Int J Clin Exp Med 2017;10(2):2755-2763
www.ijcem.com /ISSN:1940-5901/IJCEM0037192

Original Article

Study on the diagnostic value of various volume-adjusted PSA derivatives in prostate cancer in South Chinese populations

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Received August 3, 2016; Accepted October 31, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Objective: We aim to investigate the differential value of volume-adjusted prostate specific antigen (PSA) derivatives in the diagnosis of prostate cancer. Method: A retrospective study was performed among 374 cases that needed to receive prostate biopsy procedure in our hospital from 2014.1.1 to 2015.10.31. All the patients received a 10-core systemic biopsy procedure with the trans-peritoneal access guided by transrectal ultrasound. Clinical parameters were documented, including PSA, prostate volume, pathological results, etc. Patients were divided into several subgroups, according to different PSA level and transrectal ultrasound findings. The diagnosis of prostate cancer was determined by the pathological evaluation of the biopsy specimen. Result: In the 374 cases, 164 cases (43.9%) were prostate cancer. 154 cases (41.2%) had visually suspicious lesion detected by transrectal ultrasound. 136 cases (36.4%) had a serum level of PSA ≤ 10 ng/ml. Transition zone PSA density showed a better diagnostic efficacy than PSA density and peripheral zone PSA density did in all subgroups, especially in PSA grey-zone (conventionally, 4-10 ng/ml). Besides, transition zone PSA density was elevated consistently with the rise of the grade groups of Gleason score. Conclusion: Transition zone PSA density can be used as a complementary prostate specific antigen derivative for the detection of prostate cancer, and therefore it may help to reduce the incidence of the unnecessary biopsy. In addition, it is a potential predictor for the prognosis of prostate cancer, to some extent.

Keywords: Volume-adjusted PSA derivatives, transperineal prostate biopsy, prostate cancer, transrectal ultrasound

Introduction

Prostate specific antigen (PSA) seemed to be the most successful and useful tumor biomarker in the last century, since it had a great contribution to the reduction in the overall mortality of prostate cancer (PCa) during the past 30 years [1]. However, PSA testing also has brought the great controversy to physicians on the subsequent overdiagnosis and overtreatment of PCa, which reached the peak in the year of 2012 when the U.S. Preventive Services Task Force (USPSTF) made the recommendations against PSA as a routine screening tool for PCa in western countries [2]. Thus, different types of PSA derivatives, novel biomarkers, genetic scoring systems, etc. have been developed to improve the detection of PCa and the evaluation of its clinical significance.

It was implied that PSA density (PSAD) can help reduce the numbers of unnecessary prostate biopsy, but its sensitivity and specificity remained unsatisfactory [3]. Two pioneer researches have described the efficacy of peripheral zone PSA density (PZPSAD) [4, 5], which showed the promise of this PSA derivative in the detection of PCa. Nevertheless, these researches took less consideration into the two key points of the relation between PSA and PCa. One is the tissue heterogeneity in prostate gland, which means PCa, benign prostate hyperplasia (BPH), prostatic inflammation may spontaneously exist in the same prostate gland, and they all can

Table 1. Clinical variable in prostate cancer and non-prostate cancer subjects

	Benign (N=210, mean ± SD**)	Malignant (N=164, mean ± SD)	*P* value
Age (years)	67.70±8.13	71.41±7.58	<0.001
PSA* (ng/ml)	14.71±16.57	95.00±224.71	<0.001
Total prostate volume (ml)	43.76±20.11	56.01±25.23	<0.001
PSA density (ng/ml^2)	0.28±0.31	2.28±6.28	<0.001
Transition zone volume (ml)	18.86±12.33	31.23±22.06	<0.001
Transition zone PSA density (ng/ml^2)	0.74±1.47	7.17±25.60	<0.001
Peripheral zone volume (ml)	24.90±12.61	24.77±9.28	0.914
Peripheral zone PSA density (ng/ml^2)	0.68±0.99	3.93±9.32	<0.001

*PSA: prostate specific antigen. **SD: standard deviation.

