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Correlation Analysis between Apparent Diffusion Coefficient of Prostate Cancer and other Prostate Cancer Indicators

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Abstract

Background: There are very few reports on the correlation between the apparent diffusion coefficient (ADC) of magnetic resonance parameters and other laboratory indicators of prostate cancer in China, and there is no unified clinical conclusion at present from the other parts of the world. Therefore, this study analyzed the correlation between ADC and laboratory indicators, such as serum total prostate specific antigen (TPSA), complex prostate specific antigen (CPSA), free prostate specific antigen (FPSA), Gleason score, and left and right diameters of the prostate so as to provide a basis for the diagnosis and treatment of prostate cancer.

Methods: A total of 104 patients of all age groups with prostate cancer diagnosed in the General Hospital of Wanbei Coal and Electricity Group, Wanbei, China, from January 2017 to December 2022 were retrospectively analyzed as the experimental group. At the same time, 63 patients with benign prostatic hyperplasia who received health examinations were selected as the control group. TPSA, CPSA, FPSA, CPSA/TPSA, FPSA/TPSA, Gleason score, left and right diameters of the prostate, and magnetic resonance parameter ADC were detected in all patients. At the same time, we analyzed the correlation between ADC and other parameters in prostate cancer patients.

Results: The serum levels of TPSA, CPSA, and FPSA in prostate cancer patients were significantly higher (P<0.001) than in those in the control group. The differences between CPSA/TPSA and FPSA/TPSA in the two groups were not statistically significant. Meanwhile, ADC and left and right diameters of the prostate were significantly lower in prostate cancer patients than in subjects in the control group, and the differences were statistically significant (P<0.001). In addition, serum TPSA, CPSA, and FPSA in high-risk prostate cancer patients were found to be significantly higher than in cases in the medium-risk and low-risk groups. The results of our study also revealed that ADC was moderately negatively correlated with FPSA (r=-0.415, P<0.001) and weakly negatively correlated with TPSA (r=-0.222, P=0.024).

Conclusion: There is a correlation between ADC, TPSA, and FPSA in patients with prostate cancer, and there were significant differences in TPSA, CPSA, and FPSA between patients with prostate cancer and patients with benign prostatic hyperplasia. The three parameters can be combined for the diagnosis of prostate cancer.

Keywords: Apparent diffusion coefficient, Gleason score, Prostatic cancer, Prostate specific antigen

1. Background

Prostate cancer is the most common malignant tumor in men in many Western countries (1). As the population ages and lifestyle changes, the incidence of prostate cancer in male urinary and reproductive system tumors has leaped to the third rank in our country, which seriously threatens the health of elderly men (1, 2). In addition, patients with prostate cancer have atypical clinical symptoms, such as trouble urinating, blood in the urine and semen, bone pain, and erectile dysfunction, which are difficult to distinguish from prostatic hyperplasia. Early diagnosis of prostate cancer is the key to radical treatment (3). Therefore, early selection of molecular markers with high specificity and sensitivity is of great significance for the diagnosis, treatment, and prognosis evaluation of prostate cancer (4, 5). In 1979, Wang first isolated and purified prostate specific antigen (PSA) from prostate tissue in 1979 (3, 4). PSA has played a great role in the diagnosis of prostate cancer and has been widely used in the screening, diagnosis, and postoperative monitoring of prostate cancer (4, 5). In addition, the Gleason score given to prostate cancer based on its microscopic appearance of prostate biopsy has a high predictive value for the pathological staging of prostate cancer, which has been widely recognized in clinical practice. However, biopsy puncture is an invasive examination, and therefore, it has certain limitations (6, 7). Magnetic resonance imaging (MRI) of the prostate is currently the best noninvasive method to detect prostate diseases in clinical practice. MRI parameters have high sensitivity and specificity in the clinical diagnosis of prostate cancer, especially apparent diffusion coefficient (ADC), which plays an important role in the diagnosis of prostate cancer (8, 9). At present, the diagnosis of prostate cancer mainly relies on digital rectal examination, serum prostate specific antigen detection, and prostate magnetic resonance imaging (10, 11). Total PSA (TPSA) is a protease present in semen, has high organ specificity and non-tumor specificity, and is a very valuable indicator for screening prostate cancer. PSA includes complex state (CPSA) and free state (FPSA), the proportions of both being different in different patients (12-18).

