

Immunonutritional profiling for prognostic assessment in diffuse large b-cell lymphoma: an initial evaluation of the C-reactive Protein-Albumin-Lymphocyte (CALLY) Index

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ABSTRACT

Aims: Diffuse large B-cell lymphoma (DLBCL) demonstrates wide heterogeneity, complicating risk stratification with conventional prognostic instruments, particularly the International Prognostic Index (IPI). The C-reactive Protein (CRP)-Albumin-Lymphocyte (CALLY) Index, an immunonutritional marker that integrates inflammation, nutritional status, and immune competence, has demonstrated prognostic relevance in solid tumors. The present analysis was designed to determine the clinical utility of the CALLY Index for prognostication in newly diagnosed DLBCL patients and to assess its added value when integrated with traditional prognostic scores.

Methods: In this retrospective cohort, 112 patients presenting with newly diagnosed DLBCL and treated at Bursa Uludağ University between 2015 and 2019 were evaluated. The CALLY Index was calculated as (serum albumin $\times$ absolute lymphocyte count) / (CRP $\times 10^4$). An optimal cutoff value of 0.78 was derived using log-rank testing and used to stratify patients into low (≤ 0.78) and high (> 0.78) CALLY categories. Baseline clinical features were compared between groups. Kaplan-Meier curves and multivariable Cox proportional hazards modeling were applied to examine overall survival (OS). Multivariable analysis included IPI score and serum beta-2-microglobulin.

Results: Cases in the low CALLY subgroup (68.8%) were significantly older, had poorer Eastern Cooperative Oncology Group performance, lower albumin, higher CRP, and more advanced disease ($p < 0.01$ for all). They were also more frequently classified into higher-risk IPI categories ($p = 0.009$). Median OS in the low CALLY group was 14.8 months, while the high CALLY group had not reached median OS at the end of follow-up ($p = 0.0009$). Univariable analysis revealed that low CALLY (HR: 5.33, $p = 0.002$) and high IPI score were associated with worse OS. In multivariable analysis, low CALLY remained an independent predictor of mortality (HR: 3.42, 95% CI: 1.16-10.08; $p = 0.025$), even after adjusting for IPI and beta-2-microglobulin levels.

Conclusion: The CALLY Index is an independent and clinically accessible prognostic biomarker in DLBCL. Its integration of inflammatory, nutritional, and immune parameters provides complementary prognostic information beyond traditional models such as the IPI. Given its cost-effectiveness and reliance on routine laboratory data, the CALLY Index may serve as a valuable tool in real-world prognostic assessment. These findings support prospective validation and exploration of its utility in dynamic risk models and personalized treatment strategies for DLBCL.

Keywords: Diffuse large B-cell lymphoma, CALLY Index, immunonutritional profiling, prognosis, International Prognostic Index, overall survival

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), the predominant form of non-Hodgkin lymphoma, is marked by substantial heterogeneity at the clinical, pathological, and molecular levels. Although standard chemoimmunotherapy-most notably the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)-has significantly improved treatment outcomes, survival rates remain variable. This variability underscores the pressing need for more refined and biologically informed prognostic models.

The International Prognostic Index (IPI) continues to serve as the predominant clinical instrument for risk stratification in DLBCL. However, its performance in the rituximab era has been questioned due to its limited ability to discriminate high-risk patients and the large proportion of individuals falling into intermediate-risk groups, which restricts its clinical utility.¹⁻³ Moreover, IPI does not incorporate molecular or biomarker-based parameters, which have shown promise in enhancing risk prediction.⁴ Alternative models such as

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the National Comprehensive Cancer Network (NCCN)-IPI, revised (R)-IPI, and biomarker-integrated indices (e.g., double expressor status, MYC/BCL2 coexpression) offer improved stratification but are often complex or not readily available in routine clinical practice.⁵⁻⁷

Recent investigations highlight the prognostic relevance of systemic inflammation, nutritional state, and immune competence in DLBCL.⁸⁻¹⁰ Our group has also investigated systemic inflammatory and immunonutritional indices in hematologic malignancies, including myelofibrosis, Hodgkin lymphoma, myelodysplastic syndromes, and primary central nervous system (CNS) lymphoma, highlighting their potential in prognostic assessment.¹¹⁻¹⁴ Inflammatory and immunonutritional indices such as the Prognostic Nutritional Index (PNI), glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have demonstrated independent associations with survival outcomes and have been proposed as supplements to classical models.^{8,15-17} However, each of these indices captures only a single biological dimension.

