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Prognostic nutritional index as a predictor of prognosis in patients with diffuse large B cell lymphoma

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Summary
Background The prognostic nutritional index (PNI), an indicator of nutritional status and systemic inflammation, is associated with short-term and long-term outcomes of various malignancies. The prognostic value of PNI in diffuse large B cell lymphoma (DLBCL) remains unknown. The aim of the present study was to determine the prognostic value of baseline PNI in DLBCL patients.
Methods We retrospectively analyzed data from 103 DLBCL patients treated with R-CHOP or R-CHOP-like regimens. We evaluated the significance of PNI as a predictor of response to treatment, overall survival (OS) and event-free survival (EFS).
Results Patients with a PNI ≤ 44.55, where the cut-off was calculated by receiver operating characteristics (Youden index) and the same was obtained for response to treatment with 76.2 % sensitivity and a specificity of 85.4 %, for OS with 72.4 % sensitivity and a specificity of 90.5 % and for EFS with 65.6 % sensitivity and a specificity of 90.1 %, had significantly worse 5-year OS (18.3 % vs 86.4 %, $P < 0.001$, log rank test) and 5-year EFS (15.1 % vs 82.3 %, $P < 0.001$, log rank test). Regression analysis showed that PNI ≤ 44.55 was an independent prognostic factor for response to treatment with an odds ratio (OR) of 4.88 for treatment failure, 95 % confidence interval (CI) 1.077–22.105, OS hazard ratio (HR) 4.24, 95 % CI 1.451–12.392 and EFS HR 4.007, 95 % CI 1.48–10.852. Lower PNI levels were found in patients with advanced Ann Arbor clinical stage (46.6 ± 7.77 vs. 52.7 ± 5.43) and in those with poor response to therapy (40.58 ± 7.26 vs. 50.67 ± 6.26).
Conclusions The PNI is a simple and useful marker to predict long-term survival outcome in DLBCL patients. Low PNI predicted poor outcome. A limitation of the study is its retrospective design in which the prognostic value was tested in the derivation cohort only. Notwithstanding, this is the first study suggesting that PNI is an important prognostic factor in DLBCL.

Keywords Lymphoma, large B-cell, diffuse · Prognostic nutritional index · Prognostic marker · Prognosis

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most frequent type of lymphoma, accounting for 25–35 % of all non-Hodgkin's lymphomas (NHL) [1, 2]. The