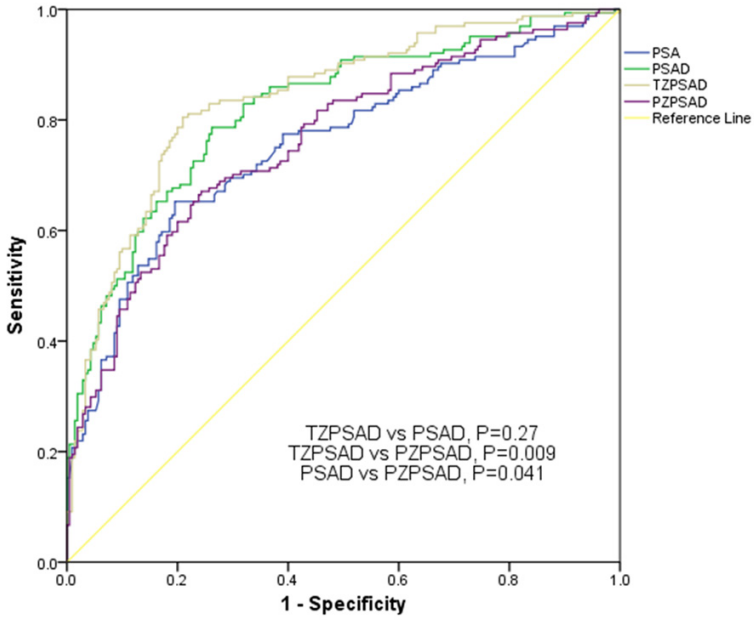

Figure 1. The ROC curve (AUCs) for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) as continuous variables in predicting PCa in all patients.

influence the serum level of PSA [6]. The other is that the expression of tissue PSA is less in PCa than normal structure while the leakage of PSA into blood has a great impact on the elevated serum level in patients with PCa [7]. As it is widely acknowledged that PCa usually occurs in peripheral zone while BPH is more likely to occur in transition zone of prostate, it seems that the influence of transition zone PSA density (TZPSAD) on PSA should also be taken into consideration for the decision making of prostate biopsy.

Therefore, our research aimed to evaluate the diagnostic efficacy of PSA derivatives (PSAD, PZPSAD and TZPSAD) in the detection of PCa in the patients from the south Chinese Han population who needed the prostate biopsy, which is probably helpful to reduce the unnecessary prostate biopsy.

Materials and methods

From 2014.1.1 to 2015.10.31, we consecutively recruited the patients who needed to receive the prostate biopsy procedure because of the suspicion of PCa in Huashan Hospital, Fudan University, China. The indication of the prostate biopsy in our hospital is the elevated PSA level above 4 ng/ml, or nodules detected by transrectal ultrasound (TRUS). 374 patients who met the criteria were included in the study and all patients signed informed consent. The study was approved by the IRB of Huashan Hospital. Patients received a 10-core systemic biopsy with the transperineal access guided by TRUS. Before the biopsy, the local anesthesia was delivered with 1% lidocaine. And all the biopsy procedures were performed by an urologist and a physician of ultrasonic medicine, both of who had the experience of over 200 cases of the collaboration in the procedures. The biopsy specimen was formalin-fixed and paraffin-embedded. The sections were stained with hematoxylin and eosin. Two pathologists independently evaluated the sections and delivered Gleason scores to the cases of PCa, which

Table 2. AUCs*, sensitivity and specificity of best cut-off value and specificity at 90% sensitivity for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) in patients with PSA of ≤ 10 and >10 ng/ml

