

Exploratory Associations of Systemic Inflammatory Markers and Prostate Volume with Predominant Gleason Pattern in Gleason Score 7 Prostate Cancer

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Abstract

Gleason score 7 prostate cancer comprises two biologically distinct subgroups—Gleason 3 + 4 and Gleason 4 + 3—with differing prognoses and therapeutic implications. However, reliable non-invasive methods to distinguish these subtypes prior to treatment remain limited. This exploratory study evaluated whether systemic inflammatory markers and prostate volume (PV) provide preliminary evidence of associations with predominant Gleason pattern. We analyzed 26 patients with biopsy-confirmed Gleason score 7 prostate cancer (3 + 4, $n = 15$; 4 + 3, $n = 11$). Pre-biopsy complete blood counts were used to calculate inflammation-based indices, including neutrophil-to-lymphocyte-to-platelet ratio (NLPR), systemic immune-inflammation index (SII), and others. Prostate volume (PV) was measured by a transrectal ultrasonography. Group comparisons used non-parametric tests, and receiver operating characteristic (ROC) analyses were performed. NLPR and PV showed modest separation between groups (NLPR AUC = 0.715; PV AUC = 0.709). Most other inflammatory markers-including NLR, PLR, MLR, AISI and SIRI-showed limited discriminatory performance. A multivariable model combining NLPR and PV yielded an AUC of 0.776, which increased to 0.8121 after adding SII. Given the very small cohort size ($n = 26$), these findings should be regarded strictly as preliminary and hypothesis-generating. This exploratory analysis suggests that NLPR and PV may reflect biological difference between Gleason 3 + 4 and 4 + 3 tumors. These observations require validation in larger, prospective, multi-institutional cohorts before any clinical interpretation or application can be considered.

Introduction

Prostate cancer (PCa) exhibits wide biological heterogeneity, ranging from indolent disease to highly aggressive tumors capable of rapid progression and metastasis [1]. Among the available grading systems, the Gleason score remains the cornerstone for prognostic stratification and treatment decision-making in PCa [2]. Gleason score 7—which encompasses the subgroups 3 + 4 and 4 + 3—presents a particularly challenging category. Although both patterns sum to 7, they differ markedly in histological architecture and clinical behavior. Gleason 3 + 4 cancers are predominantly composed of lower-grade pattern 3 glands, whereas Gleason 4 + 3 tumors contain a greater proportion of the more aggressive pattern 4 component [3]. Multiple studies have demonstrated that Gleason 4 + 3 is associated with higher risk of biochemical recurrence, adverse pathological features, and worse long-term outcomes compared with Gleason 3 + 4 disease [4, 5]. Therefore, distinguishing between these two subtypes prior to definitive treatment is clinically meaningful and may help refine management strategies.

Given these prognostic differences, there is growing interest in identifying non-invasive biomarkers that may assist in preoperative risk stratification. Prostate-specific antigen (PSA)-related metrics such as PSA density (PSAD) and prostate volume (PV), as well as systemic inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and others—have been investigated for their diagnostic or prognostic potential in PCa. These

markers which can be obtained through routine clinical testing may reflect underlying tumor burden or the host inflammatory response associated with more aggressive disease.

However, it remains unclear whether these readily available parameters can meaningfully differentiate Gleason 3 + 4 from 4 + 3 PCa, given their overlapping clinical characteristics and shared classification within intermediate-risk disease. To address this gap, we conducted a small exploratory analysis evaluating the diagnostic performance of PSAD, PV, and several systemic inflammatory indices in distinguishing these two Gleason 7 subtypes. Our aim was to determine whether a combination of simple, accessible biomarkers could generate preliminary evidence to support improved pre-treatment risk stratification within this clinically important group.

Method and Materials

Study Design and Patient Selection

We conducted retrospective analysis of patients undergoing ultrasound-guided prostate biopsy at the Urology Department of the People's Hospital of Xinjiang Uygur Autonomous Region (Xinjiang, China) between October 2018 and October 2021. Among 66 patients diagnosed with prostate cancer during this period, 26 patients with biopsy-proven Gleason score 7 PCa were included for subgroup comparison between Gleason 3 + 4 (n = 15) and Gleason 4 + 3 (n = 11).

