Araştırma

Prognostic significance of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and mean platelet volume in the early stage mycosis fungoides

ERKEN EVRE MİKOZİS FUNGOİDES'DE NÖTROFİL/LENFOSİT ORANI, TROMBOSİT/LENFOSİT ORANI VE ORTALAMA TROMBOSİT HACMİNİN PROGNOSTİK ÖNEMİ

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ABSTRACT

Objective: Mycosis Fungoides (MF) is the most common lymphoma among the primary cutaneous T-cell lymphomas. Although the prognosis is excellent in many patients diagnosed in the early stages, rapid transition to advanced stages may be seen in some patients. Recently, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and mean platelet volume (MPV) have been used as prognostic markers in lymphomas; however, there is no existing data in literature in patients with MF.

Material and Method: The data of patients diagnosed with early stage MF having at least a 5-year follow up in the Skin and Venereal Diseases Department of Dokuz Eylul University Faculty of Medicine were retrospectively reviewed.

Results: Transition to the advanced stages of the disease were observed in 15 (22.4%) of the 67 cases included in the study. The involvement ≥10% of the body surface area, presence of lymphopenia, and increased NLR (>2.60) and PLR (>138.3) were associated with poor prognosis, and NLR was found to be an independent prognostic marker.

Conclusion: NLR and PLR may prove to be a simple and low cost screening method to identify high-risk patients in early stages of MF.

Keywords: Neutrophil, lymphocyte, platelet, platelet volume

ÖZ

Amaç: Mikozis Fungoides (MF), primer kutan T hücreli lenfomalar arasında en sık görülen lenfomadır. Erken evrelerde tanı alan birçok hastada prognoz oldukça iyi olmasına rağmen, bazı hastalarda hızla ileri evrelere geçiş görülebilmektedir. Son zamanlarda nötrofil/lenfosit oranı (NLO), trombosit/lenfosit oranı (TLO) ve ortalama trombosit hacmi (OTH) lenfomalarda prognostik belirteç olarak kullanılmakla birlikte, literatürde MF'li hastalarda bu konuda veri bulunmamaktadır.

Gereç ve Yöntem: Dokuz Eylül Üniversitesi Tıp Fakültesi Deri ve Zührevi Hastalıklar Anabilim Dalı'nda erken evre MF tanısı koyulan ve en az 5 yıllık izlemi olan olguların verileri retrospektif olarak taranmıştır.

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Bulgular: Çalışmaya dâhil edilen 67 olgunun 15 (%22,4)'inde, hastalığın ileri evrelere geçiş gösterdiği belirlenmiştir. Vücut yüzey alanında ≥%10 tutulum, lenfopeni varlığı ve artmış NLO (>2,60) ve TLO'nun (>138,3) kötü prognoz ile ilişkili olduğu, NLO'nun ise bağımsız bir prognostik belirteç olduğu saptanmıştır.
Sonuç: NLO ve TLO, MF'de erken evrelerdeki yüksek riskli hastaları belirlemek amacıyla kullanılabilecek kolay ve ucuz bir tarama yöntemi olabilir.
Anahtar Sözcükler: nötrofil, lenfosit, trombosit, trombosit hacmi

Primary cutaneous T cell lymphomas (PCTL) are a heterogenous group of extranodal non-Hodgkin lymphomas characterized by monoclonal proliferations of T lymphocytes primarily involving the skin at diagnosis. Mycosis fungoides (MF) is the most common PCTL comprising approximately 50% of all primary cutaneous lymphomas and more than 70% of PCTLs. Although MF can occur at any age including the childhood, it is most common in older individuals with a median age at diagnosis of 55 to 60 years, and there is a male predominance with the prevalence being two times higher in men than women are (1, 2).

