Original Research

The diagnostic value of a new formula combining age and prostate volume in prostate cancer

Xiaobo Yang[1,†], Jiahao Shan[2,†], Qiang Zhang[1], Zhongyu Yuan[2], Haoran Xu[2], Ziyang Liu[2], Xiaojie Zhou[2], Wenzhuo Ma[2], Hongbin Shi[1,*]

[1]Department of urology, General Hospital of Ningxia Medical University, 750004 Yinchuan, Ningxia, China
[2]School of Clinical Medicine, Ningxia Medical University, 750004 Yinchuan, Ningxia, China
*Correspondence: shb0525@163.com (Hongbin Shi)
[†]These authors contributed equally.

Abstract

Background and objective: This study combined two clinical indicators (age and prostate volume (PV)) to generate age to PV (AVR) ratio, whose diagnostic value for prostate cancer (PCa) was examined based on prostate specific antigen (PSA) in the range of 4–20.0 ng/mL. **Methods**: The medical records of patients who underwent transrectal ultrasound-guided biopsy of the prostate in our hospital from June 2015 to June 2019 were examined retrospectively. According to the pathological results of the biopsy, the patients were divided into the PCa and benign prostatic hyperplasia (BPH) groups. Receiver operating characteristic (ROC) curves for TPSA, PSAD, PV, (F/T)PSA, AVR, and PSA-AV were plotted with SPSS 26.0 and GraphPad Prism 5.0, and areas under the ROC curves (AUROCs) were determined and compared by Delong test. A log-linear model was used to compare AVR and other parameters with similar high sensitivities, for specificity. **Results**: The AUROC for AVR was significantly different from those of TPSA ($p < 0.001$), PV ($p = 0.004$), (F/T)PSA ($p < 0.001$), and PSA-AV ($p = 0.006$), and similar to that of PSAD ($p = 0.064$). With the same high sensitivity (90.0%), log-linear model analysis showed that the specificity of AVR was significantly higher than those of TPSA and (F/T)PSA ($p < 0.01$), while there were no significant differences among AVR and PSAD, PV and PSA-AV. **Conclusion**: With PSA in the range of 4–20.0 ng/mL, AVR may be useful in sparing an invasive intervention for a number of patients.

Keywords: Prostate cancer; Prostate-specific antigen density; PSA-AV score; Prostate-specific antigen

1. Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the most common benign and malignant prostate diseases in middle-aged and elderly men, respectively [1]. PCa is one of the most common malignant tumors in the male genitourinary system. In the United States, it ranks first in terms of incidence among all male malignant tumors [2]. In recent years, with the improvement of living standards and the increase of aging populations, the incidence of PCa in China has steadily increased [3,4]. At present, screening of PCa mainly depends on prostate-specific antigen (PSA) and its derivatives, rectal digital exam (RDE), ultrasound, Magnetic Resonance Imaging (MRI), etc.

Wang *et al*. [5] found that PSA levels are significantly higher in patients with PCa compared with healthy men, suggesting that PSA can be used as a diagnostic indicator of PCa. However, because PSA is organ-specific rather than tumor-specific, and several factors may lead to its level increase [6,7], this biomarker has a number of limitations in distinguishing prostate hyperplasia from PCa, especially with PSA levels in the range of 4–10 ng/mL. Therefore, this interval is also known as the "diagnostic gray area" in PCa [8]. However, a previous research demonstrated that PSA at 4–20.0 ng/mL should be considered the "diagnostic gray area" in PCa [9]. In order to further improve the diagnosis of PCa in the "diagnostic gray area", a number of scholars have proposed prostate volume (PV), prostate specific antigen density (PSAD: TPSA/PV), free/total PSA ((F/T)PSA: FPSA/TPSA), and other related indicators.

Studies have shown that age and PV affect PSA levels [10,11], which may further influence the diagnosis of PCa. Some risk evaluators (e.g., ERSPC RC3 DRE, TRUS volume and ERPSC MRI) have also added factors such as age and prostate volume. In addition, compared with European and American countries, Chinese needle biopsy patients have the characteristics of older age, higher PSA, and smaller PV [12]. Therefore, we combined the two clinical indicators of age and PV to propose a new indicator, i.e., age to volume ratio (AVR), which was examined for diagnostic value comparatively to TPSA, (F/T)PSA, PV, PSAD and PSA-AV((Age × PV) / TPSA), in PCa with PSA levels of 4–20.0 ng/mL. This study provides a tool for further improving the diagnosis of PCa.