This study was approved by the institutional ethics committee, and the requirement for informed consent was waived due to the retrospective design.

Laboratory Parameters and Inflammatory Marker Calculation

Peripheral blood samples were collected on the first day after hospital admission. Laboratory tests included total PSA, free PSA, and complete blood counts (CBC) components. Based on CBC results, the following systemic inflammatory markers were calculated:

Neutrophil-to-lymphocyte ratio (NLR): $\text{neutrophil count} \div \text{lymphocyte count}$

Platelet-to-lymphocyte ratio (PLR): $\text{platelet count} \div \text{lymphocyte count}$

Monocyte-to-lymphocyte ratio (MLR): $\text{monocyte count} \div \text{lymphocyte count}$

Systemic immune-inflammation index (SII): $\text{platelet count} \times \text{neutrophil count} \div \text{lymphocyte count}$

Aggregate index of systemic inflammation (AISI): $\text{neutrophil count} \times \text{monocyte count} \times \text{platelet count} \div \text{lymphocyte count}$

Systemic inflammation response index (SIRI): $\text{neutrophil count} \times \text{monocyte count} \div \text{lymphocyte count}$

Neutrophil-to-lymphocyte-to-platelet ratio (NLPR): neutrophil count ÷ (lymphocyte count × platelet count).

Inflammatory indices were selected based on previous literature linking systemic inflammation with tumor aggressiveness.

Prostate Volume and PSA Density

Prostate volume (PV) was measured with transrectal ultrasound using the standard ellipsoid formula: $PV = \pi/6 \times \text{width} \times \text{length} \times \text{height}$.

PSA density (PSAD) was calculated as: $PSAD = \text{total PSA} \div \text{prostate volume}$.

Statistical Analysis

Given the small sample size and non-normal data distribution, group comparisons were performed using the Mann–Whitney U test. Receiver operating characteristic (ROC) curves were constructed to assess the ability of individual markers and combined models to distinguish Gleason 3 + 4 from 4 + 3 disease. Diagnostic metrics included area under the ROC curve (AUC), sensitivity, specificity, and 95% confidence intervals (CI).

Multivariable logistic regression models were constructed to evaluate whether the combination of inflammatory markers and prostate volume improved discriminatory performance.

All statistical analyses were performed using GraphPad Prism. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Baseline clinical and hematological characteristics of the 26 patients with Gleason score 7 prostate cancer are summarized in Table 1. Among them, 15 patients had Gleason 3 + 4 and 11 had Gleason 4 + 3. No statistically significant differences were observed in age, PSA, or basic hematologic parameters between the two groups.

Table 1
Baseline Clinical and Laboratory Characteristics of Patients with Gleason 3 + 4 and Gleason 4 + 3 Prostate Cancer.

Characteristic	Gleason 3 + 4 (n = 15) Median (IQR)	Gleason 4 + 3 (n = 11) Median (IQR)	P value Mann-Whitney test
Age, years	65.00 (10.50)	65.00 (9.00)	0.8282
WBC, $\times 10^9/L$	5.43 (1.69)	7.32 (3.57)	0.0892
Neutrophils, $\times 10^9/L$	3.40 (1.21)	4.73 (1.40)	0.1176
Lymphocytes, $\times 10^9/L$	1.56 (0.42)	1.55 (0.78)	0.6925
Monocytes, $\times 10^9/L$	0.42 (0.30)	0.52 (0.22)	0.4352
Platelet, $\times 10^9/L$	217.00 (78.50)	187.00 (59.50)	0.1599
tPSA	11.10 (18.03)	27.57 (55.53)	0.4130

Inflammatory Markers and Prostate Volume

Although most inflammatory indices showed no significant differences between groups, both the neutrophil-to-lymphocyte-to-platelet ratio (NLPR) and prostate volume (PV) tended to be higher values in the Gleason 4 + 3 group, NLPR: $p = 0.0687$; PV: $p = 0.0774$. These trends did not reach statistical significance. However, NLPR and PV demonstrated the strongest numerical differences and were therefore explored in subsequent analyses. (Fig. 1).

