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Are neutrophil-lymphocyte and platelet-lymphocyte ratios valuable in predicting prostate cancer?

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ABSTRACT

Introduction and Hypothesis: We retrospectively evaluated the prognostic impact of neutrophil-lymphocyte ratio (NLR) as a marker for inflammatory and immune state in men with prostate cancer.

Materials and Methods: This retrospective study was conducted in a single urology clinic to review the medical data of 558 patients who underwent transrectal prostate needle biopsies between 2007 and 2014. Prior to transrectal prostate needle biopsies, patient histories, physical examinations, and routine laboratory tests including blood biochemistry, urinalysis and urine cultures, free PSA and total PSA, rectal examination, transrectal ultrasound findings, and pathology results were evaluated.

Results: Benign biopsy results were found in 287 patients (Group 1) using neutrophil / lymphocyte (NLR) and platelet / lymphocyte ratio (PLR). When calculating malignancy in 271 patients (Group 2), there was no significantly difference in NLR and PLR values between benign and malign prostate diseases (p=0.14 and p=0.369, respectively).

Conclusion: With reference to the survey prior to the biopsy, NLR and PLR ratio values do not appear to be helpful in the differentiation of benign prostatic hyperplasia and prostate cancer.

Key words: *Prostate cancer, lymphocytes, neutrophils*

Introduction

Many clinical and laboratory parameters have been investigated to determine their utility in predicting prostate cancer. Today, prostate-specific antigen (PSA) and nomograms that employ PSA are both widely accepted; the PSA level has a high predictive value for prostate cancer. Another parameter, the PSA density, has also demonstrated a direct relationship with prostate cancer; a PSA density over 0.15 in patients with a PSA from 4-10 ng/cc and a suspicion of cancer upon digital rectal examination (DRE) following transrectal ultrasonography (TRUS) have been suggested as an indicator for prostate biopsy [1-3]. A study in patients with prostate cancer who had a PSA increase of 0.75 ng/cc or more in a year revealed a specific marker for prostate cancer, but this was not identified in those with a PSA that was lower than 4 ng/cc in patients who did not have a PSA velocity of at least 0.75 ng/cc [4]. Catalona and colleagues investigated patients with a PSA from 4-10 ng/cc along with a free/total PSA ratio that was below 25% independently of other clinical markers to determine the presence of cancer, and they

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found that these two values provide predictive information [5].

Recently, an increase in the peripheral neutrophil-to-lymphocyte ratio (NLR) has been adopted as an indicator of a poor prognosis in several types of cancers [6]. However, NLR's consistency and prognostic impact is unclear. Many studies of the NLR in solid tumors have reported that NLR provides predictive information [7]. However, publications regarding NLR in prostate cancer and the platelet-lymphocyte ratio (PLR) are limited. In this study, our aim is to compare the malignant biopsy results in patients undergoing prostate biopsy with those of patients with benign results, as well as with the pre-biopsy clinical and laboratory parameters. Neutrophil-to-lymphocyte ratio and PLR can be calculated from values that are used daily in clinical practice and are therefore readily available and inexpensive. The patients in clinical trials have been investigated for an objective foresight that can help in the differentiation of benign cases of prostate cancer.

Methods and Materials

This retrospective study, which was approved by the Ethics Committee of Clinical Research in Malatya, Turkey (protocol number 2014/173), was conducted in a single urology clinic to review the medical data of 568 patients who underwent prostate needle biopsy between January 2007 and December 2014. Prebiopsy history of the patients, DREs, transrectal ultrasonography, and routine laboratory tests, including blood biochemistry, complete blood count, urinalysis, and urine cultures, were evaluated. Patients with both malignant and benign biopsy results were divided into two groups and compared. Any subjects with hematologic, infectious, or chronic diseases were excluded from this study. Patients with missing data were also excluded.

