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ARTICLE

Analysis of risk factors for MRI-invisible prostate cancer—the significance of AGGF1 immunohistochemical detection and PSAD

Jingcheng Lyu,[1,2#] Ruiyu Yue,[1,2#] Ye Tian,[1,2*] Boyu Yang,[1,2*]

[1]Department of Urology, Capital Medical University, Beijing Friendship Hospital, Beijing, China
[2]Institute of Urology, Beijing Municipal Health Commission, Beijing, China

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Objectives: *Patients with a multi-parameter magnetic resonance imaging (mpMRI) prostate imaging report and data system (PI-RADS) score ≤ 3, but with clinically significant prostate cancer (CSPCa) detected by biopsy, are termed MRI-Invisible prostate cancer (MRI(-)PCa). This study aims to explore risk factors for MRI(-)PCa and identify immunohistochemical indicators with predictive significance.*

Methods: *A retrospective analysis was conducted on 376 patients with PI-RADS score ≤ 3 who underwent 24-needle systematic prostate biopsy at Beijing Friendship Hospital, Capital Medical University (January 2015 to October 2025). Clinical data, imaging data, and Angiogenic factor with G and FHA domain 1 (AGGF1) immunohistochemical results were collected. Patients were grouped into CSPCa ($n = 102$) and non-CSPCa ($n = 274$). t-tests, rank sum tests, and χ^2 tests were used for univariate analysis, followed by multivariate Logistic regression to determine independent risk factors. Receiver Operating Characteristic (ROC) curves were drawn. Subgroup analyses were conducted based on prostate-specific antigen (PSA) status and PI-RADS score using the same statistical methods. Moreover, we also used the Kruskal-Wallis test to compare the differences in AGGF1 expression percentages across different Gleason score groups according to ISUP in CSPCa patients.*

Results: *Multivariate Logistic regression analysis showed that prostate-specific antigen density (PSAD) [OR: 0.971, 95%CI: 0.952, 0.991] and high expression of AGGF1 [OR: 1.065, 95%CI: 1.022, 1.109] were independent risk factors for MRI(-)PCa ($p < 0.05$). Meanwhile, when the PSAD of the patient is more than 0.25 ng/mL/cm^3, it is necessary to be more suspicious that the patient may have prostate cancer ($p < 0.05$), and an AGGF1 immunohistochemical analysis should be conducted after the biopsy. In the PSA-negative subgroup, only high AGGF1 expression was an independent risk factor ($p < 0.05$). In the PSA-positive subgroup, PSAD [OR: 0.500, 95%CI: 0.279, 0.895] and AGGF1 [OR: 1.064, 95%CI: 1.037, 1.092] results were independent risk factors ($p < 0.05$). In subgroup analyses for PI-RADS 1-2 and PI-RADS 3, both PSAD and AGGF1 were accurate predictors of CSPCa ($p < 0.05$). Among all CSPCa patients, in the Gleason score 3 + 3 group, the average AGGF1 expression percentage of the patients was 48.60% ± 11.03%, which was significantly lower than that of the Gleason score 4 + 3 group (61.00% ± 6.12%) and the Gleason score 4 + 4 group (71.01% ± 4.46%), and the differences were statistically significant ($p < 0.001$).*

Conclusions: *For patients with a PI-RADS score ≤ 3, attention should be paid to PSAD before biopsy, especially for those patients with PSAD > 0.25 ng/mL/cm^3, not just PSA levels. After biopsy, AGGF1 immunohistochemical staining can be supplemented to help determine the risk and the malignancy of CSPCa.*

Key Words: prostatic neoplasms, magnetic resonance imaging, prostate-specific antigen, risk factors, immunohistochemical analysis

Introduction

Prostate cancer is one of the most common malignant tumors among men worldwide, and its incidence is increasing year by year.[1–4] In recent years, how to detect prostate cancer as early as possible and provide timely and accurate treatment has gradually become a research hotspot. Although the diagnosis of prostate cancer currently requires the results

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[#]Jingcheng Lyu and Ruiyu Yue are co-first authors

*Corresponding Authors: Ye Tian. Email: tianye166@126.com; Boyu Yang. Email: ybyurology1@163.com

of biopsy pathology, multi-parameter magnetic resonance imaging (mpMRI) combined with the Prostate Imaging Reporting And Data System (PI-RADS) score before biopsy can assist clinicians in qualitative diagnosis, risk stratification, and preoperative assessment of early prostate cancer, and further guide clinical treatment choices.[5–8]

The higher the PI-RADS score, the greater the possibility of patients developing prostate cancer. Clinically, it is recommended that patients actively undergo prostate biopsy for a clear diagnosis.[9] For patients with a PI-RADS score $\leq$ 3, other clinical results, such as prostate palpation and serum prostate-specific antigen (PSA) levels, should be combined to determine whether to further perform prostate biopsy.[10–12] However, previous studies have found that 7.8% to 19.8% of prostate cancer patients did not show obvious tumorological features on MRI before biopsy,[13–16] which is called MRI invisible prostate cancer (MRI(-)PCa).[17] Among these patients, only a small portion underwent systematic prostate biopsy to further clarify the pathology, while the vast majority of patients may choose active monitoring due to the lack of biopsy indications, resulting in disease progression.[18] It is worth noting that MRI(-)PCa may include both clinically insignificant prostate cancer (CIPCa) and clinically significant prostate cancer (CSPCa), and its pathological type also needs to be confirmed through prostate biopsy.[19]

Currently, in clinical practice, the conventional H&E staining combined with immunohistochemistry (IHC) is commonly used to identify prostate cancer.[20–22] However, it is worth noting that compared with direct microscopic observation of the morphology of cells and cell nuclei through H&E staining, IHC result can more intuitively display the staining of all cells and extracellular matrix in the pathological section, as well as the secretion amount of certain specific proteins, and can more microscopically present the metabolic state and molecular phenotype of cells at the molecular level. However, although IHC markers such as p63, α-methylacyl-CoA racemase (AMACR), and CK5/6 are widely and frequently used in prostate biopsies, recent studies have shown that in some types of prostate cancer, especially in the pathological diagnosis of early-stage prostate cancer and prostate cancer with low PSA, the sensitivity of these IHC markers is insufficient.[23–27] Therefore, more precise and earlier detection of MRI(-)PCa and finding a more efficient way to diagnose prostate cancer through pathological examination have become urgent problems to be solved in clinical practice.