	Factors	AUC	Best Cut-off value	Sensitivity %	Specificity %	Specificity at 90% sensitivity % (Cut-off value)
All patients (N=374)	PSA	0.756	17.35 ng/ml	65.2%	80.5%	32.4% (7.42 ng/ml)
	PSAD density	0.820	0.278 ng/ml^2	78.6%	73.8%	50.5% (0.184 ng/ml^2)
	Transition zone PSA density	0.839	0.694 ng/ml^2	80.5%	79,0%	51.0% (0.371 ng/ml^2)
	Peripheral zone PSA density	0.762	0.743 ng/ml^2	67.1%	75.5%	33.3% (0.317 ng/ml^2)
PSA ≤ 10 ng/ml (N=136)	PSA	0.572	7.42 ng/ml	52.9%	66.7%	22.7% (2.97 ng/ml)
	PSAD density	0.719	0.175 ng/ml^2	58.8%	79.4%	29.4% (0.095 ng/ml^2)
	Transition zone PSA density	0.769	0.265 ng/ml^2	85.3%	57.8%	36.4% (0.185 ng/ml^2)
	Peripheral zone PSA density	0.617	0.255 ng/ml^2	73.5%	51.0%	12.7% (0.125 ng/ml^2)
PSA>10 ng/ml (N=238)	PSA	0.768	17.35 ng/ml	82.3%	62.0%	33.3% (12.54 ng/ml)
	PSAD density	0.831	0.465 ng/ml^2	77.7%	73.1%	51.9% (0.295 ng/ml^2)
	Transition zone PSA density	0.835	0.795 ng/ml^2	86.9%	68.5%	73.8% (0.715 ng/ml^2)
	Peripheral zone PSA density	0.767	0.755 ng/ml^2	83.8%	58.3%	30.6% (0.535 ng/ml^2)

*AUC: areas under the receiver operator curve.

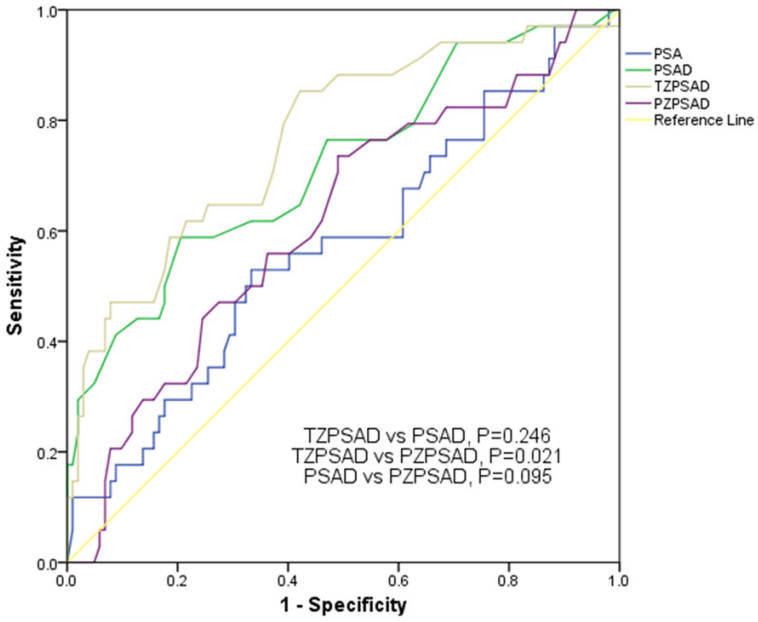

Figure 2. The ROC curve (AUCs) for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) as continuous variables in predicting PCa in patients with PSA ≤ 10 ng/ml.

would be judged by a third pathologist when two pathologists made the different diagnosis.

The clinical parameters such as age, PSA level, peripheral zone volume of prostate gland (PZV), transition zone volume of prostate gland (TZV), nodules detected by TRUS, the pathological type and Gleason score were recorded. We used TRUS to measure total prostate volume (TPV) and TZV with the formula for a prolate ellipsoid (length × width × height × 0.52). TPV minus TZV equals to PZV. Prostate-specific antigen densities (PSAD), PSAD for peripheral zone (PZPSAD), PSAD for transition zone (TZPSAD) were calculated by dividing PSA by TPV, PZV, and TZV, respectively. The nodules detected by TRUS were defined as the positive findings. According the novel prostate cancer grading system [8], we reclassified the patients by the new five grades based on the revised original Gleason score: group 1 (Gleason score ≤ 6), group 2 (Gleason score 3+4=7), group 3 (Gleason score 4+3=7), group 4 (Gleason score 8), and group 5 (Gleason score 9-10).

