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Original Article

Diagnostic value comparison of the combination of prostate-specific membrane antigen-body PET/MR and the prostate health index with each alone in early diagnosis of prostate cancer

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Abstract *Objective:* This study aimed to figure out whether the combination of the prostate health index (PHI) and prostate-specific membrane antigen (PSMA)-PET/MR could improve the diagnostic accuracy for prostate cancer (PCa) than that of each individual method used alone.
Methods: In this prospective, observational study, 41 patients who underwent the systematic prostate biopsy between June 2019 and September 2022 were enrolled. Both the PHI test and ^{18}F-PSMA-1007-PET/MR were performed prior to biopsies. The diagnostic accuracy of different models was compared by logistic regression, areas under the curve (AUCs) of the receiver operating characteristic, and net reclassification index (NRI).
Results: Among the 41 patients, 14 (34.1%) were pathologically diagnosed with PCa. The PHI in the PCa group was significantly higher than that in the benign group (44.4 *vs.* 35.0, $p=0.048$). Similarly, all the patients in the PCa group received positive results of ^{18}F-PSMA-1007-PET/MR, of which the positive rate was significantly higher than that in benign group (100% *vs.* 62.96%,

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$p=0.025$). The ^{18}F-PSMA-1007-PET/MR provided additional diagnostic values to the PHI (AUC: 0.802 *vs.* 0.692, $p=0.025$). However, there was no significant difference between the combination model and the ^{18}F-PSMA-1007-PET/MR alone (AUC 0.802 *vs.* 0.685, $p=0.071$). The optimal PHI cutoff of the combination model is 32, with which the model could significantly reduce unnecessary biopsies (NRI: 22.22%, 95% confidence interval: 6.54%—37.90%, $p=0.005$). However, among patients with the PHI of $\geq$43.5, there was no significant difference between the combination model and the PHI alone (NRI: 11.11%, 95% confidence interval: −0.74%—22.97%, $p=0.066$).

Conclusion: The combination of the PHI and ^{18}F-PSMA-1007-PET/MR outperforms the PHI alone for predicting PCa, especially in avoiding unnecessary biopsies. However, for patients with the PHI of $\geq$43.5, the addition of ^{18}F-PSMA-1007-PET/MR to the PHI does not yield additional benefits.

1. Introduction

Prostate cancer (PCa) is one of the most common cancers all over the world as well as the third leading cause of cancer death in males [1]. In Asia, with a progressively aging population, the incidence of PCa is rising annually [2].

Prostate-specific antigen (PSA) testing is currently the most approved PCa screening approach all over the world. However, the accuracy of PSA testing is not satisfied. The low specificity of PSA testing leads to high rates of unnecessary biopsies. Among patients with elevated PSA (PSA>4 ng/mL), the biopsy positive rate is about 25.5%, while the positive predictive values of the second and third biopsies in PSA-based screening are 12.0% and 15.2%, respectively [3]. How to increase the diagnostic accuracy of PCa to avoid the unnecessary prostate biopsy remains a critical clinical issue.

The prostate health index (PHI) is a diagnostic index calculated by total PSA (tPSA), free PSA (fPSA), and [−2]proPSA (p2PSA, an isoform of PSA). It has been proved to improve the diagnostic accuracy of suspected PCa with tPSA (4—20 ng/mL) and avoid the unnecessary biopsy [4,5].

The prostate-specific membrane antigen (PSMA) is a molecule which is specifically expressed in PCa cells. The PET/CT or PET/MR labeled by PSMA is a reliable imaging tool which is now widely used in diagnosis, staging, and surveillance for PCa [6,7].

Previous studies have found the combination of the PHI and multiparametric MRI (mpMRI) performs better than PHI alone or mpMRI alone when predicting PCa [8—10]. However, the accuracy of mpMRI in detecting PCa still remains several insufficiency. For example, the accuracy of mpMRI highly depends on the individual interpreting the images, resulting in potential inconsistency. As a relatively novel imaging examination, ^{18}F-PSMA-1007-PET/MR outperforms mpMRI in the diagnosis of early suspected PCa, especially increasing the sensitivity and negative predictive value [11,12]. The dependency on the manual interpretation of PSMA-PET/MR is relatively lower than that of mpMRI.

This research aimed to figure out whether the combination of PHI and ^{18}F-PSMA-1007-PET/MR can enhance the diagnostic capabilities of each individual method.

