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Which PSMA PET/CT interpretation criteria most effectively diagnose prostate cancer? a retrospective cohort study

Le Ma[1*], Yaxin Hao[1], Luoping Zhai[1], Wanchun Zhang[1*], Xiaoming Cao[2] and Kaiyuan Jia[2]

Abstract

Background PSMA PET/CT emerges as a pivotal technology in the diagnostic landscape of prostate cancer (PCa). It offers a suite of imaging interpretation criteria, notably the maximum standardized uptake value (SUVmax), the molecular imaging prostate-specific membrane antigen score (miPSMA score), and the PSMA reporting and data system (PSMA-RADS). Identifying the most valuable criteria for diagnosing PCa and standardizing imaging interpretation across various tracers is an unresolved question. Our study endeavors to pinpoint the most optimal criteria to enhance the precision of PCa diagnosis, encompassing clinically significant PCa (csPCa), by evaluating the consistency and diagnostic accuracy of these three criteria using two [^{18}F]-labeled PSMA tracers.

Method This retrospective analysis spans a five-year period, focusing on patients with clinically suspected or newly diagnosed, treatment-naïve PCa who underwent ^{18}F-PSMA PET/CT. The study is bifurcated into two segments: 1.A direct comparison assessing the consistency in SUVmax, miPSMA scores, and PSMA-RADS among PSMA PET/CT tracers ([^{18}F]DCFPyL and [^{18}F]PSMA-1007) for prostate foci in 24 patients. 2. An analysis of the diagnostic accuracy of these three criteria for both PCa and csPCa across 55 [^{18}F]DCFPyL and 65 [^{18}F]PSMA-1007 PET/CT scans, respectively.

Results 1.Our head-to-head study reveals that SUVmax and miPSMA score exhibit near-perfect consistency, with PSMA-RADS demonstrating substantial consistency. 2. The diagnostic accuracy ranking, considering both PCa and csPCa, stands as miPSMA score ≈ SUVmax > PSMA-RADS for [^{18}F]DCFPyL PET/CT, contrasting with miPSMA score > SUVmax ≈ PSMA-RADS for [^{18}F]PSMA-1007 PET/CT.

Conclusion The miPSMA score outperforms SUVmax and PSMA-RADS in terms of inter-tracer consistency and diagnostic accuracy for the detection of PCa, including csPCa, when comparing [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT scans. This underscores the miPSMA score's potential as a robust criterion for PCa and csPCa diagnosis, holding substantial promise for refining clinical decision-making and patient management strategies.

Clinical trial number not applicable.

Keywords Prostate-specific membrane antigen, Prostate cancer, PET/CT, miPSMA score, PSMA-RADS

*Correspondence:
Le Ma
male19890830@126.com
Wanchun Zhang
zhang_wanchun@126.com

[1]Department of Nuclear Medcine, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan 030032, China
[2]Department of Urology, The First Hospital of Shanxi Medical University, Taiyuan 030000, China

Introduction

Prostate cancer (PCa) is the most common malignancy in men and the second most common cause of cancer-specific mortality [1]. Within this spectrum, clinically significant prostate cancer (csPCa)(Inter-national Society of Urological Pathology grade group ≧ 2), known for its elevated risks of progression and potential lethality, stands out as a critical focus in diagnostic and therapeutic endeavors. The precision in diagnosing and staging PCa is paramount for enhancing patient care and guiding treatment strategies.

Prostate-specific membrane antigen (PSMA), a transmembrane protein located in prostate epithelial cells, is markedly overexpressed in nearly all PCa cells, with levels ranging 100 to 1,000 times higher than normal prostate tissue. This overexpression is linked to the aggressiveness of the tumor(2–3), making PSMA an ideal biomarker for PCa detection and management. PSMA positron emission tomography/ computer tomography (PET /CT), a molecular imaging modality targeting PSMA, merges molecular and morphological data to provide a comprehensive diagnostic profile. Over the past decade, the adoption of PSMA PET/CT has surged globally, solidifying its role in the initial diagnosis, staging, image-guided biopsy, monitoring of biochemical recurrence, delineating the radiotherapy target area, and assessing treatment efficacy. This widespread application is underpinned by extensive research, culminating in its endorsement within clinical guidelines [4–13].

However, the interpretation of PSMA PET/CT presents challenges due to the diversity of criteria, including the maximum standardized uptake value (SUVmax), the PSMA reporting and data system (PSMA-RADS), and the molecular imaging prostate-specific membrane antigen scoring system (miPSMA score). While SUVmax serves as a common semi-quantitative measure, its variability across different tracers(such as [^{68}Ga]PSMA-11, [^{68}Ga]PSMA-617, [^{18}F]DCFPyL, and [^{18}F]PSMA-1007)) poses a significant challenge. The SUVmax threshold for PCa diagnosis varies widely across studies, lacking a unified reference standard [14–17]. In response to this, standardized visual criteria such as PSMA-RADS and miPSMA score were introduced in 2018 to harmonize imaging outcomes. The PSMA-RADS [18] scale, ranging from 1 to 5, quantifies the probability of PCa presence by assessing the lesion's radioactive uptake and anatomical features. However, this approach is somewhat ambiguous, primarily relying on the experience of the readers, which introduces a significant degree of subjectivity in practical application. In contrast, the miPSMA score [19, 20] quantifies the likelihood of PCa presence on a scale from 0 to 3. This is based on the relative metabolic activity of prostate lesions compared to the parotid gland, blood pool, liver, or spleen. This method, while offering a more objective scoring system for PSMA expression, does have its limitations. It does not fully account for the anatomical characteristics of the lesions, which is a critical aspect in the comprehensive assessment of PCa.

The quest to identify the most valuable interpretation criteria for diagnosing PCa, particularly csPCa, and to standardize imaging interpretation across various tracers remains unresolved. Our study addresses this gap by comparing the consistency and diagnostic accuracy of SUVmax, miPSMA score, and PSMA-RADS under two [^{18}F]-labeled PSMA tracers: [^{18}F]DCFPyL and [^{18}F]PSMA-1007. This comparative analysis aims to pinpoint the optimal criteria, thereby enhancing the accuracy of PCa diagnosis and guiding future clinical practice.

Materials and methods

Patients

In this retrospective study, consecutive patients from May 2019 to November 2024 with clinically suspected PCa or newly diagnosed treatment-naive PCa who underwent PSMA PET /CT in our hospital were enrolled. Cases without complete prostate pathological results, without accurate PSA, had prostate pathology associated with other malignant tumors, or had a history of other malignant tumors were excluded.

A total of 96 patients were included in the study, of which 24 received both [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT within one week, 31 only received [^{18}F]DCFPyL PET/CT and 41 only received [^{18}F]PSMA-1007 PET/CT, resulting in a total of 55 [^{18}F]DCFPyL PET/CT scans and 65 [^{18}F]PSMA-1007 PET/CT scans.

Study design

The study was divided into two parts. Part (I) Head-to-head comparison of the consistency in SUVmax, miPSMA scores, and PSMA-RADS between PSMA PET/CT scans ([^{18}F]DCFPyL and [^{18}F]PSMA-1007) for prostate foci in 24 patients. Part (II) Analysis of the diagnostic accuracy of the three criteria for PCa in 55 [^{18}F]DCFPyL and 65 [^{18}F]PSMA-1007 PET/CT scans, respectively.

