≤55 years suspected of prostate cancer, and more significantly, to evaluate two proposed approaches.

Methods: A total of 2,599 patients (including 207 young patients) who underwent trans-perineal prostate biopsy between January 2019 and May 2023 were included in this study. Categorical variables were compared using the chi-square or Fisher exact test, while continuous variables were analyzed with the Mann-Whitney test. A multivariate logistic regression model was used to identify independent risk factors for young patients, which was then visualized with a nomogram.

Results: The positive predictive value of MRI positivity in diagnosing clinically significant prostate cancer was significantly lower for young patients than for older patients (33.9% *vs.* 61.5%). A PI-RADS score ≥4 instead of ≥3 yielded significant improvements in young patients as compared to older patients in terms of specificity (77.5% *vs.* 48.8%) and positive predictive value (51.4% *vs.* 33.9%) while providing comparable sensitivity (80.9% *vs.* 89.4%) and negative predictive value (93.2% *vs.* 94.0%). Additionally, in this population, multivariable analysis showed that prostate specific antigen density, chief complaint, and PI-RADS score were independent risk factors (P=0.009, P=0.016, and P<0.001, respectively). Receiver operating characteristic curves indicated that incorporating those three parameters yielded the highest area under the curve (0.875). Therefore, this integrated model was used to build a nomogram that could illustrate the probabilities of clinically significant prostate cancer.

Conclusions: The positive rate of MRI positivity for clinically significant prostate cancer was found to be age dependent, exhibiting a significant decline in younger patients. Among young patients suspected of

disease, both adjusting the cutoff value and incorporating a model were effective in minimizing unnecessary biopsies. Further large-scale prospective studies are warranted to validate our findings.

Keywords: Magnetic resonance imaging (MRI); clinically significant prostate cancer (csPCa); challenge; prostate-specific antigen density (PSA density); young

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Introduction

The incidence of prostate cancer (PCa) gradually increases with age; however, it is not uncommon among young patients (defined as those aged ≤55 years), and its incidence within this population is also rising year on year. The implementation of PCa screening has played a crucial role in shaping the escalating pattern of early-onset PCa. Currently, prostate-specific antigen (PSA) detection remains the primary method for the screening, with some studies having developed PSA-based risk models (1). Moreover, given the growing importance of magnetic resonance imaging (MRI) and MRI-based targeted biopsy (TB) in diagnosing PCa (2-4), the addition of MRI to PCa screening has gradually become a hotspot in PCa research (1,5).

Multiple clinical studies have demonstrated the pivotal role of MRI in PCa screening. Eklund *et al.*'s screening study (6) revealed that incorporating MRI into the screening process and conducting prostate biopsy only when MRI results were positive yielded detection rates for clinically significant PCa (csPCa) that were comparable to those achieved through standard biopsy strategies. Furthermore, their findings indicated that the inclusion of MRI can effectively address two major challenges associated with PCa screening: unnecessary biopsies and identification of clinically insignificant cancers. A recent high-quality meta-analysis (7) encompassing 12 screening studies corroborated these findings.

With the advancement of research, the challenges associated with MRI in the screening process have also gradually come to light. Through a comprehensive literature review, we found that in PCa screening, especially in the first round, patients with MRI positivity [defined as Prostate Imaging Reporting and Data System (PI-RADS) scores ≥3] exhibit lower detection rates of csPCa (5,8). We hypothesized that the suboptimal MRI performance in these studies may be partially attributable to the relatively younger age of individuals undergoing screening. The influence of age on MRI diagnosis remains unclear, with the potential evidence primarily centered on three key mechanisms. First, the peripheral zone of healthy younger patients exhibits significantly reduced signal intensity on T2-weighted imaging (T2WI) and lower apparent diffusion coefficient (ADC) values, which could be readily classified as lesions with a higher PI-RADS score (9). Second, prostatitis, a common disease among young patients, can exhibit imaging manifestations that are sometimes indistinguishable from those of PCa (10). Third, sexual activity before an MRI examination may impact the images and lead to misinterpretation of PI-RADS scores (11,12).