ROC Curve Analysis of Individual Markers and Combined Predictive Model

ROC curve analysis demonstrated that NLPR had the highest individual discriminatory ability for differentiating Gleason 4 + 3 from 3 + 4, with an AUC of 0.7152 (95% CI: 0.5109–0.9194, $P = 0.065$), followed by PV with an AUC of 0.7091 (95% CI: 0.5077–0.9105, $P = 0.073$). In contrast, PSAD showed no discriminative value (AUC = 0.5030, $P = 0.979$) (Fig. 2, Table 2). The inflammatory markers NLR, PLR, MLR, AISI, SII, and SIRI also showed poor discriminative performance, with AUCs < 0.65, and all P-values > 0.05. (Table 2). A multivariable logistic regression model combining PV and NLPR significantly improved diagnostic performance (AUC = 0.7758, 95% CI: 0.5941–0.9574, $P = 0.0182$), and the inclusion of SII further enhanced the model (AUC = 0.8121, 95% CI: 0.6468–0.9774, $P = 0.0075$) (Fig. 3, Table 3). These exploratory models demonstrated higher apparent discrimination than individual markers. However, given the limited sample size, the possibility of model overfitting cannot be excluded.

Table 2
Diagnostic performance of inflammatory markers, PSAD and PV in
Differentiating Gleason 3 + 4 from Gleason4 + 3 Prostate Cancer.

Variables	AUC	95% interval confidence	P-value
NLR	0.6242	0.3920 ~	0.8565 0.287
MLR	0.5242	0.2978~	0.7507 0.836
PLR	0.5091	0.2645~	0.7536 0.938
SII	0.5818	0.3525 ~	0.811 0.484
NLPR	0.7152	0.5109 ~	0.9194 0.065
AISI	0.5030	0.2693 ~	0.7367 0.979
SIRI	0.5697	0.3394 ~	0.8000 0.551
PV	0.7091	0.5077 ~	0.9105 0.073
PSAD	0.5030	0.2534 ~	0.7526 0.979

Table 3
Multivariable Logistic Regression Models Combing Inflammatory Markers and Prostate Volume.

Variables	AUC	PPV	NPV	95% interval confidence	P-value
PV+NLPR	0.7758	73.33%	63.64%	0.5941 ~	0.9574 0.0182
PV+NLPR + SII	0.8121	80.00%	72.73%	0.6468 ~	0.9774 0.0075
PPV=Positive Predictive value; NPV=Negative Predictive value.					

Discussion

In this exploratory analysis, PSA density (PSAD) showed minimal ability to discriminate between Gleason 3+4 and 4+3 prostate cancer, with an AUC of 0.5030, indicating no meaningful discriminatory performance in this cohort. Although PSAD is widely used to distinguish prostate cancer from benign prostatic hyperplasia and other non-malignant conditions [6–8], its utility may be limited when applied to finer stratification within Gleason score 7 disease. The substantial biological overlap between Gleason 3+4 and 4+3 tumors may reduce the discriminatory capacity of PSA-based parameters alone.

Importantly, none of the individual inflammatory markers reached statistical significance for differentiating Gleason 3+4 from 4+3 disease in the present study. However, NLPR (AUC = 0.7152, P = 0.065) and prostate volume (AUC = 0.7091, P = 0.073) demonstrated the strongest numerical trends among the evaluated variables. While these findings should be interpreted cautiously, they raise the possibility that systemic inflammatory status and prostate anatomical characteristics may be associated with differences in predominant Gleason pattern.

Previous studies have reported associations between inflammation-based indices, including NLR, PLR, and SII, and adverse pathological features or poorer outcomes in prostate cancer. Systemic inflammation has been proposed to promote tumor progression through multiple mechanisms, including immune dysregulation, angiogenesis, and remodeling of the tumor microenvironment. In this context, the observed tendency toward higher NLPR values in Gleason 4+3 disease may reflect biological differences that warrant further investigation. However, the present study was not designed to evaluate underlying mechanisms, and no causal relationship can be inferred from these data.