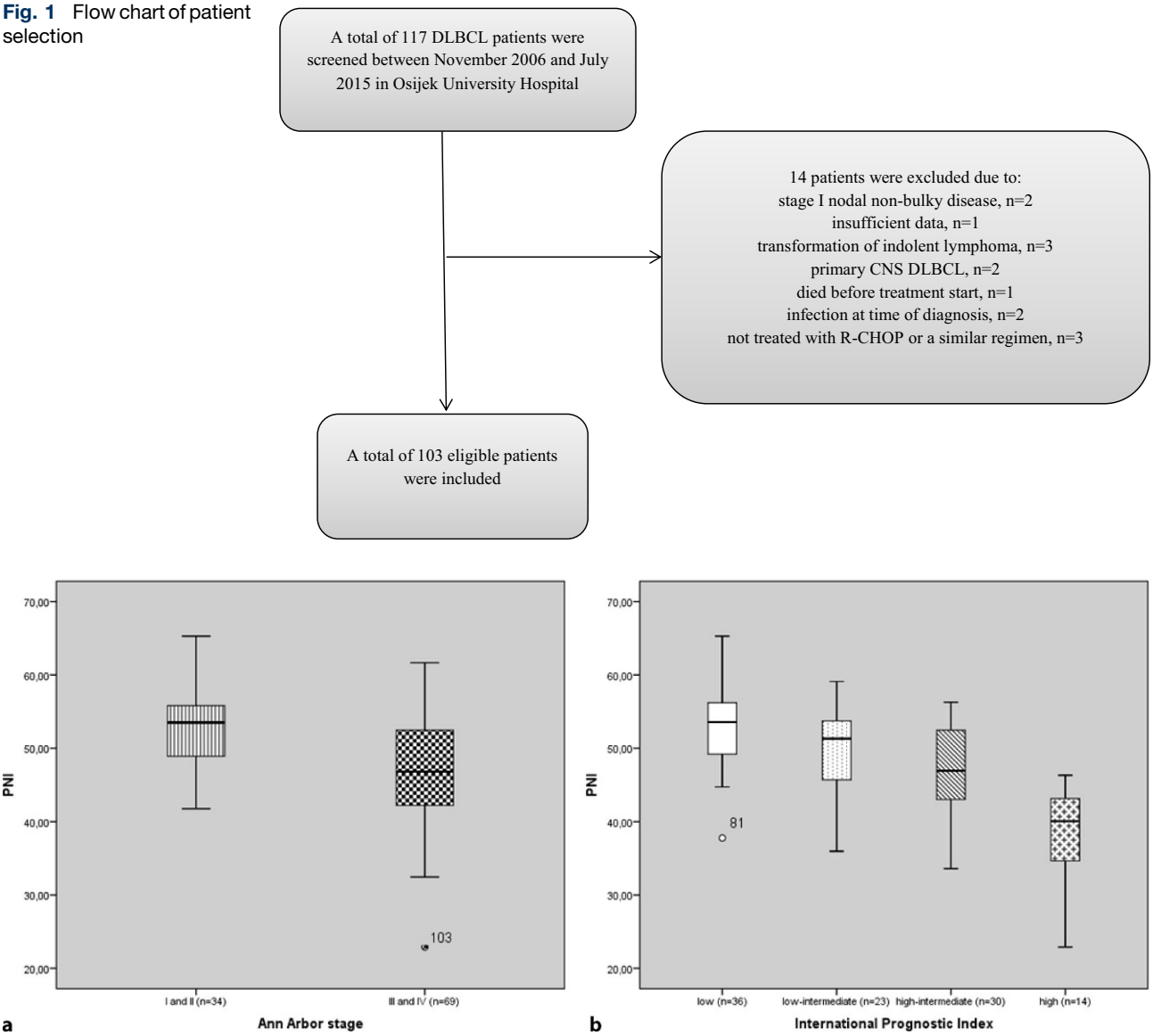

Fig. 1 Flow chart of patient selection

Fig. 2 Baseline prognostic nutritional index (PNI) in patients with diffuse large B-cell lymphoma ($N = 103$) **a** according to Ann Arbor clinical staging and **b** according to International Prognostic Index score

international prognostic index (IPI) and its variants adapted for younger, elderly (e.g. age-adjusted IPI) and patients treated with rituximab (e.g. revised R-IPI) are so far the only widely accepted and validated clinical prognostic indices for this disease [3, 4]; however, as some patients with favorable IPI fail treatment and vice versa, more precise prognostic markers are sought. Some prognostically significant molecular and immunohistochemical characteristics of DLBCL have been identified but cost and technical constraints make their routine application impractical; therefore, finding surrogate inexpensive and readily available prognostic markers could present an important contribution to improved determination of risk assessment of individual patients. Studies have shown that low baseline absolute lymphocyte count (ALC) and low serum albumin levels were negative prognostic markers in patients with DLBCL but the influence of both parameters together has not been analyzed [5–9]. The prognostic nutritional index (PNI) is an indicator of nutritional status and systemic inflammation. It is calculated according to the published formula: serum albumin (g/l) + 5 × ALC ($\times 10^9$/l) [10, 11]. The usefulness of PNI was first proposed by Buzby et al. [10] in 1980 and its importance was confirmed by Onodera et al. in 1984 [11]. Numerous studies have shown that a low PNI is an independent negative prognostic factor in many types of cancer, such as gastric cancer, pancreatic cancer, hepatocellular cancer, lung cancer, esophageal cancer and malignant pleural mesothelioma [12–14]. Studies on lymphomas are scarce [15, 16]. Recently, PNI was identified as a predictor of survival in patients with extranodal natural killer/T cell lymphoma, nasal type

