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Optimal PSA density threshold for prostate biopsy in benign prostatic obstruction patients with elevated PSA levels but negative MRI findings

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Abstract

Purpose This study was designed to identify a useful clinical parameter or model for prostate biopsy in surgery-indicated benign prostate hyperplasia (BPH) patients with elevated PSA levels and negative multiparametric prostate magnetic resonance imaging (MRI) results.

Patients and methods We retrospectively analyzed clinical and pathological data from patients who were diagnosed with BPH and admitted to the inpatient department for surgery between January 2010 and September 2020. Clinical data, including age, prostate specific antigen (PSA) level, F/T PSA ratio, prostate volume, and PSA density (PSAD), were used for comprehensive analysis. Univariate and multivariate logistic regression analyses were performed to develop a predictive model. Receiver operating characteristic (ROC) analysis and decision curve analysis (DCA) were performed to assess the diagnostic value of the predictive model, PSA concentration, F/T PSA ratio and PSAD.

Results A total of 318 patients were included in the study, 8.2% (26/318) of whom were histologically diagnosed with prostate cancer (PCa). Univariate and multivariate logistic regression analyses revealed that PSAD was the only independent predictor of PCa biopsy. ROC curve analysis of PCa detection revealed a larger area under the curve (AUC) for the predictive model (AUC 0.855) and for PSAD (AUC 0.848) than for PSA (AUC 0.722) or the F/T PSA ratio (AUC 0.635). DCA demonstrated that the optimal strategy would be to restrict biopsies to men with a PSAD of 0.30 ng/ml/cm3.

Conclusions Our study suggested that for BPH patients with surgical indications who present with PSA abnormalities and negative imaging findings, the use of a new PSAD threshold of 0.30 ng/ml/cm3 could facilitate convenient and sound biopsy decisions. This approach could reduce the complications and length of hospital stay associated with biopsies and reduce hospital costs.

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Keywords PSA density, Prostate MRI, Prostate biopsy, Benign prostate hyperplasia, Prostate cancer

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed solid malignancy worldwide, with an ever-increasing incidence [1]. The definitive diagnosis of prostate cancer relies on histopathological verification through prostate biopsy. Currently, the indication for prostate biopsy is determined by prostate specific antigen (PSA) levels, PSA density (PSAD), other biomarkers and/or suspicious digital rectal examination (DRE) and/or imaging. According to the EAU guidelines, multiparameter prostate MRI (mpMRI) should be performed before considering prostate biopsy in biopsy-naïve patients with clinical suspicion of PCa [2]. If the mpMRI demonstrates lesion(s) with features suggesting PCa, both systematic and targeted biopsy should be performed. If the mpMRI is negative, the decision to proceed with prostate biopsy should be based on the degree of clinical suspicion of PCa, which comprises indications from PSA levels, PSAD and other biomarkers. In situations where the clinical suspicion of PCa is low, prostate biopsy could be omitted when a shared decision is made with the patient.

In clinical practice, there is a large group of patients with benign prostate hyperplasia (BPH) who have indications for surgery to relieve bladder outlet obstruction. These patients present with elevated PSA levels but negative subsequent mpMRI results. Current research has proposed different PSAD thresholds (such as 0.10 ng/ml/cc, 0.15 ng/ml/cc, 0.20 ng/ml/cc, and even higher) as cutoffs to determine prostate biopsy results for patients with negative magnetic resonance results [3–6]. However, no unanimous conclusion has been reached, and these studies do not specifically focus on BPH patients with bladder outlet obstruction. Since BPH itself can cause elevated PSA levels, the findings from patients without BPH may not be applicable to those with BPH. Therefore, there is currently a lack of evidence to guide prostate biopsy for BPH patients with elevated PSA levels and negative mpMRI results before proceeding to BPH surgery. Additionally, prostate biopsy is often associated with minor bleeding, urinary symptoms, and occasionally serious infectious complications [7], which increase patients' economic, physical and psychological burdens.

To propose the best biopsy strategy for BPH patients with elevated PSA levels and negative mpMRI results, we conducted a retrospective analysis of clinical data from our center over the past ten years. The data included information on prostate biopsy and prostate surgery for BPH patients with negative mpMRI results and elevated PSA levels. We performed a comprehensive analysis to identify a sensitive threshold for predicting prostate cancer and to improve the accuracy of biopsy. Our aim was to optimize the prostate biopsy strategy for BPH patients with bladder outlet obstruction.

Patients and methods

Patients

After institutional review board approval (KY2021186) was obtained, we retrospectively analyzed the clinical data of patients who were diagnosed with BPH and admitted to the inpatient department for surgery. Surgical intervention was indicated for patients with moderate-to-severe voiding symptoms attributed to BPH refractory to medical therapy as well as for patients with clinically significant complications. We reviewed the consecutive clinical profiles of surgical candidates with BPH from January 2010 to September 2021 and enrolled patients with elevated PSA levels (PSA ≥ 4 ng/ml), negative DRE, and mpMRI PI-RADS scores ≤ 2 in our study. We excluded patients admitted for biopsy due to simply elevated PSA levels who did not present with voiding symptoms attributed to BPH. We also excluded patients whose PSA results were confounded by recent urinary obstruction or infection and who did not undergo repeated testing. Furthermore, patients without surgical or biopsy prostate pathological results were also excluded from our study. After patient selection, detailed clinical data were obtained from the patients' electronic medical records at the hospital. Follow-up assessments were conducted during scheduled postoperative visits or through consultative phone calls for patients who failed to attend routine visits. The collected results were recorded.

