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Original Article

Performance of PRIMARY Score based on PSMA-PET imaging in suspected prostate cancer patients with different PSA ranges: a retrospective study

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Abstract: Purpose: To refine the optimal PRIMARY score thresholds across different PSA ranges, enhancing diagnostic accuracy for clinically significant prostate cancer (csPCa). Methods: The study retrospectively analyzed 373 patients who underwent PSMA PET/CT scans for suspected csPCa between June 2021 and December 2023. The diagnostic efficacy of PRIMARY score was independently assessed using 68Ga-PSMA PET/CT. Receiver-operating characteristic curve analysis was used to estimate the diagnostic performance. The diagnostic efficacy of the PRIMARY score with different thresholds in different PSA ranges was also calculated and compared. Results: The PRIMARY score maintains high diagnostic accuracy either in group of PSA ≤ 20 ng/mL or PSA > 20 ng/mL, with an AUC exceeding 0.8 at appropriate thresholds. Notably, in patients with PSA > 20 ng/mL, a PRIMARY score threshold of 4 demonstrated enhanced diagnostic accuracy compared to a threshold of 3, significantly improving specificity from 70.6% to 91.2% while maintaining high sensitivity (from 99.2% to 98.4%). Consequently, 91.2% (31/34) patients could avoid unnecessary biopsies, at the expense of missing 1.6% (2/125) of csPCa cases. Conclusion: Across different PSA ranges, the PRIMARY score based on ^{68}Ga-PSMA PET/CT imaging is useful in the diagnosis of csPCa. A threshold of 3 for PSA ≤ 20 ng/mL and a threshold of 4 for 20 ng/mL < PSA ≤ 50 ng/mL respectively demonstrated favorable diagnostic performance.

Keywords: PRIMARY score, PSMA PET/CT, PSA, prostate cancer, diagnosis

Introduction

Prostate cancer (PCa) is the second-most prevalent malignancy in male and the fifth leading cause of cancer related death worldwide [1]. Thus, it is imperative to improve the accuracy of diagnosis for PCa, particularly for clinically significant PCa (csPCa) that requires curative treatment and active monitoring, so as to reduce the mortality due to malignancy [2].

PSA is the clinical first-line screening indicator for PCa [3]. However, since PSA is organ-specific but not cancer-specific, numerous trials have confirmed PSA-based PCa screening has non-ignorable risk of over-diagnosis [4], especially in the range of 4-20 ng/mL. The proportion of non-clinically significant prostate cancer (ncsPCa) in PSA levels of 4-20 ng/mL is up to 75%, which would lead to unnecessary biopsy [5]. Thus, additional imaging diagnosis is important for identifying csPCa and biopsy decision-making.

^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) has been well-established as an effective method for the csPCa diagnosis [6-12]. Recently, Emmett et al. developed a 5-level PRIMARY scoring system with a threshold of 3, incorporating intraprostatic pattern and intensity on PSMA-PET/CT, for further improving the accuracy of ^{68}Ga-PSMA PET/CT [13]. Subsequent studies confirmed its superior diagnostic value for csPCa compared to PSMA-PET intensity-based diagnosis [10, 14, 15].

It is worth noting that previous PRIMARY studies only covered the patients whose PSA ranges 4-20 ng/mL, its performance for the group of PSA > 20 ng/mL remains unclear. It is widely believed that relatively low percentage of ncsPCa, about 13%-27%, for patients with PSA > 20 ng/mL in western country, which was inconsistent with the recent data of Asia with high incidence of 30%-65%. These discrepancies may result from multiple factors, including regional variations in prostate cancer risk, the prevalence of benign prostatic conditions, and differences in screening practices [16-21]. Therefore, for populations with PSA > 20 ng/mL in Asian, there is still a need to have additional diagnosis, such as PSMA-PET, for reducing unnecessary biopsy.

Herein, this study aims to evaluate and refine the optimal PRIMARY score thresholds across different PSA ranges, enhancing diagnostic accuracy for clinically significant prostate cancer (csPCa) while reducing unnecessary biopsies.

