Original Article

Systemic Immune-Inflammation Index and Hodgkin Lymphoma: An Underexplored Relationship

Sistemik İmmün-İnflamasyon İndeksi ve Hodgkin Lenfoma: Yeterince Keşfedilmemiş Bir İlişki

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ABSTRACT

Introduction: Tumor-associated inflammation is an important feature of tumor development and progression. We aimed to investigate whether the clinicopathological and prognostic characteristics of patients with classical Hodgkin lymphoma (cHL) were associated with systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).
Materials and methods: This was a retrospective cohort study conducted between January 2012 and December 2021. A total of 77 patients with newly diagnosed cHL were included in the study.
Results: The median age of the patients was 37 (24-49) years. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR. Female patients (p=0.005), those with B symptoms (p=0.014) and subjects with extranodal involvement (p=0.011) had significantly higher PLR. Also, the SII of patients with B symptoms was significantly higher compared to those without (p=0.009). There were significant but weak correlations between international prognostic score-7 and SII (r=0.271, p=0.017), PLR (r=0.294, p=0.010) and NLR (r=0.378, p=0.001).
Discussion: SII was associated with B symptoms, but was not prognostic for cHL. PLR and NLR were also unassociated with prognosis in patients with cHL. However, considering the exceedingly limited data on this topic, further studies to assess inflammation indices are necessary.

Keywords: Hodgkin lymphoma, prognosis, inflammation, biomarkers, neutrophil, lymphocyte, platelet

ÖZET

Giriş: Tümörle ilişkili inflamasyon, tümör gelişimi ve ilerlemesinin önemli bir özelliğidir. Klasik Hodgkin lenfoma (kHL) hastalarının klinikopatolojik ve prognostik özelliklerinin sistemik immün-inflamasyon indeksi (SII), nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranı (PLO) ile ilişkili olup olmadığını araştırmayı amaçladık.
Gereç ve yöntemler: Bu, Ocak 2012 ile Aralık 2021 tarihleri arasında yürütülen retrospektif bir kohort çalışmasıdır. Çalışmaya yeni tanı almış toplam 77 kHL hastası dahil edildi.
Bulgular: Hastaların ortanca yaşı 37 (24-49) idi. Evre IV hastalığı (p=0,036), B semptomları (p=0,005) ve ekstranodal tutulumu (p=0,012) olan hastalarda NLO anlamlı olarak daha yüksekti. Kadın hastalarda (p=0,005), B semptomu olanlarda (p=0,014) ve ekstranodal tutulumu olanlarda (p=0,011) PLR anlamlı olarak daha yüksekti. Ayrıca B semptomu olan hastaların olmayanlara göre SII değeri anlamlı olarak daha yüksekti (p=0,009). Uluslararası prognostik skor-7 ile SII (r=0,271, p=0,017), PLO (r=0,294, p=0,010) ve NLO (r=0,378, p=0,001) arasında anlamlı ancak zayıf düzeyde korelasyon vardı.
Tartışma: SII, B semptomları ile ilişkili bulundu, ancak kHL için prognostik değildi. Ayrıca PLO ve NLO da kHL'li hastalarda prognozla ilişkili değildi. Ancak bu konudaki verilerin son derece sınırlı olduğu düşünüldüğünde, inflamasyon indekslerinin değerlendirilmesi için daha fazla çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Hodgkin lenfoma, prognoz, inflamasyon, biyobelirteç, nötrofil, lenfosit trombosit

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Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas [1] and has an annual incidence of 2–3 cases per 100 000 people [2]. It is characterized by B lymphocyte-derived malignant cells and a general inflammatory microenvironment [3]. Although genetic and environmental factors and various viral infections contribute to pathophysiology [3, 4], it is still unclear what causes normal B lymphocytes to turn into malignant, biologically active tumor cells [3].

HL is histopathologically classified as classical HL (cHL) and nodular lymphocyte-predominant HL. Patients with cHL constitute 95% of all cases [3]. Today, up to 90% of patients with cHL can be cured [4]; however, 5-10% of cases develop primary resistant disease [1], and approximately 50% of patients with relapse or resistance die from progressive disease [1, 3]. Defined prognostic factors for early stage HL are high erythrocyte sedimentation rate (ESR), multiple nodular involvement, extra-nodal involvement, being aged >50 years, and presence of massive spleen disease, bulky disease, and B symptoms [5-7]. International prognostic scores (IPS-7 and IPS-3) are used to assess patients with advanced cHL [8]; however, many of the parameters required to obtain scores are generally difficult to clarify and require detailed investigation. As such, there is a lack of generally accepted, simple and inexpensive prognostic markers that may be applicable to cHL prognostication, including those with early stage cHL, and it is evident that such markers could facilitate individualized treatment for patients with poor prognosis.