The onset of MF is generally insidious, typically characterized by progression from a nonspecific phase of erythematous macules to the appearance of infiltrative plaques distributed in non-sun exposed ''bathing suit'' areas, such as the breasts, buttocks, lower trunk, and groin. Early MF is defined as the disease presenting with stage IA (involvement of less than 10% of the body surface area [T1], stage IB (more than 10% of the body surface area [T2]), or stage IIA (palpable adenopathy with a negative node biopsy in T1 or T2 patients); while advanced stage is defined as the presence of tumors (T3/stage IIB), erythroderma (T4/stage III–IV), lymph node involvement (stage IVA), significant blood burden (stage IVA), or visceral metastases (stage IVB). Although most patients in the early stage of the disease show a favorable prognosis and achieve long-lasting remissions with excellent overall survival with current treatment strategies, the disease progresses to an aggressive malignancy with a poor prognosis in approximately one-third of the patients. The outcome of MF is related to the extent of skin, blood, lymph node and visceral organ involvement, but it is impossible to predict which patients will develop severe disease and will be in need of aggressive treatment at the time of diagnosis (2). While patients with limited patches and plaques can be treated with expectant policy, topical therapies (corticosteroids, nitrogen mustard, retinoids), phototherapy or total skin electron beam therapy, patients with more advanced disease need a multispecialty team at tertiary care centers and can be opted for systemic immunomodulatory agents, palliative chemotherapy or radiotherapy (3). Consequently, there is an interest in identifying simple, low-cost laboratory assessments that improve current risk stratification approaches in early-stage MF.

In recent years, increasing attention has been attached to the correlation between cancer and inflammation, which reflects the antitumor activity of the immune system. Recently, the pre-treatment neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been demonstrated to be prognostic in various types of solid tumors, and eventually in non-Hodgkin lymphomas (4-6). In addition, it has been known that platelets have been demonstrated to play an important role in cancer development and progression, and mean platelet volume (MPV) was also found to be an important prognostic factor in patients with lymphoma (7). The prognostic significance of NLR is seldom reported and remains controversial (8, 9), whereas PLR and MPV have never been explored in patients with MF.

In this study, we aimed to determine whether pre-treatment NLR, PLR and MPV are predictive for progression in early-stage MF.

MATERIAL AND METHODS

Study Design

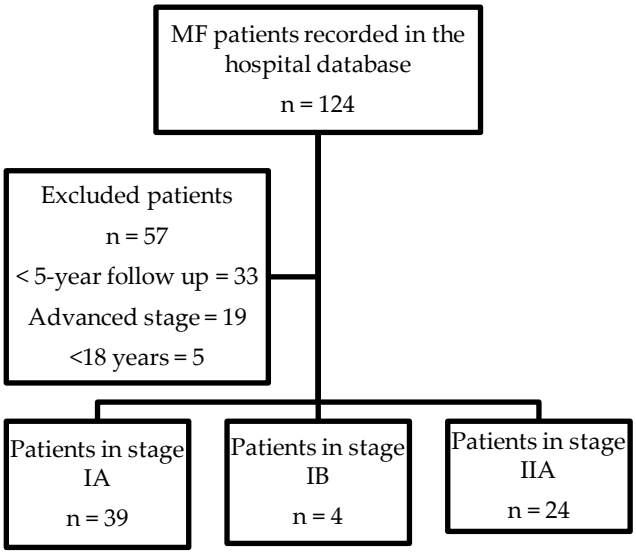
We performed a longitudinal study using retrospective information from electronic medical records of patients with early stage MF treated in Dokuz Eylul University, Department of Skin and Venereal Diseases,

between January 2008 and December 2018. The study protocol was approved by the Local Ethical Committee, which follows the guidelines set by the Declaration of Helsinki.

Collection of the data

The data of 124 histopathologically verified MF patients were reviewed from the medical records of the dermatology department, retrospectively. Inclusion criteria were age >18 years; biopsy-proven diagnosis of MF; no previous treatment; and a follow up period for at least five years. Only the patients in the early stage of the disease (Stage IA-IIA, good risk group) included in the study. Exclusion criteria included presence of immunosuppression; anti-HIV positivity; and transplantation or malignancy in the history. 57 patients were excluded from the analysis because of the lack of ≥5-year follow up period in their file records, having advanced stages of the disease (stage ≥ 2b), and the age criteria of the study. As a result, totally 67 patients were included in the study (Table I).

Table I. Summary of the selection of study population



Demographic and clinical data were collected from patients' file records. Clinical features including duration of MF, percentage of skin involvement (body surface area <10% or ≥10%), stage of the MF, treatment modalities and presence of progress in stage were noted. Lymphocyte, neutrophil, and mean platelet volume counts were obtained from standard complete blood count data before the initiation of the treatment. NLR was calculated using the formula absolute neutrophil count, which was divided through absolute lymphocyte count. PLR was calculated as the absolute platelet count, which was divided through absolute lymphocyte count. ROC curves were used to determine the best threshold values for sensitivity and specificity.

