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Original Article

Elevated plasma fibrinogen and the neutrophil-to-lymphocyte ratio as predictive risk factors for prostate cancer

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Abstract: Background: The relationship between inflammatory markers and prostate cancer (PCa) remains controversial. This study was designed to evaluate the role of inflammatory factors in predicting the risk of PCa. Methods: A retrospective analysis was performed on 460 patients who underwent prostate biopsy and pre-operative blood sample collection. Neutrophil, lymphocyte, monocyte, and platelet counts as well as fibrinogen (FBG) levels were obtained, and the ratios of neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), and platelet-to-lymphocyte (PLR) were calculated. The correlations of these factors with the demographic, clinical, and histopathologic outcomes were analyzed using the Mann-Whitney or Kruskal-Wallis tests. A logistic regression analysis was used to screen the risk indicators of PCa. Using the receiver operating curve method, we determined the optimal cut-off level for FBG to assess the predictive value of the new model. Results: NLR and FBG were determined to be independent risk factors for PCa. Furthermore, FBG was determined to be an independent risk factor for local advanced PCa. Both NLR and FBG levels were correlated positively with the clinical and pathological characteristics of PCa. Patients with higher FBG may have higher risk grades and clinical stages based on the 3.015 stratification of FBG. The new predictive model composed of NLR, FBG, and prostate-specific antigen exhibits a greater predictive value in detecting PCa. Conclusions: NLR and FBG are independent risk factors for PCa. Furthermore, pre-treatment FBG greater than 3.015 may indicate higher risk grades and clinical stages in patients with PCa. NLR and FBG may be low-cost and high-efficiency clinical biomarkers, which can be combined with prostate-specific antigen to form a new prediction model, improving the predictive efficiency for PCa.

Keywords: Biomarkers, neutrophil-to-lymphocyte ratio, plasma fibrinogen, predictive model, prostate cancer

Introduction

At present, the incidence of prostate cancer (PCa) in the United States ranks first among all male malignant tumors [1]. In China, the morbidity and mortality of PCa have continually increased in recent years [2, 3]. The early stage of PCa is usually asymptomatic, and once clinical symptoms appear, tumors are already in the advanced stages [4]. Although the incidence of PCa is high, its risk factors remain unclear. Therefore, elucidating the potential risk factors of PCa may provide more opportunities to prevent or delay the onset of PCa; however, only a few studies on this have been published to date.

The role of inflammation in the etiology of cancer has attracted attention; increasing research evidence indicates that the occurrence and development of cancer is affected not only by the characteristics of tumor cells, but also the host inflammatory reactions [5, 6]. Epidemiological investigations and clinical studies suggest that inflammation is one of the pivotal factors in the tumorigenesis of PCa [7, 8]. In the past decade, it has been found that inflammatory indicators, including fibrinogen (FBG), the neutrophil ratio, lymphocyte count, and monocyte count, reflect the state of systemic inflammation and have an important impact on the occurrence and development of tumors [9, 10]. The systemic inflammatory response has been

Table 1. Characteristics of all the patients

Parameters	BPH	PCa	P
Number of patients	208	252	
Age	68 (62-74)	70.50 (64-76)	0.658
PSA	8.46 (5.12-14.21)	51.85 (18.05-208.59)	< 0.001
Lymphocytes	1.94 (1.52-2.42)	1.76 (1.41-2.14)	0.003
Hemoglobin	137.50 (129.25-145.00)	130.50 (118.25-143.00)	< 0.001
Albumin	39.00 (36.80-41.10)	38.20 (35.55-40.85)	0.04
FBG	3.01 (2.51-3.66)	3.11 (2.60-4.14)	0.034
NLR	1.92 (1.52-2.46)	2.16 (1.59-2.83)	0.005
MLR	0.23 (0.18-0.29)	0.25 (0.19-0.33)	0.006
White blood cells	6.62 (5.40-7.65)	6.35 (5.33-7.61)	0.597
Neutrophils	3.40 (2.93-4.57)	3.75 (3.10-4.75)	0.371
Monocytes	0.43 (0.35-0.53)	0.44 (0.36-0.54)	0.412
Platelets	230 (192.75-279)	221 (179.25-267)	0.063
PLR	117.37 (93.89-154.86)	121.87 (95.53-163.30)	0.138

BPH: benign prostatic hyperplasia; FBG: fibrinogen; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PSA: prostate-specific antigen.

observed to exhibit characteristic changes in circulating leukocytes, and many studies have investigated the changes in circulating leukocytes in relation to tumors, including the ratios of neutrophils-to-lymphocytes (NLR), monocytes-to-lymphocytes (MLR), and platelets-to-lymphocytes (PLR), which were used to predict tumor occurrence and prognosis. Although research have shown that chronic inflammation makes an important impact in the tumorigenesis and development of PCa, the relationship between inflammatory markers and the risk of PCa remains controversial [11]. Therefore, this study was designed to clarify the relationship between FBG, NLR, PLR, MLR and tumorigenesis and progression of PCa and to further evaluate their predictive value.