Tumor-associated inflammation is an important feature of tumor development and progression [9, 10]. Several studies have reported that increased systemic inflammatory response may predict worse survival and prognosis for various neoplasms including lymphomas [11-13]. The literature on this topic has assessed the prognostic potential of various inflammatory markers in lymphoma, such as neutrophil-to-lymphocyte ratio (NLR) [12, 14], platelet-to-lymphocyte ratio (PLR) [12, 15] and systemic immune inflammation index (SII) [1, 11, 16]. The SII, which is based on peripheral blood neutrophil, platelet, and lymphocyte counts, has been shown to predict prognosis and/or severity in various cancer types including lymphomas [1, 16]. There have been many attempts to investigate the relationship between non-Hodgkin lymphoma (nHL) and SII [11, 16, 17]; however, to our knowledge, only one such study exists for HL [1].

Therefore, in this study, we aimed to investigate whether clinicopathological and/or prognostic parameters in patients with cHL were associated with SII, NLR and PLR values.

Material and Method

Study design and ethical considerations

This retrospective study was carried out in the Hematology department of our hospital. The protocol of this study was approved by the local ethics committee. It has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Study population

A total of 77 patients with new-onset cHL who were treated and followed up for cHL at our clinic, between January 2012 and December 2021, were included in the study. Patients younger than 18 years of age, those with known active infection, rheumatic or immunological disease at the time of blood sampling, patients with concomitant or previously treated malignancy, subjects with any known comorbid disease, patients with missing data, and those with no follow-up information were excluded from the study.

Data collection

All data about patients including age and sex information, performance status, pathology results, HL-related information, laboratory results, and follow-up data were retro-

spectively collected from hospital computer database.

Patient management and examinations

All steps of cHL management, including diagnosis, treatment and follow-up, were carried out in accordance with the current European Society for Medical Oncology Guidelines (www.esmo.org/ Guidelines/ Haematological-Malignancies) and the National Comprehensive Cancer Network, USA, Cinical Practice Guidelines (www.nccn.org /professionals/ physician_gls/ default.aspx).

The pretreatment information including B symptoms, performance score, pathological subtype, Ann Arbor stage, EBV positivity, bulky mass/mediastinal mass, diagnosis date and extranodal involvement positivity and IPS-7 score, treatment, and post-treatment data including refractory/recurrent disease and mortality were collected.

Performance status (PS) was determined in accordance with the Eastern Cooperative Oncology Group (ECOG) criteria [18]. The IPS-7 score was calculated as previously described [8]. Refractory disease was defined as a condition that either does not respond to treatment or achieves remission with treatment but relapses within six months. Relaps was defined as recurrent cHL after a documented complete remission that lasted at least six months after the first line treatment [19, 20].

Definitions for analyses

Patients with relapsed disease and/or death were defined as having a poor prognosis. However, disease (refractory/recurrent or death)-free-survival (DFS) was calculated using data from patients with poor prognosis (refractory/recurrent or death). When calculating DFS, the time between the diagnosis date and refractory/recurrent determining date or death date or data collection starting date was used. The follow-up time was calculated as the duration from the diagnosis date to data collection starting date or mortality.

Laboratory measurements and related tools

All laboratory analyses were performed in the Biochemistry department of our hospital using calibrated standard measuring devices and according to the manufacturer's recommendations. The results of the following laboratory findings, which were studied from blood samples obtained at the time of diagnosis and before any treatment, were included in the study: aspartate amino-transferase (AST), alanine amino-transferase (ALT), albumin, ESR, lactate dehydrogenase (LDH), C-reactive protein (CRP), and hemogram.

The NLR, PLR and SII were calculated using absolute neutrophil, lymphocyte, platelet counts. SII was calculated by using the following formula: SII ($\times 10^3$) = Absolute neutrophil count ($\times 10^3$) × Absolute platelet count ($\times 10^3$) / Absolute lymphocyte count ($\times 10^3$) [1].

