DOI: 10.37990/medr.944806 Med Records 2022;4(1):16-20

MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Role of Platelet Mass Index in the Differential Diagnosis of Patients with Elevated Prostate-Specific Antigen Levels

Prostat Spesifik Antijen Yüksekliğinde Trombosit Kitle Indeksinin Ayırıcı Tanıdaki Yeri

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Abstract

Aim: To evaluate the role of platelet mass index (PMI) calculated using hemogram parameters obtained from a routine blood test in the differentiation of prostate cancer in patients with prostate-specific antigen (PSA) values of 2.5-10 ng/dl.

Material and Method: Seventy-five patients with prostate cancer and 48 with prostatitis were included in the study and grouped according to their pathology results. The white blood cell (WBC), hemoglobin (HGB), thrombocyte (PLT), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV) and PMI values were compared between the two groups.

Results: The PMI and PLT levels of the prostate cancer group were statistically significantly lower than those of the prostatitis group ($p<0.05$). In predicting prostate cancer, the cut-off value for the PMI level was determined as 1.480, at which the likelihood ratio was calculated as 1.08.

Conclusion: We consider that PMI calculated using hemogram parameters in patients with a PSA value below 10 ng/dl will guide the clinician in differentiating prostate cancer from other prostate pathologies without performing an unnecessary biopsy.

Keywords: Prostate-specific antigen, platelet mass index, prostate cancer

Öz

Amaç: Bu çalışmamızda rutin bakılan bir kan tahlili olan hemogram parametlerinden faydalanılarak hesaplanan Trombosit Kitle İndeksinin 2.5-10 ng/dl arası PSA değerlerinde prostat kanserini ayırt etmedeki rolünü değerlendirmeyi amaçladık.

Bu çalışmanın amacı, embriyonik kemik gelişimi sırasında düşük (3 mg/kg) ve yüksek (6 mg/kg) doz nikotinin neden olduğu iskelet sistemi malformasyonlarını ikili iskelet boyama yöntemi ile belirleyerek; E vitamininin koruyucu rolünü ortaya koymaktır.

Materyal ve Metot: Çalışmaya patoloji sonucuna göre prostat kanseri olan 75 ve prostatit olan 48 hasta dahil edildi. Bu hastalar patoloji sonuçlarına göre gruplandırıldı. White blood cell (WBC) , hemoglobin (HGB), trombosit (PLT) , nötrofil lenfosit oranı (NLR) , trombosit lenfosit oranı (PLR), ortalama trombosit hacmi (MPV), PMI değerleri her iki grup arasında karşılaştırıldı.

Bulgular: Prostat kanserli grubun PMI ve PLT düzeyi prostatit grubundan istatistiksel olarak anlamlı şekilde düşük saptanmıştır ($p<0.05$). Prostat kanserini tahmin etmede PMI düzeyi için cut-off noktası 1480 saptanmış olup, bu noktadaki Likelihood Ratio değeri 1.08 saptanmıştır.

Sonuç: PSA değeri 10 ng/dl altında olan hemogram parametreleri kullanılarak hesaplanan PMI'nın gereksiz biyopsiden kaçınılarak prostat kanseri ayrımını yapmada klinisyene yol gösterici olacağını düşünmekteyiz.

Anahtar Kelimeler : Prostat spesific antijen, trombosit kütle indeksi, prostat kanseri

INTRODUCTION

Prostate-specific antigen (PSA) is a glycoprotein produced by both normal and neoplastic prostate tissues. The main causes of high serum PSA are benign prostatic hyperplasia (BPH), prostate cancer (PCa), prostatitis/prostate infection, and perineal trauma (1). Acute bacterial and/or inflammatory prostatitis is an important cause of increased PSA (1-2). The presence of malignancy should either be confirmed or excluded in patients with elevated PSA. There for prostate biopsy, which is invasive method, should be performed in this patient group. The procedure of transrectal ultrasound (TRUS)-guided prostate biopsy is still accepted as the standard approach in the current

Geliş Tarihi / Received: 30.05.2021 **Kabul Tarihi / Accepted:** 11.10.2021
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guidelines in the diagnosis of prostate cancer (3). However, in addition to various complications, a biopsy can be considered as an uncomfortable procedure for patients. For this reason, various non-invasive strategies have been developed to prevent unnecessary biopsies (4). In addition, various combinations of hemogram parameters have been used to facilitate the differentiation between inflammatory process and malignancy (5), which led to the development of several indexes. Platelet mass index (PMI) is a new parameter that shows platelet (PLT) functions; i.e., the inflammatory process (6). PLTs, which are also a hemogram parameter, play various and important roles in the inflammatory process (7) and also act as a modulator in other cells involved in the response to infection (8). PLTs can also interact with leukocytes and alter their functions. In addition to this parameter, the neutrophil-lymphocyte ratio (NLR) is a well-known indicator of the inflammation cascade.