Clinical data

Patient baseline data, including age, IPSS, medical treatment with 5 alpha reductase inhibitors, history of bladder stones and indwelling urinary catheters, PSA levels, F/T PSA ratio, DRE, TRUS and mpMRI findings, were collected. Specifically, since treatment with 5 alpha reductase inhibitors for more than 3 months reduces PSA levels by an average of approximately 50% [8], we doubled the PSA value of those patients in further analysis. For patients with prostate cancer (PCa), the Gleason score of the biopsy specimen was obtained. Prior to 2015, patients without PI-RADS V2 scoring information were individually scored by radiologists with over 5 years of experience in our hospital. The radiologists who scored the prostate with the PI-RADS V2 system were blinded to the pathological results. The prostate volume (PV) was calculated based on the mpMRI data (PV = 0.52 × anteroposterior diameter × transverse diameter × craniocaudal diameter). The PSAD is defined as the ratio of the PSA value to the PV.

All prostate biopsies were performed using a transrectal systematic 12-core procedure in the left lateral decubitus position under local anesthesia. BPH surgery was performed using either monopolar transurethral resection of the prostate or greenlight laser enucleation of the prostate. The histopathology of all biopsies was reported separately and analyzed by an experienced uropathologist using the 2014 International Society of Urological Pathology (ISUP) modified classification. For BPH surgery, all the removed prostatic tissues were subjected to pathological examination performed by the same uropathologist. Any PCa with an ISUP grade ≥ 2 (Gleason score ≥ 3 + 4) was defined as clinically significant PCa (csPCa).

Statistical analysis

SPSS (version 23) and R software (version 3.5.3) were used for all the statistical analyses. Continuous variables are expressed as medians and interquartile ranges. The Mann–Whitney U test was used for 2 continuous variables, and the Chi-square test or Fisher's exact test was used for categorical variables. Multivariate logistic regression analysis was performed with clinically relevant parameters and statistically significant variables identified by univariate analysis. The predictive ability was evaluated using a receiver operating characteristic (ROC) curve. Decision curve analysis (DCA) was used to identify the strategy with the greatest net clinical benefit.

Results

Descriptive characteristics of the overall population

This study included a total of 1347 patients admitted to our department from January 1, 2010, to September 1, 2020, who required prostate surgery and had a PSA level ≥ 4 ng/ml. After careful selection, 318 patients were enrolled in the study for the final analysis (Fig. 1). Among these 318 BPH patients, the median IPSS was 21, indicating that patients experienced moderate to severe voiding symptoms. Of the 318 patients, 15.7% (50/318) presented with urinary retention, 10.8% (34/318) presented with bladder stones, and 27.7% (88/318) were receiving long-term treatment with 5 alpha reductase inhibitors. Based on the current guidelines, all 318 patients were recommended for prostate biopsy. Among them, 68 patients underwent systemic transrectal prostate biopsy first and later received BPH surgery or radical prostatectomy according to the pathological results, while the remaining 250 patients refused biopsy and opted for transurethral surgery solely to relieve obstruction. Overall, 8.2% (26/318) of the patients were histologically diagnosed with PCa. Specifically, 61.5% (16/26) of the prostate cancer patients were classified as having insignificant PCa (insPCa), and 38.5% (10/16) were classified as having csPCa. Table 1 presents a comparison of the clinical characteristics between BPH patients (non-PCa) and prostate cancer patients (PCa) in the study cohort. Clinical

