

RESEARCH ARTICLE

The influence of age on prostate cancer screening index

Jiahao Shan¹ | Ziyang Liu² | Xinyu Geng¹ | Yuelong Feng³ | Xiaobo Yang⁴ |
Haoran Xu² | Xiaojie Zhou² | Wenzhuo Ma² | Hengyu Zhu² | Hongbin Shi⁴ 

¹Department of Urology, Suzhou Hospital of Anhui Medical University, Suzhou, China

²School of Clinical Medicine, Ningxia Medical University, Yinchuan, China

³Department of Urology, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China

⁴Department of urology, General Hospital of Ningxia Medical University, Yinchuan, China

Correspondence

Hongbin Shi, Department of urology, General Hospital of Ningxia Medical University, Yinchuan 750004, China. Email: shb0525@163.com

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Abstract

Purpose: This study aimed to identify parameters with a higher diagnostic value for early screening of prostate cancer (PCa) at different ages.

Materials and Methods: A total of 294 patients were included and divided into two groups according to the age of patients (≤ 66 and > 66 years). Receiver operating characteristic (ROC) curves of total prostate-specific antigen (TPSA), free PSA (FPSA), (F/T)PSA, PSA density (PSAD), PSA-AV score, the ratio of patients' age to prostate volume (AVR) and (F/T)/PSAD were constructed. The area under the ROC curve (AUC) was calculated, and differences in the AUC values among the above-mentioned parameters were compared.

Results: There were 121 patients in the ≤ 66 years age group (benign prostatic hyperplasia BPH, 103 patients; PCa 18 patients) and 173 patients in the > 66 years age group (BPH, 100 patients; PCa, 73 patients). In the ≤ 66 years age group, the AUC value of AVR for PCa diagnosis was the highest; however, there was no statistically significant difference compared with the AUC values of PSAD and (F/T)/PSAD; compared with TPSA, FPSA, (F/T)PSA and PSA-AV, the differences were statistically significant. In the > 66 years age group, the AUC values of PSAD and PSA-AV for PCa diagnosis were higher than those of TPSA, FPSA, (F/T)PSA and (F/T)/PSAD, and the difference was statistically significant; however, the difference was not statistically significant when compared with the AUC value of AVR.

Conclusion: In different age groups, screening indices for PCa diagnosis should be selected according to the age of patients.

KEYWORDS

benign prostatic hyperplasia, prostate cancer, prostate-specific antigen, prostate-specific antigen density

1 | INTRODUCTION

Prostate cancer (PCa) is one of the most common malignant tumours in men and ranks second in terms of the global incidence of cancers.¹ Prostate cancer is the sixth most common malignant tumour in men

of Chinese origin.² The incidence rate of PCa is low in China and relatively higher in developed countries³; in recent years, the annual incidence rate of PCa in China has increased.^{4,5}

Early screening of PCa mainly relies on the detection of prostate-specific antigen (PSA). Although serum PSA level is susceptible to

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various factors, it is the first choice for PCa screening worldwide.^{6,7} Currently, the clinical indicators used for early screening of PCa mainly include total PSA (TPSA), free PSA (FPSA), (F/T)PSA, PSA density (PSAD), (F/T)/PSAD⁸ and PSA-AV score.⁹ The diagnostic value of these parameters for early screening of PCa has been verified in the relevant literature; however, during clinical diagnosis and treatment, the results are often contradictory. Therefore, the right clinical indicators that have been plaguing urology physicians are yet to be discovered.

Most studies have demonstrated that age is closely related to the occurrence and development of PCa.¹⁰⁻¹³ However, a relatively small number of studies are based on parameters of diagnostic value for screening PCa. Therefore, given the correlation between age and PCa, this study aimed to compare the diagnostic value of various parameters for screening PCa in different age groups to identify clinical indicators with a higher diagnostic value for PCa screening.