Angiogenic factor with G and FHA domain 1 (AGGF1) is a nuclear chromatin-related protein that can not only promote the formation of tumor microvessels but also participate in DNA damage repair, autophagy, proliferation, and invasion processes of tumors.[28–32] Previous studies have confirmed that AGGF1 plays an important role in the proliferation and metastasis of gastric cancer, liver cancer, and esophageal cancer, but its role in prostate cancer is less studied.[33,34] Compared with traditional or other potential immunohistochemical markers for prostate cancer diagnosis, AGGF1 has been confirmed to potentially act as an upstream regulatory factor in other cancer types, participating in the occurrence and development process of tumors earlier.[35,36] However, only a few studies have discussed the diagnostic value of AGGF1 as an immunohistochemical marker in digestive tract tumors.[35] There are currently no research reports indicating whether AGGF1 is related to the occurrence, progression and malignancy of prostate cancer. At the same time, there are no studies discussing the diagnostic value of AGGF1 as an immunohistochemical marker in prostate cancer. Therefore, in-depth research on AGGF1 can make up for the deficiencies in the early diagnosis of prostate cancer and this article aims to further enhance its application value through clinical data analysis and AGGF1 immunohistochemical experiments, providing a theoretical basis for subsequent basic research. At the same time, in the clinical research field of prostate cancer, previous studies have mostly focused on how to prevent unnecessary biopsies for patients, and there have been few studies exploring the risk factors for MRI(-)PCa patients.[37–39] Through a retrospective analysis, this article explores the possible clinically relevant risk factors for MRI(-)PCa patients, with the hope of providing assistance for future clinical treatment decisions. At the same time, more clinical detection methods should be provided for cases where the cell morphology examination cannot clearly distinguish between tumors and benign lesions, in order to further increase the pathological detection rate of prostate cancer.

Methods and Materials

General information

A retrospective analysis was conducted on the clinical data of patients admitted to Beijing Friendship Hospital, Capital Medical University, who were suspected of having prostate cancer and underwent their first prostate biopsy from January 2015 to October 2025. All patients underwent mpMRI examination before the biopsy, and a total of 376 patients met the PI-RADS score of $\leq$3. This study followed the Helsinki

Declaration and was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Approval Number: 2024-P2-438-01).

Inclusion and exclusion criteria

Inclusion Criteria: (1) First time undergoing prostate biopsy; (2) Based on mpMRI examination and with a PI-RADS score ≤ 3.

Exclusion criteria: (1) Patients who had underwent transurethral prostatectomy before prostate biopsy; (2) Patients who had underwent surgery for other malignant tumors in other organs; (3) Patients who had other types of urinary system diseases, such as prostatitis or urinary calculi; (4) Patients with missing clinical data.

In this study, a total of 402 patients met the inclusion criteria. However, according to the exclusion criteria, 3 patients had undergone transurethral prostatectomy before prostate biopsy, 4 patients had undergone surgery for other malignant tumors in other organs, 12 patients had other types of urinary system diseases, and 7 patients had incomplete clinical data. All of these patients were excluded from this study. Therefore, a total of 376 patients who met the criteria were finally included in this study.

Multi-parameter magnetic resonance imaging scanning strategy

The scanning sequence includes T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and dynamic contrast-enhanced imaging (DCE). The PI-RADS scores of all patients were completed by radiologists at Beijing Friendship Hospital, Capital Medical University, who are familiar with prostate MRI scoring. DWI is the main determining sequence for the peripheral zone of the prostate, while T2WI is the main determining sequence for the transition zone.[40–42] MRI(-)PCa is defined as prostate cancer with a PI-RADS score of ≤ 3. The final MRI results and PI-RADS scores were interpreted by two radiologists with over 10 years of clinical experience. If there were any discrepancies in the interpretation results, they would be judged by another senior physician with over 15 years of clinical experience.

Puncture method and pathology

All patients underwent transrectal ultrasound-guided transperineal 24-needle system biopsy under general anesthesia. Eight needles were placed at the base, middle, and apex of the prostate, including 8 needles in the transitional zone and 16 needles in the peripheral zone.[43] The specific locations are shown in Figure 1. The pathological grading of prostate cancer biopsy specimens was based on the adenocarcinoma Gleason grading standard revised by the expert consensus meeting of the International Society of Urological Pathology (ISUP) in 2014.[44–46] CSPCa was defined as ISUP grading 2 or higher, and CIPCa was defined as ISUP grading 1. Non-CSPCa (NCSPCa) is defined as all patients who are not CSPCa patients, which includes CIPCa patients and patients with benign prostate diseases.

AGGF1 immunohistochemical (IHC) staining

For frozen sections, the specimens were fixed in 4°C acetone for 10 min, then rinsed three times with phosphate-buffered saline (PBS) solution, each time for 5 min. As for formalin-fixed paraffin-embedded (FFPE) tissues, first place the sections in the xylene gradient decalcification solution and dewaxing for 15 min each time. Then, the xylene was eluted using a gradient ethanol solution. This process was repeated for 10 min each time. Finally, double-distilled water was used to rinse off the ethanol. Then, the sample was incubated at room temperature with hydrogen peroxide for 5 min to eliminate the activity of endogenous peroxidase. Then, immerse it in PBS for 2 times, each time for 5 min. Subsequently, 10% fetal bovine serum (non-activated Charcoal Absorbed FBS) was used for blocking, and the sample was incubated at room temperature for 10 min. After removing the serum, an anti-AGGF1 dilution of 1:2000 (11889-1-AP, Proteintech, Wuhan, China) was added, and the sample was incubated at 4°C overnight. Then, the sample was rinsed three times with PBS, each time for 5 min. Then, a secondary antibody dilution of 1:1000 (SA00004-2, Proteintech, Wuhan, China) was added and incubated at room temperature for 30 min, followed by another rinse with PBS. Add an appropriate amount of alkaline phosphatase-labeled streptavidin working solution and incubate at 37°C for 30 min. After PBS washing, the chromogenic agent will develop color for 5 min. Finally, the sample was thoroughly rinsed with water, re-stained, dehydrated, cleared, sealed, and observed under a microscope (BX43, Olympus, Tokyo, Japan). The staining degree was scored according to the percentage of positive staining cells: low expression ($\leq$50%), high expression (>50%).[29–33] As for the type of staining positivity, both normal prostate epithelial cells and tumor epithelial cells cytoplasmic staining patterns were considered positive for AGGF1 expression.

