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Prognostic Values of GNRI, PNI, And CONUT in Patients with Diffuse Large B-Cell Lymphoma

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Abstract

Background: *Diffuse Large B-Cell Lymphoma (DLBCL) is a highly heterogeneous non-Hodgkin lymphoma. Emerging evidence indicates that malnourishment serves as a prognostic role in DLBCL. However, there are few studies on concurrently analysing the nutritional indices such as Geriatric nutritional risk index (GNRI), Prognostic nutritional index (PNI), and controlling nutritional status score (CONUT) in DLBCL. This retrospective study was aimed to explore and validate the prognostic value of three nutritional indices in newly diagnosed DLBCL patients.*

Methods: *A total of 236 DLBCL patients were enrolled in this study. The Continuous variables were transformed into categorical variables by Restricted cubic spline (RCS) and MaxStat analysis. Kaplan-Meier method was utilized to analyse the influence of variables on prognosis. Log-rank test was performed for evaluation of the differences between groups. Univariable and multivariable Cox proportional hazards analyses were used for the selection of the variables.*

Results: *The optimal cut-off points for GNRI, PNI, and CONUT were 107.38, 49, and 5 by using RCS and MaxStat analysis. Univariable analysis showed that CONUT, PNI, GNRI, and haemoglobin were all significantly associated with the survival of DLBCL. CONUT, PNI, Albumin, and Central involvement were independent prognostic predictors for OS after multivariable analysis ($P < 0.05$). The overall survival (OS) in patients with malnourishment determined with three nutritional indices was significantly inferior to those without poor nutritional status ($P < 0.05$).*

Conclusions: *CONUT and PNI could be used to predict the survival of DLBCL. The integration of GNRI, PNI, and CONUT could accurately distinguish the nutritional status of DLBCL patients.*

Keywords: *DLBCL, GNRI, PNI, CONUT, Prognosis.*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive disease with high heterogeneity in cell-of-origin, clinical features, and molecular pathogenesis, accounting for about 40% of Non-Hodgkin lymphoma (NHL)[1-3]. In the era of rituximab-based immunochemotherapy, R-CHOP regimen dramatically improved the survival of patients, but approximately 40% of the patients will develop relapse or refractory [4, 5]. Several prognostic models such as International Prognostic Index (IPI), Revised International Prognostic Index (R-IPI), and NCCN-IPI are widely used to stratify patients and guide individualized treatment [6-8]. Evidence is emerging that malnourishment is associated with adverse outcomes of various solid malignancies and lymphoma [9-12]. However, these prognostic models did not take nutrition status into account.

Indicators reflecting the body's nutritional status, such as serum levels of albumin, absolute lymphocyte count, total cholesterol level, and ideal body weight, were reported to correlate with survival in many malignancies and lymphoma [13-16]. Nutrition-based scores such as Geriatric nutritional risk index (GNRI), Prognostic nutritional index (PNI), and controlling nutritional status score (CONUT) were calculated from above clinical

laboratory factors. For instance, Geriatric nutritional risk index (GNRI) is a nutritional assessment tool used to detect malnutrition and is calculated from serum albumin and the ratio between actual and ideal body weight [17]. It is reported that GNRI was a prognostic factor for oesophageal, gastric, and chronic kidney diseases [18-20]. Kanemasa et al. [21] also showed that GNRI was associated with poor overall survival in DLBCL patients [21]. The other two nutritional scores such as PNI composed of serum albumin and absolute lymphocyte count and CONUT based on serum albumin, total cholesterol level, and total lymphocyte counts have also been proved to be related to DLBCL [22, 23]. These nutritional indices can be used routinely in clinical work and provide predictive information for patient survival outcomes.

So far, there have been no studies analysing the integration of GNRI, PNI and CONUT in patients with DLBCL. Therefore, we conducted this retrospective study to explore and validate three nutritional indices in predicting the prognosis of DLBCL and to analyse the prognostic value of integrated nutritional indices.

Materials and Methods

Patients

We carried out this retrospective study of 236 newly diagnosed patients with DLBCL at the Affiliated Hospital of Xuzhou Medical University from November 2014 to December 2019. All patients included in this study had a pathological diagnosis of DLBCL. The exclusion criteria included: 1) patients with other malignant diseases; 2) special types of lymphoma (primary central nervous system lymphoma, primary mediastinal DLBCL, transformed DLBCL).