Glomerular filtration rate (GFR) was calculated automatically using the short Modification of Diet in Renal Disease formula from the Turkish Society of Nephrology's internet application called “formula and calculations” (https://nefroloji.org.tr/tr/ formul-ve-hesaplamalar).

Statistical analysis

The classical $p<0.05$ threshold was accepted to show statistical significance. All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Histogram and Q-Q plots were used to determine whether variables were normally distributed. Between-group analyses were performed with the Mann-Whitney U test or Kruskal-Wallis test depending on normality of distribution. Pairwise comparisons were adjusted by the Bonferroni correction. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. DFS was calculated with the Kaplan-Meier method by using time between remission and recurrence or death. Cox regression analyses were performed to determine significant factors independently associated with poor prognosis.

Variables were analyzed with the univariable cox regression analysis and statistically significant variables were included into the multivariable cox regression model.

Results

The median age of the patients was 37 (24-49) years, and 62.34% (n=48) of them were males. Mean follow-up time was 48.74±26.46 (range 9-118) months. One patient died of ischemic heart disease 93 months after diagnosis. Patients' disease characteristics and laboratory measurements are depicted in Table 1 and Table 2.

The relationships between NLR, PLR and SII and the characteristics of patients with cHL are presented in Table 3. Patients with stage IV disease (p=0.036), B symptoms (p=0.005), and extranodal involvement (p=0.012) had significantly higher NLR than patients without these characteristics. The PLR values of female patients (p=0.005), patients with B symptoms (p=0.014) and those with extra-nodal involvement (p=0.011) were significantly higher than comparative groups. The SII values of patients with B symptoms were significantly higher than those without (p=0.009).

Correlations between NLR, PLR, SII and other continuous variables are presented in Table 4. Significant correlations were found between NLR and age (r=-0.226, p=0.048), IPS-7 score (r=0.378, p=0.001), albumin (r=-0.280, p=0.014), ESR (r=0.416, p<0.001), CRP (r=0.452, p<0.001), hemoglobin (r=-0.387, p=0.001) and hematocrit (r=-0.387, p<0.001) levels. There were significant correlations between PLR and IPS-7 score (r=0.294, p =0.010), albumin (r=-0.264, p=0.020), ESR (r=0.446, p<0.001), CRP (r=0.541, p<0.001), hemoglobin (r=-0.519, p<0.001), hematocrit (r=-0.515, p<0.001) levels and mean corpuscular volume (MCV) (r=-0.367, p=0.001) values. Also, significant correlations were found between SII and age (r =-0.278, p=0.014), IPS-7 score (r=0.271, p=0.017), GFR (r=0.252, p=0.027), AST (r=-0.300, p=0.008), ALT (r=0.263, p=0.021), ESR (r=0.390, p<0.001), CRP (r=0.519, p<0.001), hemoglobin (r=-0.369, p=0.001),

Table 1. Summary of patients and disease characteristics

Age at diagnosis	37 (24 - 49)
Sex	
Male	48 (62.34%)
Female	29 (37.66%)
ECOG performance score	
0	60 (77.92%)
1	16 (20.78%)
2	1 (1.30%)
Histological subtype	
Nodular sclerosis	39 (50.65%)
Mixed cellularity	32 (41.56%)
Lymphocyte-depleted	1 (1.30%)
Lymphocyte-rich	5 (6.49%)
Other	0 (0.00%)
EBV	
Negative	21 (27.27%)
Positive	25 (32.47%)
Unknown	31 (40.26%)
Stage	
Stage I	3 (3.90%)
Stage II	29 (37.66%)
Stage III	25 (32.47%)
Stage IV	20 (25.97%)
Bulky disease	14 (18.18%)
B symptoms	35 (45.45%)
IPS-7	2 (2 - 3)
Mediastinal mass	35 (45.45%)
Extranodal involvement	16 (20.78%)
Chemotherapy	
ABVD	72 (93.51%)
BEACOPP	1 (1.30%)
GEMOX	0 (0.00%)
Brentuximab	4 (5.19%)
Nivolumab	0 (0.00%)
Radiotherapy	19 (24.68%)
Refractory/Recurrent disease	18 (23.38%)
Autologous stem cell transplantation	18 (23.38%)
Mortality	1 (1.30%)
Follow-up time, months	48.74 ± 26.46

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables
Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, IPS-7: International prognostic scores-7