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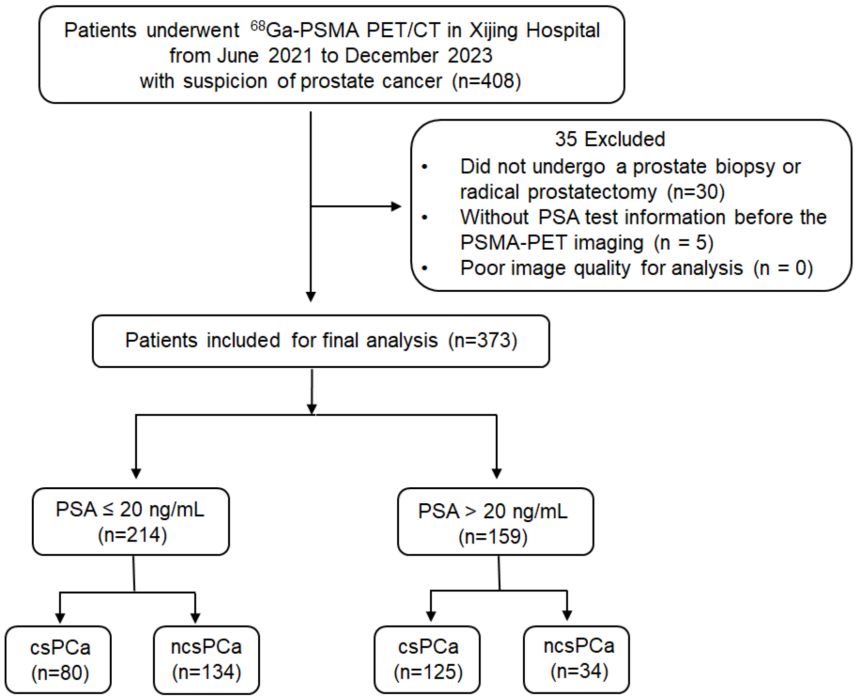

Figure 1. Descriptive flowchart of study. PSMA: PSA: prostate-specific antigen; csPCa: clinically significant prostate cancer; ncsPCa: non-clinically significant prostate cancer.

Materials and methods

Study population

Patients who underwent [^{68}Ga]Ga-PSMA-11 PET/CT in Xijing hospital for suspected prostate cancer between June 2021 and December 2023 were retrospectively enrolled. The exclusion criteria are as follows: (1) who did not receive a biopsy or radical prostatectomy; (2) without a PSA test before the PSMA-PET imaging; (3) poor image quality for analysis; The institutional review board approved this study and waived informed consent due to its retrospective nature. This study conformed with the Declaration of Helsinki and national regulations.

Imaging with [^{68}Ga] Ga-PSMA-11 PET/CT

Whole-body PET scans were obtained 60 min after intravenous injection of 1.8-2.2 MBq/kg [^{68}Ga]Ga-PSMA-11 according to the Joint EANM and SNMMI Procedure Guidelines [22]. Patients were instructed to drink plenty of water to accelerate tracer excretion and to void their bladders before the scan to clear the bladder and urethral activity. Low-dose CT scans (pitch 0.8, 50 mA, 120 kV [peak]) for PET attenuation were acquired (automatic mA, 120 keV, 512 × 512 matrix, 5-mm slice thickness, 1.0-s rotation time), followed by a PET scan with 5 bed positions (3 min/bed, from the head to the proximal thighs).

A suspicious lesion was defined as increased uptake in prostate regions that was higher than that of the background. For each lesion, the regions of interest were manually delineated, excluding areas of physiological urethral involvement. The SUV_{max} values were calculated from these regions of interest and the highest SUV_{max} value of all suspicious lesions was selected as the location of highest PSMA uptake and recorded for further analysis. The 5-level PRIMARY score was reviewed independently and blinded by two experienced board-certified nuclear medicine specialists according to the criteria in a previous study [13]. Any discrepancies were resolved by consensus with a third radiologist.

Histopathologic examination

Biopsy was performed via a transrectal ultrasound-guided 12-core systematic biopsy. For those who received radical prostatectomy, postoperative pathological result was used instead [23]. All pathology was processed and reported in accordance with 2014 International Society of Urological Pathology (ISUP) consensus guideline [24]. Clinically significant PCa was defined as the presence of any Gleason grade group (GG) ≥ 2 (Gleason score ≥ 3 + 4).