The reference standard utilized was prostate pathology, with a particular emphasis on pathology derived from radical prostatectomy. For those patients who had not undergone radical prostatectomy, biopsy pathology was adopted as the reference standard.

This study complies with the Declaration of Helsinki, ensuring the anonymity and security of data, and has been approved by the Ethics Committee of Shanxi Bethune Hospital (approval number: YXLL-2024-196). Informed consent was obtained from each participants through a mail-based process.The flowchart for participant enrollment and the study design were presented in Fig. 1.

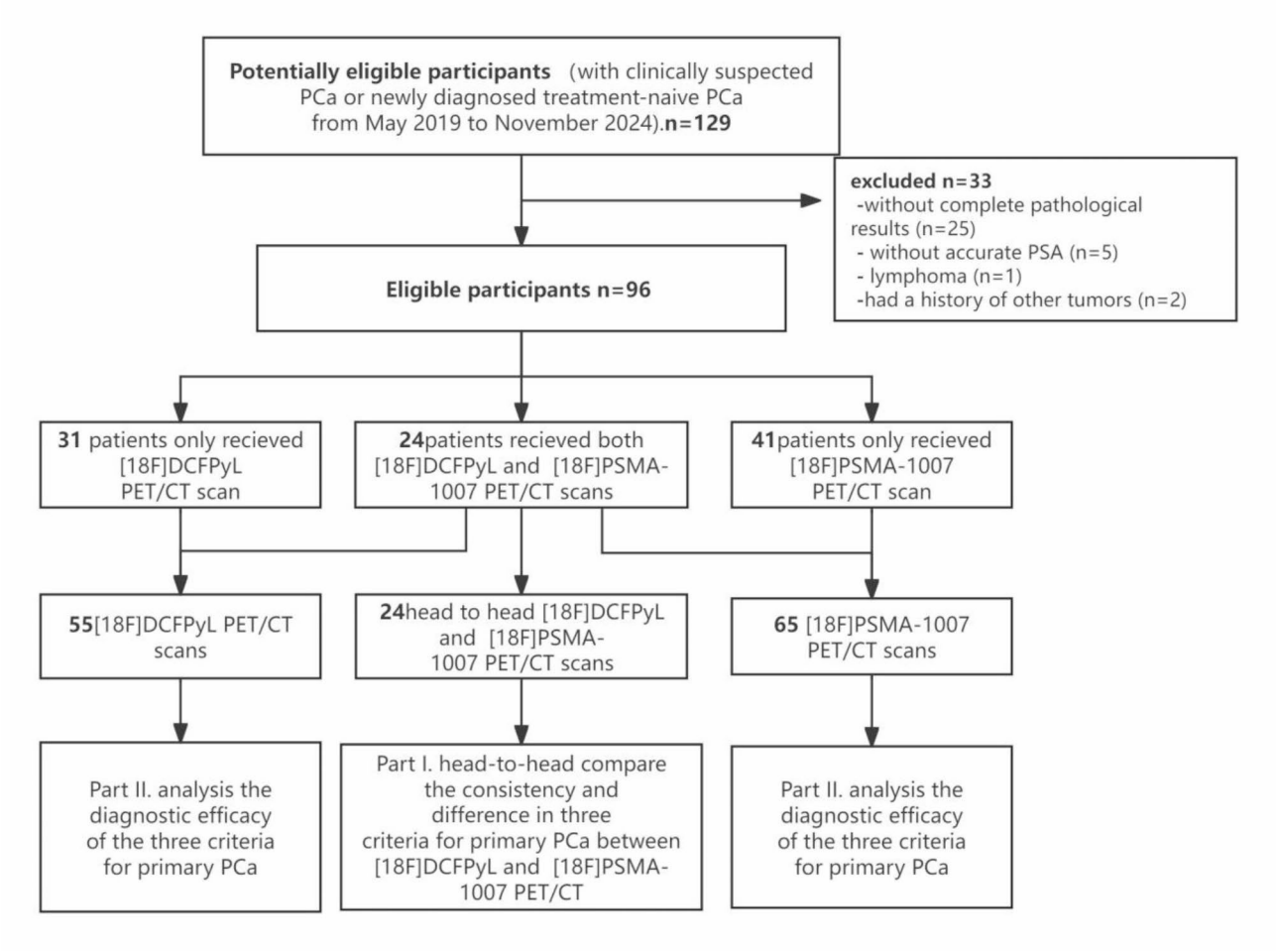

Fig. 1 Diagram of the study design

[18F]-PSMA PET/CT imaging

The injection activity of [^{18}F]DCFPyL and [^{18}F]PSMA-1007 had an average of 4.44 MBq/kg body weight. Image acquisition on a GE Discovery PET/CT Elite scanner (General Electric Company, USA) began about 90 min after injection of [^{18}F]DCFPyL and 120 min for [^{18}F] PSMA-1007. Standard whole-body acquisitions were performed from the base of the skull to the proximal thigh with an acquisition time of 1.5 min per bed position (8–9 beds in total), and the images were reconstructed in a 128 × 128 matrix with a pixel size of 5.5 mm and a slice thickness of 3.3 mm. The reconstruction method was VUE Point FX, which uses time-of-flight information and includes a fully 3-dimensional ordered-subsets expectation maximization (OSEM) algorithm with 2 iterations, 32 subsets, and a filter cutoff of 6.4 mm. The same reconstruction parameters were used for both radiotracers. A CT scan was performed using the following parameters: tube voltage of 140 kV, tube current of 300 mA, and section thickness of 3.75 mm. The CT data were used for attenuation correction.

Scan assessment and interpretation

The PSMA PET/CT images were independently evaluated by three experienced nuclear medicine physicians (Reader 1, Reader 2, and Reader 3), with each reader focusing on a set of interpretation criteria. Reader 1 assessed the images based on SUVmax values, Reader 2 utilized the miPSMA scoring system, and Reader 3 applied the PSMA-RADS criteria. All readers were blinded to the patients' clinical data. The imaging interpretation criteria are as follows:

SUVmax: As the study aim to obtain standardized results, we set a unified diagnostic threshold of 8.62 for PCa and csPCa both in [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT. The PSMA-positive prostate lesion with a SUVmax > 8.62 was considered to be PCa (or csPCa); otherwise, it was classified as a benign prostate disease (BPD) (or non-csPCa (including PCa (Gleason score 3 + 3) and BPD)).

miPSMA score: According to PROMISE V2 [20], the miPSMA scores are: 0, no expression (equal to or below blood pool); 1, low (above blood pool and lower than

or equal to liver); 2, intermediate (above liver and lower than or equal to parotid gland); 3, high (above parotid gland). For [^{18}F]PSMA-1007, the spleen is recommended as the reference organ instead of the liver. A score of 2–3 points was was considered indicative of PCa (or csPCa), while a score of 0–1 was considered indicative of BPD (or non-csPCa).

