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# Role of Prognostic Nutritional Index in Diffuse Large B-Cell Lymphoma

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**Abstract:**

**Background:** Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30–40% of all non-Hodgkin lymphomas and is characterized by aggressive clinical behavior and heterogeneous outcomes. Prognostication traditionally relies on clinical models such as the IPI, but there is growing interest in integrating host-related biomarkers. Nutritional and immune status are critical in determining treatment tolerance and survival outcomes in hematological malignancies. PNI, derived from albumin and lymphocyte counts, offers a combined measure of nutritional reserves and immune competence, which are often compromised in DLBCL patients due to tumor burden, systemic inflammation, and chemotherapy-related toxicity.

**Keywords:** Prognostic Nutritional Index, PNI, diffuse large B-cell lymphoma, DLBCL, overall survival, progression-free survival, nutritional status, immunological status.

**Introduction:**

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of non-Hodgkin lymphoma, characterized by aggressive behavior and marked heterogeneity in clinical presentation and prognosis **(1).** While the International Prognostic Index (IPI) remains the standard prognostic tool, it does not incorporate host-related factors such as nutritional and immune status, which are increasingly recognized as important determinants of treatment response and survival **(2).**

The Prognostic Nutritional Index (PNI), calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm$^3$), was initially developed to assess surgical risk in gastrointestinal cancer patients but has since been applied in various malignancies, including hematological cancers (Onodera et al., 1984). In DLBCL, low PNI values have been associated with impaired immunity, higher systemic inflammation, and reduced tolerance to chemotherapy **(3).**

Recent studies have demonstrated that PNI can serve as an independent predictor of overall survival (OS) and progression-free survival (PFS) in DLBCL patients, even after adjusting for IPI scores. This suggests that incorporating PNI into prognostic assessment could improve risk stratification and guide individualized treatment approaches **(4).**

Prognostic estimation is crucial for cancer management because it can significantly inform the selection of the treatment approach. The conventional prognostic estimation tools include medical imaging, pathological methods, demographic factors, and laboratory testing. However, none of these tools can accurately predict the prognosis of cancer patients when used alone. They each have distinct limitations, including invasiveness, high cost, requirement of special training, and subjectivity. The ideal prognostic estimation tool should be noninvasive, easy to use, low cost, and standardized. Some tools can meet these requirements, such as the prognostic nutritional index (PNI) **(5).**

PNI was first proposed by Buzby in 1980. The formula for calculating the PNI was based on 4 factors: albumin, triceps skinfold, transferrin, and skin test reactivity. Partly due to the subjectivity involved in triceps skinfold and skin test reactivity, the clinical application of PNI was limited. In 1984, Onodera modified the formula to the following: PNI=albumin (g/L) + 5 × absolute lymphocyte count ($10^9$/L). Compared to the initial formula, the modified formula has some advantages, such as being low cost and easy to perform, and having a short turnaround time and standardized design. Because albumin and absolute lymphocyte count are greatly affected by the nutritional status of individuals and because cancer patients are often malnourished, PNI is usually used to estimate the prognosis of cancer patients **(5).**

**Nutritional status and DLBCL**

A growing body of evidence indicates that malnutrition is a cluster of conditions that can aggregate different levels of both undernutrition and obesity. Evaluation of previously specified lymphoma analyses will be important to know whether the findings in this setting differ from the overall field of cancer **(6).**

Some studies assessed the risk of onset of lymphoproliferative diseases in correlation with nutritional parameters. In a nested case-control study some markers of sustained B- cell activation were predictive of B-cell lymphoma risk, namely sCD23, sCD27, sCD30, and CXCL13. Also, sCD23 and CXCL13 partly mediated the causal pathway association between positive Body Mass Index (BMI) and Diffuse Large B-Cell Lymphoma (DLBCL) risk. Associations have also been reported between increased risk of NHL and polymorphisms in obesity-related genes such as leptin (LEP) and leptin receptor,2,3 key regulators of energy balance and immune function. Indeed, polymorphisms in the LEP gene (2548G>A, 19A>G), associated with high circulating leptin levels, were identified as susceptibility loci for NHL in two independent studies **(7).**