Materials and methods

Patients

After obtaining the approval of the Ethics Committee of the Southern Hospital, Southern Medical University, a total of 549 patients who underwent prostate biopsies between January 2014 and December 2018 were retrospectively reviewed. The following selection criteria were applied: 1) patients who underwent the first prostate biopsy due to elevated prostate-specific antigen (PSA) and/or positive imaging findings; 2) patients who did not receive any anti-tumor treatment before their diagnosis; 3) patients who were not diagnosed with any systemic acute or chronic inflammation, and who did not have a history of taking antibiotics in the previous two weeks; 4) patients who had no hematological or immune diseases; 5) patients who were prostate cancer-specific; 6) patients with complete clinical data. Those who did not meet the above conditions were excluded. Finally, 460 patients were registered based on the criteria above, of which 252 were positive for PCa and 208 were negative for benign prostatic hyperplasia (BPH). The groups were as follows: patients with PSA < 10 ng/ml, a Gleason score < 7, and clinical tumor stage cT ≤ 2a were assigned to the low-risk group; patients with PSA between 10-20 ng/ml, or a Gleason score = 7, or clinical stage cT = 2b were assigned to the medium-risk group; patients with PSA > 20 ng/ml, or a Gleason score > 7, or clinical staging cT ≥ 2c were assigned to the high-risk group. Then, the PCa patients with bone metastasis and non-bone metastasis were grouped according to the results of their bone scans. Informed consent was signed by all patients, and the data were analyzed anonymously.

Data collection

The baseline characteristics (including demographic, clinical, and histopathologic outcomes) were collected through the medical records. The PSA levels (ng/ml), albumin levels, neutrophil count (10^9 cells/l), lymphocyte count (10^9 cells/l), monocyte count (10^9 cells/l), platelet count (10^9 cells/l), and plasma fibrinogen (g/l)

Table 2. Relationship between inflammatory markers and clinical pathological parameters

Parameters	FBG	NLR	PLR	MLR
PCa	3.11 (2.60-4.14)	2.16 (1.59-2.83)	121.87 (95.53-163.30)	0.25 (0.19-0.33)
BPH	3.01 (2.51-3.66)	1.92 (1.52-2.46)	117.37 (93.89-154.86)	0.23 (0.18-0.29)
p	0.034	0.005	0.138	0.006
PSA groups				
PSA<10	2.81 (2.48-3.37)	1.91 (1.55-2.45)	116.48 (92.36-154.49)	0.22 (0.18-0.28)
10≤PSA≤20	2.76 (2.44-3.56)	1.95 (1.45-2.63)	114.38 (88.76-143.37)	0.24 (0.18-0.31)
PSA>20	3.47 (2.80-4.51)	2.20 (1.58-2.92)	127.99 (101.39-173.8)	0.25 (0.19-0.33)
p	< 0.001	0.011	0.102	0.317
Gleason Score				
< 7	2.76 (2.52-3.34)	1.98 (1.50-3.10)	121.37 (94.7-162.68)	0.22 (0.18-0.30)
= 7	3.08 (2.55-4.11)	2.14 (1.63-2.67)	119.88 (93.73-161.25)	0.25 (0.20-0.32)
> 7	3.43 (2.82-4.64)	2.31 (1.55-2.92)	127.50 (100.88-173.8)	0.26 (0.19-0.36)
p	< 0.001	0.684	0.585	0.242
ISUP < 3	2.77 (2.40-3.31)	2.08 (1.56-2.76)	121.51 (94.56-160.77)	0.24 (0.18-0.31)
ISUP≥3	3.47 (2.76-4.64)	2.27 (1.59-2.87)	122.37 (96.42-170.05)	0.26 (0.19-0.34)
p	< 0.001	0.468	0.613	0.201
Clinical Stage				
T < 3	2.99 (2.54-3.80)	2.21 (1.57-2.88)	120.98 (94.63-161.50)	0.25 (0.18-0.32)
T≥3	3.40 (2.71-4.67)	2.15 (1.60-2.78)	126.87 (97.65-172.43)	0.25 (0.19-0.35)
p	0.007	0.951	0.441	0.347
Bone Metastasis				
No	2.91 (2.52-3.64)	2.10 (1.55-2.67)	118.26 (93.03-150.85)	0.25 (0.19-0.31)
Yes	3.71 (2.87-4.90)	2.23 (1.61-3.20)	133.31 (102.09-196.1)	0.26 (0.19-0.37)
p	< 0.001	0.002	0.166	0.144
Risk Stratification				
Low	2.77 (2.43-3.29)	2.01 (1.62-3.07)	120.98 (96.54-159.45)	0.21 (0.17-0.27)
Medium	2.69 (2.34-3.25)	2.38 (1.68-2.67)	116.20 (83.18-169.42)	0.29 (0.19-0.33)
High	3.30 (2.66-4.31)	2.16 (1.55-2.88)	124.65 (97.65-163.79)	0.25 (0.19-0.33)
P	0.001	0.949	0.725	0.227

