The Prognostic Significance of Prognostic Nutritional Index in Diffuse Large B Cell Lymphoma Patients

Merih Reis ARAS[1], Fatma YILMAZ[1], Mesut TIGLIOGLU[2], Bugra SAGLAM[3], Busra YUZGENC[4], Hacer Berna AFACAN OZTURK[1], Umit Yavuz MALKAN[5], Murat ALBAYRAK[1]

[1] Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Hematology
[2] Gaziantep Ersin Arslan Training and Research Hospital, Department of Hematology
[3] Sanliurfa Mehmet Akif Inan Training and Research Hopsital, Department of Hematology
[4] Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Internal Medicine
[5] Hacettepe University, Faculty of Medicine, Department of Hematology

ABSTRACT

The aim of the study was to determine the prognositc value of baseline prognostic nutritional index (PNI) in diffuse large B cell lymphoma (DLBCL) patitens. A retrospective analysis was made of patients diagnosed with diffuse large B cell lymphoma in our department between January 2012- February 2022. Patiens treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone were included the study. A receiver operating characteristic (ROC) curve analysis was used to identify the cut-off value of PNI. The prognostic role of PNI and survival outcomes were evaluated. One hundred and one patients with a median age of 66 [20-86] were included the study. The cut-off value of PNI was 48.8. Patients divided into two groups according to the PNI cut-off value. Compared to the PNI-low group (PNI ≤ 48.8), the PNI-high group (PNI > 48.8) had a significantly better overall survival and progression-free survival ($p< 0.030$ and $p< 0.11$, respectively). PNI can be used as a simple and useful predictor of prognosis in DLBCL patients.

Keywords: Diffuse large B cell lymphoma, Prognostic nutritional index, Albumin, Lymphocyte, Survival

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30-40% of all non-Hodgkin lymphomas. It is the most common subtype of non-Hodgkin lymphoma. Although it has an aggressive course, remission is achieved in 60-70% of patients with the standard chemotherapy protocol of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). However, approximately one third of the cases are resistant to the standard chemotherapy protocol. Gene expression profile and International Prognostic Index (IPI) are parameters used to identify high-risk patients.[1]

The Prognostic Nutritional Index (PNI) is a scoring system calculated by serum albumin and lymphocyte values. It reflects the nutritional and immune status of patients.[2]

It is stated that PNI, which is an indicator reflecting the nutritional and immune status of patients, can be used to predict the clinical outcomes of patients with various malignant tumors, regardless of the location and origin of the tumor in recent studies. There are studies that this prognostic index can be used to predict overall survival and disease-free survival in DLBCL.[3]

PATIENTS and METHODS

A retrospective evaluation was made of patients with DLBCL diagnosed in the Hematology Department of the University of Health Sciences Ankara Diskapı Yildirim Beyazit Training and Research Hospital in the period between January 2012- October 2022. Patient files were analyzed retrospectively. Patients treated with R-CHOP regimen were included in the study. Pregnant women, patients under the age of 18, patients diagnosed as having primary central nervous system lymphoma, acquired immunodeficiency syndrome related lymphoma, or with Richter's transformation were excluded. Patients who had a history of solid organ malignancy or who were treated with a regimen other than R-CHOP were also excluded. A total of 101 patients were included in the study. Age, gender, disease stage, ECOG performance status, R-IPI score, beta-2-microglobulin, serum albumin, serum lactate dehydrogenase and lymphocyte values at the time of diagnosis were recorded. The laboratory values of serum albumin and absolute lymphocyte count were noted and PNI scores were calculated. PNI is calculated with the formula below;

PNI= 10 x albumin (g/dL) + 0.005 x lymphocyte count (/mm^3)

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

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 our hospital, the patient records confirmed that all the study patients gave informed consent at the time of hospitalization and before the administration of any intervention. The study was approved by University of Health Sciences Turkey, Ankara Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (protocol no: 136/10 , date: 25/04/2022).

Statistical Analysis

Study data were analyzed using SPSS 21 software. Descriptive data were given as a percentage. Descriptive statistics and frequency tables were used. A receiver operating characteristic (ROC) curve analysis was used to identify the cut-off value of PNI. Examination of numerical variables in terms of this cut-off value was analyzed with the t test. The relationship between the PNI cut-off value and categorical variables was analyzed with the Chi-square test. The effect of the variables on survival was analyzed by logistic regression test.