The following baseline data were collected: age, gender, Eastern Cooperative Oncology Group (ECOG PS), International Prognostic Index (IPI), Ann Arbor stage, B symptom, extra-nodal involvement, albumin, absolute lymphocyte count, platelet count, total cholesterol, haemoglobin, lactate dehydrogenase (LDH), C-Myc, Bcl-2, Bcl-6, cell-of-origin (COO), CD5, and Ki-67. Follow-up was conducted through reviewing the inpatient medical records and making phone calls. The overall survival (OS) was calculated as the interval between the time of diagnosis and death from any cause or the last follow-up. This investigation was in line with the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Xuzhou Medical University.

Calculation of prognostic scores

GNRI was calculated from albumin and body weight using the formula:

$$GNRI = \left[1.489 \times \text{albumin}\left(g/L\right)\right] + \left[41.7 \times \left(\text{weight/WLo}\right)\right]$$

Where: WLo is the ideal weight, which was calculated with the Lorentz formula (for men: height [cm] − 100 − (height − 150)/4; for women: height − 100 − (height − 150)/2).

PNI was calculated from albumin and total lymphocyte count using the formula:

$$\text{PNI} = 10 \times \text{albumin}\left(\text{g/dL}\right) + 0.005 \times \text{lymphocyte count}\left(/\text{mm}^3\right)$$

The CONUT score was defined as the sum of following parameters [24]: (a) serum albumin, ≥3.50, 3.00-3.49, 2.50-2.99, and <2.50 g/dL were scored as 0, 2, 4, and 6 points; (b) total lymphocyte counts, ≥1600, 1200-1599, 800-1199, and <800/μL were scored as 0, 1, 2, and 3 points; (c) serum total cholesterol ≥180, 140-179, 100-139, and <100 mg/dL were scored as 0, 1, 2, and 3 points, respectively.

Statistical Analysis

Baseline clinical characteristics were described by variable type using median. Outliers were verified by the hospital medical record system. The relationship between GNRI, PNI, and CONUT was evaluated using Pearson's $\chi 2$ test. Continuous variables were transformed into categorical variables by Restricted cubic spline (RCS) and MaxStat analysis (titled as Maximally Selected Rank Statistics). Cox proportional hazard model was used to analyse the univariable association between clinical features and prognosis. All variables with $P < 0.1$ in univariable analysis were included in the multivariable model. Multivariable Cox analysis was performed to identify the predictive prognostic variables. A two-tailed P value < 0.05 was considered statistically significant. Survival curves were estimated by the Kaplan–Meier method, and log-rank test was performed for the difference between groups. All statistical analyses were conducted with SPSS software (version 19.0 (IBM, NY, USA)) and R software (version 4.0.3; http://www.Rproject.org).

Results

Basic clinical characteristics

In this study, the median GNRI, PNI, and CONUT were 107.4 (range, 70.8–146.1), 49 (range, 21.3–209.4), and 4 (range, 1–11), respectively (Table 1). The median age was 63 years (range: 10–91), and 132 (55.9%) patients were aged over

60. One hundred and sixteen (49.2%) patients were female, and only 12.3% had B symptoms. One hundred and forty-five patients (61.4%) had stages I/II tumours, while 91 patients had stages III/IV (38.6%) tumours. COO was identified as GCB and non-GCB in 151 (64.0%) and 85 (36.0%) patients, respectively. Pearson's correlation tests revealed that there was a strong correlation between PNI and GNRI ($r = 0.989$, $P < 0.01$). And there was no significant correlation between GNRI and CONUT ($r = -0.213$, $P = 0.064$). The follow-up deadline was Aug 1, 2020. The median survival time of the patients was 31.5 months (95% CI (19.6, 43.4)), and 115 patients (48.7%) died during the period of follow-up. The main baseline clinical characteristics of patients were summarized in Table 1.

Clinical characteristics	n (%)
Gender	
Female	116 (49.2)
Male	120 (50.8)
Age	
<60	104 (44.1)
≥60	132 (55.9)
ECOG PS	
0-1	186 (78.8)
≥2	50 (21.2)
Ann Arbor stage	
I-II	145 (61.4)
III-IV	91 (38.6)
Bulky disease	
absence	228 (96.6)
presence	8 (3.4)
B symptoms	
absence	207 (87.7)
presence	29 (12.3)
IPI	
0-2	166 (70.3)
≥3	70 (29.7)
COO	
GCB	151 (64.0)
Non-GCB	85 (36.0)
GNRI, median (range)	107.4 (70.8-146.1)
PNI, median (range)	49 (21.3-209.4)
CONUT, median (range)	4 (1-11)
Note: ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; COO, cell-of-origin; GCB, germinal center B cell-like; GNRI, Geriatric Nutritional Risk Index; PNI, Prognostic Nutritional Index; CONUT, Controlling Nutritional Status score.	