Considering the complications of TRUS-guided prostate biopsy performed due to elevated PSA, unnecessary invasive procedures should be avoided. As the PSA value increases, the cancer detection rate increases, while the unnecessary biopsy rate increases as the PSA value approaches 2.5 ng/dl. Cancer is not detected in the TRUS biopsy in 60-75% of patients with a PSA value of 4-10 ng/ml (9-10).

In this study, we aimed to evaluate the role of PMI calculated using hemogram parameters obtained from a routine blood test in the differentiation of PCa in patients with PSA values of 2.5-10 ng/dl.

MATERIAL AND METHOD

This study was conducted by Health Sciences University Şanlıurfa Mehmet Akif İnan Training And Research Hospital's Urology Clinic. According to the Declaration of Helsinki, approval was obtained from the ethics committee of Harran University Faculty of Medicine before the study (HRU/20.22.08). The files of 278 patients who presented to the urology outpatient clinic of the university between January 2016 and December 2020 due to increased PSA and underwent a prostate biopsy were retrospectively examined. Patients with additional diseases affecting the inflammation cascade, diabetes mellitus, renal failure or hyper/hypothyroidism, those receiving chemotherapy or radiotherapy, those with extraprostatic cancer, those without hemogram tests before the biopsy, and those with a PSA value of above 10 ng/dl were not included in the study. A total of 123 patients who met the inclusion criteria were included in the study. After the patients were divided into the PCa (n = 75) and prostatitis (n = 48) groups according to their pathology results obtained from their files, white blood cell (WBC), hemoglobin (HGB), PLT, NLR, platelet-lymphocyte ratio (PLR), mean platelet volume (MPV) and PMI values were recorded. NLR was obtained by dividing the neutrophil (NEU) count by the lymphocyte (LYM) count, PLR was calculated by dividing the PLT count by the lymphocyte count, and PMI by multiplying the PLT count by MPV. WBC, HGB, PLT, and MPV were calculated using the results of the hemogram analysis performed on the venous blood taken from the cubital vein.

IBM SPSS Statistics v. 22.0 was used for statistical analyses when evaluating the findings obtained in the study. For the evaluation of the study data, the conformance of the parameters to normal distribution was evaluated with the Kolmogorov-Smirnov test. In addition to descriptive statistical methods (mean and standard deviation), Student's t-test was used for the comparison of the two groups in relation to the parameters showing normal distribution, and the Mann-Whitney U test for the comparison of non-normally distributed data. The receiver operating characteristic (ROC) curve and likelihood ratio methods were used to determine the cut-off value. Significance was evaluated at the $p < 0.05$ level.

RESULTS

The study was conducted between January 2016 and December 2020 with a total of 123 cases, of which 75 were in the PCa group and 48 were in the prostatitis group. The ages of the cases ranged from 52 to 87 years, with a mean value of 65.94 ± 8.73 years.

The mean age of the PCa group was statistically significantly higher than that of the prostatitis group ($p < 0.01$). PSA, NLR, PLR, MPV, WBC, NEU, LYM and HGB levels did not statistically significantly differ between the two groups ($p > 0.05$). The PMI level of the PCa group was found to be statistically significantly lower than that of the prostatitis group ($p < 0.05$). The PLT level of the PCa was also statistically significantly lower compared to the prostatitis group ($p < 0.05$) (Table 1).

Table 1. Comparison of age, PSA and hemogram parameters between the prostate cancer and prostatitis groups

	Prostate cancer	Prostatitis	P
	Mean ± SD (Median)	Mean ± SD (Median)	
Age	68.89 ± 9.01	61.18 ± 5.67	10.001**
PSA	8.89 ± 1.5 (9.5)	8.99 ± 5.47 (8.5)	20.085
NLR	3.30 ± 2.04 (2.42)	4.83 ± 6.24 (2.10)	20.707
PLR	139.67 ± 78.01 (108.3)	152.33 ± 100.59 (128)	20.715
MPV	8.33 ± 1.77	8.55 ± 1.99	10.539
PMI	2136.93 ± 581.11	2466.10 ± 930.27	10.017*
WBC	9.09 ± 2.66 (8.42)	11.50 ± 11.54 (8.51)	20.957
NEU	5.63 ± 2.24 (4.95)	8.42 ± 11.63 (4.86)	20.756
LYM	2.23 ± 0.94	2.34 ± 0.94	10.528
HGB	13.51 ± 1.85	13.56 ± 2.53	10.903
PLT	262.90 ± 69.39	291.41 ± 76.91	10.035*