PSMA-RADS : According to PSMA-RADS V1 [18], the PSMA-RADS scores are: 1, with or without radiotracer uptake and definitively benign; 2, with low levels of radiotracer uptake and likely to be benign; 3, with equivocal radiotracer uptake; 4, with high radiotracer uptake but lacking a definite anatomic abnormality; 5, with high levels of radiotracer uptake and corresponding anatomic findings. A score of 4–5 points was considered to indicate a PCa (or csPCa) while a score of 1–2 indicated BPD (or non-csPCa). The physicians rating the lesions were recommended to avoid a score of 3, which might have been ambiguous.

Statistical analysis

Continuous variables with normal distribution were presented as mean ± SD, and non-normally distributed variables as median (IQR). Categorical variables were expressed as frequencies (%). Group comparisons for normally distributed variables were made using the independent samples t-test, and categorical data were compared using chi-square. Paired T-tests assessed diagnostic consistency and inter-group differences in continuous variables, while the paired rank sum test and weighted Kappa analyzed categorical variables (ICC and κ values indicated poor agreement at < 0.4, moderate 0.4–0.59, substantial 0.6–0.79, and almost-perfect 0.8–1). Diagnostic effectiveness was evaluated using sensitivity, specificity, mistake diagnostic rate, omission diagnostic rate, positive predictive value, negative predictive value, Youden index, receiver operator characteristic curve (ROC curve), and area under the ROC curve (AUC).

ICCs and weighted Kappa were calculated utilizing IBM SPSS software (version 27.0). The remaining statistical analyses were performed with Free Statistics software (Version 2.0, Beijing, China). A P value < 0.05 was considered statistically significant.

Results

Patients clinical characteristics was shown in Table 1. Of the 96 patients, 16 underwent radical prostatectomy with postoperative pathology serving as the reference standard, and the remaining 80 had biopsy pathology as the reference standard.

Head-to-head comparison of the consistency

In the 24 [^{18}F]DCFPyL and 24 [^{18}F]PSMA-1007 PET/CT scans, the average SUVmax of the prostate lesions was 13.94 ± 7.25 and 16.94 ± 7.38, respectively. This showed excellent agreement (ICC = 0.89).

For the miPSMA scores, 21 cases were consistent, including 6 cases with score 1, 7 cases with score 2, and 8 cases with score 3. Three cases were inconsistent, including 2 cases with score 2 in the [^{18}F]DCFPyL scan, but a score 1 in the [^{18}F]PSMA-1007 PET/CT scan, while 1 case had score 3 in the [^{18}F]DCFPyL scan, but score 2 in the [^{18}F]PSMA-1007 PET/CT scan. There was almost perfect agreement (Kappa = 0.81) .

For the PSMA-RADS, 21 cases were consistent, including 3 cases with score 2, 15 cases with score 4, and 3 cases with score 5. Three cases were inconsistent, with all having score 2 in the [^{18}F]DCFPyL scan, but score 4 in the [^{18}F]PSMA-1007 PET/CT scan. There was substantial agreement (Kappa = 0.74) .

The results are shown in Table 2; Figs. 2 and 3.

Table 1 Patients' clinical characteristics

			[^{18}F]DCFPyL+[^{18}F]PSMA-1007 group (n = 24)	[^{18}F]DCFPyL group (n = 55)	[^{18}F]PSMA-1007 group (n = 65)	P value
Age (yr), mean ± SD			68.33 ± 7.93	68.47 ± 8.34	69.02 ± 7.53	0.71
tPSA (ng/mL), median(IQR)			20.55 (8.34, 121.93)	27.30 (9.7, 116.68)	19.20 (9.35, 78.05)	0.86
Prostate Volume (mL), median(IQR)			48.32 (28.80, 51.94)	47.29 (29.84, 53.00)	47.29 (31.72, 55.78)	0.83
Pathology, n(%)	BPD		6 (25.00%)	11 (20.00%)	15 (23.08%)	0.68
	PCa		18 (75.00%)	44 (80.00%)	50 (76.92%)	
	Gleason score	3 + 3	3 (16.67%)	4 (9.09%)	4 (8.00%)	0.87
		3 + 4	0 (0)	5 (11.36%)	2 (4.00%)	
		4 + 2	0 (0)	0 (0)	1 (2.00%)	
		4 + 3	0 (0)	4 (9.09%)	6 (12.00%)	
		4 + 4	3 (16.67%)	7 (15.91%)	8 (16.00%)	
		4 + 5	6 (33.33%)	9 (20.45%)	13 (26.00%)	
		5 + 4	3 (16.67%)	8 (18.18%)	8 (16.00%)	
		5 + 5	3 (16.67%)	7 (15.91%)	8 (16.00%)	

PCa: Prostate Cancer; BPD: benign prostate diseases. The P value reflects the difference between [^{18}F]DCFPyL group and [^{18}F]PSMA-1007 group

Table 2 Head-to-head comparison of the inter-tracer consistency of the three interpretation criteria

		[18F]DCFPyL	[18F]PSMA-1007	*P* value	ICC/ weighted Kappa
SUVmax, mean ± SD		13.94 ± 7.25	16.94 ± 7.38	< 0.001	0.89*
miPSMA score, n	0	0	0	0.08	0.81*
	1	6	8		
	2	9	8		
	3	9	8		
PSMA-RADS, n	1	0	0	0.08	0.74**
	2	5	3		
	3	0	0		
	4	16	18		
	5	3	3		

*almost-perfect agreement; **substantial agreement

Evaluating the diagnostic accuracy in [18F]DCFPyL PET/CT

In the [18F]DCFPyL group, 55 cases were analyzed, of which 44 were diagnosed pathologically as PCa and 11 as BPD. Additionally, of which 40 were identified as csPCa and 15 as non-csPCa.

The respective primary PCa diagnostic accuracy parameters for SUVmax, miPSMA score, and PSMA-RADS were as follows: sensitivity 95.45%, specificity 90.91%, 90.91%, and 81.82%, Accuracy 94.55%, 94.55%, and 92.73%, and AUC 96.49% (91.54%, 100%), 96.28 (91.88%, 100%), and 89.87% (80.40%, 99.35%) (Table 3). The ROC curve is shown in Fig. 4a. Using prostate pathology as the reference standard, the optimal diagnostic threshold of SUVmax was 9.24.

The respective csPCa diagnostic accuracy parameters for SUVmax, miPSMA score, and PSMA-RADS were as follows: sensitivity 97.50%, specificity 73.33%, 73.33%, and 66.67%, Accuracy 92.73%, 92.73% and 89.09%, and