FBG: fibrinogen; MLR: monocyte to lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelets to lymphocytes; PSA: prostatespecific antigen.

were acquired from blood tests. Blood samples were collected in the morning within seven days before each prostate biopsy. NLR was calculated as neutrophil count divided by lymphocyte count, Similarly, the PLR and MLR were calculated as the platelet count and monocyte count divided by the lymphocyte count, respectively.

Statistical analysis

Data on the continuous variables are described as medians with their respective interquartile ranges (IQR) and differences among groups were evaluated using a Mann-Whitney or Kruskal-Wallis test, while the Chi-squared test was used for the categorical variables. A logistic regression analysis was used to screen the risk factors of PCa. Using the receiver operating characteristic (ROC) curve, we determined the optimal cut-off level for FBG to evaluate the accuracy of the prediction model. The area under the curve (AUC) of each significant factor was evaluated. All statistical analyses were conducted in IBM-SPSS version 22. Bilateral $P < 0.05$ was considered to indicate statistical significance.

Results

Higher levels of FBG and NLR suggest a greater risk of PCa

The characteristics of the patients in the PCa and BPH groups were compared (**Table 1**). The median age in the PCa group was 68 years and the median age in the BPH group was 70.5

Table 3. Variables in the logistic regression analysis for PCa detection

Parameters	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Age[a]	1.097	1.070-1.125	0.157	1.082	1.045-1.121	< 0.001
PSA[a]	1.065	1.047-1.082	< 0.001	1.069	1.049-1.090	< 0.001
Lymphocyte[a]	0.632	0.469-0.850	0.002	1.116	0.640-1.944	0.699
Hemoglobin[a]	0.974	0.963-0.985	< 0.001	0.994	0.975-1.013	0.508
FBG[a]	1.260	1.065-1.491	0.007	1.544	1.107-1.980	0.008
NLR[a]	1.396	1.153-1.691	0.001	1.520	1.032-2.240	0.034
MLR[a]	15.064	2.854-79.495	0.001	0.528	0.019-15.028	0.709
PSA[b]	1.003	1.002-1.005	< 0.001	1.004	1.002-1.005	< 0.001
Albumin[b]	1.009	0.943-1.079	0.791	0.906	0.824-0.995	0.047
FBG[b]	1.430	1.155-1.769	0.001	1.426	1.086-1.872	0.011
PSA[c]	1.005	1.003-1.007	< 0.001	1.005	1.003-1.007	< 0.001
Hemoglobin[c]	0.986	0.972-1.000	0.040	1.007	0.988-1.027	0.463
FBG[c]	1.537	1.192-1.981	0.001	1.392	1.027-1.886	0.030
PSA[d]	1.008	1.005-1.010	< 0.001	1.008	1.005-1.010	< 0.001
Hemoglobin[d]	0.972	0.958-0.985	< 0.001	0.990	0.968-1.012	0.370
FBG[d]	1.857	1.460-2.363	< 0.001	1.587	1.160-2.171	0.004

a: PCa versus control; b: LAPCa versus LPCa; c: ISUP ≥ 3 of PCa versus ISUP < 3 of PCa; d: Bone Metastasis of PCa versus non-bone Metastasis of P. PSA: prostate specific antigen; FBG: fibrinogen; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte to lymphocyte ratio; OR: odd ratio; CI: Confidence Interval.

years (*P* = 0.658). Using a univariate analysis, we observed that the FBG, NLR, and MLR of the PCa group were significantly higher than they were in the BPH patients (*P* = 0.034, *P* = 0.005, and *P* = 0.006, respectively), but PLR was not (*P* = 0.138). Further, using a multivariate logistic regression analysis, including age and PSA, it was indicated that FBG (OR = 1.544, 95% CI: 1.107-1.980, *p* = 0.008) and NLR (OR = 1.520, 95% CI: 1.032-2.240, *P* = 0.034) still remained significantly correlated with PCa (**Table 3**). In other words a higher pre-treatment level of FBG and NLR suggests a higher risk of PCa.