SD: Standart Deviation 1Student's t-test 2Mann-Whitney U test *p < 0.05 **p < 0.01
PSA: prostate specific antigen , NLR: neutrophil-lymphocyte ratio , PLR: platelet-lymphocyte ratio , MPV: mean platelet volume , PMI: platelet mass index , WBC: white blood cell , NEU: neutrophil , LYM: lymphocyte , HGB hemoglobin: , PLT: platelet

In predicting PCa, the cut-off value for the PMI level was determined as 1,480, at which it had a sensitivity of 0.95, specificity of 0.88, and a likelihood ratio of 1.08. The area under the ROC curve value was determined to be 0.375 (Figure 1).

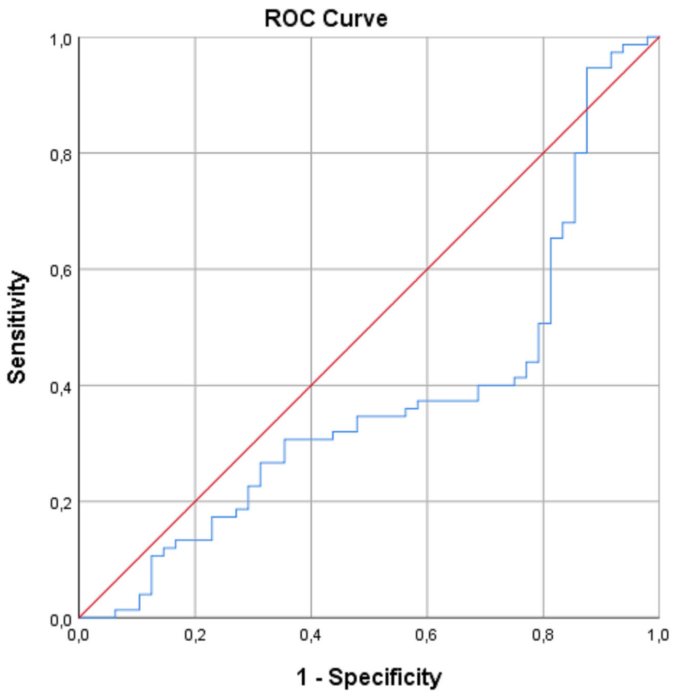

Figure 1. VROC curve and cut-off value calculation for the PMI level in predicting prostate cancer

DISCUSSION

In this study, we determined that PMI calculated using the hemogram parameters obtained before a prostate biopsy could be useful in predicting the biopsy result in patients with a PSA value of 2.5-10 ng/dl. In addition, we found that the number of PLTs was significantly lower in the PCa group compared to the chronic prostatitis group.

Currently, there is no biochemical parameter other than PSA that can predict the prostate biopsy result in PCa (11). The serum PSA level is used for the screening and early diagnosis of PCa. However, as a dilemma, this results in a significant number of unnecessary biopsies, especially when the PSA value is in the range of 4 to 10 ng/ml (12). A transrectal/transperineal prostate biopsy is currently performed to exclude PCa. However, the cost of the biopsy procedure performed due to high PSA values placing a burden on the health system of countries, as well as related complications have led scientists interested in this subject to seek alternative methods. There are publications supporting that PMI, which has recently been introduced, can help differentiate malignant-benign or malignant-inflammatory processes. Many inflammatory biomarkers, such as WBC, NEU, LYM, red blood cell distribution width, and NLR have been used in differential diagnosis studies (13). The ratio of blood cells to each other has been investigated in many cancers (14).

MPV is an early marker of activated PLTs. Lower MPV values suggest increased depletion of large PLTs in inflammatory conditions. Recent studies have confirmed that low MPV levels are associated with high-grade inflammatory diseases and return to their normal range in the anti-inflammatory treatment process (15). When MPV is interpreted together with the PLT count, a more definite result can be reached about PLT function (16). It is known that MPV is associated with PLT function and activation and affected by various inflammatory conditions (17,18). PLTs are circulating cells that play an important role in wound healing, thrombosis, hemostasis, and inflammation (19). Recent studies have found a relationship between PLT activation and the pathophysiology of inflammatory diseases. It is accepted that PLT activity and function are related to PLT size, with larger PLTs being generally younger and more reactive (20-21). It has been reported that the MPV level decreases in high-grade inflammatory conditions due to the predominance of small PLTs in peripheral blood after the increased sequestration and destruction of large and active PLTs in inflammatory areas (22).