2. Materials and methods

After approval of the study protocol by the Ethics Committee of the General Hospital of Ningxia Medical University, the medical records of patients who underwent transrectal ultrasound-guided biopsy of the prostate in our

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Table 1. Baseline clinical data in the PCa and BPH groups.

	PCa	BPH	t/Z	p
PV (mL) Mean ± SD	46.74 ± 31.36	73.23 ± 35.18	−5.00	<0.001
Age (years) Mean ± SD	71.20 ± 6.70	66.51 ± 7.72	−3.22	0.001
TPSA (ng/mL) Median (IQR)	12.68 (10.39, 16.87)	11.61 (8.63, 14.79)	−1.53	0.126
(F/T)PSA Median (IQR)	0.14 (0.09, 0.16)	0.15 (0.10, 0.20)	−1.03	0.193
PSAD (ng/mL/mL) Median (IQR)	0.31 (0.18, 0.47)	0.17 (0.11, 0.26)	−4.63	<0.001
AVR Median (IQR)	1.84 (1.48, 2.27)	0.99 (0.70, 1.35)	−5.64	<0.001
PSA-AV Median (IQR)	249.53 (141.16, 378.71)	376.83 (247.34, 637.59)	−3.89	<0.001

Age- and PV-based data were normally distributed, and compared by the Student's *t*-test. TPSA, (F/T)PSA, PSAD, AVR, and PSA-AV data were non-normally distributed, and compared by the Mann-Whitney U test. PV, prostate volume; TPSA, total prostate specific antigen; (F/T)PSA, ratio of FPSA to TPSA; PSAD, prostate specific antigen density; AVR, the ratio of age to volume; PSA-AV, prostate specific antigen-age volume score.

hospital from June 2015 to June 2019 were collected retrospectively. All blood samples were collected on the second day after admission, and tPSA and fPSA were quantitated by the laboratory department of our hospital with an electrochemical luminescence assay kit (Roche Diagnostic GmbH, Mannheim, Germany). The Chinese Urological Association (CUA) guidelines recommended the following items for puncture indications: (1) prostatic nodules found by DRE; (2) abnormal images of the prostate detected by B-scan ultrasonography, computed tomography (CT) or MRI; (3) PSA >10 ng/mL; (4) PSA = 4–10 ng/mL, abnormal (F/T)PSA or abnormal PSAD value.

A standard prostate biopsy guided by an ultrasound probe (ProFocus 2202 Ultra View, BK Medical, Herlev, Denmark) was performed by two experienced urologists [13]. Prostate specimens were diagnosed by pathologists in the pathology department of our hospital, and divided into the PCa and BPH groups according to the pathological results. PV was determined by Transrectal Ultrasonography as $0.52 \times height \times length \times width$. Inclusion criteria were: (1) >50 years of age; (2) PSA = 4–20.0 ng/mL; (3) first-time prostate needle biopsy. Exclusion criteria were: (1) urinary tract infection or obstruction; (2) digital rectal examination, prostate massage, cystoscopy or other procedures within two weeks before the PSA test; (3) diagnosis of prostatitis; or (4) other cancers.

3. Statistical analysis

All data were processed and statistically analyzed with SPSS 26.0 (IBM, Armonk, NY, USA) and GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA, USA). Continuous variables conforming to normal distribution were analyzed by the Student's *t* test [14], and non-normally distributed ones were analyzed by the Mann-Whitney U test [15]. Receiver operating characteristic (ROC) curves were employed to evaluate and compare the efficacies of PSA, PSAD, (F/T)PSA, PSA-AV, and AVR in the diagnosis of PCa, with Delong test performed to evaluate the differences among them [16]. Considering the small sample size and how much power could be provided for further analysis to support our conclusions, we used the PASS15.0 (NCSS LLC, Kaysville, UT, USA) software (log rank test) for statistical performance analysis [17]. The sensitivity of each parameter was about 90%, and the logarithmic linear model was used to analyze specificity differences among these diagnostic parameters [18]. A difference was statistically significant at $p < 0.05$.