Statistical analysis

Continuous variables were present as median and interquartile ranges. Categorical variables were presented as frequencies and percentages. Receiver-operating characteristic curve analysis was performed to evaluate the diagnostic performance of the PRIMARY score, and a 95% CI was calculated as proposed by Obuchowski [25]. The optimal cutoff value was chosen using the Youden method. The area under the curve (AUC) was compared using the DeLong test. As previous reports, the proportion of unnecessary biopsies avoided was calculated as TN/(TN + FP) × 100%, and the proportion of csPCa cases missed was calculated as FN/(TP + FN) × 100%, where TP = true positives, TN = true negatives, FP = false positives, and FN = false negatives [15, 26]. Statistical analysis was performed using IBM SPSS statistics software, version 26.0. $P < 0.05$ was considered to indicate a significant difference.

Results

Patient characteristics

As shown in **Figure 1**, 373 patients were finally included in the study. The clinical characteristics are summarized in **Table 1**. In total, 56.8% (212/373) of patients were diagnosed by biopsy only, and 43.2% (161/373) were diagnosed through radical prostatectomy. In general, 57.4% (214/373) patients with PSA ≤ 20 ng/mL, and 42.6%

Table 1. Clinical characteristics of 373 patients

Characteristics	Numbers (range)
Age, y	68 (57-79)
PSA, ng/mL	
≤ 4	7 (1.9%)
4-10	113 (30.3%)
10-20	94 (25.2%)
20-50	87 (23.3%)
> 50	72 (19.3%)
PRIMARY score	
1	10 (2.7%)
2	132 (35.4%)
3	31 (8.3%)
4	64 (17.2%)
5	136 (36.5%)
Gleason grade group	
1	21 (5.6%)
2	32 (8.6%)
3	55 (14.7%)
4	63 (16.9%)
5	34 (9.1%)
csPCa	206 (55.2%)
Diagnostic Method	
Biopsy-only	212 (56.8%)
Prostatectomy	161 (43.2%)

(159/373) patients with PSA > 20 ng/mL. 55.2% (206/373) patients were diagnosed as csPCa in total. Of all patients, 61.9% (231/373) had a score of PRIMARY ≥ 3 and 53.6% (200/373) had a score of ≥ 4.

Relationship between PSA, PRIMARY score and csPCa

The proportion of csPCa increased with PSA (**Figure 2A**). The csPCa patients accounts for 37.4% (80/214) and 97.2% in the group of PSA ≤ 20 ng/mL and group of PSA > 50 ng/mL respectively (**Figure 2A-C**). While the proportion of csPCa in patients with PSA between 20 ng/mL and 50 ng/mL was 63.2% (55/87), indicating it is necessary to have additional differential diagnosis for these patients (**Figure 2A**). Moreover, as the PRIMARY score showed, the distribution of csPCa in each score was similar between the group of PSA ≤ 20 ng/mL and PSA > 20 ng/mL, except the group of 3 (**Figure 2D** and **2E**). The PRIMARY score of 5 (SUV_{max} > 12) 100% confirmed csPCa in both groups.

Diagnostic efficacy of PRIMARY score across different PSA ranges

As shown in **Table 2**, the PRIMARY scoring system exhibited a relatively high efficiency for identifying csPCa in both PSA ≤ 20 ng/mL and PSA > 20 ng/mL groups with the AUCs remaining at a high level of ≥ 0.85, suggesting a good generalizability of the PRIMARY score in patients with PSA > 20 ng/mL.

Regarding variability in selecting thresholds, as presented in **Table 2**, for patients with PSA ≤ 20 ng/mL, the AUC remains stable across the PRIMARY score threshold of 3 and 4, with values ranging from 0.87 to 0.91. Threshold of 3 shows higher screening sensitivity than threshold of 4 (89.2% *vs.* 80.7%). Conversely, for patients with PSA levels > 20 ng/mL, the AUC value increased from 0.85 to 0.98 once the threshold was set at 4 rather than 3. This enhancement is predominantly attributed to a marked increase in specificity, which rises from 70.6% to 91.2%, while sensitivity is maintained at a high level (99.2% to 98.4%).

