RESEARCH ARTICLE

Predictive Value of the Platelet-To-Lymphocyte Ratio in Diagnosis of Prostate Cancer

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Abstract

Purpose: To predict prostatic carcinoma using a logistic regression model on prebiopsy peripheral blood samples. Materials and Methods: Data of a total of 873 patients who consulted Urology Outpatient Clinics of Fatih Sultan Mehmet Training and Research Hospital between February 2008 and April 2014 scheduled for prostate biopsy were screened retrospectively. PSA levels, prostate volumes, prebiopsy whole blood cell counts, neutrophil and platelet counts, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), biopsy results and Gleason scores in patients who had established diagnosis of prostate cancer (PCa) were evaluated. Results: This study was performed on a total of 873 cases, with an age range 48-76 years, divided into three groups as for biopsy results. with diagnoses of benign prostatic hyperplasia (BPH) (n=304, 34.8 %), PCa (n=265, 30.4 %) and histological prostatitis (n=304; 34.8 %). Intra- and intergroup comparative evaluations were performed. White blood cell and neutrophil counts in the histological prostatitis group were significantly higher than those of the BPH and PCa groups (p=0.001; p=0.004; p<0.01). A statistically significant intergroup difference was found for PLR (p=0.041; p<0.05) but not lymphocyte count (p>0.05). According to pairwise comparisons, PLR were significantly higher in the PCa group relative to BPH group (p=0.018, p<0.05, respectively). Though not statistically significant, higher PLR in cases with PCa in comparison with the prostatitis group was remarkable (p=0.067, and p>0.05, respectively). Conclusions: Meta-analyses showed that in patients with PSA levels over 4 ng/ml, positive predictive value of PSA is only 25 percent. Therefore, novel markers which can both detect clinically significant prostate cancer, and also prevent unnecessary biopsies are needed. Relevant to this issue in addition to PSA density, velocity, and PCA3, various markers have been analyzed. In the present study, PLR were found to be the additional predictor of prostatic carcinoma.

Keywords: Prostatic carcinoma - PSA - platelet-to-lymphocyte ratio - neutrophil-to-lymphocyte ratio

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Introduction

Changes in host inflammatory responses and tumor relations have been increasingly recognized in various tumor types and inflammatory cells around the tumor cells play a significant role in the progress and prognosis of tumors. The relationship between systemic inflammation markers and the outcome retains its complexity. Among these markers, increased neutrophil-to-lymphocyte ratio (NLR) may be associated with neutrophil dependent systemic inflammatory response and lower lymphocyte levels with decreased antitumoral immune response which all may correlate with poor prognosis related to aggressive tumour biology and progression of cancer. In the progression of cancer, circulatory neutrophils and mediators such as TNF alpha, IL1, IL6 and in the angiogenesis, vascular endothelial growth factor (VEGF) may play important roles (Mantovani et al., 2008; Jarnicki et al., 2010). Besides, studies performed have shown that increased Neutrophil levels decreased antitumoral immune response (Schaider et al., 2003). Especially in gynecologic malignancies thrombocytosis has been demonstrated as a prognostic criterion of poor outcome (Li et al., 2004; Gorelick et al., 2009). Still some studies have indicated that thrombocytosis is associated with tumour load, while some others have demonstrated that platelets may play a role in tumour burden (Kerpsack and Finan, 2000). Platelets release platelet derived growth factor (PDGF) and thrombospondin (Gungor et al., 2009). PDGF is a potent mitogen for various cell types of the ovarian surface epithelium. Thrombospondin is an adhesive glucoprotein which may increase adhesion of tumoral cells (Gungor et al., 2009). Though these factors seem to explain the association between platelets and cancerogenesis, lack of satisfactory information still exists.

Serum PSA levels may increase in healthy men. It is not prostate cancer (PCa) specific, it is prostate-specific. Meta-analyses performed have shown that in patients with PSA levels over 4 ng/ml, positive predictive value of PSA is nearly 25 percent (Mistry and Cable, 2003).

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In patients whose first biopsy result does not indicate malignancy, recurrent biopsies can detect cancer in 15-34 % of the specimens. (Roehl et al., 2002). Therefore, novel markers which can both detect clinically significant prostate cancer and also prevent unnecessary biopsies are needed. Relevant to this issue in addition to PSA density, velocity and prostate cancer antigen-3 (PCA3), various markers have been analyzed. In the present study our aim is evaluate predictive value of NLR and platelet-to-lymphocyte ratio (PLR) on this issue.

