# The Prognostic Value of Blood Count Parameters in Patients with Diffuse Large B Cell Lymphoma

## Diffüz Büyük B Hücreli Lenfoma Tanılı Hastalarda Tanıdaki Tam Kan Parametrelerinin Prognostik Önemi

Hacer Berna AFACAN ÖZTÜRK, Murat ALBAYRAK, Abdulkerim YILDIZ, Senem MARAL, Pınar CÖMERT, Buğra SAĞLAM, Mesut TIĞLIOĞLU

University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Hematology, Ankara, Turkey

Correspondence Address
Yazışma Adresi

**Hacer Berna AFACAN ÖZTÜRK**
University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital Department of Hematology, Hematology, Ankara, Turkey

E-mail: bernaafacan@yahoo.com

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Hacer Berna AFACAN ÖZTÜRK
ORCID ID: 0000-0001-9386-7604
Murat ALBAYRAK
ORCID ID: 0000-0003-4025-741X
Abdulkerim YILDIZ
ORCID ID: 0000-0002-9596-4042
Senem MARAL
ORCID ID: 0000-0003-4766-1861
Pınar CÖMERT
ORCID ID: 0000-0003-3829-289X
Buğra SAĞLAM
ORCID ID: 0000-0001-8342-990X
Mesut TIĞLIOĞLU
ORCID ID: 0000-0002-4111-2004

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## ABSTRACT

**Objective:** Full blood count with the associated components is a widely used marker in the diagnosis of patients with diffuse large B cell lymphoma (DLBCL) as it is simple and inexpensive and can be easily interpreted. The aim of the current study was to evaluate the prognostic role of complete blood count parameters with the associated components in patients with DLBCL.

**Material and Methods:** In this retrospective study, the neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) were evaluated and an analysis was made of the progression-free survival (PFS) and overall survival (OS) in patients who were diagnosed with DLBCL and treated with a total of 6 cycles of R-CHOP chemotherapy in the 2011-2017 period.

**Results:** 66 patients were included in the study. In the Cox-Regression Model, high NLR and the low LMR were associated with short OS and PFS; high PLR was associated with short PSF.

**Conclusion:** Pre-treatment NLR, LMR, and PLR values can be used as prognostic factors in DLBCL patients.

**Keywords:** Neutrophil/Lymphocyte ratio, Lymphocyte/Monocyte ratio, Platelet/Lymphocyte Ratio, Diffuse Large B Cell Lymphoma, Prognosis

## ÖZ

**Amaç:** Diffüz büyük b hücreli lenfoma (DBBHL) tanısı alan hastalarda tam kan sayımı ve ilişkili bileşenleri, prognozun belirlenmesinde basit, ucuz, kolaylıkla yorumlanabilen ve yaygın olarak kullanılan markerlardan biridir. Çalışmanın amacı, DBBHL hastalarında tam kan sayımı parametreleri ile ilişkili bileşenlerin prognostik rolünü değerlendirmektir.

**Gereç ve Yöntemler:** Retrospektif olarak 2011-2017 yıllarında DBBHL tanısı almış ve toplam 6 kür R-CHOP kemoterapisi ile tedavi edilmiş hastaların tanıdaki nötrofil/lenfosit oranına (NLR), lenfosit-monosit oranına (LMR) ve Platelet-lenfosit oranına (PLR) bakıldı ve progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) analizi yapıldı.

**Bulgular:** Çalışmaya 66 hasta dahil edildi. Cox-Regresyon Modelinde, yüksek NLR ve düşük LMR kısa OS ve PFS ile ilişkiliydi; yüksek PLR, kısa PSF ile ilişkiliydi.

**Sonuç:** Çalışmamızın sonucunda tedavi öncesi NLR, LMR, PLR değerlerinin DBBHL hastalarında bağımsız prognostik faktör olarak kullanılabileceğini gösterir.

**Anahtar Sözcükler:** Nötrofil/lenfosit oranı, Lenfosit-monosit oranı, Platelet-lenfosit oranı, Diffüz büyük b hücreli lenfoma, Prognoz

## INTRODUCTION

DCBCL is the major type of non-Hodgkin's lymphoma and constitutes 25%-35% of all newly-diagnosed non-Hodgkin's lymphoma cases throughout the world (1). Despite the highly important development of the addition of rituximab to the combination of cyclophosphamide, doxorubicin, vincristine and methylprednisolone (CHOP) chemotherapy, the long-term survival of relapse-refractory cases after the first remission is poor (2) and more than 30% of patients are refractory to first line treatment or relapse after that (3). Several new prognostic parameters have been suggested for the clinical identification of DLBCL patients. However, although these methods are promising, the majority are expensive, difficult to apply, cannot be interpreted easily, and require further confirmation, so there remains a need for clinical parameters that can be widely used. Full blood count and components could be the current most useful tool.

