Diagnostic and predictive value of inflammatory biomarkers on prior to prostate

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Abstract

Aim: Prostate cancer (PCa) is the second most commonly diagnosed cancer in men. The cost-effectiveness of biomarkers assessed prior to the prostate biopsy is still a matter of debate. The present study aims to investigate the predictive role of inflammation markers that do not involve additional costs, before the first biopsy to increase the detection rates of clinically significant PCa and to avoid unnecessary biopsies.

Materials and Methods: The present study was performed with a total of 236 patients who underwent prostate biopsy between January 2015 and December 2019 and who were selected by a random sampling method. The patients were divided into the two groups of benign (n = 140) and malignant (n = 96) based on the pathology results. Mann–Whitney U test and ROC analysis were used for the statistical analyses. A p value of <0.05 was considered significant.

Results: The median (mean) age of the patients participating in the study was 66 (11) years. Compared to the patients with benign pathology results, the median age, PSA, and PSAD values of the patients diagnosed with PCa were higher, whereas the median PV levels were lower (p: 0.001, p: 0.001, p: 0.001, and p: 0.008, respectively). There was no statistically significant difference between the two groups in terms of inflammation markers levels (p>0.05).

Conclusion: Inflammation biomarkers (NLR, PLR, and SII) assessed before prostate biopsy did not contribute to the predictive factors currently used in the prediction of biopsy results.

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men. Each year, 1.6 million men are diagnosed with PCa, leading to the death of 366,000 men [1]. The gold standard in the diagnosis of PCa is the histopathological examination. The two main factors for prostate biopsy indication are abnormality in digital rectal examination (DRM) and elevated age-related prostate-specific antigen (PSA). PSA is a serum protease secreted from prostate epithelial cells. The rate of PCa diagnosis has increased, thanks to the use of PSA.

PSA is not specific to cancer and is inconsistent as a diagnostic marker owing to its low cancer specificity. However, PSA elevation has a higher predictive power compared to DRM alone [2].

Currently, there is no defined, absolutely accepted biomarker that can distinguish benign from malignant for the diagnosis of PCa. Biomarkers such as prostate-specific antigen density (PSAD), the ratio of free to total PSA (f/tPSA) and 4K score have been used to avoid unnecessary prostate biopsy procedures and to differentiate benign from malignant before biopsy. However, studies on these markers continue, and the need to identify biomarkers that may support or replace PSA in due course remains [3].

In the recent years, relevant studies have reported evidence indicating a strong association between chronic inflammation and cancer [4]. Inflammation is also thought to be involved in the development of PCa [5]. There are several studies in the literature on the predictive power of inflammation markers for prostate cancer, which have investigated many markers such as platelet lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR). In this study, we evaluated for the first time the predictive role of systemic immune-inflammation index (SII) values in distinguishing benign from malignant before the first prostate biopsy.

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Materials and Methods

This descriptive retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (University of Health Sciences Hamidiye Scientific Research Ethics Committee, decision number: 14/30).

Patient population

Between January 2013 and September 2020, 236 patients selected by simple random sampling method from those who underwent prostate biyopsy in our clinic due to abnormality in DRM and/or elevated PSA were evaluated. Two groups were formed according to the pathology results; benign (n=140) and malignant(n=96).

Inclusion–exclusion criteria

Patients who presented to the clinic with lower urinary tract symptoms, who underwent prostate biopsy due to high PSA level and/or abnormal DRM upon physical examination, and who were reported as benign or malignant based on the pathology result were selected by simple random sampling method and included. Patients with a history of prostate biopsy, active infection, a systemic or local treatment for another cancer, and with no available data were excluded. Patients who were not assessed for complete blood count before the prostate biopsy were not included.

Study design

Patients' age, PSA level, prostate volume (PV), and PSAD (PSA/PV = PSAD) as well as the NLR, PLR, and SII values measured based on whole blood assays were compared against the pathology results.

Histopathology results reported as benign prostatic hyperplasia and inflammation were considered benign and included in Group 1. Those results reported as PCa were considered malignant and included in Group 2. Patients with atypical histopathology results were not included in groups.

