The Predictive Value of tPSA, fPSA, fPSA/tPSA Combined with Ultrasound Parameters in Postoperative Gleason Grading of Prostate Cancer

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AIM: Prostate cancer (PCa) is a common malignant tumor in men. This study aimed to explore the predictive value of serum biomarkers combined with ultrasound parameters for postoperative Gleason grading in PCa.
METHODS: This study included 65 PCa patients who underwent transurethral resection of the prostate in our hospital from January 2021 to December 2023. Based on postoperative Gleason grading, the study subjects were divided into a Mild Group (n = 34) and a Severe Group (n = 31). Levels of serological biomarkers such as total prostate-specific antigen (tPSA), free prostate-specific antigen (fPSA), and fPSA/tPSA (the ratio of fPSA to tPSA), along with ultrasound (US) parameters, including prostate-specific antigen density (PSAD), intraglandular prostate-specific antigen density (IGPSAD), extraglandular prostate-specific antigen density (EGPSAD), and US score were compared between the two groups to evaluate their predictive values for postoperative Gleason grading.
RESULTS: The fPSA, tPSA, fPSA/tPSA ratio, PSAD, IGPSAD, EGPSAD, and US scores in the Severe Group were significantly different from those in the Mild Group ($p < 0.05$). The combined evaluation of fPSA, tPSA, fPSA/tPSA, PSAD, IGPSAD, EGPSAD, and US score for predicting postoperative Gleason grading in PCa patients revealed an area under the curve (AUC) of 0.947, indicating a better predictive performance. The AUC of multi-parameter union was significantly higher than that of individual parameters and serum indicators union (fPSA, tPSA and fPSA/tPSA) ($p < 0.05$).
CONCLUSIONS: The combined use of multiple parameters (fPSA, tPSA, fPSA/tPSA, PSAD, IGPSAD, EGPSAD and US Score) shows better predictive performance than individual testing. The combined application has high predictive value in postoperative Gleason grading of PCa. These findings can effectively guide clinical decision-making and optimize diagnostic strategies for developing effective and targeted therapeutic interventions for PCa.

Keywords: prostate cancer; Gleason grading; prostate-specific antigen; Transrectal Ultrasound; forecast

Introduction

Prostate cancer (PCa) is a common malignancy affecting the genitourinary system in older men, with annually increasing global incidence [1]. PCa is commonly treated with surgical interventions where preoperative risk assessment is crucial for effective treatment. Early-stage PCa typically lacks clear symptoms and is difficult to distinguish clinically from benign prostatic hyperplasia (BPH). The Gleason score (GS) is a crucial predictor of the biological behavior of PCa and a significant indicator in determining its treatment [2]. Currently, GS and prostate-specific antigen (PSA) levels in serum are the common determinants for assessing preoperative risk in PCa. The isolation of limited preoperative biopsy specimens leads to a significant difference in GS for pre- and post-operative pathological tissues, reflecting limitations in the current preoperative risk assessment [3]. Therefore, investigating potential indicators is imperative for predicting more accurate preoperative Gleason grading to improve the management of PCa.

PSA can be categorized into free prostate-specific antigen (fPSA) and total prostate-specific antigen (tPSA). Although elevated levels of PSA can determine the progression of PCa, they are influenced by other prostate lesions, leading to false positive and false negative outcomes in the diagnosis of PCa [4]. The fPSA/tPSA (the ratio of fPSA to

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tPSA) represents the proportion of fPSA in the tPSA [5], which can be used to distinguish between PCa and benign prostatic hyperplasia. The smaller ratio indicates a higher probability of PCa, whereas the higher ratio represents a lower chance of PCa [6]. Additionally, Transrectal Ultrasound (TRUS) is a method for initial PCa screening, which offers real-time, simple, economical, radiation-free, high-resolution, and clear imaging. It can be used to determine the morphology and structure of the lesion, measure blood flow perfusion in prostate nodules, and evaluate postoperative prognosis of PCa [7]. Research has reported the sensitivity and specificity of TRUS, ranging from 40% to 50% in diagnosing PCa [8]. This limited efficacy of two-dimensional ultrasound (US) in diagnosing PCa is primarily due to the similarity of scattered signals between normal and cancerous tissues and the heterogeneity of these signals in the transition zone [9]. Therefore, this study aimed to compare the serum levels of tPSA, fPSA, fPSA to tPSA ratio, US parameters such as prostate-specific antigen density (PSAD), intraglandular prostate-specific antigen density (IGPSAD), extraglandular prostate-specific antigen density (EGPSAD), and US score of patients with different Gleason grades after PCa surgery. Furthermore, it sought to analyze the correlation between these factors and postoperative Gleason grading, and clinical pathological characteristics for predicting this grading, thereby providing a solid foundation for planning effective clinical treatment.