2 | MATERIALS AND METHODS

Medical records were collected from patients who underwent transrectal prostate biopsy guided by B-scan ultrasonography (10-needle puncture method) for the first time in the General Hospital of Ningxia Medical University between June 2014 and June 2021 and had serum PSA values in the range of 4–20 ng/mL. According to the results of pathological studies of prostate biopsy, all patients were divided into PCa and benign prostatic hyperplasia (BPH) groups. The guidelines recommended by the Urology Branch of Chinese Medical Association (CUA) for puncture indications were as follows: (1) digital rectal examination was performed to identify prostate nodules; (2) abnormal images of the prostate were captured using B-scan ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI); (3) PSA >10 ng/mL; and (4) PSA = 4–10 ng/mL, abnormal (F/T)PSA or abnormal PSAD value. Inclusion criteria were as follows: (1) >50 years of age; (2) PSA = 4–20.0 ng/mL; and (3) first-time prostate needle biopsy. Exclusion criteria were as follows: (1) urinary tract infection or obstruction; (2) digital rectal examination, prostate massage, cystoscopy or other procedures within 2 weeks before the PSA test; (3) diagnosis of prostatitis; or (4) other cancers.

Venous blood was drawn on the second day of admission; TPSA and FPSA were measured using an electrochemical luminescence assay kit (Roche Diagnostic GmbH). Prostate biopsy was performed by an urologist, and PV was measured before the puncture using transrectal ultrasonography (Pro Focus 2202 Ultra View, BK Medical). Age, PV, TPSA, FPSA and pathological results of the prostate biopsy were recorded. (F/T)PSA, PSAD, (F/T)/PSAD, PSA-AV and AVR values were calculated.

2.1 | Statistical methods

The Mann-Whitney *U* test was used to analyse continuous variables that did not conform to a normal distribution. The receiver operating

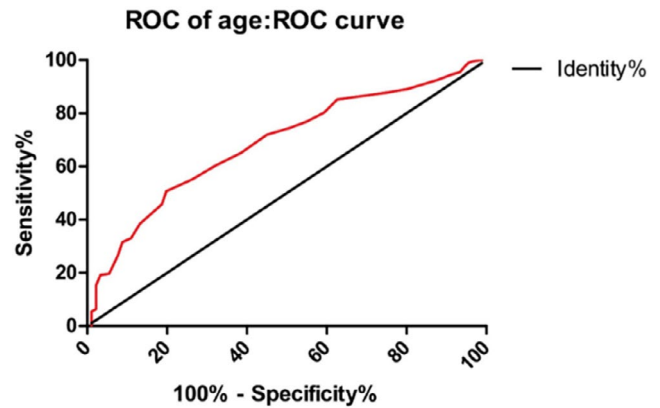


FIGURE 1 ROC curves of age groups for the diagnosis of PCa. ROC: Receiver operating characteristic

characteristic (ROC) curves of TPSA, FPSA, (F/T)PSA, PSAD, (F/T)/PSAD, PSA-AV and AVR were constructed using the GraphPad Prism 5 software. The area under the ROC curve (AUC) was calculated using the SPSS 26.0 and MedCalc software, and differences in AUC values among these parameters were compared using the Z test. The PASS 15 software was used to calculate the statistical effectiveness of AVR and other indicators. *p*-value <0.05 was considered statistically significant.

3 | RESULTS

A total of 294 patients were included in this study (232 cases of Han nationality and 62 cases of Hui nationality), of which, 91 had PCa and 203 had BPH. The average age of patients in the BPH group was 66.33 ± 7.61 years, with an average PV of 71.72 ± 42.42 mL. The average age of patients in the PCa group was 71.13 ± 6.62 years, with an average PV of 49.07 ± 30.85 mL. To calculate the cut-off value of age, ROC curves were plotted (as demonstrated in Figure 1), and the AUC value was 0.687. The 95% confidence interval (CI) was 0.630–0.739, and the cut-off value was 66 years when the maximum approximate index was considered. Considering the age of 66 years, the patients were divided into the ≤ 66 years and >66 years age groups. A total of 121 patients were included in the ≤ 66 years age group (BPH, 103 patients; PCa, 18 patients), and 173 patients were included in the >66 years age group (BPH, 100 patients; PCa, 73 patients). Table 1 provides the basic data for the diagnostic parameters of patients with BPH and PCa when grouped based on different ages. All diagnostic parameters failed to conform to a normal distribution and were represented by median (and interquartile range). The Z test was used to compare the differences between groups.