Table 2. Summary of laboratory measurements

GFR (mL/min/1.73 m^2)	115.61 ± 18.21
AST (IU/L)	18 (16 - 28)
ALT(IU/L)	17 (12.6 - 33)
Albumin (g/dL)	3.96 ± 0.66
ESR (mm/h)	46 (11 - 67)
LDH (mg/dL)	207 (179 - 270)
CRP (mg/L)	12 (2.5 - 72)
Hemoglobin (g/dL)	11.74 ± 2.62
Hematocrit (%)	36.14 ± 6.74
MCV (fl)	81.13 ± 6.89
WBC ($x10^3$)	8.32 (4.96 - 15.47)
Neutrophil ($x10^3$)	5.28 (3.20 - 11.92)
Lymphocyte ($x10^3$)	1.75 ± 0.82
Monocyte ($x10^3$)	0.78 ± 0.47
Eosinophil ($x10^3$)	0.18 (0.08 - 0.34)
Platelet ($x10^3$)	357.53 ± 168.95
NLR	4.06 (1.99 - 6.84)
PLR	180.46 (142.57 - 321.43)
SII ($x10^3$)	1045.39 (515.46 - 2598.73)

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

hematocrit (r=-0.369, p=0.001) levels and MCV (r=-0.257, p=0.024) values.

DFS was 73.54 ± 7.14 (95% CI: 59.54 - 87.54) months (Figure 1). Univariable cox regression analysis revealed that stage at diagnosis and Bulky disease were the only factors independently associated with poor prognosis. Multivariable cox regression revealed that stage at diagnosis was the only factor independently associated with poor prognosis. Patients with stage III & IV cHL at diagnosis had a 4.270-fold higher risk for refractory/ recurrent disease or death compared to patients with stage I & II cHL at diagnosis (HR: 4.270, 95% CI: 1.165 - 15.655, p=0.029, Figure 2) (Table 5).

Discussion

The main findings of the present study were as follows: Firstly, there were significant associations between SII and B symptoms, between NLR and stage IV disease, B symptoms and extranodal involvement, and between PLR and female sex. Secondly, SII, NLR and PLR were not found to be significant markers in predicting poor prognosis. Finally, only Stage III & IV disease and Bulky disease were associated with poor prognosis in the present study [7].

SII is assumed to reflect systemic inflammation in a balanced way, and has been claimed to be a stronger prognostic marker in some malignancies –compared to other systemic inflammation markers such as NLR, PLR and lymphocyte-to-monocyte ratio [1, 17, 21]. However, the relationship between SII and the clinicopathological and prognostic features of HL has not been adequately studied. In the present study, SII was only associated with the presence of B symptoms. There was also a weak correlation between SII and IPS-7 score. Although the presence of B symptoms and a high IPS-7 score are predictors of poor prognosis in HL, no strong relationship was found between SII and these factors of poor prognosis in our study. Mirilli and colleagues showed that SII was an independent predictive factor for both overall survival (OS) and progression free survival (PFS) in HL patients. They also found SII to be a more powerful indicator than other scores and inflammatory parameters including NLR, prognostic nutritional index and B2 microglobulin, as demonstrated by its predictive sensitivity of 73% and specificity of 73% [1]. To our knowledge, there have been no other studies investigating the role of SII in HL, whereas there has been research in patients with nHL [16, 22-24]. In the light of available data, although SII seems to have a prognostic role for nHL, it seems that more comprehensive studies are needed to ascertain its prognostic role in cHL.

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Table 3. Inflammation indices with regard to patient characteristics