Exploratory multivariable models incorporating NLPR and prostate volume demonstrated higher apparent discrimination than individual markers alone. The addition of SII further increased the apparent AUC. However, given the very limited sample size and the small number of events, these findings should be interpreted with considerable caution. The possibility of model overfitting cannot be excluded, and the observed improvements may not be reproducible in independent datasets. Therefore, these multivariable models should be regarded as hypothesis-generating rather than predictive tools suitable for clinical application.

From a clinical perspective, Gleason 4+3 disease is associated with a higher risk of biochemical recurrence, adverse pathological features, and poorer long-term outcomes compared with Gleason 3+4 disease [4,5,9,10]. Nevertheless, the purpose of the present study was not to replace pathological grading obtained from prostate biopsy. Rather, we sought to explore whether readily available systemic inflammatory markers may reflect biological differences between these two clinically important Gleason score 7 subgroups. Such observations may provide a rationale for future studies investigating links between peripheral inflammatory profiles and the tumor immune microenvironment.

Several limitations should be acknowledged. First, the study cohort was very small ($n = 26$), substantially limiting statistical power and increasing uncertainty around all estimates of diagnostic performance. Second, the retrospective single-center design may introduce selection bias and restrict generalizability. Third, systemic inflammatory markers can be influenced by non-cancer-related factors, including subclinical infection, medication use, and chronic inflammatory conditions, which were not fully controlled in this dataset. Fourth, Gleason classification was based on biopsy pathology rather than radical prostatectomy specimens. Because upgrading and downgrading between Gleason 3+4 and 4+3 diseases are well recognized, some degree of pathological misclassification cannot be excluded. Finally, no external validation cohort was available to assess the robustness of the observed findings.

Future studies should evaluate these observations in larger, prospective, multi-institutional cohorts with external validation. In addition, mechanistic studies examining the relationship between peripheral inflammatory indices and the tumor immune microenvironment may help clarify whether markers such as NLPR reflect underlying biological processes associated with predominant Gleason pattern.

In summary, no individual inflammatory marker significantly differentiated Gleason 3+4 from 4+3 prostate cancer in this small exploratory cohort. However, NLPR and prostate volume demonstrated the strongest numerical trends, and exploratory multivariable models showed higher apparent discriminatory

performance. These findings should be considered preliminary and hypothesis-generating. Further validation in larger studies is required before any clinical interpretation or application can be considered.

Declarations

Disclosure Statement

The authors have nothing to disclose.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

This research received no external funding.

Ethics Statement

This retrospective study was approved by the Medical Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region, Xinjiang, China. All methods were performed in accordance with the relevant guidelines and regulations.

Informed Consent Statement

Informed consent was waived due to the retrospective nature of the study and the use of anonymous clinical data.

Registry and the Registration No. of the study: N/A

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Animal Studies: N/A

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17–48.
2. Epstein JI, Egevad L, Amin MB, et al. The 2014 ISUP Gleason grading system: Definition and implications. *Am J Surg Pathol.* 2016;40(2):244–252.

3. Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29(9):1228–1242.
4. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Contemporary Gleason grading and the risk of prostate cancer mortality: a population-based study. *Eur Urol*. 2013;63(3):428–435.
5. Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. The prognostic significance of Gleason score 3+4=7 versus 4+3=7 prostate cancer: a retrospective analysis of radical prostatectomy outcomes. *BJU Int*. 2007;99(3):545–550.
6. Brawer MK. "Prostate-specific antigen: current status." *CA Cancer J Clin*. 1999;49(5):264–281.
7. Loeb S, et al. "The role of PSA density in the diagnosis of prostate cancer." *Nat Rev Urol*. 2012;9(7):369–377.
8. Maolake A, et al. Combination of PSA density and MLR improves the diagnostic accuracy of prostate cancer. *Front Oncol*. 2025;15:1570584. doi:10.3389/fonc.2025.1570584.
9. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int*. 2013 Oct;111(5):753-60. doi:10.1111/j.1464-410X.2012.11611.
10. Van Leenders GJ, et al. Gleason 4+3 versus Gleason 3+4 prostate cancer: implications for prognosis and treatment. *Histopathology*. 2016;69(6):874-81.