4. Results

4.1 Patient baseline characteristics

A total of 120 patients were enrolled in this study, including 39 (32.5%) cases in the PCa group and 81 (67.5%) in the BPH group. Average age in the PCa group was 71.20 ± 6.70 years, and PV averaged 46.74 ± 31.36 mL; the median TPSA was 12.68 (10.39–16.87) ng/mL. Average age in the BPH group was 66.51 ± 7.72 years, and PV averaged 73.23 ± 35.18 mL; the median TPSA was

Table 2. AUROC values and 95% CIs for various parameters in the diagnosis of PCa.

	TPSA	PSAD	PV	(F/T)PSA	AVR	PSA-AV
AUROC	0.586	0.761	0.783	0.573	0.819	0.720
95% CI	0.478–0.695	0.669–0.853	0.692–0.873	0.465–0.682	0.734–0.903	0.623–0.817
p	0.126	<0.001	<0.001	0.194	<0.001	<0.001

TPSA, total prostate specific antigen; PSAD, prostate specific antigen density; PV, prostate volume; (F/T)PSA, free/total prostate specific antigen; AVR, ratio of age to volume; PSA-AV, prostate specific antigen age volume score.

11.61 (8.63–14.79) ng/mL. After comparing data between the PCa and BPH groups, it was concluded that age- and PV-based data were normally distributed (Table 1). However, TPSA, (F/T)PSA, PSAD, AVR, and PSA-AV were non-normally distributed. Table 1 indicates that there were no significant differences in TPSA and (F/T)PSA between the PCa and BPH groups (p_{TPSA} = 0.126 and $p_{(F/T)PSA}$ = 0.193). There were significant differences in age (p = 0.001), PV ($p < 0.001$), PSAD ($p < 0.001$), AVR ($p < 0.001$), and PSA-AV ($p < 0.001$) between the two groups.

4.2 The diagnostic value of AVR in PCa

Figs. 1,2 show ROC curves for TPSA, PV, (F/T)PSA, PSAD, AVR, and PSA-AV. As presented in Table 2, AUROC values for TPSA, PSAD, PV, (F/T)PSA, AVR, and PSA-AV were 0.586, 0.761, 0.783, 0.573, 0.819, and 0.720, respectively, and their corresponding 95% CIs were 0.478–0.695, 0.669–0.853, 0.692–0.873, 0.465–0.682, 0.734–0.903 and 0.623–0.817, respectively. These findings indicated that TPSA and (F/T)PSA had low diagnostic values in PCa, while PSAD, PV, AVR, and PSA-AV have moderate diagnostic values. Delong test was used to compare differences in AUROC values for various diagnostic parameters. As shown in Table 3, the AUROC for TPSA was significantly different from those of PSAD ($p < 0.001$), PV (p = 0.007), AVR ($p < 0.001$), and PSA-AV (p = 0.008), with no significant difference compared with that of (F/T)PSA (p = 0.868). The AUROC for PSAD was noticeably different from those of (F/T)PSA (p = 0.002) and PSA-AV ($p <$ 0.001), with no significant differences compared with those of AVR (p = 0.064) and PV (p = 0.499). The AUROC for PV was remarkably different from those of (F/T)PSA ($p <$ 0.001) and AVR (p = 0.004), with no significant difference compared with that of PSA-AV (p = 0.055). The AUROC for (F/T)PSA was markedly different from those of AVR ($p < 0.001$) and PSA-AV (p = 0.014). The AUROC for AVR was significantly different from that of PSA-AV (p = 0.006).