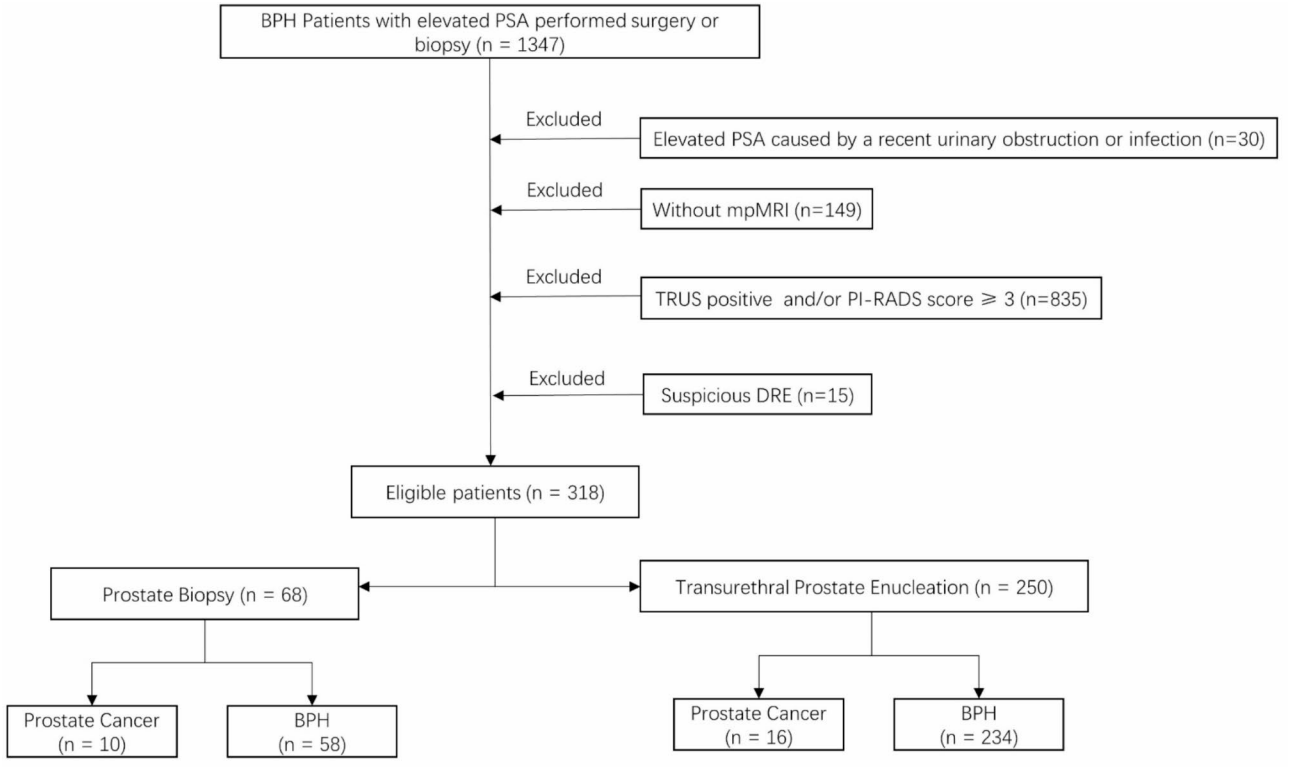

Fig. 1 Flowchart of patient selection

Table 1 Comparison of clinical characteristics between prostate cancer and nonprostate cancer patients in the study cohort

Group	Non PCa	PCa	*P* value	Total
Cases number, n(%)	292	26		318
Median Age, yr(IQR)	74(67–79)	73(67–79)	0.902	74(67–79)
Median PSA, ng/ml(IQR)	8.83(6.17–11.62)	14.71(8.98–21.33)	< 0.001	9.03(6.31–12.08)
Median prostate volume, cm^3 (IQR)	65.27(50.14–87.67)	44.54(38.57–57.27)	< 0.001	63.92(49.20–86.20)
PSAD, ng/ml/cm^3 (IQR)	0.13(0.09–0.20)	0.36(0.19–0.45)	< 0.001	0.14(0.09–0.21)
Median IPSS Score, (IQR)	23(21–26)	24(22–25)	0.969	21(23–25)
Indwelled Catheter, n(%)			0.961	Fisher exact
No	246(84.2)	22(84.6)		268(84.3)
Yes	46(15.8)	4(15.4)		50(15.7)
5α reductase inhibitor usage, n(%)			0.315	
No	209(71.6)	21(80.8)		230(72.3)
Yes	83(18.8)	5(19.2)		88(27.7)
Bladder Stones, n(%)			0.176	Fisher exact
No	263(90.1)	21(80.8)		284(89.3)
Yes	29(9.9)	5(19.2)		34(10.7)
F/T Ratio, n(%)			0.076	
<0.16	127(43.5)	16(61.5)		143(45.0)
>0.16	165(56.5)	10(38.5)		175(55.0)
PSA Group, n(%)			0.011	
4–10 ng/ml	176(60.3)	9(34.6)		185(58.2)
≥10 ng/ml	116(39.7)	17(65.4)		133(41.8)
PSAD Group, n(%)			< 0.001	
<0.10 ng/ml/cm^3	95(32.5)	1(3.8)		96(30.2)
0.10–0.14 ng/ml/cm^3	73(25.0)	2(7.7)		75(23.6)
0.15–0.19 ng/ml/cm^3	53(18.2)	5(19.2)		58(18.2)
≥0.20 ng/ml/cm^3	71(24.3)	18(69.2)		89(28.0)
Management			< 0.001	
Encleation	234(80.1)	0(0)		234(73.6)
Encleation + AS	0(0)	9(34.6)		9(2.8)
Encleation + RP	0(0)	7(26.9)		7(2.2)
Biopsy + Encleation	58(19.9)	1(3.8)		59(18.6)
Biopsy + RP	0(0)	9(34.6)		9(2.8)
FollowUp			0.458	
Available, n(%)	229(78.4)	22(84.6)		251(78.9)
Median Time, months(IQR)	33(12–67)	16(5–59)	0.133	33(12–66)
Median PSA Value, ng/ml (IQR)	1.23(0.54–1.96)	1.17(0.55–1.89)	0.903	1.23(0.55–1.95)

parameters such as IPSS, percentage of patients with urinary retention, bladder stones and receiving 5 alpha reductase inhibitor treatment did not significantly differ between the BPH and PCa groups. However, there were significant differences in the PSA level, prostate volume, and PSAD between the two groups (all $P < 0.05$). Patients with PCa exhibited higher levels of PSA and PSAD but lower prostate volume.