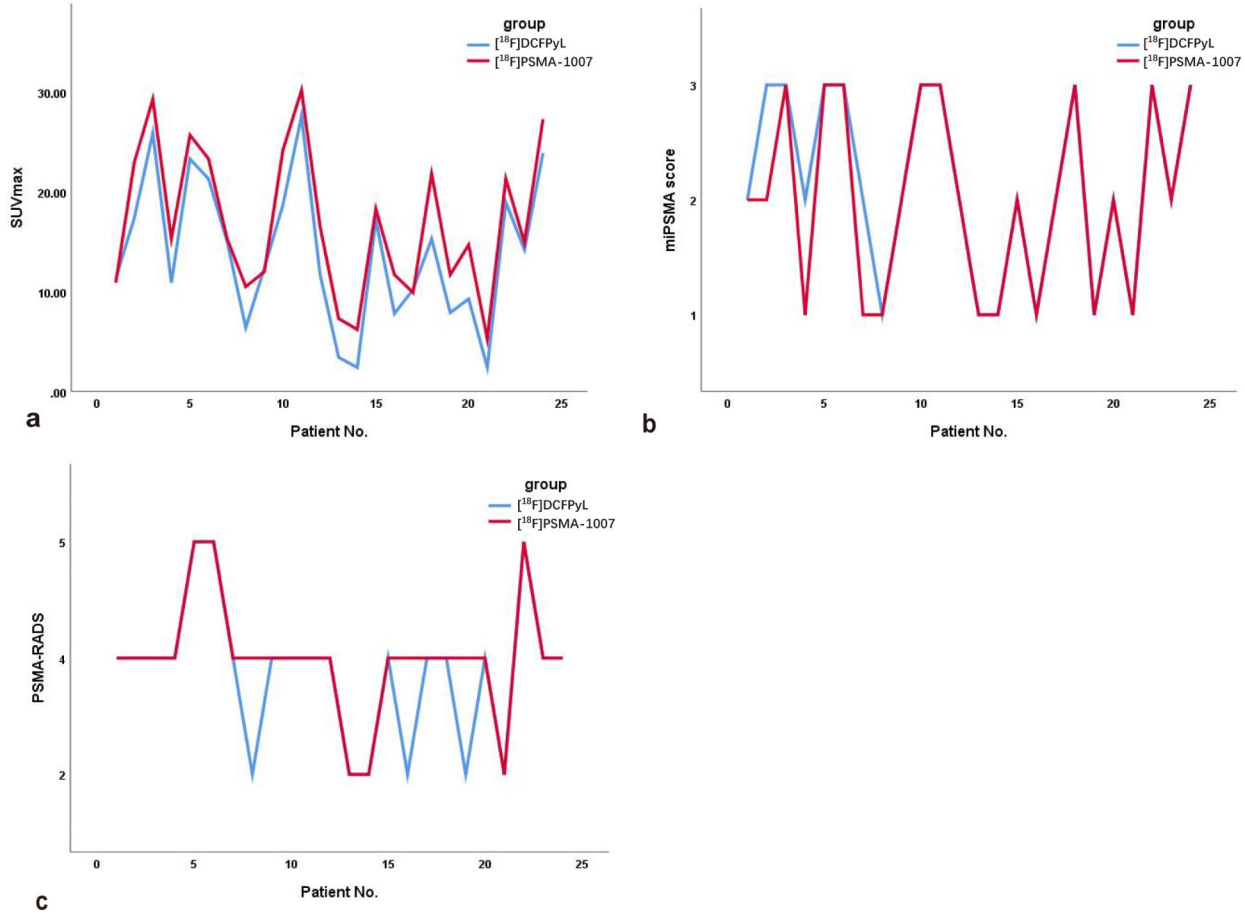

Fig. 2 Head-to-head comparison of the diagnostic results of the three criteria. Legend: In a head-to-head comparison across 24 patients, three interpretation criteria were evaluated for their diagnostic results: SUVmax (Panel a), miPSMA (Panel b), and PSMA-RADS (Panel c). The comparison was made between the results obtained from [18F]DCFPyL PET/CT scans (blue line) and [18F]PSMA-1007 PET/CT scans (red line). Panel a demonstrates an excellent agreement and a significant difference in SUVmax between the two groups. Panel b shows an almost perfect agreement and no significant difference in miPSMA score between the two groups. Panel c illustrates a considerable difference in PSMA-RADS scores, indicating a divergence in diagnostic classification when using the two tracers

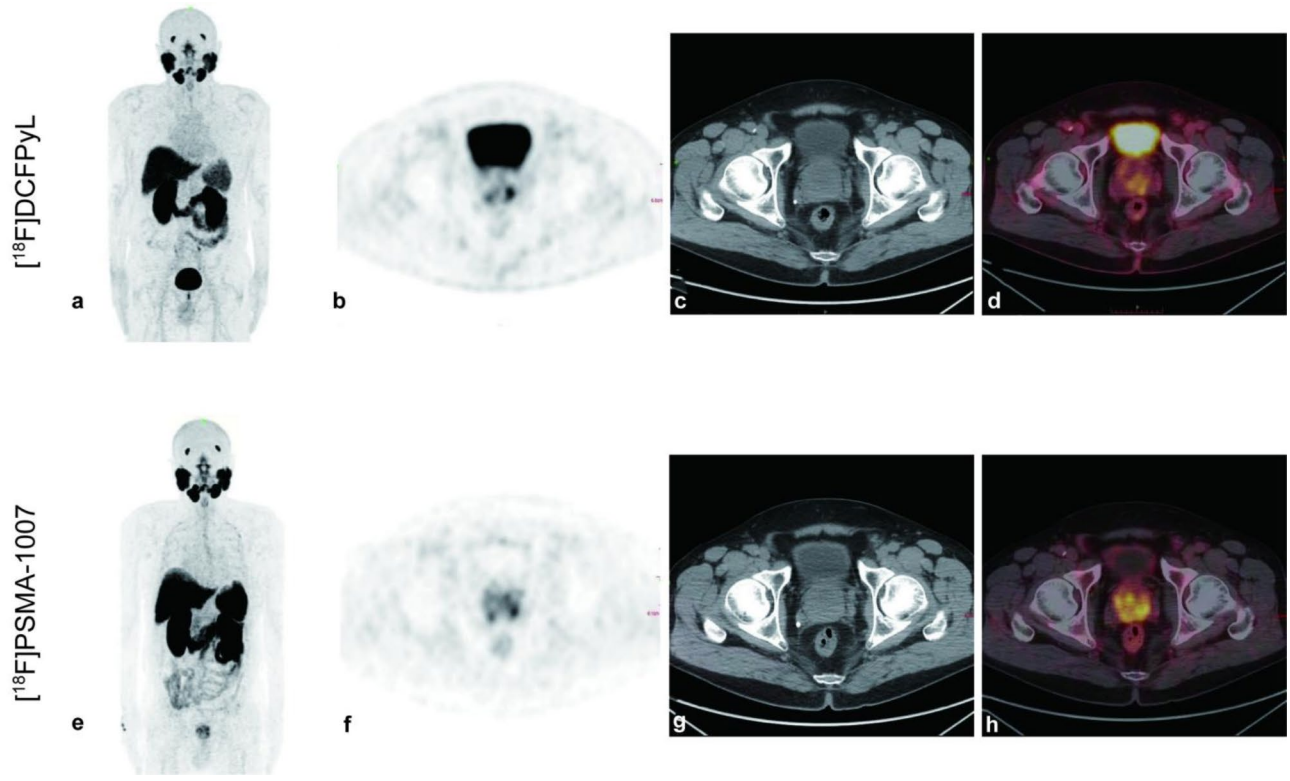

Fig. 3 A case of an inconsistent imaging diagnostic result in the [^{18}F]DCFPyL+[^{18}F]PSMA-1007 group. Legend: A patient with clinically suspected PCa (total PSA serum-level of 11.9 ng/mL) was examined using [^{18}F]DCFPyL (**a**-**d**) and [^{18}F]PSMA-1007 (**e**-**h**) PET/CT scans. Prostatic hyperplasia with focal low-grade neoplasia of glands was finally diagnosed by systematic transrectal ultrasonography-guided 18-core biopsy. The results of the [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT scans were as follow: SUVmax of the prostate lesion were 6.39 (true negative) and 10.9 (false positive), miPSMA score were both 1 (true negative), and PSMA-RADS were 2 (true negative) and 4 (false positive), respectively