Little clinical research has been conducted to elucidate and address the impact of young age on the MRI diagnosis of csPCa. Gielchinsky *et al.* (13) retrospectively examined the distribution of PI-RADS scores among patients with csPCa and found that the sensitivity of PI-RADS score ≥4 in the younger group (≤50 years) was significantly lower than that in the older group (>55 years). Another study by Stabile *et al.* (12), which only included patients with positive MRI findings, revealed age-related differences in the diagnostic performance of MRI for csPCa. Recently, Boschheidgen *et al.* (8) also reported a low positive predictive value (32–36%) of the PI-RADS score ≥3 for csPCa in PCa screening at age 45 years and described the complexities of interpreting MRI scans for young patients. In addressing these issues, an approach of double readings has been suggested (8), but no additional suitable solution to this challenge has yet been proposed.

Therefore, we conducted this study to further validate the limited efficacy of MRI positivity in younger patients suspected of PCa, and more importantly, to evaluate our two proposed approaches designed to enhance the clinical utility of MRI in this population, thereby minimizing unnecessary biopsies. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1017/rc).

Methods

A total of 2,842 patients who underwent transperineal prostate biopsy at Jiangsu Province Hospital between January 2019 and May 2023 and who had accessible bi-parametric MRI images were included in this study. Patients excluded were those with PSA levels exceeding 100 ng/mL (n=171), incomplete data (n=57), and nonadenocarcinoma PCa (n=9). Ultimately, 2,599 patients were included in this study.

The age criterion for young patients with PCa remains a subject of controversy (14-16). We typically employ 55 years as the cutoff value, in line with the majority of relevant studies (14,16-18). This cutoff value is supported not only by Hussein *et al.*'s explicit recommendation to use 55 years as the cutoff value in their review (15) but also because it aligns with the peak age for morbidity and mortality changes. The incidence and mortality rates of PCa are low before the age of 55 years but significantly increase after this age. Considering these factors, we categorized 207 patients with suspected disease aged ≤55 years into a group for subsequent analysis. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Jiangsu Province Hospital (No. 2023-SR-715). The requirement for individual consent was waived due to the retrospective nature of the analysis.

General data, including age at biopsy, body mass index (BMI), chief complaint, PSA value, prostate volume (PV), digital rectal examination (DRE) result, PSA density (PSAD), PI-RADS score and pathological findings were collected for each patient. The chief complaint was categorized into two groups: those with only elevated PSA levels and those presenting clinical symptoms such as lower urinary tract symptoms (LUTS) and hematospermia. For MRI, all imaging scans were conducted using a 3-T MRI system (MAGNETOM, Verio, Siemens Healthineers, Erlangen, Germany), with the sequences primarily consisting of T2WI, diffusion-weighted imaging (DWI) with a b value of 2,000 s/mm^2, and ADC measurements. The PI-RADS v. 2.1 scores were assigned independently by two experienced radiologists, and in cases of discrepancy, a final score was determined through consultation with a third radiologist. Additional MRI parameters such as lesion number and location, as well as lifestyle factors, were also recorded. Metabolic syndrome (MS) was included as a potential risk factor in this study due to the growing evidence supporting its correlation with PCa risk (19). The diagnosis of MS followed the 2004 guidelines established by the Chinese Diabetes Society (20). The details of our prostate biopsy strategies are described elsewhere (21). In general, patients with PI-RADS score <3 underwent systematic biopsy (SB), while TB or a combination biopsy (TB + SB) was adopted for those with higher scores. csPCa was defined as PCa with Gleason score equal to or greater than 7.

Statistical analysis

The patients were first divided into two groups based on their age at biopsy (cutoff, 55 years). A univariate linear model was employed to assess the interaction effect between age group and PI-RADS score in csPCa detection. Additionally, chi-square tests were conducted to examine the association between age group and csPCa detection rate among patients with different PI-RADS scores.

Subsequently, patients aged ≤55 years were categorized into csPCa and non-csPCa groups based on their pathological results. Categorical variables were compared using the chi-squared test or Fisher exact test, while continuous variables were compared with the Mann-Whitney test and are presented as the median and interquartile range (IQR) due to their nonnormal distributions. Univariate and multivariate logistic regression analyses were conducted to identify potential risk factors, followed by construction of receiver operating characteristic (ROC) curves for comparative evaluation of predictive accuracy. Finally, a specialized nomogram was developed to predict csPCa among young patients.