Figures

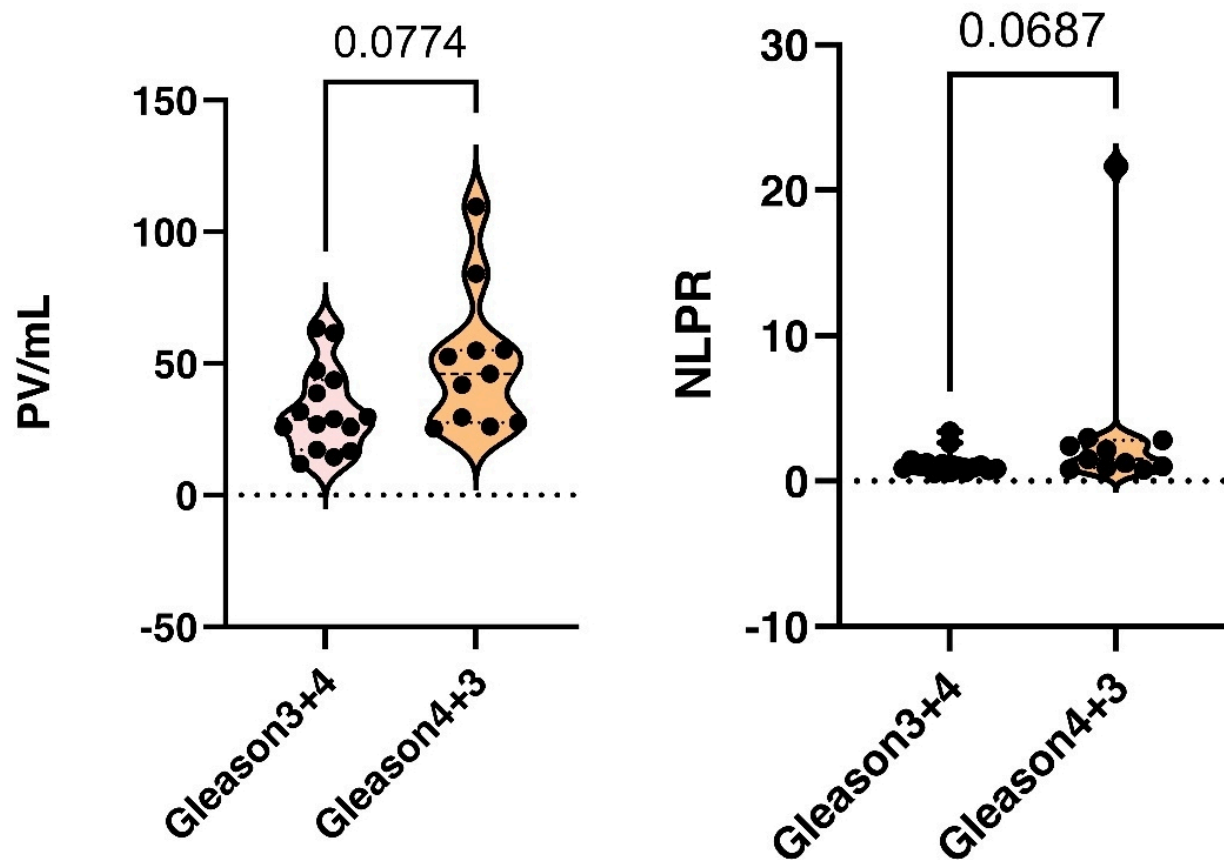


Figure 1

Violin Plots of NLPR and Prostate Volume between Gleason 3+4 and 4+3 Prostate Cancer

Distribution of NLPR and PV in patients with Gleason 3+4 and 4+3 scores. Median and interquartile ranges are displayed. Statistical comparison was conducted using the Mann–Whitney U test. NLPR ($P = 0.0687$); PV ($P = 0.0774$).