A total of 251 patients were successfully followed up. After a median of 33 months postoperative follow-up, based on their latest PSA results, all patients showed a reduction compared to the preoperative PSA value in BPH patients. Specifically, no patients with prostate cancer experienced recurrence after radical prostatectomy.

Risk factors for prostate cancer

To explore the potential risk factors for prostate cancer, we conducted univariate and multivariate logistic regression comparing 26 non-PCa patients and 292 PCa patients. Univariate analysis revealed that greater PSA levels (odds ratio [OR] 1.16, 95% confidence interval [CI] 1.09–1.24; $p < 0.001$), lower F/T ratios (OR 0.01, 95% CI 0-0.35; $p = 0.023$) and greater PSAD levels (OR 207738.27, 95% CI 3990.48-10814523.29; $p < 0.001$) were predictors of PCa biopsy in patients with negative MRI findings. Multivariate analysis excluded the PSA value and F/T ratio and confirmed that PSAD (OR 1638230, 95% CI 9803-525887770; $p < 0.001$) was the only independent predictor of PCa biopsy (Table 2). Based on the logistic regression model, a predictive model for PCa was created (see Supplement).

Table 2 Risk factors for prostate Cancer

	Univariate analysis		Multivariate analysis	
	OR(95%CI)	P	HR(95%CI)	P
Age	1.01(0.96–1.06)	0.786	-	-
IPSS Score	0.97(0.87–1.08)	0.560	-	-
Catheter Indwelled	0.97(0.32–2.95)	0.961	-	-
Bladder Stones	2.16(0.76–6.16)	0.150	-	-
5 alpha reductase usage	0.60(0.22–1.64)	0.320	-	-
PSA Value	1.16(1.09–1.24)	< 0.001	0.94(0.84–1.05)	0.300
F/T Ratio	0.01(0.00-0.35)	0.023	3.36(0.00-1137)	0.700
PSAD	207738.27(3990.48-10814523.29)	< 0.001	1,638,230(9803-525887770)	< 0.001

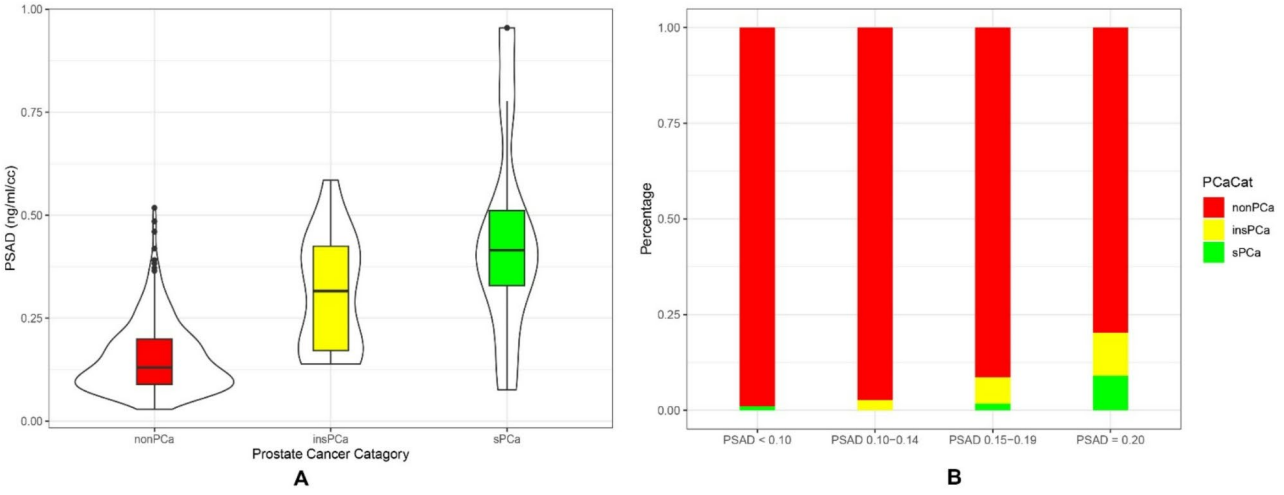

Fig. 2 The distribution of prostate cancer between different prostate cancer category **(A)** and different PSAD threshold **(B)**

Diagnostic variables for prostate cancer

PSAD was proven by a multivariate logistic regression model to be an independent predictor of PCa. The distribution of prostate cancer between different PSAD thresholds showed that the number of PCa cases detected increased with increasing PSAD (Fig. 2).

To explore the best clinical parameters that would help to discriminate nonPCa from PCa, we performed ROC analysis between the four clinical parameter candidates, PSAD, PSA, F/T ratio and the logistic model created above. ROC curve analysis of PCa detection revealed a larger AUC for the predictive model (AUC = 0.855) and PSAD (AUC = 0.848) than for the PSA (AUC = 0.722) or F/T ratio (AUC = 0.635) (Fig. 3a). The best threshold for PSAD was 0.30 ng/ml/cc, and by setting a cutoff of 0.30 for PSAD, the maximal AUC was achieved.