All tests were two-sided, with a significance level of $P < 0.05$. R version 4.3.0 (The R Foundation for Statistical Computing) was used for nomogram development and internal validation, while the SPSS 27 (IBM Corp., Armonk, NY, USA) for Windows was used for other statistical analyses.

Results

Lower positive predictive value of csPCa for young patients with positive MRI findings

Among the 2,599 patients included in this study, 58.1% were diagnosed with PCa and 47.2% with csPCa. Initially, 207 patients aged ≤55 years were assigned to the younger group while remaining 2,392 were assigned to the older group. Using a univariate linear model, we observed an

Table 1 The detection rates of csPCa stratified by PI-RADS score varied across the different age groups

PI-RADS score	Age ≤55 years (n/N)	Age >55 years (n/N)	P value
<3	6.0% (5/83)	9.8% (55/564)	0.274†
3	8.0% (4/50)	30.3% (195/643)	<0.001*†
4	36.0% (18/50)	69.9% (455/651)	<0.001*†
5	83.3% (20/24)	89.0% (475/534)	0.602†

†, Chi-square test. *, statistically significant. csPCa, clinically significant prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System.

interaction effect between age groups and PI-RADS scores on the detection rate of csPCa ($P_{interaction}$=0.008). The positive predictive value of MRI positivity in diagnosing csPCa was significantly lower for younger patients compared to older patients (33.9% *vs.* 61.5%). We then examined the association between age groups and detection of csPCa across different PI-RADS score stratifications (*Table 1*). Specifically, for patients with a PI-RADS score <3, both groups had low rates of csPCa detection (6.0% and 9.8%; P=0.274). Conversely, for patients with a PI-RADS score 5, both the younger and older groups exhibited high and comparable detection rates (83.3% and 89.0%, respectively; P=0.602). However, among patients with a PI-RADS score 3 or 4, the younger group showed significantly lower positive rates of csPCa compared to the older group (PI-RADS score 3: 8.0% and 30.3%; PI-RADS score 4: 36.0% and 69.9%; both P values <0.001). *Figure 1* presents three cases of young males with a PI-RADS scores of 3 or 4, with the pathological findings indicating prostatitis or clinically insignificant PCa (Gleason score: 3+3).

PI-RADS scores of 4 or 5 were suitable for prostate biopsy in young patients with suspected disease

This study enrolled 207 young patients with suspected disease, among whom 69 were ultimately diagnosed with PCa and 47 with csPCa (*Table 2*). Regarding the PI-RADS scores, there were 83 patients with a score <3, 50 patients with a score of 3, 50 patients with a score of 4, and 24 patients with a score of 5 (*Table 3*). Among patients with positive MRI findings, we observed high sensitivity (89.4%) and negative predictive value (94.0%) but low specificity (48.8%) and positive predictive value (33.9%). However, by employing PI-RADS score ≥4 as the threshold, we could achieve a significant improvement in specificity (77.5%) and positive predictive value (51.4%) while maintaining comparable sensitivity (80.9%) and negative predictive value (93.2%) (Table S1).

Chief complaint and PSAD enhanced the value of PI-RADS score in predicting csPCa in young patients with suspected disease

Among young patients, the csPCa and non-csPCa groups showed significant differences in age at biopsy, chief complaint, PSA value, PV, PSAD, PI-RADS score, MS, and histological location of the main lesion on MRI (*Table 3*). However, factors including BMI, DRE findings, smoking status, alcohol intake, number of lesions, and anatomical location of the main lesion on MRI were not significantly different.