It is evident from Table 1 that TPSA, FPSA, (F/T)PSA and (F/T)/PSAD were not significantly different between the PCa and BPH groups in the ≤ 66 years age group. However, statistically significant differences were observed between PSAD, PSA-AV and AVR. In the >66 years age group, no significant differences were observed in FPSA and (F/T)PSA between the PCa and BPH groups; however,

TABLE 1 Basic data of each diagnostic parameter

	TPSA (ng/mL) median (IQR)	FPSA (ng/mL) median (IQR)	(F/T)PSA median (IQR)	PSAD (ng/mL/mL) median (IQR)	PSA-AV median (IQR)	AVR median (IQR)	(F/T)/PSAD median (IQR)
Age ≤66 years old							
BPH	10.55 (8.26–14.97)	1.54 (0.89–2.21)	0.14 (0.10–0.18)	0.20 (0.13–0.30)	307.11 (199.91–478.73)	1.08 (0.69–1.64)	0.68 (0.35–1.41)
PCa	9.67 (7.20–15.19)	1.16 (0.84–1.62)	0.11 (0.08–0.17)	0.33 (0.17–0.43)	186.99 (145.24–356.37)	1.90 (1.46–2.35)	0.43 (0.18–0.91)
<i>p</i>	0.429	0.123	0.270	0.016	0.035	<0.001	0.052
Age >66 years old							
BPH	11.13 (7.58–13.98)	1.59 (1.07–2.48)	0.16 (0.12–0.21)	0.16 (0.11–0.22)	455.81 (334.87–668.74)	1.02 (0.75–1.70)	1.03 (0.57–1.78)
PCa	12.68 (9.75–16.78)	1.68 (1.18–2.49)	0.14 (0.10–0.20)	0.28 (0.18–0.44)	263.25 (163.18–419.37)	1.70 (1.24–2.02)	0.55 (0.22–1.02)
<i>p</i>	0.004	0.518	0.205	<0.001	<0.001	<0.001	0.001

Abbreviations: (F/T) PSA, FPSA/TPSA; (F/T)/PSAD: (F/T) PSA/PSAD; AVR, ratio of patients' age to prostate volume; BPH, Benign prostatic hyperplasia; FPSA, Free prostate-specific antigen; PCA, Prostate cancer; PSA-AV, Age multiplied by previous gland volume divided by total prostate-specific antigen; PSAD, Prostate-specific antigen density; TPSA, Total prostate-specific antigen.

significant differences were observed in TPSA, PSAD, PSA-AV, AVR and (F/T)/PSAD.

The ROC curves of all diagnostic parameters were subsequently constructed (as demonstrated in Figure 2). In Figure 2, (1) and (2) represent the ≤66 years age group and (3) and (4) represent the >66 years age group. AUC, cut-off values and 95% CI for PCa were calculated for each diagnostic parameter (see Table 2). According to Table 2, in the ≤66 years age group, it was found that AVR (AUC = 0.764) had moderate diagnostic value for PCa. In the >66 years age group, it was found that PSAD (AUC = 0.740), PSA-AV (AUC = 0.735) and AVR (AUC = 0.712) had moderate diagnostic value for PCa.

Table 3 shows the comparison between the AUC of each diagnostic parameter in the ≤66 years age group. It also shows that in the ≤66 years age group, the AUC value of AVR (AUC = 0.764) was higher than that of TPSA (AUC = 0.559), FPSA (AUC = 0.614), (F/T) PSA (AUC = 0.581) and PSA-AV (AUC = 0.656), and the difference was statistically significant. The AUC value of PSAD (AUC = 0.679) was higher than that of PSA-AV (AUC = 0.656), with the difference being statistically significant. Pairwise comparison of AUC values of other indicators for PCa diagnosis revealed no significant statistical difference.

Table 4 shows that in the >66 years age group, The AUC value of AVR (AUC = 0.712) was higher than that of FPSA (AUC = 0.529) and (F/T)PSA (AUC = 0.556). The AUC values of PSAD (AUC = 0.740) and PSA-AV (AUC = 0.735) were higher than those of TPSA (AUC = 0.629), FPSA (AUC = 0.529), (F/T)PSA (AUC = 0.556) and (F/T)/PSAD (AUC = 0.687).

