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Predictive Significance of Preoperative Neutrophil to Lymphocyte Ratio versus Platelet to Lymphocyte Ratio for Gleason score in Prostate Cancer Patients

ORIGINAL ARTICLE

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ABSTRACT

Objective: Inflammation plays a critical role in the development and progression of cancer. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are easily accessible basic inflammatory parameters. In this study, we aimed to analyze the association between the NLR, PLR, and the Gleason score in prostate cancer, which is main parameter used in the prostate cancer prognosis.

Materials and Methods: A total of 173 patients with prostate cancer (mean age, 63±6.2 years) who underwent radical prostatectomy were included into this retrospective study. The NLR and PLR were derived from the complete blood cell count results from the preoperative period. Patients were divided into two groups, as the low grade prostate cancer (Gleason score≤7 [3+4]) and the high-grade prostate cancer (Gleason score≥7 [4+3]) group. A logistic regression analysis was performed to determine the association.

Results: A univariate logistic regression analysis showed that the Ln-prostate specific antigen (PSA) (1.83, 95% confidence interval [CI] [1.01, 3.3] p=0.04), Ln-lymphocyte (0.38, 95% CI [0.15, 0.94] p=0.03), and Ln-NLR (1.9, 95% CI 1.9 [1.13, 3.38] p=0.01) levels were significantly associated with the high-grade Gleason score. However, the Ln-PLR levels revealed the association with marginal statistical significance (2.06, 95 % CI [0.95, 4.4] p=0.06). In multiple analyses, after adjusting the analysis for age, Ln-NLR (1.96, 95% CI [1.12, 3.42] p=0.01) and Ln-lymphocyte levels (0.38, 95% CI [0.15, 0.97] p=0.04) were still statistically significantly associated with high-grade prostate cancer.

Conclusion: Higher NLR levels were significantly associated with high-grade prostate cancer. However, PLR levels were not a significant predictor of higher Gleason scores.

Keywords: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prostate carcinoma, gleason score

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INTRODUCTION

Prostate cancer is the second most common cancer and sixth leading cause of cancer death among men worldwide. With aging and an increased use of the PSA as a screening marker, there has been a substantial increase in the prostate cancer diagnosis documented in many countries (1). In Turkey, several reports have documented that the prevalence of prostate cancer is almost 2 to 3 times higher than in Asian population and that it shows rates similar to Europe's (2). Also, the first multicenter, population-based report from Turkey documented that the prostate cancer incidence rate is 35 cases per 100,000, highlighting its importance with regard to economic and health-related quality of life of the patients (3).

Chronic inflammation plays a crucial role in the development of cancer (4) The traditional risk factors for prostate cancer are age, genetics, and Western lifestyle (4) Besides genetic, environmental factors that lead to chronic prostate inflammation, such as infection, diet, or other exposures are important in prostate cancer etiopathogenesis (4). Moreover, chronic inflammation has a considerable effect on the progression and metastasis through angiogenesis and epithelial mesenchymal transition (EMT), impacting the dynamics of the tumor microenvironment in prostate cancer (5).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory parameters that are easily reachable from a routine complete blood count and have been reported as a prognostic value in solid organ cancers (6, 7-10). They also have been suggested as an emerging marker of systemic inflammation, tumor hypoxia, and necrosis. Several reports have documented the use of these basic clinic parameters to differentiate malign form benign in prostate lesions (11, 12) However, the evidence about the prognostic values of NLR and PLR in prostate cancer is scarce. Hence, in this retrospective study, we aimed to analyze the prediction effect of preoperative NLR and PLR levels for prostate carcinoma histological grade using the Gleason scoring system for radical prostatectomy specimens.

MATERIALS and METHODS

Study Population

A total of 173 men in whom biopsy proved the presence of prostate carcinoma and who underwent a robot-assisted radical prostatectomy between October 2012 and January 2018 at the Yuksek Ihtisas University Faculty of Medicine Koru Ankara Hospital Department of Urology were included into these retrospective analyses. We have excluded the patients with an infectious or inflammatory disease (i.e., active connective tissue disorder, HIV, any other proven infections) or who had no sufficient medical records. Also, none of the patients received anticancer therapy before operation. The Institutional Review Board of the Yuksek Ihtisas University Faculty of Medicine, Koru Ankara hospital approved the study protocol.