Subsequently, univariate logistic regression analyses demonstrated that age at biopsy, chief complaint, PSAD, PI-RADS score, MS, number of lesions, anatomical location, and histological location of the main lesion in MRI were identified as risk factors for csPCa (*Table 4*). In the multivariable analysis, only chief complaint (P=0.016), PSAD (P=0.009), and PI-RADS score (P<0.001) remained significantly associated with csPCa, indicating their independent predictive values for young patients. Through ROC analyses, we observed that the incorporation the PI-RADS score, chief complaint, and PSAD yielded the highest area under the curve (AUC: 0.875) (*Figure 2*). Consequently, this integrated model was employed to construct a nomogram depicting the probabilities of csPCa (*Figure 3*). Notably, internal validation demonstrated the excellent calibration of this nomogram (Figure S1).

Discussion

Our study confirmed that age is associated with the diagnosis of csPCa by MRI, with a reduced positive predictive value for young patients with positive MRI findings. Therefore, we developed two approaches:

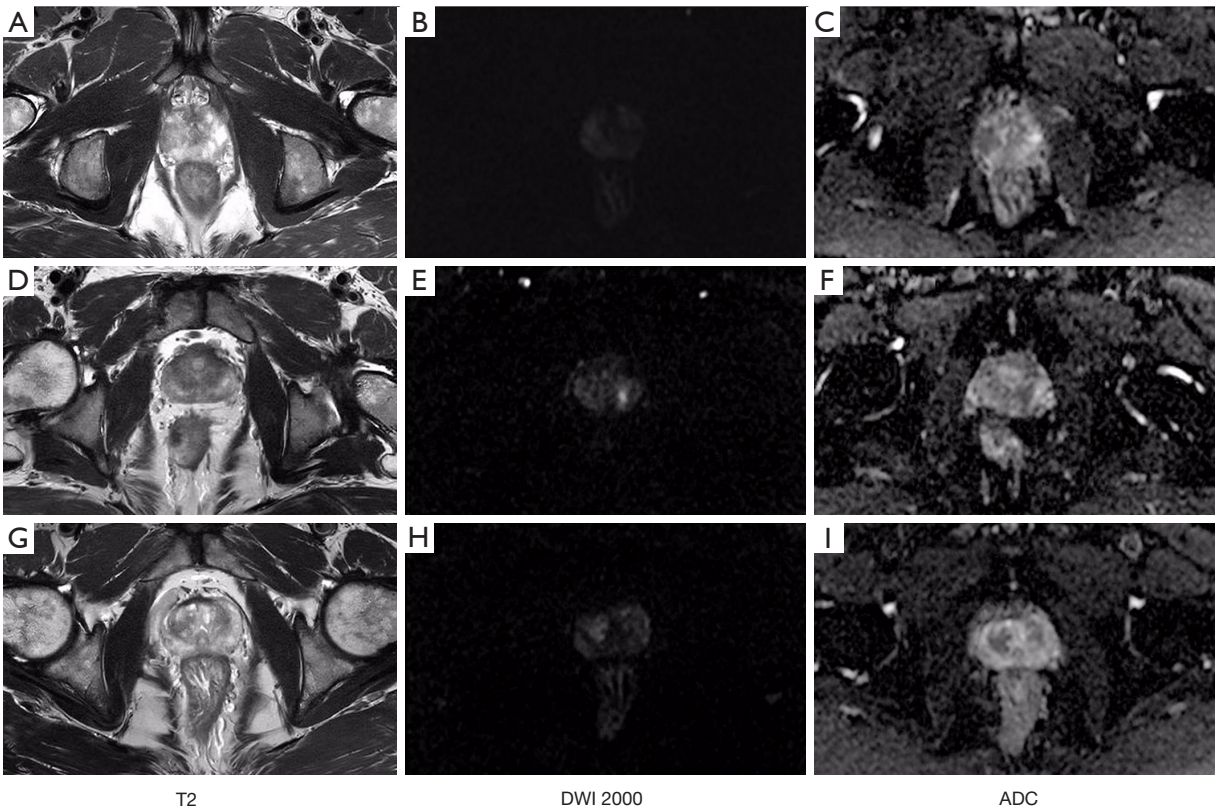

Figure 1 MRI of three young men with PI-RADS scores of 3 or 4 who were eventually pathologically confirmed to have prostatitis or clinically insignificant prostate cancer. (A) T2WI, (B) DWI (b value =2,000 s/mm^2), and (C) ADC image of a 52-year-old patient with a PI-RADS score of 3 and pathologically confirmed prostatitis. (D) T2WI, (E) DWI (b value =2,000 s/mm^2), and (F) ADC image of a 43-year-old patient with a PI-RADS score of 4 and pathologically confirmed prostatitis. (G) T2WI, (H) DWI (b value =2,000 s/mm^2), and (I) ADC image of a 54-year-old patient with a PI-RADS score of 4 and pathologically confirmed clinically insignificant prostate cancer. MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