We also calculated the statistical power between AVR and TPSA, FPSA, (F/T)PSA, PSAD, (F/T)/PSAD and PSA-AV, and the results

are demonstrated in Table 5. It is evident from Table 5 that in the ≤66 years age group, the statistical efficacy of AVR and TPSA, FPSA, (F/T)PSA, PSAD, PSA-AV and (F/T)/PSAD was 88.07%, 63.83%, 80.15%, 26.75%, 39.23% and 46.27%, respectively. In the >66 years age group, the statistical efficacy of AVR and TPSA, FPSA, (F/T) PSA, PSAD, PSA-AV and (F/T)/PSAD was 59.34%, 99.72%, 98.17%, 10.85%, 8.61% and 10.00%, respectively.

4 | DISCUSSION

Although many men may harbour PCa despite having low serum PSA,^{14,15} at present, as recommended by various guidelines, the PSA threshold of prostate biopsy is 4 ng/mL. Some studies have reported that when PSA >4 ng/mL and PSA >10 ng/mL, the incidence of PCa is only 22.2% and 67%, respectively.^{16,17} These data further illustrate the limitations of PSA in the diagnosis of PCa. At the same time, considering that the median PSA level of newly diagnosed prostate cancer patients in China is higher than that in Western countries,¹⁸ some scholars also suggested that the 'diagnostic grey area' in PCa should be relaxed to the range of 4–20.0 ng/mL.¹⁹ Therefore, in this study, PSA was set in the range of 4–20 ng/mL.

Oesterling et al. reported that as age increases, the physiological barrier in the prostate duct is further weakened, thus increasing the permeability of PSA and serum PSA levels. Therefore, it is recommended that different PSA reference ranges should be used at different ages to increase the diagnosis rate of PCa.²⁰ Age is not only related to the serum PSA level but also correlated with the diagnosis and treatment of PCa. The age of onset of PCa is mainly concentrated in the middle-aged and elderly population.¹² The peak age of onset of