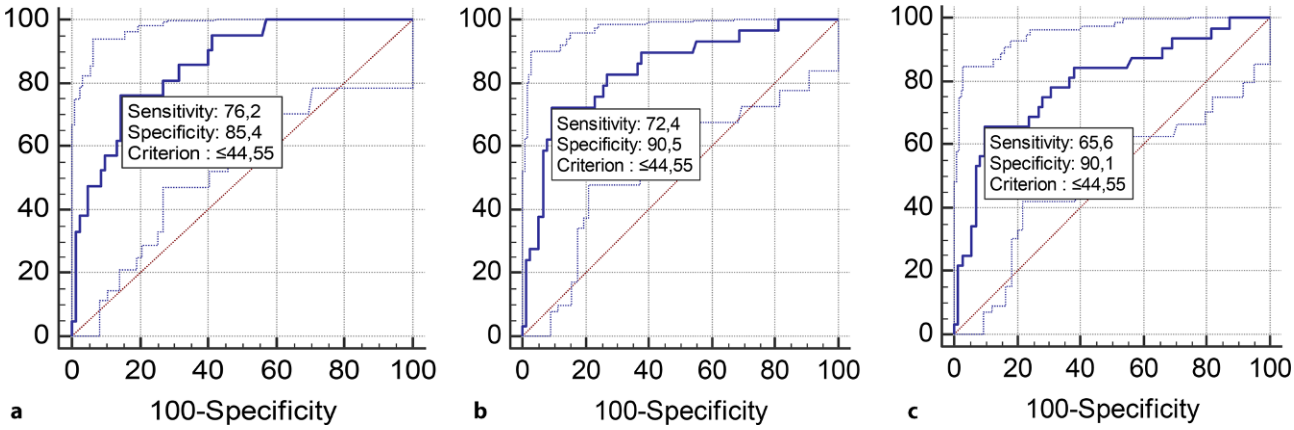

Fig. 3 Receiver operating characteristic curves (ROC) of prognostic nutritional index (PNI) in patients with diffuse large B-cell lymphoma (DLBCL) ($N = 103$) for differentiating **a** response to treatment ($P < 0.001$), **b** overall survival ($P < 0.001$), **c** event-free survival ($P < 0.001$)

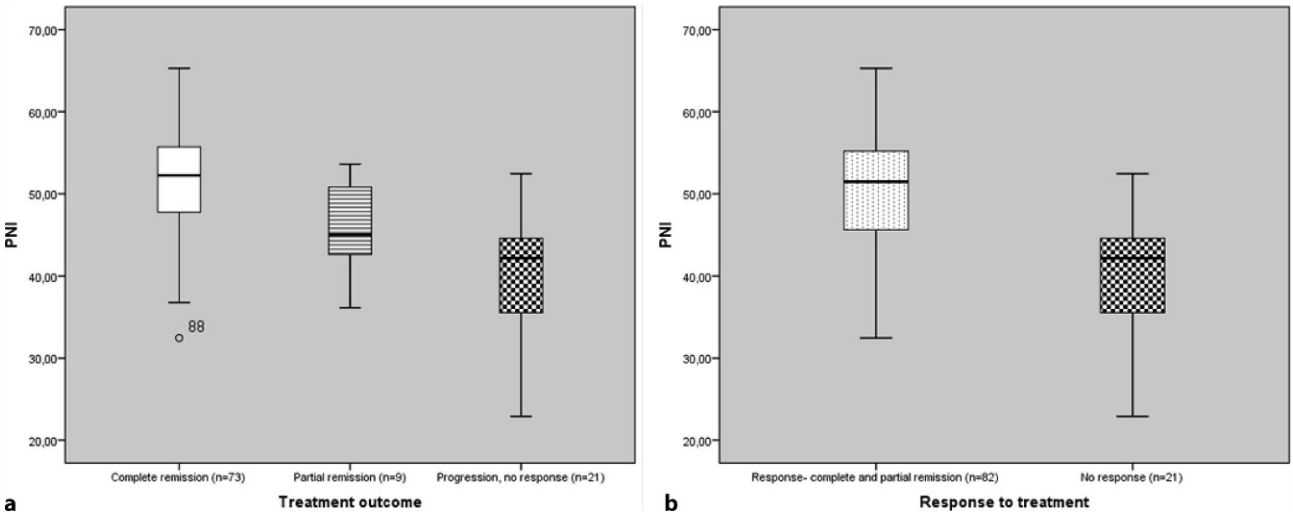

Fig. 4 Baseline prognostic nutritional index (PNI) in patients with diffuse large B-cell lymphoma (DLBCL) ($N = 103$) **a** according to the treatment outcome and **b** according to response to treatment

[15] and in human immunodeficiency virus (HIV) patients with NHL [16].

So far, there have been no reports on the prognostic value of PNI in patients with DLBCL. The aim of our study was to determine whether baseline PNI was an independent prognostic factor for response to treatment, overall survival (OS) and event-free survival (EFS) in patients with DLBCL.