	NLR	p	PLR	p	SII	p
Sex						
Male	3.40 (1.92 - 6.79)	0.223	155.02 (133.80 - 271.51)	**0.005**	950.60 (445.10 - 2890.10)	0.185
Female	4.88 (2.16 - 7.07)		227.92 (168.31 - 391.20)		1499.18 (794.92 - 2548.65)	
ECOG performance score						
0	4.14 (1.96 - 7.17)	0.778	171.24 (143.14 - 329.73)	0.615	963.64 (495.73 - 3281.13)	0.893
1 & 2	3.42 (2.54 - 6.57)		218.95 (141.00 - 321.43)		1212.39 (809.34 - 2246.51)	
Histological subtype						
Nodular sclerosis	6.02 (1.99 - 7.90)		195.00 (154.49 - 349.60)		2246.51 (476.77 - 3641.94)	
Mixed cellularity	3.30 (2.05 - 6.06)	0.195	163.62 (140.68 - 315.72)	0.355	902.81 (529.50 - 1425.97)	0.194
Other	2.41 (1.66 - 4.64)		157.32 (136.56 - 218.95)		797.19 (286.51 - 1928.93)	
EBV						
Negative	4.88 (1.66 - 7.07)	0.275	212.03 (158.48 - 310.00)	0.434	1352.75 (448.98 - 3454.05)	0.700
Positive	5.64 (3.11 - 10.42)		280.00 (150.79 - 418.02)		1204.61 (583.10 - 2598.73)	
Stage						
Stage I & II	2.75 (1.75 - 6.63) [a]		160.58 (138.45 - 229.60)		827.90 (402.35 - 2238.79)	
Stage III	4.47 (2.19 - 6.08) [ab]	**0.036**	181.08 (143.70 - 391.20)	0.115	1357.43 (562.49 - 2492.16)	0.118
Stage IV	6.80 (3.27 - 9.15) [b]		214.67 (159.77 - 347.31)		1425.97 (905.88 - 4232.40)	
Bulky disease						
No	3.55 (1.94 - 6.84)	0.345	170.31 (140.91 - 280.00)	0.107	941.92 (476.77 - 2548.65)	0.316
Yes	6.29 (3.19 - 6.84)		306.25 (158.48 - 391.20)		1483.56 (861.43 - 4143.38)	

Table 1 continued next page

B symptom						
No	2.99 (1.58 - 6.08)	**0.005**	155.66 (136.56 - 280.00)	**0.014**	640.06 (395.79 - 2492.16)	**0.009**
Yes	4.88 (2.62 - 8.12)		217.30 (168.75 - 391.20)		1274.81 (867.31 - 3380.79)	
Mediastinal mass						
No	3.25 (1.94 - 6.31)	0.111	157.20 (136.56 - 231.28)	**0.011**	940.11 (476.77 - 2492.16)	0.260
Yes	4.88 (2.43 - 9.37)		217.30 (163.55 - 418.02)		1499.18 (543.54 - 3641.94)	
Extranodal involvement						
No	3.34 (1.94 - 6.31)	**0.012**	170.31 (141.00 - 238.00)	0.058	938.30 (476.77 - 2492.16)	0.092
Yes	6.96 (5.03 - 10.29)		306.25 (157.98 - 385.94)		1479.67 (905.88 - 4963.06)	
R/R or Death						
No	3.78 (1.94 - 7.07)	0.911	180.77 (154.19 - 321.43)	0.408	940.11 (514.69 - 2548.65)	0.339
Yes	5.64 (2.19 - 6.63)		153.11 (126.87 - 396.88)		1499.18 (583.10 - 2689.67)	

Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. Same letters denote the lack of statistically significant difference between groups. The letters in the table represent pairwise comparison results. Each letter provides contextual information regarding the comparative groups and are coded with an approach that reduces clutter. For example: The lettering “a b b” indicates that the first measurement/group is different from the others, and there is no difference between the second and third measurements/groups. The lettering “a ab b” indicates that the first measurement/group and the third measurement/group are different, and the second measurement/group is similar to both other measurements/groups
Abbreviations: EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, R/R: Refractory/Recurrent, SII: Systemic immune inflammation index.

Table 4. Relationships between inflammation indices and other continuous variables

		NLR	PLR	SII
Age at diagnosis	r	**-0.226**	-0.142	**-0.278**
	p	**0.048**	0.219	**0.014**
IPS-7	r	**0.378**	**0.294**	**0.271**
	p	**0.001**	**0.010**	**0.017**
GFR (mL/min/1.73 m2)	r	0.192	0.150	**0.252**
	p	0.095	0.192	**0.027**
AST (IU/L)	r	-0.172	-0.068	**-0.300**
	p	0.135	0.555	**0.008**
ALT (IU/L)	r	-0.155	-0.123	**-0.263**
	p	0.178	0.287	**0.021**
Albumin (g/dL)	r	**-0.280**	**-0.264**	-0.221
	p	**0.014**	**0.020**	0.054
ESR (mm/h)	r	**0.416**	**0.446**	**0.390**
	p	**<0.001**	**<0.001**	**<0.001**
LDH (mg/dL)	r	0.009	-0.105	-0.024
	p	0.939	0.365	0.835
CRP (mg/L)	r	**0.452**	**0.541**	**0.519**
	p	**<0.001**	**<0.001**	**<0.001**
Hemoglobin (g/dL)	r	**-0.387**	**-0.519**	**-0.369**
	p	**0.001**	**<0.001**	**0.001**
Hematocrit (%)	r	**-0.387**	**-0.515**	**-0.369**
	p	**<0.001**	**<0.001**	**0.001**
MCV (fl)	r	-0.193	**-0.367**	**-0.257**
	p	0.093	**0.001**	**0.024**