There are few reports on the correlation between the apparent diffusion coefficient of magnetic resonance parameters and other indicators of prostate cancer in China, and there is no unified clinical conclusion at present from the other parts of the world.

2. Objectives

Based on this, this study analyzed the correlation between magnetic resonance parameters ADC and laboratory indices, such as serum TPSA, CPSA, FPSA, Gleason score, and left and right diameters of prostate cancer patients to provide a basis for the diagnosis and treatment of prostate cancer.

3. Methods

3.1. Study design and participants

Hospital data records of 104 patients with prostate cancer diagnosed in the General Hospital of Wanbei Coal and Electricity Group from January 2017 to December 2022 were retrospectively analyzed as the experimental group, and 63 patients with benign prostatic hyperplasia who received health examination in General Hospital of Wanbei Coal and Electricity Group during the same period were selected as the control group. All patients and their families signed the written informed consent, and the study was approved by the Medical Ethics Committee of General Hospital of Wanbei Coal and Electricity Group.

Inclusion criteria were: (1) All patients with prostate cancer were diagnosed by multipoint biopsy or pathological biopsy after surgery. (2) All patients had no surgical contraindication. (3) None of the patients had undergone medical treatment or prostate biopsy prior to prostate MRI. (4) Patients with suspicious lesions on prostate examination images and image quality meeting diagnostic requirements. (5) Patients with complete laboratory testing and clinical data. Exclusion criteria were: (1) The image quality of prostate MRI examination does not meet the effective standard and cannot be used for examination and diagnosis of patients. (2) Patients with contraindications to surgery. (3) Patients with incomplete laboratory tests and clinical data.

The sample size was calculated using the following formula:

$$n = \frac{2(Z_\alpha + Z_{1-\beta})^2 * \sigma^2}{\Delta^2}$$

where n is the required sample size. Z_α, Z is a constant and for Z1-, β, Z is a constant set by convention according to the power of the study, σ is the standard deviation (estimated),and Δ the difference in the effect of two interventions which is required (estimated effect size).

3.2. MRI scan

A Siemens MagnetomVerio 3.0 TMR scanner was used to perform routine MRI of the prostate in all subjects (Figure 1). Select phased array coil, conventional sequence; T1-and T2-weighted axial imaging (T1WI axial position, FOV 200 mm×187.5 mm, layer thickness 2.5 mm, layer spacing 0.25 mm, TR 667 ms, TE 12 ms), T2-weighted axial imaging (T2WI axial position, FOV 200 mm×187.5 mm, layer thickness 2.5 mm, layer spacing 0.25 mm, TR 3050 ms, TE 102 ms); DWI shaft can (b value=50, 800, 1,200 s/mm^2, matrix 122 x 128, FOV 200 mm x 200 mm, layer thickness 3.0 mm, layer distance 0 mm, TR 4600 ms, TE 72 ms, incentive number 4 times).

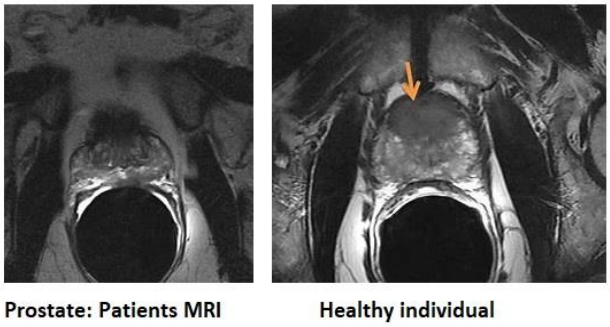

Figure 1. MRI of prostate cancer patients and healthy individuals

3.3. Puncture pathological biopsy

Transrectal needle biopsy ultrasound guided was used to examine the prostate region 6 (Under the guidance of transrectal ultrasound, a standard 12-needle needle system is used to perform a needle biopsy of the prostate, and an additional 1-2 needles are taken for the echogenic areas that indicate abnormal lesions on MRI or suspicious lesions on rectal ultrasonography). The biopsy tissue was embedded in paraffin and then sectioned and stained with HE.