It is worth noting that since all patients underwent transperineal 24-needle system biopsy, each patient received 24 samples after the biopsy. However, we

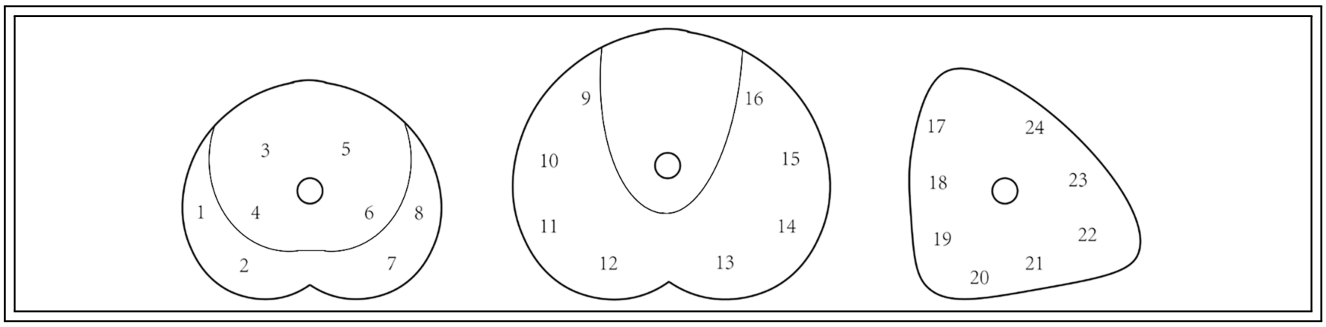

FIGURE 1. Schematic diagram of the 24-needle systematic puncture site for the prostate under transrectal ultrasound guidance through the perineum

only selected the two samples with the highest Gleason scores for IHC analysis (we preferred to use two specimens from the transition zone and the peripheral zone, respectively. If the two specimens with the highest Gleason scores were from the same zone of the prostate, then only these two specimens from the same zone could be selected). If the expression of AGGF1 in any one of these samples was greater than 50%, it was considered that the patient had positive AGGF1 expression. Conversely, if the IHC results of both tissues indicated that the expression of AGGF1 was lower than 50%, it was considered that the patient had negative AGGF1 expression.[29–33] All IHC results were interpreted by two pathologists with over 10 years of clinical experience. In case of any discrepancy in the interpretation results, a senior physician with over 15 years of clinical experience would make the final judgment.

Other clinical data

This study retrospectively collected all patients' demographic data, including their previous medical histories such as age, body mass index (BMI), hypertension, diabetes, coronary heart disease (CHD), etc., previous pelvic surgery history, smoking history, drinking history, and medication history of α-receptor inhibitors and 5α-reductase inhibitors, as well as serum biochemical indicators such as white blood cell count, PSA level, corrected PSA level, free prostate specific antigen/total prostate specific antigen (f/tPSA), and prostate-specific antigen density (PSAD). Additionally, in terms of imaging data, this study collected and analyzed factors including prostate volume, suspected lesion locations on mpMRI, presence of abnormal signals on MRI-weighted sequences, and PI-RADS score.

The collected PSA represents the final test result before the prostate biopsy for the patients. The surgical indications for prostate biopsy in the PSA-positive group were PSA $>$ 10 ng/mL or 4 ng/mL $<$ PSA $\leq$ 10 ng/mL and f/tPSA $\leq$ 0.16; in the PSA-negative group, it was defined as PSA $<$ 4 ng/mL or 4 ng/mL $<$ PSA $\leq$ 10 ng/mL and f/tPSA $>$ 0.16. The use history of 5α-reductase inhibitors (5α-reductase inhibitor, 5-ARI) was defined as being currently taking 5-ARI and having used it for $\geq$2 months. The corrected PSA was defined as the actual measured PSA $\times$ 2 (when the patient had a 5-ARI use history).

Statistical methods

The data were statistically analyzed using SPSS 26.0 (IBM Corp, Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) with 'dcurves' package. Firstly, the patients were grouped based on whether they had CSPCa to explore the risk factors of MRI(-)PCa. The measurement data with normal distribution were expressed as mean $\pm$ standard deviation (SD), and the comparison between groups was conducted using the *t*-test; the measurement data with non-normal distribution were expressed as median (interquartile range) [median (Q_1, Q_3)], and the comparison between groups was conducted using the rank sum test. The count data were expressed as the number of cases and percentage [cases (%)], and the comparison between groups was conducted using the χ^2 test. The indicators with statistically significant differences were included in the multivariate Logistic regression to further explore the independent risk factors of MRI(-)PCa. The Receiver Operating Characteristic (ROC) curve was drawn and adjusted by bootstrap optimism correction (1000 repetitions of sampling) as an internal validation. Select the point with the maximum Youden index as the optimal threshold, then calculate the corresponding PSAD value. In terms of evaluating the clinical application value, decision-curve analysis (DCA) has been further improved,

and the relevant curve diagrams were drawn. Subsequently, further subgroup analyses were conducted based on whether the PSA before biopsy was positive and the PI-RADS score to further determine the risk factors of prostate cancer in different serological indicators and PI-RADS score subgroups. Moreover, we also used the Kruskal-Wallis test to compare the differences in AGGF1 expression percentages across different Gleason score groups according to ISUP in CSPCa patients. p-value < 0.05 was considered statistically significant.

Result

Analysis of risk factors for MRI(-)PCa

The mean age of the patients was 66.48 ± 7.86 years, the median PSA was 8.75 (6.05, 13.24) ng/mL, and the median prostate volume was 53.25 (38.98, 73.99) cm^3. The biopsy results showed that 273 patients had benign diseases, 1 patient had CIPCa, and 102 patients had CSPCa.

There were 102 patients in the CSPCa group and 274 patients in the NCSPCa group. The clinical data results are shown in Table 1. The results of univariate analysis showed that the proportion of patients with high AGGF1 expression in the CSPCa group was 72.5%, significantly higher than 4.0% in the NCSPCa group, and the differences were statistically significant ($p < 0.001$). At the same time, the f/tPSA level was lower and the prostate volume was smaller in the CSPCa group, but the corrected PSA level, PSAD, and PSA positive rate were higher than those in the NCSPCa group, and the differences were statistically significant ($p < 0.05$). This study also found that if the patient's MRI indicated abnormal signals in the peripheral zone, it was more likely to indicate the

TABLE 1. **Comparison of clinical data between the CSPCa group and the NCSPCa group patients**