Next, we examined the ability of various PSAD thresholds and conventional clinical parameters, such as a PSA concentration of 10 ng/ml and an F/T ratio of 0.16, to predict PCa (Table 3). The specificity for PCa was 60% for 10 ng/ml PSA and 57% for an F/T ratio of 0.16, with corresponding sensitivities of 65% and 62%, respectively. The specificity was 93% for a PSAD of 0.30 ng/ml/cm3, 76% for a PSAD of 0.20 ng/ml/cm3, and 57% for a PSAD of 0.15 ng/ml/cm3, with corresponding sensitivities of 65%, 69% and 92%, respectively. The highest Youden's J index among the various clinical parameters was 0.58 for patients with a PSAD of 0.30 ng/ml/cm3. a PSAD cutoff of 0.30 outperformed the other thresholds and was the most suitable predictive marker.

We also performed DCA to validate the diagnostic value of different biopsy strategies. According to the DCA for the different biopsy strategies (Fig. 3b), biopsy PSAD ≥ 0.30 and the predictive model showed the greatest net benefit at each probability threshold compared to the other strategies. With a probability of 0.05–0.15, the net benefit of a biopsy PSAD ≥ 0.30 surpassed that of the predictive model. In accordance with previous findings, the optimal strategy would be to restrict biopsies to men with a PSAD of 0.30 ng/ml/cm3.

Discussion

In this study, we focused on a specific group of patients: those with benign prostatic hyperplasia (BPH) who were admitted to our center and required surgery to relieve bladder outlet obstruction (with a median IPSS of 21 and a median prostate volume of 63.92 ml). Preoperative assessment revealed elevated PSA levels but negative

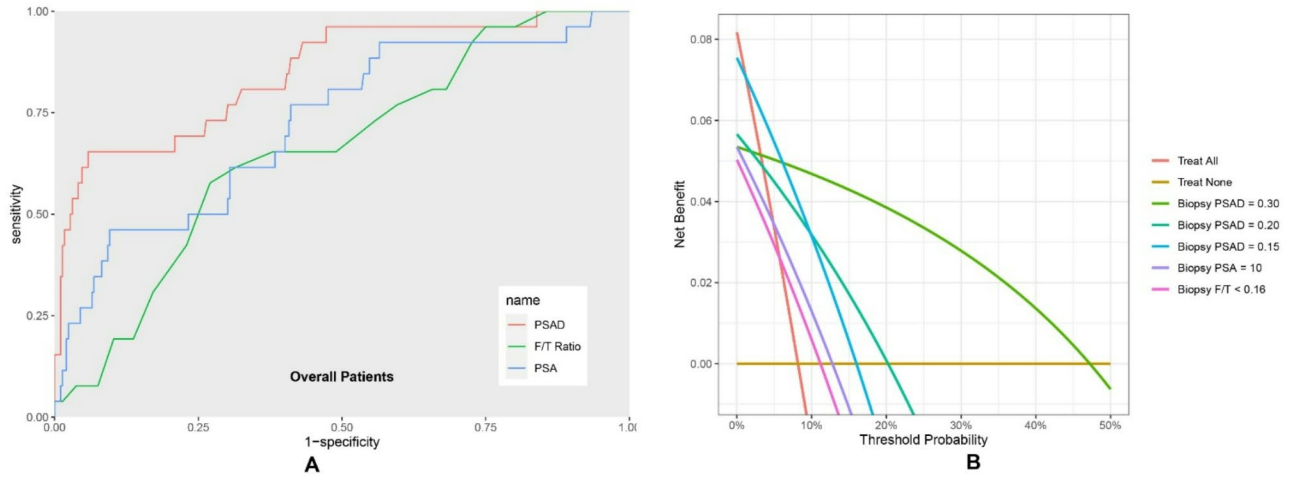

Fig. 3 ROC for performance of PSAD, PSA, F/T PSA Ratio in detecting prostate cancer in BPH patients with elevated PSA value, normal mpMRI results **(A)**. Decision Curve analysis of different biopsy strategies. Biopsy PSAD ≥ 0.30 and Predictive Model showed the highest net benefit at each probability threshold compared to other strategies. During a probability of 0.05–0.15, the net benefit of Biopsy PSAD ≥ 0.30 surpass the Predictive Model **(B)**

Table 3 Sensitivity, specificity, and predictive values for prostate cancer detection at various thresholds