Table 1: Baseline Clinical characteristics of DLBCL patients.

Determination of the optimal cut-off points of PNI, GNRI, and CONUT

We used the RCS model with 3 knots to simulate the relationship between PNI and the risk for DLBCL. A significant nonlinear dose-response association was shown in the relationship between PNI and the risk ($P < 0.0001$). And dose-response relationship analysis showed that with the continuous change of PNI, the association strength of risk decreased nonlinearly (Figure. 1A). Similarly, we used this method to calculate the optimal cut-off point of GNRI. Our results showed that when the optimal cut-off value of GNRI was 107.38, the relationship between GNRI and risk also showed a significant nonlinear dose-response relationship ($P = 0.0003$, Figure. 1B). By using MaxStat analysis, we determined that the most discriminative cut-off value for CONUT was 5.

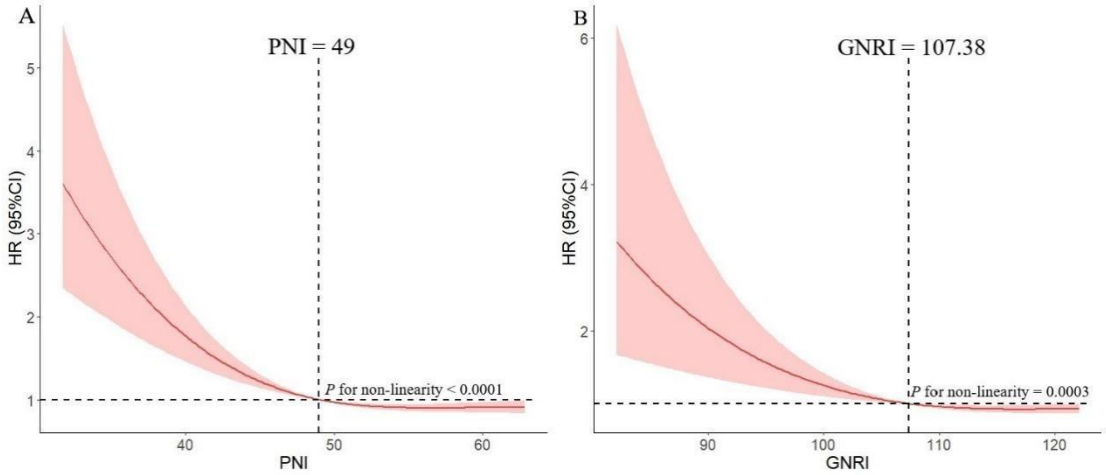

Figure 1: A: Association between PNI and the risk of DLBCL allowing for nonlinear effects. B: Association between GNRI and the risk of DLBCL allowing for nonlinear effects.

Survival analysis in patients with DLBCL

In univariable analysis, CONUT, PNI, and GNRI were all associated with the survival of DLBCL (P < 0.1). Absolute lymphocyte count had only borderline significance (P = 0.187). B symptom was not associated with OS (P = 0.265, HR = 1.340, 95% CI (0.801-2.242). CONUT, PNI, Albumin, Ann Arbor stage, haemoglobin, and IPI appeared to be stronger predictors (P < 0.001). Multivariable analysis demonstrated that CONUT, PNI, Albumin, and Central involvement were significantly associated with OS (P < 0.05). Nevertheless, GNRI in the current multivariable analysis was not predictive (P > 0.05). Univariable and multivariable analysis results have been illustrated in Table 2.

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
CONUT	2.057(1.394-3.035)	<0.001	1.154(0.034-0.702)	0.015
PNI	0.406(0.280-0.591)	<0.001	0.170(0.050-0.568)	0.004
Albumin	0.323(0.218-0.478)	<0.001	0.174(0.042-0.714)	0.042
Ann Arbor stage	1.343(1.130-1.596)	<0.001		
Hemoglobin	0.978(0.969-0.986)	<0.001		
IPI	1.521(1.301-1.779)	<0.001		
GNRI	0.425(0.228-0.791)	0.007		
BCL-2	2.033(1.166-3.545)	0.012		
Central involvement	1.696(1.104-2.606)	0.016	6.716(2.431-18.5)	<0.001
ECOG PS	1.290(1.001-1.663)	0.049		
Note: CONUT, Controlling Nutritional Status score; PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; IPI, International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group performance status.				