Disease staging in patients

TNMB staging of the cases were performed in accordance with International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) criteria during the first diagnosis (1). The development of tumors, erythrodermia, lymph node or internal organ involvement, and progression to an advanced stage were approved as disease progression.

Statistical Analysis

The statistical analyses were performed with the SPSS/PC software (Version 23.0 for Windows; SPSS Inc., Chicago,Ill). Mann Whitney U-test was used to compare mean values of quantitative variables as the two samples were obtained independently. Qualitative variables were analyzed with chi-squared test and Fisher's exact test. We derived cross-validated areas under the curve (AUC); afterwards we chose the best cut-off values based on the cross-validated sensitivity, specificity and the Youden's indices (sensitivity+specificity−1). Respective NLR, PLR and MPV cut-off values were determined at a point with the maximum Youden's index on the receiver operating characteristic (ROC) curve. The univariate Cox proportional model was applied to identify prognostic factors for disease progression, and variables with statistical significance in the univariate analyses were subsequently used to construct the multivariate Cox model. The results were considered to be statistically significant when the p-value was less than 0.05.

RESULTS

Patient Characteristics

67 patients with MF were involved in the study; 35 (52.2%) were female and 32 (47.8) were male giving a female: male ratio of 1.09: 1. The age range was 22-90 years (58.42±15.15). Based on ISCL/EORTC staging, 39 (58.2%) patients were stage IA, 4 (6%) were stage IB, and 24 (35.8%) were stage IIA. The treatments applied were topical corticosteroids in 15 (22.4 %) patients and PUVA in 55 (77.6%) patients (Table II).

Table II. Clinical and demographic characteristics of the study population

Patient characteristics	
Gender, n (%)	
Female	35 (52.2)
Male	32 (47.8)
Age, mean±SD	58.42±15.15
Age group, n(%)	
<60 years	35 (52.2)
≥60 years	32 (47.8)
Percentage of skin involvement, n (%)	54 (80.6)
<%10	13 (19.4)
≥%10	
Lymphopenia, n (%)	8 (11.9)
Stage, n (%)	
IA	39 (58.2)
IB	4 (6)
IIA	24 (35.8)
Treatment modality	
Topical corticosteroids	15 (22.4)
Phototherapy	52 (77.6)
Progress in disease, n (%)	
Stage IA	5 (12.8)
Stage IB	1 (25)
Stage IIA	9 (37.5)
NLR, mean±SD	2.62 ± 1.43
PLR, mean±SD	146.77 ± 65.57
MPV, mean±SD	8.63 ± 1.78

Overall, disease progression was observed in 15 (22.4%) patients in the present study. Death related to the disease occurred in none of the patients. We found that disease progression was significantly higher in patients with a percentage of ≥10% skin involvement at the time of the diagnosis ($p = 0.006$), and in patients with stage II disease ($p = 0.027$) (Table III).

In complete blood count, lymphopenia was seen in eight (11.9 %) patients, and six of those were among the patients with disease progression ($p = 0.001$). The mean value of lymphocyte count also showed a significant association with disease progression (1.47 vs. 2.18, $p<0.001$), whereas the mean values of neutrophyl and platelet count did not ($p>0.05$).

Determining the Cut-off Values of the NLR, PLR and MPV

ROC curves of the NLR, PLR and MPV according to disease were generated to determine the cut-off values. The area under the curve (AUC) was recorded as 0.80 (95% CI, 0.67-0.93), a NLR value of 2.60 corresponded to the maximum combined sensitivity and specificity on the ROC curve (a 69.2% spesivity and a 73% sensitivity). The AUC was recorded as 0.79 (95% CI, 0.66-0.91), a PLR value of 138.3 corresponded to the maximum combined sensitivity and specificity on the ROC curve (a 69.2% spesivity and a 67% sensitivity). The AUC was recorded as 0.48 (95% CI, 0.31 – 0.66), a MPV value of 8.56 corresponded to the maximum combined sensitivity and specificity on the ROC curve (a 50% spesivity and a 53.3% sensitivity (Figure 1)

Table III. Clinical and demographic differences in patients with and without disease progression