Materials and Methods

Data of a total of 873 patients who consulted to our urology outpatient clinics between February 2008 and April 2014 and scheduled for prostate biopsy because of increased PSA levels were screened retrospectively. For this retrospective study, we reviewed the pathological reports of 873 patients with prostate biopsy between 2008 and 2014 under the permission of the ethical committee of the hospital. Myeloproliferative disorders, autoimmune diseases, splenectomies and patients using drugs which may affect platelet count and function were excluded from the study. At the study period, our standart protocol for transrectal prostat biopsy included followings; After preoperative administration of a single dose antibiotic prophylaxis and distal gastrointestinal system cleaning, all patients underwent standard 12 quadrant prostate biopsy under local anesthesia. Biopsy specimens were evaluated in the same histopathology clinic. PSA levels, prebiopsy whole blood cell counts, neutrophil and platelet counts, biopsy results and Gleason scores (GS) in patients who had established diagnosis of PCa were evaluated. Patients who were diagnosed non-metastatic PCa after performing imaging methods, were included in the study. Besides NLR and PLR were estimated.

PSA is a member of the kallikrein-related peptidase family and is secreted by the epithelial cells of the prostate gland. PSA levels measures in blood samples. PSA is present in small quantities in the serum of men with healthy prostates, but is often elevated in the presence of prostate cancer or other prostate disorders.

Statistical Analysis: For statistical analysis NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used. For the evaluation of data descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) and also for comparison of the variables with non-normal distribution in 3 or more than 3 groups Kruskal-Wallis test was used. For the determination of the group which was the cause of difference Mann Whitney U Test was used. For the assessment of correlations between parameters, Spearman Correlation Analysis was used. Statistical significance was evaluated at $p<0.01$ and $p<0.05$, respectively.

Results

Distribution of biochemical data among groups are shown in Table 1. Age range of the patients was 48-76 years. White blood cell (WBC) and Neutrophil counts were significantly higher in the histological prostatitis group when compared with benign prostatic hyperplasia (BPH) and PCa groups ($p=0.001$, $p=0.004$ and $p<0.01$, respectively). However Lymphocyte counts did not differ statistically significantly among groups ($p>0.05$). A statistically significant difference was not detected as

Table 1. Evaluation of Biochemical Parameters

	[1]BPH (n=304) Mean±SD (Median)	[2]Prostate Cancer (n=265) Mean±SD (Median)	[3]Histological Prostatitis (n=304) Mean±SD (Median)	[a]p	[b]Post hoc Evaluation
WBC	7632.3±2099.2 (7300.0)	7733.2±2200.6 (7500.0)	8506.5±2949.1 (7900.0)	0.001**	1<3=0.001** 2<3=0.004**
NEUTROPHIL	4715.3±1761.6 (4400.0)	4860.7±2005.9 (4500.0)	5607.5±2901.4 (4850.0)	0.002**	1<3=0.001** 2<3=0.006**
LYMPHOCYTE	2154.9±769.2 (2100.0)	2017.3±679.1 (2000.0)	2081.9±847.3 (1950.0)	0.166	-
PLT	236870.7±65861.0 (226000.0)	239479.2±65511.5 (230000.0)	232296.0±7837.5 (220000.0)	0.094	-
HCT	54.9±5.9 (42.5)	41.5±4.3 (42.0)	41.2±4.9 (42.0)	0.003**	1>2=0.019* 1>3=0.001**
PSA	9.4±9.7 (7.3)	29.9±45.9 (9.2)	10.4±18.7 (7.3)	0.001**	2>1=0.001** 2>3=0.001**
NLR	2.5±2.1 (2.0)	3.0±3.8 (2.2)	3.5±4.0 (2.4)	0.004**	1<3=0.001** 2<3=0.094
PLR	124.4±76.2 (108.2)	134.4±70.7 (118.2)	136.5±115.8 (108.3)	0.041*	2>1=0.018* 2>3=0.067

[a]Kruskal Wallis Test; [b]Mann Whitney U Test; *p<0.05; **p<0.01; WBC: white blood cell counts; Plt: platelet; Hct: hematocrit; PSA: prostate- specific antigen; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; BPH: Benign prostatic hyperplasia; Neu: Neutrophil; Lym: Lymphocyte

for platelet counts between groups, while platelet counts in cases with PCa group were remarkably higher than the histological prostatitis group (p=0.094 and p>0.05, respectively).