The statistical analysis was conducted with the software of IBM SPSS Statistics Version 20 (IBM Corp. U.S.A.). The difference of the means of age, PSA level, TPV, PSAD, PZV, TZV, PZPSAD, TZPSAD were compared by the independent samples t-test. Areas under the receiver operating characteristic (ROC) curve (AUC) were applied to evaluate the performances of PSA, PSAD, PZPSAD and TZPSAD in detecting PCa. The cut-off value was simultaneously identified

Table 3. AUCs*, sensitivity and specificity of best cut-off value and specificity at 90% sensitivity for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) in patients with positive & negative TRUS** findings, and negative TRUS findings accompanied with PSA ≤ 10 ng/ml

	Factors	AUC	Best Cut-off value	Sensitivity %	Specificity %	Specificity at 90% sensitivity % (Cut-off value)
Positive TRUS findings (N=154)	PSA	0.769	11.37 ng/ml	77.1%	67.3%	38.8% (6.99 ng/ml)
	PSAD density	0.808	0.285 ng/ml^2	78.1%	73.5%	49.0% (0.185 ng/ml^2)
	Transition zone PSA density	0.827	0.671 ng/ml^2	81.9%	71.4%	49.0% (0.380 ng/ml^2)
	Peripheral zone PSA density	0.764	0.496 ng/ml^2	79.0%	65.3%	36.7% (0.335 ng/ml^2)
Negative TRUS findings (N=220)	PSA	0.751	19.95 ng/ml	61.0%	85.1%	29.8% (7.73 ng/ml)
	PSAD density	0.801	0.278 ng/ml^2	79.7%	74.5%	24.2% (0.125 ng/ml^2)
	Transition zone PSA density	0.820	0.710 ng/ml^2	78.0%	82.6%	43.5% (0.305 ng/ml^2)
	Peripheral zone PSA density	0.750	0.755 ng/ml^2	69.5%	77.6%	25.5% (0.295 ng/ml^2)
Negative TRUS findings accompanied with PSA ≤ 10 ng/ml (N=90)	PSA	0.650	7.42 ng/ml	81.8%	58.0%	17.4% (5.41 ng/ml)
	PSAD density	0.680	0.225 ng/ml^2	54.5%	91.3%	15.9% (0.095 ng/ml^2)
	Transition zone PSA density	0.742	0.575 ng/ml^2	63.6%	89.9%	17.8% (0.175 ng/ml^2)
	Peripheral zone PSA density	0.582	0.385 ng/ml^2	45.5%	75.4%	17.4% (0.195 ng/ml^2)

*AUC: areas under the receiver operator curve. **TRUS: transrectal ultrasound.

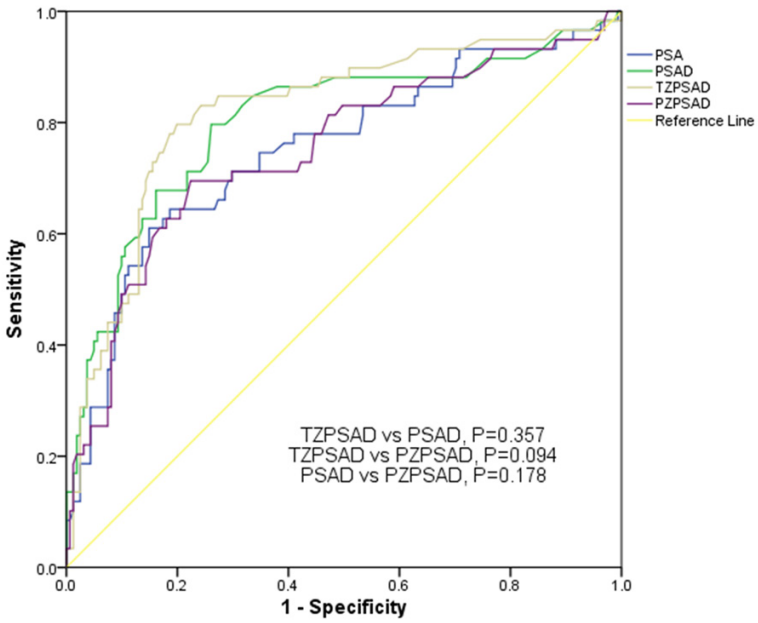

Figure 3. The ROC curve (AUCs) for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) as continuous variables in predicting PCa in patients with negative TRUS findings.

using the ROC curve and the best cut-off value was defined as the maximum value of sensitivity plus specificity (%). Spearman rank correlation analysis was used to find the association between the novel Gleason grading system and PSA derivatives. *P* value below 0.05 was considered statistically significant.