Diagnostic performance of PRIMARY score in different PSA range

As detailed in **Table 3** and **Figure 3**, the analysis in this study concentrates on three PSA subgroups: 4-10, 10-20, and 20-50 ng/mL, due to the absence of positive results in patients with PSA < 4 ng/mL and the minimal negative results in patients with PSA > 50 ng/mL. The diagnostic performance in the 4-10 ng/mL and 10-20 ng/mL groups was comparable between a threshold of 3 and 4. The Youden index (YI) and AUC demonstrated minimal variation within these two PSA ranges, the difference is the threshold option of 3 has a greater improvement in the sensitivity for screening, while threshold option of 4 will improve the specificity of the identification for csPCa. In contrast, the diagnostic performance improved significantly as the threshold increased from 3 to 4 in the 20-50 ng/mL group. The Youden index (YI) increased markedly from 0.621 to 0.870, with corresponding AUCs rising from 0.84 (95% CI: 0.74-0.90) to 0.98 (95% CI: 0.92-0.99). The sensitivity analysis was conducted to patients with PSA 20-50 ng/mL, where radical prostatectomy confirmation was more frequent (64/87). At a threshold of 3, the sensitivity and specificity were 97.5% and 62.5%, respectively. When the threshold increased to 4, the sensitivity slightly decreased to 95.0%, whereas the specificity markedly improved to 91.7%, yielding an AUC of 0.867 (Supplementary Table 1). This enhancement was primarily attributed to a significant increase in specificity, while sensitivity remained stable. An illustrated case was presented in **Figure 4**.

Comparison of unnecessary biopsy rates

As shown in **Table 3**, neither a threshold value of 3 nor 4 impact the unnecessary biopsy rate in group of PSA < 4 ng/mL and group of PSA > 50 ng/mL. For PSA range of 4-10 ng/mL or 10-20 ng/mL, setting the threshold value at 4 would indeed reduce about 10% unnecessary biopsies, while result in 10% increase in missed csPCa cases when compared with a threshold of 3. Importantly, for PSA range of 20-50 ng/mL, a threshold of 4 could obviously avoid unnecessary biopsy (90.6% *vs.* 68.8%) at the cost of only 1.8% increase in missed csPCa cases when compared with a threshold of 3.