Statistical analysis

SPSS Statistics version 20.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) and Microsoft Excel software programs were used for the statistical analyses. The normality hypothesis was tested using the Shapiro–Wilk Test during data analysis. Descriptive levels were presented as median and interquartile range for the non-normally distributed data. Mann–Whitney U test was applied to compare the groups according to normality test results. ROC curve analysis was performed to detect of cut-off levels of test variables. $p < 0.05$ were considered statistically significant.

Results

The median age of the patients participating in the study was 66 years. The median PV, PSA, and PSAD values of all the patients included in the study were 44 mL, 6.425 ng/mL , and 0.15 ng/mL/cc , respectively.

Table 1. Descriptive features and statistical analysis of patients in groups according to pathology results.

	Benign (n=140) Median (IQR)	Malign (n=96) Median (IQR)	p
Age (year)	64 (10)	67.5 (11)	0.001*
Prostate volume (ml)	46 (32)	40 (23.75)	0.008*
tPSA (ng/mL)	5.69 (3.80)	8.7 (14.11)	0.001*
PSA density(ng/mL/cc)	0.12 (0.09)	0.24 (0.34)	0.001*

*p<0.05.

Table 2. Inflammatory marker levels of the patients in the groups according to the pathology results and statistical analysis of the two groups.

	Benign (n=140) Median (IQR)	Malign (n=96) Median (IQR)	p
NLR	2.005 (1.14)	2.03 (1.09)	0.557
PLR	105.905 (51.31)	103.42 (57.05)	0.487
SII	434.4589 (296.02)	421.6224 (324.75)	0.793

*p<0.05. NLR: Neutrophil/Lymphocyte Ratio; PLR: Platelet/ Lymphocyte Ratio; SII: Neutrophil x Platelet / Lymphocyte Ratio.
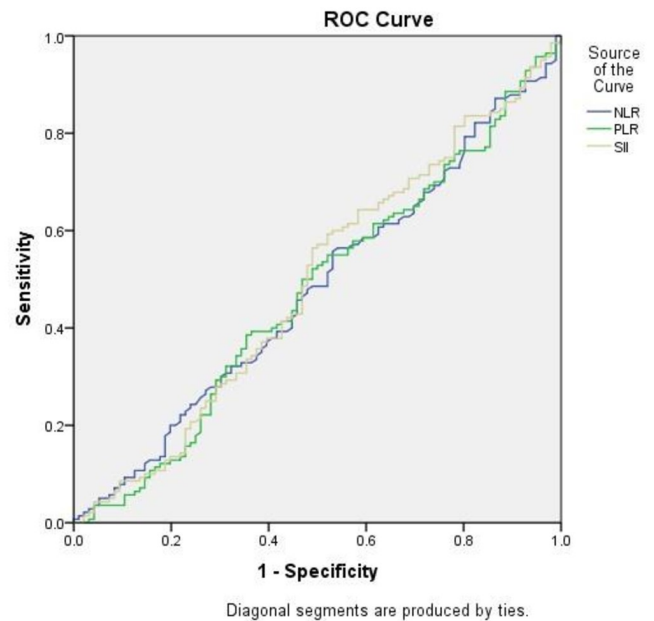

Figure 1. ROC Analysis.

Compared to the patients with benign pathology results, the median age, PSA, and PSAD values of the patients with PCa were higher, whereas the median PV levels were lower (p: 0.001, p: 0.001, p: 0.001, and p: 0.008, respectively) (Table 1).

A statistical comparative investigation of the inflammation biomarkers for both groups indicated that the median NLR, PLR, and SII values were 2 , 105.9, and 434.45 , respectively, for Group 1 and 2 , 103.42 , and 421.62 , respectively, for Group 2. There was no statistically significant difference between the two groups in terms of NLR,

Table 3. ROC analyse and curve of inflammatory marker levels of the patients in the groups according to the pathology results and statistical analysis of the two groups.