adjusting the cutoff value and constructing a multivariate model incorporating relevant indicators. Through these, we observed that using a PI-RADS score ≥4 significantly improved specificity for diagnosing csPCa in this population while maintaining comparable sensitivity to that of the clinically used PI-RADS score ≥3. Meanwhile, chief complaint and PSAD could enhance the predictive ability of PI-RADS score for csPCa.

Clinically, a PI-RADS score of 3 or higher is commonly used as an indication for prostate biopsy; however, it might not be suitable for younger patients. In this specific population, we compared the detection rate of csPCa at different PI-RADS score cutoffs. When a PI-RADS score ≥3 was used, the diagnostic sensitivity and negative predictive value were 89.4% and 94.0%, respectively, while the specificity and positive predictive value were 48.8% and 33.9%, respectively. Nevertheless, by raising the cutoff to 4, there was a substantial improvement in specificity and positive predictive value without significant compromise to the sensitivity and positive predictive value. These findings suggest that a PI-RADS score ≥4 might serve as a more appropriate indicator for prostate biopsy in young patients with suspected disease. This is in line with a recent study by Möller *et al.* (5), who conducted a screening study among relatively younger individuals and also found a PI-RADS score ≥4 to be a superior indicator for prostate biopsy. Indeed, the reason for adjusting the cutoff value is to determine whether lesions with a PI-RADS score of 3 should undergo biopsy. According to our data, the positive rate of csPCa among patients with a PI-RADS score of 3

Table 2 Quantitative histology of young men with PCa stratified by PI-RADS scores

Parameter	PI-RADS score				Total
	<3	3	4	5	
PCa, n	10	10	29	20	69
csPCa, n	5	4	18	20	47
Biopsy ISUP grade group, n					
1	5	6	11	0	22
2	5	0	6	6	17
3	0	3	7	6	16
4–5	0	1	5	8	14
Maximal cancer percentage					
Mean	32	44	71	91	67
Median [IQR]	30 [10–50]	30 [9–90]	80 [55–100]	100 [83–100]	80 [38–100]
Number of cores, n					
Mean	15	13	14	12	13
Median [IQR]	15 [14–16]	13 [8–16]	14 [12–16]	13 [8–16]	14 [12–16]
Number of positive cores, n					
Mean	4	4	5	7	6
Median [IQR]	3 [2–5]	3 [1–6]	5 [4–7]	7 [6–9]	6 [3–8]

PCa, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; csPCa, clinically significant prostate cancer; ISUP, International Society of Urological Pathology; IQR, interquartile range.

was 8% (4/50). In Stabile *et al.*'s study (12), which included 87 patients under the age of 50 years, 47 patients exhibited lesions with a PI-RADS score of 3, and the csPCa-positive rate was 8.5% (4/47). According to the European Association of Urology (EAU) guidelines (22), individuals with a risk range of 5–10% for csPCa should be classified as low-risk patients and may forego biopsy. However, we also conducted pathologic analyses on four patients with csPCa with a PI-RADS score of 3, three of whom had an International Society of Urological Pathology (ISUP) grade of 3 and one an ISUP grade of 4. The percentage of positive cores in the three patients with ISUP 3 ranged from 66.7% to 76.5%, while the maximum cancer percentage ranged from between 50% and 90%. Additionally, we evaluated the post-radical prostatectomy pathology of these four patients, revealing that three had pT2 stage and one had pT3a stage. All three pT2 stage patients exhibited multifocal lesions, with the largest lesion diameter exceeding 1 cm. These findings suggested that refraining from performing biopsies on PI-RADS 3 lesions in young patients could avoid unnecessary biopsies in approximately 92% of cases and prevent detection of clinically insignificant cancers by around 12%. However, this approach might potentially miss approximately 8% of cases of csPCa that could be relatively aggressive. Therefore, even if a higher PI-RADS cutoff value is employed, we nonetheless advocate systematic follow-up for patients with PI-RADS 3 lesions. Given the subjective variability in MRI interpretations, seeking the expertise of experienced imaging specialists for a secondary reading may be advisable. Notably, Pepe *et al.*'s study (23) revealed that approximately 35% and 15% of PI-RADS score 3 lesions initially diagnosed by affiliated radiological centers were subsequently downgraded and upgraded upon reassessment by experienced radiologists. Moreover, numerous studies (24,25) have demonstrated that prostate-specific membrane antigen on positron emission tomography-computed tomography contributed equally to the early detection of PCa as did MRI. Consequently, for diagnosing lesions with a PI-RADS score of 3, integrating multiple imaging modes could serve

