Does Systemic Immun Inflammation Index Predict Survival in Diffuse Large B Cell Lymphoma Patients?

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Abstract

Objective: The systemic immune inflammation index has been considered a novel prognostic biomarker in several malignant tumors. The aim of the current study was to determine the association between the systemic immune inflammation index and prognosis of patients with Diffuse Large B Cell Lymphoma.

Material and Method: The study included 101 patients diagnosed diffuse large B cell lymphoma. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the systemic immune inflammation index for predicting survival.

Results: The results of ROC curve analysis showed a cut-off value for the systemic immune inflammation index of 500. No statistically significant difference was determined between the groups with systemic immune inflammation index ≤ 500 and >500 groups in respect of overall-survival and progression-free survival. The mortality risk was determined to be significantly higher in patients with systemic immune inflammation index ≤ 500 (*p:0.017*). There was no significant relationship between the systemic immune inflammation index values and lactat dehydrogenase, age, R-IPI risk groups,ECOG performance status, and disease stage.

Conclusion: The results of this study demonstrated that there is no association between the systemic immune inflammation index and survival in patients with diffuse large B cell lymphoma. Larger prospective studies are needed to investigate the association between the systemic immune inflammation index and Diffuse Large B Cell Lymphoma.

Keywords: Diffuse large B cell lymphoma, Lymphocyte, Neutrophil, Platelet, Survival, Systemic immune inflammation index

Özet

Amaç: Sistemik immün inflamasyon indeksi, birçok malign tümörde kullanılan yeni bir prognostik biyobelirteçtir. Bu çalışmanın amacı, Diffüz Büyük B Hücreli Lenfoma hastalarında sistemik immün inflamasyon indeksi ile prognoz arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Çalışmaya Diffüz Büyük B Hücreli Lenfoma tanılı 101 hasta dahil edildi. Sağkalımı öngören optimum sistemik immün inflamasyon indeksi kesme değerini saptamak için receiver operating charecteristic curve analizi kullanıldı.

Bulgular: Receiver operating charecteristic curve analizi ile sistemik immün inflamasyon indeksi kesme değeri 500 saptandı. Sistemik immün inflamasyon indeksi ≤ 500 ve sistemik immün inflamasyon indeksi >500 grupları arasında progresyonsuz sağkalım ve genel sağkalım açısından istatistiksel olarak anlamlı fark yoktu. Ancak sistemik immün inflamasyon indeksi ≤ 500 olan hastalarda mortalite riski anlamlı olarak yüksekti (p:0,017). Sistemik immün inflamasyon indeksi ile laktat dehidrogenaz, yaş, R-IPI risk grupları, ECOG performans durumu ve hastalık evresi arasında anlamlı bir ilişki yoktu.

Sonuç: Çalışmamızın sonuçları, Diffüz Büyük B Hücreli Lenfoma hastalarında sistemik immün inflamasyon indeksi ile sağkalım arasında bir ilişki olmadığını göstermiştir. Sistemik immün inflamasyon indeksi ve DBBHL arasındaki ilişkiyi araştırmak için daha büyük prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Diffüz büyük B hücreli lenfoma, Lenfosit, Nötrofil, Platelet, Sağkalım, Sistemik immün inflamasyon indeksi

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. It develops as a result of the combined effects of immunosuppression, immune stimulation, and genetic predisposition. Although 75-80% of patients achieve complete remission after first line treatment. Approximately 40% of all patients relapse (1).

Therefore, it is very important to stratify the prognosis of patients at the time of diagnosis, and to individualize the treatment according to this prognostic stratification. A more intensive or longer period of chemotherapy may be required for patients with poor prognosis (2).

Inflammation has an important role in tumor progression and treatment response. Peripheral blood count values are closely associated with the progression of malignancy and reflect the inflammation status to some degree. Previous studies have shown that inflammatory markers such as pretreatment neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) affect the outcomes of DLBCL patients. Blood biomarkers are also easier and cheaper to obtain than molecular biomarkers (3).

The systemic immune inflammation index (SII) is calculated from lymphocyte, platelet and neutrophil counts, and is a relatively new inflammatory index, which reflects the inflammatory status and correlates with circulating tumor cells. Platelets have important roles in angiogenesis, tumor cell immuneinvasion, and extravasation to other organs. There is growing evidence of the importance of SII in solid tumors. A high SII value has been associated with poor outcomes in renal cell carcinoma, hepatocellular carcinoma, small cell lung cancer, and gastrointestinal cancer, but there are limited data on SII in hematopoietic tumors (2).