Test Result Variable(s)	Area Under the Curve				
	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR	.477	.038	.557	.403	.552
PLR	.473	.039	.487	.398	.549
SII	.490	.039	.793	.414	.566

PLR, and SII levels (p>0.05) (Table 2).

ROC analysis and curve of NLR, PLR, and SII values of the patients in the groups according to the pathology results and statistical analysis of the two groups were summarized in Figure 1 and Table 3.

Discussion

The inflammation effect, which has been frequently implicated in the recent years to be involved in the etiopathogenesis of PCa, is further supported by new biomarkers in the relevant literature. It has previously been reported that prostate cancer was associated with inflammation and that certain inflammation markers were increased in those diagnosed with prostate cancer [6]. Epidemiological studies have shown that chronic inflammation induced by various reasons was one of the greatest risks for cancer development. Accordingly, recruitment of lymphocytes, production of cytokines and chemokines, and inflammatory processes that progress with angiogenesis were valid for prostate cancer similar to other cancers [7]. In the study in which we investigated the predictive effect on PCa diagnosis of SII, a biomarker with recently increased popularity, as well as known parameters such as NLR are PLR that have been previously investigated in the literature, we could not obtain a statistically significant result.

The search for new biomarkers continues due to the relatively limited role of PSA in predicting PCa. Sathinathen et al. investigated biomarkers such as 4K score and Select-Mdx and concluded that the number of unnecessary biopsies decreased from 34% to 24% [8]. The number of studies suggesting that biomarkers using pre-biopsy serum as well as urine samples and genomic biomarkers were successful in predicting PCa and also cost effective is increasing day by day [9,10].

The idea that inflammation biomarkers could be used to predict cancer, prognosis of cancer, survival time, metastasis, and recurrence probability arose based on the information regarding the association between inflammation and cancer. It was concluded in a meta-analysis aimed to predict the prognosis of certain cancer types that an increase in SII level was associated with poor survival [11]. It has also been shown that inflammation markers had an independent role in predicting cancer prognosis and survival [12,13]. Chen et al. suggested that SII values might be helpful in identifying high-risk patients among the patients with the same TNM staging in predicting colorectal cancer survival [14]. A study by Getzler et al., which suggested that elevated NLR value was an important predictor of recurrence in non-muscle invasive bladder cancer, and another study by Lolli et al., which suggested that an increase or decrease in NLR values before and at the 6th week of sunitinib therapy in metastatic renal cell kidney cancer affected survival rates, show that inflammation markers may play a role in cancer follow-up [15,16].

Inflammation biomarkers may prove to be useful in predicting prognosis in patients with metastatic castration-resistant PCa [17,18]. Elevated NLR was associated with poor survival in PCa [19]. Studies on the predictive role of inflammation markers in PCa are limited. These studies are mostly focused on NLR. In a prospective study with 1223 patients, Murray et al. investigated PSAD and circulating prostate cells together with NLR but could not make any differentiation regarding PCa positivity in the first biopsy [20]. Kamali et al. explored NLR and neutrophil count in their study and concluded that there was no predictive value before prostate biopsy [21].

Considering the data in the present study, the effectiveness of inflammatory biomarkers in the diagnosis of PCa was weak. In addition to parameters such as NLR and PLR, which can be effective in predicting the prognosis, survival time, possibility of metastasis, and recurrence of cancer, the pre-biopsy assessment of SII, which has started to prove itself in many stages of PCa, did not make a significant contribution in terms of cancer prediction. SII was the least statistically significant parameter among all three parameters.

Limitations

The limitations of the study include retrospective planning, single-center evaluation, and relatively low number of patients. Notwithstanding these limitations, presenting for the first time the hypothesis that pathology results can be predicted from the evaluation of the SII level before prostate biopsy is the powerful aspect of the study. Prospective studies with large sample sizes are needed.

Conclusion

Inflammatory parameters (NLR, PLR, and SII) assessed before prostate biopsy did not contribute adequately to predict the biopsy results; therefore, the routine assessment of such parameters before biopsy is not recommended. Nevertheless, in the future, the SII may prove to be especially useful in the diagnosis phase as it is relevant in many stages of PCa.

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