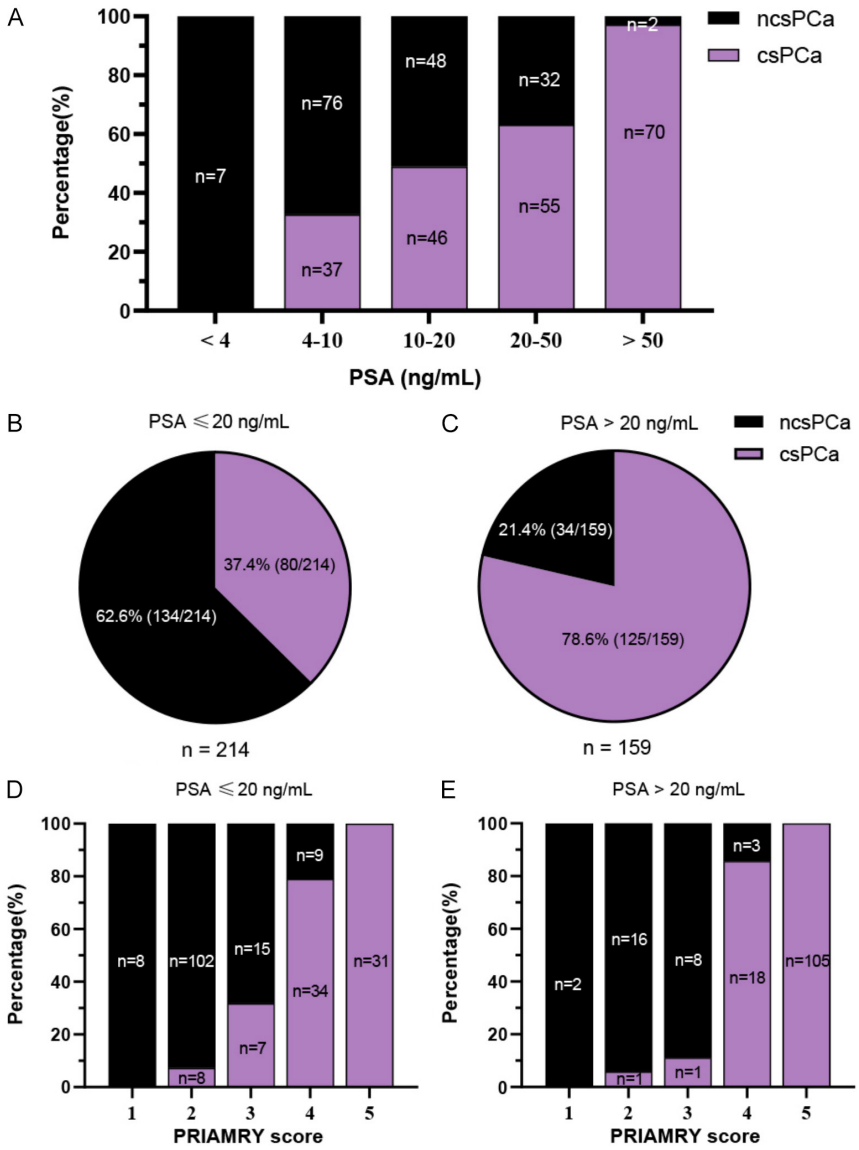

Figure 2. (A) Distribution of csPCa and ncsPC at stratified PSA levels (ng/mL). Proportion of csPCa and ncsPCa in patients of PSA levels ≤ 20 ng/mL (B) and > 20 ng/mL (C). Proportion of csPCa and ncsPCa in different PRIMARY score in patients of PSA levels ≤ 20 ng/mL (D) and > 20 ng/mL (E). csPCa: clinically significant prostate cancer; ncsPCa: non-clinically significant prostate cancer; PSA prostate-specific antigen.

Disscussion

To the best of our knowledge, this is the first study to systematically evaluate the performance of PSMA-PET imaging and the PRIMARY score across different PSA ranges. Two main findings yielded in this study. Firstly, the PRIMARY score based on ^{68}Ga-PSMA PET/CT imaging is useful in the diagnosis of csPCa across different PSA ranges. Secondly, the optimal threshold of the PRIMARY score potentially variable in different PSA ranges, a threshold of 3 for PSA ≤ 20 ng/mL and a threshold of 4 for PSA > 20 ng/mL respectively demonstrating favorable diagnostic performance.

PSA screening is widely used for the early detection of PCa, and PSA > 20 ng/mL was generally defined as "high-risk" of prostate cancer thereby recommending a biopsy [27]. Previous reports suggested about 12%-15% patients with PSA over 20 ng/mL in the USA [16, 17]. In this Chinese database, 42.6% of patients had a PSA level greater than 20 ng/mL. Notably, 36.8% of patients with PSA levels of 20-50 ng/mL were diagnosed with ncsPCa. This finding aligns with data from Thailand and Kuwait, where approximately 52% of patients had ncsPCa. The high proportion of ncsPCa patients with elevated PSA levels is a distinctive feature in Asian populations, potentially due to genetic and environmental differences between Asian and Western populations [19, 21, 28]. Thus, it is necessary to have an additional diagnosis for Asian male with PSA > 20 ng/mL before a biopsy.

In recent years, the PRIMARY scoring system based on ^{68}Ga-PSMA PET imaging showed high diagnostic accuracy for diagnosis csPCa in male with abnormal PSA ≤ 20 ng/mL [13]. Subsequently, we and other groups revealed it was superior to MRI based PI-RADS scoring for detecting csPCa [13, 14, 26, 29, 30]. In this study, we extended our analysis to populations with varying PSA levels and observed comparable diagnostic performance overall. Notably, the most significant improvement was seen in the 20-50 ng/mL group compared to lower PSA ranges, suggesting the broad applicability of the PRIMARY score.