The higher the FBG concentration, the greater the risk of local advanced PCa

The prognosis of local advanced prostate cancer (LAPCa) is very different from localized prostate cancer (LPCa). In non-metastatic PCa patients, we observed that the FBG levels in patients with clinical stage cT ≥ 3 were significantly higher than in patients with cT < 3 (2.99 vs 3.40, *P* = 0.007, **Table 2**). Similarly, using the multivariate logistic regression model, it was found that PSA (OR = 1.004, 95% CI: 1.002-1.005, *P* < 0.001) and FBG (OR = 1.426, 95% CI: 1.086-1.872, *P* = 0.011) were independent risk factors for LAPCa, while albumin is a protective factor (**Table 3**). The above results indicated that the higher the FBG concentration, the greater the risk of LAPCa. However, there was no significant difference in NLR, PLR, or MLR (*P* > 0.05).

The association between NLR, FBG, and clinical pathological characteristics

The 460 patients were separated into three groups based on their PSA values: the low PSA group (< 10 ng/ml), the medium PSA group (10-20 ng/ml), and the high PSA group (> 20 ng/ml). We observed that FBG, NLR, PLR, and MLR were increased with increasing PSA levels, as shown in **Table 2**. First, the Shapiro-Wilk test was performed to verify that the data in each group were normally distributed (*P* > 0.05), and Levene's test indicated that the data in each group had an uneven variance (*P* < 0.001). A Welch's variance analysis showed that NLR [welch F (2, 217.975) = 7.823, *P* = 0.011] and FBG [welch F (2, 220.576) = 25.982, *P* < 0.001] increased with the PSA level, unlike PLR (*P* = 0.102) and MLR (P = 0.317) (**Table 2**). Further, using a Games-Howell multiple comparison, the results showed that FBG in the high PSA group was higher than in the medium and low PSA groups (*P* < 0.001, **Figure 1A**). Similarly, NLR in the high PSA group was higher than in the low group (*P* = 0.0114, **Figure 1B**).