Increasing evidence has shown a close relationship between chronic inflammation and the immune factors of immune insufficiency, autoimmunity, infections, and lymphoma (4, 5). Abnormal inflammatory reactions and immune status are closely related to the pathobiology of lymphoma. Studies in recent years have suggested that the lymphocyte – monocyte ratio (LMR) is a prognostic marker of the tumour micro-environment in DLBCL patients (6, 7). For example, it has been shown that long-term survival is reduced in DLBCL patients with low LMR (8-11).

The relationship between NLR and survival in cases of hematological malignancy has attracted great interest in research. In DLBCL patients treated with a total of 6 cycles of R-CHOP, it has been shown that the pre-treatment NLR value in diagnosis functions as an independent predictor of survival and it has been seen that survival is poor in patients with high NLR (12). In studies related to PLR, survival has been shown to be generally poor in cancer patients with high PLR (13).

In the light of these previous studies, the aim of this study was to investigate the effect on survival of the LMR, PLR, and NLR at diagnosis of DLBCL patients subsequently treated with a total of 6 cycles of R-CHOP and to show the utility of these as independent prognostic factors.

## MATERIAL and METHODS

### Patients

A retrospective scan was made of the records of 66 patients newly diagnosed with de novo DLBCL between 2011 and 2017 at our tertiary referral hospital. The clinical characteristics of the patients at the time of diagnosis were recorded and these are shown in Table I.

### Ethical Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. As a standard of care/action of Ankara Diskapi Yildirim Beyazit Research and Training Hospital, the patient records confirmed that all the study patients gave informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care. This study was approved by Ankara Diskapi Yildirim Beyazit Research and Training Hospital's Ethics Committee and the approval date/number: 25.03.2019-61/03.

### Statistical Analysis

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, the LMR by dividing the absolute lymphocyte count by the absolute monocyte count, and the PLR by dividing the platelet count by the absolute lymphocyte count. Receiver operating characteristic (ROC) curve analysis was applied to the NLR, LMR, and PLR separately to determine the cut-off value for each one. In the comparison of the clinical characteristics of the NLR, LMR and PLR, the Pearson Chi-square test or Fisher's Exact test was used. Progression-free survival was defined as the time from diagnosis to relapse or progression of the disease. Comparison of the PFS and overall survival (OS) times with the NLR, LMR and PLR cut-off values was made according to the Kaplan-Meier method (log-rank test) and the Cox proportional hazards model. Analyses of all the data were applied using the SPSS 20.0 software (IBM Corp., Armonk, NY, USA).

## RESULTS

As of 1 December 2017, 25 of the 66 patients included in the study were exits and 41 survived. The basal clinical characteristics of the patients at the time of diagnosis were recorded and these are shown in Table I.

Using ROC curve analysis between the surviving and non-surviving patients, the cut-off values were determined as 3.5 for NLR, 1.3 for LMR, and 216.8 for PLR (Figure 1).

The NLR value was seen to be high in 36 (54.5%) patients, the LMR was high in 48 (72.7%), and the PLR was low in 38 (57.6%). A total of 41 (62.1%) patients were determined to have survived.

### Survival Analysis

A statistically significant difference was determined between survival times according to the NLR, LMR, and PLR cut-off values as a result of the Log Rank test (Mantel-Cox) applied for median OS (Figure 2) (respectively $\chi^2$=5.258;p=0.022,