Table 3 The diagnostic efficacy parameters of the three criteria for PCa in the [^{18}F]DCFPyL PET/CT

[^{18}F]DCFPyL group ($n=55$)	SUVmax		miPSMA score		PSMA-RADS	
Pathology	**Positive ($n=43$)**	**Negative ($n=12$)**	**Positive ($n=43$)**	**Negative ($n=12$)**	**Positive ($n=44$)**	**Negative ($n=11$)**
PCa ($n=44$)	42	2	42	2	42	2
BPD ($n=11$)	1	10	1	10	2	9
Sensitivity (95% CI)	95.45% (89.30%, 100%)		95.45% (89.30%, 100%)		95.45% (89.30%, 100%)	
Specificity (95% CI)	90.91% (73.92%, 100%)		90.91% (73.92%, 100%)		81.82% (59.03%, 100%)	
Accuracy (95% CI)	94.55% (88.55%, 100%)		94.55% (88.55%, 100%)		92.73% (85.87%, 99.59%)	
Mistake diagnostic rate (95% CI)	9.09% (0%, 26.08%)		9.09% (0%, 26.08%)		18.18% (0%, 40.97%)	
Omission diagnostic rate (95% CI)	4.55% (0%, 11.21%)		4.55% (0%, 11.21%)		4.55% (0%, 11.21%)	
Positive predictive value (95% CI)	97.67% (93.16%, 100%)		97.67% (93.16%, 100%)		95.45% (89.30%,100%)	
Negative predictive value (95% CI)	83.33% (62.24%, 100%)		83.33% (62.24%, 100%)		81.82% (59.03%, 100%)	
Youden Index (95% CI)	86.36% (77.29%, 95.43%)		86.36% (77.29%, 95.43%)		77.27% (66.19%, 88.35%)	
AUC (95% CI)	96.49% (91.54%, 100%)		96.28% (91.88%, 100%)		89.87% (80.40%, 99.35%)	

PCa: Prostate Cancer; BPD: benign prostate diseases

AUC 95.17% (89.66%,100%), 95.42% (90.93%, 99.90%), and 87.58% 78.66%, 96.51%) (Table 4). The ROC curve is shown in Fig. 4c. Using prostate pathology as the reference standard, the optimal diagnostic threshold of SUVmax was 11.35.

Regardless of whether it is diagnosing PCa or csPCa, both SUVmax and miPSMA scores performed well in independent diagnosis. However, PSMA-RADS performed poorly with a higher misdiagnosis rate (18.18% for PCa, 33.33 for csPCa). In conclusion, the diagnostic accuracy for PCa in [^{18}F]DCFPyL PET/CT was graded as miPSMA score ≈ SUVmax > PSMA-RADS.

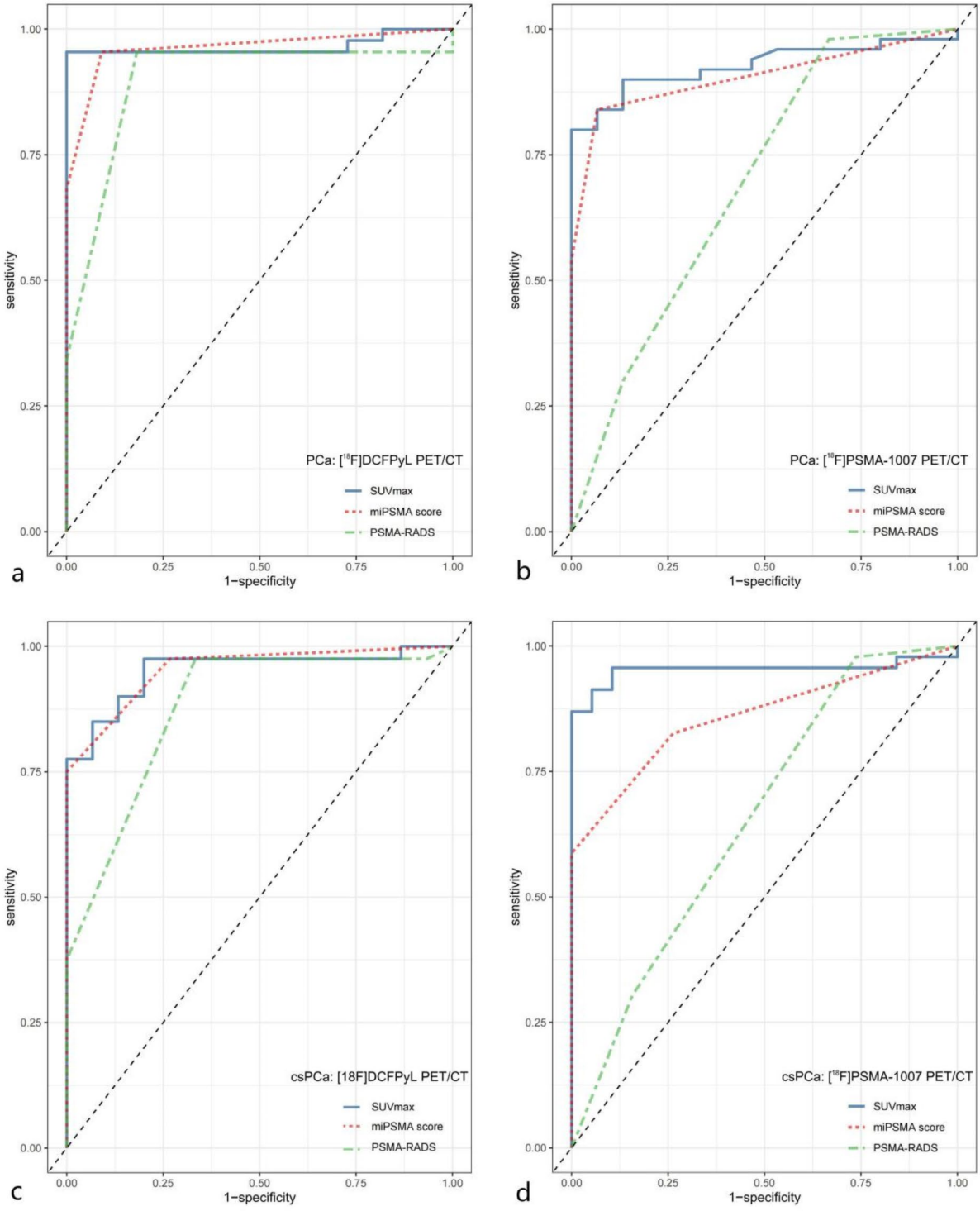

Fig. 4 The ROC curve of the three imaging criteria in PSMA PET/CT scans. Legend: **a**. In [^{18}F]DCFPyL PET/CT, the AUC values for diagnosing Prostate Cancer (PCa) using the three criteria are as follows: SUVmax (solid blue line) is 96.49% (91.54%, 100%), miPSMA (dotted red line) is 96.28 (91.88%, 100%), and PSMA-RADS (dashed green line) is 89.87% (80.40%, 99.35%). **b**. In [^{18}F]PSMA-1007 PET/CT, the AUC values for diagnosing PCa using the three criteria are 92.73% (86.50%, 98.96%), 90.47% (84.31%, 96.62%), and 69.13% (54.46%, 83.80%), respectively. **c**. In [^{18}F]DCFPyL PET/CT, the AUC values for diagnosing Clinical Significant Prostate Cancer (csPCa) using the three criteria are 95.17% (89.66%, 100%), 95.42% (90.93%, 99.90%) and 87.58% (78.66%, 96.51%), respectively. **d**. In [^{18}F]PSMA-1007 PET/CT, the AUC values for diagnosing csPCa using the three criteria are 95.31% (89.69%, 100%), 85.87% (77.91%, 93.83%) and 65.56% (52.23%, 78.89%), respectively