Table 2: Analysis of prognostic factors for OS in patients with DLBCL.

Prognostic values of nutrition-based prognostic scores in DLBCL

We investigated the effects of different GNRI, PNI, or CONUT levels on overall survival (OS) of DLBCL patients. The Kaplan-Meier results showed that patients with low PNI (PNI < 49) were associated with poor OS compared with high PNI patients (P < 0.001, 3-y: 33.2% vs 57.3%, Fig. 2A). Similarly, patients with low GNRI (GNRI < 107.38) were related to poor OS (P = 0.006, 2-y: 24.3% vs 52.0 %, Fig. 2B). However, patients with a CONUT ≥ 5 had significantly lower OS than those with a CONUT < 5 (3-y: 28.6% vs 54.8%, P < 0.001, Fig. 2C).

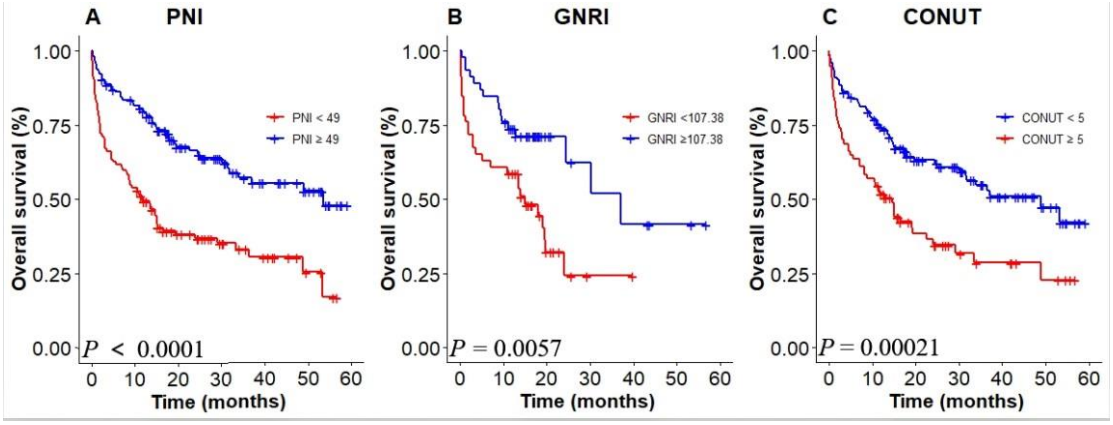

Figure 2: Three indices predicted the survival of DLBCL patients according to (A) PNI, (B) GNRI, and (C) CONUT.

Subgroup analysis

Subgroup analyses of patients with GCB-type disease, malnourishment determined with PNI, GNRI, and CONUT predicted significantly worse OS (PNI, 3-y: 34.7% vs 66.1%, P < 0.001; GNRI, 2-y: 37.7% vs 66.1%, P = 0.002; CONUT, 2-y: 35.7% vs 60.1%, P = 0.003; Figure. 3A-C).

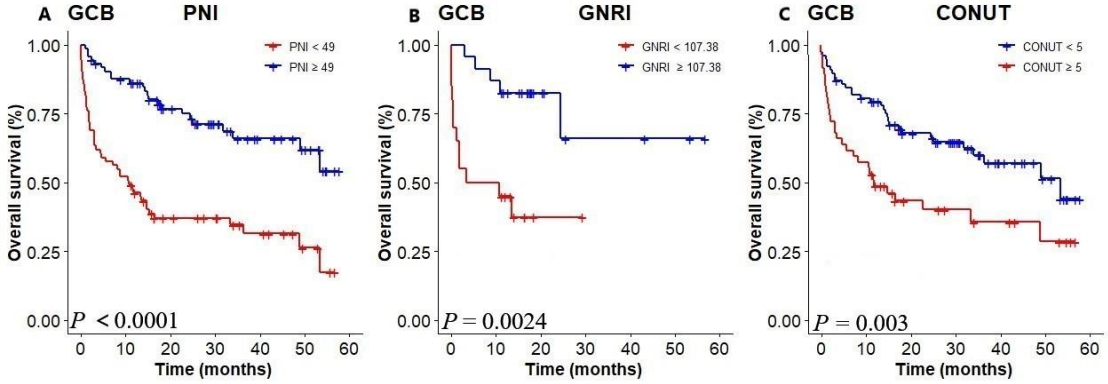

Figure 3: Kaplan-Meier survival curves of the DLBCL patients. Prognosis of different (A)PNI, (B)GNRI, and (C)CONUT levels in GCB group.