Factors	CSPCa Group (n = 102)	NCSPCa Group (n = 274)	$t/Z/\chi^2$	p value
Age (years), mean ± SD	67.67 ± 6.48	66.47 ± 7.05	1.16	0.121
BMI (kg/m^2), mean ± SD	25.08 ± 3.02	24.90 ± 3.14	0.51	0.609
Hypertension, N (%)	50 (49.0)	133 (48.5)	0.01	0.934
Diabetes Mellitus, N (%)	23 (22.5)	44 (16.1)	2.14	0.144
CHD, N (%)	12 (11.8)	23 (8.4)	1.00	0.317
Pelvic Surgery, N (%)	2 (2.0)	6 (2.2)	0.02	0.891
Smoking, N (%)	27 (26.5)	88 (32.1)	0.74	0.391
Drinking, N (%)	16 (15.7)	53 (19.3)	0.66	0.415
Using α-receptor Blocker, N (%)	25 (24.5)	87 (31.8)	1.86	0.172
Using 5α-reductase inhibitor, N (%)	13 (12.7)	52 (19.0)	2.02	0.155
High expression of AGGF1, N(%)	74 (72.5)	11 (4.0)	199.55	<0.001
White Blood Cell ($\times 10^9$/L), median (Q_1, Q_3)	6.05 (5.06, 7.10)	6.33 (5.17, 7.34)	1.13	0.261
f/tPSA, median (Q_1, Q_3)	0.12 (0.12, 0.18)	0.16 (0.13, 0.20)	−2.57	0.011
Adjusted PSA (ng/mL), median (Q_1, Q_3)	10.64 (6.52, 20.14)	8.31 (6.02, 12.02)	5.64	<0.001
PSAD (ng/mL/cm^3), median (Q_1, Q_3)	0.25 (0.15, 0.44)	0.14 (0.10, 0.21)	−7.62	<0.001
PSA Positive, N (%)	84 (82.4)	147 (63.5)	25.85	<0.001
Prostate Volume (cm^3), median (Q_1, Q_3)	42.18 (32.35, 49.50)	59.37 (42.37, 78.82)	−5.61	<0.001
Location of Lesion, N (%)			23.824	<0.001
peripheral zone	89 (87.3)	167 (61.7)		
transition zone	11 (10.8)	96 (35.0)		
both	2 (2.0)	11 (4.0)		
Abnormal signal of DWI, N (%)	40 (39.2)	84 (30.7)	2.46	0.117
PI-RADS, N (%)			2.27	0.132
1~2	70 (58.3)	209 (76.3)		
3	32 (41.7)	65 (23.7)		

Abbreviations: BMI, Body Mass Index; CHD, Coronary Heart Disease; PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging; PI-RADS, Prostate Imaging Reporting And Data System.

TABLE 2. **Multivariate logistic regression analysis of risk factors for MRI-invisible prostate cancer (MRI(-)PCa)**

Factors	B	SE	Wald χ^2	OR	95%CI	*p* value
High expression of AGGF1	0.063	0.021	9.137	1.065	1.022, 1.109	0.003
f/tPSA	0.010	0.037	0.069	1.010	0.940, 1.085	0.793
PSAD	−0.029	0.010	8.152	0.971	0.952, 0.991	0.004
Adjusted PSA	−3.076	1.926	2.550	0.046	0.001, 2.012	0.110
Prostate Volume	−0.071	0.076	0.876	0.931	0.802, 1.081	0.349
Location of Lesion	3.046	1.839	2.743	21.034	0.572, 773.514	0.098
PSA Positive	0.019	0.055	0.121	1.019	0.915, 1.136	0.728

Abbreviations: PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

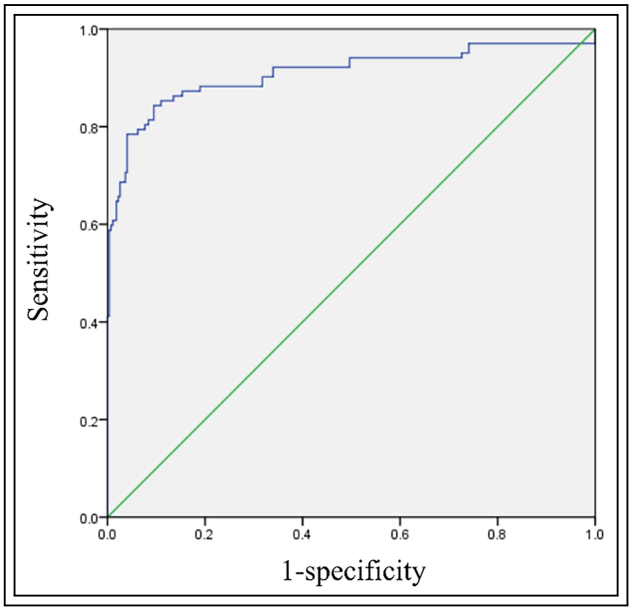

FIGURE 2. Receiver operating characteristic (ROC) curve analysis of risk factors for patients with MRI-invisible prostate cancer (MRI(-)PCa)

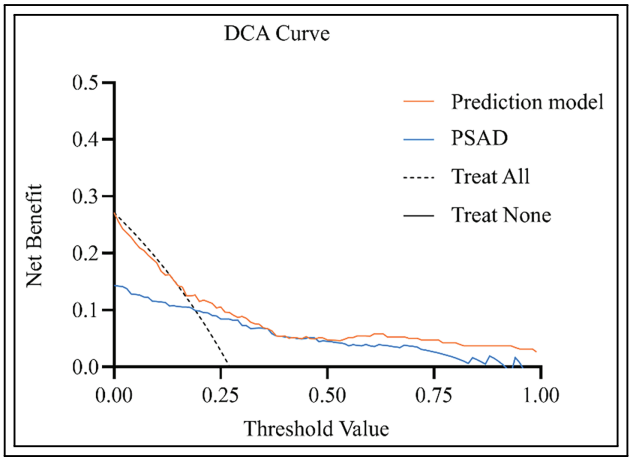

FIGURE 3. Decision-curve analysis (DCA) curve to evaluate the clinical application value of the predictive model. The curve labeled "Treat None" coincides with the horizontal axis

presence of CSPCa compared to abnormal signals in the transition zone.

The results of multivariate Logistic regression analysis showed that only AGGF1 expression level and PSAD were independent risk factors for MRI(-)PCa. The results are shown in Table 2. In terms of result verification, the area under the ROC curve calculated by the multivariate Logistic regression equation after bootstrap optimism correction was 0.909 (95% CI: 0.866, 0.953), indicating good predictive accuracy, as shown in Figure 2. When the Youden index is at its maximum, the sensitivity of the model is 84.3%, the specificity is 90.5%, and the threshold of PSAD at this time is 0.25 ng/mL/cm^3. The DCA results show that when the threshold is 0.13 or higher, the clinical practical benefits of using this prediction model can be significantly improved, and the clinical benefits for patients are higher than the diagnostic effect achieved by simply considering PSAD. The results are shown in Figure 3.

