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# Benign prostatic hyperplasia and prostate cancer differentiation via platelet to lymphocyte ratio

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**Abstract.**
**BACKGROUND:** The aim of the current study is to evaluate NLR and PLR inflammation markers in PCa and BPH.
**METHODS:** Clinical and pathological data such as age, prostate volume, PSA, NLR, and PLR levels of 201 patients were retrospectively reviewed. Pathological sample results of these patients were categorized either as benign or malign. The benign group consisted of chronic prostatitis and BPH and the malign group of PCa. The PSA levels were divided into three categories as PSA: 0–4 ng/ml, PSA: 4–10 ng/ml, and 10 ng/ml and above.
**RESULTS:** In the benign category, the mean PLR values for PSA: 0–4 ng/ml is 131.8 $\pm$ 31.2, for PSA: 4–10 ng/ml 124.7 $\pm$ 83.9 and 10 ng/ml and above 124 $\pm$ 53 in chronic prostatitis group and in the BPH group for PSA: 4–10 ng/ml 120.3 $\pm$ 45.1, for PSA: 4–10 ng/ml 126 $\pm$ 54,2,and 10 ng/ml and above 191.4 $\pm$ 176.1. In the malign category, the mean PLR values of PCa patients is for PSA: 0–4 ng/ml 122.8 $\pm$ 43.8, for PSA: 4–10 ng/ml 123 $\pm$ 43.8, and above 10 ng/ml 179.1 $\pm$ 94. Related to the variables of age, NLR, and mean prostate volume, there were no statistically significant differences. Statistically significant differences were observed in the mean PLR values only if the PSA level was 10 ng/ml and above (p: 0.044) in the BPH and PCa groups. The correlation of the PCa Gleason score and PSA, NLR and PLR parameters in the malign category revealed no statistically significant differences ($P > 0.05$).
**CONCLUSION:** Effective malign and benign differentiation of prostate pathologies based on noninvasive inflammation biomarkers such NLR and PLR necessitate clinical studies with larger patient series.

Keywords: Benign prostatic hyperplasia, prostate cancer, platelet to lymphocyte ratio

## 1. Introduction

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are among serious health problems emerging with old age in the increasing male population worldwide. BPH and PCa are both epidemiologically and histopathologically hormone dependent diseases and prostatic inflammation associated chronic diseases requires long time both for development and progression [1]. In both malign and benign prostate diseases there is an imbalance between prostate cell growth and apoptosis because of intrinsic and extrinsic factors having a direct or indirect impact on prostate tissue growth and differentiation. Moreover, the microenvironment of the prostate cells significantly contributes to cell growth and differentiation [2].

Although definite malign and benign differentiation is only possible with histopathologic evaluation, to avoid unnecessary biopsies, prediagnostic nomograms taking factors such as age, race, family history, digital rectal examination (DRE), PSA, PSA intensity, and

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TRUS findings are proposed [3]. Out of these factors, PSA is widely used in PCa prediction. Hereby, the routine practice is for patients with PSA levels of 4.0 ng/ml and above is needle biopsy. However, several reports reveal the possible contribution of histological inflammation within the prostate to abnormal PSA elevation of [4].

To clarify the interaction mechanisms between chronic inflammation and BPH or PCa, various biomarkers such as IL-6, interleukin 8 (IL-8), CRP, and transforming growth factor beta (TGF-$\beta$), amalondialdehide have been reported [5]. Secreted group IIA phospholipase A2 (sPLA2-IIA), and CRP serum levels of BPH and PCa patients are significantly higher than those of healthy individuals; yet, concentrations of these inflammatory biomarkers do not vary between BPH and PCa patients [6]. Increased ferritin, LDH, CRP, ESR, IL-1a, and IL-6 levels, associated with chronic infections, are also associated with reactive thrombocytosis (RT). RT is seen in clinical situations including chronic inflammation and malignancy [7,8]. It is considered to be related to the excessive production of some hematopoetic growth factors that act on megakaryocytes [8].

PSA is the most widely used screening test in PCa; however, elevated serum PSA levels are common in differing urologic conditions, such as BPH, acute/chronic prostatitis, or urinary tract infection. Therefore, PSA related studies, not only enabling more definitive PCa diagnosis but also preventing unnecessary biopsies are still in progress [9]. Compared to men with normal PSA levels, patients with elevated PSA levels had significantly higher serum CRP, plasma fibrinogen, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) means; yet, their lymphocyte counts were significantly lower [10]. Preoperative PLR was also used with CA19-9 marker in periampullary cancer diagnosis. Their combined use revealed positive predictive values and increased specificity rates [11]. PLR can be used for the differentiation of endometrial hyperplasia and endometrial cancer [12].