Results

Among all 374 cases, there were 164 cases (43.9%) diagnosed as PCa. 136 cases (36.4%) with the level of PSA ≤ 10 ng/ml. And 154 cases (41.2%) had the visually suspicious lesion detected by transrectal ultrasound. The clinical information of all the patients with and without PCa was shown in **Table 1**. Age, TPV, TZV, PSA, PSAD, TZPSAD and PZPSAD were all found significantly different between the PCa patients group and the non-PCa patients group (P<0.001).

The AUCs for PSA, PSAD, TZPSAD and PZPSAD as continuous variables in predicting PCa in all patients were 0.756, 0.820, 0.839 and 0.762, respectively. ROC curve analyses implied that the AUC regarding the TZPSAD and PSAD was higher than that regarding PZPSAD with a *P* value of 0.009 and 0.041, respectively (**Figure 1**; **Table 2**). This suggested that the TZPSAD had higher accuracy in predicting PCa. When the best TZPSAD cut-off as 0.694 ng/ml^2 was chosen, the sensitivity on predicting PCa was 80.5%, which was higher than those in the cases of PSA (65.2%), PSAD (78.6%) and PZPSAD (67.1%); the specificity was 79.0%, which was approximated to that in the cases of PSA (80.5%) and higher than those with PSAD (73.8%) and PZPSAD (75.5%). With 90% sensitivity for detecting PCa in all patients, TZPSAD revealed 51.0% specificity at the cutoff value of 0.371 ng/ml^2, which was higher than the specificity with PSA, PSAD and PZPSAD (32.4%, 50.5% and 33.3%, respectively).

We then divided the study cohort into two groups by the PSA levels. In the group of patients with a PSA level ≤ 10 ng/ml (PSA grey-zone), the AUCs for PSA, PSAD, TZPSAD and PZPSAD as continuous variables in predicting PCa were 0.572, 0.719, 0.769 and 0.617, respectively (**Table 2**). TZPSAD still had a better diagnostic efficacy than PZPSAD did (P=0.02) (**Figure 2**). At 90% sensitivity for detecting PCa, TZPSAD revealed a specificity of 36.4%, which was higher than those with PSA, PSAD and PZPSAD. When we chose 0.185 ng/ml^2 as the cut-off value, it can reduce unnecessary biopsy by 7.0% and 23.7% compared to PSAD and PZPSAD, respectively. Similar results were also found in patients with a PSA level above 10 ng/ml (**Table 2**).

In order to investigate the diagnostic efficacy of TZPSAD further, we re-divided patients into two groups by the TRUS findings (positive & negative findings in TRUS). From **Table 3** and **Figure 3**, it implied that TZPSAD still had a higher AUC than PSA, PSAD and PZPSAD in detecting PCa. However, we didn't find any statistical significance among them in ROC analysis. In the group with negative TRUS findings, when we chose 0.305 ng/ml^2 as the cut value of TZPSAD