Patients and methods

This retrospective study used data from 103 consecutive patients with histologically proven DLBCL, diagnosed between November 2006 and July 2015 and treated with R-CHOP or R-CHOP-like regimens at the University Hospital Osijek, Osijek, Croatia. Patients with disease stages II–IV, IE (i.e. localized involvement of a single extranodal organ or site in the absence of any lymph node involvement) or I bulky (i.e. measurable tumor mass >10 cm in diameter or a mediastinal mass >1/3 of the chest diameter) who were initially planned for at least 4 cycles of immunochemotherapy and for whom all necessary laboratory and clinical data were available, were included in the study. Those with transformed indolent lymphoma, post-transplant DLBCL, HIV-associated DLBCL, primary central nervous system (CNS) DLBCL and with clinical evidence of infection or active chronic inflammatory disease (e.g. asthma, arthritis, inflammatory bowel disease and psoriasis) at the time of diagnosis were excluded from the study.

The following demographic characteristics, clinical features and laboratory parameters were collected from medical records: age, disease stage, IPI, presence of B symptoms, red blood cell (RBC), white blood cell (WBC), platelet count, absolute neutrophil count (ANC), ALC, lactate dehydrogenase (LDH), C-reactive protein (CRP), albumin, hemoglobin (Hb) and ferritin levels, Eastern Cooperative Oncology Group performance status (ECOG-PS) and the number of involved

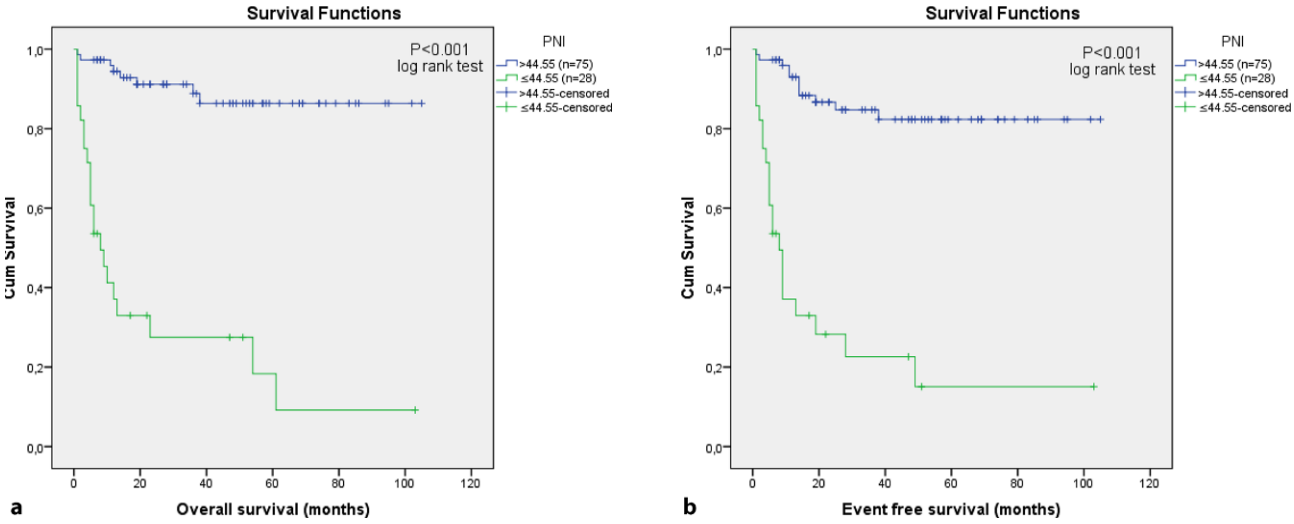

Fig. 5 Survival curve for **a** overall survival according to baseline prognostic nutritional index (PNI) level (≤44.55, >44.55) in patients with diffuse large B-cell lymphoma (DLBCL) (*N* =103), **b** event-free survival according to baseline prognostic nutritional index (PNI) level (≤44.55, >44.55) in patients with DLBCL (*N* =103)

extranodal localizations. The IPI used five baseline characteristics, i.e. age, ECOG PS, serum LDH, Ann Arbor (AA) disease stage and number of extranodal involvement, to stratify patients into low (IPI = 0–1), low–intermediate (IPI = 2), high–intermediate (IPI = 3) and high-risk (IPI = 4–5) groups.

The PNI was calculated according to the published formula [10, 11]. Initial PNI and laboratory parameters were defined as values obtained within 2 weeks before treatment start.

Most patients (89 %) were treated with standard R-CHOP 21 immunochemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. The remaining 11 patients received R-CHOP-like regimens.

The outcomes analyzed were response to treatment, EFS and OS. Response to treatment was determined according to the International Working Group criteria [17]. The EFS was calculated from the date of diagnosis until the date of one of the following events: disease progression, initiation of another antilymphoma treatment, relapse or death irrespective of cause. The OS was calculated from the date of the diagnosis until the date of death due to any cause or until the latest control.