Materials and Methods

Study Subjects

Clinical Data

This retrospective analysis included 65 PCa patients who underwent transurethral resection of the prostate in Qingdao Municipal Hospital from January 2021 to December 2023. This study was conducted following the guidelines of the Helsinki Declaration and approved by the Ethics Committee of Qingdao Municipal Hospital with the ethical number 20240122. Since this study was a retrospective analysis based on the data obtained from previous clinical diagnosis and treatment, acquiring the informed consent was exempted by the Ethics Committee of Qingdao Municipal Hospital.

Inclusion Criteria

The inclusion criteria were as follows: (1) male patients aged over 18 years; (2) prostate cancer patients treated with transurethral resection; and (3) those with complete case data.

Exclusion Criteria

(1) The patients with a history of acute or chronic prostatitis or acute urinary retention before admission; (2) The patients with a history of prostate surgery, such as prostate massage, prostate puncture, and cystoscopy, before admission; (3) Patients who underwent α-reductase inhibitors treatment before admission.

Detection of Serum PSA

A fasting venous blood sample (5 mL) was collected from each study subject one day before surgery and centrifuged at 4000 r/min for 10 minutes to isolate the serum. Serum tPSA and fPSA levels were determined using Cobas 6000 fully automatic electrochemiluminescence analyzer (6000, Shanghai Hanfei Medical Equipment Co., Ltd., Shanghai, China) along with its specified detection kit (Shanghai Yaji Biotechnology Co., Ltd., Batch No.: 20201125231, Shanghai, China). To ensure accuracy, these measurements were performed one week after prostate massage, 48 hours after urethral cystoscopy, digital rectal examination, and catheterization, one month after prostate puncture biopsy, and 24 hours after ejaculation.

TRUS Examination Method

All patients were subjected to TRUS examination using the PHILIPS iu22 ultrasound machine (iu22, Royal Philips Electronics Group of the Netherlands, Amsterdam, Netherlands), adjusted at 7.5 MHz, with the 3D9-3V 3D probe. The probe was inserted transrectally to observe the morphology, hemodynamic changes, and internal echogenicity of the prostate lesion area. Additionally, the inner gland prostate volume (IGPV), anterior-posterior diameter (AP), transverse diameter (TR), and superior-infra diameter (SI) of the prostate were obtained. The corresponding prostate volume (PV) was calculated using the following formula: $PV = 0.52 \times AP \times TR \times SI$. Furthermore, PSAD, IGPSAD, EGPV, and EGPSAD were determined using the following formulas: PSAD = tPSA/PV; IGPSAD = tPSA/IGPV; EGPV = PV – IGPV; and EGPSAD = tPSA/EGPV, respectively. According to the two-dimensional US examination of the prostate, US scores were obtained as follows: asymmetric lobes on both sides of the prostate (1 point), uneven echo in the parenchyma (1 point), incomplete capsule (1 point), unclear boundary between the inner and outer glands (1 point), diffuse lesions in the glands (1 point), and blood flow within the echo nodules (1 point). In addition, operators should possess relevant medical knowledge and skills, and have more than 2 years of operating experience. They should be familiar with the use and operation procedures of B-ultrasound equipment, and strictly follow the disinfection and cleaning requirements of medical devices to ensure the hygiene and safety of equipment and probes. Moreover, regular calibration and maintenance of ultrasound equipment are necessary to ensure optimal performance. Finally, the US images were evaluated by two associate chief physicians with more than 3 years of experience in US analysis.

Gleason Scoring Method

The Gleason scoring system categorizes the differentiation degree of PCa cells into 5 levels, with level 1 representing the best differentiation and low malignancy, and level 5 indicating the worst differentiation and high malignancy. Specific manifestations associated with each level are as

Table 1. Comparison of baseline characteristics between the two groups of patients.

Variables	Mild Group	Severe Group	$t/Z/\chi^2$	*p*-values
	n = 34	n = 31		
Age (years)	63.82 ± 10.46	64.58 ± 11.14	–0.282	0.779
BMI (kg/m^2)	23.89 ± 2.96	23.95 ± 2.58	–0.078	0.938
PV (cm^3)	83.10 (63.76, 95.04)	75.14 (69.39, 83.76)	–0.473	0.636
Smoking history (n (%))	11 (32.35)	10 (32.26)	0.001	0.993
Alcohol consumption history (n (%))	19 (55.88)	18 (58.06)	0.031	0.859
T stage			1.275	0.528
T2 stage (n (%))	12 (35.29)	9 (29.03)		
T3 stage (n (%))	14 (41.18)	17 (54.84)		
T4 stage (n (%))	8 (23.53)	5 (16.13)		
Surgical results			1.223	0.542
Positive margin (n (%))	10 (29.41)	12 (38.71)		
Lymph node invasion (n (%))	15 (44.12)	14 (45.16)		
Seminal vesicle invasion (n (%))	9 (26.47)	5 (16.13)		

Note: BMI, body mass index; PV, prostate volume.