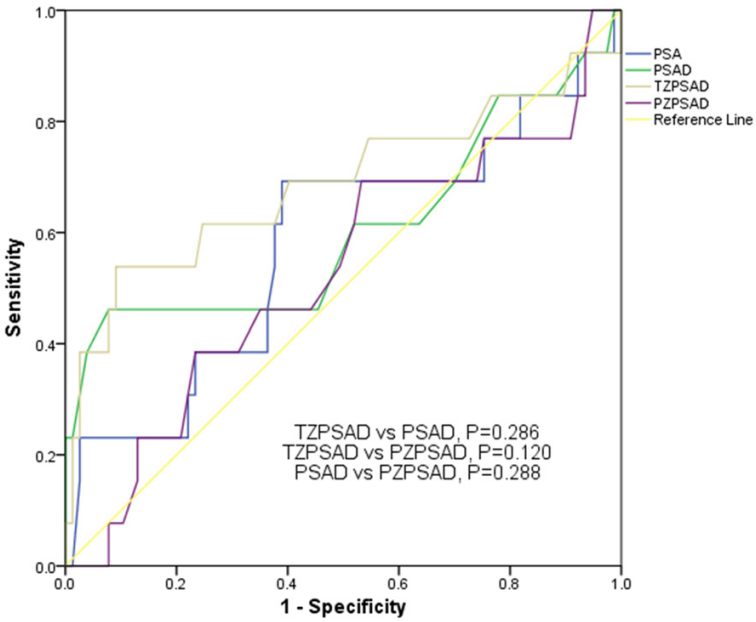

Figure 4. The ROC curve (AUCs) for prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD) as continuous variables in predicting PCa in patients with negative TRUS findings accompanied with PSA ≤ 10 ng/ml.

at 90% sensitivity, it can reduce unnecessary biopsy by 19.3% and 18.0% compared to PSAD and PZPSAD, respectively. We then analyze the diagnostic efficacy of TZPSAD in patients who had both negative TRUS findings and a PSA level of ≤ 10 ng/ml. Though TZPSAD had a highest AUC, no difference was found between them and their specificity at 90% sensitivity was similar (**Table 3**; **Figure 4**).

Spearman rank correlation analysis showed that PSA level, PSAD, TZPSAD and PZPSAD were all significantly associated with the grade groups of Gleason score (P<0.001). The correlation coefficients were 0.492, 0.484, 0.469 and 0.484, respectively, which means these four derivatives were elevated with the rise of the grades of the novel Gleason groups, (**Table 4**).

Discussion

PSA is a serine proteinase synthesized by prostate epithelial cells. It is widely used in the early detection and surveillance of PCa. However, PSA is just an organ-specific biomarker, but not cancer-specific. An increase in the serum level of PSA can be observed in many other occasions such as BPH, prostatitis, acute urinary retention, and some urological procedure, e.g. DRE, TRUS and cystoscopy [9]. Besides, PSA level also increases with aging. Therefore, PSA alone is probably no longer a best indicator of prostate biopsy. Moreover, the prostate biopsy can cause some complications such as infection, hematuria and hematospermia [10-12]. Recently, more and more researches have focused on the approaches developed to reduce the unnecessary biopsy and the missing diagnosis of PCa. For example, PSAD, TZPSAD and several other PSA derivatives were often used to guide the indication of biopsy in clinical trials [4, 5, 13].

In our study, we revealed that TZPSAD was a rational complementary derivative in predicting PCa, which was similar to other studies [13]. Our findings showed that TZPSAD owned a higher diagnostic efficacy than PZPSAD, especially in the patients with a PSA level ≤ 10 ng/ml, which indicated that TZPSAD could be used as a better complementary index in PSA grey-zone. Using TZPSAD would reduce the unnecessary biopsy compared to PZPSAD. However, some of studies suggested that PZPSAD was a more effective predictor [4, 5]. The main reason of the difference might be as follows: PCa usually occurs in peripheral zone and seldom causes the hyperplasia in transition zone. The tumor can damage prostate basal membrane, causing the leakage of PSA into the blood circulation [7]. On the other side, BPH is more likely to occur in transition zone of prostate [14]. Both peripheral and transition zone of prostate contribute to the PSA level. When the PSA level of two patients is the same, the one who has a higher TZPSAD means he owns a smaller transition zone volume. In another word, the peripheral zone of prostate or the leakage of PSA in it makes more contribution to his total serum PSA level. Thus, he is more likely to have PCa. Therefore, TZPSAD is a more accurate variable than PZPSAD in predicting PCa. It can eliminate

Table 4. The relationship between Gleason Grade Group and prostate specific antigen (PSA), PSA density (PSAD), transition zone PSA density (TZPSAD) and peripheral zone PSA density (PZPSAD)

Gleason Grade Group	PSA*	PSA density*	Transition zone PSA density*	Peripheral zone PSA density*
1 (N=36)	19.82±18.42	0.55±0.60	1.32±1.54	1.09±1.44
2 (N=27)	24.23±27.60	0.75±1.31	2.19±3.13	1.22±2.30
3 (N=41)	55.26±78.39	1.15±1.32	3.49±4.04	1.94±2.28
4 (N=37)	169.32±3.76	3.91±9.66	14.16±42.58	6.00±12.58
5 (N=23)	246.99±279.68	6.18±10.14	17.48±39.21	11.74±16.28

*Spearman rank correlation analysis: P<0.01.

some cases of PSA elevation caused by BPH and thereby avoid the unnecessary ultrasound-guided biopsy.