Subgroup analysis of whether PSA levels are abnormal

In this study, there were a total of 145 PSA-negative patients, among which 18 were in the CSPCa group and 127 were in the NCSPCa group. The univariate analysis showed that there were statistically significant differences in the expression levels of AGGF1,

TABLE 3. **Comparison of clinical data between the CSPCa group and the NCSPCa group in PSA-negative patients**

Factors	CSPCa Group (n = 18)	NCSPCa Group (n = 127)	$t/Z/\chi^2$	p value
Age (years), mean ± SD	68.56 ± 6.03	67.30 ± 6.33	0.83	0.414
BMI (kg/m^2), mean ± SD	23.67 (21.75, 25.47)	24.61 (22.58, 26.67)	−0.83	0.415
Hypertension, N (%)	8 (44.4)	60 (47.2)	0.05	0.824
Diabetes Mellitus, N (%)	1 (5.6)	22 (17.3)	1.64	0.201
CHD, N (%)	1 (5.6)	13 (10.2)	0.40	0.529
Pelvic Surgery, N (%)	0 (0.0)	2 (1.6)	0.29	0.592
Smoking, N (%)	5 (27.8)	29 (22.8)	0.22	0.643
Drinking, N (%)	2 (11.1)	21 (16.5)	0.35	0.555
Using α-receptor Blocker, N (%)	4 (22.2)	38 (29.9)	0.45	0.500
Using 5α-reductase inhibitor, N (%)	3 (16.7)	27 (21.3)	0.20	0.653
High expression of AGGF1, N (%)	18 (100.0)	11 (8.7)	82.21	<0.001
White Blood Cell ($\times 10^9$/L), median (Q_1, Q_3)	5.29 (4.86, 6.64)	6.20 (4.89, 7.26)	−0.32	0.754
f/tPSA, median (Q_1, Q_3)	0.19 (0.18, 0.26)	0.19 (0.17, 0.24)	−0.77	0.446
Adjusted PSA (ng/mL), median (Q_1, Q_3)	6.60 (4.25, 8.16)	6.28 (4.38, 8.10)	−0.62	0.539
PSAD (ng/mL/cm^3), median (Q_1, Q_3)	0.12 (0.07, 0.19)	0.11 (0.07, 0.13)	−0.88	0.388
Prostate Volume (cm^3), median (Q_1, Q_3)	45.40 (37.03, 65.40)	56.28 (39.24 74.00)	−0.40	0.695
Location of Lesion, N (%)			0.79	0.675
peripheral zone	15 (83.3)	99 (78.0)		
transition zone	3 (16.7)	23 (18.1)		
both	0 (0.0)	5 (3.9)		
Abnormal signal of DWI, N (%)	1 (5.6)	44 (34.6)	6.23	0.013
PI-RADS, N (%)			5.02	0.025
1~2	8 (44.4)	90 (70.9)		
3	10 (55.6)	37 (29.1)		

Abbreviations: BMI, Body Mass Index; CHD, Coronary Heart Disease; PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging; PI-RADS, Prostate Imaging Reporting And Data System.

the abnormal DWI signal conditions, and the PI-RADS scores between the two groups ($p < 0.05$), as shown in Table 3. The multivariate Logistic regression analysis results indicated that only when the AGGF1 immunohistochemical result of the prostate biopsy pathology of the patients was positive, the incidence of CSPCa was higher. The results are detailed in Table 4.

On the other hand, there were a total of 231 PSA-positive patients, among which 84 patients were in the CSPCa group and 147 patients were in the NCSPCa group. The results of univariate analysis showed that the expression levels of AGGF1, corrected PSA levels, prostate volume, PSAD, abnormal DWI signals, and suspected lesion locations on MRI images in both groups were statistically different ($p < 0.05$) (Table 5). The results of multivariate Logistic regression analysis showed that only PSAD and the immunohistochemical results of AGGF1 were related to the incidence of CSPCa. The details are shown in Table 6.

Subgroup analysis of different PI-RADS scores

A total of 279 patients had a PI-RADS score of 1–2. Among them, 70 patients were in the CSPCa group and 209 patients were in the NCSPCa group. The results of the univariate analysis showed that 70% of the patients in the CSPCa group had high AGGF1 expression, which was significantly higher than 5.3% in the NCSPCa group, and the difference was statistically significant ($p < 0.001$). At the same time, patients in the CSPCa group had higher corrected PSA levels, PSAD, and lower prostate volume than those in the NCSPCa group. Moreover, the proportion of patients with lesions located in the peripheral zone or with abnormal signals on the DWI sequence was higher in the CSPCa group than in the NCSPCa group, and the differences were statistically significant ($p < 0.05$).

TABLE 4. **Multivariate logistic regression analysis of MRI-invisible prostate cancer (MRI(-)PCa) in PSA-negative patients**

Factors	B	SE	Wald χ^2	OR	95%CI	*p* value
High expression of AGGF1	0.055	0.012	19.484	1.056	1.031, 1.082	<0.001
Abnormal signal of DWI	−0.071	0.071	0.989	0.932	0.811, 1.071	0.320
PI-RADS	0.038	0.039	0.940	1.039	0.962, 1.121	0.332

Abbreviations: DWI, Diffusion Weighted Imaging; PI-RADS, Prostate Imaging Reporting And Data System; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

TABLE 5. **Comparison of clinical data between the CSPCa group and the NCSPCa group in patients with positive PSA**

Factors	CSPCa Group (n = 84)	NCSPCa Group (n = 147)	$t/Z/\chi^2$	*p* value
Age (years), mean ± SD	67.48 ± 6.59	65.76 ± 7.57	1.80	0.073
BMI (kg/m^2), mean ± SD	25.23 (23.03, 27.55)	24.91 (22.32, 27.44)	−0.587	0.558
Hypertension, N (%)	42 (50.0)	73 (49.7)	0.00	0.960
Diabetes Mellitus, N (%)	22 (26.2)	22 (15.0)	3.67	0.055
CHD, N (%)	11 (13.1)	10 (6.8)	2.56	0.110
Pelvic Surgery, N (%)	2 (2.4)	4 (2.7)	0.02	0.876
Smoking, N (%)	22 (26.2)	56 (38.1)	3.39	0.066
Drinking, N (%)	14 (16.7)	32 (21.8)	0.87	0.350
Using α-receptor Blocker, N (%)	21 (25.0)	49 (33.3)	1.758	0.185
Using 5α-reductase inhibitor, N (%)	10 (11.9)	25 (17.0)	1.08	0.298
High expression of AGGF1, N (%)	56 (66.7)	0 (0.0)	129.36	<0.001
White Blood Cell ($\times 10^9$/L), median (Q_1, Q_3)	6.10 (5.18, 7.12)	6.36 (5.52, 7.44)	−1.86	0.064
f/tPSA, median (Q_1, Q_3)	0.15 (0.06, 0.14)	0.13 (0.11, 0.16)	−1.69	0.093
Adjusted PSA (ng/mL), median (Q_1, Q_3)	12.92 (8.15, 23.12)	11.13 (8.21, 15.98)	−3.007	0.003
PSAD (ng/mL/cm^3), median (Q_1, Q_3)	0.31 (0.19, 0.63)	0.18 (0.14, 0.26)	−4.40	<0.001
Prostate Volume (cm^3), median (Q_1, Q_3)	41.37 (32.34, 48.97)	61.35 (45.43, 81.63)	−7.46	<0.001
Location of Lesion, N (%)	39 (46.4)	40 (27.2)	8.773	0.003
peripheral zone			40.224	<0.001
transition zone	74 (88.1)	68 (46.3)		
both	8 (9.5)	73 (49.7)		
Abnormal signal of DWI, N (%)	2 (2.4)	6 (4.1)		
PI-RADS, N (%)			1.608	0.205
1~2	62 (73.8)	119 (81.0)		
3	22 (26.2)	28 (19.0)		