After DWI scanning, the ADC map was automatically generated, regions of interest (ROI) were manually delineated on the ADC map, and the corresponding ADC values were measured. ROI with an area of 10-40mm^2 was placed in the suspicious lesion area.

Selection methods: Avoid the junction of the peripheral zone and central gland and the junction of prostate and rectum; avoid urethra, ejaculatory duct, and seminal vesicle root; avoid hemorrhage, cysts, and calcifications. The results were judged by three experienced radiologists, and the average of the three results was taken.

3.4. Laboratory examination

Fasting venous blood was collected from untreated patients and normal physically-examined subjects, and prostate examinations, such as digital rectal examination, massage, and puncture, were not performed 3 days before blood collection. Serum was

separated within 30 min after blood collection, and laboratory indices (TPSA, CPSA, and FPSA) were measured immediately by Bay ER: ACS-180Plus CLIA. Reagents and standards were supplied by Bayer.

3.5. Gleason score for prostate cancer

The grading of cancer was done using the Gleason score. The Gleason grading score is the sum of the major structural grading score and the minor structural grading score, and the criterion ranges from 2 to 10, having three categories, mainly Gleason 6 or lower, which indicates healthy or similar to healthy cells also called well-differentiated cells. Gleason 7-grade cells look somewhat similar to healthy cells, which is called moderately differentiated. Gleason scores of 8, 9, and 10 look very different from healthy cells, which are called poorly differentiated or undifferentiated. Grade groups were defined according to the below system. Grade Group 1 = Gleason 6 (or fewer), Grade Group 2 = Gleason 3+4 = 7, Grade Group 3 = Gleason 4+3 = 7, Grade Group 4 = Gleason 8, Grade Group 5 = Gleason 9-10. Gleason rating and scoring were performed on the results by two experienced pathologists. Gleason score < 7 was classified as a low-risk group, 7 as a moderate-risk group, and > 7 as a high-risk group. As the Gleason score rises, the tumor becomes more aggressive and more likely to develop metastases and recurrences.

3.6. Statistical analysis

In this study, SPSS 24.0 software was used for data analysis, and GraphPad Prism 8.0 software was used for analysis and mapping. In the baseline data, the continuous variables conforming to the positive distribution were expressed as mean ± standard deviation, the continuous variables not conforming to the positive distribution were described as median, and the categorical variables were expressed as rates or constituent ratios. The Kolmogorov-Smirnov test was used to verify the normality of the data. When the continuous variables did not conform to the normal distribution, the Mann-Whitney rank sum test was used for comparison between groups. When the continuous variables conformed to the normal distribution, the independent sample t-test and one-way analysis of variance were used for comparison between two groups and multiple groups of continuous variables. Spearman correlation analysis was used to analyze the relationship between magnetic resonance parameters ADC and laboratory indices, Gleason score, and left and right diameters of the prostate. $P < 0.05$ was considered statistically significant.

4. Results

4.1. General data

There was no significant difference in the general data between the two groups ($P>0.05$), which was comparable.

4.2. Comparison of laboratory indices, ADC, and left and right diameters of the prostate between the two groups

The serum levels of TPSA, CPSA, and FPSA in prostate cancer patients were significantly higher than in those in the control group. The differences between CPSA/TPSA and FPSA/TPSA in the two groups were not statistically significant. Meanwhile, the ADC and left and right diameters of the prostate were lower in prostate cancer patients than in those in the control group, and the differences between them were statistically significant ($P<0.001$, Table 1).

4.3. Comparison of laboratory indices, ADC, and left and right diameters of the prostate between different groups of prostate cancer patients

Serum TPSA, CPSA, and FPSA in high-risk prostate cancer patients were significantly higher than in those in the medium-risk and low-risk groups. However, there were no statistically significant differences in CPSA/TPSA, FPSA/TPSA, magnetic resonance parameters ADC, and left and right diameters of the prostate among the three groups (Table 2).