Statistical analysis

The MedCalc statistical software, version 11.4.2.0 (Ostend, Belgium) was used for receiver operating characteristics (ROC) curve calculation and SPSS, version 15.0 (Chicago, IL) for all other statistical analyses. Variables were tested for normality using the Kolmogorov-Smirnov test. Descriptive statistics are presented as follows: continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and those with not normal distribution as median and range (minimum–maximum), categorical variables are expressed as absolute and relative frequencies. Survival curves were estimated using Kaplan-Meier method and differences in survival were assessed using the log-rank test. The ROC curve of PNI was calculated to determine the optimal predictive cut-off values for response to treatment, OS and EFS. To determine the optimal cut-off values of PNI for response to treatment, OS and EFS, the Youden index [18] was calculated (sensitivity + specificity – 1) and the maximum value of the Youden index was considered as the optimal cut-off point. Univariable and multivariable analyses with a Cox proportional hazards model or logistic regression model were performed to assess significant predictors. A *P*-value < 0.05 was considered statistically significant.

Results

Study subjects and PNI

Between 2006 and 2015 a total of 117 patients with DLBCL were diagnosed and treated at our institution of which 14 were excluded from the analysis: 2 with stage I nodal non-bulky disease, 11 due to insufficient data, 3 due to transformation of indolent lymphoma, 2 for primary CNS disease, 1 who died before treatment start, 2 due to infection at the time of diagnosis and 3 who were not treated with R-CHOP or a similar regimen. The details of the patient selection process are shown in Fig. 1. Of the patients 66 were women and the median age was 63 years (range 22–87 years) (Table 1.). The median value of the PNI was 50.26, with a range from 22.91 to 65.3.

Table 1 Baseline characteristics and treatment outcome in DLBCL patients (overall and divided according to PNI value)

Variable	Overall	PNI	
	N (103)	>44.55 (*n* = 75)	≤44.55 (*n* = 28)
Age in years, median (minimum – maximum)	63 (22–87)	62 (22–81)	67.5 (37–87)
Age group, *n* (%)			
≤60 years	43 (41.7)	37 (49.3)	6 (21.4)
>60 years	60 (58.3)	38 (50.7)	22 (78.6)
Gender, *n* (%)			
Male	37 (35.9)	26 (34.7)	11 (39.3)
Female	66 (64.1)	49 (65.3)	17 (60.7)
ECOG-PS, *n* (%)			
<2	78 (75.7)	65 (86.7)	13 (46.4)
≥2	25 (24.3)	10 (13.3)	15 (53.6)
IPI risk, *n* (%)			
Low	36 (35)	35 (46.7)	1 (3.6)
Low-intermediate	23 (22.3)	20 (26.7)	3 (10.7)
High-intermediate	30 (29.1)	19 (25.3)	11 (39.3)
High	14 (13.6)	1 (1.3)	13 (46.4)
LDH, *n* (%)			
Normal	58 (56.3)	52 (69.3)	6 (21.4)
>241 U/l	45 (43.7)	23 (30.7)	22 (78.6)
B symptoms†, *n* (%)			
No	49 (47.6)	45 (60)	4 (14.4)
Yes	54 (52.4)	30 (40)	24 (85.7)
Infiltration of bone marrow, *n* (%)			
No	65 (63.1)	54 (72)	11 (39.3)
Yes	38 (36.9)	21 (28)	17 (60.7)
AA clinical stage, *n* (%)			
I and II	34 (33)	32 (42.7)	2 (7.1)
III and IV	69 (67)	43 (57.3)	26 (92.9)
RBC ($\times 10^{12}$/l, mean ± SD)	4.27 ± 0.63	4.39 ± 0.56	3.97 ± 0.73
Hemoglobin (g/l, mean ± SD)	121 ± 19	126 ± 18	110 ± 19
WBC* ($x10^9$/l, mean ± SD)	7.37 ± 2.71	7.15 ± 2.5	7.97 ± 3.19
ANC (cells × 10^9/l, mean ± SD)	4.89 ± 2.07	4.62 ± 1.94	5.63 ± 2.27
ALC (cells × 10^9/l, mean ± SD)	1.57 ± 0.75	1.72 ± 0.72	1.19 ± 0.7
Platelets ($x10^9$/l, mean ± SD)	264 ± 121	257 ± 120	280 ± 124
CRP (mg/l), median (minimum–maximum)	9.7 (0.5–247.7)	6.2 (0.5–136.1)	37.55 (1.3–247.7)
Albumin (g/l, mean ± SD)	40.67 ± 6.47	43.3 ± 4.79	33.62 ± 5
Iron (μmol/l, mean ± SD)	10.02 ± 6.42	11.18 ± 6.23	6.72 ± 5.88
Ferritin (μg/l), median (minimum–maximum)	112.35 (5.8–2350)	87.6 (5.8–2350)	325.25 (7.7–1288.7)
Treatment outcome, *n* (%)			
Response	82 (79.6)	70 (93.3)	12 (42.9)
No response	21 (20.4)	5 (6.7)	16 (57.1)