The aim of this study was to evaluate the association between the systemic immune inflammation index (SII) and the prognosis of patients with DLBCL.

Material and Method

A retrospective analysis was made of the data of patients with DLBCL diagnosed in a-tertiary-level hospital between January 2012 and September 2022. Patients treated with R-miniCHOP and R-CHOP regimens were included in the study. Patients were excluded from the study if they were aged <18 years,were pregnant, had primary central nervous system lymphoma, acquired immunodeficiency syndrome related lymphoma,HIV positivity,another concominant malignancy,heart failure,chronic kidney disease,hepatic cirrhosis,Richter's transformation, a history of solid organ malignancy, or who were treated with a regimen other than R-CHOP or R-miniCHOP. Age,gender,disease stage,ECOG performance status,IPI score,beta-2-microglobulin,serum lactate dehydrogenase (LDH), neutrophil, platelet, and lymphocyte values were recorded at the time of diagnosis. The SII values were calculated from the laboratory values of serum neutrophil,platelet and lymphocyte counts.

Disease staging was made according to the Ann-Arbor classification Cotswold modification. The treatment regimen, treatment response and follow-up duration were recorded for all patients. Overall survival (OS) was defined as the time from diagnosis to death from any cause, and progression free survival (PFS) was defined as the time from diagnosis to progression or death.

Ethical approval and informed consent

All the study procedures complied with the principles of the Helsinki Declaration. Approval for the study was granted by the Clinical Research Ethics Committee (Approval number: 2023/138, date: 03/05/2023). Written informed consent was obtained from each patient.

Statistical Analysis

The study data were analyzed using SPSS 21 software. Descriptive data were stated as number and percentage. Descriptive statistics and frequency tables were used. Receiver operating characteristic (ROC) curve analysis was used to identify a cut-off value for SII. The numerical variables were analyzed in terms of this cut-off value using the Student's t-test. The relationship between the SII cut-off value and categorical variables was analyzed with the Chi-square test.

The effect of the variables on survival was examined using logistic regression analysis. A value of $p<0.05$ was considered statistically significant.

Results

The study population of 101 patients comprised, 45 (44.6%) males and 56 (55.4%) females, with a median age of 64 years (min 20-max 86 years). When the patients were analysed by age, 34 (33.7%) patients were ≤60 years old and 67 (66.3%) were older than 60 years. At the time of diagnosis, 45 (44.6%) patients had stage I-II disease, and 56 (55.4%) had stage III-IV disease. The patients were classified according to R-IPI score as very good, good, and poor-risk groups. According to the R-IPI scores, 10 (9.9%) patients were in the very good risk group, 42 (41.6%) were in the good risk group, and 49 (48.5%) were in the poor risk group. The clinical and demographic features of the patients at the time of diagnosis are given in Table I and the laboratory findings at the time of diagnosis are shown in Table II.

Table I. The clinical and demographic features of the patients at the time of diagnosis

Characteristics		n (%)
Gender	Female	56 (55.4)
	Male	45 (44.6)
Age (years)	≤ 60	34 (33.7)
	> 60	67 (66.3)
Ann-Arbor Stage	1-2	45 (44.6)
	3-4	56 (55.4)
ECOG PS	0-2	91 (90.1)
	3-4	10 (9.9)
LDH	N	39 (38.6)
	>N	62 (61.4)
R-IPI	Very good (0)	10 (9.9)
	Good (1-2)	42 (41.6)
	Poor (3-5)	49 (48.5)

ECOG PS: Eastern Cooperative Oncology Group Performance Status
LDH: Lactat dehydrogenase, **R-IPI:** Revised International Prognostic Index

Table II. Laboratory findings of the patient at the time of diagnosis

	Median	Min-Max
White blood cell count (x10^6/L)	8493	1800-20550
Lymphocyte count (x10^6/L)	1574	300-4470
Hemoglobin (gr/dl)	11.9	6.8-16.2
Platelet count (x10^6/L)	284276	10000-1089000
SII	1373	38-7687

SII: Systemic Immune Inflammation Index

In ROC analysis, the cut-off value for the SII was calculated as 500 (Figure I). The patients were then separated into two groups according to the SII cut-off value. There was no significant relationship between the SII cut-off value and LDH, age, R-IPI risk groups, ECOG performance status, and disease stage. Comparisons of the parameters between the groups according to the SII cut-off value are given in Table III.