Table 3 Baseline characteristics of young patients with and without csPCa

Variable	csPCa group (n=47)	Non-csPCa group (n=160)	P value
Age at biopsy (years), median [IQR]	53 [52–55]	52 [48–54]	0.006‡*
BMI (kg/m^2), median [IQR]	24.8 [22.3–27.3]	24.3 [22.5–26.3]	0.448‡
Chief complaint, n (%)			0.013†*
Elevated PSA	37 (78.7)	94 (58.8)	
Clinical symptoms	10 (21.3)	66 (41.2)	
PSA value (ng/mL), median [IQR]	12.1 [7.7–24.6]	8.3 [6.0–11.2]	<0.001‡*
Prostate volume (mL), median [IQR]	32.8 [24.7–42.4]	37.8 [28.9–51.3]	0.036‡*
PSAD (ng/mL), median [IQR]	0.38 [0.20–0.69]	0.21 [0.14–0.31]	<0.001‡*
DRE, n (%)			0.113§
Negative	39 (83.0)	146 (91.3)	
Positive	8 (17.0)	14 (8.7)	
PI-RADS score, n (%)			<0.001†*
<3	5 (10.6)	78 (48.8)	
3	4 (8.5)	46 (28.7)	
4	18 (38.3)	32 (20.0)	
5	20 (42.6)	4 (2.5)	
Number of lesions, n (%)¶			0.450†
1	29 (69.0)	51 (62.2)	
≥2	13 (31.0)	31 (37.8)	
Anatomical location, n (%)¶			0.064†
Apex	15 (35.7)	16 (19.5)	
Basal	6 (14.3)	24 (29.3)	
Middle	21 (50.0)	42 (51.2)	
Histological location, n (%)¶			0.016†*
Peripheral zone	30 (71.4)	40 (48.8)	
Other	12 (28.6)	42 (51.2)	
Smoking, n (%)	17 (36.2)	43 (26.9)	0.217†
Alcohol intake, n (%)	12 (25.5)	25 (15.6)	0.119†
Metabolic syndrome, n (%)	8 (17.0)	7 (4.4)	0.007§*

†, Chi-square test; ‡, Mann-Whitney test; §, Fisher exact test; ¶, these analyses focused solely on main lesions and patients with PI-RADS ≥3; *, statistically significant. csPCa, clinically significant prostate cancer; IQR, interquartile range; BMI, body mass index; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; DRE, digital rectal examination; PI-RADS, Prostate Imaging Reporting and Data System.

as an additional alternative approach. Furthermore, it is worth noting that biomarkers exhibited relatively high negative predictive values, and their combined used with MRI could significantly reduce the number of patients with PI-RADS score 3 with suspected csPCa. Furthermore, examining MRI parameters, such as ADC values (26), or conducting MRI-based radiomics analysis (27,28) might also contribute significantly to enhancing the detection

Table 4 Univariate and multivariate logistic regression analyses for csPCa in young patients with suspected prostate cancer