Table 1. Characteristics of the study patients

	n=173
Age (years, mean±SD)	63±6.2
PSA (ng/mL, median IQR)	8.4 (5.1, 16.4)
Gleason Score (n, %)	
Low Grade [6(3+3), 7(3+4)]	106 (61%)
High Grade [7(4+4) and higher]	67 (39 %)
Lymph node metastasis (n, %)	9 (5.1%)
Positive resection margin (n, %)	41 (24%)
Hemoglobin (g/dL, mean±SD)	14.5±1.2
Leukocyte (/ µL, median, IQR)	7420 (6320, 8840)
Neutrophil (/ µL, median, IQR)	4380 (3700, 5890)
Lymphocyte (/ µL, median, IQR)	2110 (1760, 2560)
Platelet (/ µL, median, IQR)	222000 (181000, 262000)
NLR (median, IQR)	2.1 (1.6, 2.9)
PLR (median , IQR)	103.4 (84.7, 135.4)

PSA: prostate specific antigen; SD: standard deviation; IQR: interquartile range; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Clinical and Laboratory Analysis

The NLR was calculated using the neutrophil and lymphocyte counts from the complete blood count (CBC) obtained before surgery, and the PLR was calculated using the platelet count divided by the lymphocyte count as in same CBC results. All surgeries were performed by the same surgery team. The tumor grade of the radical prostatectomy specimens was determined according to the International Society of Urological Pathology (ISUP) consensus on the Gleason grading (13).

Statistical Analysis

Continuous variables were presented as the mean±SD or median (interquartile range) according to the distributions and categorical variables as frequencies and percentage. The comparison of variables between the two groups was performed according to the normality, either t-test or Mann-Whitney U test for continuous variables, and Chi-squared test for categorical variables. Logistic regression analyses were used to evaluate the possible association between the NLR, PLR, and Gleason score. All leukocyte, neutrophil, lymphocyte, platelet, PSA, NLR, and PLR values were log transformed to reach the normal distribution, and transformed values were used in the regression analysis. Since it was not possible to obtain the body mass index values for all patients, multiple analyses were adjusted by age. Independent variables were not put together in the model for possible interaction. The Gleason score results were grouped as the low grade and high-grade for the analyses. A p-value under 0.05 was considered as statistically significant. A statistical analysis was carried out using the Statistical package for social sciences, version 25.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Our study group comprised of 173 men with biopsy-proven prostate carcinoma. The demographics of study population are depicted in Table 1. The mean age was 63±6.2 years, with the median preop-

Table 2. The comparison of parameters between study groups

	Low Grade [Gleason≤ 7(3+4)] n=106	High Grade [Gleason ≥7(4+3)] n=67	p
Age (years, mean±SD)	62±6	63±6	0.17
PSA (ng/mL, median IQR)	6.6 (4.8, 11.9)	11.1 (6.3, 32.2)	0.04
Lymph node metastasis (n, %)	0	9	<0.001
Positive resection margin (n, %)	18	23	0.01
Hemoglobin (g/dL, mean±SD)	14.6±1.2	14.2±1.3	0.05
Leukocyte (/ µL, median, IQR)	7470 (6352, 8767)	4680 (6160, 8850)	0.81
Neutrophil (/ µL, median, IQR)	4375 (3800, 5800)	4680 (3560, 6020)	0.80
Lymphocyte (/ µL, median, IQR)	2160 (1785, 2632)	2100 (1670, 2450)	0.11
Platelet (/ µL, median, IQR)	227000 (192000,269000)	217000 (188000,257000)	0.46
NLR (median, IQR)	2.03 (1.6, 2.6)	2.3 (1.6, 3.3)	0.06
PLR (median , IQR)	102 (83, 129)	109 (89, 149)	0.14

PSA: prostate specific antigen; SD: standard deviation; IQR: interquartile range; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Table 2. The comparison of parameters between study groups