Figure I. ROC analysis acoording to the SII cut-off value

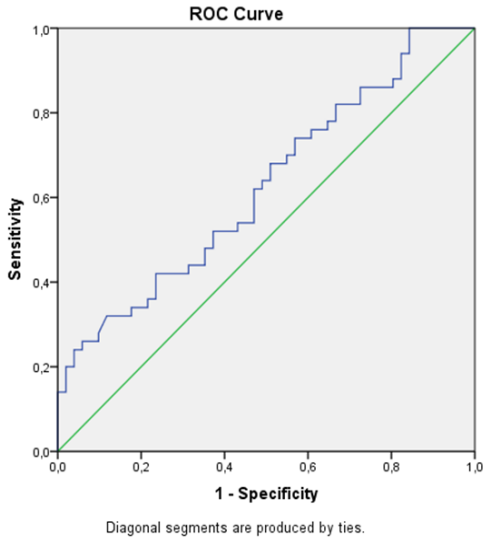

Table III. Comparison of parameters between the groups according to SII

		SII cut-off value				Chi-square	*p*
		≤500		>500			
		n	%	n	%		
Age (years)	≤60	6	17.6	28	82.4	0.214	*.644*
	>60	16	23.9	51	76.1		
LDH	N	6	15.4	33	84.6	0.976	*.323*
	>N	16	25.8	46	74.2		
ECOG	0-2	20	22.0	71	78.0	.021	*.886*
	3-4	2	20.0	8	80.0		
Stage	1-2	7	15.6	38	84.4	1.247	*.264*
	3-4	15	26.8	41	73.2		
R-IPI	very good	0	0.00	10	100	3.097	*.213*
	good	10	23.8	32	76.2		
	poor	12	24.5	37	75.5		

SII: Systemic Immune Inflammation Index
LDH: Lactat dehydrogenase
R-IPI: Revised International Prognostic Index (very good:0, good: 1-2, poor:3-5)
ECOG: Eastern Cooperative Oncology Group

Mean OS was 33.82 months in the SII ≤ 500 group and 45.66 months in the SII> 500 group, with no significant difference determined between groups (*p<0.221*). The mean PFS was 21.41 months in the SII ≤ 500 group and 31.15 months in the SII> 500 group, with no significant difference determined between groups (*p<0.225*). The comprasion of overall survival and progression free survival according to the SII values are presented in Table IV.

Table IV. Comprasion of progression free survival (PFS) and overall survival (OS) according to SII

	SII cut-off value				t	*p*
	≤ 500		> 500			
	Mean	SD	Mean	SD		
OS (months)	33.82	39.31	45.66	40.01	-1.232	*.221*
PFS (months)	21.41	33.94	31.15	32.90	-1.220	*.225*

SII: Systemic Immune Inflammation Index
OS: Overall survival, PFS: progression free survival
SD: Standart deviation

The results of the univariate and multivariate logistic regression analyses for survival are given in Table V.

The univariate logistic regression analysis was performed to identify the risk factors for poor survival. Revised-IPI poor risk group,elevated LDH,age>60 years,SII ≤ 500, and stage 3-4 disease were determined to be risk factors for poor survival. The risk of mortatilty was 9.067 fold higher in the R-IPI poor risk group than in the very good risk group. Patients with an elevated LDH value were seen to be at a 4.316 fold higher risk of mortality than those with a normal LDH value. In patients older than 60 years, the mortality risk was 2.402 fold higher than for those ≤60 years. In the low SII group, the risk of mortality was 3.551 fold higher than for those in the high SII group

In the multivariate logistic regression analysis there was any significant risk factors for survival.

Table V. Univariate and multivariate logistic regression analysis results for survival

	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	*p*	Odds ratio	95 % CI	*p*
R-IPI (good)	2.000	0.374_10.700	*.418*	1.912	0.151_24.139	*.616*
R-IPI (poor)	9.067	1.716_47.891	*.009**	2.117	0.136_33.004	*.593*
LDH (>N)	4.316	1.813_10.273	*.001**	1.694	0.512_5.599	*.388*
SII ≤ 500	3,529	1.249_9.981	*.017**	3.551	0.815_15.470	*.092*
Age (≥60)	2.402	1.023_5.640	*.044**	1.015	0.240_4.287	*.984*
Stage (3-4)	2.801	1.243_6.312	*.013**	1.126	0.321_3.950	*.853*

CI: Confidence Interval, SII: Systemic Immune Inflammation Index
LDH: Lactat dehydrogenase
R-IPI: Revised International Prognostic Index (very good:0, good: 1-2, poor:3-5)

Discussion

The host immune response and inflammatory response are closely related to cancer occurrence, progression and disease biology (4). An association between inflammation and cancer was hypothesized by Virchow in 1863 from the obervation of the presence of leukocytes in neoplastic tissues (5,6). Several prognostic parameters have been used for non-Hodgkin lymphomas, of which the International Prognostic Score (IPI) is the most commonly used (7). The hosts inflammatory response and the clinicopathological characteristics of the tumor are associated with prognosis, although, IPI does not reflects the inflammatory response (8).