Then we found a significant deterioration of OS in BCL-2 positive group with malnourishment identified by PNI and GNRI (PNI, 3-y: 27.9% vs 52.9%, P＜0.001, Fig. 4A; GNRI, 2-y: 21.7% vs 63.0%, P = 0.048, Fig. 4B). However, CONUT did not significantly affect OS in this subgroup.

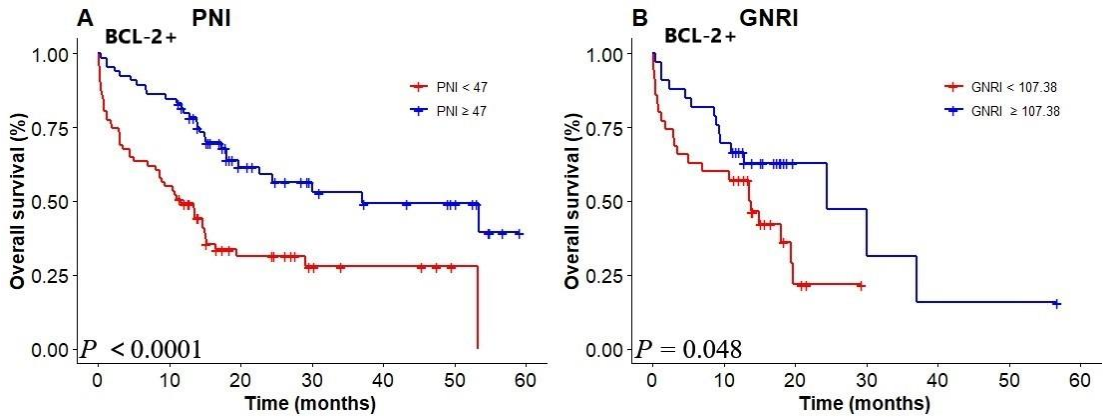

Figure 4: Kaplan-Meier survival curves of the DLBCL patients. (A-B) prognosis of different PNI and GNRI levels in BCL-2 positive expression group.

Besides, we found that only CONUT could accurately distinguish DLBCL patients in BCL-2 negative groups (P = 0.002). In BCL-6 positive group, all three nutrition indices conferred a significantly worse OS (CONUT, 3-y: 29.2% vs 56.0%, P = 0.001; GNRI, 2-y: 22.9% vs 76.0%, P < 0.001; PNI, 3-y: 35.1% vs 58.7%, P < 0.001; Figure. 5).

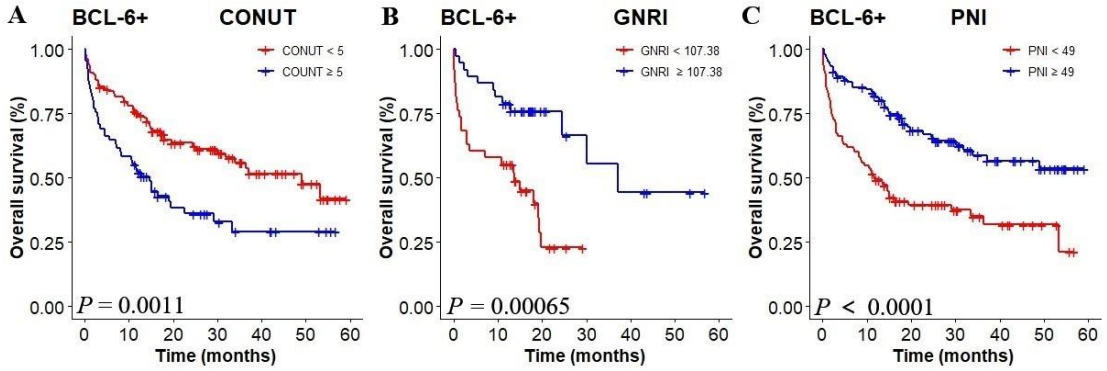

Figure 5: Kaplan-Meier survival curves of the DLBCL patients. Prognosis of different (A)CONUT, (B)GNRI and (c)PNI levels in BCL-6 positive expression group.