DLBCL diffuse large B cell lymphoma, *PNI* prognostic nutritional index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *IPI* International prognostic index, *LDH* lactate dehydrogenase, *AA* Ann Arbor, *RBC* red blood cells, *SD* standard deviation, *WBC* white blood cells, *ANL* absolute neutrophil count, *ALC* absolute lymphocyte count, *CRP* C-reactive protein

† fever, nights sweats, weight loss

Table 2 Univariable and multivariable logistic regression analysis for response to treatment in patients with diffuse large B-cell lymphoma (*N* = 103)

	Univariable			Multivariable		
	Odds ratio	95 % confidence interval	*P-value*	Odds ratio	95 % confidence interval	*P*-value
PNI (≤44.55)	18.667	5.758–60.516	<0.001	4.88	1.077–22.105	0.04
Age group (>60 years)	–	–	0.175	–	–	–
Gender (male)	–	–	0.214	–	–	–
ECOG-PS (≥2)	12.909	4.265–39.072	<0.001	–	–	0.293
LDH (>241 U/L)	4.333	1.519–12.358	0.006	–	–	0.183
Clinical stage AA (III and IV)	13.469	1.723–105.289	0.013	–	–	0.928
B symptoms (yes)	12.757	2.786–58.405	0.001	–	–	0.089
IPI (as a linear parameter)	5.608	2.511–12.522	<0.001	3.699	1.183–11.568	0.025

PNI prognostic nutritional index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *AA* Ann Arbor, *IPI* International prognostic index

PNI, clinical stage and International Prognostic Index score

Lower values of PNI were found in patients with advanced disease (stages III and IV) in comparison with those with localized disease (stages I and II), i.e. 46.6 ± 7.77 vs. 52.7 ± 5.43 (Fig. 2a) and with a higher IPI score (38.49 ± 6.42 vs. 46.83 ± 6.63 vs. 50 ± 5.85 vs. 53.15 ± 5.47, respectively, Fig. 2b).

PNI category and clinical laboratory parameters

The patients were divided into two groups, based on cut-off PNI values for response to treatment, OS and EFS, according to the ROC analysis (Fig. 3). Optimal cut-off value was 44.5 and the same was obtained for response to treatment, OS, EFS; for response to treatment area under the curve (AUC) for PNI was 0.861 with a 95 % confidence interval (CI) 0.779–0.921 (Z = 8.756, $P < 0.001$) with 76.2 % sensitivity and a specificity of 85.4 % (Fig. 3a); for OS the AUC for PNI was 0.842 (95 % CI 0.757–0.906, Z = 7.629, $P < 0.001$) with 72.4 % sensitivity and a specificity of 90.5 % (Fig. 3b); for EFS the AUC for PNI was 0.796 (95 % CI 0.705–0.869, Z = 5.887, $P < 0.001$) with 65.6 % sensitivity and a specificity of 90.1 % (Fig. 3c). Of the patients 75 had a PNI > 44.55 while 28 patients had PNI ≤ 44.55. Patients with PNI ≤ 44.55 had significantly lower ECOG-PS, higher AA stage, higher IPI, higher CRP, higher ferritin, lower RBC, lower serum Hb, more frequent expressed B symptoms, had bone marrow infiltration and worse response to treatment (Table 1).

PNI and treatment outcome

The patients with better response to treatment had higher PNI values, complete remission (CR) versus (vs.) partial remission (PR) vs. no response or progression (NR) (51.3 ± 6.09 vs. 45.6 ± 5.53 vs. 40.58 ± 7.26, respectively, Fig. 4a; CR + PR vs. NR, 50.67 ± 6.26 vs. 40.58 ± 7.26, respectively, Fig. 4b).