2. Patients and methods

2.1. Patients

We prospectively enrolled 87 patients with elevated PSA levels (4—20 ng/mL) who underwent ^{18}F-PSMA-1007-PET/MR and the systematic 12-core prostate biopsy in Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, from June 2019 to September 2022. ^{18}F-PSMA-1007-PET/MR information was collected prior to the biopsy. Patients were excluded if (1) had urinary infections such as prostatitis, which may affect the serum test; (2) ever used 5-alpha reductase inhibitors; (3) had not been tested p2PSA before biopsy. Finally, 41 patients who met the criteria were included in this study.

This study was approved by the Ethics Committee of Ruijin Hospital (approval number: 2022277). All participants provided written informed consents to take part in the study. The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable request.

2.2. The collection of clinical variables

We collected clinical characteristics of the patients, including age, prostate volume (PV), tPSA, fPSA, p2PSA, maximum standardized uptake value (SUV_{max}), results of ^{18}F-PSMA-1007-PET/MR, the site and diameter of lesions, previous biopsy experience, and biopsy results.

The ratio f/tPSA was calculated by dividing tPSA by fPSA. PSA density (PSAD) was calculated by dividing PSA by PV. PHI was calculated using the formula:

$$PHI=(p2PSA/fPSA)\times\sqrt{tPSA}.$$

2.3. ^{18}F-PSMA-PET/MR protocol

All the patients receiving ^{18}F-PSMA-1007-PET/MR were intravenously injected with ^{18}F-PSMA-1007. One hour after the injection, patients received a full body scan using an integrated PET/MR system (Biograph mMR, Siemens Healthcare, Erlangen, Germany). The images were analyzed with dedicated software (Syngovia version VB10,

Siemens Healthcare, Erlangen, Germany) and interpreted independently by experienced nuclear medicine physicians. The agreements were achieved by discussion.

2.4. Statistical analysis

The results of combination of ^{18}F-PSMA-1007-PET/MR and PHI were defined positive when both two examinations suspected malignant. If one of these two indicators showed the benign result, the combination was explained as negative.

Continuous variables were reported as medians and interquartile ranges and categorical variables were reported as numbers and proportions. Shapiro–Wilk test was performed to exam the normality of variables. In the univariate analysis, continuous variables that fit a normal distribution were compared by Student's *t*-test and the others were compared by Mann–Whitney *U* test. The comparison between categorical variables was using Chi-square corrected test.

PHI and p2PSA are more accurate than PSA and f/tPSA in predicting a positive repeat prostate biopsy. Consequently, the comparison of previous biopsy rates between the two positive and negative groups was conducted using the Chi-square corrected test to eliminate potential biases.

PHI was explored as both a continuous variable and a categorized variable according to different cutoffs. The cutoff choosing refers to previous studies [8,13]. The diagnostic ability of PHI and the combination under different cutoffs were evaluated respectively.

The univariate logistic regression was used to evaluate the influence weight of different variables. Since there was zero in the four-fold table of ^{18}F-PSMA-1007-PET/MR and biopsy results, the logistic regression involving ^{18}F-PSMA-1007-PET/MR was performed with Firth's corrections. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to evaluate the predictive ability. The diagnostic indicators including sensitivity, specificity, positive predictive value, and negative predictive value of different diagnostic methods were calculated. We used McNemar's test to compare the diagnostic value of different methods, and the DeLong test was used to compare different ROC curves. The net reclassification index (NRI) [14] was also used to compare the performance of different models.

A two-side $p<0.05$ was regarded as statistical significant. All statistical analyses were performed using R version 4.2.2 (R Core Team 2022, Vienna, Austria).

3. Results

From June 2019 to September 2022, 41 patients who met the criteria were included in this study.

Table 1 shows the population characteristics. Among the 41 patients, 14 (34.1%) were pathologically proved to be PCa and 27 (65.9%) patients were pathologically benign.

Patients in the biopsy positive group have a higher but not statistically significant median age than those in biopsy negative group (67.0 years *vs.* 59.0 years, $p=0.054$). Additionally, the data revealed comparable repeat biopsy rates between the biopsy positive and negative groups (14.29% *vs.* 18.52%, $p=0.750$). The median PHI of patients in biopsy positive group is significantly higher than that in biopsy negative group (44.4 *vs.* 35.0, $p=0.048$). ^{18}F-PSMA-1007-PET/MR results were also significantly different between these two groups. More patients were suspected having PCa according to the image in the positive group than in the negative group (100% *vs.* 62.96%, $p=0.025$). The rest features including tPSA, fPSA, f/tPSA,

Table 1 Basic patient characteristics.