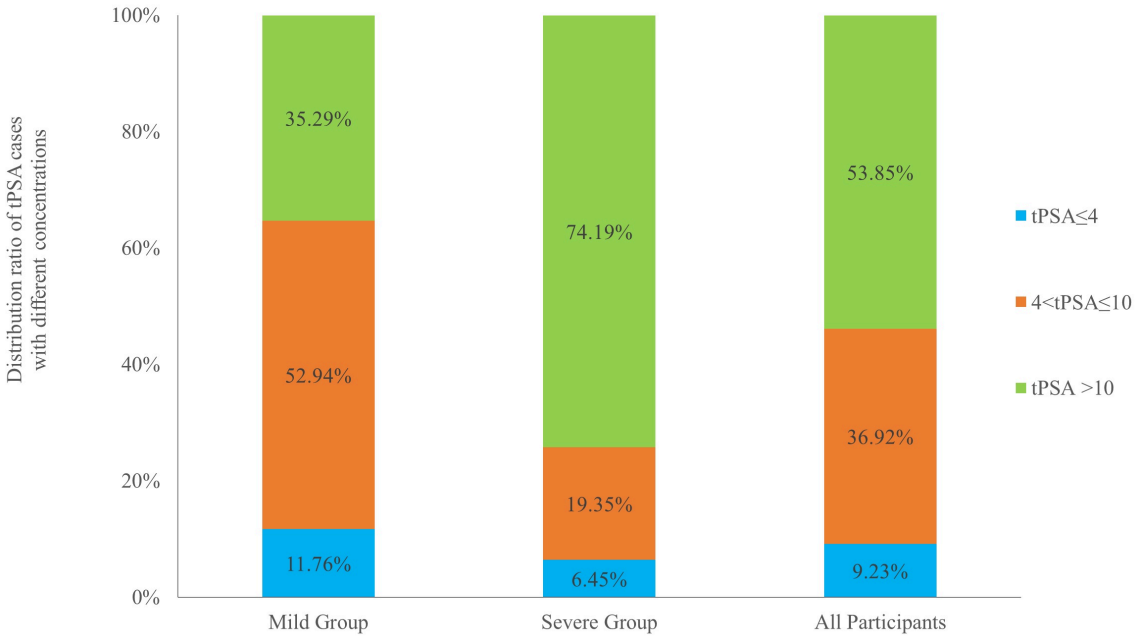

Fig. 1. Comparison of serum tPSA levels between the two groups of patients. tPSA, total prostate-specific antigen.

follows: Level 1 indicates large, densely packed, and well-organized glands forming small nodules. Level 2 represents large, densely packed, and irregular glands forming small nodules with no glandular fusion. Level 3 indicates the infiltrating growth of small glands or acini, often forming small sieve-like structures. Level 4 is associated with large sieve-like and fused glands. Level 5 is identified by single-cell infiltration, solid cancer nests without glandular structures, and acne-like cancer. The final Gleason score is determined by adding the scores of the two most prevalent patterns of cancerous cell differentiation, ranging from 2–10. The grades ranging from 2–4 indicate well-differentiated, 5–7 represent moderately differentiated, and 8–10 correspond to poorly differentiated or undifferentiated prostate adenocarcinoma.

Experimental Grouping

Based on the postoperative Gleason grading, the study subjects were divided into two categories. The Mild Group included 34 patients, with a Gleason score of $\leq$7, whereas 31 patients were grouped in the Severe Group with a Gleason score of $\geq$8.

Table 2. Comparison of serum fPSA, tPSA, and fPSA/tPSA between the two groups.

Experimental groups	n	fPSA (ng/mL)	tPSA (ng/mL)	fPSA/tPSA (%)
Mild Group	34	0.93 ± 0.10	6.86 ± 0.44	13.62 ± 1.17
Severe Group	31	0.80 ± 0.13	6.47 ± 0.56	12.55 ± 2.68
t		4.587	3.118	2.061
p-values		<0.001	0.003	0.046

tPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; fPSA/tPSA, the ratio of fPSA to tPSA.

Table 3. Comparison of PSAD, IGPSAD, EGPSAD, and US score between the two groups.