Laboratory Data

Hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC), neutrophil, lymphocyte and platelet counts, mean platelet volume (MPV), and red blood cell distribution width (RDW) were obtained using Beckman Coulter LH780 and Beckman Coulter LH750 (California, USA) analyzers. Neutrophil-to-lymphocyte ratio and PLR values were calculated by dividing the total neutrophil and platelet counts by the total lymphocyte count, respectively.

Statistics

The data were outlined by calculating the median (min-max) values. The Mann-Whitney U test was used for the comparison of NLR, PLR, and Free / Total PSA values between the two groups. The optimal cut-

Table 1. Median values of properties (min-max).

Variable	Group 1 (n=287)	Group 2 (n=281)	P value (p<0.05)
Age	65(38-84)	67(45-108)	0.001
Total PSA	8(3-305)	9(1-819)	0.008
Free PSA	1.3(0.2-71.4)	2.1(0.1-114)	p<0.001
f/t PSA	0.15(0.01-0.75)	10(0.04-48)	p<0.001
Total vol.(cc)	60(15-288)	40(15-323)	p<0.001
RBC	4.85(3.02-6.83)	4.84(3.03-6.12)	0.22
HGB	14.5(1.5-45.6)	14.5(8.6-17.7)	0.978
HCT	43(19.1-56.7)	42.9(5.2-53)	0.423
MCV	89.3(68.4-116)	89.9(61.8-103.6)	0.086
MCH	30.1(21.5-39.4)	30.4(18.5-35.6)	0.301
Neutrophils	3,900(2,490-4,310)	3,960(2,000-7,900)	0.818
Lymphocytes	1,650(1,200-3,460)	1,780(910-4,200)	0.059
RDW	13.8(12.4-22.4)	14(12.4-22.7)	0.31
Platelet	234,000(80,000-450,000)	231,000(80,000-450,000)	0.924
MPV	7.7(5.8-12.3)	7.8(6.2-69.9)	0.61
WBC	7,600(2,000-15,000)	7,600(3,700-15,000)	0.45

PSA: Prostate specific antigen; **RBC:** red blood cell; **HGB:** Hemoglobin; **HCT:** Hematocrit; **MCV:** Mean corpuscular volume; **RDW:** Red blood cell distribution width; **MPV:** Mean platelet volume; **WBC:** white blood cell

Table 2. Results of univariate and multivariate regression models.

Variable	Youden Index	95% CI	P < 0.05
NLR	0.1141	0.06657 - 0.1813	0.1419
PLR	0.1096	0.06924 - 0.1335	0.3720

NLR: Neutrophil and lymphocyte ratio; **PLR:** platelet and lymphocyte ratio

off points for NLR, PLR, and Free / Total PSA were analyzed by receiver operating curve (ROC) analysis. The optimum cut-off point was determined using the Youden Index criteria. A value of $P < 0.05$ was considered significant. The data were analyzed using the SPSS software program for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The results of 568 patients were evaluated; 287 patients with benign pathology (Group 1) and 281 patients with malignant pathology (Group 2) were separated. The average age of Group 1 was 65 (38-84) years, while that of Group 2 was 67 (45–108) years. The malignant group had a higher average age, and this difference was statistically significant ($p = 0.001$). PSA and Free PSA values, which were higher in malignant group, and prostate volume and Free / Total PSA ratio, which were higher in benign group, were significantly different between two groups (respectively, $p = 0.008$, $p < 0.001$, $p < 0.001$, $p < 0.001$).

Complete blood count parameters between the two groups showed no significant differences (Table 2). Group 1 and Group 2 also had no statistically significant differences between NLR and the PLR results ($p = 0.140$ and $p = 0.369$, respectively) (Figures 1,2).