Logistic regression analysis of potential prognostic markers is shown in Table 2. A PNI ≤ 44.55 was shown to be an independent prognostic factor for response to treatment. Patients with PNI ≤ 44.55 had higher risk of treatment failure with odds ratio (OR) of 4.88 (95 % CI 1.077–22.105, $P = 0.04$) compared to patients with PNI > 44.55. Higher IPI score was also an independent prognostic factor for response to treatment with OR for treatment failure of 3.699 (95 % CI 1.183–11.568, $P = 0.025$) in our population study.

Survival and prognostic factors

The median follow-up was 27 months (range 1–105 months), 29 (28.2 %) patients died and 32 (31.1 %) experienced one of the events (e.g. disease progression, initiation of another antilymphoma treatment, relapse or death irrespective of cause). The 5-year OS was 68.1 % for all patients, significantly lower in those with PNI ≤ 44.55 (18.3 % vs. 86.4 %, $P < 0.001$, log rank test) (Fig. 5a). The 5-year EFS was 64.3 % for all patients, significantly lower in those with PNI ≤ 44.55 (15.1 % vs. 82.3 %, $P < 0.001$, log rank test) (Fig. 5b). Univariable Cox regression analysis of potential prognostic markers is shown in Table 3 for OS and in Table 4 for EFS. A PNI ≤ 44.55 was shown to be a significant predictor of OS with a hazard ratio (HR) of 12.785 (95 % CI 5.585–29.265, $P < 0.001$) and EFS (HR 9.642, 95 % CI 4.581–20.296, $P < 0.001$). Elevated LDH values ($P = 0.001$), high clinical stage (stages III and IV, $P = 0.004$), presence of B symptoms ($P = 0.001$) and high ECOG-PS (≥2, $P < 0.001$) were also significant prognostic factors for OS. Elevated LDH values ($P = 0.003$), high clinical stage (stages III and IV, $P = 0.005$), age (>60, $P = 0.021$), presence of B symptoms ($P = 0.001$), and high ECOG-PS (≥2, $P < 0.001$) were also significant prognostic factors for EFS. Age >60 years was not prognostic for OS ($P = 0.059$). A one-level increase in IPI also

Table 3 Univariable and multivariable logistic regression analysis for overall survival (OS) in patients with diffuse large B-cell lymphoma ($N = 1\,03$)

	Univariable			Mutlivariable		
	Odds ratio	95 % confidence interval	*P*-value	Odds ratio	95 % confidence interval	*P-value*
PNI (≤44.55)	12.785	5.585–29.265	<0.001	4..24	1.451–12.392	0.008
Age group (>60 years)	–	–	0.059	–	–	–
Gender (male)	–	–	0.071	–	–	–
ECOG-PS (≥2)	6.152	2.876–13.161	<0.001	–	–	0.132
LDH (>241 U/L)	4.146	1.832–9.383	0.001	–	–	0.323
Clinical stage AA (III and IV)	18.224	2.475–134.205	0.004	–	–	0.23
B symptoms (yes)	4.442	1.804–10.94	0.001	–	–	0.383
IPI (as a linear parameter)	2.96	2.066–4.24	<0.001	–	–	0.077

PNI prognostic nutritional index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *AA* Ann Arbor, *IPI* International prognostic index

was prognostic for OS and EFS in our population ($P <$ 0.001 for OS as well as EFS).

Multivariable Cox regression analysis results for OS are shown in Table 3 and in Table 4 for EFS. Patients with PNI ≤ 44.55 had higher risk of death with the HR of 4.24 (95 % CI 1.451–12.392, P = 0.008) compared to patients with PNI > 44.55. Multivariable analysis found that PNI was an independent prognostic factor for EFS, patients with PNI ≤ 44.55 having higher risk for an event with HR of 4.007 (95 % CI 1.48–10.852, P = 0.006) compared to patients with PNI > 44.55. Higher IPI score was also an independent prognostic factor for EFS with HR of 1.931 (95 % CI 1.038–3.592, P = 0.038) in our population study. The IPI as a linear parameter was not prognostic for OS in the multivariable analysis perhaps due to small sample size.