According to the IPI score, all patients were divided by low-risk group (LR), low intermediate risk group (LIR), high intermediate risk group (HIR), and high-risk group (HR). Further subgroup analyses showed that PNI successfully found the patients with worse prognosis in LR group (PNI, 3-y: 52.6% vs 68.3%, P = 0.015, Figure 6A).

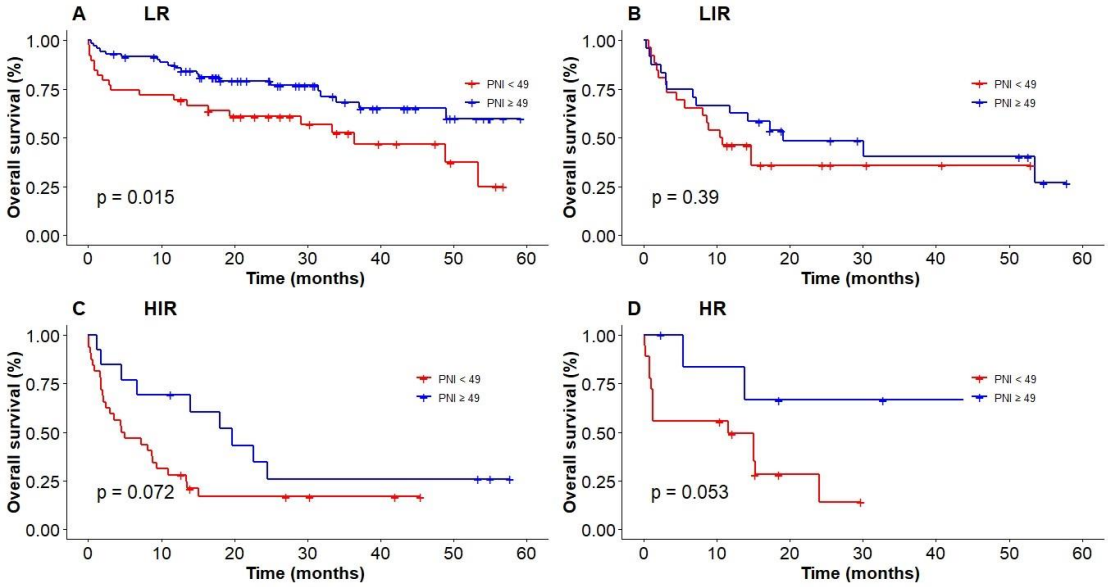

Figure 6: Kaplan-Meier survival curves of the DLBCL patients; Prognosis of different PNI levels in (A) LR, (B) LIR, (C) HIR, and (D) HR groups.

In contrast, PNI did not successfully differentiate patients with poor prognosis in LIR, HIR, and HR groups (Fig. 6B-D). In this study, we defined patients with PNI < 49, GNRI < 107.38, and CONUT≥5 as malnourishment and evaluated patient survival with a combination of three indicators. KM analysis showed that patients in status with malnourishment determined with PNI, GNRI, and CONUT had the worst survival (P = 0.021; Fig. 7A), but there was no difference between the group of normal and other groups. Furthermore, we also found that malnourishment determined with PNI, GNRI, and CONUT can successfully identify the patients with worse prognosis both in IPI-LR group (P = 0.010; Fig. 7B) and IPI-LIR group (P = 0.019; Fig. 7C).

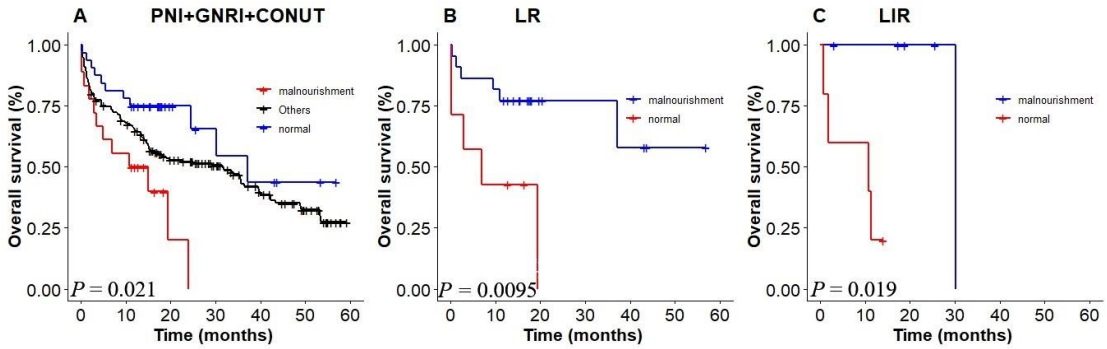

Figure 7: OS according to malnourishment determined with (A) GNRI, PNI, and CONUT; Prognosis of malnourishment patients in (B) IPI-LR group and (C) IPI-LIR group.

