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A Novel Prognostic Indicator in Testicular Cancer Patients: Mean Platelet Volume

Testis Kanseri Hastalarında Yeni Bir Prognoz Göstergesi: Ortalama Trombosit Volümü

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ABSTRACT

Objective: Testicular cancer (TCa) is still the most frequent solid organ cancer in men aged 15-35 years. Mean platelet volume (MPV) alteration is used as an indicator in some cancer. We evaluated MPV levels and their significance as one of the prognostic factors in TCa.

Methods: Between January 2006 and October 2019, all TCa data of our clinic were researched. Total of 133 patients diagnosed with TCa enrolled. Age, tumor size, blood tests, clinicopathological data including lymphovascular invasion, pathological stage, invasion of epididymis, spermatic cord, surgical margin, retroperitoneal lymph node involvement in radiological examinations, and metastasis were recorded. The potential prognostic value of MPV was evaluated using receiver operating characteristics (ROC) curves. Prognostic factors were analyzed. Significant p was p<0.05.

Results: The mean age was 39.22±10.25 years old and optimal cut-off value of MPV for disease-specific survival (DSS) was 7.9 fL in ROC curve analysis. Progression for DSS was worse for decreased MPV in Kaplan-Meier analyses (p<0.001). Univariate analyses showed that preoperative human chorionic gonadotropin and MPV were statistically significant prognostic factors (respectively; p=0.002, p<0.001). MPV was the only factor that was determined as an independent prognostic factor in multivariate cox regression model (p<0.001). The optimal cut-off value of MPV for DSS was 8.37 fL in ROC analysis. Decreased MPV levels also presented poor progression for overall survival (OAS) (p<0.001).

Conclusion: Decreased MPV levels can be defined as one of the risk factors in TCa patients for DSS. There is also a risk of poor OAS in TCa patients with decreased MPV.

Keywords: Mean platelet volume, prognosis, survival, testicular cancer

ÖZ

Amaç: Testis kanseri (TCa), 15-35 yaş arası erkeklerde halen en sık görülen solid organ kanseridir. Ortalama trombosit hacmi (MPV) değişikliği bazı kanserlerde gösterge olarak kullanılmaktadır. TCa'da prognostik faktörlerden biri olarak MPV düzeylerini ve önemini değerlendirmeyi amaçladık.

Yöntem: Ocak 2006 ile Ekim 2019 tarihleri arasında kliniğimize ait tüm TCA verileri araştırıldı. Toplam 133 hasta TCA tanısı aldı. Yaş, tümör boyutu, kan testleri, lenfovasküler invazyon, patolojik evre, epididim invazyonu, spermatik kord, cerrahi sınır, radyolojik incelemelerde retroperitoneal lenf nodu tutulumu ve metastaz gibi klinikopatolojik veriler kaydedildi. MPV'nin potansiyel prognostik değeri, ROC eğrileri kullanılarak değerlendirildi. Prognostik faktörler analiz edildi. Anlamlı p, p<0,05 idi.

Bulgular: ROC eğrisi analizinde ortalama yaş 39,22±10,25 idi ve MPV'nin hastalığa özgü sağkalım (HÖS) için optimal cut-off değeri 7,9 fL idi. DSS için ilerleme Kaplan-Meier analizlerinde azalmış MPV için daha kötüydü (p<0,001). Tek değişkenli analizler, ameliyat öncesi insan koryonik gonadotropini ve MPV'nin istatistiksel olarak anlamlı prognostik faktörler olduğunu gösterdi (sırasıyla; p=0,002, p<0,001). MPV, çok

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değişkenli cox regresyon modelinde bağımsız prognostik faktör olarak belirlenen tek faktördü (p<0,001). HÖS için MPV'nin optimal cut-off değeri ROC analizinde 8,37 fL idi. Azalan MPV seviyeleri ayrıca genel sağkalım (GS) için kötü ilerleme gösterdi (p<0,001).