**Table I: Clinical characteristics of patients.**

| Variable (n=66) | Results | | Percentage |
|---|---|---|---|
| **Age (years)** | Median (min-max) | 63.50 (22-85) | |
| **Gender** | Female | 36 | 54.5 |
| | Male | 30 | 45.5 |
| **Stage** | I / II | 23 | 34.8 |
| | III / IV | 43 | 65.2 |
| **IPI** | 0-1 | 15 | 23.4 |
| | 2-3 | 44 | 68.8 |
| | 4-5 | 5 | 7.8 |
| **Hemoglobin (gr/dl)** | Median (min-max) | 12.00 (6.60-15.60) | |
| | Mean ± Standard deviation | 11.98±2.13 | |
| **Leukocyte (number /µl)** | Median (min-max) | 7200.00 (13.10-17500.00) | |
| | Mean ± Standard deviation | 7780.78±3486.53 | |
| **Platelet (number /µl)** | Median (min-max) | 271000 (76000-600000) | |
| | Mean ± Standard deviation | 295709.09±114250.32 | |
| **Lymphocyte (number/µl)** | Median (min-max) | 914.83(450-4800) | |
| | Mean ± Standard deviation | 1449.45±914.83 | |
| **Ki67** | Median (min-max) | 80 (10-100) | |
| | Mean ± Standard deviation | 75.16±19.67 | |
| **NLR** | Median (min-max) | 3.86 (0.33-14.19) | |
| | Mean ± Standard deviation | 4.57±3.13 | |
| **NLR cut off** | < 3.5 | 30 | 45.5 |
| | ≥ 3.5 | 36 | 54.5 |
| **LMR** | Median (min-max) | 2.06 (80.42-8.87) | |
| | Mean ± Standard deviation | 2.61±1.89 | |
| **LMR cut off** | < 1.3 | 18 | 27.3 |
| | ≥ 1.3 | 48 | 72.7 |
| **PLR** | Median (min-max) | 187.49 (14.38-1142.55) | |
| | Mean ± Standard deviation | 246.79±183.15 | |
| **PLR cut off** | < 216.8 | 38 | 57.6 |
| | ≥ 216.8 | 28 | 42.4 |
| **Status** | Survived | 41 | 62.1 |
| | Exitus | 25 | 37.9 |

**NLR:** Neutrophil/Lymphocyte ratio, **LMR:** Lymphocyte /Monocyte ratio, **PLR:** Platelet/Lymphocyte ratio, **IPI:** International prognostic index

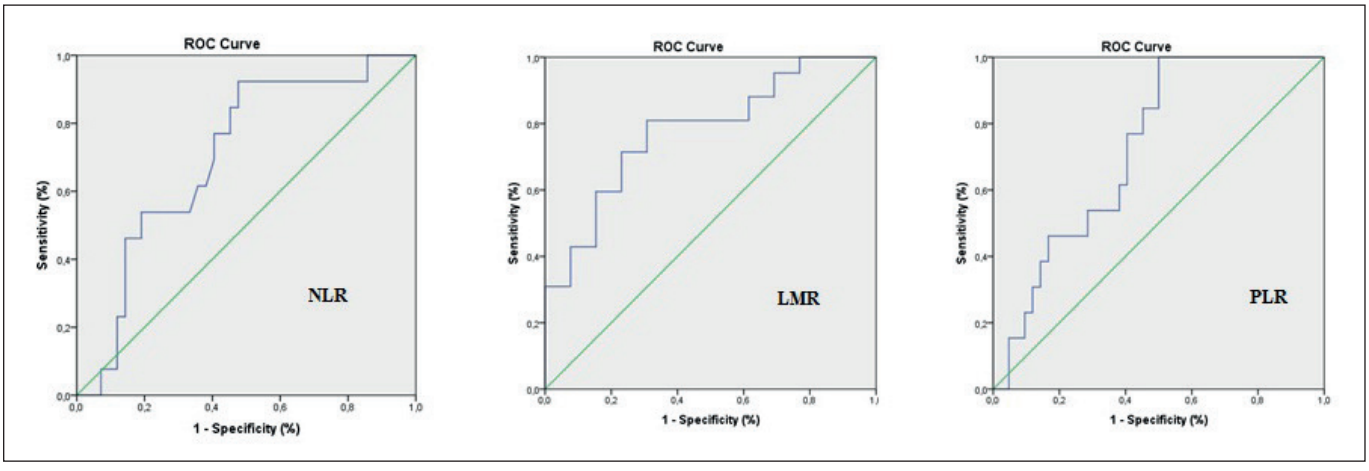


**Figure 1:** Receiver operating characteristic (ROC) curve for the NLR, LMR and PLR value.

$\chi^2$=13.330;p=0.000 and $\chi^2$=3.954;p=0.047) and PFS (Figure 3) (respectively $\chi^2$=5.194;p=0.023, $\chi^2$=14.055;p=0.000 and $\chi^2$=4.589;p=0.032). The median survival times of those in the high NLR group and high PLR group were determined to be lower. The median survival times of those in the high LMR group were determined to be higher.