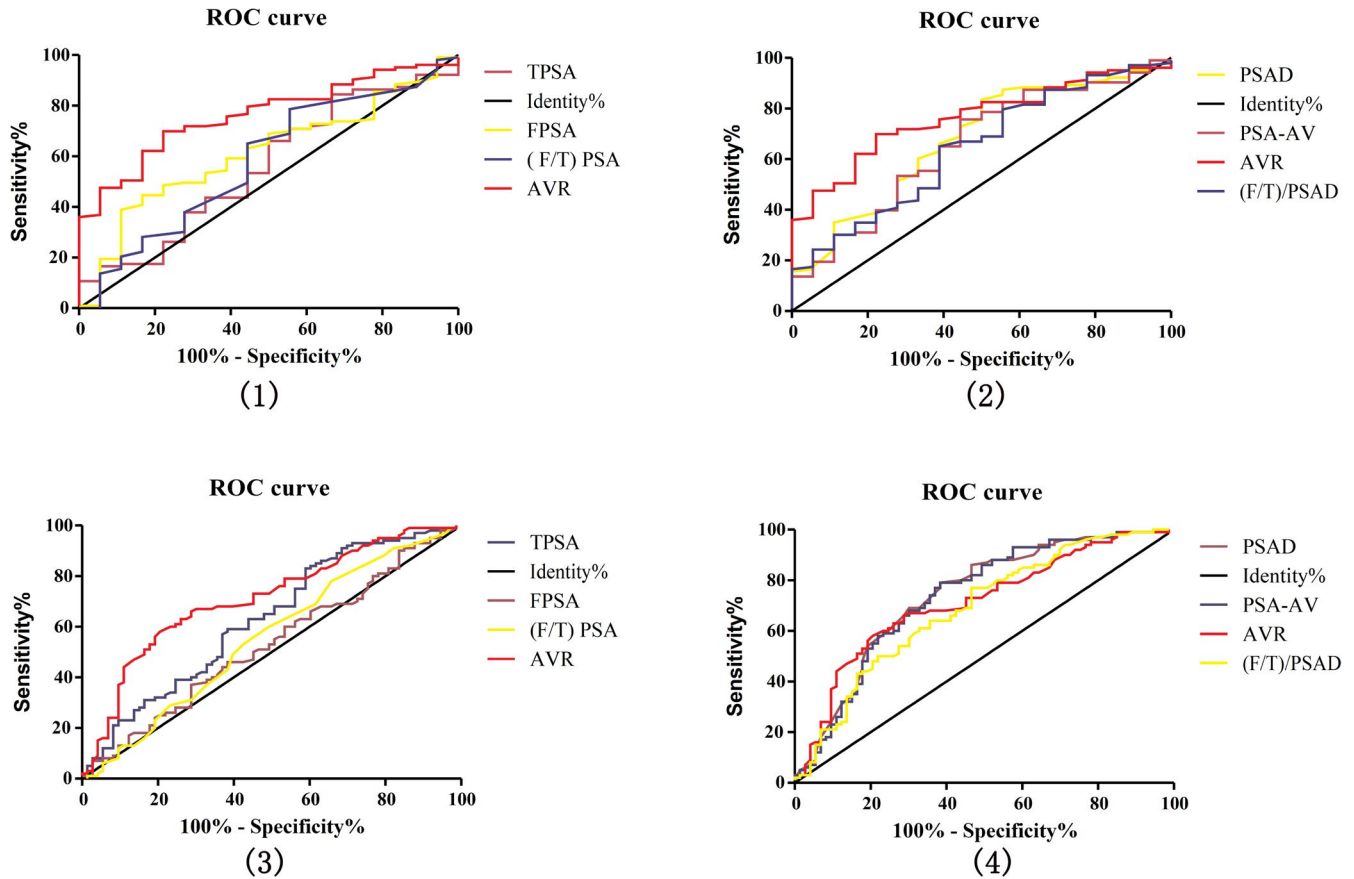


FIGURE 2 (1) and (2) ROC curves of clinical indicators used for diagnosing PCa when age was ≤ 66 years; (3) and (4) ROC curves of clinical indicators used for diagnosing PCa when age was > 66 years. ROC, Receiver operating characteristic; TPSA, Total prostate-specific antigen; FPSA, Free prostate-specific antigen; (F/T)PSA, Free/Total prostate-specific antigen; PSAD, Prostate-specific antigen density; PSA-AV, Age multiplied by the previous gland volume divided by the total prostate-specific antigen; AVR, Ratio of age to volume; (F/T)/PSAD, (F/T)PSA/PSAD

TABLE 2 AUC, critical value and 95% CI of each diagnostic parameter

	TPSA	FPSA	(F/T)PSA	PSAD	PSA-AV	AVR	(F/T)/PSAD
Age ≤ 66 years old							
AUC	0.559	0.614	0.581	0.679	0.656	0.764	0.644
95% CI	0.465–0.649	0.521–0.701	0.488–0.670	0.588–0.761	0.588–0.761	0.678–0.836	0.552–0.729
Age > 66 years old							
AUC	0.629	0.529	0.556	0.74	0.735	0.712	0.687
95% CI	0.552–0.701	0.452–0.605	0.479–0.632	0.721–0.900	0.662–0.799	0.639–0.778	0.612–0.755

Abbreviations: (F/T) PSA, FPSA/TPSA; (F/T)/PSAD, (F/T) PSA/PSAD; AVR, ratio of age to volume; FPSA, Free prostate-specific antigen; PSA-AV, Age multiplied by previous gland volume divided by total prostate-specific antigen; PSAD, Prostate-specific antigen density; TPSA, Total prostate-specific antigen.

PCa is mainly > 60 years in China and > 50 years in the United States.²¹ With increasing age, the incidence of PCa gradually increases.¹⁰ At present, the gold-standard method for diagnosing PCa is prostate biopsy. Complications after biopsy are also different according to age. Studies have demonstrated that men aged > 70 years have more complications after biopsy.¹¹ Treatment varies depending on the age of patients with PCa: non-surgical treatment is mainly used for elderly patients, whereas surgical treatment is mainly used for older patients.

The postoperative prognosis of patients of different age groups also has certain differences. Studies have demonstrated that patients aged ≤ 59 years have the best prognosis, with a 5-year survival rate of 58.31%.²² In conclusion, age is related to PCa screening, diagnosis, treatment and prognosis and has also been identified as a risk factor for PCa.²³ However, the division of age groups in elderly patients with PCa remains controversial, and patients are mainly classified based on the following age limits: 70, 75 and 80 years.^{24,25} In this study,

TABLE 3 Comparison of AUC among diagnostic parameters (Age ≤ 66 years old)