A statistically and extremely significant difference was detected between groups as for PSA measurements (p=0.001 and p<0.01, respectively). PSA measurements of the cases in the PCa group were significantly higher in the groups with BPH and histological prostatitis (p=0.001, p=0001 and p<0.01, respectively).

NLR values were statistically and extremely significant different between groups (p=0.004 and p<0.01, respectively). NLR estimates in the group with histological prostatitis were significantly higher than those of the BPH group (p=0.001 and p<0.01, respectively). Increased NLR estimates of the cases in the histological prostatitis group relative to the PCa group were remarkable, though not statistically significant (p=0.094 and p>0.05, respectively).

PLR values were statistically significantly different between groups (p=0.041 and p<0.05, respectively). PLR values of the cases in the PCa group were significantly higher when compared with the BPH group (p=0.018 and p<0.05, respectively). Higher PLR values in the PCa group relative to the prostatitis group were striking, though not statistically significant (p=0.067 and p>0.05, respectively).

PSA values over 4 ng/ml has a 98.1 % sensitivity, 1.97 % specificity, 30.3 % positive and 70.6 % negative predictive values with a test accuracy of 31.16 percent.

Cut-off value of PLR in the detection of prostate cancer has been determined as 110 with a 60.75 % sensitivity, 51.64 % specificity, 35.38 % positive, and 75.12 % negative predictive values with a test accuracy of 54.41 percent.

Mean NLR values of patients with and without prostate cancer were 3.03±3.88 (2.27) and 3.04±3.28 (2.21), respectively without any significant intergroup difference (p:0.944; p>0.05)(Table 4).

In the BPH group; A weakly positive but statistically significant correlation was found at a level of 15.5 % between PSA and NLR values. (PSA levels increased in parallel with NLR) (r=0.156, p=0.007 and p<0.01, respectively). A weakly positive but statistically significant correlation was found at a level of 15.5 % between PSA and PLR values (PSA levels increased in parallel with PLR) (r=0.156, p=0.006 and p<0.01, respectively) (Table 2).

In the PCa group; A positive correlation between PSA and NLR at a level of 11.0 % was not found to be

Table 2. Analysis of the Correlations among PSA, NLR, PLR and Gleason Scores for BPH, Prostatitis and Prostate Cancer

	PSA			GLEASON SCORE
	BPH	Prostate cancer	Histological Prostatitis	Prostate cancer
NLR				
r	0.156	0.11	0.162	0.048
p	0,007**	0.074	0,005**	0.441
PLR				
r	0.156	0.144	0.097	0.033
p	0,006**	0,019*	0.092	0.597
PSA				
r				0.436
p				0,001**

r= Spearman Correlation Coefficient; *p<0.05; **p<0,01; PSA, prostate-specific antigen; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; BPH: Benign prostatic hyperplasia

Table 3. Analysis of the Correlations among BPH and PCa

	BPH (n=304)	Prostate Cancer (n=265)	p
	Mean±SD (Median)	Mean±SD (Median)	
NLR	2.54±2.15	3.03±3.88	0.121
	-2	-2.2	
PLR	124.4±76,2	134.4±70.7	0.018*
	-108.2	-118.2	
PSA	9.47±9.78	29.9±45.9	0.001**
	-7.3	-9.2	

*Mann Whitney U Test; *p<0,05; **p<0,01; PSA: prostate- specific antigen; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; BPH: Benign prostatic hyperplasia; Pca: Prostate cancer

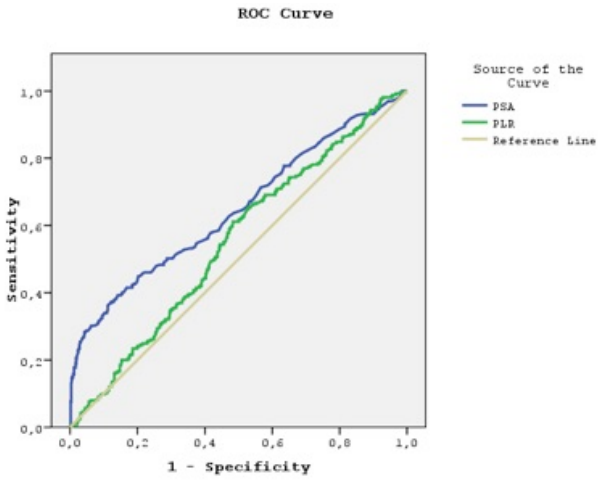

Figure 1. PSA: prostate- specific antigen; PLR: Platelet/lymphocyte

Table 4. Degrees of Sensitivity, Specificity, PPV, NPV and Accuracy for PSA, and PLR