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, r: Spearman correlation coefficient

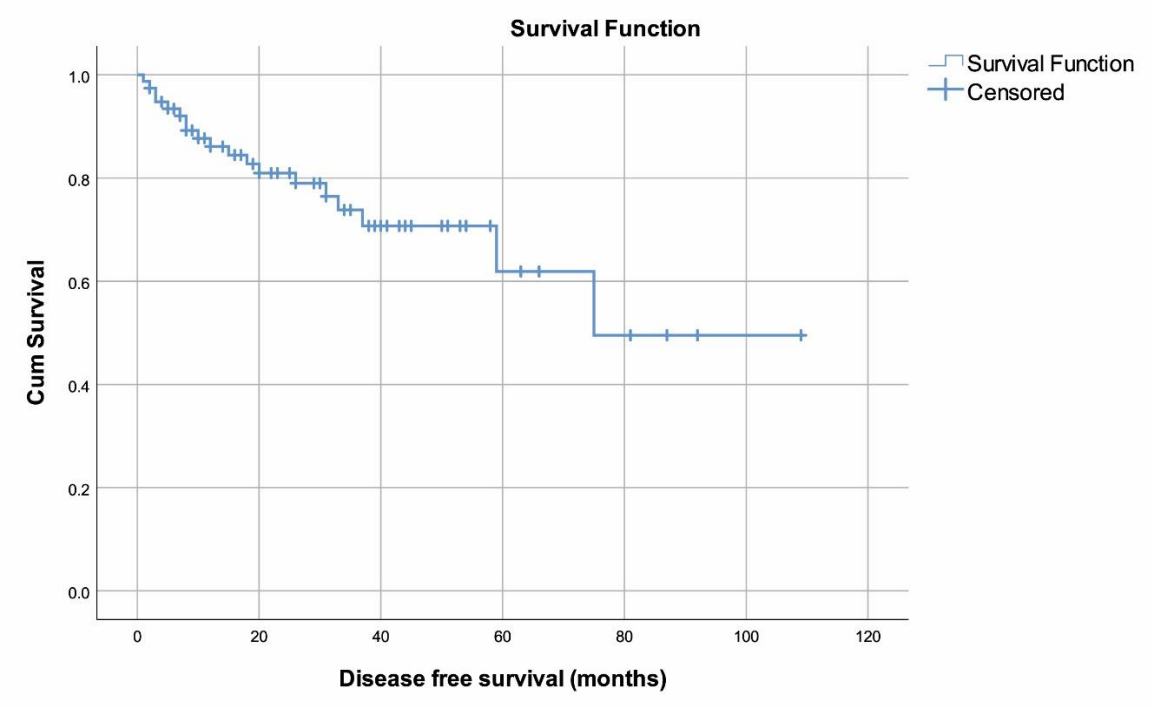

Figure 1. Disease free survival plot

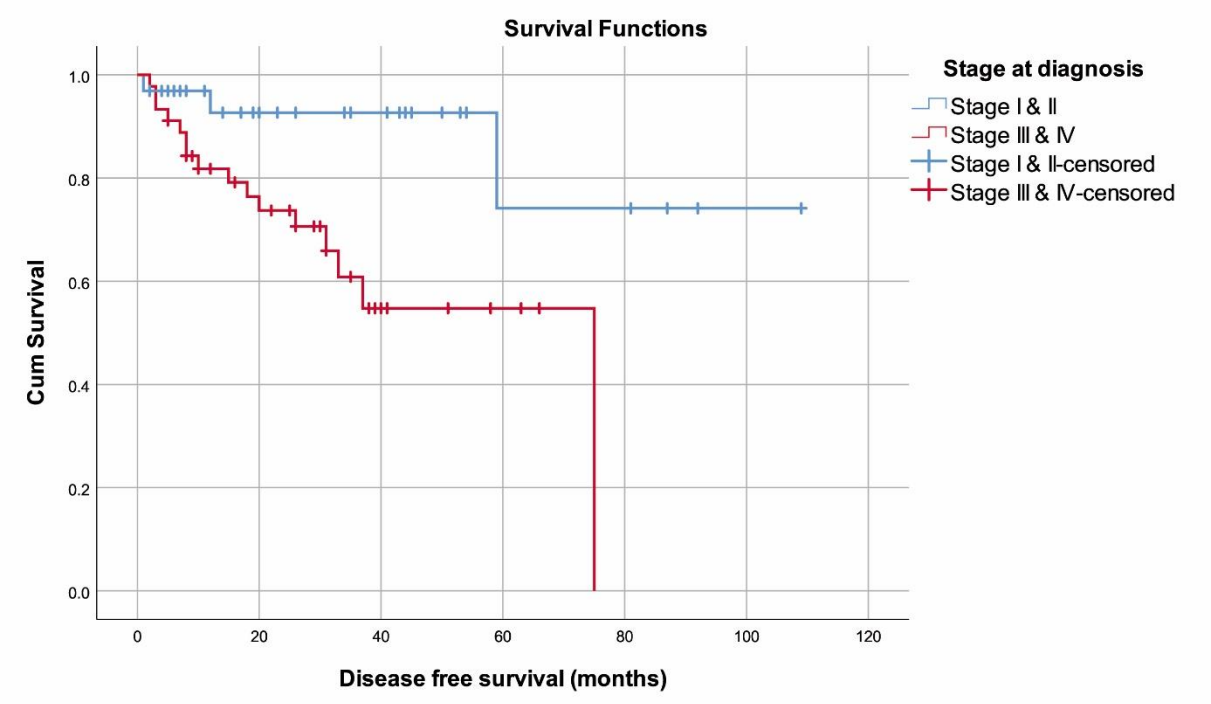

Figure 2. Disease free survival plot with regard to stage

Table 5. Association between variables and poor prognosis (refractory/recurrent disease or death), Cox Regression

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Age at diagnosis	0.981 (0.948 - 1.014)	0.255		
Sex (based female)	0.538 (0.192 - 1.505)	0.237		
ECOG performance score (based ECOG≥1)	1.328 (0.472 - 3.738)	0.591		
Histological subtype (based mixed cellularity)	1.440 (0.577 - 3.590)	0.434		
EBV (based positive)	2.453 (0.651 - 9.252)	0.185		
Stage (based stage III & IV)	4.970 (1.407 - 17.564)	**0.013**	4.270 (1.165 - 15.655)	**0.029**
Bulky disease (based present)	2.986 (1.098 - 8.119)	**0.032**	2.004 (0.722 - 5.557)	0.182
B symptom (based present)	1.662 (0.674 - 4.100)	0.270		
IPS-7	1.027 (0.725 - 1.454)	0.882		
Mediastinal mass (based present)	1.526 (0.594 - 3.924)	0.380		