	Patients with progressive disease	Patients without progressive disease	p value
Gender, n(%) Male Female	 8 (25) 7 (20)	 24 (75) 28 (80)	 0.624
Age group, n(%) <60 years ≥60 years	 5 (14.3) 10 (31.3)	 30 (85.7) 22 (68.8)	 0.096
Percentage of skin involvement, n(%) <10% ≥10%	 8 (14.8) 7 (53.8)	 46 (85.2) 6 (46.2)	 0.006*
Stage, n(%) I A, B II	 6 (14) 9 (37.5)	 37 (86) 15 (62.5)	 0.027*
Lymphopenia, n(%) Absent Present	 9 (15.3) 6 (75)	 50 (84.7) 2 (25)	 0.001*
Treatment modality Topical corticosteroids Phototherapy	 3 (20) 12 (23.1)	 12 (80) 40 (76.9)	 1.000
NLR, n(%) ≤ 2.60 >2.60	 4 (10) 11 (40.7)	 36 (90) 16 (59.3)	 0.003*
PLR, n(%) ≤ 138.3 >138.3	 3 (7.9) 12 (41.4)	 35 (92.1) 17 (58.6)	 0.001*
MPV, n(%) ≤ 8.56 >8.56	 7 (21.2) 8 (23.5)	 26 (78.8) 26 (76.5)	 0.820
NLR, mean±SD	3.95 ± 2.16	2.24 ± 0.84	<0.001*
PLR, mean±SD	199.13 ± 75.30	131.66 ± 54.49	0.001*
MPV, mean±SD	8.43 ± 1.04	8.69 ± 1.95	0.839

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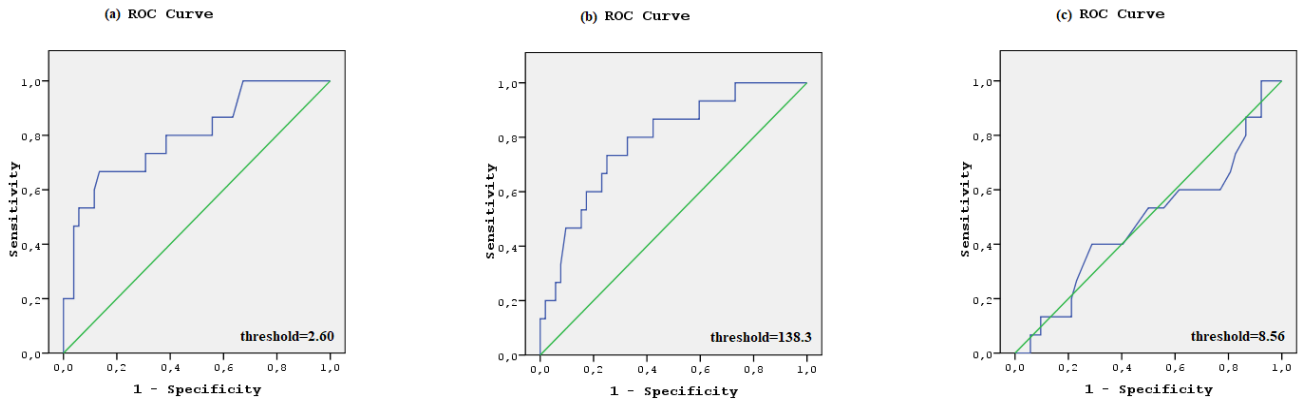

Figure 1: Receiver operating characteristic curve and area under the curve for the NLR (a), PLR (b) and MPV (c) at diagnosis.
Abbreviations: NLR neutrophil/lymphocyte ratio, PLR platelet/lymphocyte ratio, MPV mean platelet volume

Association of NLR, PLR and MPV with disease progression

Both NLR and PLR values were significantly higher in patients with disease progression ($p < 0.001$ and $p = 0.001$, respectively), and the number of patients with higher NLR and PLR values were significantly higher in patients with disease progression compared to the patients without disease progression ($p = 0.003$ and $p = 0.001$, respectively). However, no significant differences were observed in mean MPV and in number of patients with higher MPV between patients with and without disease progression ($p>0.05$) (Table III).