4.3 Statistical power analysis of AVR and other parameters

Next, we calculated the statistical powers of AVR and TPSA, PSAD, PV, (F/T)PSA and PSA-AV. The results indicated that the statistical powers that could distinguish AUROC differences between AVR and TPSA, PV, (F/T)PSA
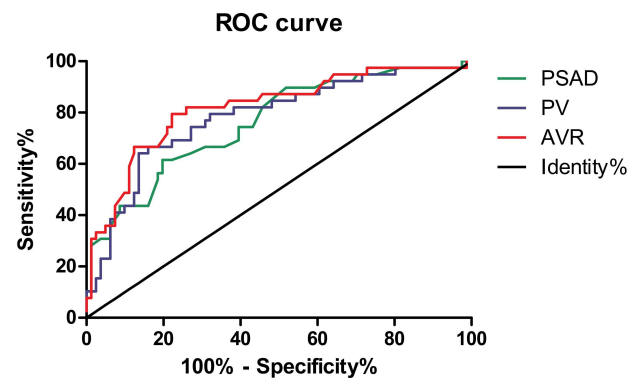
Fig. 1. ROC curves for PV, PSAD and AVR in the diagnosis of prostate cancer. ROC, Receiver operating characteristic; PV, Prostate volume; PSAD, Prostate-specific antigen density; AVR, Ratio of age to volume.
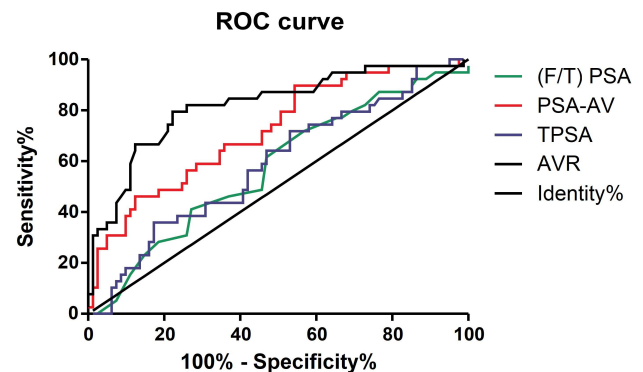
Fig. 2. ROC curves for PSA-AV, (F/T)PSA and TPSA in the diagnosis of prostate cancer. ROC, Receiver operating characteristic; PSA-AV, Prostate specific antigen age volume score; (F/T)PSA, Free/total prostate-specific antigen; TPSA, Total prostate-specific antigen; AVR, Ratio of age to volume.

and PSA-AV were 99.87%, 14%, 99.96% and 63.11%, respectively. The statistical power of the non-significant difference between AVR and PSAD in the AUROC for PCa diagnosis was 28.41% (Table 4).

Table 3. AUROC value comparisons between each pair of diagnostic indices.

	TPSA	PSAD	PV	(F/T)PSA	AVR	PSA-AV
TPSA	–	–	–	–	–	–
PSAD	<0.001	–	–	–	–	–
PV	0.007	0.499	–	–	–	–
(F/T)PSA	0.868	0.002	<0.001	–	–	–
AVR	<0.001	0.064	0.004	<0.001	–	–
PSA-AV	0.008	<0.001	0.055	0.014	0.006	–

TPSA, total prostate specific antigen; PSAD, prostate specific antigen density; PV, prostate volume; (F/T)PSA, free/total prostate specific antigen; AVR, ratio of age to volume; PSA-AV, prostate specific antigen age volume score.

Table 4. Statistical power analysis of AVR and other parameters.

	TPSA	PSAD	PV	(F/T)PSA	AVR	PSA-AV
AUC	0.586	0.761	0.783	0.573	0.819	0.720
Power (%)	99.87*	28.41*	14.00*	99.96*	—	63.11*

TPSA, total prostate specific antigen; PSAD, prostate specific antigen density; PV, prostate volume; (F/T)PSA, free/total prostate specific antigen; AVR, ratio of age to volume; PSA-AV, prostate specific antigen age volume score. *: Comparison of other indicators with AVR.

4.4 Specificities of diagnostic parameters with high sensitivity

After adjusting the sensitivities of TPSA, PSAD, PV, (F/T)PSA, AVR and PSA-AV to about 90% (35 true positive and 4 false positive cases in the PCa group), the cut-off points (it is generally considered that the value with the largest sum of sensitivity and specificity is the best diagnostic cut-off point) of various diagnostic parameters were 7.30, 0.16, 77.82, 0.26, 0.89 and 514.26, respectively, and their specificities were 15%, 41%, 37%, 15%, 40% and 33%, respectively. Logarithmic linear model analysis showed that the specificity of AVR was significantly higher than those of TPSA and (F/T)PSA ($p < 0.01$), with no statistically significant differences compared with those of PSAD, PV and PSA-AV (Table 5).

5. Discussion

PSA is a serine protease secreted by the prostate tissue [19]. Under normal circumstances, only a small portion of PSA enters the blood stream and becomes serum PSA. However, in case of pathological changes in the gland tissue, the barrier composed of endodermis, basal cell layer, and basement membrane may be destroyed, and PSA may leak into the lymphatic system and enter the circulation, increasing serum PSA levels [20,21]. It was reported that urinary tract infection, RDE, medical operations, and other factors can affect the serum content of PSA [22]. Therefore, PSA has some limitations in the early screening of PCa, especially with values in the "PSA gray zone".