The aim of the current study is to evaluate NLR and PLR inflammation markers in PCa and BPH patients based on their PSA levels, retrospectively.

## 2. Material and method

Subsequent to local ethics committee approval, clinical and pathological data such as age, prostate volume, PSA, NLR, and PLR levels of the patients' hospitalized between June 2011 and March 2014 were collected in line with convenience sampling method from the medical records archived. Routine full blood count results of the patients intervened for BPH, PCa, or abnormally elevated PSA levels had been collected as part of the pre-intervention protocols such open prostatectomy, radical prostatectomy, transurethral resection, and prostate biopsy. The widely accepted threshold level for biopsy is 4 ng/ml PSA level. PSA levels ranging from 4–10 ng/ml are commonly referred as the diagnostic grey zone and 10 ng/ml and above as the high malignity rate. Thus, pathological sample results were categorized as chronic prostatitis, BPH, and PCa. PSA levels were also categorized PSA: 0–4 ng/ml, PSA: 4–10 ng/ml, and 10 ng/ml and above.

NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count; similarly, PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Patient demographics, pre-intervention full blood count, operative details, and standard histologic tumor characteristics were recorded. The diagnosis of PCa, BPH, and Chronic prostatitis was histologically confirmed according to prostate biopsy, open prostatectomy, transurethral resection of the prostate, radical prostatectomy.

Exclusion criteria were; incomplete pre-intervention laboratory data, incomplete blood count, lack of available medical records, and/or surgical pathological reports. As well as the presence of conditions that may affect the number of leukocytes or proportion of differential count (e.g., immediate past or current history or signs or symptoms of infection, bone marrow or hematologic disorders, steroid intake, or receiving blood transfusion, presence of other cancer types.).

### 2.1. Statistical analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The mean+ standard deviation (SD) of the data was presented. Groups were compared using one-way (ANOVA) analysis of variance for variables that showed a normal distribution differences, followed by a post hoc Turkey multiple comparison test to estimate the significance of between groups, and the Mann-Whitney U test was used for variables that did not show a normal distribution. A correlation analysis between Gleason score and different parameters was performed, calculating Pearson's or Spearman's coefficient as appropriate. Differences were considered to be statistically significant at $P <$

Table 1
Demographic data

| | Chronicprostatitis (n: 15) | | | BPH (n: 110) | | | PCa (n: 76) | | |
|---|---|---|---|---|---|---|---|---|---|
| | PSA: 0–4 | PSA: 4–10 | PSA: >10 | PSA: 0–4 | PSA: 4–10 | PSA: >10 | PSA: 0–4 | PSA: 4–10 | PSA: >10 |
| Age | 66.8 ± 8.9 | 66.4 ± 5.84 | 67.7 ± 5.28 | 65.8 ± 8.9 | 64.7 ± 8.48 | 68.9 ± 9.1 | 71.5 ± 8.1 | 67.1 ± 8.49 | 73.9 ± 7.25 |
| PSA | 1.78 ± 1.1 | 6.37 ± 1.65 | 15.02 ± 6.33 | 1.95 ± 1.01 | 6.23 ± 1.63 | 23.7 ± 16.7 | 1.6 ± 1.27 | 6.45 ± 1.66 | 27.03 ± 18.5 |
| Volume | 98.2 ± 27.2 | 101.5 ± 38.3 | 90.6 ± 33.1 | 88.4 ± 27.8 | 92 ± 31.9 | 105.6 ± 45.8 | 97.3 ± 28.4 | 85 ± 31.3 | 77.1 ± 40.4 |
| NLR | 2.6 ±3 | 2.07 ± 1.65 | 2.88 ± 1.97 | 2.5 ± 1.3 | 2.7 ± 0.92 | 2.84 ± 1.5 | 2.49 ± 0.68 | 2.21 ± 1.48 | 2.59 ± 1.3 |
| PLR | 131.8 ± 31.2 | 124.7 ± 83.9 | 124 ± 53.6 | 120.3 ± 45.1 | 126 ± 54.2 | 191.4 ± 176.1 | 122.8 ± 43.8 | 123 ± 43.8 | 179.1 ± 94 |

Table 2
Univariate and multivariate analyses of the variables according to the Gleason score of the PCa