Previous study defined PRIMARY score of 3 as the threshold for discriminating csPCa. Consistently, we found, for the patients with PSA ≤ 20 ng/mL (either in "gray zone" group of 4-10 ng/mL or higher group of 10-20 ng/mL), a threshold of 3 could achieve higher screening sensitivity than a threshold of 4. Thus, from the perspective of highly-sensitive screening, threshold of 3 is proper for PSA ≤ 20 ng/mL whatever in Western or Asia country. Interestingly, for patients with PSA of 20-50 ng/mL, though a threshold of 3 could avoid 70.6% unnecessary biopsies, setting threshold at 4 could significantly improve the specificity (90.6% *vs.* 68.8%) meanwhile maintaining a high level of sensitivity (98.3% *vs.* 96.4%) when compared with a threshold of 3. Consequently, 91.2% patients could avoid unnecessary biopsies at the expense of missing only 1.6% csPCa cases. The reasons underlying these observations remain unclear. However, it is suspected that the high incidence of csPCas in the peripheral zone and the high prevalence of benign prostate lesions in the transitional zone among patients with PSA of 20-50 ng/mL may

Table 2. Performance of the PRIMARY score with a threshold of 3 or 4 in patients with PSA levels ≤ 20 and > 20 ng/mL

PSA	≤ 20 ng/mL (n = 214)		> 20 ng/mL (n = 159)	
Threshold	3	4	3	4
AUC	0.87 (0.80-0.90)	0.91 (0.87-0.95)	0.85 (0.78-0.90)	0.98 (0.95-0.99)
Sensitivity	89.2 (80.4-94.9)	80.7 (70.6-88.6)	99.2 (95.6-100.0)	98.4 (94.3-99.8)
Specificity	82.2 (74.7-88.3)	93.3 (87.7-96.6)	70.6 (52.5-84.9)	91.2 (76.3-98.1)
PPV	75.5 (68.0-81.7)	88.2 (79.7-93.4)	92.5 (88.0-95.4)	97.6 (93.3-99.2)
NPV	92.5 (86.9-95.8)	88.7 (83.5-92.5)	96.0 (77.1-99.4)	93.9 (79.6-98.4)

Data are percentages, with 95% CIs in parentheses. CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; AUC area under the curve.

Table 3. Performance of the PRIMARY score with a threshold of 3 or 4 in patients with stratified PSA levels

PSA (ng/mL)	Threshold	Sensitivity%	Unnecessary biopsies avoided (%)	csPCa cases missed (%)	PPV%	NPV%	AUC
< 4.0 (n = 7)	3	100 (7/7)	-	0	100 (7/7)	-	-
	4	100 (7/7)	-	0	100 (7/7)	-	-
4.0-10.0 (n = 113)	3	89.2 (33/37)	81.6 (62/76)	10.8 (4/37)	70.2 (33/47)	93.9 (62/66)	0.85 (0.78-0.91)
	4	78.4 (29/37)	92.1 (70/76)	21.6 (8/37)	82.9 (29/35)	89.7 (70/78)	0.87 (0.79-0.92)
10.0-20.0 (n = 94)	3	89.1 (41/46)	85.4 (41/48)	10.9 (5/46)	85.4 (41/48)	89.1 (41/46)	0.87 (0.83-0.94)
	4	82.6 (38/46)	93.8 (45/48)	17.4 (8/46)	92.7 (38/41)	84.9 (45/53)	0.92 (0.85-0.97)
20.0-50.0 (n = 87)	3	98.3 (54/55)	68.8 (22/32)	1.8 (1/55)	84.4 (54/64)	95.7 (22/23)	0.84 (0.74-0.90)
	4	96.4 (53/55)	90.6 (29/32)	3.6 (2/55)	94.6 (53/56)	93.5 (29/31)	0.98 (0.92-0.99)
> 50.0 (n = 72)	3	100 (70/70)	100 (2/2)	0 (0/70)	100 (70/70)	100 (2/2)	1.00 (0.95-1.00)
	4	100 (70/70)	100 (2/2)	0 (0/70)	100 (70/70)	100 (2/2)	1.00 (0.95-1.00)

Data are percentages, with 95% CIs in parentheses. CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; AUC area under the curve.