	Sensitivity	Specificity	PPV	NPV	Accuracy
PSA>4 ng/ml	98.1	1.97	30.3	70.6	31.16
PLR>110	60.75	51.64	35.38	75.12	54.41

*PSA, prostate- specific antigen; PPV, positive predictive value; PLR, platelet- to- lymphocyte ratio; NPV, negative predictive value

statistically significant (unidirectional increases in PSA levels and NLR values) (r=0.110; p=0.074; p>0.05). A weakly positive correlation (parallel increases in both PSA and PLR values) between PSA and PLR was found to be statistically significant at a level of 14.4 percent (r=0.144; p=0.019; p<0.05 and r=0,436; p=0.001, p<0.01, respectively). A statistically significant correlation was not detected between GS, NLR and PLR (r=0.048, and r=0.033, respectively; p>0.05) (Table 2).

In the histological prostatitis group; Positive correlation (concurrent increases in PSA and NLR) between PSA and NLR at a level of 16.2 % was found to be statistically significant (r=0.162; p=0.005 and p<0.01, respectively). Positive correlation (concurrent increases in PSA and PLR) between PSA and PLR was remarkable but not statistically significant (r=0.097; p=0.092 and p>0.05, respectively) (Table 2).

For the BPH - PCa Groups; NLR estimates between groups did not differ statistically significantly (p>0.05). However a statistically significant difference was detected as for PLR values of groups (p=0.018 and p<0.05, respectively). PLR estimates in the prostate cancer group were higher than the BPH group. PSA measurements of the cases differed statistically and extremely significantly between groups (p=0.001 and p<0.01, respectively). PSA measurements of the cases in the prostate cancer group were significantly higher relative to the BPH group. PLR and PSA parameteres were detected to be statistically significant in the detection of BPH and Pca (p=0.018, p=0.001 and p<0.05, respectively) (Table 3).

Area under curve (AUC) value for PSA was 0.647 with a standard error of 0.021 (95% CI 0.605-0.689). AUC for PLR was 0.551with a standard error of 0.021 (95 %CI 0.510-0.592). When areas under curve for PSA and PLR were analyzed using ROC curve analysis, a statistically significant difference was found between both AUC values (p:0.001; p<0.01) (Figure 1).

For the BPH – Histological Prostatitis Groups; A statistically significant and extremely meaningful intergroup differences were found between NLR estimates (p=0.001 and p<0.01, respectively). NLR values in the prostatitis group were significantly higher when compared with the BPH group. A statistically significant difference was not detected between groups as for PLR estimates and PSA levels (for both, p>0.05). NLR parameter was found to be statistically significant for the detection of both BPH and histological prostatitis (p=0.001 and p<0.01, respectively). Area under ROC curve was calculated as 57.7 % with a standard error of 2.3 percent.

For the Groups with PCa and Histological Prostatitis; Any statistically significant intergroup difference was not found as for NLR and PLR estimates (p>0.05). A statistically and extremely significant intergroup difference was found regarding PSA levels (p=0.001 and p<0.01). PSA levels measured in the prostatitis group were significantly lower when compared with the prostate cancer group. Since significant differences were not detected between groups with prostate cancer and histological prostatitis as for NLR and PLR estimates, evaluations based on a ROC curve could not be performed.