Neutrophils and lymphocytes are crucial components of the immune system. Reactive oxygen species (ROS) and nitric oxide (NO) released by neutrophils can lead to T-cell activation disorders. ROS and NO increases the incidence of tumor dissemination by downregulation of peripheral lymphocytes (9).

The first inflammatory marker from leukocyte subsets, the neutrophil-lymphocyte ratio (NLR) was first defined by Zahorec et al. (10) in oncological intensive care unit patients. Numerous studies have investigated NLR as an inflammatory and prognostic marker in malignant and benign disorders (11). Platelets play an important pro-inflammatory role, and platelet-lymphocyte ratio (PLR) was the second defined cellular immun inflammatory marker obtained from leukocyte subsets (11,12). The PLR has been shown to be an inflammatory and prognostic marker in malignant and benign disorders, similar to NLR (11).

SII was defined as the third cellular immune inflammation marker by Hu et al. Both NLR and PLR are calculated as ratios of two different blood count parameters, whereas the SII is calculated from three blood parameters (11,13). The SII is a relatively new inflammatory index that has been shown to be correlated with circulating tumor cells (2,14). Based on lymphocyte, neutrophil and platelet counts,the SII is calculated using the formula of neutrophil count × platelet count/lymphocyte count (15,16).

In a meta-analysis of 7657 cancer patients, a higher SII was reported to be correlated with poor disease free survival(DFS),poor PFS, and poor OS. In that meta-analysis, a SII value over the cut-off value was shown to predict poor OS in gastric carcinoma, esophageal squamous cell carcinoma, hepatocellular carcinoma, urinary system cancer,and small cell, and non-small cell lung cancer (15). In another meta-analysis to evaluate the prognostic role of SII in solid tumors, high SII was associated with worse OS in hepatocellulary carcinoma, urinary cancers, small cell lung lung cancer, gastrointestinal tract cancers, and acral melanoma (17). Yang et al. (18) evaluated the prognostic value of blood-based biomarkers in 28 patients with testicular DLBCL, and determined a SII cut-off value of 428. No significant associations was observed between SII and OS or PFS. However, SII was found to be significantly associated with the risk of disease progression. Similar to that study , there was no significant association between SII and OS or PFS in the current study. Only the risk of mortality was higher in the low SII group than in the high SII group Wu et al. (1) aimed to determine associations between DLBCL and SII, the lymphocytes to monocytes (LMR) ratio, the LMR to LDH (LMR/LDH) ratio, and prognosis. A total of 68 patients diagnosed with DLBCL were included in that study. The SII of patients with an Ann Arbor stage of III–IV and ECOG score of ≥ 2 was found to be significantly higher than that of patients with an Ann Arbor stage of I–II and ECOG score of < 2 ($p < 0.05$). Patients with a low SII had better PFS than those with a high SII ($p < 0.05$) .

In the current study, stage 3-4 disease, elevated LDH, R-IPI poor risk group,and age>60 years were found to be poor prognostic factors.

R-IPI and ECOG performance status are known prognostic factors for DLBCL. In this study 90.1% of the patients were in the ECOG 0-2 group and 51.2 % in R-IPI were in the very good and good risk group. This could explain why the results of this study differ from previous reports in the literature. Serum soluble interleukin-2 receptor and serum-soluble tumor necrosis factor receptor 2 levels have been used for DLBCL prognosis together with the IPI score in recent studies (19,20). The combination of serum soluble interleukin-2 receptor and serum-soluble tumor necrosis factor receptor 2 levels with the IPI score can be compared with SII in further studies.

The results of the current study are not consistent with the literature. There seen to be better survival rates in the high SII group, which was in contrast with the findings of other studies. There were some limitations to this study, primarily the retrospective, single-centre design, and small number of patients.There is a need for larger prospective studies to further investigate the association between SII and DLBCL.

Conclusion

In conclusion,the results of this study demonstrated that elevated LDH, R-IPI poor risk group, age>60 years, and stage 3-4 disease were poor prognostic factors in patients with DLBCL. No significant relationship was determined between SII and OS or PFS. Blood cell counts are low cost parameters. There may be also other prognostic parameters that can be determined from the avaliable blood cell counts.

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