The C-reactive Protein (CRP)-Albumin-Lymphocyte (CALLY) Index is a novel composite biomarker that integrates inflammation (CRP), nutritional status (serum albumin), and immunity (absolute lymphocyte count). The CALLY Index has shown strong independent prognostic value across various solid tumors, including gastric, colorectal, esophageal, hepatocellular, lung, breast, and ovarian cancers.¹⁸⁻²² Compared to single-parameter models, it offers a more comprehensive biological assessment and has outperformed traditional markers such as CRP or albumin alone in several malignancies.^{18,20,22}

The appeal of the CALLY Index lies in its simplicity, cost-effectiveness, and reliance on readily accessible laboratory parameters, making it feasible for use in daily clinical practice and in resource-limited settings. While its usefulness has been documented in solid cancers, the prognostic role of the CALLY Index remains unexplored in hematologic neoplasms, including DLBCL.¹⁸

Our primary aim was to determine the prognostic relevance of the CALLY Index in the setting of newly diagnosed DLBCL. We hypothesize that this composite biomarker, encompassing inflammatory, nutritional, and immune parameters, may serve as a reliable and accessible adjunct to current clinical models, ultimately supporting more personalized risk stratification strategies.

METHODS

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Bursa Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Decision No: 2021-7/30, Date: 02.06.2021).

Study Design and Patient Selection

The study retrospectively analyzed individuals diagnosed with DLBCL at Bursa Uludağ University, Division of Hematology, between January 2015 and December 2019. Eligibility

criteria were age ≥ 18 years, availability of baseline laboratory parameters for CALLY Index calculation, and accessible survival data. Patients with incomplete laboratory or clinical information were excluded. Altogether, 112 individuals satisfying these requirements were analyzed in the study.

Data Collection and Definitions

Baseline clinical and laboratory information at diagnosis was retrieved from the institutional electronic database. Variables collected included patient age, sex, serum albumin (g/dl), absolute lymphocyte count (cells/ μ L), CRP (mg/dl), Eastern Cooperative Oncology Group performance status (ECOG PS), serum lactate dehydrogenase (LDH), beta-2-microglobulin concentration, number of extranodal sites involved, Ann Arbor stage, and IPI score. The CALLY Index was calculated as:

$$\frac{\text{Serum albumin (g/dl)} \times \text{absolute lymphocyte count (/}\mu\text{L)}}{\text{CRP (mg/dl)} \times 10^4}$$

CALLY Stratification

The optimal stratification point of the CALLY Index for predicting overall survival (OS) was determined using log-rank test p-values across a range of potential thresholds. Based on this analysis, a CALLY score of 0.78 was selected as the discriminative cutoff (Figure 1). Patients were subsequently categorized into low (≤ 0.78) and high (> 0.78) CALLY groups.

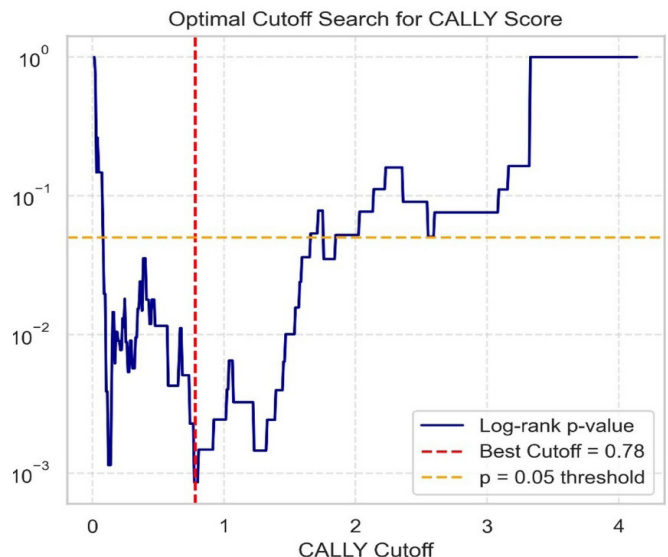


Figure 1. Optimal CALLY Index cutoff determination using log-rank test p-values

Blue Line: Log-rank p-values calculated at each potential CALLY cutoff. Red Dashed Line: Best discriminative cutoff for overall survival (CALLY=0.78). Orange Dashed Line: Statistical significance threshold ($p=0.05$)