Variable	Total ($n=41$)	Biopsy positive ($n=14$)	Biopsy negative ($n=27$)	*p*-Value
Age, year	62.0 (56.0–67.0)	67.0 (63.0–74.0)	59.0 (56.0–62.5)	0.054[a]
tPSA, ng/mL	9.01 (6.04–10.63)	7.42 (5.77–10.82)	9.73 (7.24–10.55)	0.394[b]
fPSA, ng/mL	1.18 (0.71–1.80)	1.05 (0.67–1.73)	1.40 (0.82–1.76)	0.450[b]
f/tPSA	0.13 (0.10–0.17)	0.13 (0.09–0.18)	0.14 (0.10–0.17)	0.847[b]
p2PSA	14.3 (10.1–25.1)	15.0 (12.1–25.0)	13.1 (9.8–23.4)	0.322[b]
PHI	38.1 (30.6–47.7)	44.4 (33.1–55.1)	35.0 (28.8–43.6)	0.048[b]
PV, cm^3	48.1 (39.4–56.3)	41.5 (27.4–64.0)	48.2 (38.7–54.2)	0.711[b]
PSAD, ng/mL^2	0.20 (0.15–0.24)	0.16 (0.12–0.23)	0.20 (0.17–0.25)	0.294[b]
SUV_{max}	7.70 (5.73–13.20)	10.15 (7.03–14.60)	7.30 (5.44–10.60)	0.132[b]
^{18}F-PSMA-PET/MR positive	31 (75.61)	14 (100)	17 (62.96)	0.025[c]
Leision				
Central zone	5 (12.20)	1 (7.14)	4 (14.81)	NA
Peripheric zone	13 (31.71)	8 (57.14)	5 (18.52)	NA
Transitional zone	13 (31.71)	5 (35.71)	8 (29.63)	NA
Diameter, cm	0.80 (0.65–1.20)	1.10 (0.73–1.50)	0.70 (0.50–1.10)	NA
Repeated biopsy	7 (17.07)	2 (14.29)	5 (18.52)	0.750

PSA, prostate-specific antigen; tPSA, total PSA; fPSA, free PSA; PHI, prostate health index; PV, prostate volume; PSAD, PSA density; SUV_{max}, maximum standardized uptake value; f/tPSA, the ratio of fPSA and tPSA; p2PSA, an isoform of PSA; NA, not applicable.
Note: data are presented as median (interquartile range) or *n* (%), and percentages may not sum up to 100% due to rounding.
[a] Student's *t*-test.
[b] Mann–Whitney *U* test.
[c] Chi-square corrected test.

p2PSA, PV, PSAD, and SUV_{max} were proved insignificant in this study (all these $p>0.05$).

In the ROC analysis (Fig. 1), the combination model provided a significant larger AUC than PHI (AUC 0.802 *vs.* 0.692, $p=0.025$). However, the difference between the ROC of the combination model and the ^{18}F-PSMA-1007-PET/MR model was not significant (AUC 0.802 *vs.* 0.685, $p=0.071$). There was also no significant difference between the ROC of PHI and ^{18}F-PSMA-1007-PET/MR alone (AUC 0.692 *vs.* 0.685, $p=0.950$).

Fig. 2 shows the changing trend of the AUC of the PHI and combination under different cutoffs. In this analysis, the PHI was regarded as a categorical variable. The PHI result is considered as positive if it exceeds the cutoff value. The combination result is defined as positive if both the PHI and ^{18}F-PSMA-1007-PET/MR are positive, otherwise is negative. The performance of the combination was significantly better than that of PHI alone when the cutoff was $\leq$40 (0.601 *vs.* 0.742, $p=0.033$). However, if the PHI cutoff was $\geq$43.5, there was no significant difference (0.620 *vs.* 0.676, $p=0.071$).

Table 2 shows the NRI of the combination model and ^{18}F-PSMA-1007-PET/MR alone in comparison with the PHI alone. There were no significant differences between the PHI and ^{18}F-PSMA-1007-PET/MR alone whatever the cutoffs were (all $p>0.05$). Although ^{18}F-PSMA-1007-PET/MR can help to detect more PCa, it also led to more unnecessary biopsies in those patients who only have benign hyperplasia. However, the combination model gave a better performance. When the cutoff ranges from 25 to 40, the diagnostic capability of the combination model outperforms PHI alone, especially in avoiding unnecessary biopsy ($p=0.002$, 0.005, 0.013, and 0.030 under PHI cutoffs of 25, 30, 35, and 40, respectively). However, once PHI was $\geq$43.5, there was no significant improvement according to the NRI (NRI=11.11%, 95% CI: −0.74%–22.97%, $p=0.066$), which is consistent with the aforementioned ROC analysis (Fig. 2).