Table 1. Comparison of laboratory indices, ADC, and left and right diameters of prostate between the two groups

Group	Prostate cancer	BPH	*P*-value*
TPSA, ng/mL	176.80±413.93	11.26±7.40	< 0.001
CPSA, ng/mL	150.45±393.43	8.83±6.06	< 0.001
FPSA, ng/mL	27.14±57.60	2.43±2.10	< 0.001
FPSA/TPSA	0.19±0.15	0.22±0.11	0.164
CPSA/TPSA	0.80±0.17	0.78±0.11	0.407
ADC, mm²	0.58±0.12	1.02±0.12	< 0.001
Left and right diameters of prostate, cm	4.83±0.62	5.40±0.54	< 0.001

* Mann-Whitney rank sum test
ADC: Apparent diffusion coefficient, BPH: Benign prostatic hyperplasia, CPSA: Complex prostate specific antigen, FPSA: Free prostate specific antigen, TPSA: Total prostate specific antigen

Table 2. Comparison of laboratory indices, ADC, and left and right diameters of the prostate between different groups of prostate cancer patients

Group	High-risk group	Moderate-risk group	Low-risk group	*P*-value*
TPSA, ng/mL	251.67±540.62	180.77±369.83	22.65±18.01	<0.001**
CPSA, ng/mL	220.13±529.95	149.53±332.62	17.83±15.38	<0.001**
FPSA, ng/mL	33.29±60.15	32.09±66.29	4.62±7.05	0.001
FPSA/TPSA	0.28±0.60	0.21±0.16	0.18±0.17	0.727
CPSA/TPSA	0.89±0.51	0.77±0.20	0.81±0.17	0.362
ADC, mm²	0.56±0.11	0.59±0.12	0.62±0.15	0.202
Left and right diameters of prostate, cm	4.80±0.57	4.80±0.66	5.01±0.65	0.603

* One-way ANOVA** High-risk groups were significantly higher than moderate- and low-risk groups
ADC: Apparent diffusion coefficient, BPH: Benign prostatic hyperplasia, CPSA: Complex prostate specific antigen, FPSA: Free prostate specific antigen, TPSA: Total prostate specific antigen

4.4. Correlation analysis of ADC with Gleason score, serum PSA, and left and right diameters of prostate cancer

ADC was moderately negatively correlated with FPSA and weakly negatively correlated with TPSA. The correlation between ADC and CPSA in prostate cancer patients, CPSA/TPSA, FPSA/TPSA, Gleason score, and left and right diameters of the prostate were extremely weak and non-significant (Table 3, Figure 2).

Table 3. Correlation analysis of ADC with Gleason score, serum PSA, and left and right diameters of prostate cancer

Index	Median (range)	*r*	*P*-value*
ADC, mm²	0.60（0.23-0.94）		
Gleason score	7.00（5.00-10.00）	-0.14	0.166
TPSA, ng/mL	51.35（3.78-3172.00）	-0.222	0.024
CPSA, ng/mL	36.67（2.99-3161.80）	-0.175	0.079
FPSA, ng/mL	7.27（0.18-342.00）	-0.415	0
FPSA/TPSA	0.17（0.01-0.89）	-0.016	0.875
CPSA/TPSA	0.83（0.11-0.99）	0.011	0.912
Left and right diameters of prostate, cm	4.79（3.40-6.50）	0.025	0.803

* Spearman correlation analysis
ADC: Apparent diffusion coefficient, BPH: Benign prostatic hyperplasia, CPSA: Complex prostate specific antigen, FPSA: Free prostate specific antigen, TPSA: Total prostate specific antigen