CALLY: C-reactive Protein-Albumin-Lymphocyte Index

Statistical Analysis

Continuous variables were described using medians with corresponding interquartile ranges (IQR) and their distributions were compared through the Mann-Whitney U test. Categorical variables were presented as counts and percentages, with group differences assessed using either the Chi-square test or Fisher's exact test, depending on suitability.

OS was defined as the interval between the date of diagnosis and either death from any cause or the most recent follow-up. Survival distributions were estimated by the Kaplan–Meier method, and differences between groups were examined using the log-rank test. Both univariate and multivariable Cox proportional hazards regression models were applied to explore the impact of clinical variables on OS. Candidate variables with a p-value <0.10 in univariate analysis were subsequently incorporated into the multivariable model. Effect sizes were expressed as hazard ratios (HRs) together with 95% confidence intervals (CIs).

All statistical procedures were performed in Python (version 3.13.2) using the lifelines package. A two-sided p-value <0.05 was considered to indicate statistical significance.

RESULTS

The final analysis comprised 112 patients with DLBCL for whom CALLY index values could be calculated. At the time of diagnosis, the study cohort had a median age of 55 years (IQR: 43.8–66.0), with an overall range of 18 to 89 years. Males represented the majority of the study population (60.6%, n=67).

Baseline Laboratory and Clinical Characteristics

At baseline, patients exhibited a median serum albumin level of 3.8 g/dl (IQR: 3.4–4.3), median absolute lymphocyte count of 1575/μL (IQR: 953–2238), and median CRP level of 2.2 mg/L (IQR: 0.5–7.2). The resulting median CALLY Index was 0.2 (IQR: 0.1–1.3), reflecting a broad spectrum of inflammatory and nutritional status across the cohort (Figure 2).

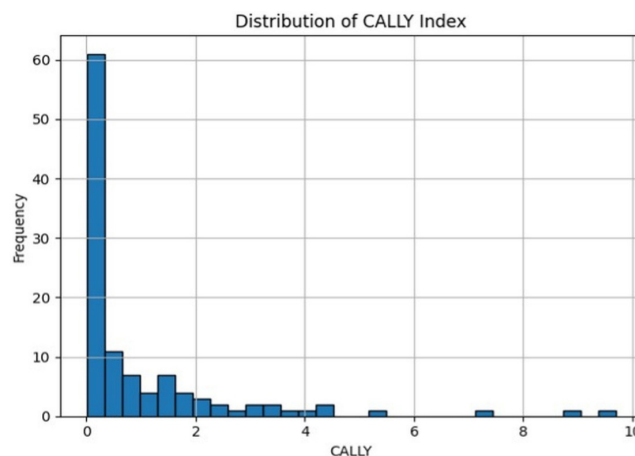


Figure 2. Histogram of CALLY Index distribution among DLBCL patients

The CALLY Index is calculated as: (serum albumin × lymphocyte count) / (CRP × 10⁴). Values are right-skewed, with most patients exhibiting low scores

CALLY: C-reactive Protein–Albumin–Lymphocyte Index, DLBCL: Diffuse large B-cell lymphoma, CRP: C-reactive protein

Patients were stratified into low CALLY (≤0.78, n=77, 68.8%) and high CALLY (>0.78, n=35, 31.3%) groups based on the optimal cutoff derived from survival analyses.

Comparison Between CALLY Groups

Individuals in the low CALLY cohort were significantly older (median age: 59.0 vs. 48.0 years, p=0.005), had lower serum albumin (3.7 vs. 4.4 g/dl, p<0.001), lower lymphocyte counts (1360/μL vs. 1980/μL, p<0.001), and markedly elevated CRP levels (4.6 vs. 0.3 mg/dl, p<0.001) compared to those in the high CALLY group (Table 1).