	TPSA	FPSA	(F/T)PSA	AVR	PSAD	PSA-AV	(F/T)/PSAD
TPSA	N	N	N	N	N	N	N
FPSA	0.441	N	N	N	N	N	N
(F/T) PSA	0.852	0.599	N	N	N	N	N
AVR	0.025	0.044	0.030	N	N	N	N
PSAD	0.368	0.528	0.214	0.102	N	N	N
PSA-AV	0.471	0.687	0.348	0.045	0.010	N	N
(F/T)/PSAD	0.509	0.705	0.121	0.059	0.434	0.795	N

Abbreviations: (F/T) PSA, FPSA/TPSA; (F/T)/PSAD, (F/T) PSA/PSAD; AVR, ratio of age to volume; FPSA, Free prostate-specific antigen; PSA-AV, Age multiplied by previous gland volume divided by total prostate-specific antigen; PSAD, Prostate-specific antigen density; TPSA, Total prostate-specific antigen.

TABLE 4 Comparison of AUC among diagnostic parameters (Age > 66 years old)

	TPSA	FPSA	(F/T) PSA	AVR	PSAD	PSA-AV	(F/T)/PSAD
TPSA	N	N	N	N	N	N	N
FPSA	0.018	N	N	N	N	N	N
(F/T)PSA	0.214	0.738	N	N	N	N	N
AVR	0.153	0.007	0.001	N	N	N	N
PSAD	0.004	0.000	0.000	0.323	N	N	N
PSA-AV	0.006	0.000	0.000	0.442	0.334	N	N
(F/T)/PSAD	0.199	0.024	0.000	0.405	0.016	0.030	N

Abbreviations: (F/T) PSA, FPSA/TPSA; (F/T)/PSAD, (F/T) PSA/PSAD; AVR, ratio of age to volume; FPSA, Free prostate-specific antigen; PSA-AV, Age multiplied by previous gland volume divided by total prostate-specific antigen; PSAD, Prostate-specific antigen density; TPSA, Total prostate-specific antigen.

TABLE 5 Statistical power analysis of A-PSAD and other parameters

	TPSA	FPSA	(F/T)PSA	PSAD	PSA-AV	(F/T)/PSAD	AVR
Age ≤ 66 years old							
AUC	0.559	0.614	0.581	0.679	0.656	0.644	0.764
Power (%)	88.07 ^a	63.83 ^a	80.15 ^a	26.75 ^a	39.23 ^a	46.27 ^a	N
Age > 66 years old							
AUC	0.629	0.529	0.556	0.740	0.735	0.687	0.712
Power (%)	59.34 ^a	99.72 ^a	98.17 ^a	10.85 ^a	8.61 ^a	10.00 ^a	N

Abbreviations: (F/T) PSA, FPSA/TPSA; (F/T)/PSAD, (F/T) PSA/PSAD; AVR, ratio of age to volume; FPSA, Free prostate-specific antigen; PSA-AV, Age multiplied by previous gland volume divided by total prostate-specific antigen; PSAD, Prostate-specific antigen density; TPSA, Total prostate-specific antigen.

^aComparison of other indicators with AVR.

the cut-off age corresponding to the maximum Youden index for the diagnosis of PCa was 66 years, which was selected as the limit to further investigate the diagnostic value of AVR and PSA-based clinical indicators in the ≤ 66 years old and > 66 years age groups.

At present, the diagnostic value of various clinical indices depends on PSA (PSA in the range of 4–10 or 4–20 ng/mL) because there is a certain overlap between the increase in serum-borne PSA in patients with BPH and PCa in this range. Scholars propose new indicators or scoring systems based on some clinically accessible indicators or imaging data such as PSA, age and PV to improve the

screening and diagnostic rate of PCa. With the continuous progress of science and technology, imaging tests such as CT and MRI are used for screening PCa, and the diagnostic rate of imaging is higher than that of PSA and PSA-based clinical indicators. However, the cost of these sophisticated imaging procedures may lead to heavy economic burden on some patients. Although the screening rate of PCa based on PSA is lower than that of CT and MRI, it is more suitable for early screening of PCa and hence serves as a general screening method that is easily accessible in a clinic and more easily accepted by patients. However, a few studies have investigated the

impact of various clinical indicators on the diagnosis of PCa at different ages. Given the influence of age on the level of serum PSA and the occurrence and development of PCa, we further investigated the diagnostic value of clinical indicators of PCa. Based on the results demonstrated in Table 2, it is evident that in the ≤ 66 years age group, AVR has a moderate diagnostic value for PCa; however, TPSA, FPSA, (F/T)PSA, PSAD, PSA-AV and (F/T)/PSAD have a lower diagnostic value for PCa. In the > 66 years age group, PSAD, PSA-AV and AVR have a moderate diagnostic value for PCa, whereas TPSA, FPSA, (F/T)PSA and (F/T)/PSAD have a low diagnostic value for PCa.

