Original Research

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

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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 PCas in China has steadily increased [3, 4]. At present, screening of PCas 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 PCas compared with healthy men, suggesting that PSA can be used as a diagnostic indicator of
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 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 0.5 × height × length. 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, prostat 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 in diagnostic efficiency between the two methods.
Table 2. AUROC values and 95% CIs for various parameters in the diagnosis of PCa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC</th>
<th>PSAD</th>
<th>PV</th>
<th>(F/T)PSA</th>
<th>AVR</th>
<th>PSA-AV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPSA</td>
<td>0.586</td>
<td>0.761</td>
<td>0.783</td>
<td>0.573</td>
<td>0.819</td>
<td>0.720</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.478–0.695</td>
<td>0.669–0.853</td>
<td>0.692–0.873</td>
<td>0.465–0.682</td>
<td>0.734–0.903</td>
<td>0.623–0.817</td>
</tr>
<tr>
<td>p</td>
<td>0.126 &lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.194 &lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 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 (pTPSA = 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).
TABLE 3. AUROC value comparisons between each pair of diagnostic indices.

<table>
<thead>
<tr>
<th></th>
<th>TPSA</th>
<th>PSAD</th>
<th>PV</th>
<th>(F/T)PSA</th>
<th>AVR</th>
<th>PSA-AV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPSA</td>
<td>0.586</td>
<td>0.761</td>
<td>0.783</td>
<td>0.573</td>
<td>0.819</td>
<td>0.720</td>
</tr>
<tr>
<td>PSAD</td>
<td>0.001</td>
<td>0.064</td>
<td>0.004</td>
<td>0.001</td>
<td>0.064</td>
<td>0.001</td>
</tr>
<tr>
<td>PV</td>
<td>0.007</td>
<td>0.499</td>
<td>0.868</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>(F/T)PSA</td>
<td>0.014</td>
<td>0.055</td>
<td>0.014</td>
<td>0.014</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>PSA-AV</td>
<td>0.008</td>
<td>0.055</td>
<td>0.014</td>
<td>0.006</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 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 4. Statistical power analysis of AVR and other parameters.

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>PSAD</th>
<th>PV</th>
<th>(F/T)PSA</th>
<th>AVR</th>
<th>PSA-AV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power (%)</td>
<td>99.87*</td>
<td>28.41*</td>
<td>14.00*</td>
<td>99.96*</td>
<td>—</td>
<td>63.11*</td>
</tr>
</tbody>
</table>

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 cutoff 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 cm$^3$ [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 significant 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 PCAs 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 PCAs, 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 PCAs mainly relies on PSA, which is easily affected by many factors, including age and PV, so the diagnosis rate of PCAs 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 PCAs 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 PCAs, 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 PCAs.
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-AV: 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.

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Conflict of interest
The authors declare no conflict of interest.

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