Predictive Value of Systemic Inflammatory Markers in the Prognosis of Prostate Cancer with Variant Histology

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Objective: This study aimed to investigate the potential role of systemic inflammatory markers in the management of Prostate Cancer (PCA) with variant pathology.

Materials and Methods: A retrospective analysis was conducted on 302 patients who underwent radical prostatectomy between 2014 and 2023. After applying exclusion criteria, 279 patients were included: 207 with adenocarcinoma and 72 with variant pathologies. Systemic inflammatory markers such as Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune-Inflammation Index (SII), and Systemic Inflammation Response Index (SIRI) were compared between the groups.

Results: Patients in the variant group were significantly older ($p = 0.005$). The frequencies of lymphovascular invasion (LVI), perineural invasion (PNI), and positive surgical margins (SM) were significantly higher in the variant histology group ($p < 0.001$, $p = 0.014$, and $p < 0.001$, respectively), as were ISUP grades ($p < 0.001$). Pretreatment PSA values were also significantly higher in the variant group ($p < 0.001$), as was the rate of subsequent radiotherapy ($p < 0.001$). However, no significant differences were found in NLR, PLR, SIRI, or SII values between the groups. Recurrence rates were significantly higher in the variant group ($p < 0.05$), but overall mortality did not differ.

Conclusion: Systemic inflammation markers have limited value in predicting prognosis among patients with variant PCA. This highlights the complex role of inflammation in cancer progression and underscores the need for further research to identify more specific biomarkers for different PCA variants.

Keywords: prostate cancer; systemic inflammation; variant pathology

INTRODUCTION

Prostate cancer (PCA), one of the most prevalent types of cancer globally, especially affects the elderly population.[1] The incidence of PCA is rapidly increasing in the Middle East, and many etiological factors are being studied.[2] PCA is generally considered a slow-progressing cancer, ranking as the second most common cancer but only fifth in terms of mortality compared to other cancer types.[3] However, mortality and disease progression can vary depending on various factors. The D'Amico classification, which categorizes risk groups, is one of the main systems used in this regard.[4] Additionally, age, comorbidities, and potential variant pathologies can all influence prognosis and mortality.[5] In recent years, the clinical significance of variant pathologies in PCA has gained increased importance.[6] Variant pathologies refer to deviations in the cellular characteristics of PCA cells and can have profound effects on the aggressiveness of the disease and the response to treatment. Therefore, understanding and addressing variant pathologies in PCA is of critical importance for better patient classification and the development of personalized treatment strategies.

Furthermore, the relationship between PCA and inflammation has garnered increasing interest. In this context, systemic inflammatory indices such as the Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), Systemic Inflammation Response Index (SIRI), and Systemic Immune-Inflammation Index (SII) have emerged as important tools for evaluating the prognosis of PCA patients and predicting treatment responses. In this article, we aimed to investigate the differences in treatment strategies between patients with conventional PCA and those with variant pathologies, as well as the plausible role of systemic inflammatory markers in the management of PCA.

MATERIALS AND METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Istanbul Training and Research Hospital Clinical Research Local Ethics Committee, Istanbul, Turkey (04/08/2023, Decision No: 193).

Selection of Participants

This single-center study included 302 patients who underwent radical prostatectomy for PCA in our urology clinic between January 2014 and March 2023. The data of these patients were retrospectively analyzed. Twen-

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Table 1. Demographic and baseline clinical characteristics of study patients (n=279)