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | r | p | r | p |
| Age | 0.388 | 0.002 | 0.673 | 0.001 |
| PSA | 0.168 | 0.195 | 0.244 | 0.060 |
| PLR | 0.096 | 0.462 | 0.243 | 0.074 |
| NLR | 0.022 | 0.866 | 0.167 | 0.201 |

0.05. The correlation of the PCa Gleason score and PSA, NLR and PLR parameters were made using multivariate analysis.

## 3. Results

Out of 285 patients, 201 patients meeting the necessary inclusion criteria were included in the present retrospective study. There were 125 patients in the benign category. Out of these 125 patients, 15 were chronic prostatitis and 110 BPH patients. In the malign category, there were 76 PCa patients. The mean age, prostate volume, and serum PSA levels of are presented in Table 1. In the chronic prostatitis group; the mean NLR for PSA: 0–4 ng/ml is 2.6 ± 3, for PSA: 4–10 ng/ml 2.07 ± 1.65, and for 10 ng/ml and above 2.88 ± 1.97. In the BPH group, the mean NLR is for PSA: 0–4 ng/ml 2.5 ± 1.3, for PSA: 4–10 ng/ml 2.7 ± 0.92, and for 10 ng/ml and above 2.84 ± 1.5. In the PCa group, the mean NLR is for PSA: 0–4 ng/ml 2.49 ± 0.68, for PSA: 4–10 ng/ml 2.21 ± 1.48, and for 10 ng/ml and above 2.59 ± 1.3. In the chronic prostatitis group, the mean PLR is for PSA: 0–4 ng/ml 131.8 ± 31.2, for PSA: 4–10 ng/ml 124.7 ± 83.9 and for 10 ng/ml and above 124 ± 53.6. In the BPH group, the mean PLR is for PSA: 4–10 ng/ml 120.3 ± 45.1 for PSA: 4–10 ng/ml 126 ± 54.2, and 10 ng/ml and above 191.4 ± 176.1. In the PCa group, the mean PLR is for PSA: 0–4 ng/ml 122.8 ± 43.8, for PSA: 4–10 ng/ml 123 ± 43.8, and for 10 ng/ml and above 179.1 ± 94 (Table 1). No statistically significant differences were observed between the malign and benign groups in terms of age, NLR, and mean prostate volume. Statistically significant differences were present only in the PSA 10 ng/ml and above groups related to mean PLR-values (p: 0.044). The other PSA level groups revealed no significant differences ($P > 0.05$). Likewise the correlation of the PCa Gleason score and PSA, NLR and PLR parameters made using multivariate analysis revealed no statistically significant differences ($P > 0.05$). Yet, positive correlation was evident for age and Gleason score parameters (r: 0,388 p: 0,002) (Table 2).

## 4. Discussion

BPH and prostate cancer are similar diseases as both emerge with old age are androgen dependent, that respond to androgen-deprivation treatments, share similar genetic alterations, and with inflammation having an important role in both conditions. Yet, differences in the histology and anatomic location of these diseases support the widely accepted belief that BPH does not affect PCa risk [13]. The role of prostatic inflammation, as a crucial part of PCa, BPH pathogenesis, and progression, was indicated in numerous epidemiologic, histopathological, and molecular studies [14]. Histological inflammation distribution in the prostate gland differs significantly according to the prostate volume. The chronic inflammation of the prostate increases from smaller to larger ones, suggesting a simple relationship and correlates with clinical BPH progression. Considering that histological inflammation is related with acinar atrophy, it is apt to increase with age and is associated with PCa distribution [15]. According to National Institutes of Health (NIH) consensus classification, the prevalence of type IV: asymptomatic prostatic inflammation (histological prostatitis) is in fact much higher, as evidenced with studies examining men who had undergone biopsy for PCa due to elevated PSA levels and had tested negative for cancer. Similarly, results from a prospective randomized controlled trial of 328 men with PSA levels between 2.5 and 10 ng/ml and normal DRE indicated that more than 45% of them had leucocytes in

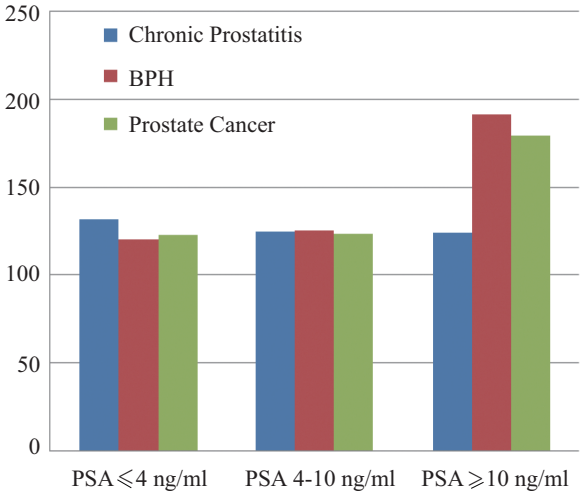


Fig. 1. PLR values according to the PSA levels on different prostatic diseases. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/CBM-150458)

expressed prostatic secretions (EPS). Finally, histological specimens of prostate cancer tissue frequently exhibit unexplained acute and chronic inflammation and lesions [16].