Table 4 The diagnostic efficacy parameters of the three criteria for csPCa in the [^{18}F]DCFPyL PET/CT

[^{18}F]DCFPyL group ($n=55$)	SUVmax		miPSMA score		PSMA-RADS	
Pathology	**Positive ($n=43$)**	**Negative ($n=12$)**	**Positive ($n=43$)**	**Negative ($n=12$)**	**Positive ($n=44$)**	**Negative ($n=11$)**
csPCa ($n=40$)	39	1	39	1	39	1
Non-csPCa ($n=15$)	4	11	4	11	5	10
Sensitivity (95% CI)	97.50% (92.66%, 100%)		97.50% (92.66%, 100%)		97.50 (92.66%, 100%)	
Specificity (95% CI)	73.33% (50.95%, 95.71%)		73.33% (50.95%, 95.71%)		66.67% (42.81%, 90.53%)	
Accuracy (95% CI)	92.73% (85.87%, 99.59%)		92.73% (85.87%, 99.59%)		89.09% (80.85%, 97.33%)	
Mistake diagnostic rate (95% CI)	26.67% (4.29%, 49.05%)		26.67% (4.29%, 49.05%)		33.33% (9.47%, 57.19%)	
Omission diagnostic rate (95% CI)	2.50% (0, 7.36%)		2.50% (0, 7.36%)		2.50% (0, 7.36%)	
Positive predictive value (95% CI)	90.70% (82.02%, 99.38%)		90.70% (82.02%, 99.38%)		88.64(79.26%, 98.02%)	
Negative predictive value (95% CI)	91.67% (76.03%, 100%)		91.67% (76.03%, 100%)		90.91(73.92%, 100%)	
Youden Index (95% CI)	70.83% (58.82%, 82.84%)		70.83% (58.82%, 82.84%)		64.17(51.50%, 76.84%)	
AUC (95% CI)	95.17% (89.66%, 100%)		95.42% (90.93%, 99.90%)		87.58% (78.66%, 96.51%)	

csPCa: Clinically Significant Prostate Cancer; non-csPCa: including PCa (Gleason score 3 + 3) and benign prostate diseases

Table 5 The diagnostic efficacy parameters of the three criteria for PCa in the [^{18}F]PSMA-1007 PET/CT

[^{18}F]PSMA-1007 group($n=65$)	SUVmax		miPSMA score		PSMA-RADS	
Pathology	**Positive ($n=57$)**	**Negative ($n=8$)**	**Positive ($n=43$)**	**Negative ($n=22$)**	**Positive ($n=59$)**	**Negative ($n=6$)**
PCa ($n=50$)	48	2	42	8	49	1
BPD ($n=15$)	9	6	1	14	10	5
Sensitivity (95% CI)	96.00% (90.57%, 100%)		84.00% (77.37%, 90.63%)		98.00% (95.24%, 100%)	
Specificity (95% CI)	40.00% (15.21%, 64.79%)		93.33% (82.24%, 100%)		33.33% (13.73%, 52.93%)	
Accuracy (95% CI)	83.08% (77.08%, 89.18%)		86.15% (80.28%, 92.02%)		83.08% (72.65%, 93.51%)	
Mistake diagnostic rate (95% CI)	60.00% (39.00%, 81.00%)		6.67% (0%, 34.38%)		66.67% (40.25%, 93.09%)	
Omission diagnostic rate (95% CI)	4.00% (0%, 10.00%)		16.00% (8.40%, 23.60%)		2.00% (0%, 8.17%)	
Positive predictive value (95% CI)	84.21% (77.21%, 91.21%)		97.67% (94.42%, 99.92%)		83.05% (71.98%, 94.13%)	
Negative predictive value (95% CI)	75.00% (58.00%, 91.98%)		63.64% (47.31%,79.97%)		83.33% (67.31%, 99.35%)	
Youden Index (95% CI)	36.00% (15.18%, 100%)		77.33% (59.58%, 95.58%)		31.33%(9.45%, 53.21%)	
AUC(95% CI)	92.73% (86.50%, 98.96%)		90.47% (84.31%, 96.62%)		69.13% (54.46%, 83.80%)	

PCa: Prostate Cancer; BPD: benign prostate diseases

Evaluating the diagnostic efficacy in [18F]PSMA-1007 PET/CT

In the [^{18}F]PSMA-1007 group, 65 cases were analyzed, of which 50 were diagnosed pathologically as PCa and 15 as BPD. Additionally, of which 46 were identified as csPCa and 19 as non-csPCa.

As shown in Table 5, the respective primary PCa diagnostic efficacy parameters for SUVmax, miPSMA score, and PSMA-RADS were as follows: sensitivity 96.00%, 84.00%, and 98.00%, specificity 40.00%, 93.33%, and 33.33%, Accuracy 83.08%, 86.15% and 83.08%, and AUC 92.73% (86.50%, 98.96%), 90.47% (84.31%, 96.62%), and 69.13% (54.46%, 83.80%). The ROC curve is shown in Fig. 4b. Using prostate pathology as the reference standard, the optimal diagnostic threshold of SUVmax was 14.20.

As shown in Table 6, the respective csPCa diagnostic efficacy parameters for SUVmax, miPSMA score, and PSMA-RADS were as follows: sensitivity 95.65%, 82.60%, and 97.82%, specificity 31.58%, 73.68%, and 26.32%, Accuracy 76.92%, 0.00% and 76.92%, and AUC 95.31% (89.69%, 100%), 85.87% (77.91%, 93.83%), and 65.56% (52.23%, 78.89%). The ROC curve is shown in Fig. 4d. Using prostate pathology as the reference standard, the optimal diagnostic threshold of SUVmax was 14.20.

Regardless of whether it is diagnosing PCa or csPCa, the miPSMA score performed well in independent diagnosis. However, SUVmax and PSMA-RADS performed poorly with a higher misdiagnosis rate (60.00% and 66.67% for PCa, 68.42% and 73.68% for csPCa). In conclusion, grading of the diagnostic accuracy for diagnosing PCa in [^{18}F]PSMA-1007 PET/CT was miPSMA score > SUVmax ≈ PSMA-RADS.