PSA in serum mainly exists in free and bound states. When PCa occurs in the actual glands, TPSA levels may increase, whereas FPSA may not noticeably change. Therefore, (F/T)PSA can be used for the early screening of PCa in patients with PSA in the gray area. Multiple studies have demonstrated that (F/T)PSA has a higher diagnostic value than PSA, especially with PSA levels of 4–10 ng/mL [23,24]. However, a meta-analysis indicated that the determination of (F/T)PSA is associated with low sensitivity and specificity in the diagnosis of PCa, and is not therefore recommended for the diagnosis of PCa alone [25]. In the present study, when PSA levels were 4–20.0 ng/mL, no significant difference was found between the PCa and BPH groups. According to AUROC values, the diagnostic values of TPSA and (F/T)PSA in PCa were insignificant. With the sensitivities of TPSA and (F/T)PSA set to 90%, the specificity in PCa diagnosis was low, corroborating a meta-analysis [23]. Since there are differences in serum PSA levels in patients with BPH of different ages [26,27], it may also cause a certain degree of bias.

A previous study showed that PV in patients with PCa is smaller than that of patients with BPH, and the detection rate of PCa increases with decreasing PV [28,29]. Previous reports demonstrated that the diagnostic value of PSAD in the PSA gray area (4–10 ng/mL) is noticeably higher than those of PSA and TPSA. It was suggested that the critical value for PSAD should be set to 0.15; the greater the value, the greater the possibility of PCa diagnosis [30,31]. In the present study, although the AUROC for PV (0.783) was higher than that of PSAD (0.761), there was no significant difference between them ($p = 0.499$). A previous study reported that with PSA levels of 2–20 ng/mL, PV and PSAD have the same diagnostic values in PCa, being superior to TPSA and (F/T)PSA [32], consistent with the results of the present study.

Studies have demonstrated that age is closely associated with PCa. PCa often occurs in middle-aged and elderly men, and its morbidity and mortality are positively correlated with age [33,34]. In addition, the detection rate in the "PSA gray zone" increases with age. A study similarly showed that utilizing different cutoff points for PSA in different age-based groups could prevent unnecessary prostate biopsy. Patel *et al*. [35] proposed the PSA-AV score by combining the three clinical indexes of age, PV, and PSA for the first time. A study conducted in Turkey revealed no superiority of PSA-AV score in patients with PV values of 20–60 cm³ [36]. However, Chinese scholars further studied the clinical significance of PSA-AV score in the Chinese population, and found that with a critical value of PSA-AV score of 400, it has the same diagnostic value as PSAD in the diagnosis of PCa, being superior to TPSA [37]. In the present research, the PSA-AV score was assessed, and a sig-

Table 5. Specificities of diagnostic parameters with high sensitivity.

	Cutoff point	True positive	False positive	True negative	False negative	Specificity	Z	p
TPSA	7.30	35	69	12	4	0.15	3.39*	0.001
PSAD	0.16	35	48	33	4	0.41	0.16*	0.873
PV	77.82	35	51	30	4	0.37	0.32*	0.748
(F/T)PSA	0.26	35	69	12	4	0.15	3.39*	0.001
AVR	0.89	35	49	32	4	0.40	–	–
PSA-AV	514.26	35	54	27	4	0.33	0.81*	0.418

TPSA, total prostate specific antigen; PSAD, prostate specific antigen density; PV, prostate volume; (F/T)PSA, free/total prostate specific antigen; AVR, ratio of age to volume; PSA-AV, prostate specific antigen age volume score. *: Comparison of other indicators with AVR.

nificant difference was found between the PCa and BPH groups ($Z = -3.89$, $p < 0.01$). In addition, PSA-AV score had the same diagnostic value as PSAD in the diagnosis of PCa, and was superior to TPSA and (F/T)PSA. The current results corroborate Wu *et al.* With the sensitivity of PSA-AV set to 90%, its specificity for PCa diagnosis was 33%, which was lower than that of PSAD, but not significantly ($Z = 0.81$, $p = 0.418$).