It is also acknowledged that undernutrition will further aggravate lymphoma evolution as well as promoting or causing new illness, as is the case for infections, which in the presence of malnutrition become more difficult to treat. Epidemiological studies reinforce biological findings, suggesting an association between nutritional indicators and lymphoma risk and outcomes. Indeed, several case-control and prospective studies have found increased risk of NHL in association with BMI $\geq 30$ **(8).**

Tumors actively perturb nutritional status through a variety of mechanisms. The anatomical site of presentation of the lymphoma, such as the gastrointestinal, oropharyngeal and central nervous system sites, can impair food intake. Beyond the mechanical causes that induce reduced intake, weight loss is a B-symptom which can be found more frequently in high-grade lymphoma or in those with faster replication. In cancer patients, important contributors of nutritional deterioration are represented by metabolic disturbance and changes in resting energy expenditure. Hypermetabolism and increased gluconeogenesis are not counterbalanced by adaptation mechanisms to preserve lean body mass. These deep metabolic disturbances are generated by a cascade of events triggered by biological mediators. The final outcome is that of a cancer metabolic syndrome. The intense production of pro-inflammatory cytokines is attributable to the tumor itself or to the systemic response to the tumor. For lymphoma, a key clinical study highlighted the role of IL-6 in causing anorexia and cachectic state that improved after treatment with anti-IL-6 monoclonal antibodies. Furthermore, depending on the treatment modality and on the type of regimen, therapy for lymphoma can impact nutritional status by means of side effects that accelerate the appearance of nutritional decline **(8).**

**PNI and DLBCL**

Prognostic Nutritional Index (PNI) is a simple biomarker calculated on the basis of serum albumin level and total lymphocyte count in peripheral blood. It is used as prognostic parameter for various diseases, including solid tumors and hematological malignancies. Its prognostic value in lymphomas may reflect both the role of hypoalbuminemia and malnutrition in negatively affecting the outcome of the disease, both the intrinsic biological aggressiveness of lymphoma that induces immunosuppression as well as malnutrition through the action of cytokine mediators. In a retrospective study, PNI was identified as an independent predictor of response to treatment, OS and Event-Free Survival (EFS) in patients with DLBCL. Furthermore, a significant correlation was observed between PNI and other poor prognostic factors including ECOG-PS, bone marrow involvement, advanced disease stage and presence of B symptoms **(9).**

In another retrospective study, low-PNI was associated with more frequent therapy-related toxicities and mortality and early withdrawal from treatment in patients treated with first-line R-CHOP for DLBCL. PNI also predicted both OS and EFS in a group of 98 patients with DLBCL in an additional retrospective study **(8).**

A number of studies in recent years have shown that malnutrition, which is a frequently-encountered issue in patients with DLBCL, is associated with the poor overall survival (OS). Lymphoma patients with poor nutrition supply have a higher risk of developing febrile neutropenia that can lead to delays in chemotherapy treatment due to decreased drug usage. Recent studies have found that PNI, an indicator that reflects the nutritional and immune status of patients, can be used to predict the clinical outcomes of patients with various malignant tumors, regardless of the tumor location and origin. Some studies have focused on exploring the prognostic value of PNI for DLBCL, however the results were inconsistent and contradictory, possibly due to small sample sizes and patient heterogeneity in individual studies **(10).**

**PNI and Hematologic malignancies**

Some studies have investigated the prognostic value of PNI in lymphomas, including follicular lymphoma (Abu Sabaa et al.), extranodal natural killer/T cell lymphoma (ENKTL), nasal type, classic Hodgkin lymphoma (cHL), and diffuse large B cell lymphoma (DLBCL). PNI was found to be associated with worse OS and/or PFS in ENKTL and FL. However, the results from studies concerning cHL varied. One study of 122 patients with classic cHL reported that low PNI was associated with worse OS and PFS in univariate analysis; however, low PNI lost its significance in the multivariate analysis. In another study with large sample size (n=1,012), low PNI was an independent risk factor for OS and PFS in cHL **(11).**

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