RESULTS

Of the 101 DLBCL patients included the study, 48 (47.5%) were female and 53 (52.5 %) were male. The median age was 66 [min 20-max 89]. Thirty-five (34.7%) of patients were ≤ 60 years and 66 (% 65.3) were > 60 years. At the time of diagnosis, 44 (43.6%) patients were stage I-II and 57 (56.4%) were stage III-IV. Patients were classified as very good, good, and poor-risk groups according to R-IPI score. According to R-IPI score, 11 (10.9 %) patients were very good, 39 (38.6%) were good and 51 (63.4%) were poor risk group. The demographic and clinical features of the patients at the time of diagnosis are given in Table 1.

In laboratory findings of patients, median lymphocyte value was 1460 x10^6/L (min 300-max 4470) and median albumin value was 3.7 g/dl (min 1,5-max 5,3). The laboratory findings of patient at the time of diagnosis are given in Table 2.

In ROC analyse, the cut-off value for the PNI was 48.8 (Figure 1). Patients divided into two groups according to the cut-off value for the PNI. There is a significant relationship between PNI cut-off value and LDH, age, R-IPI risk group. In R-IPI very good risk group 63.6% of patients PNI cut-off value was > 48.8. While PNI cut-off value was ≤48.8 in 61.5% of patients in R-IPI good risk group and 80.4% of patients in R-IPI poor risk group (p< 0.009). PNI cut-off value was > 48.8 in 51.4 of ≤ 60

Table 1. The demographic and clinical features of the patients at the time of diagnosis

Characteristics		n (%)
Gender	Female	48 (47.5)
	Male	53 (52.5)
Age	≤ 60	35 (34.7)
	> 60	66 (65.3)
Ann-Arbor Stage	1	17 (16.8)
	2	27 (26.7)
	3	38 (37.6)
	4	19 (18.8)
ECOG PS	0	22 (21.8)
	1	47 (46.5)
	2	23 (22.8)
	3	7 (6.9)
	4	2 (2)
LDH	N	37 (36.6)
	> N	64 (63.4)
R-IPI	Very good (0)	11 (10.9)
	Good (1-2)	39 (38.6)
	Poor (3-5)	51 (63.4)

ECOG PS: Eastern Cooperative Oncology Group Performance Status LDH: Lactate dehydrogenase; R-IPI: Revised International Prognostic Index

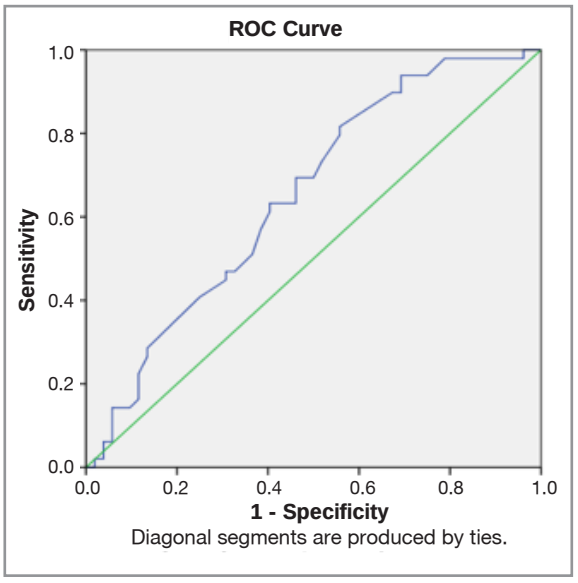

Figure 1. ROC analyse for PNI

Table 2. Laboratory findings of patient at the time of diagnosis

	Median	Min-Max
White blood cell (x10⁶/L)	8200	1740-20550
Lymphocyte (x10⁶/L)	1460	300-4470
Hemoglobin (gr/dl)	12,2	6.8-16.2
Platelet (x10⁶/L)	267000	10-1089
LDH (U/L)	257	120-4527
Albumin (gr/dl)	3.7	1.5-5.3
PNI	44	16.5-66

PNI: Prognostic Nutritional Index, LDH: Lactate dehydrogenase

aged patients and ≤ 48.8 in 78.8% of > 60 aged patients (p< 0.004). PNI > 48.8 in 56.8 % of LDH normal patients and PNI ≤ 48.8 in 82.8 of LDH elevated patients (p< 0.000). Comparison of parameters between groups according to PNI cut-off value are given in Table 3.

Overall survival was singificantly longer in PNI> 48.8 group compaired with PNI ≤ 48.8 group (53.97 months and 35.6 months, respectively, p< 0.030). Progression free survival was singificantly longer in PNI> 48.8 group compaired with PNI≤ 48.8 group (41.59 months and 20.8 months, respectively, p< 0.011). Comprasion of overall survival and progression free survival according to PNI are given in Table 4. Univariate and multivariate logistic regression analysis for survival are given in Table 5. Univariate logistic regression analysis was performed to identify the risk factors for survival.