	Univariate		Multiple*	
	B (95% CI)	p	B (95% CI)	p
Age (years, mean±SD)	1.03 (0.98, 1.08)	0.17	-	
Ln-PSA (ng/mL, median IQR)	1.83 (1.01, 3.3)	0.04	1.79 (0.99, 3.26)	0.05
Ln-Leukocyte (/ µL, median, IQR)	0.90 (0.42, 1.96)	0.80	0.91 (0.42, 1.98)	0.81
Ln-Neutrophil (/ µL, median, IQR)	1.41(0.69, 2.87)	0.33	1.40 (0.68, 2.87)	0.35
Ln-Lymphocyte (/ µL, median, IQR)	0.38 (0.15, 0.94)	0.03	0.38 (0.15, 0.97)	0.04
Ln-Platelet (/ µL, median, IQR)	1.09 (0.38, 3.08)	0.86	1.15 (0.39, 3.36)	0.79
Ln-NLR (median, IQR)	1.9 (1.13, 3.38)	0.01	1.96 (1.12, 3.42)	0.01
Ln-PLR (median , IQR)	2.06 (0.95, 4.4)	0.06	2.1 (0.96, 4.6)	0.06

*age adjusted multiple analyses. PSA: prostate specific antigen; NLR: neutrophil to lymphocyte ratio; PLr: platelet to lymphocyte ratio; LN: log transformed

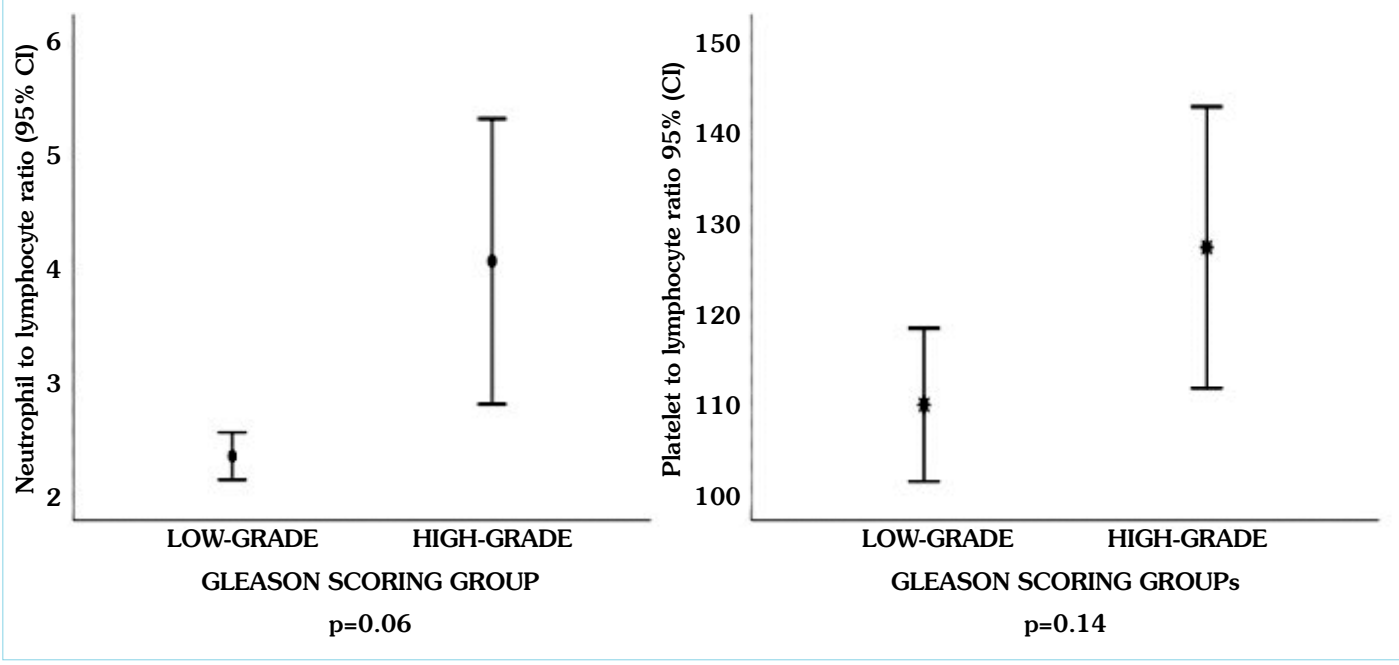

Figure 1. NLR and LR values among study subgroups: Both NLR and PLR values were higher in high-grade group, the difference in NLR showed near statistical significance (p=0.06), however PLR was not significantly different (p=0.14).