Prognostic Significances of NLR, PLR and MPV in disease progression

In the univariate model, skin involvement ≥10%, presence of lymphopenia, NLR value of >2.60, and a PLR value of >138.3 were found to be the significant prognostic factors for disease progression. Only the variables with statistical significance in the univariate analyses were used in the multivariate model, and NLR continued to be an independent prognostic marker, whereas PLR had less significance and lost its prognostic value in the presence of potential confounding factors (Table III). MPV was not found to be a prognostic marker for disease progression in the univariate analysis ($p>0.05$) (Table IV).

Table IV. Risk factor analysis for progression in patients with MF

Parameters	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Male vs. female	1.25 (0.45 – 3.45)	0.666		
Age, ≥60 years vs. <60 years	2.19 (0.75 – 0.40)	0.153		
Skin involvement ≥10% vs. <10%	3.64 (1.32 – 10.02)	0.013*	1.78 (0.56 –5.70)	0.003*
Stage II vs. stage I	2.69 (0.96 – 7.56)	0.061		
Topical therapy vs. phototherapy	1.58 (0.44 – 5.69)	0.487		
Lymphopenia	4.62 (1.48 –14.51)	0.009*	2.51 (0.62 –10.07)	0.195
NLR >2.60	4.07 (1.30 – 12.80)	0.016*	1.36 (1.06 – 1.74)	0.016*
PLR>138	5.24 (1.48 – 18.57)	0.010*	1.00 (0.99 – 1.01)	0.676
MPV>8.55	1.11 (0.40 – 3.06)	0.841		

DISCUSSION

In the present study, we evaluated the prognostic significances of mean NLR, PLR and MPV values in early stage MF in a sample of patients. Whereas no significant association was found between mean MPV and disease progression in this study, we found that higher NLR and PLR values showed significant associations with disease progression, and NLR was also found to be an independent prognostic marker. Although the association of NLR and PLR with prognosis in hematological malignancies is under strong research interest, only two studies investigated pre-treatment NLR's prognostic role in patients with MF, and revealed conflicting results. Our study adds a new data on the prognostic implication of pre-treatment NLR in patients with MF, and furthermore, this study is the first to evaluate the prognostic association of pre-treatment PLR and MPV in patients with MF.

As a surrogate marker of inflammation, absolute neutrophil count produced by the tumor, is used in the form of peripheral blood NLR at diagnosis to predict the prognosis in many forms of solid organ tumors, and recently in hematological malignancies. The rationale behind using this ratio is to consider the interaction among components of host immunity represented by lymphocytes and inflammation produced by the tumor and the tumor microenvironment. Lymphocytes are the main components of immune cells, which have important anti-tumor effects, and reduced lymphocytes in the blood and in the tumor stroma reflect the down regulation of the immune response against the tumor (4, 5, 7, 10). The prognostic value of NLR in non-hodgkin lymphomas was first demonstrated by Porrata et al. on 255 diffuse large B-cell lymphoma patients (11). After that, this hypothesis was supported from new studies analyzing NLR levels in various types of lymphomas (12-17). Beltran et al studied the prognostic value of NLR on 93 patients with unspecified PTCL (PTCL-U), and commented that NLR could be used as a prognostic factor for survival in patients with a diagnosis of PTCL-U (18).

The first study evaluating the prognostic role of NLR in patients with MF was recently published by the study of Eren et al. including 117 MF patients (60 in stage IA, 18 in stage IB, 35 in stage IIA, 1 in stage IIIA and 3 in stage IVA). The median NLR was 1.96, and the cut-off score for NLR was determined as 2 according to the median NLR level in their study. They found no significant difference in progression in stage, time to progression in stage, treatment demand, and time to treatment between patients with NLR < 2 and NLR ≥ 2 in that study. The subgroup analysis was also done according to the lymph node involvement and on a stage-based approach dividing patients into stage I and stage II. While 17 (28.8 %) patients had lymph node involvement in patients with NLR < 2, 26 (44.8 %) patients had lymph node involvement in patients with NLR ≥ 2. There was no difference regarding progression in stage, time to progression in stage, treatment demand, and time to treatment in patients with NLR < 2 and NLR ≥ 2; either they were stage I or stage II (8). On the contrary, this association was evaluated in a second study conducted by Cengiz et al. including 119 MF patients (56 in stage IA, 21 in stage IB, 21 in stage IIA, 10 in stage IIB, 3 in stage IIIA, 3 in stage IIIB, 4 in stage IVA and 1 in stage IVB). The investigators found that a high NLR at diagnosis of MF was positively correlated with advanced disease stage, and disease progression. The cut-off score for NLR was determined as 2.85 according to the generated ROC curve in their study, and the patients were divided according to this NLR value. The group with a NLR value less than 2.85 contained 92 patients (77.3 %), and the group with a NLR value of 2.85 or more contained 27 patients (22.7 %). They found that a NLR value of 2.85 or higher at diagnosis were positively correlated with elevated Beta-2-microglobulin, advanced disease stage, and disease progression (9). Our result was also similar with this previous study that we also found high mean levels of NLR, and the ratio of patients with a NLR value higher than 2.60 at diagnosis in patients in which the disease progression developed.