	Pathological Results		Diagnostic Value				
	Non PCa	PCa	Sensitivity	Specificity	PPV	NPV	Youden's J index
PSAD ≥ 0.30	19	17	0.65	0.93	0.47	0.96	0.58
PSAD < 0.30	273	9					
PSAD ≥ 0.20	71	18	0.69	0.76	0.20	0.97	0.45
PSAD < 0.20	221	8					
PSAD ≥ 0.15	126	24	0.92	0.57	0.16	0.98	0.49
PSAD < 0.15	166	2					
PSA ≥ 10	116	17	0.65	0.60	0.13	0.95	0.25
PSA < 10	176	9					
F/T < 0.16	127	16	0.62	0.57	0.11	0.94	0.19
F/T ≥ 0.16	165	10					

mpMRI results. While men with negative mpMRI findings have a low risk of high-grade prostate cancer, there is still a small chance of missed csPCa, ranging from 5 to 15% in one recent systematic review. Therefore, identifying patients with prostate cancer is still necessary [9]. Currently, evidence on the management of these patients is lacking. In our study, we proposed that a PSAD cutoff of 0.30 could be used for initiating prostate biopsy in patients with negative MRI by retrospectively analyzing clinical data and follow-up data. To the best of our knowledge, our study is the first to focus on this specific subset of patients who face the dilemma of whether to undergo prostate biopsy. We also developed a predictive model based on logistic regression analysis that incorporates the PSA concentration, F/T ratio, and PSAD. However, this model, via ROC analysis, only showed slightly better performance than PSAD alone (AUC 0.855 vs. 0.848). Furthermore, according to the decision curve analysis, the net benefit of the predictive model was lower than that of PSAD alone for a clinically relevant threshold probability of 0.05–0.15. Therefore, we conclude that applying a PSAD cutoff of 0.30 is a better risk stratification option than using the predictive model.

PCa and BPH are both common diseases among older men, and often coexist, affecting each other's management strategies [10]. Ideally, urologists should accurately diagnose prostate cancer before performing surgery for BPH to reduce the incidence of incidental prostate cancer and guide men toward the appropriate initial treatment option. Incidental prostate cancer refers to the discovery of PCa after prostate surgery for benign prostate hyperplasia and is found in 5–11% of BPH/LUTS patients who undergo appropriate diagnostic evaluation [11]. Previous studies have identified several clinical parameters, such as patient age [12, 13], PSA [13–15], PSAD [12, 15, 16], preoperative prostate biopsy [17], and the presence of suspicious lesions on prostate MRI [18] or ultrasound [19], as predictive variables for incidental PCa. However, most of these studies were retrospective and did not specifically focus on patients with negative prostate MRI results. Furthermore, research on incidental PCa has not provided a practical prostate biopsy strategy to

target patients with PCa and avoid unnecessary biopsies in patients without PCa.

Elevated PSA levels should prompt a PCa screening process for individuals who meet specific criteria, such as being over 55 years of age or having a strong family history, as outlined in current guidelines. In China, as well as the United States, a PSA level of 4.0 ng/ml is the generally accepted threshold for prostate biopsy [20]. Prostate biopsy is an invasive urological procedure associated with complications such as infection, bleeding, and substantial discomfort to patients. Therefore, after a positive PSA screening is confirmed, further assessments should be conducted to minimize unnecessary biopsies. Systematic analysis has shown that compared with systematic biopsy, mpMRI, which has an average sensitivity of 91% and specificity of 37%, can reduce the number of biopsies by 30% while maintaining the detection of significant cancers [21]. However, recent systematic reviews have reported false-negative rates of MRI results ranging from 5 to 15%, highlighting the need for risk-adapted strategies in biopsy selection [9]. 68GaPSMA PET/CT, another emerging diagnostic imaging modality for PCa, demonstrated a diagnostic accuracy equal to 92% in the diagnosis of csPCa in men high risk for cancer [22], however, it is not yet routinely utilized in our clinical practive due to its relatively high cost. PSA derivatives (F/T ratio, PSA velocity, and PSAD) and urine- or blood-based molecular markers (Stockholm-3 model, the Prostate Health Index, the 4 K score Test, PCA3 test, and ExoDx test) have all been reported to effectively stratify high risk patients for biopsy and improve the diagnostic accuracy of PCa [20]. F/T ratio could be used to indicated prostate cancer risk in patients with a PSA level less than 10 ng/ml, in a study of a case-finding protocol on 14,453 patients, PCa prevalence in case of tPSA ≤ 2.5 ng/ml (F/T ratio < 0.15), 2.6–4 ng/ml (F/T ratio < 0.20) and 4.1–10 ng/ml (F/T ratio < 0.25) was equal to 29.1%, 37.4% and 28.8%, respectively [23]. PCA3 test, which measures the expression of the prostate cancer antigen 3 gene in post DRE urine, is a well-established urine-based biomarker. Pepe et al. reported that an AUC for a 25 cutoff of PCA3 compared to 35 cutoff was 0.678 vs. 0.634 respectively for detecting PCa in repeated saturation prostate biopsy [24]. However, according to guidelines, these biomarkers are not yet recommended as first-line screening tests in combination with serum PSA. These methods are mainly recommended for individuals who have previously undergone a negative prostate biopsy or are listed as options with weak evidence to guide biopsy decision making in those with PSA levels between 2 and 10 ng/ml [2, 25]. Furthermore, the additional cost of urine and blood-based biomarkers still hinders their widespread application. On the other hand, PSA derivatives are easily accessible and commonly used in clinical practice. Among the PSA derivatives, PSAD has been identified as a strong predictive variable for incidental PCa [12, 15, 16], and multiple studies suggest the combination of MRI findings and PSAD to define patients who can safely avoid biopsy [5, 26–28]. However, the exact cutoff for selecting patients at high risk of harboring PCa despite negative MRI results is still under debate [4]. According to a recent meta-analysis, EAU guidelines recommend using a cutoff of 0.20 ng/ml/cc in patients with negative MRI results [29], while other studies propose different thresholds. Distler et al. [30] reported that obtaining a biopsy in patients with negative MRI results and a PSAD ≥ 0.15 increased the detection of csPCa by 10% compared to that of MRI alone, and this approach could avoid approximately 20% of unnecessary biopsies. Other researchers have recommended alternative thresholds for PSAD. Hansen et al. [6] categorized patients in three groups based on PSAD (≤ 0.10, 0.10–0.20, and > 0.20) and found that a PSAD of ≤ 0.20 was associated with low detection of csPCa in patients undergoing repeated biopsy with negative MRI. By incorporating PSAD, the NPV of negative MRI increased from 0.71 to 0.91. Pellegrino et al. [4] suggested that a PSAD cutoff of 0.15 is appropriate only when MRI accuracy is very low. For average MRI accuracy, a higher cutoff of at least 0.20 should be used, assuming that MRI accuracy has improved over the years. In our study, we proposed a cutoff of 0.30 to detect PCa, which is higher than the literature proposed above. The difference may reflect the different patient characteristic between our study and the literature. Our study specifically targeted patients with bladder outlet obstruction due to benign prostatic hyperplasia while the literature primarily focused on the general population.