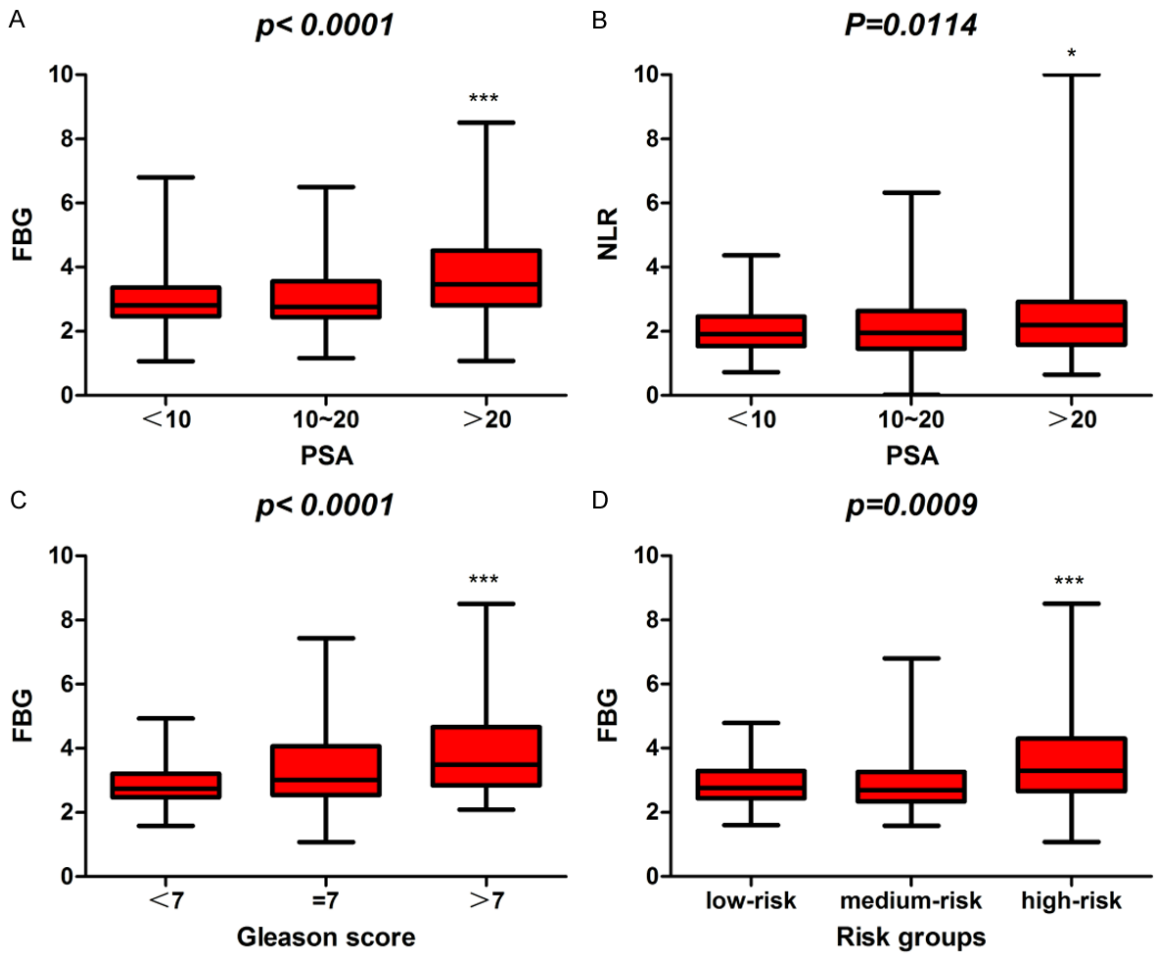

Figure 1. Comparison of NLR and FBG in different PCa groups with the Kruskal-Wallis test. The concentration of FBG in the high PSA group is higher than it is in the medium and low PSA groups (A). The NLR values in the high PSA group are higher than those in the low PSA group (B). The concentrations of FBG in the high and medium Gleason score groups are higher than the concentration in the low Gleason score group (C). The concentration of FBG in the high risk group is higher than it is in the low and medium risk groups (D). FBG: fibrinogen; NLR: neutrophil-to-lymphocyte ratio; PCa: prostate cancer; PSA: prostate-specific antigen.

Similarly, we divided the PCa patients into three groups according to their Gleason scores, including the low (< 7), medium (= 7), and high (> 7) groups. Using Welch's variance analysis, it was indicated that plasma FBG was significantly different between the different Gleason scores groups (P < 0.001, **Table 2**). Further using the Games-Howell multiple comparison test, the results showed that FBG in the high and medium Gleason score groups was higher than it was in the low group (P < 0.0001, **Figure 1C**). However, NLR, PLR, and MLR were not (P = 0.684, P = 0.585, and P = 0.242, respectively). In the same way, FBG increased with increasing risk grades, and FBG in the high risk group was significantly higher than it was in the low and medium risk groups (P = 0.0009, **Figure 1D**).

As we all know, the prognosis of Gleason 3+4 and Gleason 4+3 with a total score of 7 Gleason is very different in PCa. The new grouping distinguished Gleason 3+4 from Gleason 4+3 into level 2 and level 3 based on the current International society of Urological Pathology (ISUP) grading system. In our research, the results of a Mann-Whitney test showed that the FBG level in the ISUP ≥ 3 group was higher than it was in the ISUP < 3 group (P < 0.0001, **Figure 2A**). The Univariate analysis results showed that hemoglobin, PSA, and FBG had statistically significant relationships with ISUP ≥ 3 in patients with PCa (P < 0.05, **Table 2**). The result of the multivariable logistic regression analysis demonstrated that FBG (OR = 1.392; 95% CI = 1.027-1.886; P = 0.030) still remained an inde-