Variable	Univariate analysis		Multivariate analysis[†]	
	OR (95% CI)	P value	OR (95% CI)	P value
Age at biopsy (≥50 *vs.* <50 years)	5.03 (1.71–14.77)	0.003	NI	
PSAD (>0.36 *vs.* ≤0.36 ng/mL^2)	6.10 (3.00–12.39)	<0.001*	3.28 (1.34–8.01)	0.009*
Chief complaint				
Elevated PSA	Reference		Reference	
Clinical symptoms	0.39 (0.18–0.83)	0.015*	0.28 (0.10–0.79)	0.016*
PI-RADS score				
<3	Reference		Reference	
3	1.36 (0.35–5.31)	0.661	1.68 (0.41–6.81)	0.625
4	8.78 (3.00–25.66)	<0.001*	7.97 (2.58–24.63)	0.001*
5	78.00 (19.17–317.43)	<0.001*	86.21 (18.55–400.66)	<0.001*
Number of lesions			NI	
0	Reference			
1	8.87 (3.22–24.42)	<0.001*		
2	6.54 (2.15–19.89)	<0.001*		
Anatomical location			NI	
Apex	Reference			
Basal	0.27 (0.09–0.83)	0.023*		
Middle	0.53 (0.22–1.28)	0.160		
Not applicable	0.07 (0.02–0.22)	<0.001*		
Histological location			NI	
Peripheral zone	Reference			
Other	0.38 (0.17–0.85)	0.018*		
Not applicable	0.09 (0.03–0.24)	<0.001*		
MS (yes *vs.* no)	4.48 (1.53–13.12)	0.006*	NI	

[†], the multivariate analysis model included PSAD, chief complaint, and PI-RADS score. *, statistically significant. csPCa, clinically significant prostate cancer; OR, odds ratio; CI, confidence interval; NI, not included; PSAD, prostate-specific antigen density; PSA, prostate-specific antigen; PI-RADS, Prostate Imaging Reporting and Data System; MS, metabolic syndrome.

rates of csPCa. Generally, the determination of biopsy strategy for young individuals with a PI-RADS score of 3 remains unclear and requires verification from large-scale, multicenter clinical studies.

Model construction based on multivariate logistic analysis was another approach employed to address the limited performance of the PI-RADS score in young patients. Via the construction if multiple models, PSAD and chief complaint were ultimately identified as two parameters that significantly enhanced the prediction of csPCa by PI-RADS score. It is worth noting that PSAD has gained considerable recognition among urologists in clinical practice, and its value in distinguishing between benign prostatic hyperplasia and tumors was extensively demonstrated at the end of the 20th century (29). In recent years, PSAD has increasingly emerged as a crucial factor in the research related to PCa diagnosis (30,31). Its combination with the PI-RADS score has yielded promising outcomes for the diagnosis of

csPCa. Through a retrospective analysis of 630 patients who underwent prostate biopsy, Massanova *et al.* (32) found that both the PSAD and PI-RADS score independently predicted csPCa, while their combined use demonstrated exceptional risk stratification capabilities. Notably, for patients with negative MRI results and PSAD levels below 0.3 ng/mL^2, prostate biopsies are unnecessary. Schoots and Padhani (33) systematically analyzed the relevant literature and proposed a risk-adapted biopsy decision model based on PI-RADS and PSAD, which was endorsed by the EAU guidelines (22). Additionally, PSAD has also demonstrated the potential to enhance the reassessment of csPCa risk in patients undergoing active surveillance, thereby supplementing the evaluation provided by PI-RADS scores (34). Based on its diagnostic value in the overall population with csPCa, we also sought to assess its utility in diagnosing early-onset PCa. The results of the multivariable analysis further substantiated its significance; however, it should be noted that a different cutoff value was employed. The cutoff value for this parameter was not fixed; however, a commonly used threshold was 0.15. In our study, we determined the optimal cutoff value based on the Youden index and identified it to be 0.36. To determine the most appropriate threshold, we compared the area under the ROC curve for both values (0.36 and 0.15) within multivariate model analysis. Notably, the area under the ROC curve was larger for 0.36 (0.875 *vs.* 0.865), indicating that the cutoff value of 0.36 was more suitable in this specific context.