Sonuç: Azalmış MPV seviyeleri, TCA hastalarında HÖS için risk faktörlerinden biri olarak tanımlanabilir. MPV'si azalmış TCa hastalarında kötü GS riski de vardır.

Anahtar Kelimeler: Ortalama trombosit hacmi, prognoz, sağkalım, testis kanseri

INTRODUCTION

The incidence of the testicular cancer (TCa) is gradually increased and recently the TCa has occurred in 1% of male neoplasms.[1,2] The incidence is slightly higher in men living in industrialized countries.[3,4] The germ cell TCa is more common and at the time of diagnosis 1-2% of the cases are bilateral.[5,6]

To use tumor markers are essential from diagnosis to follow-up period.[6] An increased level of tumor markers shows clear TCa. Alpha fetoprotein (AFP) and human chorionic gonadotropin (β-hCG) increased 50-70% and 40-60% in non-seminomatous germ cell tumor patients, respectively. Additionally, 90% of nonseminomatous germ cell tumor is presented with a rise in one or both of the markers. The β-hCG level may elevate up to 30% in seminoma patients during the disease.[7]

The lactate dehydrogenase (LDH) level depends on tumor volume.[7] Thus, LDH is the less specific marker in TCa. However, low levels of LDH cannot be used to eliminate TCa, high levels of TCa (up to 80%) can be associated with advanced TCa.[7]

The other diagnostic tool is placental alkaline phosphatase (PLAP) and it is frequently used for following up procedures of pure seminoma patients. However, it not useful in smokers.[8] As it is a very well-known surgical treatment, radical orchiectomy is the back bone of the treatment in TCa.[9]

However, the interaction of platelets with other cell types is associated with human carcinogenesis.[10] Besides, this formation provides platelets that are inclusive of the processing process of many malignancies.[10] Platelet activation is determined by counting the numbers and mean platelet volume (MPV).[11] Recent studies have pointed that platelet activation could be part of some processes related to cancer occurrence and its metastasis.[12-14] MPV is altered in several malignancies, however, there is no information about the impact of MPV in survival in TCa patients undergo radical orchiectomy.

We investigated the importance of MPV on survival in TCa patients. We used receiver operating characteristics (ROC) curves and statistical analyse. were Our hypothesis iss lower MPV can be determined by a worse prognosis in TCa.

METHODS

Clinicopathological data of 133 patients who were admitted to the urology outpatient clinic at our university hospital and diagnosed with TCa between January 2006 and October 2019 were evaluated. The clinicopathological information of each patient included age, tumor size, lymphovascular invasion, pathological stage, invasion of the epididymis and spermatic cord, retroperitoneal lymph node involvement, surgical margin, metastasis, blood serum levels (preoperative LDH, β-hCG, AFP, hemoglobin level, MPV and leukocyte) were collected from the patients' medical records. Laboratory data were collected within one week before radical orchiectomy. Exclusion criteria that can affect MPV were diabetes mellitus, smoking, any infections, any hematological disease. The study was approved by our Institute's Ethical Board.

The TCa was classified with using 2009 tumor, lymph node, metastasis classification.[15] Normal range of laboratory tests for β-hCG; <2 mU/mL, MPV; 6.5-12 fL, AFP; 0-8.1 ng/mL and LDH; 125-220 U/L.

The ROC curve was used to determine prediction power of the MPV in TCa. The area under the ROC curve (AUC) was used to calculate the sensitivity and specificity. Multivariate cox regression model was used to define the optimal cutoff of MPV. Kaplan-Meier method was used to assign the impact of the MPV on patient disease-specific survival (DSS) and log-rank test was used to compare the variables.

Statistical Analysis

Statistical analyses were performed with using Statistical Package for the Social Sciences software version 22. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether variables are normally distributed or not. Descriptive analyses were presented using means (±standard deviations) and medians (minimum-maximum).