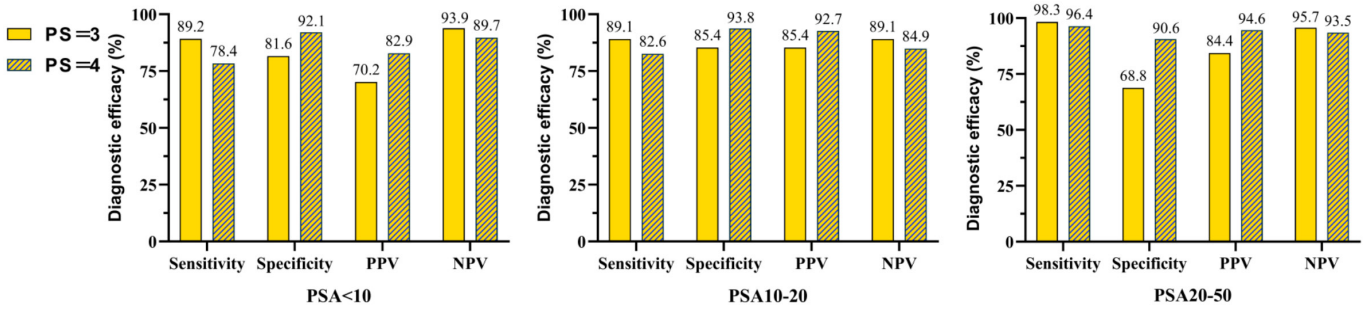

Figure 3. Bar chart showing the diagnostic efficacy of the PRIMARY score within stratified PSA levels (ng/mL) at threshold of 3 and 4. PS: PRIAMRY score; PSA: prostate-specific antigen; PPV: positive predictive value; NPV: negative predictive value.

be interrelated [31, 32]. Therefore, the optimal threshold of the PRIMARY score may vary across different PSA ranges in Asian populations. Physicians need to select the appropriate PRIMARY threshold for specific PSA levels to balance the benefits of high screening efficiency and the need for necessary biopsies.

Another important finding in this study was that choosing a threshold of 3 or 4 did not impact the performance of PRIMARY score in patients with PSA > 50 ng/mL. Though the using of PSMA-PET imaging could further support the diagnosis of csPCa, only 2.8% diagnosis were finally rectified. Considering the high incidence of csPca (97.2%) in these population, a direct biopsy is recommended for csPca differentiation. Thereby, we suggested the application of PRIMARY score could be detailed to the patients with PSA ranges from 4 to 50 ng/mL. Collectively, the PRIMARY score is a promising tool for identifying csPCa and reducing unnecessary invasive biopsy in Asian whose PSA range from 4 ng/mL to 50 ng/mL.

There are also some limitations in this study. First, it was a retrospective, single-center study in China, the present results should be further validated in multicenter among Asia countries with a larger number of patients. Second, a large-scale study with 17,598 cases indicated that 55.7% of biopsy GG1 patients have experienced GG upgrading after RP [33]. In this study, radical prostatectomy was not performed on all individuals, may lead to bias in pathological results in a small number of patients.