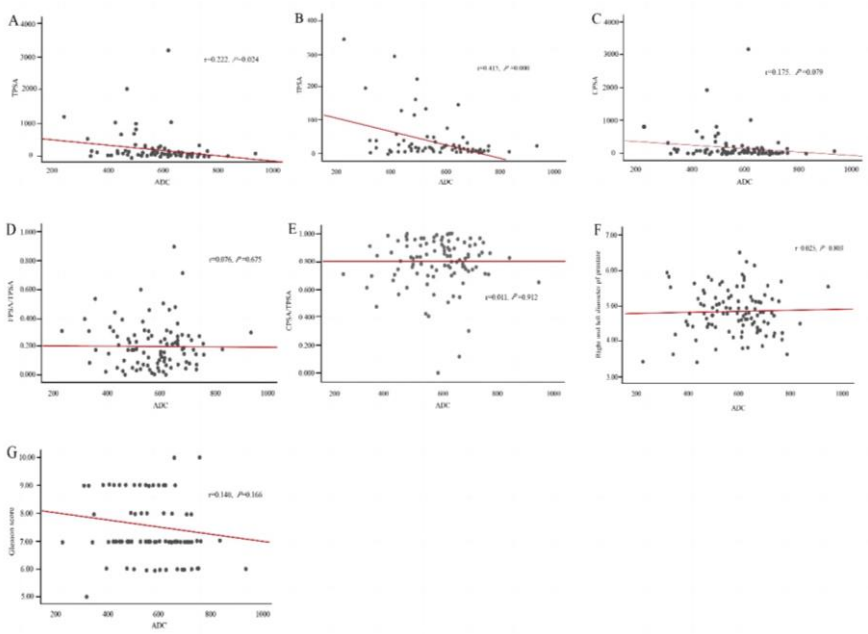

Figure 2. Correlation analysis of ADC with Gleason score, serum PSA, and left and right diameters of prostate cancer

5. Discussion

In the present study, both groups were comparable in terms of general data. The serum TPSA, CPSA, and FPSA were significantly higher in patients as well as in the high-risk group compared to the control and other groups, while the ADC and left and right diameters of the prostate in patients were less comparatively. Study results showed a correlation between ADC, TPSA, and FPSA in patients

with prostate cancer, and significant differences in TPSA, CPSA, and FPSA between prostate cancer and benign prostatic hyperplasia patients.

The serum levels of TPAS, CPSA, and FPSA in prostate cancer patients were significantly higher; however, CPSA/TPSA and FPSA/TPSA ratios in the two groups were not statistically significant. Although TPSA is the most commonly used screening indicator for prostate cancer, it is not specific to prostate cancer. It is affected by various factors, and all transurethral operations or urethral stimulation can affect the change of TPSA (19, 20). Generally, based on clinical diagnosis, it is indicated that serum TPSA<4.0 ng/mL belongs to the normal level, 4.1-10.0 ng/mL belongs to the gray area, and >10.0 ng/mL belongs to the abnormal level (21). Prostate cancer or other pathological changes, such as prostatitis, acute urinary retention, and prostate trauma necrosis, cause the destruction of the prostate tissue barrier. As a result, a large amount of PSA is diffused into the blood circulation by disrupting the tissue barrier, which eventually leads to an increase in the level of TPSA in the peripheral blood of patients (22). In addition, the more aggressive the prostate cancer, the greater the damage to normal tissue and the greater the rise in PSA levels (23). There is a close relationship between PSA level and the clinicopathological stage of prostate cancer. The later the stage, the more serious the damage to normal physiological barrier structure, the more PSA penetration content, and the higher the serum PSA level (24). The results showed that the level of serum TPSA was higher in patients with prostate cancer than in those in the control group. Likewise, the serum TPSA in patients with high-risk prostate cancer was significantly higher than that in the medium-risk and low-risk groups. The increase in TPSA may increase the risk of prostate cancer and has higher accuracy in the diagnosis of prostate cancer.

To improve the accuracy of prostate cancer screening, this study evaluated various parameters, such as FPSA, CPSA, FPSA/TPSA, and CPSA/TPSA. It was reported that with increased CPSA/TPSA ratio and decreased FPSA/TPSA ratio in elderly men, prostate cancer was highly suspected (25-27), which was exactly what we observed in our study. FPSA and CPSA can be used as auxiliary indicators. The results of this study showed that the CPSA level of patients in the prostate cancer group was higher than that in the control group, and the FPSA was also higher than that in the control group. In addition, the differences between the two groups in FPSA/TPSA and CPSA/TPSA were non-significant. On the one hand, the sample size was insufficient and the study was biased. On the other hand, there was a possibility that prostate cancer patients might also have other benign diseases that affected the FPSA index.