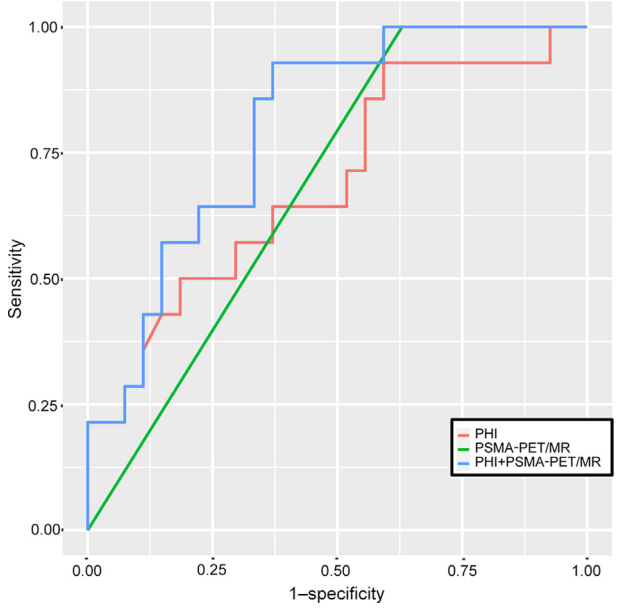

Figure 1 Receiver operating characteristic curves analysis: comparing PHI, ^{18}F-PMSA-PET/MR, and the combination. PHI, prostate health index; PSMA, prostate-specific membrane antigen.

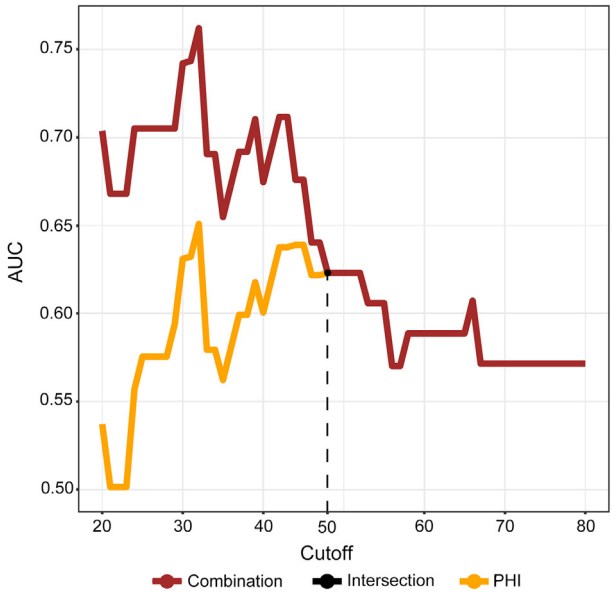

Figure 2 The changing trend of the AUC of the PHI and combination under different cutoffs. The vertical line represents the cutoff point where AUC values of both the PHI and combination model reach equality. AUC, area under the curve; PHI, prostate health index.

Table 3 shows diagnostic values of the combination model under different PHI cutoffs. Choosing 32 as the cutoff, the combination performs best according to Youden index with a sensitivity of 85.71% and a specificity of 66.67%. Also taking PHI $\geq$32 as an optimal cutoff of the combination model can help to avoid 22.22% unnecessary biopsies according to the NRI analysis ($p=0.005$) (Table 2).

4. Discussion

To our knowledge, this is the initial prospective observational research to evaluate the additive diagnostic value of the combination of PHI and ^{18}F-PSMA-1007-PET/MR. The purpose of this study was to figure out whether ^{18}F-PSMA-1007-PET/MR can add diagnostic values to the PHI alone in detecting PCa or in avoiding the unnecessary biopsy.

Based on our research, we concluded that among patients with a suspected PSA elevation of 4–20 ng/mL: (1) there is limited value to perform an additional PHI test to those patients who had already experienced ^{18}F-PSMA-1007-PET/MR; (2) for those patients who had experienced PHI test, if ^{18}F-PSMA-1007-PET/MR is further performed, the decision making should be based on the combination of these two rather than only taking the image result into account; (3) for patients with 25<PHI<43.5, an additional ^{18}F-PSMA-1007-PET/MR can help to avoid unnecessary biopsy; (4) it is not recommended for patients with PHI$\geq$43.5 to take an ^{18}F-PSMA-1007-PET/MR examination (Supplementary Table 1).