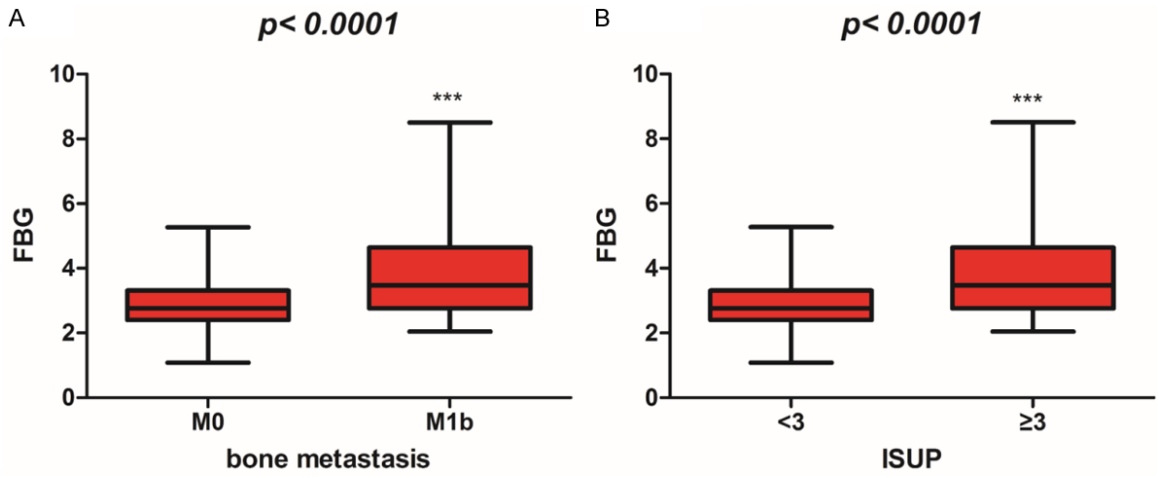

Figure 2. Comparisons of FBG in the different PCa groups with the Mann-Whitney test. The FBG level in the ISUP ≥ 3 group is higher than it is in the ISUP < 3 group (A). The FBG level in the bone metastasis group is higher than it is in the non-bone metastasis group (B). FBG: fibrinogen; PCa: prostate cancer; ISUP: International society of Urological Pathology.

Table 4. Clinical characteristics of prostate cancer patients according to FBG

Parameters	FBG		*P*	OR	95% CI
	< 3.015 (n = 116)	≥ 116 (n = 136)			
Age (median, IQR)	68 (62-73)	73 (67-77.75)	< 0.001		
PSA (median, IQR)	36.14 (11.93-93.40)	97.72 (26.93-347.38)	< 0.001		
ISUP < 3/ISUP26	60/56	28/108	< 0.001	4.477	2.565-7.816
cT < 3/cT ≥ T	79/37	75/61	0.035	1.737	1.036-2.910
Metastasis (no/yes)	86/30	64/72	< 0.001	3.225	1.889-5.506
Risk Stratification (low-medium/high)	37/79	17/119	< 0.001		

PSA: prostate-specific antigen; FBG: fibrinogen.

pendent predictor in PCa patients with ISUP ≥ 3 (**Table 3**). Similarly, we found that FBG in the bone metastasis group was significantly higher than it was that in the non-bone metastasis group (*P* < 0.0001, **Figure 2B**), and FBG still remained an independent predictor of PCa with bone metastasis (OR = 1.587, 95% CI: 1.160-2.171, *P* = 0.004, **Table 3**).

Comparison of the clinical parameters between the high and low FBG PCa patients

We determined the optimal cut-off level for FBG using the ROC method. The PCa patients were divided into a low FBG (< 3.015, n = 116) and a high FBG group (≥ 3.015, n = 136) based on their cut-off levels. There were significant differences between the two groups in age, PSA, Gleason score, risk stratification, incidence of metastasis (*P* < 0.001), and clinical stage (*P* = 0.036). The odds ratio (OR) of the ISUP ≥ 3 group versus the ISUP < 3 group was 4.437 (95% CI: 2.565-7.816, *P* < 0.001); The OR of the bone metastasis versus non-bone metastasis group was 3.225 (95% CI: 1.889-5.506, P < 0.001); The OR of the clinical stage T ≥ 3 versus clinical stage T < 3 group was 1.737 (95% CI: 1.036-2.910, *P* = 0.036). The data are shown in **Table 4**.