The univariate analyses of Odds ratios (OR) were calculated for determining the testis tumor patients' prognosis according to overall survival by univariate and multivariate cox regression. For the multivariate analysis, the possible prognostic factors identified with univariate analyses were further entered into the cox regression model. In the multivariate model for patient outcome, OR and

95% confidence interval (95% CI) values were calculated after adjusting for age, preoperative hCG and MPV with enter selection. A 5% type-1 error level was used to infer statistical significance.

RESULTS

The mean age of 133 patients with TCa was 39.22±10.25. The mean follow-up was 40.92±32.28 months (range, 1-124 months). Of the 12 patients died during the follow-up period. For the T stage, 87 patients (65.4%) were stage T1, 34 patients (25.6%) were stage T2 and 12 patients (9.0%) were stage T3. Parameter values of were as follows: hemoglobin 12.53±1.24 g/dL; MPV, 9.1 (5.7-13.7) fL; leukocyte 8.5 (4.64-14.80) K/uL; AFP, 5 (1-54260) U/L; β-hCG, 2 (0-1164157) U/L; LDH, 221 (114-2782) U/L and maximum tumor size, 4.20 (0-17) cm (0.8-5.9 cm) (Table 1).

The cut-off value of MPV was determined as 7.9 fL for DSS (Figure 1; AUC: 0,928, 95% CI: 0.860-0.997). The decreased MPV group showed poor prognosis in DSS (p<0.001) (Figure 2).

On univariate analyses, preoperative HCG and MPV under 7.9 fL were risk factors (Table 2). On multivariate logistic regression model, MPV under 7.9 fL was a statistically significant prognostic factor (OR: 15.838; 95% CI: 3.131-80.102, p<0.001) (Table 3).

DISCUSSION

In this study, we investigated the prognosis of TCa patients according to their MPV values. The diagnosis of TCa is completed with clinical manifestations, laboratory, preoperative radiology findings, biological tissue markers in the pathology specimen.[16] Serum tumor markers are principal tracking tools from preoperative to the end for TCa. Tumor markers need to be recalculated after orchiectomy to determine half-life kinetics. The decrease in tumor markers should be evaluated until the normal range has been measured in patients with clinical "stage 1" disease. Markers are inevitable to determining the level of TCa in patients before chemotherapy.[17] Elevated serum tumor markers may show disease persistence after orchiectomy however normal range cannot be proved of disease-free status exactly.[18] Moreover, serum tumor markers should abate during chemotherapy.[19]

We found preoperative decreased MPV levels were related to poor prognosis in terms of DSS and OSS in TCa patients who underwent radical orchiectomy. The relationship between inflammation and status cancer has been identified.[20] MPV is a marker of activated platelets and decreased MPV levels might be considered an increased consumption of platelets in inflammatory status.[21]

Recent studies concluded that platelet activation is substantial in malignant tumors. Briefly, tumor cells effuse to tissues via blood and platelets are essential part of this process according to malign cells to be aggregated and be leaved from vessels.[22,23] The soluble P-selectin, soluble CD40 ligand, and platelet factor 4 are the major platelet activation indices in cancer patients.[24-26] Moreover, MPV levels were reported as increased in patients with tumor and that showed poor prognosis in gastric cancer patients.[27-29] However, Wang et al.[30] found that decreased MPV was associated with tumor's stage, pathology, and a poor OSS in muscle invasive bladder cancer patients. Seles et al.[31] concluded that small platelet volume was associated