Table 2 The NRI of the combination model and ^{18}F-PSMA-1007-PET/MR compared to the PHI under different cutoffs.

PHI cutoff	PHI *vs.* combination				PHI *vs.* ^{18}F-PSMA-1007-PET/MR			
	PCa missed (%)	Biopsy avoided (%)	NRI (95% CI) (%)	*p*-Value	PCa missed (%)	Biopsy avoided (%)	NRI (95% CI) (%)	*p*-Value
25	0	25.93	25.93 (9.40–42.46)	0.002	−7.14	14.81	21.96 (−4.08–47.99)	0.098
30	0	22.22	22.22 (6.54–37.90)	0.005	−7.14	3.70	10.85 (−16.72–38.41)	0.441
32[a]	0	22.22	22.22 (6.54–37.90)	0.005	−7.14	−14.29	6.88 (−25.77–39.53)	0.680
35	0	18.52	18.52 (3.87–33.17)	0.013	−35.71	−11.11	24.60 (−11.42–60.62)	0.181
40	0	14.81	14.81 (1.41–28.21)	0.030	−42.86	−25.93	16.93 (−20.04–53.90)	0.369
43.5[b]	0	7.32	11.11 (−0.74–22.97)	0.066	−37.04	−50.00	12.96 (−23.56–49.49)	0.487
45	0	7.41	7.41 (−2.47–17.29)	0.142	−50.00	−40.74	9.26 (−25.96–44.48)	0.606
50	0	0	0	NA	−64.29	−51.85	12.43 (−18.95–43.82)	0.438

NRI, net reclassification index; PSMA, prostate-specific membrane antigen; PHI, Prostate Health Index; PCa, prostate cancer; CI, confidence interval; NA, not applicable.

[a] The optimal cutoff.

[b] The selected PHI cutoff for the combination model to discriminate between positive and negative cases is <43.5, as at higher cutoffs (≥43.5), the combination model does not show a significant improvement over the PHI alone.

Table 3 Sensitivity, specificity, PPV, and NPV of the combination under different PHI cutoffs.

PHI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
25	92.86	48.15	48.15	92.86	0.410
30	92.86	55.56	52.00	93.75	0.484
32[a]	85.71	66.67	57.14	90.00	0.524
35	64.29	66.67	50.00	78.26	0.310
40	57.14	77.78	57.14	77.78	0.349
45	50.00	85.19	63.64	76.67	0.352
50	35.71	88.89	62.50	72.73	0.246

PHI, prostate health index; PPV, positive predictive value; NPV, negative predictive value.

[a] The optimal cutoff.

Both PHI and ^{18}F-PSMA-1007-PET/MR are reliable examinations in detecting PCa. The PHI improves the diagnostic ability both in patients with tPSA 4–10 ng/mL and 10–20 ng/mL [15,16]. PSMA-PET/MR has also been proved to be more sensitive than mpMRI in early predicting PCa [17]. We have noticed that the combination of these two examinations showed similar AUCs compared to ^{18}F-PSMA-1007-PET/MR alone, but a significant larger AUC than PHI alone, which means for those patients who had already had ^{18}F-PSMA-1007-PET/MR examination, it is no need for performing an additional PHI test. However, it could be valuable for those patients who only test the PHI to take ^{18}F-PSMA-1007-PET/MR.

The diagnostic ability of PHI is correlated with the selected cutoff values. Chiu et al. [5] suggested that different cutoffs of PHI should be <25, 25–35, and >35. Na el al. [16] evaluated the diagnostic accuracy of PHI across the range of 18–35.

The definition of the combination result is based on experience and previous studies. Hsieh et al. [9] combined Prostate Imaging-Reporting and Data System (PI-RADS) with PHI in a similar way as we did and found that among patients with PI-RADS 3 or 4, adding a PHI test and using ≥30 as the threshold can avoid an unnecessary biopsy. However, it is important to note that the PHI alone may not be sufficiently specific, which could lead to overdiagnosis and an unnecessary biopsy. For example, in a multicenter study in China, among patients with tPSA of 10–20 ng/mL, the specificity of the PHI was 38.68% at the cutoff of 32 [16]. In another meta-analysis, the pooled specificity of PHI was 34% [18]. Besides, the specificity of PSMA-PET/MR was 40%, referring to a study by Emmett et al. [17]. Combining these two methods in such a way we have aforementioned, regarding the combination result as being negative if anyone of these two examinations gives a negative outcome, can raise the specificity to avoid an unnecessary biopsy. Our analysis outcomes have proved the hypothesis.