The multivariate predictive model (NLR+FBG+PSA) is of greater value in predicting PCa and LAPCa

Applying the ROC method, we evaluated the clinical usefulness of PSA, NLR, FBG and the new model (combined with NLR, FBG and PSA) in discriminating PCa. The results revealed that the area under the curve (AUC) for PSA was 0.855 (95% CI: 0.820-0.889), for NLR it was 0.577 (95% CI: 0.525-0.629), and for FBG it was 0.557 (95% CI: 0.505-0.610), as shown in

Table 5. Factors to predict PCa or LAPCa

Parameters	AUC	Std. Error	*P*	95% CI
Age[a]	0.701	0.024	0.001	0.654Irrora
PSA[a]	0.855	0.018	0.001	0.820Irrora
NLR[a]	0.577	0.027	0.005	0.525Irrora
FBG[a]	0.557	0.027	0.034	0.505Irrora
TPSA+NLR+FBG[a]	0.891	0.016	0.001	0.862NLR+FB
TPSA[b]	0.755	0.033	0.001	0.692NLR+FB
FBG[b]	0.701	0.034	0.001	0.629NLR+FB
TPSA+FBG[b]	0.771	0.031	0.001	0.708FBG+FB

a: PCa versus control; b: LAPCa versus LPCa; PSA: prostate-specific antigen; FBG: fibrinogen; NLR: neutrophil-to-lymphocyte ratio; AUC: area under the curve.

Table 5. In the new model combined with PSA, NLR, and FBG, the ROC curve generated an AUC of 0.891 (95% CI: 0.862-0.921) with a sensitivity of 75.40%, a specificity of 85.58%, a negative predictive value of 74.17%, a positive predictive value of 86.36%, and a coincidence rate of 80.00%. Accordingly, the new model exhibited the highest accuracy rate with 0.891, which was statistically significant in comparison with PSA alone (P = 0.0105). Our results demonstrated that the new multivariate predictive model (combined with PSA, NLR, and FBG) is of greater value in predicting PCa. The ROC curve is shown in **Figure 3A**.

Similarly, we also assessed the clinical usefulness of PSA and FBG in discriminating LAPCa. The results revealed that PSA had an AUC of 0.755 (95% CI: 0.692-0.819) and FBG had an AUC of 0.701 (95% CI: 0.629-0.763). In the new model combined with PSA and FBG, the ROC curve had an AUC of 0.771 (95% CI: 0.708-0.833) with a sensitivity of 75.14%, a specificity of 60.14%, and a coincidence rate of 71.40%. Although the new model obtained the highest accuracy rate with 0.771, it exhibited no statistical significance in comparison with the PSA alone (P = 0.3007). The ROC curve is shown in **Figure 3B**.

Discussion

Inflammatory and immune cells are essential components of the tumor microenvironment. By creating a favorable microenvironment and inhibiting anti-tumor immunity, systemic inflammation is importantly involved in the stages of tumor initiation, promotion, malignant transformation, invasion and metastasis [12]. Systemic inflammation disrupts the balance of circulating leukocyte components, which affects the number of neutrophils and lymphocytes during cancer development [13]. NLR is an index of tumor-related inflammatory reaction, which has previously been shown to be a representative prognostic marker for systemic inflammatory responses in various malignancies, including breast cancer [14], lung cancer [15], gallbladder cancer [16], and PCa [17]. Meanwhile, many studies have confirmed that hyperfibrinogenemia is closely related to tumor progression [18-20]. FBG is an acute phase protein and FBG levels are increased in malignancy and systemic inflammation, which may be associated with infectious diseases, cancer, and venous thromboembolism [21]. Our data showed that increased FBG is significantly associated with higher age, PSA, the Gleason score, risk stratification, clinical stage and the incidence of bone metastasis in PCa, which means that high FBG indicates higher tumor grade. Our results were consistent with previous studies. For example, Ziaran et al. found that FBG was observably increased in patients with PCa after 12 months of androgen deprivation therapy, suggesting that the plasma FBG level may be associated with the progression of hormone resistance [22]. Thurner et al. showed that increased plasma FBG levels in PCa patients who received radiation therapy were significantly associated with poor prognoses in LAPCa [23].

The proposed mechanisms involved in the relationship between inflammation factors and tumor progression include the fact that FBG interacts with multiple integrin and non-integrin receptors of cancer cells to regulate tumor cell proliferation, migration, and other signaling transduction [24, 25]. O'Byrne et al. found that increased NLR and tumor progression includes the fact that inflammatory cytokine networks had a considerable influences on the survival, proliferation, and differentiation of tumor cells through DNA damage, angiogenesis, and other signal transduction pathways [26]. In this study, the inflammation factors (including NLR and FBG) are closely related to the occurrence and development of PCa, so we have established a new prediction model, which was composed of NLR, FBG and PSA, to assess the accuracy for