REDUCE clinical trial made with a series of 8,824 patients revealed a high incidence of chronic prostatic inflammation in BPH and confirmed this by comparing prostate volume and IPSS chronic prostatic inflammation reports made by 77.6% of the patients who had undergone prostate biopsies and prostatic inflammation. Inflammation presence was significantly associated with higher prostate volume and higher IPSS score [17]. Likewise a histological examination of 3942 BPH patients revealed prostatic inflammation in 43%. In 69% out of these 43% with prostatic inflammation, it was chronic. In 78% of the patients suffering from chronic inflammation, it was mild inflammation highly associated with age and prostate volume [18].

These studies about the relation between prostatic diseases and inflammation have also led to the emergence of various inflammation markers attempting to clarify this situation.

The presence chronically activated T cells and macrophages in the BPH nodules indicate the association between inflammation and histological BPH [19].

Potential nonspecific BPH markers such as CRP, IL-8, markers of oxidative stress, have been generally evaluated for PCa or BPH. Especially in BPH there is a positive correlation between serum malondialdehyde measures, an index of inflammation and oxidative stress, and PSA. Likewise, serum CRP concentration, a nonspecific marker of inflammation, and lower urinary tract symptoms (LUTS), association suggests BPH [20]. Several cytokines including IL-1, IL-3, IL-6, IL-11, leukemia inhibitory factor (LIF), granulocyte macrophage colony-stimulating factor (GM-CSF) lead to thrombocytosis resulting from chain reactions [21]. In addition IL-1, IL-2, and IL-6 stimulation of megakaryocytes leads to thrombosytosis. The association of thrombocytosis with prognosis that has been shown in numerous studies can be attributed to the fact that an elevated platelet count is an indicator of inflammation severity [22].

Throughout recent years, systemic inflammatory response markers have been studied as prognostic and predictive markers in various cancer populations. Platelets play a key role in hemostasis, inflammation, and recovery in a great variety of cancers. They are activated in inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, arterial thrombosis, asthma, and transplant rejection. In chronic inflammations, the stimulation of megakaryocytes by proinflammatory mediators leads to reactive thrombocytosis [22]. An elevated risk of prostate cancer among men with syphilis, gonorrhea infection related prostatitis history or chronic inflammation suggests a very high association with prostate cancer. This fact demonstrates that chronic inflammation may lead to prostate carcinogenesis [23]. Including homeostasis and inflammation; platelets have various roles in physiological and pathological pathways. Thrombocytosis is related with the majority of all common cancer types including breast, lung, colon, esophageal, gastric, renal transitional cell, endometrial and ovarian cancers, as well for melanoma and glioblastoma [21]. Wang et al. compared NLR and PLR with Glasgow Prognostic Score combined with CRP and albumin as prognostic indicators for gastric cancer patients' survival rates. Glasgow Prognostic Score independently, unlike NLR or PLR, was associated with disease-free and overall survival rates [24].

Although no statistically significant relationship was determined between MPV, NLR, and PLR and histopathological subgroups and TNM stages, elevated serum NLR and PLR might facilitate lung cancer diagnosis [25].

In urogenital cancer types such as prostate cancer and renal cell carcinoma, IL-6 expression directly released from tumor cells have been shown and increased IL-6 levels have significant impact on clinical outcome. Especially serum IL-6 was significantly correlated with the PCa clinical stage [26,27]. In PCa diagnosis, despite the fact that novel genetic and im-