Discussion

Serum PSA levels may increase in without any clinical prostatic disease men. However in our study, PCa detection rate was 34.8 percent. In an epidemiological study, patients with higher PSA, but without any clinical prostatic disease were analyzed as for systemic inflammation markers. This study demonstrated that higher serum PSA levels were correlated with especially fibrinogen and NLR (McDonald et al., 2014). However in our study, intergroup correlations with respect to PSA and NLR values were evaluated. Contrary to insignificant correlation in BPH groups, a statistically significant positive correlation was found as for PSA and NLR values in the histological prostatitis and BPH groups. However considering PLR values, a weak correlation was observed in the histological prostatitis and BPH groups, while statistically significant correlation was detected in the prostate cancer group. Current studies analyzing the correlations between inflammation and PCa have demonstrated the presence of a correlation between NLR and metastatic PCa resistant to castration (Gueron et al., 2012; Nuhn et al., 2013; Templeton al., 2014; Sonpavde et al., 2014; Sumbul et al., 2014; Keizman et al., 2014). Similar studies indicated C- reactive protein (CRP) as an indicator of poor prognosis in metastatic prostate cancer (Prins et al., 2012; Pond et al., 2012). A study analyzed 5-year survival and cancer aggressivity in PCa patients and demonstrated that Glasgow prognostic score (GPS) was more effective in the prediction of these parametres than NLR (Shafique et al., 2012). The same authors performed a study on 5-year survival rates and revealed that GPS score was especially more significant in low-risk Pca (Shafique et al., 2013). In a study performed on one of urological malignancies i.e. localized renal clear cell cancer, potential importance of GPS during follow-up period of curative nephrectomy was demonstrated. Necessity of closer monitorization of the patients especially with GPS scores indicating high-risk patients was emphasized (Tai et al., 2014).

Even though, many studies have demonstrated the association between systemic inflammation markers as NLR and PLR in various malignancies, hypothetical interrelationships have not been accepted completely. Therefore, we think that studies on prostate tissue which is the only tissue that yields clinical manifestations in both malignant and benign conditions, can convey important implications. Relevant to this issue, in a study comparing BPH and PCa, higher IL-7 levels in the PCa patients were detected (Mengus et al., 2011). In another study, increased Neutrophil counts were demonstrated as a good prognostic criterion of BPH (Fujita et al., 2014). In another study performed by the same authors, increased PSA and lower Neutrophil values were reported as indicators of poorly differentiated Pca (Fujita et al., 2012). Also in this study, lower Neutrophil counts were demonstrated in PCa, rather than BPH. Some studies indicated that higher Neutrophil counts herald benign prostate biopsy and asserted that lower Neutrophil counts and higher serum PSA levels were strong indications for prostate biopsy (Fujita et al., 2012). In our study, any significance was observed between groups with BPH and PCa regarding Neutrophil

counts and hence NLR, while PLR differed statistically significantly between these groups. In the same group a weakly positive (increase in PSA levels in parallel with PLR) correlation between PSA and PLR at a level of 14.4 % was found to be statistically significant. However a significant correlation was not detected among GS, NLR and PLR.

The pathogenesis of PCa and BPH is still largely unresolved. The common key mechanisms involved in the development and progression of PCa and BPH are represented by ageing, hormonal alterations, metabolic syndrome and inflammation (Kramer et al., 2007). Currently, a vast literature suggests a link between chronic inflammation and prostatic disease (Palapattu et al., 2005; Karazanashvili, 2008). However, whether intraprostatic inflammation may contribute to carcinogenesis and hypertrophy of prostate is still unknown. In our study, a very strong and statistically significant difference was detected between NLR measurements in groups with BPH or histological prostatitis. PSA measurements did not differ statistically significantly between groups. NLR and PLR estimates of the cases did not reveal statistically significant differences between groups with PCa and histological prostatitis. However a statistically and extremely significant difference was detected between PSA values of these groups.

Studies on responses to cancer and systemic inflammatory markers have gained increasing popularity recently, and have taken their place in the current urology practice. These markers have been studied in every type of urological malignancy and even BPH. (Tanik et al., 2014). These studies make contribution to the diagnostic, prognostic and therapeutic armamentorium. Recently, within this concept, thanks to the development of treatment modalities as sipuleucel-t immunotherapy, survival rates in patients with urinary cancers improved considerably (Kantoff et al., 2010).

It is well known from our daily practice that the diagnosis of PCa made by prostate biopsies after elevation of psa levels and/ or suspicious digital rectal exemination. However, despite of the new markers and imaging methods, unnecessary biopsy rates are still considerably higher. In this study each BPH, histological prostatitis and PCa groups were evaluated individually and comparatively in terms of NLR and PLR. The main purpose of this evaluation was to separate benign and malignant tissues by a simple blood examination.

Relevant to this issue in addition to PSA density, velocity and prostate cancer antigen-3 (PCA3), various markers have been analyzed. In the present study, PLR were found to be the additional predictor of prostatic carcinoma and can prevent unnecessary biopsies in the diagnosis of PCa. Furter prospective studies are needed to confirm this topic.

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