Abbreviations: BMI, Body Mass Index; CHD, Coronary Heart Disease; PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging; PI-RADS, Prostate Imaging Reporting And Data System.

See Table 7 for details. The results of the multivariate Logistic regression analysis showed that only PSAD before biopsy and the immunohistochemical indication of AGGF1 high expression after prostate biopsy were independent risk factors for CSPCa, as shown in Table 8.

A total of 97 patients had a PI-RADS score of 3. Among them, 32 patients were in the CSPCa group and 65 patients were in the NCSPCa group. The results of the univariate analysis showed that 78.1% of the patients in the CSPCa group had high expression of AGGF1, while no patients in the NCSPCa group showed positive immunohistochemical results

TABLE 6. **Multivariate Logistic regression analysis of MRI(-) prostate cancer in PSA-positive patients**

Factors	B	SE	Wald χ^2	OR	95%CI	*p* value
High expression of AGGF1	0.062	0.013	22.139	1.064	1.037, 1.092	<0.001
Adjusted PSA	−0.086	0.074	1.349	0.918	0.794, 1.061	0.245
Prostate Volume	0.031	0.040	0.608	1.032	0.954, 1.116	0.435
PSAD	−0.694	0.297	5.449	0.500	0.279, 0.895	0.020
Abnormal signal of DWI	0.022	0.018	1.225	1.023	0.987, 1.060	0.221
Location of Lesion	0.655	0.393	2.780	1.925	0.891, 4.157	0.095

Abbreviations: PSA, Prostate Specific Antigen; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

TABLE 7. **Comparison of clinical data between the CSPCa group and the NCSPCa group in patients with PI-RADS 1-2 classification**

Factors	CSPCa Group (n = 70)	NCSPCa Group (n = 209)	$t/Z/\chi^2$	*p* value
Age (years), mean ± SD	67.00 (63.75, 70.00)	66.00 (62.00, 71.00)	−0.73	0.469
BMI (kg/m^2), mean ± SD	25.18 ± 3.05	25.00 ± 3.13	0.43	0.671
Hypertension, N (%)	33 (47.1)	94 (45.0)	0.10	0.753
Diabetes Mellitus, N (%)	16 (22.9)	36 (17.2)	1.097	0.295
CHD, N (%)	8 (11.4)	19 (9.1)	0.33	0.567
Pelvic Surgery, N (%)	1 (1.4)	5 (2.4)	0.23	0.630
Smoking, N (%)	19 (27.1)	57 (27.3)	0.00	0.983
Drinking, N (%)	11 (15.7)	38 (18.2)	0.22	0.639
Using α-receptor Blocker, N (%)	21 (30.0)	66 (31.6)	0.06	0.805
Using 5α-reductase inhibitor, N (%)	9 (12.9)	38 (18.2)	1.06	0.303
High expression of AGGF1, N (%)	49 (70.0)	11 (5.3)	130.184	<0.001
White Blood Cell ($\times 10^9$/L), median (Q_1, Q_3)	6.01 (5.17, 7.04)	6.35 (5.16,7.34)	−0.81	0.4198
f/tPSA, median (Q_1, Q_3)	0.12 (0.07, 0.17)	0.16 (0.13, 0.19)	−1.917	0.056
Adjusted PSA (ng/mL), median (Q_1, Q_3)	11.67 (6.39, 21.61)	8.31 (6.06, 12.02)	−3.449	0.001
PSAD (ng/mL/cm^3), median (Q_1, Q_3)	0.24 (0.14, 0.54)	0.14 (0.10, 0.21)	−3.997	<0.001
Prostate Volume (cm^3), median (Q_1, Q_3)	43.72 (33.27, 56.14)	60.68 (42.32, 79.95)	−4.599	<0.001
Location of Lesion, N (%)			12.07	0.002
peripheral zone	59 (73.5)	130 (43.9)		
transition zone	9 (12.2)	71 (51.9)		
both	2 (14.3)	8 (4.2)		
Abnormal signal of DWI, N (%)	18 (25.7)	28 (13.4)	5.78	0.016

Abbreviations: BMI, Body Mass Index; CHD: Coronary Heart Disease; PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging.

for AGGF1 in the biopsy pathology. At the same time, the CSPCa group had lower f/tPSA and prostate volume compared to the NCSPCa group, but the PSAD of the CSPCa group was higher than that of the NCSPCa group, and the differences were statistically significant ($p < 0.05$). Additionally, the proportion of patients in the CSPCa group with MRI imaging indicating lesions located in the peripheral zone was higher than that in the NCSPCa group, and the differences were also statistically significant ($p < 0.05$), as shown in Table 9. The results of the multivariate Logistic regression analysis showed that only the PSAD level before prostate biopsy and the immunohistochemical result of AGGF1 were independent risk factors for CSPCa, as shown in Table 10.