Our study also found that adjusting PSA to respective prostate volume, especially for transition zone volume, can increase the specificity of PSA in detecting PCa. Similar results were reported in a multicenter study which compared various PSA derivatives. The authors showed 14.3%, 20.2%, and 26.2% specificity for PSA, PSAD, and TZPSAD at 90% sensitivity, respectively [15]. The results were lower than those in our study. Our smaller sample might attribute to this difference. Besides, our patients were all from south China. It was always reported that Asian men had a much lower incidence of PCa, compared with other races [16].

Furthermore, we analyzed the association between Gleason score and TZPSAD. Gleason score is the most commonly used and most important histopathological grading system for PCa. As Gleason grading has a good relationship with biological behavior and prognosis, it has become one of the important indicators for the treatment and prognosis of PCa [17]. However, the prognosis of patients with a Gleason score of 3+4=7 and 4+3=7 was different according to the clinical practice, which didn't show in the current Gleason system. The novel PCa grading system published in 2015 [8] has a more accurate grade stratification than the current Gleason system and a potential to reduce overtreatment of PCa. Therefore, we introduced the novel PCa grading system into our study. Our results showed that TZPSAD was elevated with the increase of grade group of Gleason score, which suggested that TZPSAD may predict the clinical significance of PCa.

There remained several limitations in our study. First, the sample size of our study is relatively small. We recruited only 23 patients with PSA of <4 ng/ml and detected 5 cases of PCa. Therefore, it's difficult and meaningless to analyze the diagnostic efficacy of PSA and its derivatives in this range. Secondly, as mentioned before, PSA is elevated with the increase of age. The age of our sample ranges from 51 to 93. We didn't divide our cases by the age, which needs a further investigation in the future research. Thirdly, in addition to PSA derivatives, the novel diagnostic biomarkers and imaging tools have recently been introduced such as single nucleotide polymorphisms (SNPs) [18] and multiparametric magnetic resonance imaging (mpMRI) [19, 20]. Further studies are required to compare the diagnostic efficacy of TZPSAD and these new tools for detecting PCa.

In conclusion, TZPSAD can be used as a more reliable index of PSA for diagnosis of PCa than PZPSAD do, especially in the patients who have elevated PSA within grey-zone. It can reduce the cases of the unnecessary prostate biopsy and may be utilized as a potential predictor for the prognosis of PCa. TZPSAD also shows the best performance in predicting PCa in both patients with and without visually suspicious lesion detected by TRUS.

Acknowledgements

The study was supported by Scientific Research Foundation of Huashan North Hospital (Grand No.2015101). We thank all the study participants, urologists and study coordinators for participating in the study.

Disclosure of conflict of interest

None.

Authors' contribution

Yang T: Project development, data analysis, manuscript writing; Zhang LM: Project development, data collection, data analysis; Cai YH: Project development, data collection; Wu YS: Data collection; Liu SH: Data collection; Tong SJ: Data collection; Xiong ZQ: Data collection; Jiang HW: Manuscript Revision; Ding Q: Manuscript Revision. All authors reviewed and approved the manuscript.

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References

[1] Lilja H, Ulmert D, Bjork T, Becker C, Serio AM, Nilsson JA, Abrahamsson PA, Vickers AJ and Berglund G. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol 2007; 25: 431-436.

[2] Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012; 157: 120-134.

[3] Huang M, Lin Y, Xu A, Deng X, Lin X, Wu S, Diao P, Xie K, Tang P. Percent free prostate-specific antigen does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: a multicenter study. Med Oncol 2014; 31: 925-925.

[4] Zhang HM, Yan Y, Wang F, Gu WY, Hu GH, Zheng JH. Ratio of prostate specific antigen to the outer gland volume of prostrate as a predictor for prostate cancer. Int J Clin Exp Pathol 2014; 7: 6079-6084.