Experimental groups	n	PSAD (ng/mL·cm^3)	IGPSAD (ng/mL·cm^3)	EGPSAD (ng/mL·cm^3)	US score (point)
Mild Group	34	0.26 ± 0.03	0.95 ± 0.08	1.44 ± 0.14	3.19 ± 0.49
Severe Group	31	0.35 ± 0.04	0.70 ± 0.07	1.06 ± 0.14	4.14 ± 0.84
t		–9.166	12.975	10.689	–5.499
p-values		<0.001	<0.001	<0.001	<0.001

PSAD, prostate-specific antigen density; IGPSAD, intraglandular prostate-specific antigen density; EGPSAD, extraglandular prostate-specific antigen density; US, ultrasound.

Observation Indices

We comparatively analyzed the serum tPSA, fPSA, fPSA/tPSA levels, and US parameters such as PSAD, IGPSAD, EGPSAD, and US Score, in these two experimental groups with different clinical characteristics. Furthermore, we assessed the predictive value of preoperative serum indicators and US parameters based on postoperative Gleason grading. Additionally, we compared variations in the area under the curve (AUC) between different predictive indicators.

Statistical Analysis

The data were statistically analyzed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Initially, all data were examined for normal distribution. Normally distributed data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm$ s), and *t*-test was used to compare the two groups, whereas non-normally distributed data were represented as the median (P25, P75), and the two groups were compared using the Mann-Whitney test. The count data were expressed as percentages (%) and analyzed using the χ^2 test. Statistically significant indicators identified from inter-group comparisons were further analyzed using multiple logistic regression analysis to derive the formula for measuring the joint predictive factor. The predictive value of serum indicators and US parameters for postoperative Gleason grading was assessed using the receiver operating characteristic (ROC) curve and AUC. AUC of 0.85–0.95 indicated good diagnostic performance, AUC of 0.7–0.85 indicated moderate diagnostic performance, and AUC of less than 0.7 indicated poor diagnostic performance. A *p*-value < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics between the Two Groups

This study included 65 patients, aged from 46 to 83 years, with an average age of 62.61 ± 12.61 years. The body mass index (BMI) ranged from 19.21 to 29.03 kg/m^2, with an average of 23.53 ± 2.07 kg/m^2. The prostate volume ranged from 8.24 to 296.24 cm^3, with an average volume of 63.97 $\pm$ 24.35 cm^3; The tPSA ranged from 3.31 to 95.14 ng/mL, with an average of 30.12 ± 3.25 ng/mL. There were no significant differences between the two groups regarding age, BMI, PV, smoking history, alcohol consumption history, T stage, and surgical outcomes, with $p > 0.05$, as shown in Table 1.

Serum tPSA Distribution

When serum tPSA >10 ng/mL, the total incidence rate of PCa accounted for 53.85% of the total PCa population. Within the normal range of serum tPSA $\leq$4 ng/mL, 6 patients (9.23%) were still diagnosed with PCa. And in the gray area between the two (4 ng/mL < tPSA $\leq$ 10 ng/mL), 24 patients (36.92%) were diagnosed with PCa. In the Mild Group, there were 12 cases (35.29%) with tPSA >10 ng/mL, and in the Severe Group, there were 2 cases (6.45%) with tPSA $\leq$4 ng/mL. Therefore, it is difficult to determine the Gleason grading of PCa by measuring the serum tPSA levels in patients (Fig. 1).

The comparison results of serological indicators fPSA, tPSA, and fPSA/tPSA between two groups of patients are shown in Table 2. The results of the above indicators are significantly lower in the Severe Group than in the Mild Group, and the differences between the two groups are statistically significant ($p < 0.05$).

Table 4. Multivariate Logistic regression analysis of various indicators in two groups.

Variables	B	SE	Wald χ^2	*p*-values	OR	95% CI	
						Lower	Upper
fPSA	–1.421	0.369	14.817	<0.001	0.241	0.117	0.498
tPSA	–1.225	0.268	20.866	<0.001	0.294	0.174	0.497
fPSA/tPSA	–1.249	0.332	14.193	<0.001	0.287	0.150	0.549
PSAD	1.371	0.226	36.737	<0.001	3.939	2.529	6.137
IGPSAD	–2.157	0.272	62.861	<0.001	0.116	0.068	0.197
EGPSAD	–1.714	0.425	16.280	<0.001	0.180	0.078	0.414
US score	1.524	0.200	58.072	<0.001	4.591	3.102	6.794

B, partial regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; Lower, minimum interval value; Upper, maximum interval value.

Table 5. The data results of the application of ROC curve to various parameters for predicting postoperative Gleason grading.