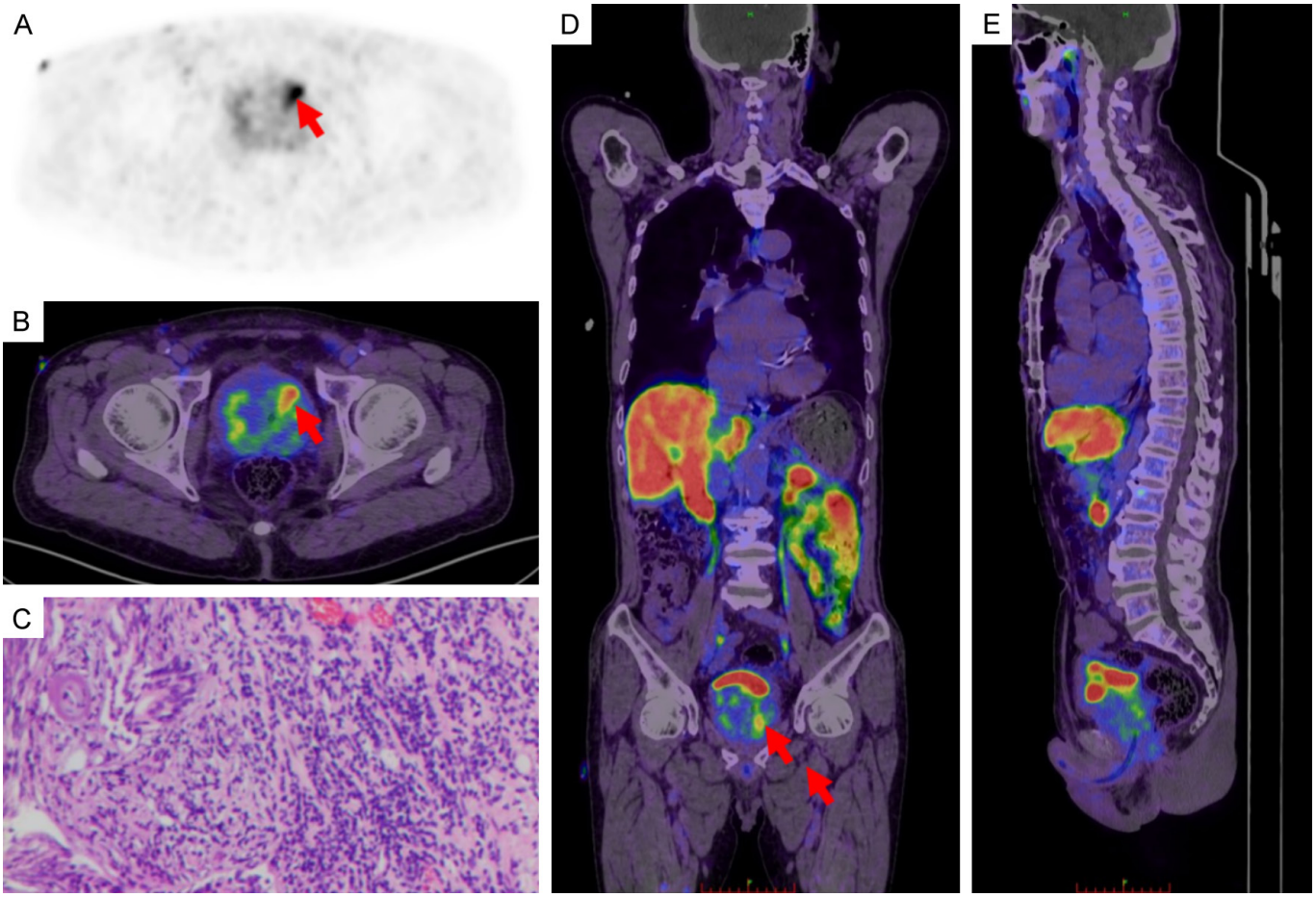

Figure 4. A 72-year-old male with total serum PSA level of 28.7ng/mL. The corresponding [^{68}Ga]Ga-PSMA-11 PET/CT imaging revealed a focal PSMA activity lesion (red arrow) involving the left transitional zone of the prostate (SUV_{max} = 8.3) (A, B, D and E), defined as PRIMARY score 3. (C) The histopathology confirmed the focal lesion as benign nodules with inflammatory cell infiltration. CD68(KP1)(+), CK8/18(-), 34βE1(+), Ki-67(10%), P504S(+), P63(+), PSA(+).

In conclusion, across different PSA ranges, the PRIMARY score based on ^{68}Ga-PSMA PET/CT imaging is useful in the diagnosis of csPCa. A threshold of 3 for PSA ≤ 20 ng/mL and a threshold of 4 for 20 ng/mL < PSA ≤ 50 ng/mL respectively demonstrated favorable diagnostic performance.

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Written informed consent obtained from each patient prior to enrollment.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Performance of the PRIMARY score at thresholds 3 and 4 among prostatectomy patients with PSA levels of 20-50 ng/mL

PSA	20-50 ng/mL (n=64)	
Threshold	3	4
AUC	0.80 (0.69-0.92)	0.97 (0.89-0.99)
Sensitivity	97.5 (86.8-99.9)	95.0 (83.1-99.4)
Specificity	62.5 (40.6-81.2)	91.7 (73.0-99.0)