Characteristic	Value (Median, IQR or n, %)
Age (years)	63 (59 – 68)
BMI (kg/m²)	26.73 (24.22 – 29.41)
Hypertension (yes)	115 (41.2%)
Diabetes Mellitus (yes)	55 (19.7%)
Cardiovascular Disease (yes)	43 (15.4%)
Lymphovascular Invasion (yes)	48 (17.2%)
Perineural Invasion (yes)	197 (70.6%)
Surgical Margin (positive)	87 (31.3%)
Hormone therapy (yes)	68 (24.4%)
ISUP-Grade	
ISUP-1	104 (37.3%)
ISUP-2	107 (38.4%)
ISUP-3	35 (12.5%)
ISUP-4	15 (5.4%)
ISUP-5	18 (6.5%)
PSA (ng/mL)	8.00 (6.00 – 13.00)
Prostate Volume (mL)	40.0 (30.0 – 52.0)
WBC (×10³/uL)	7.67 (6.35 – 9.35)
Hemoglobin (g/dL)	14.3 (13.4 – 15.1)
Hematocrit (%)	42.9 (40.4 – 45.4)
Platelet (×10³/uL)	240 (205 – 276)
Neutrophil (×10³/uL)	4.81 (3.80 – 6.00)
Lymphocyte (×10³/uL)	2.05 (1.55 – 2.66)
Monocyte (×10³/uL)	0.55 (0.42 – 0.70)
Eosinophil (×10³/uL)	0.03 (0.01 – 0.18)
Basophil (×10³/uL)	0.03 (0.02 – 0.05)
NLR	2.23 (1.62 – 3.23)
PLR	116.53 (94.37 – 155.06)
SIRI	1.22 (0.80 – 1.90)
SII	540.40 (393.07 – 818.38)

BMI, Body Mass Index; CVD, Cardiovascular Disease; ISUP, International Society of Urological Pathology; LVI, Lymphovascular Invasion; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; PNI, Perineural Invasion; PSA, Prostate-Specific Antigen; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index; WBC, White Blood Cell.

ty-three patients were excluded from the study for reasons such as other malignancies, recurrent blood transfusions due to anemia, autoimmune diseases, and the use of immunosuppressive drugs. Of the remaining 279 patients, 207 (74.2%) had adenocarcinoma pathology, while 72 (25.8%) had variant pathologies (ductal, mucinous, intraductal, neuroendocrine, foamy, or signet-ring cell).

Patients included in the study were selected from those who underwent radical prostatectomy in our clinic. Blood parameters measured within one week prior to surgery were used for analysis.

Those with autoimmune diseases, additional oncological conditions apart from PCA, patients who received steroid or immunosuppressive agents, those on antibiotic treatment for an active infection, and those who had undergone a blood transfusion in the last 30 days were excluded from the study.

Study Variables

The PLR, NLR, SIRI, and SII values were calculated using the following formulas:

- PLR = Platelet Count / Lymphocyte Count
- NLR = Neutrophil Count / Lymphocyte Count
- SIRI = (Neutrophil Count × Monocyte Count) / Lymphocyte Count
- SII = (Neutrophil Count × Platelet Count) / Lymphocyte Count

Statistical Analysis

The Kolmogorov-Smirnov test was used to check the normality of data for quantitative variables. Descriptive data were expressed as median and interquartile range (IQR) or as frequency and percentage. The Pearson chi-square, Fisher's Exact, and Mann-Whitney *U* tests were used where appropriate. Survival analysis was performed using the Kaplan-Meier method. For survival analysis, the day of surgery was considered the start date, and the date of the patient's last outpatient visit or the date of death was considered the end date. SPSS version 28.0 software was used for the analyses. A p-value < 0.05 was considered statistically significant.

Table 2. Postoperative oncological parameters of study patients (n=279)

Parameter	Value (n, % or Mean ± SD)
Radiotherapy (yes)	87 (31.2%)
Radiotherapy-Hormone Therapy Time (months)	10.6 ± 18.0
Chemotherapy (yes)	5 (1.8%)
Biochemical Recurrence (yes)	73 (26.2%)
Disease-Specific Survival Event (yes)	14 (5.0%)
All-Cause Mortality (Exitus) (yes)	26 (9.3%)
Follow-up period (months)	66.5 ± 30.9

RESULTS

After applying the exclusion criteria, the demographic, pathological, oncological, and inflammatory marker parameters of the remaining 279 patients are shown in (**Table 1**). The median age was 63 (IQR 59–68) years, and the median BMI was 26.73 (IQR 24.22–29.41) kg/m².