Discussion

In the present study, a simple prognostic score based on nutritional status and the presence of systemic inflammation (PNI) was identified as an independent predictor of response to treatment, OS and EFS in DLBCL patients. To our knowledge, this is the first report on the prognostic value of PNI in patients with DLBCL. Our results thus contribute to the previous knowledge on the significant relationship between PNI and prognosis for cancers, specifically for this particular hematologic malignancy. Our findings suggest a common pathophysiological relationship between PNI and the course of malignancy in general. The PNI was initially designed to assess immunological and nutritional aspects of patients undergoing digestive tract surgery, predominantly as an indicator of their nutritional status [10, 19–21]. Recently, it was reported to be a reflection of systemic inflammation in cancer patients [22]. Our study suggests that this is also true for DLBCL patients. The PNI correlated negatively with CRP and ferritin and positively with RBC and Hb. In our study, low PNI was associated with known negative prognostic factors including ECOG-PS, bone marrow involvement, advanced disease stage and presence of B symptoms. These results indicate that PNI may reflect the growth and invasive potential of the tumor and the inadequacy of patient response mechanisms. We found a negative association between clinical stage according to AA and PNI. This result also reflects an association between PNI and increased inflammation or malnutrition caused by cancer progression. The precise mechanisms of the association between low PNI and poor prognosis remain unclear. Several possible explanations have been offered so far: (i) hypoalbuminemia may reflect malnutrition and undernourished patients may respond to and tolerate treatment less well than well-nourished patients, (ii) decreased serum albumin concentration and lymphopenia may be caused by the increased release of cytokines by tumors, such as interleukin 6 and tumor necrosis factor-alpha, which is characteristic of more aggressive disease, (iii) low ALC is a consequence of pre-existing immunosuppression, suggesting that the host had an inadequate antitumor immunological reaction and (iv) low ALC may be a consequence of lympholytic cytokines produced by lymphoma cells and such lymphomas may be intrinsically resistant to treatment [5, 23–27]. Future studies are needed to elucidate if this, at least in part, explains the nature of the association between mortality and low PNI in DLBCL patients. Also, further investigations are needed to explain the relationships of PNI with inflammation and the response to cancer treatment. Altogether, the baseline PNI, which consists of serum albumin concentration and lymphocyte count, correlates with survival in DLBCL patients. Our results suggest that an early nutritional intervention with dietary counseling and parenteral or enteral nutritional supplementation might improve the outcome for DLBCL patients undergoing immunochemotherapy and enhance palliative care.

Protein expression and molecular biological analysis (e. g. c-myc, Bcl-2, Bcl-6 and p53 expression [28–31]) have recently attracted a lot of interest but

Table 4 Univariable and multivariable logistic regression analysis for event-free survival (EFS) in patients with diffuse large B-cell lymphoma ($N = 103$)

	Univariable			Mutlivariable		
	Odds ratio	95 % confidence interval	*P-value*	Odds ratio	95 % confidence interval	*P-value*
PNI (≤44.55)	9.642	4.581–20.296	<0.001	4.007	1.48–10.852	0.006
Age group (>60 years)	2.573	1.155–5.734	0.021	–	–	0.663
Gender (male)	–	–	0.167	–	–	–
ECOG-PS (≥2)	4.795	2.363–9.729	<0.001	–	–	0.297
LDH (>241 U/L)	3.09	1.486–6.422	0.003	–	–	0.133
Clinical stage AA (III and IV)	9.642	4.581–20.296	0.005	–	–	0.824
B symptoms (yes)	4.347	1.874–10.079	0.001	–	–	0.164
IPI (as a linear parameter)	2.517	1.812–3.497	<0.001	1.931	1.038–3.592	0.038

PNI prognostic nutritional index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *AA* Ann Arbor, *IPI* International prognostic index

this was not in the focus of our interest. Further research should investigate the relationship of PNI with protein expression and molecular biological analysis and try to elucidate the pathophysiological nature of our results. We demonstrated that PNI was a prognostic marker and that, in addition to IPI, PNI should be regularly assessed in DLBCL. Further investigations are warranted to provide a better understanding of the mechanisms underlying the relationship between PNI and clinical outcome.

A limitation of the study is its retrospective design and the fact that it was conducted in a single center with a relatively small number of patients. This was a retrospective study in which prognostic value was tested in the derivation cohort only. As this makes the analysis prone to overfitting, our results should be validated in an independent cohort. To confirm that PNI can be used as a prognostic marker our findings require validation in larger independent cohorts of patients, preferably in a prospective study. Despite the limitations, this is the first study suggesting that PNI is an important prognostic factor in DLBCL, in addition to and independent of the IPI. Factors included in PNI are routinely available and the index can be easily calculated. The easy availability and inexpensiveness of PNI should encourage its use in every day clinical practice. In conclusion, PNI may emerge as a simple, fast, easy to use and inexpensive new prognostic marker for DLBCL patients in routine clinical practice.

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Conflict of interest V. Periša, L. Zibar, A. Knezović, I. Periša, J. Sinčić-Petričević, and I. Aurer declare that they have no competing interests.

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