[5] Koo KC, Lee DH, Lee SH and Chung BH. Peripheral zone prostate-specific antigen density: an effective parameter for prostate cancer prediction in men receiving 5alpha-reductase inhibitors. Prostate Int 2013; 1: 102-108.

[6] Edlin RS, Heyns CF, Van Vuuren SP and Zarrabi AD. Prevalence of histological prostatitis in men with benign prostatic hyperplasia or adenocarcinoma of the prostate presenting without urinary retention. S Afr J Surg 2012; 50: 127-130.

[7] Hasui Y, Marutsuka K, Asada Y, Ide H, Nishi S, Osada Y. Relationship between serum prostate specific antigen and histological prostatitis in patients with benign prostatic hyperplasia. Prostate 1994; 25: 91-96.

[8] Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, Magi-Galluzzi C, Vickers AJ, Parwani AV, Reuter VE, Fine SW, Eastham JA, Wiklund P, Han M, Reddy CA, Ciezki JP, Nyberg T and Klein EA. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016; 69: 428-435.

[9] Abdel-Meguid TA, Mosli HA and Al-Maghrabi JA. Prostate inflammation. Association with benign prostatic hyperplasia and prostate cancer. Saudi Med J 2009; 30: 1563-1567.

[10] Abdelkhalek MA, Abdelshafy M, Elhelaly HA and El Nasr MK. Hemospermia after transrectal ultrasound (TRUS)-guided prostatic biopsy: a prospective study. J Egypt Soc Parasitol 2012; 42: 63-70.

[11] Gil-Vernet Sedo JM and Alvarez-Vijande Garcia R. Effect of intrarectal povidone-iodine in the incidence of infectious complications after transrectal prostatic biopsy. Arch Esp Urol 2012; 65: 463-466.

[12] Wagenlehner FM, van Oostrum E, Tenke P, Tandogdu Z, Çek M, Grabe M, Wullt B, Pickard R, Naber KG, Pilatz A, Weidner W, Bjerklund-Johansen TE; GPIU investigators. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol 2013; 63: 521-527.

[13] Tang P, Du W, Xie K, Deng X, Fu J, Chen H and Yang W. Transition zone PSA density improves the prostate cancer detection rate both in PSA 4.0-10.0 and 10.1-20.0 ng/ml in Chinese men. Urol Oncol 2013; 31: 744-748.

[14] Chopra S, Rowe E, Laniado M, Walker M. Relationship between chronic inflammation at prostate biopsy and transition zone prostate volume enlargement in a prospectively UK screened population. Br J Med Surg Urol 2012; 5: 115-119.

[15] Djavan B, Remzi M, Zlotta AR, Ravery V, Hammerer P, Reissigl A, Dobronski P, Kaisary A and Marberger M. Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial. Urology 2002; 60: 4-9.

[16] Matsuda T and Saika K. Comparison of time trends in prostate cancer incidence (1973-2002) in Asia, from cancer incidence in five continents, Vols IV-IX. Jpn J Clin Oncol 2009; 39: 468-469.

[17] Moussa AS, Li J, Soriano M, Klein EA, Dong F, Jones JS. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. BJU Int 2009; 103: 43-48.

[18] Kader AK, Sun J, Reck BH, Newcombe PJ, Kim ST, Hsu FC, D'Agostino RB Jr, Tao S, Zhang Z, Turner AR, Platek GT, Spraggs CF, Whittaker JC, Lane BR, Isaacs WB, Meyers DA, Bleecker ER, Torti FM, Trent JM, McConnell JD, Zheng SL, Condreay LD, Rittmaster RS, Xu J. Potential impact of adding genetic markers to clinical parameters in predicting prostate biopsy outcomes in men following an initial negative biopsy: findings from the REDUCE trial. Eur Urol 2012; 62: 953-961.

[19] Borkowetz A, Platzek I, Toma M, Laniado M, Baretton G, Froehner M, Koch R, Wirth M and Zastrow S. Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer. BJU Int 2015; 116: 873-879.

[20] Tonttila PP, Lantto J, Paakko E, Piippo U, Kauppila S, Lammentausta E, Ohtonen P and Vaarala MH. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016; 69: 419-25.