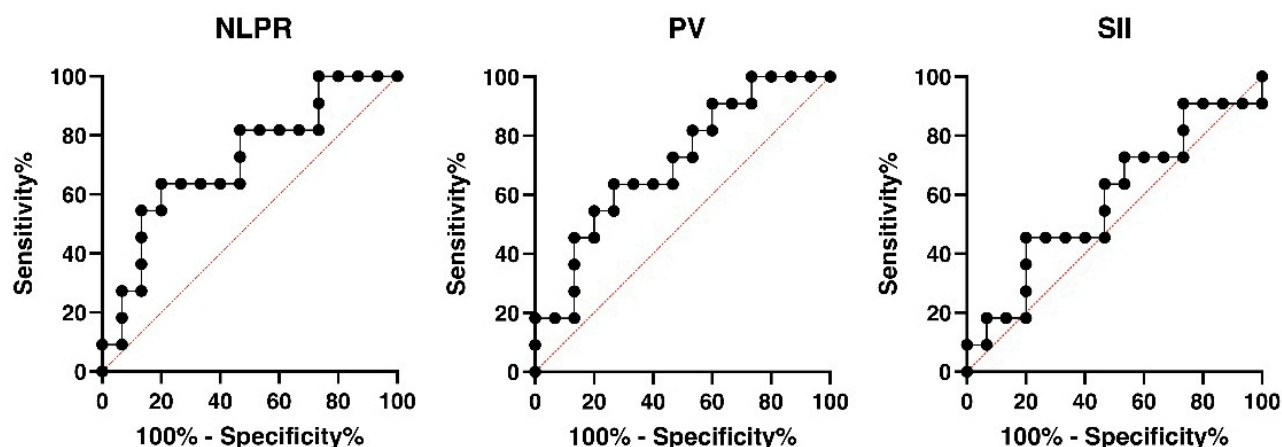


Figure 2

Receiver Operating Characteristic (ROC) Curves for Individual Markers

ROC curves showing the discriminatory ability of NLPR (AUC = 0.7152), PV (AUC = 0.7091), and SII (AUC = 0.5818) in distinguishing Gleason 3+4 from 4+3. NLPR and PV showed fair discrimination.

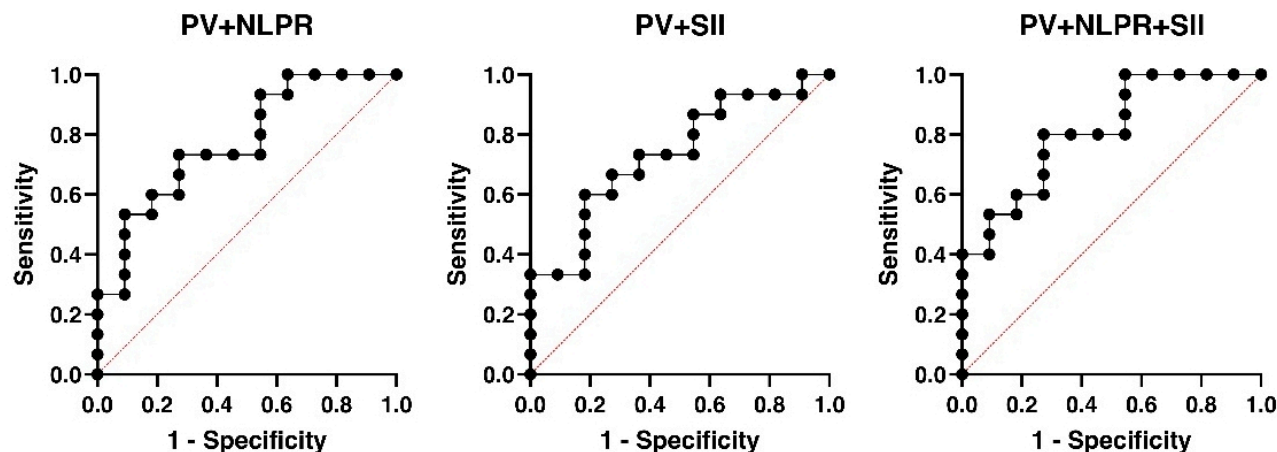


Figure 3

ROC Curve of Combined Predictive Model: PV + NLPR + SII

Multivariable model combining prostate volume, neutrophil-to-lymphocyte-platelet ratio (NLPR), and systemic immune-inflammation index (SII) achieved an AUC of 0.8121 (P = 0.0075), with improved discrimination between Gleason 3+4 and 4+3 tumors.