In the current study, median age was elevated in patients with PCa compared with BPH cases, while the median volume was smaller. As shown above, the PCa and BPH groups significantly differed in age (71.20 ± 6.70 years vs 66.51 ± 7.72 years, $p < 0.001$) and size (46.74 ± 31.36 mL vs 73.23 ± 35.18 mL, $p < 0.001$). Therefore, the age to volume ratio was proposed in this study for further analysis. Our findings unveiled that AVR had a diagnostic value similar to that of PSAD in the diagnosis of PCa, being superior to TPSA, PV, (F/T)PSA, and PSA-AV. For general diagnostic experiments, the cut-off point corresponding to the maximum Youden index is the best critical value, but some scholars believe that in tumor diagnostic assays, less than 90% sensitivity is hardly suitable for clinical diagnosis and treatment [38]. Therefore, in order to further evaluate the diagnostic efficacy of PCa, we set the sensitivities of TPSA, PSAD, PV, (F/T)PSA, AVR and PSA-AV to 90%, and compared the specificities of the diagnostic parameters by logarithmic linear model analysis. The results showed that under the premise of high sensitivity, the specificity of AVR in the diagnosis of PCa was significantly higher than those of TPSA and PSA, with no significant differences compared with those of PSAD, PV and PSA-AV. In other words, if AVR is used for PCa screening, 32 of the 81 patients in the BPH group would be exempted from prostate biopsy in case of high sensitivity.

With the sample size of 39 cases and 81 controls, and given a two-side type one error of 0.05, we could detect statistical differences between AVR (AUC = 0.819) and TPSA (AUC = 0.586), PV (AUC = 0.783), (F/T)PSA (AUC = 0.573) and PSA-AV (AUC = 0.720) with powers of 99.87%, 14.00%, 99.96% and 63.11%, respectively. The power with no statistically significant difference between

AVR and PSAD (AUC = 0.761) was 28.41%. In view of low statistical powers between AVR and PSAD and PV, this may be related to the following reasons. (1) There was no statistical difference in the diagnosis of PCa between AVR and PSAD, as well as between AVR and PV. However, due to the small sample size of this study, it could not be further assessed. (2) Differences between AVR and PSAD and PV had statistical significance in the diagnosis of PCa, but due to the small sample size, they could not provide enough evidence. (3) AVR and PSAD, as well as AVR and PV overlapped in their 95% CIs (AVR, 95% CI 0.734–0.903; PSAD, 95% CI 0.669–0.853; PV, 95% CI 0.692–0.873) and ROC curves (Fig. 1), which may also lead to a lower statistical power. Based on the above results, we believe that in the range of 4–20.0 ng/mL PSA, AVR may be used as a new diagnostic parameter for PCa screening, However, these results may need larger studies for further verification.

At present, the screening of PCa mainly relies on PSA, which is easily affected by many factors, including age and PV, so the diagnosis rate of PCa is low. This is the first study to propose AVR as a clinical indicator in combination with age and PV, for the early screening of PCa. Unlike other indicators, AVR does not depend on PSA but combines two easily accessible clinical indicators to further diagnose PCa. According to the above results, AVR has a certain diagnostic value in PCa, which may reduce the influences of age and PV on PSA levels, thereby further improving PCa diagnosis. This may further confirm the influences of age and prostate volume on PSA. The above findings indicate that in the range of 4–20.0 ng/mL PSA, AVR may be useful in sparing an invasive intervention in a number of patients, but the sample size of this study was small, and further research is needed. In addition, considering that all data in this study were collected in a population of Chinese descent, the conclusion may not be applicable to other races.

6. Conclusions

In this study, compared to PSAD, AVR showed the same diagnostic value in the screening of PCa with PSA at the range of 4–20.0 ng/mL, with superiority to TPSA, PV,

(F/T)PSA, and PSA-AV. Therefore, AVR may be used as a new diagnostic parameter for the early screening of PCa, and may help spare an invasive intervention in a number of patients. However, since this was a single-center study, multicenter large studies are still required to further examine AVR's clinical significance in the early screening of PCa.

Abbreviations

PCa, Prostate cancer; PSA, prostate specific antigen; CUA, Chinese Medical Association; BPH, Benign Prostate hyperplasia; PV, prostate volume; TPSA, Total prostate specific antigen; FPSA, Free prostate specific antigen; (F/T)PSA, FPSA/TPSA; PSAD, Prostate specific antigen density; PSA-A, prostate specific antigen age volume score; PSA-AV, prostate specific antigen age volume score.

Author contributions

HS and XY conceived and designed the experiments; XY and JS performed the experiments; JS analyzed the data; QZ, ZY, HX, ZL, XZ and WM, contributed materials; XY and JS, wrote the paper.