erative PSA of 8.4 (5.1, 16.4) ng/mL. All patients underwent robot-assisted radical prostatectomy, and surgery specimens' pathology report showed that 106 patients had low grade tumor (Gleason under 7[3+4]), and 67 patients had high-grade tumor (Gleason higher than 7[4+3]). Only nine patients had lymph node metastasis. Among 173 patients, 41 (24%) had a positive resection margin.

The median leukocyte level was 7420 (6320, 8840)/µL, the median neutrophil level was 4380 (3700, 5890)/µL, the median lymphocyte level was 2110 (1760, 2560)/µL, the median platelet level was 222000 (181000, 262000)/µL, and the mean Hb level was 14.5±1.2 g/dL. The median NLR was 2.1 (1.6, 2.9), and PLR was 103.4 (84.7, 135.4) (Table 1).

We also compared all characteristics among the study subgroups assigned as low grade and high-grade according to the Gleason scoring system. The comparison analysis is depicted in Table 2. The comparison regarding the serum PSA levels showed that the high-grade group had statistically significantly higher values than low grade (p=0.04; Table 2). Although both the NLR and PLR values were higher in the high-grade group, the difference in NLR showed a marginal statistical significance (p=0.06); however, the PLR was not significantly different (p=0.14; Figure 1).

Association Between the NLR, PLR, and Gleason Score

A univariate logistic regression analysis showed that the Ln-PSA (1.83, 95% confidence interval [CI] [1.01, 3.3] p=0.04), Ln-lymphocyte (0.38, 95% CI [0.15, 0.94] p=0.03), and Ln-NLR (1.9, 95%CI 1.9 [1.13, 3.38] p=0.01) levels were statistically significantly associated with a high-grade Gleason score. However, the Ln-PLR levels revealed the association with marginal statistical significance [2.06, 95 % CI (0.95, 4.4) p=0.06]. In multiple analy-

ses, after adjusting the analysis for age, the Ln-NLR (1.96, 95% CI [1.12, 3.42] p=0.01) and Ln-lymphocyte levels (0.38, 95% CI [0.15, 0.97] p= 0.04) were still statistically significantly associated with high-grade prostate cancer. Also, the slight association for Ln-PSA [1.79, 95% CI (1.79, 0.99, 3.26) p=0.05] and Ln-PLR [2.1, 95% CI (0.96, 4.6) p=0.06] were still observed in multiple analyses. All results are summarized in Table 3.

DISCUSSION

Recently, there were several studies that aimed to find parameters that would be inexpensive, easily available, and practical in clinical use in the diagnosis, follow-up, and prediction of prognosis of solid organ cancers. Measuring of serum PSA levels, rectal digital examination, and prostate biopsy are standard techniques for the diagnosis among men who are suspected to have prostate cancer. The possibility of finding prostate cancer ranges between 20% and 67% by trans-rectal prostate biopsy (14) However, false negative results have been reported at the rate as high as 23% in the first prostate biopsy. It is known that repeated biopsies are needed to detect cancer, especially in patients whose previous pathology reports showed an atypical small acinar proliferation or high-grade prostate intraepithelial neoplasia (15, 16). Thus, several tests have been developed to clarify diagnosis prior to biopsy, such as magnetic resonance imaging. However, those tests are not easy to perform and are also expensive. Accordingly, all research has been focused on the development of markers that would be cheaper and easy to use in clinical practice.