Revised-IPI poor risk group, elevated LDH, PNI≤ 48.8, age > 60 and stage 3-4 were poor risk factors for survival. In R-IPI poor risk group, exitus risk was 21.875 times higher than good risk group. In R-IPI good risk group, exitus risk was 5.00 times higher than very good group. Patients with elevated LDH value had 4.122 times higher risk of exitus those patients with normal LDH value. In PNI≤48.8 group, patients had 3.521 times higher risk of exitus than PNI > 48.8 group.

In > 60 aged patients, exitus risk was 2.961 times higher than ≤ 60 aged patients. In > 60 aged patients according to PNI cut off value, median OS was 29.62±33.84 months in PNI ≤ 48.8 group and 41.64±34.3 months in PNI > 48.8 group, median PFS was 19.58±25.13 months in PNI ≤ 48.8 group and 25.93±24.06 months in PNI > 48.8 group (p=

Table 3. Comparison of parameters between groups according to PNI

		PNI cut-off value				Chi-square	p
		≤48.8		>48.8			
		n	%	n	%		
Age	≤ 60	17	48,6	18	51,4	8,302	0,004*
	> 60	52	78,8	14	21,2		
LDH	N	16	43,2	21	56,8	15,181	0,000*
	> N	53	82.8	11	17.2		
ECOG	0-2	62	67.4	30	32.6	0.409	0.523
	3-4	7	77.8	2	22.2		
Stage	1-2	28	63.6	16	36.4	0.452	0.501
	3-4	41	71.9	16	28.1		
R-IPI	very good	4	36.4	7	63.6	9.452	0.009*
	good	24	61.5	15	38.5		
	poor	41	80.4	10	19.6		

R-IPI: Revised International Prognostic Index (very good:0, good: 1-2, poor:3-5)

0.244 and p= 0.400, respectively). Median OS and PFS values according to PNI cut off value are given in Figure 2.

Exitus risk was 2.858 times higher in stage 3-4 patients than stage 1-2 patients. In multivariate logistic regression analysis there was any significant risk factors for survival.

DISCUSSION

Nutritional status is a key factor affecting treatment response and prognosis in patients with malignancy. 30-40% of malignant patients suffer from malnutrition. Malnutrition can lead to many adverse clinical outcomes, mainly increased mortality and morbidity and decreased survival.[4,5]

Table 4. Comprasion of overall survival (OS) and progression free survival (PFS) according to PNI

	PNI cut-off value				t	p
	≤ 48,8		> 48			
	Mean	SD	Mean	SD		
OS (months)	35.64	36.23	53.97	44.30	-2.201	0.030*
PFS (months)	20.80	24.91	41.59	40.92	-2.656	0.011*

OS: Overall survival, PFS: progression free survival; SD= standard deviation

Table 5. Univariate and multivariate logistic regression analysis for survival

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
R-IPI (good)	5.000	0.576-43.388	0.144	2.144	0.107-42.811	0.618
R-IPI (poor)	21.875	2.576-185.745	0.005*	2.658	0.122-57.973	0.534
LDH (> N)	4.212	1.743-10.179	0.001*	1.761	0.462-6.714	0.407
PNI (> 48.8)	0.284	0.115-0.703	0.006*	0.575	0.149-2.213	0.421
Age (≥ 60)	2.961	1.247-7.03	0.014*	1.494	0.334-6.677	0.599
Stage (3-4)	2.858	1.262-6.474	0.012*	1.464	0.408-5.26	0.559-

CI: Confidence Interval

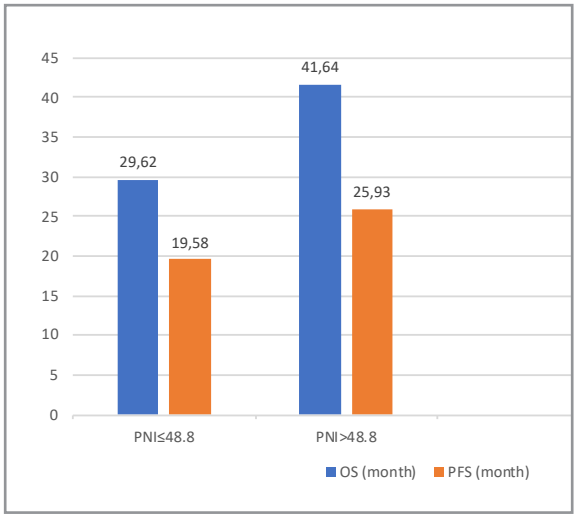

Figure 2. Median OS and PFS values according to PNI cut off value in > 60 aged patients