Discussion

PSMA PET/CT emerges as a pivotal technology in the diagnostic landscape of PCa. It offers a suite of imaging interpretation criteria, notably SUVmax, miPSMA score and PSMA-RADS. The development and validation of standardized imaging diagnostic criteria are crucial for harmonizing outcomes across different studies, enhancing comparability, and facilitating communication with clinically relevant physicians. The standardized diagnosis values of three criteria in PSMA PET/CT for primary PCa should be evaluated using the following two aspects: the inter-tracer consistency observed in PSMA PET/CT

Table 6 The diagnostic efficacy parameters of the three criteria for csPCa in the [^{18}F]PSMA-1007 PET/CT

[^{18}F]PSMA-1007 group($n=65$)	SUVmax		miPSMA score		PSMA-RADS	
Pathology	**Positive ($n=57$)**	**Negative ($n=8$)**	**Positive ($n=43$)**	**Negative ($n=22$)**	**Positive ($n=59$)**	**Negative ($n=6$)**
csPCa ($n=46$)	44	2	38	8	45	1
Non-csPCa ($n=19$)	13	6	5	14	14	5
Sensitivity (95% CI)	95.65% (87.32%, 100%)		82.60% (72.50%, 92.71%)		97.82% (95.00%, 99.39%)	
Specificity (95% CI)	31.58% (13.34%, 49.82%)		73.68% (57.66%, 89.70%)		26.32% (5.01%, 50.55%)	
Accuracy (95% CI)	76.92% (65.63%, 88.21%)		80.00% (68.49%, 91.51%)		76.92% (65.78%,88.02%)	
Mistake diagnostic rate (95% CI)	68.42% (32.38%, 100%)		26.32% (10.34%, 42.30%)		73.68% (51.53%, 92.91%)	
Omission diagnostic rate (95% CI)	4.35% (0, 15.88%)		17.39% (9.16%, 25.62%)		2.17% (0, 4.61%)	
Positive predictive value (95% CI)	77.19% (67.20%, 87.18%)		88.37% (76.24%, 100%)		76.27% (66.21%, 86.33%)	
Negative predictive value (95% CI)	75.00% (32.59%, 100%)		63.64% (46.20%, 81.08%)		83.33% (53.13%, 100%)	
Youden Index (95% CI)	27.23% (7.97%, 46.49%)		56.28% (35.80%, 76.76%)		24.14% (10.27, 38.01%)	
AUC(95% CI)	95.31% (89.69%, 100%)		85.87% (77.91%, 93.83%)		65.56% (52.23%, 78.89%)	

csPCa: Clinically Significant Prostate Cancer; non-csPCa: including PCa (Gleason score 3 + 3) and benign prostate diseases

scans, and their diagnostic accuracy in detecting PCa. Currently, the literature is sparse, with a limited number of studies focusing on miPSMA score and PSMA-RADS, predominantly concentrating on interobserver and intraobserver agreement analyses [21–27]. This scarcity of comprehensive data underscores a significant gap in confirming the diagnostic value of these criteria in PCa. Moreover, no studies have yet compared these three criteria across various radiotracers. Our retrospective study addresses this gap by comparing and analyzing the consistency and diagnostic accuracy of these three criteria in standardized diagnosis. We utilized two representative ^{18}F-labelled radiotracers with distinct metabolic pathways: [^{18}F]DCFPyL, which is excreted by the urinary system, and [^{18}F]PSMA-1007, excreted by the hepatobiliary system. This comparative analysis is pivotal for advancing the field and potentially influencing clinical guidelines by providing a more nuanced understanding of the strengths and limitations of each criterion in the context of PSMA PET/CT.

In contrast to the miPSMA score and PSMA-RADS, SUVmax serves as a widely recognized diagnostic criterion for PCa. However, the diagnostic threshold for PCa, which is significantly influenced by the choice of radiotracer, varies considerably. Drawing from the existing literature [11, 13–17, 28–31], the SUVmax threshold for diagnosing PCa ranged from “radiation uptake above background"levels to specific values such as 2.5, 6.94, 8.62 and and beyond.This variability is further complicated by the fact that different tracers exhibit distinct thresholds, which complicates the standardization of diagnosis in PSMA PET/CT. Given the aim of our study is to evaluate the standardized diagnostic value of indicators under different tracer conditions, we assumed that the SUVmax threshold would be consistent across both tracers. During the study design phase, we reviewed extensive literature to determine our threshold value. A study by Bodar Y et al. [28] (which used the same tracer as ours, [^{18}F]DCFPyL), utilized radical prostatectomy pathological findings (which are more accurate than biopsy) as the gold standard to determine the SUVmax diagnostic threshold for PCa, which was found to be 8.62. Therefore, we adopted this value for our research. Our study showed that SUVmax exhibits high consistency across different tracers. However, using the identical SUVmax threshold for diagnostic assessment, it uncovers discrepancies between the two tracers. The specificity for diagnosing PCa was 90.91% and 40.00% for [^{18}F]DCFPyL and [^{18}F]PSMA-1007, respectively, with misdiagnosis rates of 9.09% and 60.00%. For csPCa, the specificity was 77.33% and 31.58%, with misdiagnosis rates of 26.67% and 68.42%. Further analysis revealed that the true SUVmax thresholds vary between the tracers: 9.24 for PCa and 11.35 for csPCa with [^{18}F]DCFPyL, compared to 14.20 for both PCa and csPCa with [^{18}F]PSMA-1007. This contradicts the findings of Giesel et al. [32], who found no significant SUVmax difference in their self-controlled study for identifying tumor lesions with these tracers ($P=0.175$). These results suggest that each center should establish a tailored SUVmax threshold for PCa diagnosis, based on prostate pathology, rather than relying on thresholds from other centers. Moreover, SUVmax values from various research centers should not be directly compared, as they may not accurately reflect treatment response.

In our study, the miPSMA scores demonstrated not only an almost-perfect inter-tracer agreement between [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT scans. This consistency was not only observed in the scoring system but also translated into perfect diagnostic accuracy for PCa and csPCa, irrespective of the tracer used. Our findings mirror those of a prospective [^{68}Ga]PSMA PET/CT study by Liu et al. [33], which utilized puncture pathology as the gold standard. That study demonstrates that the miPSMA score has a sensitivity, specificity, and accuracy of 93.3%, 75.0%, and 83.9% for diagnosing PCa,