There are several limitations to this study. First, our study was a single-center retrospective study and was limited by the inherent flaws of its retrospective design. Second, the pathological results in the study were obtained from biopsies and transurethral prostate enucleation specimens. The latter lacked a peripheral zone of prostate tissue, which may have led to a reduced proportion of PCa patients. However, this limitation is mitigated by the follow-up results. During a minimum follow-up time of 12 months (median of 33 months), patients with negative pathological findings showed no progression of PSA, and no patients were diagnosed with PCa after BPH surgery. Thus, we can safely conclude that these patients did not have PCa before management. Third, our study analyzed the whole population of PCa patients rather than focusing solely on patients with conventional csPCa. Since csPCa accounts for only 3.1% of the entire population, this small proportion could substantially influence the results of the univariate and multivariate analyses, making the identified risk factors unreliable. Finally,

further multicenter clinical trials are needed to validate this conclusion.

Conclusion

Our study suggested that for BPH patients with surgical indications, in the case of PSA abnormalities and negative imaging findings, using a PSAD threshold of 0.30 could be a useful tool for making personalized biopsy decisions. This approach can help reduce the complications and length of hospital stay associated with biopsies as well as reduce hospital costs.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12894-025-01719-5 .

Supplementary Material 1

Author contributions

Wenhao Shen participated in designing the protocol of the study. Yiji Peng, Chengcheng Wei, Yin Li, Fuhan Zhao, Yuan Liu, Tao Jiang, Zhipeng Chen, Jun Zheng, Jiong Fu, and Peng Wang were responsible for data collection, and management. Yiji Peng and Chengcheng Wei were responsible for data analysis. Yiji Peng drafted the manuscript and prepared Figure and Table. Chengcheng Wei and Wenhao Shencritically revised the manuscript. Each of the authors had carefully read and approved the final manuscript for publication.

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Data availability

The raw data that support the findings of this study are available from the corresponding author, Wenhao Shen, upon reasonable request.