Postoperative treatment requirements, biochemical recurrence, disease-specific survival (DSS), and mortality rates are shown in (**Table 2**). The mean follow-up period was 66.5 ± 30.9 months.

A comparison of demographic and blood parameters between the two groups is demonstrated in (**Table 3**). Patients in the variant group were significantly older (p = 0.005). No significant difference was observed in terms of BMI, hypertension (HT), diabetes mellitus (DM), or cardiovascular disease (CVD) between the groups (p > 0.05 for each). In the variant histology group, the frequencies of lymphovascular invasion (LVI) and perineural invasion (PNI) were significantly higher (p < 0.001 and p = 0.014, respectively). The rate of positive surgical margins (SM) was also significantly higher in the variant group (p < 0.001). Higher ISUP grades in prostatectomy specimens were observed in the variant histology group (p < 0.001). There were no statistically significant differences between the groups in terms of prostate volume, WBC count, hemoglobin levels, hematocrit levels, or counts of neutrophils, platelets, monocytes, lymphocytes, basophils, or eosinophils. Consequently, there were no significant differences in NLR, PLR, SIRI, and SII values (p > 0.05 for each).

A comparison of oncological parameters between the two groups is shown in (**Table 4**). In the variant group, pretreatment PSA values were statistically significantly higher (p < 0.001). There were no significant differences between the groups in terms of PSA values at postoperative months 1, 12, 24, 36, 48, and 60 (p > 0.05 for each). In the variant group, the rate of radiotherapy was significantly higher (p < 0.001). The recurrence rate was significantly higher in the variant group (p < 0.05). No significant difference was observed in terms of PCA-related deaths or overall mortality rates between the two groups (p > 0.05).

A comparison of the cumulative projected disease-free

Table3. Comparison of demographic and blood parameters between groups

Parameter	Adenocarcinoma (n=207)	Variant Histology (n=72)	*p*-value
Age (years)	62 (58 – 67)	65 (62 – 69)	0.005*
BMI (kg/m²)	26.57 (24.22 – 29.40)	26.93 (24.22 – 29.58)	0.702
Hypertension (yes, n (%))	83 (40.1%)	32 (44.4%)	0.519
Diabetes Mellitus (yes, n (%))	45 (21.7%)	10 (13.9%)	0.149
Cardiovascular Disease (yes, n (%))	32 (15.5%)	11 (15.3%)	0.971
LVI (yes, n (%))	23 (11.1%)	25 (34.7%)	< 0.001*
PNI (yes, n (%))	138 (66.7%)	59 (81.9%)	0.014*
Surgical Margin (positive, n (%))	52 (25.2%)	35 (48.6%)	< 0.001*
Hormone therapy (yes, n (%))	36 (17.4%)	32 (44.4%)	< 0.001*
ISUP-Grade (n, %)			< 0.001*
ISUP-1	90 (43.5%)	14 (19.4%)	
ISUP-2	82 (39.6%)	25 (34.7%)	
ISUP-3	22 (10.6%)	13 (18.1%)	
ISUP-4	8 (3.9%)	7 (9.7%)	
ISUP-5	5 (2.4%)	13 (18.1%)	
Prostate Volume (mL)	40.0 (30.0 – 52.0)	39.5 (30.0 – 50.0)	0.559
WBC (×10³/uL)	7.75 (6.14 – 9.36)	7.62 (6.66 – 9.35)	0.440
NLR	2.27 (1.63 – 3.33)	2.11 (1.56 – 2.96)	0.197
PLR	118.25 (93.28 – 158.99)	114.29 (97.74 – 140.94)	0.388
SIRI	1.21 (0.81 – 1.95)	1.22 (0.75 – 1.70)	0.620
SII	548.83 (396.69 – 866.34)	525.96 (357.32 – 752.19)	0.329

Values are Median (IQR) or n (%). *p < 0.05. Abbreviations are defined in Table 1.

survival time between the groups is shown in (**Figure 1**).