As well as NLR, PLR is another commonly used proinflammatory marker, and its value at time of cancer diagnosis has also been reported to predict poor prognosis in patients with various types of malignancies and lymphomas (19-22). Studies on platelets have shown that they might play an essential role in tumor spreading and growth, and preliminarily activated platelets have tumor promoting properties. Because of their greater content in

granules, larger platelet size reflects the increased platelet reactivity, thus the MPV is one of the most commonly used laboratory markers related platelet functions. However, on the contrary of this classical knowledge, recent clinical reports proved the negative effect of a low MPV on the cancer patients with multiple myeloma, non small cell lung carcinoma, and diffuse large B cell lymphoma (23-25). Despite the existence of confusing data in literature, no research has been published to date, evaluating the prognostic role of PLR and MPV in patients with MF. In our study, we did not find any correlation between the MPV and MF progression, while PLR was found to be significantly higher in patients with disease progression. However, in multivariate analysis, PLR had less significance, and did not remain its prognostic value to be an independent prognostic factor in the presence of the potential confounding factors.

This study has some limitations. First, this was a retrospective study with unavoidable selection bias and systematic error; and the recruitment was performed in a single institution, which might have posed a further limitation. The small sample size may render the results inconclusive at most, and the results should be confirmed in larger prospective series. Nevertheless, our study differs from these prior analyses in that it focuses on early stage patients in which lymph node involvement, tumors, and erythroderma were absent at the time of the diagnosis, and we examined both NLR and PLR, as well as MPV simultaneously.

CONCLUSION

In this study, the pre-treatment NLR and PLR were found to be significantly associated with the increased risk of disease progression in early stage MF. Elevated levels of these parameters were associated with poor MF progression on the univariate analysis, however only NLR was found to be an independent prognostic factor in the multivariate analysis. These parameters can be easily determined using widely available complete blood count tests, and can be used as non-invasive, simple and cost-effective alternatives to future risk stratification schema that merit further investigation. Larger prospective studies are necessary to validate the results of our study and to evaluate the exact clinical significance.

REFERENCES

1. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2017. Eur J Cancer 2017; 77: 57 - 74.
2. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 2014; 70: 205.
3. Berg S, Villasenor-Park J, Haun P, Kim EJ. Multidisciplinary Management of Mycosis Fungoides/Sézary Syndrome. Curr Hematol Malig Rep 2017; 12: 234 – 243.
4. Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017; 58: 1 – 13.
5. Deng M, Ma X, Liang X, Zhu C, Wang M. Are pretreatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio useful in predicting the outcomes of patients with small-cell lung cancer? Oncotarget 2017;8:37200-37207.
6. Han Y, Wang J, Hong L, Sun L, Zhuang H, Sun B et al. Platelet-lymphocyte ratio is an independent prognostic factor in patients with ALK-positive non-small-cell lung cancer. Future Oncol 2017; 13: 51 – 61.
7. Reddy JP, Hernandez M, Gunther JR, Dabaja BS, Martin GV, Jiang W et al. Pre-treatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are prognostic of progression in early stage classical Hodgkin lymphoma. Br J Haematol 2018; 180: 545 – 549.
8. Eren R, Nizam N, Doğu MH, Mercan S, Erdemir AV, Suyanı E. Evaluation of neutrophil-lymphocyte ratio in patients with early-stage mycosis fungoides. Ann Hematol 2016; 95: 1853 – 7.

9. Cengiz FP, Emiroglu N, Ozkaya DB, Bahali AG, Su O, Onsun N. Prognostic Evaluation of Neutrophil/Lymphocyte Ratio in Patients with Mycosis Fungoides. Ann Clin Lab Sci 2017; 47: 25 – 28.