Discussion

Neutrophil-to-lymphocyte ratio is elevated in gastrointestinal tumors and kidney tumors. When postoperative values are compared with preoperative ones, a predictive value can often be identified. Complete blood count facilitates this simple comparison and is also used to determine the applicability of this ratio. This ratio can also be used in the management of chronic events unrelated to a tumor; for example, NLR is often used as an indicator of cellular immune responses. Neutrophil-to-lymphocyte ratio does not provide a complete predictive value, but it offers some information about the progression of the disease. Cancer cells

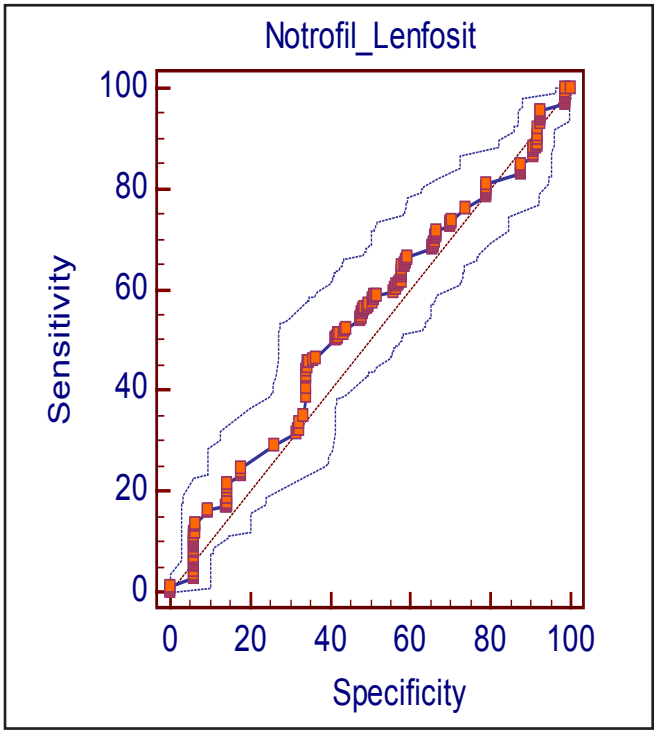

Figure 1. ROC analysis for neutrophil to lymphocyte ratio. **NLR:** Neutrophil/Lymphocytes P=0.14.

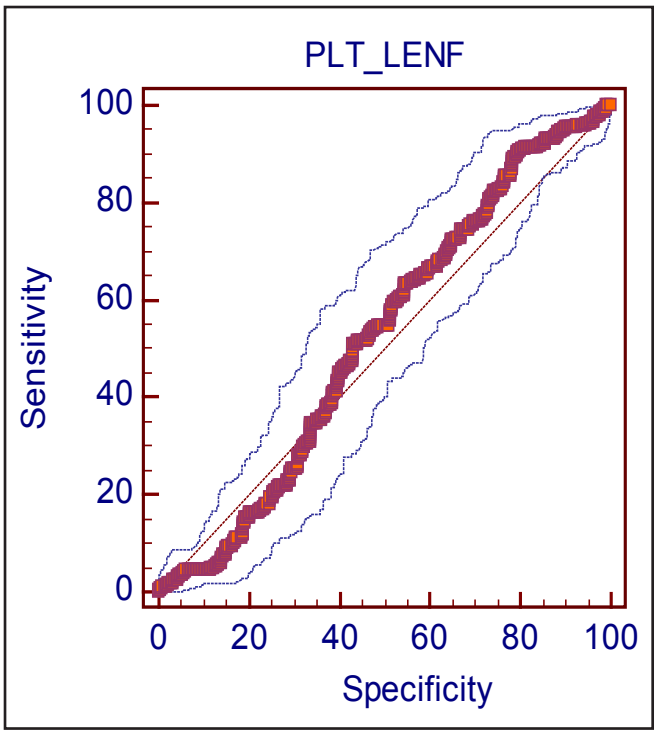

Figure 2. ROC analysis for platelet to lymphocytes ratio. **PLR:** Platelet and lymphocyte ratio P=0.369.

in peripheral blood impact the number of circulating erythrocytes, leukocytes, and platelets. However, the reason for the increase in the number of neutrophils and monocytes remains unclear.