However, none of these methods alone can provide an accurate prognosis estimation. Each of these methods has its own limitations; These can be listed as high costs, invasive methods, subjectivity, and the need for special methods. The ideal prognostic estimation method; it should be noninvasive, easy to use, low cost and standardized.[6]

The prognostic nutritional index (PNI) was first proposed by Buzby in 1980; It was calculated by albumin, transferrin, triceps skinfold and skin test reactivity. However, its clinical application was limited due to the subjectivity of triceps skinfold and skin test reactivity.[6,7] Onodera modified the formula in 1984 to the following: PNI=albumin (g/L)+ 5 × absolute lymphocyte count (10^9/L). Compared to the initial formula, the modified formula was easy to perform, low cost and standardized design.[6,8]

Some studies have investigated the prognostic value of PNI in Hodgkin lymphoma, Diffuse large B-cell lymphoma, Follicular lymphoma and Extranodal NK/T-cell lymphoma.[6] In the meta-analysis of Luan et al.[3] data from 7 studies involving a total of 1311 patients were analyzed. The prognostic value of PNI in DLBCL patients was evaluated in this meta-analysis. The results of the study revealed low PNI was an important prognostic marker for poor OS and poor PFS, regardless of ethnicity.

Perisa et al.[9], evaluated the significance of PNI as a predictor of response to treatment, overall survival (OS) and event-free survival (EFS). They analyzed data from 103 DLBCL patients treated with R CHOP or R CHOP-like regimens. In ROC analyse, the cut-off value for the PNI was 44.55. Lower PNI levels were were associated with poor response to treatment and Ann Arbor advanced clinical stage.

Ozturk· et al.[10] evaluated the effect of PNI score on prognosis and survival in patients with high risk DLBCL. One hundred an one patients diagnosed with DLBCL and treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone were included to the study. Patients were divided into three groups according to the cut-off value for the PNI: patients with PNI < 33 were classified as high-risk, 33-42 intermediate-risk, and ≥ 42 as low-risk. According to PNI, median durations of PFS and OS were 2 months and 3 months in the high-risk group, 9 months and 19 months in the intermediate-risk group respectively (p= 0.001). The median duration for PFS and OS could not be reached in the low risk group.

In our study, compared to the PNI-low group, the PNI-high group had a significantly better overall survival and progression-free survival. In univariate analyses, age > 60 years, increased LDH, stage 3-4 disease, R-IPI poor risk group was found to be associated with poor survival. These findings supports previous studies.

The exact mechanism for the association of low PNI values with poor prognosis is unclear, but several possible explanations exist

1. Hypoalbuminemia may be due to malnutrition. Malnourished patients may have weaker treatment tolerance and shows poor response to treatment compared to wellnourished patients.

2. The cytokines released from tumoral cells (TNF-alfa and IL-6) can cause lymphopenia and a decrease in serum albumin concentration. This indicates the disease is stromgly aggressive.

3. Pre-existing immunosupression can be caused low absolute lymphocyte count. Low absolute lymphocyte count indicates that the antitumor immunological reaction of the host was insufficient.

4. Lympholytic cytokines arising from lymphoma cells was possibly caused low absolute lymphocyte count. Therefore, intrinsic treatment resistance could be seen in these lymphomas .[3,11-15]

Conclusion

In concluson, our study demostrated that low PNI correlated with unfavorable survival. PNI is an accessible, easy and reliable tool . Therefore, PNI can be used as a simple and useful predictor of prognosis in DLBCL patients. Patients with a low PNI value should be evaluated more carefully for possible poor prognosis.

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Correspondence:

Dr. Merih Reis ARAS

Diskapi Yildirim Beyazit Egitim ve Arastirma Hastanesi

Hematoloji Bolumu

Diskapi, ANKARA / TURKIYE

Tel: (+90-506) 661 16 18

e-mail: merihreis@gmail.com

ORCIDs:

Merih Reis Aras	0000-0002-9161-5582
Fatma Yilmaz	0000-0001-6112-3950
Mesut Tiglioglu	0000-0002-4111-2004
Bugra Saglam	0000-0001-8342-990X
Busra Yuzgenc	0000-0001-7366-8165
Hacer Berna Afacan Ozturk	0000-0001-9386-7604
Umit Yavuz Malkan	0000-0001-5444-4895
Murat Albayrak	0000-0003-4025-741X