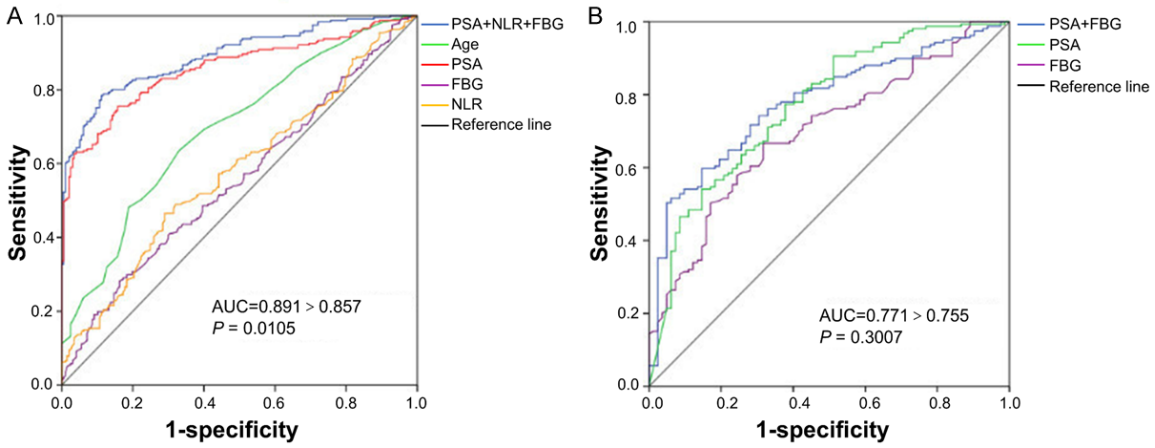

Figure 3. The predictive model used the ROC method to predict PCa and LAPCa. The ROC method for the prediction of PCa (A) and LAPCa (B). The new multivariate predictive model (combined with PSA, NLR, and FBG) exhibits a greater value of 0.891 in predicting PCa (P = 0.0105). The new model (combined with PSA and FBG) exhibited the highest AUC of 0.771 in predicting LAPCa, but was not statistically significant in comparison with PSA alone (P = 0.3007). AUC: area under the curve; FBG: fibrinogen; LAPCa: locally advanced prostate cancer; NLR: neutrophil-to-lymphocyte ratio; PCa: prostate cancer; PSA: prostate-specific antigen; ROC: receiver operating characteristic.

PCa prediction. As far as we know, this is the first study to investigate its clinical value in PCa patients.

Our results demonstrated the relationship between systemic inflammatory markers (including NLR, PLR, MLR, and FBG) and the risk of PCa. A new approach is put forward here that combines PSA, NLR, and FBG, which was found to have significantly improved the PCa detection accuracy. The results support the concept that inflammatory factors are thought to be associated with a higher risk of the growth and progression of PCa. However, in the second prediction model which combined FBG and PSA to predict LAPCa, the result demonstrated an AUC increase from 0.755 to 0.771, but it was not statistically significant.

One question that needs to be asked is that previous studies suggested that high white blood cell and monocyte counts were positively correlated with the risk and prognosis of PCa [10, 17]. Also a low serum neutrophil count may be a positive predictor of prostate biopsy [27]. Additionally, Yuksel et al. demonstrated that PLR can be used to distinguish BPH from PCa [28]. However, different conclusions were obtained in our study. The conclusion can be drawn from this study that only NLR is an independent risk factor for PCa, but white blood cells, monocyte counts, PLR and MLR were not.

The limitations of our study should be acknowledged. First, this was a retrospective investigation that involved a manual extraction of clinical data and unavoidable selection biases. Second, many demographic and environmental factors are known to affect neutrophils, lymphocytes, monocytes, and FBG levels, such as diet, drug use, age, smoking, and body mass [29, 30]. Despite strict registration criteria, we cannot completely rule out conditions that may lead to changes in blood. Third, it is difficult to assure that the surgical pathologic gradations and the PCa stages are consistent with the prostate biopsy results. Fourth, further studies are needed to fully describe all of these findings and their correlations.

Conclusion

This study demonstrated that NLR and FBG are independent risk factors for PCa. The higher the level of NLR and FBG, the greater the risk of PCa. Furthermore, preoperative FBG greater than 3.015 may indicate higher risk grades and clinical stages in patients with PCa. NLR and FBG may be low-cost and high-efficiency clinical biomarkers, which can combine with prostate-specific antigen form a new prediction model, improving the predictive efficiency for PCa.

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For this type of study, formal consent was not required.

Disclosure of conflict of interest

None.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee.

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