We compared AUCs of the PHI and combination by different cutoffs. It turns out that there was no significant difference between AUCs of the combination and PHI alone when the cutoff value was set to 43.5, which implies among patients with the PHI≥43.5, the clinical utility of performing an additional ^{18}F-PSMA-1007-PET/MR examination may be limited.

The difference between the combination and ^{18}F-PSMA-1007-PET/MR was insignificant. Thus, in the subsequent NRI analysis, we compared the reclassification between the PHI model alone and ^{18}F-PSMA-1007-PET/MR alone. In the PHI spectrum from 25 to 50, there was no significant reclassification between these two models. That indicates the result of ^{18}F-PSMA-1007-PET/MR should be considered together with the PHI result rather than independently. The NRI analysis was consistent with the ROC analysis. The reclassifications were significant when the cutoff of PHI was set between 25.0 and 43.5. The Youden index shows that a PHI of 32 is the optimal cutoff for the combination model, with a sensitivity of 85.71% and a specificity of 66.67%. The combination can help to avoid 22.22% unnecessary biopsies without missing PCa.

The strength of our study mainly includes following four points.

Firstly, this is the first study combining the ^{18}F-PSMA-1007-PET/MR and PHI to predict PCa. There are some studies that had evaluated the mpMRI-PHI

combination and the PSMA-PET/MR-PSA combination. Hsieh et al. [9] found that AUCs of the combination of PHI and PI-RADS were higher than each alone (0.873 *vs.* 0.735, $p=0.002$; 0.873 *vs.* 0.830, $p=0.035$, respectively). Zhou et al. [8] found that the combination of PI-RADS and the PHI performed better than PI-RADS alone among patients with tPSA of 10—20 ng/mL (AUC 0.936 *vs.* 0.824, $p=0.029$). However, as a more sensitive image examination than mpMRI, ^{18}F-PSMA-1007-PET/MR and its additive value among patients experienced a PHI test have not been evaluated before. There is a slight difference between the combination of the PHI and ^{18}F-PSMA-1007-PET/MR and the combination of the PHI and mpMRI. The improvement brought by the PHI among patients who had undergone ^{18}F-PSMA-1007-PET/MR was not significant in our study according to either the ROC analysis or NRI analysis. One possible reason is the better diagnostic accuracy brought by ^{18}F-PSMA-1007-PET/MR than mpMRI in diagnosing early PCa.

Secondly, based on the insignificant reclassification between the PHI and ^{18}F-PSMA-1007-PET/MR, we recommend that if patients have experienced both, the result of them should be considered together. Although ^{18}F-PSMA-1007-PET/MR is such a powerful image tool, the PHI still has its own additive values.

Thirdly, we find out a PHI threshold to avoid a further ^{18}F-PSMA-1007-PET/MR examination. For those patients with the PHI$\geq$43.5, there is no need to perform an excess ^{18}F-PSMA-1007-PET/MR examination.