The serum PSA level is not only related to age but also correlated with PV.^{1,26,27} Considering the influence of age and PV on serum PSA, we proposed a new indicator: the ratio of age to volume (AVR) and verified the diagnostic value of AVR in a small-sample clinical retrospective study.¹⁷ In this study, we discussed its diagnostic value for PCa in different age groups. Based on the data provided in Tables 2–4, it is evident that AVR had a moderate diagnostic value for PCa in different age groups, and when age was ≤ 66 years, although the AUC value of AVR for PCa diagnosis was higher than that of PSAD and (F/T)/PSAD, the difference was not statistically significant. Therefore, the three may have the same diagnostic value for PCa. When the age was > 66 years, the AUC values of PSAD and PSA-AV were higher than those of TPSA, FPSA, (F/T)PSA and (F/T)/PSAD, and the difference was statistically significant. However, compared with AVR, the difference was not statistically significant. PSAD and PSA-AV had the same diagnostic value as that of AVR and better diagnostic values than those of TPSA, FPSA, (F/T)PSA and (F/T)/PSAD.

In addition, we also calculated and compared the statistical performance between AVR and TPSA, FPSA, (F/T)PSA, PSAD, PSA-AV and (F/T)/PSAD. Based on data provided in Table 5, in the ≤ 66 years age group, statistical power of 88.07%, 63.83%, 80.15% and 39.23% demonstrates that the AUC value of AVR had statistical significance compared with that of TPSA, FPSA, (F/T)PSA and PSA-AV, respectively. Statistical efficiencies of PSAD and (F/T)/PSAD were 26.75% and 46.27%, respectively, and were not statistically different from the efficiency of AVR. In the > 66 years age group, FPSA and (F/T)PSA had a statistical power of 99.72% and 98.17%, respectively, which signifies the statistical difference between the AUC values of AVR and FPSA and (F/T)PSA. The statistical power of insignificant differences between the AUC value of AVR and TPSA, PSAD, PSA-AV and (F/T)/PSAD was 59.34%, 10.85%, 8.61% and 10.00%, respectively. The low statistical power between AVR and PSAD in the age group ≤ 66 years and between AVR and PSAD, PSA-AV and (F/T)/PSAD in the age group > 66 years may be related to the limited sample size. The results of this study indicate that at different ages, the clinical indicators have different diagnostic values for PCa. Therefore, it is suggested that different clinical indicators should be used for screening and diagnosing PCa at different ages.

The limitations of this study are as follows: the present study was a single-centre study; the included subjects were from a north-western district in China; and the results of this study may have a certain bias, which may prevent the application of our findings in other populations. In addition, owing to a limited sample size, we

could not further subdivide the age groups to explore the diagnostic value of various clinical indicators for PCa at different ages. Therefore, the results of this study may require further verification from multi-centre and large-sample studies.

5 | CONCLUSIONS

Different clinical indicators should be used for screening PCa at different ages. Therefore, it is recommended that different clinical indicators should be used when screening and diagnosing PCa at different ages. AVR, as a new clinical indicator, has a certain diagnostic value in the setting of PCa at different ages. However, considering that this study followed a single-centre study design, the clinical significance of AVR in the diagnosis of PCa requires further verification from multi-centre and large-sample studies to facilitate discussion and confirmation of the work reported herein.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Jiahao Shan involved in research conception and design. Ziyang Liu, Xinyu Geng, Yuelong Feng, Haoran Xu, Xiaojie Zhou, Wenzhuo Ma and Hengyu Zhu involved in data acquisition. Jiahao Shan, Yuelong Feng and Xiaobo Yang involved in statistical analysis. Jiahao Shan involved in data analysis and interpretation. Jiahao Shan drafted the manuscript. Hongbin Shi, critically revised the manuscript. Hongbin Shi obtained funding. Hongbin Shi approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Hongbin Shi  <https://orcid.org/0000-0001-7082-7327>

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