Parameters	AUC	SE	*p*-values	95% CI	
				Lower	Upper
fPSA	0.672	0.069	0.017	0.536	0.807
tPSA	0.694	0.066	0.007	0.565	0.824
fPSA/tPSA	0.657	0.071	0.030	0.517	0.796
PSAD	0.751	0.063	0.001	0.629	0.874
IGPSAD	0.737	0.064	0.001	0.613	0.862
EGPSAD	0.811	0.054	0.000	0.706	0.916
US score	0.766	0.064	0.000	0.640	0.891
Serum indicators union	0.823	0.054	0.000	0.716	0.929
US parameters union	0.879	0.042	0.000	0.795	0.962
All parameter union	0.947	0.030	0.000	0.887	1.000

AUC, area under the curve; ROC, receiver operating characteristic.

Comparison of US Parameters between the Two Groups of Patients

The comparison results of US parameters such as PSAD, IGPSAD, EGPSAD and US score between two groups of patients are shown in Table 3. The results of PSAD and US score are significantly higher in the Severe Group than in the Mild Group, the results of IGPSAD and EGPSAD are significantly lower in the Severe Group than in the Mild Group, and the differences between the two groups are statistically significant ($p < 0.05$).

Multivariate Logistic Regression Analysis

Multivariate Logistic regression analysis was performed on the levels of fPSA, tPSA, fPSA/tPSA, PSAD, IGPSAD, EGPSAD, and US score between the two groups to assess the impact of each indicator on the severity of PCa. The identified values of the regression coefficients (Table 4) were used to calculate the weight of each indicator for measuring the joint predictive factors using the following formulas:

$$L_{\text{Serum indicators union}} = -1.421 \times fPSA - 1.225 \times tPSA - 1.249 \times fPSA/tPSA$$

$$L_{US\ \text{parameters union}} = 1.371 \times PSAD - 2.157 \times IGPSAD - 1.714 \times EGPSAD + 1.524 \times \text{US Score}$$

$$L_{\text{All parameter union}} = -1.421 \times fPSA - 1.225 \times tPSA - 1.249 \times fPSA/tPSA + 1.371 \times PSAD - 2.157 \times IGPSAD - 1.714 \times EGPSAD + 1.524 \times \text{US Score}$$

The Predictive Effect of Various Parameters on Postoperative Gleason Grading

The ROC curve of serological indicators to predict postoperative Gleason grading was drawn, and the predictive values of fPSA, tPSA, and fPSA/tPSA indicators were measured. As shown in Fig. 2 and Table 5, according to the AUC results of each indicator, it can be seen that the predictive effect of the above serological indicators on Gleason grading is less than 0.7, indicating that directly applying these three indicators to predict postoperative Gleason grading in PCa patients has poor predictive effect.

The ROC curves of various US parameters for predicting postoperative Gleason grading are shown in Fig. 3 and Table 5. Through these curves, the predictive value of US parameters (PSAD, IGPSAD, EGPSAD, and US Score) can be observed. According to the AUC results of each parameter, it can be seen that the predictive effect of the above US parameters on Gleason grading is between 0.7 and 0.85, in-

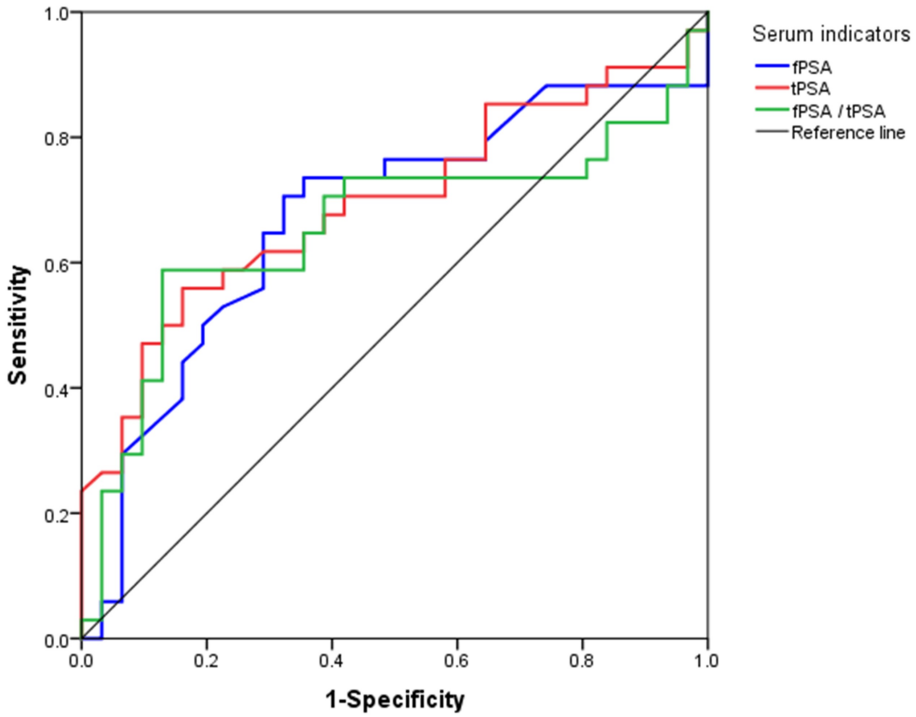

Fig. 2. ROC curves of various serum indicators for predicting postoperative Gleason grading. ROC, receiver operating characteristic; fPSA, free prostate-specific antigen; fPSA/tPSA, the ratio of fPSA to tPSA.