TABLE 8. **Multivariate logistic regression analysis of MRI(-) prostate cancer in patients with PI-RADS 1-2 classification**

Factors	B	SE	Wald χ^2	OR	95%CI	*p* value
High expression of AGGF1	0.081	0.016	25.989	1.084	1.051–1.118	<0.001
Adjusted PSA	−0.052	0.074	0.491	0.949	0.821–1.098	0.484
PSAD	−0.044	0.007	36.737	0.957	0.943–0.971	<0.001
Prostate Volume	−0.388	0.365	1.134	0.678	0.332–1.386	0.287
Location of Lesion	−0.527	0.317	2.768	0.590	0.317–1.098	0.096
Abnormal signal of DWI	−2.498	1.442	3.001	0.082	0.005–1.389	0.083

Abbreviations: PSA, Prostate Specific Antigen; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

TABLE 9. **Comparison of clinical data between the CSPCa group and the NCSPCa group in patients with PI-RADS 3 classification**

Factors	CSPCa Group (n = 32)	NCSPCa Group (n = 65)	$t/Z/\chi^2$	*p* value
Age (years), mean ± SD	68.00 (64.25, 73.00)	67.00 (62.00, 72.00)	−1.70	0.093
BMI (kg/m^2), mean ± SD	24.86 ± 3.01	24.58 ± 3.18	0.43	0.666
Hypertension, N (%)	17 (53.1)	39 (60.0)	0.42	0.519
Diabetes Mellitus, N (%)	7 (21.9)	8 (12.3)	1.50	0.220
CHD, N (%)	4 (12.5)	4 (6.2)	1.14	0.285
Pelvic Surgery, N (%)	1 (3.1)	1 (1.5)	0.27	0.605
Smoking, N (%)	8 (25.0)	28 (43.1)	3.00	0.083
Drinking, N (%)	5 (15.6)	15 (23.1)	0.73	0.394
Using α-receptor Blocker, N (%)	4 (12.5)	21 (32.3)	3.42	0.064
Using 5α-reductase inhibitor, N (%)	4 (12.5)	14 (21.5)	1.16	0.282
High expression of AGGF1, N (%)	25 (78.1)	0 (0.0)	68.41	<0.001
White Blood Cell ($\times 10^9$/L), median (Q_1, Q_3)	6.39 (4.70, 7.21)	6.10 (5.22, 7.28)	−0.79	0.430
f/tPSA, median (Q_1, Q_3)	0.12 (0.08, 0.19)	0.18 (0.14, 0.23)	−3.84	<0.001
Adjusted PSA (ng/mL), median (Q_1, Q_3)	9.41 (7.43, 14.40)	8.10 (5.96, 12.28)	−1.70	0.098
PSAD (ng/mL/cm^3), median (Q_1, Q_3)	0.23 (0.15, 0.40)	0.13 (0.09, 0.20)	−2.57	0.015
Prostate Volume (cm^3), median (Q_1, Q_3)	38.42 (27.48, 44.96)	56.45 (42.43, 72.31)	−4.45	<0.001
Location of Lesion, N (%)			13.68	0.001
peripheral zone	30 (93.7)	37 (56.9)		
transition zone	2 (6.3)	25 (38.5)		
both	0 (0.0)	3 (4.6)		
Abnormal signal of DWI, N (%)	22 (68.8)	56 (86.2)	3.09	0.079

Abbreviations: BMI, Body Mass Index; CHD, Coronary Heart Disease; PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; DWI, Diffusion Weighted Imaging.

The differences in AGGF1 expression among patients in different gleason score

A total of 102 patients were confirmed to have CSPCa by pathology. According to the ISUP grading standard, there were 52 patients in the Gleason score 3 + 3 group, 38 patients in the Gleason score 4 + 3 group, and 12 patients in the Gleason score 4 + 4 group. The IHC results showed that the expression percentage of AGGF1 in each group of patients was 48.60% ± 11.03%, 61.00% ± 6.12%, and 71.01% ± 4.46% respectively, and there was a significant statistical difference ($p < 0.001$), as shown in Figure 4.

TABLE 10. **Multivariate Logistic regression analysis of MRI(-) prostate cancer in patients with PI-RADS 3 classification**

Factors	B	SE	Wald χ^2	OR	95%CI	*p* value
High expression of AGGF1	0.088	0.017	26.442	1.092	1.056–1.129	<0.001
f/tPSA	−0.554	0.356	2.420	0.575	0.286–1.155	0.120
PSAD	−1.506	0.321	22.005	0.222	0.118–0.416	<0.001
Prostate Volume	−0.382	0.303	1.596	0.682	0.377–1.235	0.207
Location of Lesion	0.049	0.042	1.364	1.050	0.967–1.141	0.243

Abbreviations: PSA, Prostate Specific Antigen; f/tPSA, Free PSA/Total PSA; PSAD, Prostate Specific Antigen Density; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

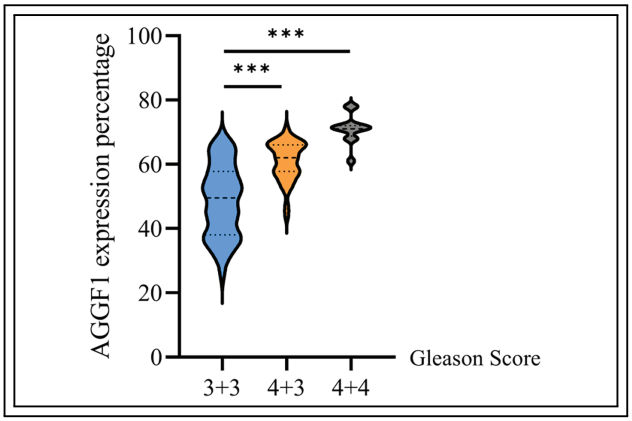

FIGURE 4. The violin plot is used to illustrate the differences in AGGF1 expression among patients with different Gleason scores. ***$p < 0.001$

Discussion

In recent years, with the development of MRI technology, mpMRI has become the imaging examination with the highest accuracy for diagnosing prostate cancer.[47,48] However, although some patients were clinically confirmed to have prostate cancer through biopsy, the preoperative MRI imaging examination might not have indicated the presence of a clear tumor lesion.[49–51] This type of tumor is also known as MRI invisible prostate cancer (MRI(-)PCa). Therefore, how to improve the detection rate of these patients and avoid further tumor progression has become an urgent problem to be solved. In our study, the detection rate of CSPCa in patients with PI-RADS score ≤ 3 was 27.13% (102/376). Failure to perform a prostate biopsy in time may delay the disease, depriving the patient of the opportunity for radical treatment, and seriously affecting the patient's quality of life and life expectancy. Therefore, understanding the risk factors of CSPCa is of great significance for guiding clinical decisions.

Many studies have strongly demonstrated that AGGF1 directly participates in the proliferation of tumor cells and may be related to the occurrence and development of tumors.[29–31] Unfortunately, in the field of prostate cancer, studies on the correlation between AGGF1 and the malignancy of tumors and the prognosis of patients are very few. The results of this study found that the positive immunohistochemical result of AGGF1 in prostate biopsy tissues was an independent risk factor for MRI invisible prostate cancer, even if the patient's preoperative magnetic resonance imaging did not find a clear lesion and the PSA level was not high. In subgroup analyses based on PSA or PI-RADS scores, we also found that regardless of the patient's PSA level, if AGGF1 is positive, the risk of prostate cancer should be considered. This also indicates that AGGF1 can be further promoted as an immunohistochemical indicator for the diagnosis of prostate cancer after prostate biopsy, to increase the detection rate of prostate cancer.