When the OS and PFS were examined in the Cox-Regression Model (Table II), a relationship was seen in the high NLR group and the low LMR group with short survival for OS and PFS. A relationship was seen in the high PLR group with short survival for PFS.

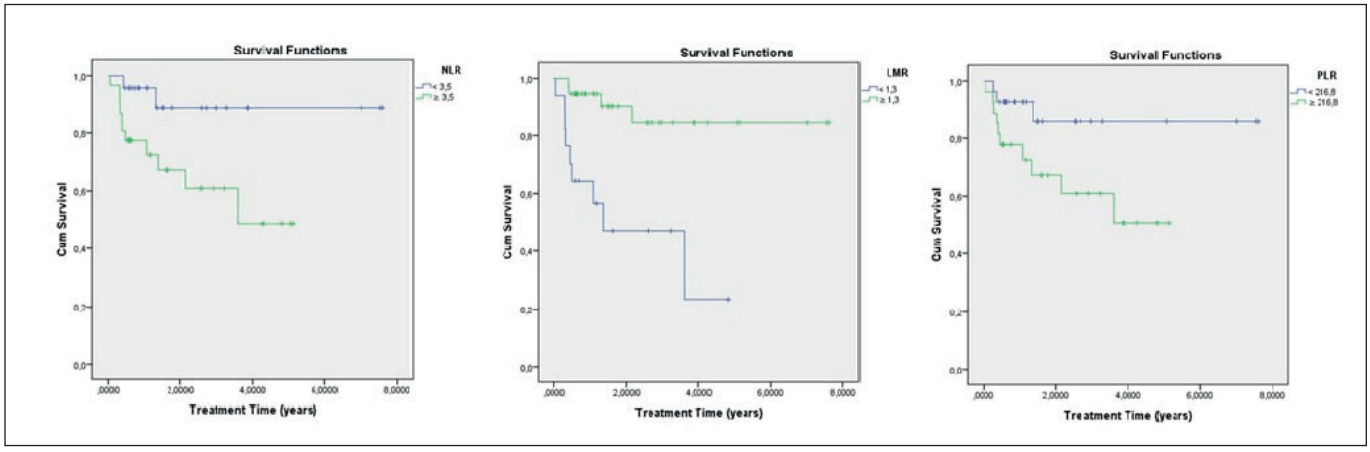


**Figure 2:** Overall survival times with the NLR, LMR and PLR cutoff values.

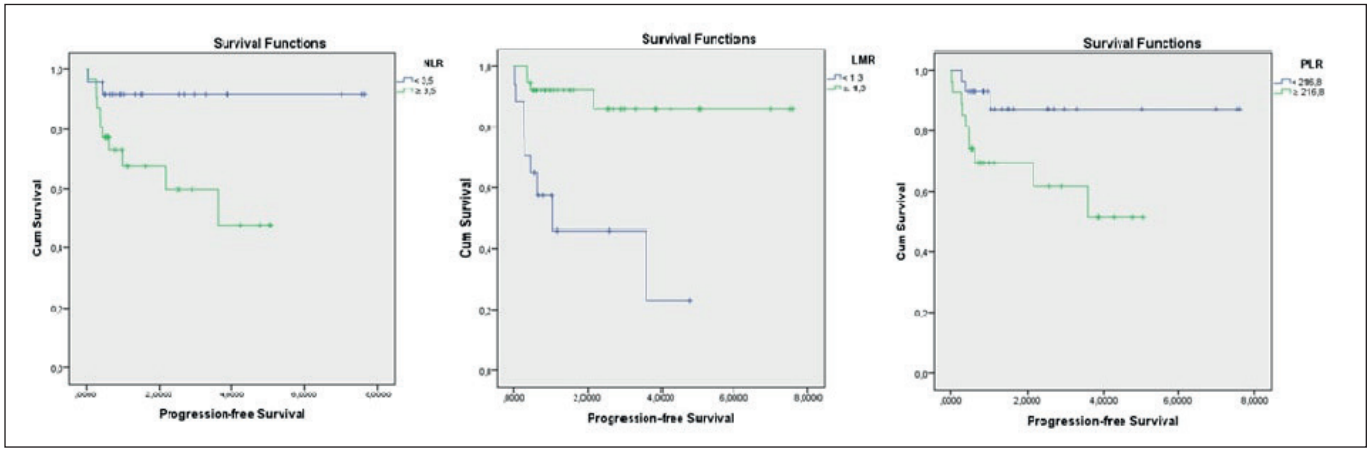


**Figure 3:** The Progression-free survival times with the NLR, LMR and PLR cutoff values.

**Table II:** Overall survival and Progression-free survival analysis.

| Variable | Overall Survival | | | Progression-free Survival | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | P |
| **Gender** | 1.861 | 0.573-6.047 | 0.302 | 1.808 | 0.556-5.875 | 0.325 |
| **Age** | 0.992 | 0.956-1.026 | 0.675 | 0.988 | 0.951-1.025 | 0.509 |
| **Stage** | 1.008 | 0.540-1.884 | 0.979 | 0.999 | 0.535-1.864 | 0.997 |
| **IPI** | 0.931 | 0.644-1.346 | 0.705 | 0.958 | 0.670-1.369 | 0.814 |
| **Ki67** | 1.014 | 0.982-1.048 | 0.384 | 1.012 | 0.980-1.046 | 0.451 |
| **NLR** | 0.204 | 0.045-0.920 | **0.039** | 0.205 | 0.045-0.927 | **0.040** |
| **LMR** | 6.722 | 2.062-21.906 | **0.002** | 7.037 | 2.153-22.995 | **0.001** |
| **PLR** | 0.292 | 0.080-1.062 | 0.062 | 0.268 | 0.073-0.976 | **0.046** |

**NLR:** Neutrophil/Lymphocyte ratio, **LMR:** Lymphocyte/Monocyte ratio, **PLR:** Platelet/Lymphocyte ratio, **IPI:** International prognostic index

## DISCUSSION

Prognostic factors in cancer patients provide information that can help in classification according to the various risk groups of the patients and potential clinical outcomes. The IPI is a simple prognostic marker based on 5 clinical factors in aggressive non-Hodgkin's lymphoma and has been widely used for more than 20 years. However, with the addition of rituximab to conventional chemotherapy for DLBCL, there has been a dramatic improvement in the survival of all risk groups and the predictive capacity of the IPI has decreased. Advanced techniques related to new prognostic parameters have provided very important information on several issues, but these are expensive and technically difficult and have not been standardised in clinical practice. In several recent studies, the use of NLR, LMR, and PLR as prognostic factors in DLBCL patients has been reported.