and 100.0%, 68.4%, and 80.6% for csPCa, respectively. The miPSMA scoring system offers two key advantages. Firstly, it provides an objective and clear definition of the radioactive uptake degree of suspicious lesions, enhancing diagnostic confidence, especially concerning uptake in the blood pool, salivary glands, liver, and/or spleen, aspects not covered by PSMA-RADS. Secondly, by quantifying the likelihood of PCa on a scale of 0–3 points, this standardized scoring system facilitates clearer communication between clinicians and radiologists and offers more reliable reference values for comparative clinical studies. This underscores the miPSMA score's potential as a robust criterion for PCa and csPCa diagnosis, holding substantial promise for refining clinical decision-making and patient management strategies. However, the miPSMA score is not without its limitations. For instance, in [^{18}F]PSMA-1007 PET/CT scans, the miPSMA score performed worse than in [^{18}F]DCFPyL scans, with an omission diagnostic rate of 16.00% for PCa and 17.39% for csPCa. This discrepancy is believed to be associated with differences in the tracer's metabolic pathway and scoring criteria [32]. The reference organ for [^{18}F]DCFPyL in the PROMISE standard is the liver, as opposed to the spleen for [^{18}F]PSMA-1007 scans. Our preliminary analysis of miPSMA scores, based on liver references, revealed that among 8 false-negative patients for PCa, 4 could be reclassified with a score upgrade from 1 to 2 points. The degree of uptake (SUVmax) of the spleen and liver appeared to be irregular. In our [^{18}F]PSMA-1007 PET/CT scans, SUVmax in the liver was higher than in the spleen in 26/65 cases, while it was lower in 39/65 cases. Additionally, we encountered other areas of confusion: the SUVmax of the parotid gland was not consistently higher than that of other reference organs; it was lower than the spleen or liver in 9/65 cases. The study by Donswijk, M.L., et al. [27] highlights "remarkably low interobserver agreement rates" for the miPSMA score in [^{18}F]PSMA-1007. The potential reasons for this could include variability in liver and spleen radioactive activity levels, as previously mentioned in our manuscript, and the challenge posed by the proximity of SUVmax values in primary prostate tumors to those of the liver and spleen. These factors significantly impact the results of the miPSMA score. Both our study and Donswijk's research highlight that the miPSMA scoring rules have certain deficiencies, which to some extent limit the robustness of the results. When Eiber et al. [19] proposed the miPSMA scoring standard, they showed that there was a lack of detailed data comparing the biological distribution of different PSMA ligands in vivo, although it was not considered relevant to all tracers given their biological similarity. Therefore, it is necessary to further optimize the miPSMA scoring rules, such as selecting the most appropriate reference organ, and determining the most suitable parameter (SUVmax, SUVmean, SUVpeak, etc.).

In 2023, PROMISE V2 introduced the PRIMARY score, a comprehensive assessment tool that incorporates both PSMA expression levels and detailed lesion characteristics, including location and extent. In the prospective study by Emmett et al. [34], this scoring system demonstrated excellent diagnostic performance for csPCa. Specifically, when the PRIMARY score was 3 or higher, the sensitivity for detectinhg csPCa was 88%, specificity was 64%, positive predictive value was 76%, negative predictive value was 81%, and the AUC was 0.85 (0.71–0.81)). However, this performance was found to be inferior to that of the miPSMA score in our study. We have delved into the reasons behind the variance in diagnostic performance, suggesting that the primary reason may stem from differences in scoring rules. While the PRIMARY score enriches the assessment with anatomical details of lesions based on PSMA expression, it lacks an objective quantification of PSMA expression levels. We hypothesize that integrating the PRIMARY score with the miPSMA score, which combines anatomical insights with an objective quantification of PSMA scoring, could enhance diagnostic accuracy for csPCa. This integration is the direction we wish to pursue in our future work, as we continuously optimize the diagnostic efficacy of PSMA PET/CT for both PCa and csPCa.

In this study, PSMA-RADS showed substantial interscan agreement between [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET /CT. However, it exhibited relatively poor diagnostic performance, with a high misdiagnosis rate of 18.18%, 66.67% for PCa, and 33.33%, 73.68% for csPCa, respectively. In all cases of misdiagnosis, the scans were erroneously assigned a score of 4, suggesting a potential overestimation in the presence of disease. The underlying issue stems from the absence of a clear, objective criterion for assessing the level of radioactive uptake by suspicious lesions iwithin the PSMA-RADS scoring system. This lack of clarity makes it challenging to define 2 points (low uptake) and 4 points (high uptake). Consequently, the PSMA-RADS scoring is predominantly reliant on the subjective interpretation and experience of the readers, leading to variability in practical application. This is detrimental to the value of PSMA-RADS in the standardization of PSMA PET/CT diagnostics. To enhance the reliability and objectivity of PSMA-RADS, further refinement is necessary. The process should mirror the rigorous development and application of PI-RADS in MRI, where standardized criteria have been established to guide clinical practice and improve diagnostic accuracy.

In summary, our findings hold significant value for the development of clinical practice and imaging interpretation criteria. We have proposed several recommendations: (1) The need for each center to establish tailored

SUVmax threshold values; (2) Further exploration and refinement of the miPSMA scoring system in terms of reference organs, semi-quantitative indicators and the integration of anatomical information of the lesions; and (3) The necessity for the PSMA-RADS scoring criteria to be more objectively refined.

Our study, while providing valuable insights, does have certain limitations that should be considered. Firstly, it is a retrospective, single-center study with a relatively small number of patients, which may lead to statistical insufficiency and underpowered conclusions. Secondly, the reference standard for diagnosing PCa in some patients relies on biopsy specimens, which can underestimate the clinical value of PSMA PET imaging due to the potential for missed diagnoses that are inherent to biopsy procedures. Lastly, our research data were derived from [^{18}F]-labeled PSMA tracers, which limits the generalizability of our findings. Whether our findings are applicable to [^{68}Ga]-labeled PSMA tracers and other tracers, as well as their applicability to PSMA PET/MRI, requires further investigation. To address the limitations mentioned above, the direction of our future research will focus on: conducting further prospective studies, particularly in the form of multicenter trials, to substantiate our results. Additionally, we will explore the application of our findings in the context of other tracers and PSMA PET/MRI. Furthermore, we will endeavor to investigate the potential of combining the miPSMA score with the PRIMARY score in the diagnostic process for PCa, aiming to enhance diagnostic accuracy and provide a more comprehensive assessment tool for clinicians.

Conclusions

The miPSMA score outperforms SUVmax and PSMA-RADS in terms of inter-tracer consistency and diagnostic accuracy for the detection of PCa, including csPCa, when comparing [^{18}F]DCFPyL and [^{18}F]PSMA-1007 PET/CT scans. This underscores the miPSMA score's potential as a robust criterion for PCa and csPCa diagnosis, holding substantial promise for refining clinical decision-making and patient management strategies.

Abbreviations

PSMA	Prostate-specific membrane antigen
Pca	Prostate cancer
csPCa	Clinically significant PCa
BPD	Benign prostate diseases
PET /CT	Positron emission tomography/ computer tomography
SUVmax	Maximum standardized uptake value
PSMA-RADS	The PSMA reporting and data system
miPSMA	The molecular imaging prostate specific membrane antigen scoring system
PSA	Serum prostate-specific antigen
DRE	Digital rectal examination
ICCs	Intra-class correlation coefficients
ROC curve	Receiver operator characteristic curve
AUC	Area under the ROC curve

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Author contributions
Le Ma was responsible for the design of the study, imaging interpretation of PSMA PET/CT, statistical analysis of data, drafting and revising the manuscript; Yaxin Hao was in charge of imaging interpretation of PSMA PET/CT and data collection; Luoping Zhai was tasked with synthesizing the [^{18}F]-labeled PSMA tracers and conducting quality control, as well as providing consultation on the study design; Wanchun Zhang was responsible for imaging interpretation of PSMA PET/CT, project administration, and reviewing the manuscript. Xiaoming Cao played a pivotal role in guiding the research and reviewing the manuscript. Kaiyuan Jia was instrumental in collecting and organizing the data.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study complies with the Declaration of Helsinki, ensuring the anonymity and security of data, and has been approved by the Ethics Committee of Shanxi Bethune Hospital (approval number: YXLL-2024-196). Informed consent was obtained from each participants through a mail-based process.

Consent for publication
Informed consent was obtained from all individual participants included in the study.

Competing interests
The authors declare no competing interests.

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