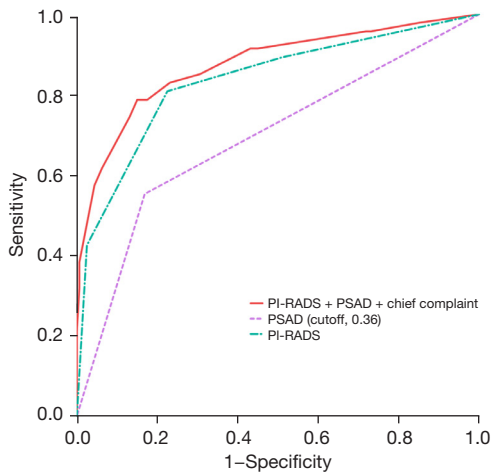

Figure 2 The ROC curves for predicting csPCa in young patients with suspected disease of PI-RADS, PSAD, and an integrated model incorporating PI-RADS, PSAD, and chief complaint. ROC, receiver operating characteristic; csPCa, clinically significant prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; PSAD, prostate-specific antigen density.

Our study involved several limitations that should be considered. First, we employed a retrospective analysis, which was inevitably influenced by recall bias. Fortunately, the majority of our data were obtained from a paper-based prostate biopsy database, thereby mitigating the impact of recall bias to a significant extent. Second, family history was not included as a variable due to its relatively low incidence in our dataset. Interestingly, Shiekh *et al.* (35) examined 1,032 patients with positive MRI findings and found no association between family history and csPCa detection (P=0.06). However, given the association of family history

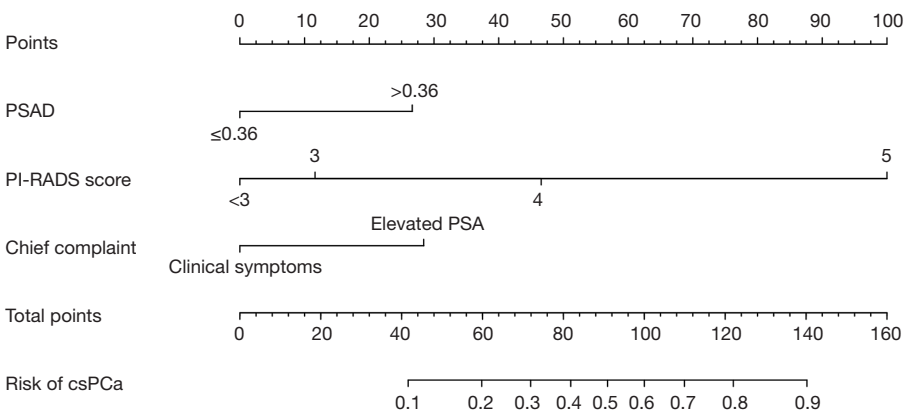

Figure 3 Nomogram for csPCa prediction among young patients with suspected disease. csPCa, clinically significant prostate cancer; PSAD, prostate-specific antigen density; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen.

with early-onset disease, further investigation into its relationship with csPCa in young patients with suspected disease is warranted. Third, the sample size used for model development was small, potentially leading to model instability. In this study, the concordance index of our nomogram was 0.875, partially indicating good predictive performance. Nevertheless, external validations using large-scale, multicenter data are needed. Finally, it is important to note that this study was an exploratory in nature, and its purpose was to preliminarily establish a suspected phenomenon and propose two potential solutions. The overarching aim is to bring this issue to the attention of urologists, who should exercise caution when interpreting MRI results in young patients, particularly lesions with a PI-RADS score of 3.

Conclusions

The positive predictive value of MRI positivity for csPCa was found to be age dependent, with a significant decrease in the positive rate observed in young patients with suspected disease, especially those with a PI-RADS score of 3 or 4. As an indicator, PI-RADS score ≥4 could optimize the tradeoff between specificity and sensitivity in young patients. Meanwhile, the integration of PI-RADS score, chief complaint, and PSAD improved the prediction of csPCa risk, and their combined use may mitigate excessive concern regarding young patients with a PI-RADS score of 3 and minimize unnecessary biopsies. Further large-scale prospective studies are warranted to validate our findings.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Jiangsu Province Hospital (No. 2023-SR-715). The requirement for individual consent was waived due to the retrospective nature of the analysis.

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