In a similar study by Ho et al., it was shown that a high pre-treatment NLR value (NLR>4.5) and a low pre-treatment LMR value (LMR <2.11) were related to a poor prognosis in patients diagnosed with DLCB (14). In a retrospective study by Keam et al., NLR ≥ 3 at diagnosis was seen to be independently related to a poor prognosis in DLBCL patients taking rituximab (15). In a systematic review and meta-analysis by Xia et al., it was reported that reduced LMR showed a poor prognosis in DLCBL patients and it could be helpful to clinicians for the determination of individual treatment strategies for patients (16).

In another study of patients treated with R-CHOP, statistically significantly poor OS and PFS were determined in those with a high NLR level at diagnosis (12). It has been shown that high PLR (>170) and low LMR (<2.5) in patients diagnosed with primary gastrointestinal DLBCL showed a poor prognosis (13). In the current study, OS and PFS were seen to be related to short survival in the group with high NLR and low LMR. A relationship with short PFS was observed in the high PLR group. Thus, the results of this study show that the pre-treatment values of NLR, LMR ,and PLR in DLBCL patients can be used as independent prognostic factors.

In the light of these studies, the components of the full blood count, which is a simple, inexpensive, and easily interpreted test and has widespread use, can be of benefit in determining the prognosis of DLCBL patients treated with R-CHOP, and the NLR, LMR, and PLR values can be used as independent prognostic factors in DLCBL patients. Thus, an evaluation could be made before treatment and this can be taken into consideration in treatment planning for patients who could have a poor prognosis.

To conclude; pre-treatment NLR, LMR, and PLR values could be used as independent prognostic factors in DLBCL patients.

**Conflict of Interest:** None Declared.

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**Author Roles:** **HBAO:** Designing the study, writing the article, collecting data, **MA:** Reviewing the article, **AY:** Writing the article, reviewing the article, **SM:** Collecting data, **PC:** Collecting data, **BS:** Working with statistics, **MT:** Working with statistics.

**Ethics Committee Approval:** This study was approved by Ankara Diskapi Yildirim Beyazit Research and Training Hospital's Ethics Committee and the approval date/number: 25.03.2019-61/03.