munological biomarkers are developed, they have not become so far a part of routine clinical practice. The Kwon et al. study suggests that PLR compared to NLR was a significant, independent, prognosticfactor in colorectal cancer. Similarly, like in a number of studies using NLR and PLR as prognostic markers, Smith established that PLR was a superior prognostic marker in ovarian cancer and pancreatic cancer [28–30]. PLR had also the potential clinical value in the prognosis of advanced stage disease or suboptimal surgery. PLR was a better indicator of survival rate in ovarian cancer patients compared with thrombocytosis or NLR. PLR, on the other hand had better predictive values for determining surgical outcome or residual disease [31]. Immunohistochemistry marker analyses of 282 patients who were surgically treated for Clinical BPH, revealed that the majority had inflammatory cells infiltrating BPH tissues: 81% had T-lymphocytes markers (CD3), 52% had B-lymphocytes markers (CD20), and 82% had macrophages markers (CD163). IPSS scores and prostate volumes were significantly higher in patients with high-grade prostatic inflammation indicating a strong correlation between histological inflammation, IPSS, and prostate volume [32]. The fact that no statistical differences emerged between NLR, PLR inflammatory markers and prostate volumes in the present study, can be attributed to the fact that all participants had been treated earlier for LUTS symptoms.

Inflammation, by promoting cellular turnover and thus creating a tissue microenvironment inducing cell replication, angiogenesis, and tissue repair, plays a major role in carcinogenesis. An environment rich in proinflammatory cytokines, inflammatory mediators, and growth factors in chronic inflammation are also observed in carcinogenesis. Current data indicate differences in leukocyte/lymphocyte cell subpopulations in the peripheral zone and transitional zone of the prostate. These differences do not clarify which T cells in both zones and which components predispose malignant or benign growth. Moreover, they do not show zone dependent differences in leukocyte/lymphocyte subtypes and what the determining triggers are [33].

In the present study, NLR, an inflammatory marker, revealed no differences regarding BPH and PCa. This can be attributed to the fact that PCa and BPH coexists approximately in 20% of the cases in the same prostate zone and both are related to inflammation [34]. In chronic prostatitis, BPH, and prostate cancer, as a result of the destruction of the prostatic ducts integrity, PSA is released into the blood stream leading to an increase in the PSA quantities [35]. The decrease of PSA threshold level necessitates leads to changing diagnosis demands and unnecessary overtreatment of clinically non-significant prostate cancer.

The National Health and Nutrition Examination Survey (NHANES) determined a significant relation between systemic inflammation markers and elevated serum PSA levels of 4 ng/ml or greater in their survey of 3,164 healthy men aged $> 40$ years without prostatic diseases [36].

The measurement of PSA level has revolutionized PCa diagnosis. Its definite diagnosis depends on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens. The need for prostate biopsies should be determined on the basis of the PSA level and/or a suspicious DRE. However, although PSA levels of 4 ng/ml is widely accepted as threshold level, there is no standard since PCa had been diagnosed in patients with PSA levels under 4 ng/ml because PSA marker is organ but not cancer-specific. Thus, serum levels may be elevated in the presence of BPH, prostatitis and other non-malignant conditions [37]. In the present study, a noninvasive inflammatory marker PLR was statistically significant if the PSA value was 10 ng/ml and above. Yet, it can be only suggested as an additional predictor marker for taking biopsy decision and histopathologic PCa diagnosis.

Therefore, in the current study, in BPH patients with PSA levels of 10 ng/ml and above, PLR levels are significantly higher than that in the PCa group An increase in the histological aggressiveness related to inflammation in the prostate, corresponds to an increase in mean PSA levels [38]. This aspect emphasize a possible correlation between inflammatory effect in prostate tissue and a clinical marker of prostate tissue proliferation and progression such as PSA.

In the current study, NLR, an inflammation marker, was above 2 in BPH, PCa, and chronic prostatitis since it is directly related with inflammation. Thus, in the present study, we assume this to be the underlying reason for the difference PLR in PCa and BPH. There is a high prevalence of chronic inflammation infiltrates in pathologic prostate samples obtained from RP specimens, biopsy, and transurethral resection of the prostate also suggests a link between chronic inflammation and PCa [33]. This is in line with the findings of the present study, since we do expect increases in the PLR levels of PCa patients with PSA levels of 10 ng/ml and above.

## 5. Conlusion

There are many hypotheses about the association of chronic prostatic inflammation with BPH, PCa, or both. Yet, our current knowledge may represent the tip of a large iceberg and further studies on inflammatory responses within the prostate are needed in order to clarify the mechanisms involved in the interaction among inflammatory infiltrates, prostatic stroma, and prostatic epithelium. There is a great demand for noninvasive biomarker clinical studies with larger patient series for the differentiation between benign and malign prostatic diseases. Moreover, understanding the function and role of inflammation will enable elaboration of prostatic disease pathogenesis, histological and clinical progression, and enable risk stratification for PCa and BPH as well as pave the way for novel treatment strategies.

## Conflicts of interest

The authors have nothing to disclose.

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