Discussion

In this retrospective study, we evaluated the predictability of nutrition-based scores including GNRI, PNI, and CONUT concurrently in newly diagnosed DLBCL patients. Our results indicated that GNRI, PNI, and CONUT were all associated with the survival of DLBCL in univariable analysis. In multivariable analysis, only PNI and CONUT were powerful predictors. Another important finding of the current study was that malnourishment groups had significantly inferior OS compared with normal groups. To the best of our knowledge, this is the first study that had simultaneously analysed and integrated three nutritional indices for the prognosis of DLBCL patients.

It is now accepted that malnutrition is a common problem in cancer patients, occurring in 30% to 85% of individuals with advanced disease [25, 26]. And emerging results indicate that many nutritional assessment tools have been proven to be used as prognostic predictors to predict the prognosis of DLBCL, such as GNRI, PNI, and CONUT. For instance, previous studies by Kanemasa et al. [21] supported that GNRI was an independent prognostic factor in DLBCL patients. However, Li et al. [27] demonstrated that GNRI was not an independent predictor for OS in DLBCL patients, which was contrary to the former research finding. Our study demonstrated that GNRI was not an independent prognostic factor for OS in multivariable analysis. This discrepancy may be due to the differences among studies including different cut-off values and the stages of disease. Many studies have demonstrated that low PNI was associated with poor prognosis of DLBCL [22, 28-30]. In the study of Go et al, the optimal cut-off value of PNI was 40 [30]. However, our study demonstrated that the optimal cut-off value for PNI was 49, and the cut-off value in our study enabled more accurate stratification of patients ($P < 0.001$). High CONUT score was also shown to be associated with significantly worse prognosis of DLBCL regardless of their age [23]. Interestingly, our study has shown that GNRI, PNI, and CONUT were associated with prognosis of DLBCL. As mentioned above, it has been shown that the results of our study are consistent with previous study findings.

Matsukawa et al. [31] demonstrated that poor nutritional status determined based on GNRI or CONUT was an independent risk factor of newly diagnosed DLBCL, and GNRI was a useful independent prognostic factor for patients with non-GCB-type DLBCL. In our study, we found that patients with low GNRI (GNRI < 107.38), low PNI (PNI < 49), and high CONUT (CONUT ≥ 5) were respectively related to the worse prognosis of patients who had DLBCL. Then we integrated three nutritional indicators and defined patients with GNRI < 107.38, PNI < 49, and CONUT ≥ 5 as malnourishment. It was interesting to note that malnourishment determined with PNI, GNRI and CONUT could successfully identify the patients with worse prognosis in the IPI-LR group ($P = 0.0095$) IPI-LIR group ($P = 0.019$). Our study showed that PNI and CONUT were significantly associated with OS after multivariable analysis. The overall survival in patients with malnourishment determined with three nutritional indices was significantly inferior compared to those without nutritional risks. In addition, subgroup analyses of patients with GCB-type, BCL-2 positive and BCL-6 positive disease, patients with high levels of GNRI and PNI had significantly higher OS than those with low levels of GNRI and PNI. Another important finding of the subgroup analyses was that malnourishment determined with CONUT, GNRI, and PNI had a more substantial effect on OS in patients with GCB-type lymphoma. But further analyses will be required to clarify the mechanism by which prognosis of GCB-type DLBCL is more strongly affected by nutritional status. In the end, we also found that PNI could accurately distinguish low-risk group of patients in IPI prognostic system but not in those with IPI LIR/HIR/HR group.

Conclusions / Recommendations

The aforementioned findings of the current study must be seen in light of a few of limitations. Due to the limitation of single-centre retrospective study and lack of some survival data, we only evaluated OS but not PFS, QOL and other vital information. Therefore, further prospective and multicentre studies are urgently needed to confirm our findings in the future.

Conflicts of Interest and Source of Funding: The authors declare no conflicts of interest.

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