AGGF1 was initially known as a vascular endothelial growth factor, but in recent years, more and more studies have confirmed that it is also directly involved in the proliferation, metastasis, and invasion processes of tumor cells.[31] Previous basic research has found that in malignant tumors of the digestive tract, AGGF1 can indirectly activate the Wnt/β-catenin pathway by activating the PI3K/Akt signaling pathway, thereby stabilizing the β-catenin protein, causing it to accumulate in the cytoplasm and transfer into the nucleus to promote tumor cell proliferation.[32–36] Furthermore, these studies have also found that in early-stage tumors, the expression level of AGGF1 is relatively higher than that in normal tissues. Similarly, the tumor specificity and sensitivity of AGGF1 are not lower than those of

traditional biomarkers such as p53, VEGF, or Ki-67. Furthermore, Si et al.[30] also discovered that AGGF1 can regulate the post-transcriptional modification and stability of p53 through MDM2, thereby influencing the occurrence and development of tumors. This further indicates that AGGF1 may be an upstream regulatory gene of p53, and its intracellular content changes may be more significant than those of p53. Therefore, the significance of AGGF1 as an IHC marker in the tumor diagnosis process may be higher than p53. Zhang et al.'s research also suggests that AGGF1 can even better predict the prognosis of colorectal cancer patients compared to traditional biomarkers.[31] Moreover, although it has not been widely used in clinical practice yet, AGGF1 may still serve as a new IHC marker for differentiating tumors from benign tissues.

Meanwhile, although previous studies have confirmed that mpMRI may have the potential for missing diagnoses of prostate cancer, they have not further explored how to screen for the population prone to such missed diagnoses.[52–54] This study provides preliminary results through subgroup analysis: For patients with positive PSA, in addition to the immunohistochemical result of AGGF1, further attention should be paid to their prostate volume and PSAD. Meanwhile, although previous studies have confirmed that mpMRI may have the potential for missing diagnoses of prostate cancer, they have not further explored how to screen for the population prone to such missed diagnoses.[52,53] If the patient has a small prostate volume and a high PSAD, the risk of having CSPCa should be considered. This study provides preliminary results through subgroup analysis: For patients with positive PSA, in addition to the immunohistochemical result of AGGF1, further attention should be paid to their prostate volume and PSAD. Fiard et al.[52] also put forward a similar viewpoint to the one in this study. When the patient's PSAD is less than 0.15 ng/mL/cm^3, the combined application of PSAD with mpMRI is helpful to rule out clinically significant cancer. Kortenbach et al.[53] conducted a prospective study to evaluate the relationship between PSA levels and the incidence of prostate cancer in the patient population with MRI results classified as PI-RADS scores 1–3. It was found that in the subgroup of patients with PSAD level cut-off by 0.15 ng/mL/cm^3, 1.3% of the patients developed PCa within a 2-year follow-up period. Therefore, the researchers believe that for patients with a PI-RADS score 1–3, it is essential to combine PSAD to further determine whether a prostate biopsy should be performed. Choe et al.'s study also further evaluated the accuracy of MRI combined with PSAD in detecting PCa. The results showed that the diagnostic accuracy rate was significantly higher in patients with smaller prostate volumes compared to those with larger prostate volumes.[54] In our study, the optimal threshold point was also selected through ROC curve analysis. The results indicated that when the patient's PSAD value before biopsy was simultaneously more than 0.25 ng/mL/cm^3, it was necessary to suspect that the patient might have prostate cancer, and an additional AGGF1 IHC should be conducted after the biopsy. This expanded the previous traditional definition range. Combined with the AGGF1 immunohistochemical analysis after the biopsy, it can more accurately screen out patients with prostate cancer, further avoiding missed diagnoses, and at the same time, it also provides a theoretical basis for the clinical further and more detailed stratified diagnosis and treatment of patients. In our research, we also found that for patients with negative PSA, only the immunohistochemical result of AGGF1 can be focused on, without paying too much attention to the PSAD result. If the patient has a small prostate volume and a high PSAD, the risk of having CSPCa should be considered. We believe that this may allow the PSAD indicator to further correct the influence caused by the increase in prostate volume and the increase in PSA level due to the coexistence of benign prostatic hyperplasia in patients. For patients with negative PSA, only the immunohistochemical result of AGGF1 can be focused on, without paying too much attention to the PSAD result.

However, this study has some limitations: due to the constraints of being a single-center and retrospective study, the majority of the patients included in this study had indicators such as elevated PSA and abnormal digital rectal examination for prostate biopsy, which led to selection bias and affected the interpretation of the final results; in addition, this study lacked long-term follow-up for patients with negative first biopsy; at the same time, further large-sample clinical studies and further external verification are still needed; in the future, whether AGGF1 directly participates in the proliferation and invasion processes of prostate cancer cells, and whether its expression level has an impact on the prognosis and survival of patients, all require further basic research and *in vitro/in vivo* experiments to confirm.

Conclusions

This study suggests that for patients with clinical suspicion of prostate cancer but whose MRI indicates a PI-RADS score ≤ 3, further attention should be paid to

PSAD. If the PSAD is more than 0.25 ng/mL/cm^3, the possibility of CSPCa should be fully considered, and after prostate biopsy, AGGF1 immunohistochemical staining can be performed to assist pathologists in determining whether the patient has a risk of CSPCa. A diagnosis of prostate cancer should be more likely considered for patients who show a positive reaction for AGGF1.

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Author Contributions

Jingcheng Lyu: Paper writing, experimental design, statistical analysis; Ruiyu Yue: Data organization and data analysis; Ye Tian and Boyu Yang: Research guidance, paper revision. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to ethical restrictions and the inclusion of sensitive patient information. However, data may be made available from the corresponding author, Boyu Yang, upon reasonable request and following review and approval by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University.

Ethics Approval

This study was conducted in accordance with the Helsinki Declaration. The study protocol was reviewed and approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Approval Number: 2024-P2-438-01).

Informed Consent

As this was a retrospective analysis of clinical data, all patient information was anonymized prior to analysis. The manuscript does not contain any personal data or information that could be used to identify individual participants. Hence, the informed consent was waived.

Conflicts of Interest

The authors declare no conflicts of interest.

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