Table 1. Demographic and clinical data of the patients

Age (mean±SD)	39.22±10.25 years
Haemoglobin (mean±SD)	12.53±1.24 g/dL
Mean platelet volume [median (min-max)]	9.1 (5.7-13.7) fL
Leukocyte [median (min-max)]	8.5 (4.64-14.80) K/uL
Preoperative AFP [median (min-max)]	5 (1-54260) U/L
Preoperative b-hCG [median (min-max)]	2 (0-1164157) U/L
Preoperative LDH [median (min-max)]	221 (114-2782) U/L
Tumor size [median (min-max)]	4.20 (0-17)
Lymphovascular invasion (%) **Negative** **Positive**	 87 (65.4) 46 (34.6)
Pathological T stage (%) **T1** **T2** **T3** **T4**	 87 (65.4) 34 (25.6) 12 (9.0) 0 (0.0)
Epididymis invasion (%) **Negative** **Positive**	 122 (91.7) 11 (8.3)
Spermatic cord invasion (%) **Negative** **Positive**	 121 (91.0) 12 (9.0)
Surgical margin (%) **Negative** **Positive**	 130 (97.7) 3 (2.3)
Retroperitoneal lymph node involvement (%) **Negative** **Positive**	 84 (63.6) 48 (36.4)
Lung metastasis (%) **Negative** **Positive**	 115 (86.5) 18 (13.5)
Extrapulmonary metastasis (%) **Negative** **Positive**	 124 (93.2) 9 (6.8)

SD: Standard deviation, AFP: Alpha fetoprotein, βhCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, min-max: Minimum-maximum

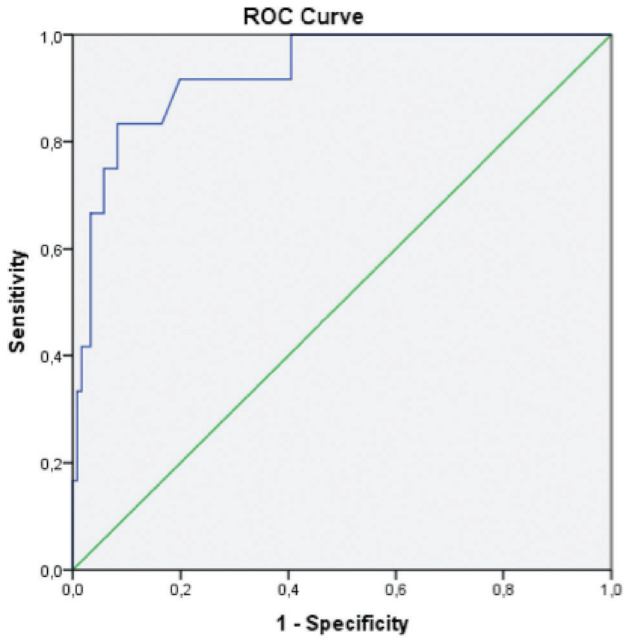

Figure 1. ROC analysis for disease spesific survival according to preoperative mean platelet volume

ROC: Receiver operating characteristic

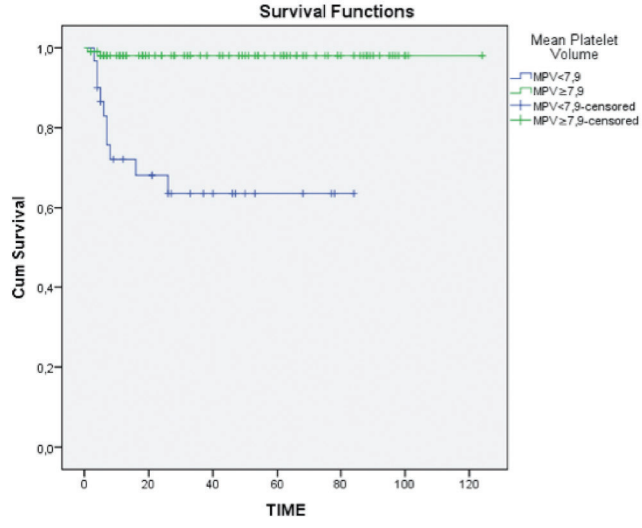

Figure 2. Kaplan-Meier analysis of disease spesific survival according to MPV for testis tumor