DISCUSSION

White blood cell counts, their derived ratios (NLR, PLR), and systemic inflammatory markers (SII, SIRI) have been increasingly used in cancer-related studies in recent years. In clinical practice, hemogram parameters are routinely implemented for patients diagnosed with cancer and for those who are candidates for surgery. Moreover, systemic inflammatory indices are considered to represent an activation of the innate immune inflammation cascade in cancer patients.[7]

Neutrophils, monocytes, and platelets, which are cells involved in inflammation, create a suitable environment for the angiogenesis and metastasis of mutated cells.[8] Neutrophils, which play a primary role in inflammation, contribute to angiogenesis with matrix metalloproteinase-9 (MMP-9).[9,10] They also suppress the formation of CD8+ T lymphocytes, leading to immunosuppression and an increased likelihood of metastasis.[11] Furthermore, the release of leukotrienes from inflammatory cells like neutrophils increases the potential for cancer cells to metastasize.[12]

Platelet aggregation amplifies intercellular interactions and causes the adhesion of platelets to cancer cells. Consequently, cancer cells are shielded from the immune system and protected from lysis.[13] Lucotti et al. reported that administering aspirin to inhibit the COX-1/TXA2 pathway effectively blocked platelet function and reduced the formation of a pre-metastatic niche.[14] Cytokines secreted by lymphocytes, one of the main components of the immune system, reduce tumor cell proliferation and the risk of metastasis. Macrophages, CD4+ T cells, CD8+ cytotoxic T cells, and natural killer cells are effective in the anti-tumor response.[15] Monocytes, on the other hand, can facilitate metastasis through the secretion of molecules related to tumor-associated macrophages. Unlike lymphocytes, neutrophils, platelets, and monocytes are generally considered poor prognostic factors.[16]

The relationship between cancer and inflammation has led to the development of inflammation markers such as NLR, PLR, SII, and SIRI, which are derived from affordable and accessible blood tests. These markers have been evaluated for prognosis and survival in different cancer types.[17,18] Zhang et al. used SIRI to assess post-chemotherapy survival and found that this index was statistically significant and associated with patient survival over 3 and 5 years, identifying SIRI as a strong prognostic factor.[17] A study published in 2012 regarding PCA reported that high NLR and PLR were indicators of a worse prognosis.[19] A meta-analysis in 2019 also emphasized the high predictive power of inflammatory markers for PCA prognosis.[20] Furthermore, a study conducted in 2021 by Rajwa et al. evaluated SII in non-metastatic PCA patients who underwent radical prostatectomy and found that it was closely related to biochemical recurrence.[21] The estimation of SII before starting treatment in castration-resistant PCA patients demonstrated a strong correlation with non-response to treatment.[22] According to a meta-analysis published in 2021, there is a significant relationship between SII and not only PCA but also other urinary system cancers, and this index can be used as a prognostic tool.[23]

Studies have reported that SII is a prognostic factor for overall survival in metastatic castration-resistant prostate cancer.[24] Another prostate cancer study showed that systemic inflammation markers were related to both overall and disease-specific mortality.[25] High SIRI and SII values are associated with a higher risk of metastasis in renal cell carcinoma patients.[26] In addition, a meta-analysis reported that an increase in SII value is associated with poor prognosis in patients with urological cancer.[27] These studies, conducted over a broad range from localized to castration-resistant PCA, indicate the efficacy of these biomarkers in predicting prognosis. Nevertheless, there is a lack of research examining the relationship between inflammation markers and variant histopathologies. Variant pathologies are often considered more aggressive, and various variant types have been associated with biochemical recurrence, metastasis risk, and resistance to androgen deprivation therapy and chemotherapy.[28] In our study, we compared patients with variant prostate cancer, who are known to have worse oncological outcomes, with