Inflammation is crucial in prostatic carcinogenesis and tumor progression by immune cell infiltration in prostate tissue and fibroblast activation along with several different mechanisms (4, 17) The NLR ratio and PLR are inexpensive and practical parameters that can be checked by one CBC during routine clinic visits. The NLR has been studied in several different solid organ tumor areas (18) and found to be predictive for both the cancer development and prognosis. In our study, we demonstrated that the NLR levels were independent predictors for high-grade prostate carcinoma in both univariate and multiple analyses with almost the same prediction level with serum PSA levels. Similar to our findings, previous studies also found the NLR as an independent prognostic marker in prostate carcinoma (10, 19) The Gleason scoring system correlates closely with clinical features of prostate carcinoma (13). Higher scores indicate worse cancer outcomes (20, 21). Hence, finding of the close association between high NLR levels and high Gleason scores suggests the NLR usefulness regarding the prediction of high-grade histology with respect to poor tumor prognosis. Our results are similar to those by Lu et al., demonstrating the higher the levels of NLR, the higher the degree of Gleason score and malignancy of prostate cancer (22) Langsenlehner et al. (23) have also reported similar findings by demonstrating that a high NLR is associated with prostate carcinogenesis and concluded that inflammation associated with an increased neutrophil count and tumor response associated with a decreased lymphocyte count might be a part of carcinogenesis. Jang et al. (24) demonstrated the higher NLR levels obtained before radical prostatectomy are associated with a higher biochemical relapse along with poor survival among 2067 prostate cancer patients. Considering the above-mentioned, large, multicenter validation studies, which would analyze the cut-off level of NLR in the prediction of grading prostate carcinoma, would use the NLR as an inexpensive, accessible, and promising marker for estimating the cancer clinical behavior in these patients.

The other simple inflammation-based parameter that we studied is PLR, which is also obtainable from the CBC. Many studies disclosed that the higher pretreatment levels of PLR are associated with poor prognosis in several types of solid cancers (25-27). In our study, although the patients with high-grade prostate carcinoma tend to have much higher levels of PLR, and although the regression analysis showed a positive relation with the Gleason score, we were unable to find statistically significant association. The reports in the literature regarding the prediction value of PLR for the diagnosis and prognosis of prostate carcinoma are conflicting. Yuksel et al. (12) suggested the PLR is an additional predictor marker for distinguishing prostate lesions benign from malign nature. Wang et al. (10) also suggested to use the PLR as an additional marker to predict the prognosis in patients with prostate cancer. Also in another report, in which the PLR and NLR levels were studied together in urological cancers, both inflammatory parameters were found to be associated with poor prognosis in prostate carcinoma (28). The evidence indicates that a higher PLR level reflects the elevated platelet-dependent tumor growth (pro-tumor reaction) and decreased lymphocyte-mediated anti-tumor immune response, and both are attributed to progression and poor tumor outcomes (17, 23). On the contrary, Zanaty et al. (29) have studied both the predictive effect of preoperative NLR and PLR levels among organ-confined prostate cancer patients and were unable to find any significant association for both markers concluding the localized tumors might not trigger the systemic inflammatory response. Likewise, we were unable to find strong association between the PLR and Gleason degree in our study. The inflammatory pathways in the tissue level and its reflection in clinical laboratory results might not be always correlated. The lack of power of the relation between the PLR and histological status in our study might be a signal that neutrophils have a more important role in the development and progression in malignancy than platelets. However, this issue should be further clarified with the studies that would conduct a simultaneous blood and specimen evaluation.

We believe that we performed our analysis on the substantial sample size. However, the design of our study is retrospective, which might limit our interpretation of results causality, although data were obtained in a prospective manner. Here our goal was to determine the relation between the histological grading of prostate cancer, but a longer follow-up period to see if there is a link with long-term clinical prognosis would provide more accurate and clinically applicable results.

CONCLUSION

Overall, our study confirms that higher NLR levels are an indicator of high-grade prostate carcinoma, suggesting a significant clinical significance for these patients. We were unable to reach statistical significance regarding the association with PLR levels. Further large-scale, follow-up studies are needed to validate these results with certain cut-off levels of these inflammatory parameters.

Ethics Committee Approval: The Institutional Review Board of the Yuksek Ihtisas University Faculty of Medicine, Koru Ankara hospital approved the study protocol at March 2018.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: GE, BK, MK, YK, HB. Performed the experiments or case: GE, BK, MK, YK, HB. Analyzed the data: GE, BK, MK, YK, HB. Wrote the paper: GE, BK, MK, YK, HB. All authors have read and approved the final manuscript.

Conflict of Interest: The authors have no conflicts of interest to declare.

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