Ethics approval and consent to participate

This work was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (approval number: 2020-08). All subjects gave their informed consent for inclusion before they participated in the study.

Acknowledgment

Funding

Conflict of interest

The authors declare no conflict of interest.

References

[1] Daniyal M, Siddiqui ZA, Akram M, Asif HM, Sultana S, Khan A. Epidemiology, Etiology, Diagnosis and Treatment of Prostate Cancer. Asian Pacific Journal of Cancer Prevention. 2014; 15: 9575–9578.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA: A Cancer Journal for Clinicians. 2018; 68: 7–30.

[3] Li M, Zhang SW, Ma JH, Chen WQ, Na YQ. Comparative study on the incidence trend of prostate cancer in some cities and counties in China. Chinese Journal of Urology. 2009; 6: 10–12.

[4] Han SJ, Zhang SW, Chen WQ, LI. CL. Analysis on the status and prevalence of prostate cancer in China. Clinical Oncology. 2013; 18: 330–334.

[5] Wang MC, Papsidero LD, Kuriyama M, Valenzuela LA, Murphy GP, Chu TM. Prostate antigen: a new potential marker for prostatic cancer. Prostate. 1981; 2: 89–96.

[6] Gui-zhong L, Libo M, Guanglin H, Jianwei W. The correlation of extent and grade of inflammation with serum PSA levels in patients with IV prostatitis. International Urology and Nephrology. 2011; 43: 295–301.

[7] Lee A, Lim J, Gao X, Liu L, Chia SJ. A nomogram for prediction of prostate cancer on multi-core biopsy using age, serum prostate-specific antigen, prostate volume and digital rectal examination in Singapore. Asia-Pacific Journal of Clinical Oncology. 2017; 13: e348–e355.

[8] Gupta M, McCauley J, Farkas A, Gudeloglu A, Neuberger MM, Ho Y, et al. Clinical practice guidelines on prostate cancer: a critical appraisal. Journal of Urology. 2015; 193: 1153–1158.

[9] Xie SW, Li HL, Du J, Xia JG, Guo YF, Xin M, et al. Influence of serum prostate-specific antigen (PSA) level, prostate volume, and PSA density on prostate cancer detection with contrast-enhanced sonography using contrast-tuned imaging technology. Journal of Ultrasound in Medicine. 2013; 32: 741–748.

[10] Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. Journal of the American Medical Association. 1993; 270: 860–864.

[11] Xie GS, Huang YH, Yan CY, Pu JX, Li G, Ouyang J, et al. Age-specific analysis of prostate-specific antigen and related parameters in 22055 middle-aged and elderly men. Chinese Journal of Urology. 2013; 34: 613–617.

[12] Chen R, Xie LP, Zhou LQ, Huang YR, Fu Q, He DL, et al. Investigation report on the status of prostate biopsy in member hospitals of China Prostate Cancer Alliance. Chinese Journal of Urology. 2015; 36: 342–345.

[13] Sighinolfi MC, Rocco B. Re: EAU Guidelines: Prostate Cancer 2019. European Urology. 2019; 76: 871.

[14] Page BR. The 'student'' of the student's t-test. Physics Teacher. 1995; 33: 490–496.

[15] Pacut A. How to use the Mann-Whitney test to detect a change in distribution for groups. Acta Neurobiologiae Experimentalis. 1987; 47: 19–26.

[16] Song HL, He J, Yu HT, Li L. Using the area under the ROC curve to evaluate and compare two related diagnostic tests. Journal of Second Military Medical University. 2006; 5.

[17] Qian J, Chen PY. Discussion on the Significance of Computational Observation Test Power in Hypothesis Test. Chinese Health Statistics. 2005; 3.

[18] Ma LM, Wang Jun. Application of log-linear model in clinical trial data analysis. Chinese Journal of Clinical Pharmacology. 2011; 3.

[19] Papsidero LD, Kuriyama M, Wang MC, Horoszewicz J, Leong SS, Valenzuela L, et al. Prostate antigen: a marker for human prostate epithelial cells. Journal of the National Cancer Institute. 1981; 66: 37–42.

[20] Bigler SA, Deering RE, Brawer MK. Comparison of microscopic vascularity in benign and malignant prostate tissue. Human Pathology. 1993; 24: 220–226.

[21] Ford TF, Butcher DN, Masters JR, Parkinson MC. Immunocytochemical Localisation of Prostate-specific Antigen: Specificity and Application to Clinical Practice. British Journal of Urology. 1985; 57: 50–55.