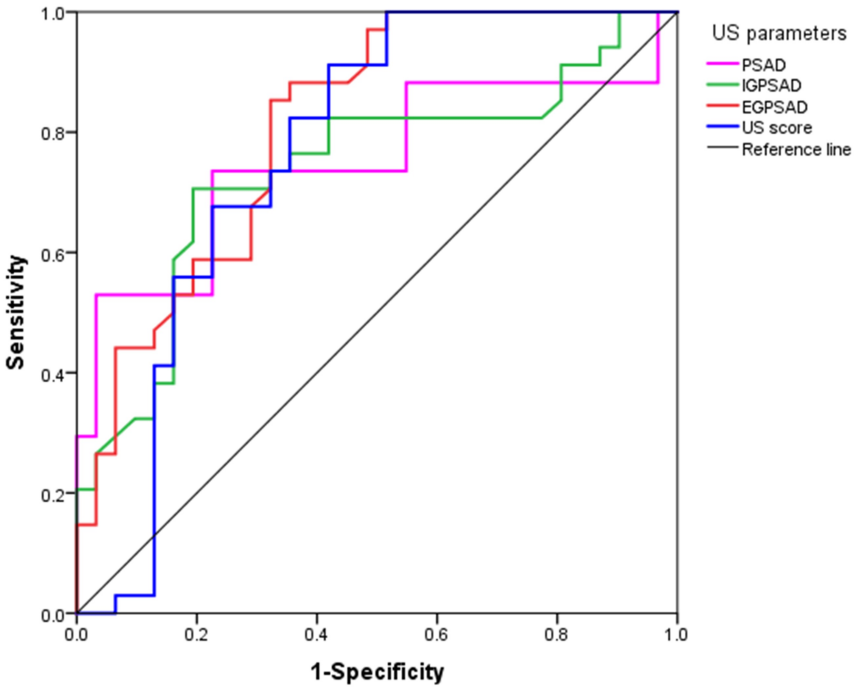

Fig. 3. ROC curves of various US parameters for predicting postoperative Gleason grading. PSAD, prostate-specific antigen density; IGPSAD, intraglandular prostate-specific antigen density; EGPSAD, extraglandular prostate-specific antigen density; US, ultrasound.

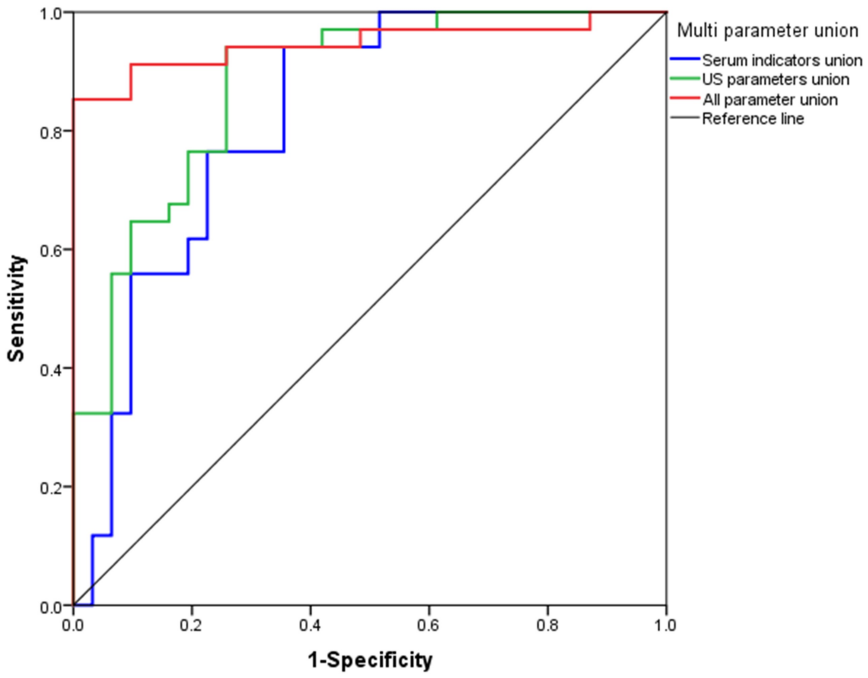

Fig. 4. ROC curves of multi-parameter union for predicting postoperative Gleason grading.