MPV: Mean platelet volume

with tumor's diameter, high Fuhrman grade, sarcomatous components, pathologic tumor necrosis and vascular invasion in renal cell carcinoma (RCC). Furthermore, they revealed that CSS and RCC recurrence could be predicted with platelet volume.[31]

Platelets comprise micro-particles that provide interactions between platelets and tumor cells.[32] This is because platelets include growth factors, chemokines, adhesive

Table 2. OR's on univariate and multivariate analyses for disease specific survival in testis tumor patients

Parameters	Disease specific survival (univariate)	
	OR (95% CI)	p value
Age	0.978 (0.922-1.038)	0.467
Tumor size	0.977 (0.798-1.197)	0.824
Preoperative β-hCG (<5000 U/L vs. 5000 U/L≤)	6.369 (2.020-20.078)	0.002*
Lymphovascular invasion (negative vs. positive)	0.871 (0.262-2.893)	0.820
Rete testis involvement (negative vs. positive)	0.769 (0.099-5.959)	0.802
MPV (7.9 fL≤ vs. <7.9 fL)	18.666 (4.088-85.236)	<0.001*
Type of tumor (seminom vs non-seminom)	1.947 (0.527-7.193)	0.318

*Statistically significant p value.

β-hCG: Human chorionic gonadotropin, MPV: Mean platelet volume, CI: Confidence interval, OR: Odds ratio

Table 3. Adjusted OR and 95% confidence intervals for clinical outcomes in testis tumor patients

Parameter	Disease specific survival (multivariate)	
	OR (95% CI)	p value
Preoperative β-hCG (<5000 vs. 5000≤)	1.480 (0.435-5.040)	0.53
MPV (7.9≤ vs. <7.9)	15.838 (3.131-80.102)	0.001*

*Statistically significant p value.

β-hCG: Human chorionic gonadotropin, MPV: Mean platelet volume, CI: Confidence interval, OR: Odds ratio

particles and coagulation factors.[32] After activation, the platelets adhere to tumor cells and to vessel surface.[33] These interactions cause prolonged tumor cell's survival and by this way, platelet aggregation provides tumor cells to more resist against intravascular shear forces and to protect tumor cells from the host's immunity.[34] Platelets may play an important role during cancer progression by using mediators and pathways like in inflammation.[35]

Additionally, platelets indirectly induce phenotypic differentiation to tumor cells by releasing transforming growth factor-β1. Thus, tumor cells might extravasation to distant sites during metastasis. At the end of these process, chemokines, proteolytic enzymes, and microparticles within the microenvironment to promote tumor cell invasion become by secretory factors from activated platelets.[34] By the way, use of antiplatelets is logical as a complementary to cancer adjuvant therapy.[36]

Study Limitations

We know the limitations of this study. Retrospective pattern is the first and small numbers of the patients are the second. Additionally, molecular studies are lacking. However, this is the first study on the impact of the preoperatively assessed MPV on the prognosis of patients with TCa in the literature. MPV is the most commonly used serum biomarker in daily clinical practice. According to our results, decreased level of MPV can be related to poor prognosis in TCa patients. We found that the threshold MPV was 7.9 fL and if the preoperative MPV is lower than 7.9 fL, poor prognosis of TCa might come into question.

CONCLUSION

The decreased preoperative MPV can be an independent prognostic factor in TCa patients who undergo radical orchiectomy. If the preoperative MPV is less than 7.9 fL, DSS would be poor in TCa patients. Our results should be confirmed by large and properly designed prospective, randomized trials with molecular studies to reveal the tangible results of MPV on TCa.

Ethics

Ethics Committee Approval: The study were approved by the İzmir Katip Çelebi University of Local Ethics Committee (protocol number: 169, date: 13.08.2015).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.N.G., Y.Y., Concept: Y.A., O.K., Design: Y.A., S.Ö., Data Collection or Processing: S.N.G., E.M.K., Analysis or Interpretation: E.M.K., O.K., Literature Search: Y.Y., S.Ö., Writing: S.N.G., Y.A.

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