Declarations

Ethics approval

The study was approved by the institutional ethics committee of Southwest Hospital, Army Medical University (KY2021186) and conducted according to the ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent. Clinical trial number: not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate Cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2021;79(2):243–62.
3. Regis L, Celma A, Planas J, Lopez R, Roche S, Lorente D, et al. The role of negative magnetic resonance imaging: can we safely avoid biopsy in P.I.-R.A.D.S. 2 as in P.I.-R.A.D.S. 1? Scand J Urol. 2019;53(1):21–5.
4. Pellegrino F, Tin AL, Martini A, Vertosick EA, Porwal SP, Stabile A, et al. Prostate-specific antigen density cutoff of 0.15 Ng/ml/cc to propose prostate biopsies to patients with negative magnetic resonance imaging: efficient threshold or legacy of the past?? Eur Urol Focus. 2023;9(2):291–7.
5. Falagario UG, Martini A, Wajswol E, Treacy PJ, Ratnani P, Jambor I, et al. Avoiding unnecessary magnetic resonance imaging (MRI) and biopsies: negative and positive predictive value of MRI according to Prostate-specific antigen density, 4Kscore and risk calculators. Eur Urol Oncol. 2020;3(5):700–4.
6. Hansen NL, Barrett T, Koo B, Doble A, Gnanapragasam V, Warren A, et al. The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7–10 prostate cancer in a repeat biopsy setting. BJU Int. 2017;119(5):724–30.
7. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. Eur Urol. 2013;64(6):876–92.
8. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010;362(13):1192–202.
9. Sathianathen NJ, Omer A, Harriss E, Davies L, Kasivisvanathan V, Punwani S, et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate Cancer in the prostate imaging reporting and data system era: A systematic review and Meta-analysis. Eur Urol. 2020;78(3):402–14.
10. Lee MS, Assmus MA, Guo J, Siddiqui MR, Ross AE, Krambeck AE. Relationships between holmium laser enucleation of the prostate and prostate cancer. Nat Rev Urol. 2023;20(4):226–40.
11. Capitanio U, Autorino R, Bandini M, Briganti A, Cheng L, Cooperberg MR et al. Incidental prostate Cancer (cT1a-cT1b) is a relevant clinical and research entity and should be fully discussed in the international prostate Cancer guidelines. Eur Urol Oncol. 2021.
12. Herlemann A, Wegner K, Roosen A, Buchner A, Weinhold P, Bachmann A, et al. Finding the needle in a haystack: oncologic evaluation of patients treated for LUTS with holmium laser enucleation of the prostate (HoLEP) versus transurethral resection of the prostate (TURP). World J Urol. 2017;35(11):1777–82.
13. Bhojani N, Boris RS, Monn MF, Mandeville JA, Lingeman JE. Coexisting prostate cancer found at the time of holmium laser enucleation of the prostate for benign prostatic hyperplasia: predicting its presence and grade in analyzed tissue. J Endourol. 2015;29(1):41–6.
14. Klein C, Marquette T, Capon G, Yacoub M, Alezra E, Bernhard JC, et al. Incidental prostate cancer after holmium laser enucleation of the prostate: incidence and predictive factors for clinical progression. Int J Clin Oncol. 2022;27(6):1077–83.
15. Otsubo S, Yokomizo A, Mochida O, Shiota M, Tatsugami K, Inokuchi J, et al. Significance of prostate-specific antigen-related factors in incidental prostate cancer treated by holmium laser enucleation of the prostate. World J Urol. 2015;33(3):329–33.
16. Elkoushy MA, Elshal AM, Elhilali MM. Incidental prostate Cancer diagnosis during holmium laser enucleation: assessment of predictors, survival, and disease progression. Urology. 2015;86(3):552–7.
17. Capogrosso P, Capitanio U, Vertosick EA, Ventimiglia E, Chierigo F, Oreggia D, et al. Temporal trend in incidental prostate Cancer detection at surgery for benign prostatic hyperplasia. Urology. 2018;122:152–7.
18. Wenzel M, Welte MN, Grossmann L, Preisser F, Theissen LH, Humke C, et al. Multiparametric MRI May help to identify patients with prostate Cancer in a contemporary cohort of patients with clinical bladder outlet obstruction scheduled for holmium laser enucleation of the prostate (HoLEP). Front Surg. 2021;8:633196.
19. Kim M, Song SH, Ku JH, Oh SJ, Paick JS. Prostate cancer detected after holmium laser enucleation of prostate (HoLEP): significance of transrectal ultrasonography. Int Urol Nephrol. 2014;46(11):2079–85.
20. Pinsky PF, Parnes H. Screening for prostate Cancer. N Engl J Med. 2023;388(15):1405–14.

21. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019;4(4):Cd012663.
22. Pepe P, Pennisi M. Targeted biopsy in men high risk for prostate cancer: (68) Ga-PSMA PET/CT versus MpMRI. Clin Genitourin Cancer. 2023;21(6):639–42.
23. Pepe P, Aragona F. Incidence of insignificant prostate cancer using free/total PSA: results of a case-finding protocol on 14,453 patients. Prostate Cancer Prostatic Dis. 2010;13(4):316–9.
24. Pepe P, Fraggetta F, Galia A, Skonieczny G, Aragona F. PCA3 score and prostate cancer diagnosis at repeated saturation biopsy. Which cut-off: 20 or 35? Int Braz J Urol. 2012;38(4):489–95.
25. Wei JT, Barocas D, Carlsson S, Coakley F, Eggener S, Etzioni R, et al. Early detection of prostate cancer: AUA/SUO guideline part I: prostate Cancer screening. J Urol. 2023;210(1):46–53.
26. Washino S, Okochi T, Saito K, Konishi T, Hirai M, Kobayashi Y, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy Naïve patients. BJU Int. 2017;119(2):225–33.
27. Boesen L, Nørgaard N, Løgager V, Balslev I, Bisbjerg R, Thestrup KC, et al. Prebiopsy biparametric magnetic resonance imaging combined with prostate-specific antigen density in detecting and ruling out Gleason 7–10 prostate Cancer in Biopsy-naïve men. Eur Urol Oncol. 2019;2(3):311–9.
28. Schoots IG, Osses DF, Drost FH, Verbeek JFM, Remmers S, van Leenders G, et al. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease. Transl Androl Urol. 2018;7(1):132–44.
29. Schoots IG, Padhani AR. Risk-adapted biopsy decision based on prostate magnetic resonance Imag Ing and prostate-specific antigen density for enhanced biopsy avoidanc e in first prostate cancer diagnostic evaluation. BJU Int.127(2):175–8.
30. Distler FA, Radtke JP, Bonekamp D, Kesch C, Schlemmer HP, Wieczorek K, et al. The value of PSA density in combination with PI-RADS™ for the accuracy of prostate Cancer prediction. J Urol. 2017;198(3):575–82.

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