Extranodal involvement (based present)	1.982 (0.693 - 5.671)	0.202		
Chemotherapy (based ABVD)	0.773 (0.101 - 5.894)	0.803		
Radiotherapy (based present)	0.507 (0.147 - 1.755)	0.284		
GFR (mL/min/1.73 m2)	1.015 (0.991 - 1.039)	0.231		
AST (IU/L)	0.987 (0.953 - 1.023)	0.480		
ALT (IU/L)	0.990 (0.965 - 1.016)	0.445		
Albumin (g/dL)	1.230 (0.598 - 2.529)	0.574		
ESR (mm/h)	1.003 (0.989 - 1.018)	0.655		
LDH (mg/dL)	1.000 (0.997 - 1.003)	0.947		
CRP (mg/L)	1.002 (0.995 - 1.010)	0.583		
Hemoglobin (g/dL)	0.951 (0.802 - 1.128)	0.567		
Hematocrit (%)	0.984 (0.922 - 1.052)	0.642		
MCV (fl)	1.078 (0.994 - 1.168)	0.070		
WBC ($x10^3$)	1.045 (0.986 - 1.108)	0.141		
Neutrophil ($x10^3$)	1.047 (0.977 - 1.123)	0.193		
Lymphocyte ($x10^3$)	1.628 (0.918 - 2.885)	0.095		
Monocyte ($x10^3$)	1.681 (0.717 - 3.939)	0.232		
Eosinophil ($x10^3$)	1.327 (0.546 - 3.228)	0.533		
Platelet ($x10^3$)	1.002 (0.999 - 1.004)	0.197		
NLR	0.990 (0.913 - 1.074)	0.811		
PLR	0.999 (0.997 - 1.002)	0.656		
SII ($x10^3$)	1.000 (1.000 - 1.000)	0.917		