[22] Rosenberg S, Stracher A, Burridge K. Isolation and characterization of a calcium-sensitive alpha-actinin-like protein from human platelet cytoskeletons. Journal of Biological Chemistry. 1981; 256: 12986–12991.

[23] Yamamoto S, Maruyama T, Kondoh N, Nojima M, Takiuchi H, Hirota S, et al. Diagnostic efficacy of free to total ratio of prostate-specific antigen and prostate-specific antigen velocity, singly and in combination, in detecting prostate cancer in patients with total serum prostate-specific antigen between 4 and

10 ng/mL. International Urology and Nephrology. 2008; 40: 85–89.

[24] Caliskan S. Diagnostic efficacy of free prostate-specific antigen/total prostate-specific antigen ratio for the diagnosis of prostate cancer in low concentration (≤4 ng/mL) and intermediate levels of total prostate-specific antigen (4.01-10.0 ng/mL). Journal of Cancer Research and Therapeutics. 2017; 13: 279–283.

[25] Huang Y, Li ZZ, Huang YL, Song HJ, Wang YJ. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10 ng/mL: a meta-analysis. Medicine. 2018; 97: e0249.

[26] Zhou LQ, Chen WM, Na YQ, Huang YY, Feng T HJ. Comparison of serum PSA level and free PSA ratio in patients with benign prostatic hyperplasia and prostate cancer %. Chinese Journal of Urology. 2002; 33–36.

[27] Bo CL, Ma TL. Sichuan province in the central and western regions apparent healthy elderly prostate specific antigen reference range. Mark Immune Analysis and Clinical. 2019; 26: 1710–1713.

[28] Ozden E, Turgut AT, Talas H, Yaman O, Gogus O. Effect of dimensions and volume of the prostate on cancer detection rate of 12 core prostate biopsy. International Urology and Nephrology. 2007; 39: 525–529.

[29] Tang P, Jin X, Uhlman M, Lin Y, Deng X, Wang B, *et al*. Prostate volume as an independent predictor of prostate cancer in men with PSA of 10-50 ng ml-1. Asian Journal of Andrology. 2013; 15: 409–412.

[30] Zheng XY, Xie LP, Wang YY, Ding W, Yang K, Shen HF, *et al*. The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL.

Journal of Cancer Research and Clinical Oncology. 2008; 134: 1207–1210.

[31] Yusim I, Krenawi M, Mazor E, Novack V, Mabjeesh NJ. The use of prostate specific antigen density to predict clinically significant prostate cancer. Scientific Reports. 2020; 10: 20015.

[32] Nan LB, Yin XT, Gao JP. Significant Diagnostic Value of Free-Serum PSA (FPSA)/Prostate-Specific Antigen Density (PSAD) and (F/T)/PSAD for Prostate Cancer of the Chinese Population in a Single Institution. Medical Science Monitor. 2019; 25: 8345–8351.

[33] JL. Q. Disease burden analysis of prostate cancer in Chinese men from 1990 to 2013. Chinese Journal of Epidemiology. 2016; 6.

[34] Feletto E, Bang A, Cole-Clark D, Chalasani V, Rasiah K, Smith DP. An examination of prostate cancer trends in Australia, England, Canada and USA: is the Australian death rate too high? World Journal of Urology. 2015; 33: 1677–1687.

[35] Patel S, Issa MM, El-Galley R. Evaluation of novel formula of PSA, age, prostate volume, and race in predicting positive prostate biopsy findings. Urology. 2013; 81: 602–606.

[36] Uçer O, Yücetas U, Çelen I, Toktas G, Müezzinoglu T. Assessment of PSA-Age volume score in predicting positive prostate biopsy findings in Turkey. International Brazilian Journal of Urology. 2015; 41: 864–868.

[37] Wu YS, Wu XB, Zhang N, Jiang GL, Yu Y, Tong SJ, *et al*. Evaluation of PSA-age volume score in predicting prostate cancer in Chinese population. Asian Journal of Andrology. 2018; 20: 324–329.

[38] Gjengstø P, Paus E, Halvorsen OJ, Eide J, Akslen LA, Wentzel-Larsen T, *et al*. Predictors of prostate cancer evaluated by receiver operating characteristics partial area index: a prospective institutional study. Journal of Urology. 2005; 173: 425–428.