**Informed Consent:** All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

## REFERENCES

1. Cultrera JL, Dalia SM. Diffuse large B-cell lymphoma: Current strategies and future directions. Cancer Control 2012; 19(3):204-13.
2. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program 2011; 498-505.
3. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M. ESMO Guidelines Committee. Diffuse Large B-cell Lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 5:116-25.
4. Bizjak M, Selmi C, Praprotnik S, Bruck O, Perricone C, Ehrenfeld M, Shoenfeld Y. Silicone implants and lymphoma: The role of inflammation. J Autoimmun 2015; 65:64-73.
5. Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders-what are the driving forces? Semin Cancer Biol 2014; 24:61-70.
6. Li ZM, Huang JJ, Xia Y, Sun J, Huang Y, Wang Y, Zhu YJ, Li YJ, Zhao W, Wei WX, Lin TY, Huang HQ, Jiang WQ. Blood lymphocyte-to-monocyte ratio identifies high-risk patients in diffuse large B-cell lymphoma treated with R-CHOP. PLoS One 2012; 7(7):e41658.

7. Aoki K, Tabata S, Yonetani N, Matsushita A, Ishikawa T. The prognostic impact of absolute lymphocyte and monocyte counts at diagnosis of diffuse large B-cell lymphoma in the rituximab era. Acta Haematol 2013; 130:242-6.
8. Koh YW, Park CS, Yoon DH, Suh C and Huh J. Should the cut-off values of the lymphocyte to monocyte ratio for prediction of prognosis in diffuse large B-cell lymphoma be changed in elderly patients? Eur J Haematol 2014; 93:340-8.
9. Wilcox RA, Ristow K, Habermann TM, Inwards DJ, Micallef IN, Johnston PB, Colgan JP, Nowakowski GS, Ansell SM, Witzig TE, Markovic SN, Porrata L. The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large- B-cell lymphoma. Leukemia 2011; 25:1502-9.
10. Porrata LF, Inwards DJ, Ansell SM, Micallef IN, Johnston PB, Hogan WJ, Markovic SN. Infused autograft lymphocyte to monocyte ratio and survival in diffuse large B cell lymphoma. Biol Blood Marrow Transplant 2014; 20:1804-12.
11. Watanabe R, Tomita N, Itabashi M, Ishibashi D, Yamamoto E, Koyama S, Miyashita K, Takahashi H, Nakajima Y, Hattori Y, Motohashi K, Takasaki H, Ohshima R, Hashimoto C, Yamazaki E, Fujimaki K, Sakai R, Fujisawa S, Motomura S, Ishigatsubo Y. Peripheral blood absolute lymphocyte/monocyte ratio as a useful prognostic factor in diffuse large B-cell lymphoma in the rituximab era. Eur J Haematol 2014; 92:204-10.
12. Wang J, Zhou M, Xu JY, Yang YG, Zhang QG, Zhou RF, Chen B, Ouyang J. Prognostic role of pretreatment neutrophil/lymphocyte ratio in patients with diffuse large B-cell lymphoma treated with RCHOP. Medicine (Baltimore) 2016; 95(38):e4893.
13. Zhao P, Zang L, Zhang X, Chen Y, Yang H, Zhao H, Yu Y, Wang Y, Zhang Y, Wang X. The lymphocyte-monocyte ratio and the platelet-lymphocyte ratio at diagnosis as independent prognostic factors in primary gastrointestinal diffuse large B cell lymphoma. Indian J Hematol Blood Transfus 2017; 33(3):333-41.
14. Ho CL, Lu CS, Chen JH, Chen YG, Huang TC, Wu YY. Neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, and absolute lymphocyte count/absolute monocyte count prognostic score in diffuse large B-Cell lymphoma: Useful prognostic tools in the rituximab era. Medicine (Baltimore) 2015; 94(24):e993.
15. Keam B, Ha H, Kim TM, Jeon YK, Lee SH, Kim DW, Kim CW, Heo DS. Neutrophil to lymphocyte ratio improves prognostic prediction of International Prognostic Index for patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Leuk Lymphoma 2015; 56:2032-8.
16. Xia WK, Lin QF, Shen D, Liu ZL, Su J, Mao WD. Prognostic significance of lymphocyte-to-monocyte ratio in diffuse large B-cell lymphoma: A systematic review and meta-analysis. FEBS Open Bio 2016; 6(6):558-65.