The proliferation of leukocytes can be partially explained by the action of cytokines [8]. The epithelium-originated malignant tumors, such as those in stomach, liver, colon, lung, pancreas, esophagus, bladder, and gallbladder, have been reported to be a result of chronic inflammation; pruning leads to an increase in the number of leukocytes [9-11]. Margalis and colleagues reported that in endometrial cancer patients, neutrophils, monocytes, and the average number of leukocytes were significantly higher than in healthy individuals [11]. Although the exact underlying mechanism is unclear, activated monocytes and the movement of neutrophils into the neoplastic tissue have been suggested to cause a toxic granular inflammation [12-14]. Other studies have shown that inflammatory processes involving cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and kappa B (NF-KB) play an important role in the different types of gynecological cancers [14-16]. At the same time, increased neutrophil count was a strong and independent prognostic factor predicting recurrence in the patients with head and neck tumors and kidney tumors, as well as cancer-specific and overall survival [17-19].

A few studies have investigated the relationship between chronic inflammation and prostate cancer [20]. To date, several biochemical markers that might play a role in prostate cancer carcinogenesis have been examined. In a study reported by Mengus and colleagues that was conducted in patients with localized prostate cancer and benign prostatic hyperplasia (BPH), prostate cancer patients had higher levels of IL-7 [20]. Similarly, according to Bear et al., an increased C-reactive protein (CRP) level was found to be associated with a poor prognosis in metastatic prostate cancer [21]. At the same time, some studies have reported that high levels of neutrophils in gastric cancer patients and in those with low-grade prostate cancer were associated with a good prognosis [22,23]. In addition, a rise in serum PSA levels and a reduction in the number of circulating neutrophils have been associated with poor differentiation in prostate cancer. However, this correlation between the low neutrophil count and poor differentiation was not statistically significant. Moreover, a higher level of neutrophils was found in patients with BPH. In contrast, in our study, the difference between the benign disease group and the prostate cancer group in regards to neutrophil count and NLR was not significant.

In a study by Tanja et al. that was conducted to predict the prognosis of patients with prostate cancer, PLR value was shown to predict disease progression in patients with prostate cancer [24]. Our study focused on the differentiation of benign events from prostate cancer; however, PLR value was unable to assist in this distinction.

Mean platelet volume is an indicator of the average platelet volume. Increased MPV is a marker of young platelets, which are more actively involved in the processes of enzymatic and metabolic homeostasis [25]. Colon cancer may cause inflammation of the colon in patients and result in a constant increase in MPV, and elevated levels of cytokines, particularly IL-6 [26]. Additionally, a decrease in MPV has been found to be associated with the completeness of the resection of cancerous mass in colon; by this relationship, the increase in MPV after colon cancer surgery has been suggested to be used in detection of recurrence in this disease [26]. Moreover, this value could also be used for the monitoring of TNM staging, regardless of whether the colon cancer recurs after surgical resection. On the other hand, in our study, we could not identify any benefit of change in MPV values in the differentiation of benign events from prostate cancer.

The retrospective collection of data, the design of the study in a single center, and the effect of nonspecific inflammatory processes on NLR, PLR, and MPV are the limitations of our study. According to our knowledge, any inflammatory or malignant process could cause an increase of these parameters; therefore, when used alone, these markers appear not to have a positive predictive value in the screening of asymptomatic populations.

Conclusion

Prostate cancers vary greatly in their behavior; thus, this study was unable to identify a positive predictive value for screening of individuals without any

sign, such as the increase in PSA and DRE findings, of this disease. Neutrophil-to-lymphocyte ratio, PLR, and MPV were useful for the differentiation of benign events from prostate cancer, but could not by itself predict whether the disease would progress. To evaluate the diagnostic utility of this method in prostate cancer, a prospective study including a larger number of participants will be required to confirm our findings by using other diagnostic and monitoring tests.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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