Table 1. Baseline clinical and laboratory characteristics of patients with DLBCL stratified by CALLY Index (cut-off: 0.78)

Variable	All patients (n=112)	Low CALLY (≤0.78) n=77	High CALLY (>0.78) n=35	p-value
Age, years, median (IQR)	55.0 (43.8–66.0)	59.0 (47.0–70)	48.0 (38.5–56.5)	0.005 ^a
Sex, male, n (%)	65 (58.0%)	46 (59.7%)	19 (54.3%)	0.737 ^b
Albumin, g/dl, median (IQR)	3.8 (3.4–4.3)	3.7 (3.1–4.0)	4.4 (4.1–4.5)	<0.001 ^a
Lymphocyte count (/μL), median (IQR)	1575 (953–2238)	1360 (730–1950)	1980 (1540–2525)	<0.001 ^a
CRP, mg/dl, median (IQR)	2.2 (0.5–7.2)	4.6 (2.1–11.0)	0.3 (0.3–0.6)	<0.001 ^a
Serum beta-2 microglobulin, normalized ratio, n (%)				0.003 ^b
≤1		28 (36.4%)	24 (68.6%)	
>1		49 (63.6%)	11 (31.4%)	
ECOG PS, median (IQR)	2 (1–3)	2 (1–3)	1 (1–2)	0.026 ^a
Extranodal site count, median (IQR)	1 (0–2)	1 (1–2)	1 (0–1)	0.001 ^a
Serum LDH, normalized ratio, n (%)				0.024 ^b
≤1		25 (32.5%)	20 (57.1%)	
>1		52 (67.5%)	15 (42.9%)	
Ann arbor stage, median (IQR)	3 (2–4)	4 (2–4)	3 (2–4)	0.008 ^a
IPI group distribution, n (%)				0.009 ^b
Low		15 (23.4%)	16 (50.0%)	
Low-intermediate		9 (14.1%)	7 (21.9%)	
High-intermediate		17 (26.6%)	6 (18.8%)	
High		23 (35.9%)	3 (9.4%)	
CALLY Index, median (IQR)	0.2 (0.1–1.3)	0.12 (0.04–0.27)	2.03 (1.46–3.44)	<0.001 ^a

DLBCL: Diffuse large B-cell lymphoma, CALLY: C-reactive Protein–Albumin–Lymphocyte, IQR: Interquartile range, CRP: C-reactive protein, ECOG PS: Eastern Cooperative Oncology Group Performance Status, LDH: Lactate dehydrogenase, IPI: International Prognostic Index, a: Mann–Whitney U test, b: Chi-square or Fisher's exact test

Furthermore, the median ECOG PS was poorer in the low CALLY category [2 (IQR: 1-3)] than in the high CALLY category [1 (IQR: 1-2), $p=0.026$]. Similarly, the extent of extranodal involvement was greater [median: 1 (IQR: 1-2) vs. 1 (IQR: 0-1), $p=0.001$] (**Table 1**).

Analysis of Ann Arbor staging revealed a higher stage distribution in the low CALLY group [median: 4 (IQR: 2-4)] versus the high CALLY group [3 (IQR: 2-4), $p=0.008$] (**Table 1**).

Risk Stratification by IPI Score

Distribution of patients according to the IPI revealed a significantly greater representation of higher-risk categories in the low CALLY group ($p=0.009$) (**Table 1** and **Figure 3**). Risk stratification revealed that 71.9% of individuals in the high CALLY group were categorized as low or low-intermediate risk, compared with 37.5% among those with low CALLY scores. Conversely, 62.5% of patients in the low CALLY group fell into the high-intermediate or high-risk categories, whereas this proportion was only 28.1% among patients in the high CALLY group (**Figure 3**).

Collectively, these findings suggest that a lower CALLY Index at diagnosis is significantly associated with older age, poor nutritional and inflammatory profiles, greater tumor burden, and more unfavorable prognostic features, as reflected by ECOG PS, extranodal site involvement, Ann Arbor stage, and IPI risk group distribution.