Table 4. Comparison of oncological parameters between groups

Parameter	Adenocarcinoma (n=207)	Variant Histology (n=72)	*p*-value
Radiotherapy (yes, n (%))	44 (21.3%)	43 (59.7%)	< 0.001*
Chemotherapy (yes, n (%))	2 (1.0%)	3 (4.2%)	0.110
Biochemical Recurrence (yes, n (%))	35 (16.9%)	38 (52.8%)	< 0.001*
All-Cause Mortality (Exitus) (yes, n (%))	17 (8.2%)	7 (9.7%)	0.807
Follow-up period (months)	70.8 (Median)	73.2 (Median)	0.945
Preoperative PSA (ng/mL)	7.00 (5.00 – 12.00)	11.00 (7.00 – 18.00)	< 0.001*
Postoperative PSA month-1 (ng/mL)	0.010 (0.008 – 0.060)	0.030 (0.010 – 0.840)	< 0.001*
Postoperative PSA month-12 (ng/mL)	0.008 (0.008 – 0.010)	0.008 (0.008 – 0.010)	0.659
Postoperative PSA month-24 (ng/mL)	0.008 (0.008 – 0.010)	0.008 (0.008 – 0.010)	0.409
Postoperative PSA month-36 (ng/mL)	0.008 (0.008 – 0.010)	0.008 (0.008 – 0.010)	0.923
Postoperative PSA month-48 (ng/mL)	0.008 (0.008 – 0.010)	0.008 (0.008 – 0.010)	0.976
Postoperative PSA month-60 (ng/mL)	0.008 (0.008 – 0.020)	0.008 (0.008 – 0.027)	0.327

Values are Median (IQR) or n (%). *$p < 0.05$. PSA, Prostate-Specific Antigen.

the non-variant group in terms of systemic inflammatory markers.

The lack of significant differences in these inflammation markers, contrary to what might be expected from the literature, could possibly be attributed to the unique biological nature of variant pathologies. The impact of inflammation on cancer is determined by a multitude of variables, such as the tumor microenvironment, immune response, and genetic factors. While inflammation is closely associated with cancer and plays a significant part in its initiation and advancement, our findings suggest this relationship may differ in variant PCA.[29] Consistent with the literature, our study found higher initial PSA values, higher ISUP scores, and more frequent positive surgical margins in the variant group. Early biochemical recurrence rates were also higher in the variant group, resulting in higher rates of subsequent hormone therapy and radiotherapy.

Our study indicates that these common inflammation markers do not show significant differences between variant PCA and prostate adenocarcinoma. This may suggest that these markers could be specific to certain cancer types or that the capacity of variant histopathologies to influence systemic inflammation is limited. However, the lack of differences in inflammation markers does not imply that inflammation is ineffective in the evolution or progression of cancer. Instead, it suggests the role of inflammation is complex and can have multifaceted effects on cancer development.