Table 6. Comparison of AUC between multi-parameter union and other parameter predictions.

Parameters	Difference in AUC	SE	95% CI		Z	*p*-values
			Lower	Upper		
fPSA	0.275	0.0814	0.116	0.435	3.381	0.0007
tPSA	0.253	0.0618	0.131	0.373	4.086	<0.0001
fPSA/tPSA	0.290	0.0813	0.131	0.450	3.571	0.0004
PSAD	0.196	0.0783	0.048	0.355	2.570	0.0102
IGPSAD	0.210	0.0621	0.092	0.336	3.443	0.0006
EGPSAD	0.136	0.0650	0.009	0.264	2.094	0.0362
US score	0.181	0.0719	0.040	0.322	2.520	0.0117
Serum indicators union	0.124	0.0613	0.004	0.244	2.027	0.0426
US parameters union	0.068	0.0527	–0.035	0.172	1.295	0.1952

dicating that the direct application of these four US parameters for predicting postoperative Gleason grading in PCa patients is generally ineffective.

The ROC curve of serum indicators union, US parameters union and all parameter union for predicting postoperative Gleason grading was drawn, and the predictive value of multi parameter union was observed. As shown in Fig. 4 and Table 5, the AUC of the combined application of fPSA, tPSA, and fPSA/tPSA is 0.823. This combined prediction method has a moderate predictive effect on postoperative Gleason grading in PCa patients. The combined application of PSAD, IGPSAD, EGPSAD, and US score parameters resulted in an AUC of 0.879. This combined prediction method has a good predictive effect on postoperative Gleason grading in PCa patients. The combined application of the above serological indicators and US parameters resulted in an AUC of 0.947, indicating that the combination of fPSA, tPSA, fPSA/tPSA, PSAD, IGPSAD, EGPSAD and US score can effectively predict postoperative Gleason grading in PCa patients. The comparison results of AUC between all parameter union and other predictive parameters are shown in Table 6. The AUC of all parameter union was significantly higher than that of each parameter alone and serum indicators union (fPSA, tPSA and fPSA/tPSA) ($p < 0.05$). The AUC of all parameter union was higher than that of US parameters union (PSAD, IGPSAD, EGPSAD and US Score), however, the difference between the groups was not statistically significant ($p > 0.05$).

Discussion

PSA is a glycoprotein secreted by prostate epithelial cells. When prostate epithelial cells are damaged due to tumors,

inflammation, or other lesions, it allows the PSA to enter the bloodstream, elevating serum PSA level, which indicates PCa [10, 11]. PSA is crucial in screening PCa in clinical practice [12]. Serum tPSA levels greater than 10 ng/mL indicate the incidence of prostate malignancy when other PSA-influencing factors are excluded [13]. In such conditions, a routine prostate biopsy is performed, even though other auxiliary examinations are negative. Since tPSA <4 ng/mL is often associated with negative biopsy results, it was recommended to collectively assess the serum tPSA levels with other auxiliary examinations for better PCa screening. However, the current study found that 9.23% of participants with surgically confirmed PCa still showed tPSA ≤4 ng/mL. Therefore, evaluating other biomarkers for accurate diagnosis and predicting tumor properties is highly recommended.

An ideal tumor marker exhibits minimal rates of missed diagnosis and misdiagnosis, along with the ability to predict staging and prognosis accurately. Numerous studies have been conducted but have failed to identify such an ideal indicator for diagnosing PCa. The combined evaluation of various indicators has been a novel approach for effective diagnosis, which might address the limitations of single-marker-based diagnosis. The detection of individual indicators may have poorer sensitivity and specificity. Some scholars have believed that the combined evaluation of multiple serum tumor biomarkers can improve the diagnostic rate of PCa to a certain extent [14]. Research has shown that calculating the ratio of fPSA/tPSA is significant in diagnosing PCa. The value of fPSA/tPSA >16% corresponds to lower probability, whereas, the ratio of fPSA/tPSA <16% indicates the higher chances of having PCa [15]. This ratio can detect variations in tPSA elevation and distinguish between PCa and BPH [16]. This study included 64 PCa patients categorized into Mild and Severe Groups. The mean fPSA/tPSA values for both groups were 4.06% and 4.62%, respectively, lower than 16%. These results further validate the association of a lower fPSA/tPSA ratio with the incidence of PCa. We also assessed the impact of combined fPSA, tPSA, fPSA/tPSA with US parameters on predicting postoperative Gleason grading. We identified that evaluating multi-parameter union could be the best approach for accurately diagnosing the PCa.