10. Zeng Q, Liu Z, Li Q, Liu T. Prognostic value of neutrophil to lymphocyte ratio and clinicopathological characteristics for multiple myeloma: A meta-analysis. Medicine (Baltimore) 2018; 97: e12678.

11. Porrata LF, Ristow K, Habermann T, Inwards DJ, Micallef IN, Markovic SN. Predicting survival for diffuse large B-cell lymphoma patients using baseline neutrophil/lymphocyte ratio. Am J Hematol 2010; 85: 896 – 9.

12. Wang S, Ma Y, Sun L, Shi Y, Jiang S, Yu K et al. Prognostic Significance of Pretreatment Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Patients with Diffuse Large B-Cell Lymphoma. Biomed Res Int 2018; 2018: 9651254.

13. Koh YW, Kang HJ, Park C, Yoon DH, Kim S, Suh C et al. Prognostic significance of the ratio of absolute neutrophil count to absolute lymphocyte count in classic Hodgkin lymphoma. Am J Clin Pathol 2012; 138: 846 – 54.

14. Lee SF, Luque-Fernandez MA. Prognostic value of lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio in follicular lymphoma: a retrospective cohort study. BMJ Open 2017; 7: e017904.

15. Kaito S, Kanemasa Y, Sasaki Y, Okuya T, Yamaguchi T, Funasaka C et al. A new prognostic score comprising lactate dehydrogenase, albumin and neutrophil to lymphocyte ratio to predict sensitivity to first-line chemotherapy in patients with peripheral T-cell lymphomas. Int J Hematol 2018; 107: 451 – 459.

16. Marcheselli R, Bari A, Tadmor T, Marcheselli L, Cox MC, Pozzi S et al. Neutrophil-lymphocyte ratio at diagnosis is an independent prognostic factor in patients with nodular sclerosis Hodgkin lymphoma: results of a large multicenter study involving 990 patients. Hematol Oncol 2017; 35: 561 – 566.

17. Feng X, Li L, Wu J, Zhang L, Sun Z, Li X et al. Complete Blood Count Score Model Integrating Reduced Lymphocyte-Monocyte Ratio, Elevated Neutrophil-Lymphocyte Ratio, and Elevated Platelet-Lymphocyte Ratio Predicts Inferior Clinical Outcomes in Adult T-Lymphoblastic Lymphoma. Oncologist 2019. pii: theoncologist. 2018-0789.

18. Beltran BE, Aguilar C, Quiñones P, Morales D, Chavez JC, Sotomayor EM et al. The neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with peripheral T-cell lymphoma, unspecified. Leuk Lymphoma 2016; 57: 58 – 62.

19. Zhu Y, Zhou S, Liu Y, Zhai L, Sun X. Prognostic value of systemic inflammatory markers in ovarian Cancer: a PRISMA-compliant meta-analysis and systematic review. BMC Cancer 2018; 18: 443.

20. Lin WF, Zhong MF, Zhang YR, Wang H, Zhao HT, Cheng BB. Prognostic Role of Platelet-to-Lymphocyte Ratio in Hepatocellular Carcinoma with Different BCLC Stages: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract 2018; 2018: 5670949.

21. Hu G, Liu Q, Ma JY, Liu CY. Prognostic Significance of Platelet-to-Lymphocyte Ratio in Cholangiocarcinoma: A Meta-Analysis. Biomed Res Int 2018; 2018: 7375169.

22. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014; 23: 1204 – 12.

23. Zhuang Q, Xiang L, Xu H, Fang F, Xing C, Liang B et al. The independent association of meanplatelet volume with overall survival in multiple myeloma.Oncotarget 2016; 7: 62640 - 62646.

24. Inagaki N, Kibata K, Tamaki T, Shimizu T, Nomura S. Prognostic impactof the mean platelet volume/platelet count ratio in terms of survival inadvanced non-small cell lung cancer. Lung Cancer 2014; 83: 97 - 101.

25. Zhou S, Ma Y, Shi Y, Tang L, Zheng Z, Fang F et al. Mean platelet volume predicts prognosis in patients with diffuse large B-cell lymphoma. Hematol Oncol 2018; 36: 104 – 109.