Our study has several limitations. First, it was a ret-

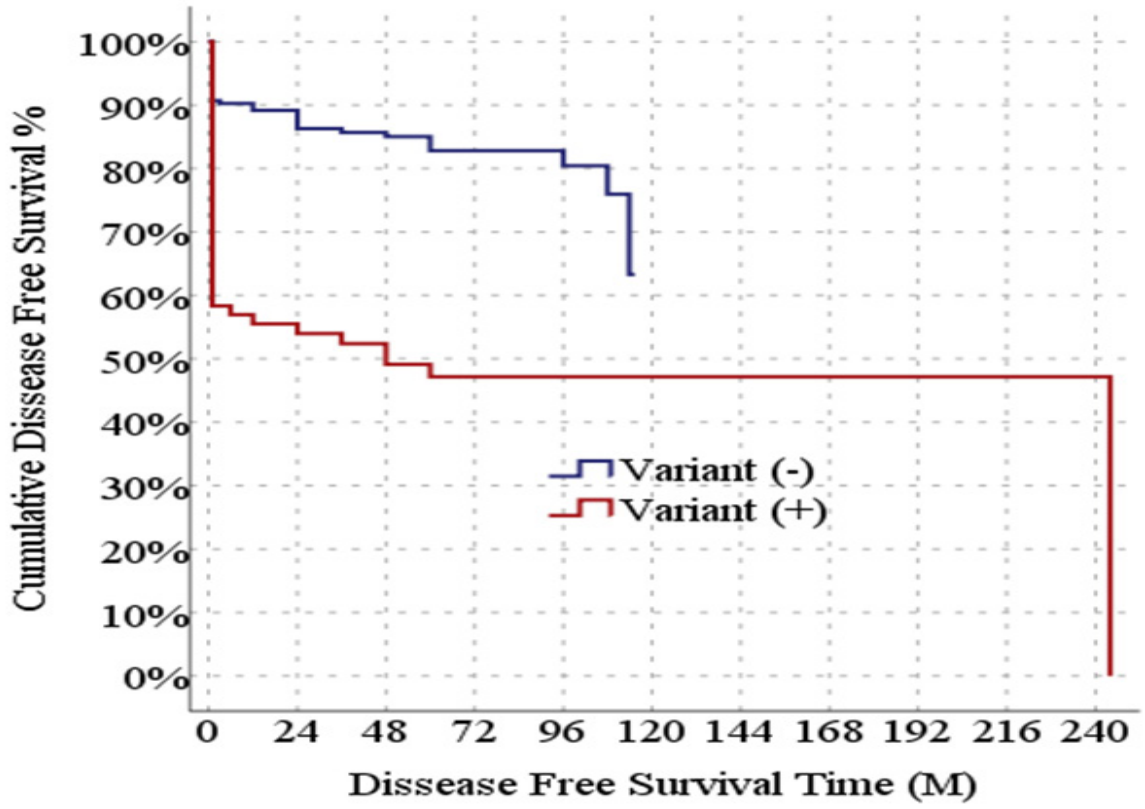

Figure 1. Comparison of cumulative projected Disease-Free Survival Time between groups. The Kaplan-Meier analysis showed that the predicted disease-free survival duration was significantly different between the groups ($p < 0.05$, log-rank test), with a mean survival of 97.3 months in the non-variant group and 119.4 months in the variant group.

rospective observational study conducted at a single institution, which may introduce selection bias. A multicenter study is needed to validate these findings. Moreover, a limitation of the study was the relatively small number of patients in the variant group. More comprehensive results and possible mechanisms could be revealed by evaluating a larger cohort. Nevertheless, to the best of our knowledge, this is the first study to investigate the relationship between variant prostate cancer and systemic inflammation markers.

CONCLUSIONS

This study demonstrates that there is no significant difference in common systemic inflammation indices between patients with variant PCA and those with conventional adenocarcinoma. These results indicate that the capacity of PCA variants to influence systemic inflammation may be limited, and these indices have limited value in predicting prognosis among these variants. This highlights the complex role of inflammation in cancer development and progression. Therefore, future research should focus on developing more specific biomarkers for different PCA variants to better understand their unique characteristics and improve clinical management strategies.

SUMMARY

This study found that while variant prostate cancers have worse pathological features and higher recurrence rates than typical adenocarcinoma, common blood inflammation markers (NLR, PLR, SII, SIRI) do not differ between the groups, limiting their prognostic use.

AUTHORS' CONTRIBUTIONS

- Research conception and design: Huseyin Aytac Ates and Emrah Okucu
- Data acquisition: Semih Aktas, Muhammet Hilmi Enes Araci and Berrin Yalcin
- Statistical analysis: Hikmet Koseoglu
- Data analysis and interpretation: Hikmet Koseoglu
- Drafting of the manuscript: Huseyin Aytac Ates and Emrah Okucu
- Supervision: Huseyin Aytac Ates and Berrin Yalcin
- Approval of the final manuscript: All authors

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

Derived data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This study was approved by the Clinical Research Ethics Committee (04/08/2023, Decision No: 193).
Informed consent and follow-up details were obtained by examining medical records and conducting telephone interviews.

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