Last but not least, there was prior research explored the relationship between SUV_{max} and clinically significant PCa (csPCa) (International Society of Urological Pathology [ISUP] grade Group $\geq$2), identifying an optimal SUV_{max} cutoff to predict csPCa [19]. In this research, we mainly focused on PCa rather than csPCa as the major outcome in this research because in the context of the treatment pattern for PCa in China, recent research suggests that a mere 2.33% of low-risk PCa patients received active surveillance or observation, despite active surveillance being widely recommended for such patients according to guidelines [20]. The reason for this phenomenon is probably (1) the cultural background which makes it hard to tolerate a malignancy without a dissection; (2) the relatively low accessibility of persistent health care and follow-up service. However, we still incorporated a detailed and comprehensive analysis of the clinical variables and their correlation with csPCa in the supplementary material. As exhibited in the Supplementary Table 2, the PHI of patients in the csPCa group demonstrated significantly higher values compared to those in the non-csPCa group (46.8 *vs.* 34.2, $p=0.015$). The ^{18}F-PSMA-PET/MR results in csPCa diagnosis was 100% versus 65.5% in the non-csPCa ($p=0.052$). Additionally, the SUV_{max} in the csPCa group is comparable with than that in the non-csPCa group (11.00 *vs.* 7.30, $p=0.053$). Based on the ROC analysis (Supplementary Fig. 1), the combination model showed superiority in predicting csPCa compared to either the ^{18}F-PSMA-1007-PET/MR alone (AUC 0.830 *vs.* 0.672, $p=0.018$) or the PHI alone (AUC 0.830 *vs.* 0.746, $p=0.046$). Similar to the PCa diagnosis, the diagnostic ability of the combination model was significantly higher than that of the PHI alone when the cutoff was $\leq$43.5 (0.764 *vs.* 0.695, $p=0.034$, Supplementary Fig. 2). Supplementary Table 1 showed the NRI, indicating that once the PHI was set higher than 43.5, there was no significant improvement for the combination model compared to the PHI alone in terms of NRI (NRI: 10.34%, 95% CI: −0.74%—21.43%, $p=0.067$), consistent with the aforementioned ROC analysis. In the diagnostic value analysis, we found the optimal SUV_{max} for predicting csPCa to be 9.90, demonstrating a sensitivity of 66.67% and a specificity of 75.86% (Supplementary Table 3). However, the combination of the ^{18}F-PSMA-PET/MR and PHI yielded a higher Youden index, with a sensitivity of 85.71% and a specificity of 66.67%, when selecting 32 as the PHI cutoff.

There are several limitations in our study. Firstly, owing to the high cost associated with ^{18}F-PSMA-PET/MR, the current study was conducted with a relatively small sample size, potentially impacting the robustness of our findings. To mitigate this concern, we employed Firth's logistic regression as a standard approach to analyze binary outcomes in small samples, reducing potential bias [21]. The significant reclassification rates observed in this exploratory observational research suggest the potential prospects of the combined methods. This lays the groundwork for future investigations. Due to the restricted sample size, certain clinical parameters such as PSAD, previously proven significant in predicting PCa [22], could not be integrated into the logistic regression model. Since the number of events per variable in logistic regression analysis should be 10 or greater [23,24], incorporating additional variables could result in unreliability. Therefore, we focused on integrating the PHI and PSMA-PET/MR results, two pivotal variables, into the model to ensure the reliability of our analysis. Nevertheless, a comprehensive larger-scale study is necessary to validate and strengthen the findings of our research. Furthermore, a larger sample size would facilitate additional subgroup analyses, exploring the model performance among patients with different ISUP grade groups.

Secondly, limited to the equipment, we only used the systematic biopsy rather than the targeted biopsy on these patients. Consequently, we rely on an ultrasound-targeted systematic biopsy approach. However, based on a previous multicenter study that compared the diagnostic efficacy of the targeted biopsy and systematic biopsy, there was no significant difference between these two methods for detecting PCa with ISUP grade group 2 or higher. Notably, the systematic biopsy demonstrated superior diagnostic performance in detecting PCa with ISUP grade group 1 [25].

Thirdly, it is important to note that our study is based on the data from a single center. However, being a tertiary hospital with a significant patient volume, the inclusivity of patients in our study can be considered representative with minimal bias.

5. Conclusion

The combination of the PHI and ^{18}F-PSMA-1007-PET/MR outperforms the PHI alone for predicting PCa, especially in

avoiding the unnecessary biopsy. However, for patients with PHI of ≥43.5, the addition of ^{18}F-PSMA-1007-PET/MR to the PHI does not yield additional benefits.

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Conflicts of interest

The Shanghai Yuye Medical Technology Co. Ltd (Shanghai, China) supplied part of the tPSA, fPSA, and p2PSA tests. The collection of samples, analysis of data, and composition of the manuscript were carried out autonomously by the investigators and were not influenced by Shanghai Yuye Medical Technology Co. Ltd. There are no additional possible conflicting interests. The authors assert that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2023.10.003.