MPV is an early marker of activated PLTs. Lower MPV values suggest increased depletion of large PLTs in inflammatory conditions. Recent studies have confirmed that low MPV levels are associated with high-grade inflammatory diseases and return to their normal range in the anti-inflammatory treatment process (15). It is known that MPV is associated with PLT function and activation and affected by various inflammatory conditions (17). Recent studies have shown that MPV is also associated with inflammatory diseases (18). When MPV is interpreted together with the PLT count, it can provide more precise information about PLT function (16). In our study, when comparing the PCa and prostatitis groups were compared in terms of MPV, no significant difference was found, but there was a significant difference in relation to PMI. This shows that assessing the volume and the count together leads to the results being less affected by factors affecting only the volume.

In a study by Fukuokaya et al., MPV was used to predict castration-resistant PCa and it was reported that MPV and PLT count were low in patients with PCa (23). This can be considered to support our findings considering that this situation would result in a decrease in PMI. In addition, since the increase in PLT count in inflammation is proportionally higher than MPV, we indirectly obtained similar results.

Watts et al. found evidence for the relationship of hematological parameters with PCa risk in British men (24). They found that higher red blood cell and PLT counts were associated with a higher risk of PCa while higher mean values of corpuscular volume, corpuscular hemoglobin concentration and spherical cell volume were associated with a lower risk of PCa. In contrast, WBC count was not determined to be associated with a risk of PCa, but higher WBC and NEU counts were related to increased

PCa mortality. Tumors can increase PLT indexes even in the onset period (25). Tumors can also increase the half-life of NEU, which can then promote tumor growth and metastasis (24).

PLTs play an important role in tumor growth and metastasis through tumor cell-derived platelet aggregation. Rudzinki et al. found that increased PLT aggregation in PCa (26), which is in agreement with our results because the number of PLTs in circulation decreases with aggregation, resulting in a lower PMI value.

Fu et al., investigating the role of hemogram parameters in combination with PSA in the differentiation of BPH from PCa, found that MPV was lower and platelet distribution width (PDW) was significantly higher in PCa, and MPV was significantly reduced in patients with PCa compared to those with BPH. In addition, the authors stated that the combination of PSA, MPV and PDW had a significantly increased ability to distinguish PCa from BPH (5). In our study, the difference is that the PSA level was selected from the range considered as the gray zone and we used the mass index including the PLT count in addition to the volume. In our study, there was no significant difference between the PCa and prostatitis groups in terms of NLR and MPV, but a significant difference was observed in PMI.

In another recent study conducted retrospectively, Yüksel et al. also compared the whole blood values of 873 patients who underwent a TRUS biopsy (27). Unlike our study, the authors also included patients with BPH in the sample and found that PLR was the highest in the prostatitis group, followed by the PCa group while the lowest value was obtained from the BPH group (27). In addition, they also examined the PLT level alone and found that it did not significantly differ between the groups but they did not investigate PMI values.

Huang et al. evaluated NLR in 662 patients who underwent a TRUS-guided prostate biopsy (28). When they classified the patients similar to our study, they determined that a high NLR rate, especially in the range of 4-10 ng/dl, was associated with a significant increase in PCa according to the pathology results. Unlike similar publications in which hemogram parameters were evaluated, the authors performed their evaluation according to the PSA ranges. In our study, patients in the same PSA range, which is considered to be the gray zone, was evaluated. The reason for choosing this PSA range in our study is that non-cancerous factors that cause PSA elevation are mostly in this range. In addition, the highest negative biopsy rate is also in this range.

The most important advantage of the platelet mass index is that it is non-invasive and inexpensive, and it can be widely examined wherever a hemogram test can be undertaken. However, the most important disadvantage of the method is that it is not an organ-specific indicator and it is affected by conditions that affect the PLT volume and number. The limitations of the study include the retrospective design, the small number of patients, and the exclusion of patients diagnosed with BPH.

CONCLUSION

We consider that in patients with a PSA value below 10 ng/dl, PMI calculated using hemogram parameters combined with a detailed history and physical examination findings can guide the clinician in the differentiation of PCa from other prostate pathologies and prevent unnecessary biopsies. Further studies with a prospective randomized design and larger series are needed to confirm our findings.

Financial disclosures: *The authors declared that this study hasn't received no financial support.*

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *According to the Declaration of Helsinki, approval was obtained from the ethics committee of Harran University Faculty of Medicine before the study (HRU/20.22.08).*

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