TRUS examination provides quantitative parameters, including PSAD, IG-PSAD, EGPSAD, and US score, which help evaluate the existence of arteriovenous shunting in the newly formed tumor blood vessels and analyze differences in arterial resistance in the supply region [17]. Ye *et al*. [18] investigated the differences in PV obtained from TRUS and multiparametric magnetic resonance imaging (mpMRI) and assessed the roles of TRUS-PASD and mpMRI-PASD in diagnosing PCa. They revealed that TRUS-PV and MRI-PV were similar, and TRUS-PSAD and mpMRI-PASD had comparable efficiency in detecting PCa; TRUS can be used for PV estimation and dynamic monitoring of PSAD. These results are consistent with the findings of our study, which illustrated that TRUS-PSAD can effectively improve clinical decision-making and optimize diagnostic strategies. Additionally, our study revealed that PSAD and US scores were higher in the Severe Group than the Mild Group, IG-PSAD and EGPSAD were lower in the Severe Group than the Mild Group, which might be due to the weaker invasiveness of lesions in the Mild Group.

Conversely, the lesions in the high-risk group showed stronger invasiveness, with significant tumor cell proliferation causing a space-occupying effect. This promotes nodule formation, further impacting the surrounding capsule and adjacent organs. During the malignant progression of the disease, neovascularization, and micro-vascular density increase, with abundant blood supply in the lesion [19]. Additionally, higher postoperative Gleason grades indicate enhanced tumor invasiveness and micro-vascular density, as well as an abundant blood supply to the lesion. TRUS examination can determine blood flow distribution, tumor size, and adjacent tissue status, whereas the US parameters can reveal the heterogeneity and multifocal nature of PCa [20]. This study used ROC analysis to find that the AUC of predicting postoperative Gleason grading by combining serum fPSA, tPSA, fPSA/tPSA, PSAD, IGPSAD, EGPSAD, and US score was greater than that predicted by each indicator alone. This suggests that clinical use of combined detection of serum indicator levels and US parameters can assist in determining postoperative Gleason grading of PCa. The reason may be that different detection methods can provide complementary information. The detection of serum fPSA, tPSA, and fPSA/tPSA levels can to some extent compensate for the shortcomings of US parameters, and combined detection can improve the predictive value of postoperative Gleason grading.

In summary, serum PSA biomarkers and US parameters are significantly associated with the postoperative Gleason grading and clinical pathological characteristics of PCa. Since the combined detection of various indicators has better predictive performance, it may be used to predict the degree of postoperative disease progression. The current study has limitations due to the relatively small sample size (n = 65), which might have impacted the statistical accuracy of measuring the predictive values, leading to possible variations between predicted and experimental values. Therefore, it is highly recommended to conduct such analyses with a larger sample size to remove any biases and validate the existing findings. For instance, conducting multi-center trials encompassing distinct geographical regions and population groups would enhance the reliability and applicability of the trial results. Furthermore, this approach would broaden the acceptability of the findings and promote the integration of these findings into clinical practices. In addition, conducting experiments simultaneously at multiple centers can reduce the impact of individual center biases on the experimental results. We believe that in the

future, better biomarkers will be discovered and validated, and prediction methods will be simpler and faster, forming a unique predictive system for postoperative Gleason grading of PCa. This will play a role in reducing the incidence, mortality, and recurrence rates of PCa in the late stage of initial diagnosis.

Conclusions

For predicting postoperative Gleason grading in PCa diagnosis, the combined evaluation of multiple parameters is more effective than utilizing individual serological indicators such as fPSA, tPSA, and fPSA/tPSA ratio, as well as US parameters including PSAD, IGPSAD, EGPSAD, and US Score. The multi parametric diagnostic markers identified in this study can effectively guide clinical decision-making, and optimize diagnostic strategies, thereby leading to effective management of PCa in clinical practice.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

LJL and YZS designed this paper; XYM and LJL collected and organized data; WLW, FYW and MZ conducted data analysis, while YZS and FYW conducted literature search and collected and organized relevant references. YZS completed the final review of the manuscript. YZS is responsible for the integrity of the work from the beginning to the publication of the article, and is designated as the "guarantor". XYM, FYW, and WLW wrote the manuscript. All authors made critical revisions to the important knowledge content of the manuscript. All authors gave final approval of the version to be published. All authors fully participated in this work, took public responsibility for the appropriate parts of the content, and agreed to be responsible for all aspects of the work to ensure that any issues related to the accuracy or completeness of any part of the work are properly investigated and resolved.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Qingdao Municipal Hospital with the ethical number 20240122. Patients who participated in the study had complete clinical data. Since this study was a retrospective analysis based on the data obtained from previous clinical diagnosis and treatment, acquiring the informed consent was exempted by the Ethics Committee of Qingdao Municipal Hospital. This study was conducted following the guidelines of the Helsinki Declaration.

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Conflict of Interest

The authors declare no conflict of interest.

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