References

[1] Rebecca S, Miller Kd, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7—30.
[2] Kimura T, Egawa S. Epidemiology of prostate cancer in Asian countries. Int J Urol 2018;25:524—31.
[3] Bokhorst LP, Zhu X, Bul M, Bangma CH, Schröder FH, Roobol MJ. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial. BJU Int 2012;110:1654—60.
[4] Zhang G, Li Y, Li C, Li N, Li Z, Zhou Q. Assessment on clinical value of prostate health index in the diagnosis of prostate cancer. Cancer Med 2019;8:5089—96.
[5] Chiu PK, Ng CF, Semjonow A, Zhu Y, Vincendeau S, Houlgatte A, et al. A multicentre evaluation of the role of the prostate health index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. Eur Urol 2019;75:558—61.
[6] Liu A, Zhang M, Huang H, Zhang C, Ruan X, Lin W, et al. Clinical utility of ^{18}F-PSMA-1007 positron emission tomography/magnetic resonance imaging in prostate cancer: a single-center experience. Front Oncol 2021;10:612701. https://doi.org/10.3389/fonc.2020.612701.
[7] Sprute K, Kramer V, Koerber SA, Meneses M, Fernandez R, Ried C, et al. Diagnostic accuracy of ^{18}F-PSMA-1007 PET/CT imaging for lymph node staging of prostate carcinoma in primary and biochemical recurrence. J Nucl Med 2021;62:208—13.
[8] Zhou Y, Qi W, Cui J, Zhong M, Lv G, Qu S, et al. Construction and comparison of different models in detecting prostate cancer and clinically significant prostate cancer. Front Oncol 2022;12:911725. https://doi.org/10.3389/fonc.2022.911725.
[9] Hsieh PF, Li W, Lin W, Chang H, Chang C, Huang C, et al. Combining prostate health index and multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in an Asian population. World J Urol 2020;38:1207—14.
[10] Druskin SC, Tosoian JJ, Young A, Collica S, Srivastava A, Ghabili K, et al. Combining prostate health index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer. BJU Int 2018;121:619—26.
[11] Lopci E, Saita A, Lazzeri M, Lughezzani G, Colombo P, Buffi NM, et al. ^{68}Ga-PSMA positron emission tomography/-computerized tomography for primary diagnosis of prostate cancer in men with contraindications to or negative multiparametric magnetic resonance imaging: a prospective observational study. J Urol 2018;200:95—103.
[12] Donato P, Morton A, Yaxley J, Ranasinghe S, Teloken P, Kyle S, et al. ^{68}Ga-PSMA PET/CT better characterises localised prostate cancer after MRI and transperineal prostate biopsy: is ^{68}Ga-PSMA PET/CT guided biopsy the future? Eur J Nucl Med Mol Imag 2020;47:1843—51.
[13] Zhou Y, Fu Q, Shao Z, Qi W, Zhong M, Lv G, et al. The function of prostate health index in detecting clinically significant prostate cancer in the PI-RADS 3 population: a multicenter prospective study. World J Urol 2023;41:455—61.
[14] Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157—72.
[15] Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/mL: results of a prospective study in a clinical setting. Eur Urol 2011;60:214—22.
[16] Na R, Ye D, Qi J, Liu F, Helfand BT, Brendler CB, et al. Prostate health index significantly reduced unnecessary prostate biopsies in patients with PSA 2—10 ng/mL and PSA >10 ng/mL: results from a multicenter study in China. Prostate 2017;77:1221—9.
[17] Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging

triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682—9.

[18] Gi Russo, Regis F, Castelli T, Favilla V, Privitera S, Giardina R, et al. A systematic review and meta-analysis of the diagnostic accuracy of prostate health index and 4-kallikrein panel score in predicting overall and high-grade prostate cancer. Clin Genitourin Cancer 2017;15:429—39.e1. https://doi.org/10.1016/j.clgc.2016.12.022.

[19] Pepe P, Pepe L, Tamburo M, Marletta G, Savoca F, Pennisi M, et al. ^{68}Ga-PSMA PET/CT and prostate cancer diagnosis: which SUV_{max} value? In Vivo 2023;37:1318—22.

[20] Zhao F, Shen J, Yuan Z, Yu X, Jiang P, Zhong B, et al. Trends in treatment for prostate cancer in China: preliminary patterns of care study in a single institution. J Cancer 2018;9:1797—803.

[21] Puhr R, Heinze G, Nold M, Lusa L, Geroldinger A. Firth's logistic regression with rare events: accurate effect estimates and predictions? Stat Med 2017;36:2302—17.

[22] Roscigno M, Stabile A, Lughezzani G, Pepe P, Galosi AB, Naselli A, et al. The use of multiparametric magnetic resonance imaging for follow-up of patients included in active surveillance protocol. Can PSA density discriminate patients at different risk of reclassification? Clin Genitourin Cancer 2020;18:e698—704. https://doi.org/10.1016/j.clgc.2020.04.006.

[23] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373—9.

[24] Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol 1995;48:1495—501.

[25] Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Lechevallier FM, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100—9.