Abbreviations: ABVD: Doxorubicin, bleomycin, vinblastine and dacarbazine, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CI: Confidence interval, CRP: C-reactive protein, EBV: Epstein-Barr virus, ECOG: The Eastern Cooperative Oncology Group, ESR: Erythrocyte sedimentation rate, GFR: Glomerular filtration rate, HR: Hazard ratio, IPS-7: International prognostic scores-7, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune inflammation index, WBC: White blood cell count

It is known that platelets play an important role in the spread and growth of tumors [25] and platelet related markers are suggested to be prognostic factors for solid tumors [26, 27]It has also been shown that platelets play a critical role in the spread of Hodgkin-Reed Sternberg cells, especially in the spleen [28]. In the current study, a significant association was found between PLR and B symptoms and mediastinal mass. There was also a weak correlation between PLR and IPS-7 score. However, PLR was not found to be a significant marker for cHL prognosis. Reddy et al. showed that 2-year PFS was 84.3% for early cHL patients with a PLR of ≥266.2, which was significantly lower compared to the 96.1% 2-year PFS of patients with a PLR of <266.2. PLR remained a significant, independent prognostic factor. Also, high PLR (≥266.2) was also associated with advanced Ann-Arbor stage, B symptoms, and Bulky disease [12]. In another study high PLR was shown to be associated with lower likelihood of complete treatment response in patients with HL, and high PLR was independently associated with shorter PFS [15]. In contrast, similar to our findings, PLR was not found to be a prognostic factor for HL in other studies [29]. PLR seems to have the potential to be a prognostic marker for HL but available evidence needs to be supported by randomized controlled trials.

NLR has also been used for the prognostication of many types of

malignancies, including lymphomas [1, 6, 12]. Our results showed that NLR was associated with Stage IV disease, B symptoms, and extranodal involvement. Also, there was a weak correlation between NLR and IPS-7 score, but NLR was not a reliable predictor for poor cHL prognosis. In a comprehensive retrospective study, it was reported that 2-year PFS for early cHL patients with an NLR of ≥6.4 was 82.2% versus 95.7% among those with an NLR of <6.4. Similar to high PLR, having high NLR (≥6.4) was also associated with advanced Ann-Arbor stage, B symptoms and Bulky disease [12]. In another study in pediatric HL patients, it was reported that patients with an NLR of >3.5 had significantly higher stage and greater frequency of Bulky disease and B symptoms [14]. High NLR values have also been associated with disease stage, early-stage risk scoring, and response to treatment [6]. We did not find any notable association between prognostic characteristics and NLR in the present study, which has been reported before in patients with HL [29].

As a general comment, unfortunately, current prognostic models have not shown satisfactory success in early detection of HL patients at high risk of shortened survival [30]. For example, IPS has little clinical benefit, because only 19% of patients with scores of 4 and 5 are found to have a less than 50% probability of 7-year PFS [31, 32]. IPS calculation is usually preferred for high-stage HLs. Considering these disadvantages, it is undoubtedly crucial to obtain further data to assess the roles of inflammation markers such as NLR, PLR and SII in cHL, particularly since these markers are readily-available, easy to access and low cost.

Despite being one of the first studies to assess these markers in patients with cHL, the limitations of the present study must be considered when interpreting the results. This is a single-center retrospective study with a relatively small sample size, and thus, there were a low number of deaths in the study group which made OS-related analyses impossible. In addition, the number of recurrences may be considered insufficient, which may impact the results concerning DFS. Although factors thought to affect the inflammatory markers were assessed to exclude patients, some relevant data of patients may not have been recorded in the database. The follow-up period of the patients who were diagnosed towards the end of the study may have been short. The patients included in the study were diagnosed between 2012 and 2021, and changes or advances in patient management may have affected the findings. As the number of similar studies was limited (especially for SII), there were inadequacies in comparative analyses with the literature.

Conclusion

SII was associated with B symptoms, NLR with Stage IV disease, and PLR with B symptoms and mediastinal mass. There were weak correlations between all three markers and IPS-7; however, none of the inflammation indices were found to be prognostic for cHL. Taken together with the limited literature, it is evident that current data is insufficient for the use of pretreatment SII, NLR, and PLR in the prognostication of cHL disease

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