The Gleason score system combined with other indicators or systems will be a good predictor of surgical outcomes and recurrence risk in patients with prostate cancer, especially when Gleason score = 7 is considered to be an important dividing line to judge whether the prognosis of patients with prostate cancer is good (27-30). Therefore, it is closely related to distant uterine metastasis and lymph node metastasis; it also has certain predictive values for the prognosis of patients, this was an exclusion criterion for the current study and hence these patients were not recruited (31). Although transrectal ultrasound-guided prostate biopsy has become a common method for the diagnosis of prostate cancer and Gleason grading score, it is an invasive examination. Most patients are older, which may lead to severe infections and complications, and prostate cancer showed multiple lesions, and the differentiation degree of various lesions causes diversity in the results of the Gleason score. In addition, prostate biopsy technology cannot evaluate the whole prostate condition since there is the possibility of missing some lesions. At the same time, the Gleason scoring system is based on the observation and analysis of pathological specimens from prostate cancer patients. Even the same physician may make inconsistent judgments at the same level of pathological specimens. Therefore, comprehensive and non-invasive examination is of great clinical significance to evaluate the biological characteristics and Gleason score of prostate cancer.

As the only non-invasive medical technology to detect the movement of water molecules in living tissues, diffusion-weighted magnetic resonance imaging (DWI) plays an important role in the examination of diseases, and its application in the diagnosis of prostate diseases has an important value that cannot be ignored. DWI is completely different from traditional conventional MRI imaging methods in the past. The main basis of DWI is to provide effective information about the physiological state of functional parts of the body according to the movement of water molecules to a certain extent, so as to effectively judge the sensitivity of symptomatic parts (32-34). During the examination of prostate diseases, in patients with benign prostate tissue, the stromal cells and epithelial cells are hyperplastic and active, and the endothelium and stroma can lead to the proliferation of prostate glands under the interaction, enhance the ability of water molecules to disperse and move, and increase the fluid composition in the gland. If patients suffer from prostate cancer, the structure of the gland and normal prostate gland epithelial structure would be differentially damaged, in which high moisture acinar cell structure is replaced by cancer cells, leading to the organization ability is greatly restricted (33, 34).

ADC value is a quantitative index to measure the diffusion effect of water molecules in the human tissue microenvironment, which can directly reflect the diffusion characteristics and the degree of water molecules in tissue. Therefore, ADC value has

high clinical application value in the diagnosis and differential diagnosis of prostate cancer. ADC value can not only reflect the overall appearance of tumor morphology and tissue but also evaluate the necrosis of the tumor. The tumor cells of prostate cancer are closely arranged, and the epithelial cells have a greater density. Compared with normal cells, the epithelial cells have more intercellular and intimal structures (35). In the present study, we also noticed that ADC and left and right diameters of the prostate in prostate cancer patients were significantly lower, and a correlation was observed between ADC, TPSA, and FPSA in patients with prostate cancer.

In this study, ADC values of magnetic resonance parameters were significantly lower in prostate cancer patients than in those in the control group, and were negatively correlated with FPSA and TPSA, which might be due to the differences in clinical tissue staging and differentiation of tumor cells, leading to great variations in biological characteristics of different patients. Generally speaking, the more highly differentiated tumor cells, the less tissue and cell structural atypia, the slower cell proliferation and metabolism, the lower the requirement for blood supply, the smaller the surrounding tissue involvement, and the less severe the degree. However, tumor cells with low differentiation degree have greater structural atypia of tissues and cells, faster cell proliferation and metabolism, higher requirements for blood supply, wider and heavier involvement of surrounding tissues, and earlier occurrence of tumor metastasis. A decrease in tumor ADC value can also reflect the relative balance between cancer cell proliferation and blood supply from the perspective of imaging (33-35). The only limitation of this study was that patients with other systematic diseases were excluded only when it was documented and were verified with repeated tests. However, these were small numbers and did not affect the significance of the results.

6. Conclusion

The results of our study showed that serum TPSA, CPSA, and FPSA in high-risk prostate cancer patients were significantly higher than in those in the medium-risk and low-risk groups. There was a correlation between ADC, TPSA, and FPSA in patients with prostate cancer, and significant differences were observed between TPSA, CPSA, and FPSA in patients with prostate cancer and patients with benign prostatic hyperplasia, which can be used as an effective indicator for the diagnosis and prognosis evaluation of patients with prostate cancer. Combined evaluation can effectively improve the diagnosis rate of prostate cancer.

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Footnotes

Conflicts of Interest: The authors declare that they have no conflicts of interest.
Data Availability: The data used to support this study is available from the corresponding author upon request.
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