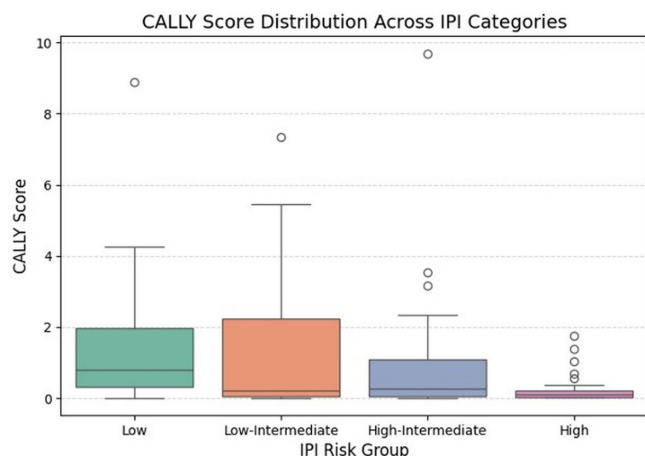


Figure 3. Distribution of CALLY scores across IPI risk groups

IPI categories: Low, low-intermediate, high-intermediate, high. Boxes: IQRs. Lines inside boxes: Medians. Whiskers: $1.5 \times \text{IQR}$. Circles: Outliers

CALLY: C-reactive Protein-Albumin-Lymphocyte Index, IPI: International Prognostic Index, IQR: Interquartile range

Survival Analysis by CALLY Score

Patients with CALLY values ≤ 0.78 demonstrated significantly worse OS than those with scores above 0.78, as illustrated by Kaplan-Meier survival analysis. Specifically, the median OS for the low CALLY group was 14.8 months, whereas it was not reached for the high CALLY group within the follow-up period, suggesting superior long-term survival in this subgroup. The survival curves began to diverge early during follow-up and remained consistently separated over time, indicating a sustained prognostic distinction. OS varied significantly between groups, with the log-rank test confirming statistical significance ($p=0.0009$) (**Figure 4**). The results provide evidence for the prognostic significance of the CALLY Index at diagnosis in stratifying survival outcomes among patients with DLBCL.

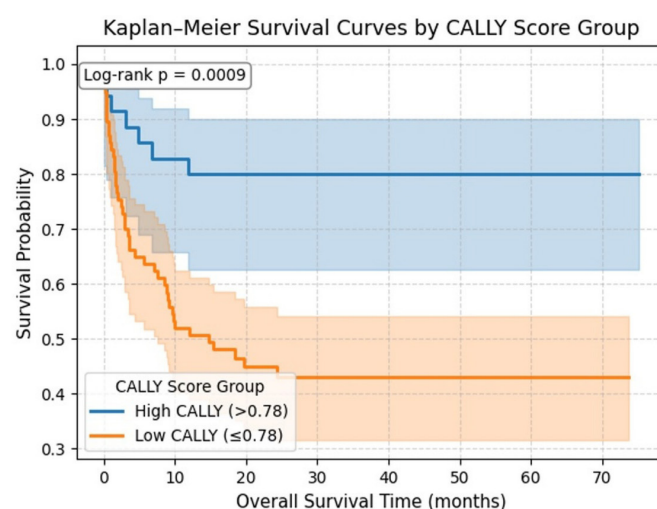


Figure 4. Kaplan-Meier overall survival curves according to CALLY Index stratification

Blue line: High CALLY (>0.78). Orange line: Low CALLY (≤ 0.78). Shaded areas: 95% confidence intervals. Log-rank $p=0.0009$

CALLY: C-reactive Protein-Albumin-Lymphocyte Index

Cox Proportional Hazards Analysis

In univariable Cox regression analysis, both IPI risk category and low CALLY Index were significant predictors of OS. Specifically, cases in the low CALLY category had significantly worse survival compared to those with high CALLY (HR: 5.33, 95% CI: 1.88-15.12; $p=0.002$). Similarly, increasing IPI category showed a significant relationship with increased mortality, with the high-risk group showing a particularly elevated hazard (HR: 14.02, 95% CI: 4.08-48.26; $p<0.001$) (**Table 2**).

Table 2. Cox regression analysis of factors associated with overall survival in DLBCL patients

Variable	Univariate HR (95% CI)	Univariate p	Multivariate HR (95% CI)	Multivariate p
CALLY score (low)	5.33 (1.88-15.12)	0.002	3.42 (1.16-10.08)	0.025
IPI (low-intermediate)	3.25 (0.73-14.52)	0.123	0.27 (0.09-0.85)	0.025
IPI (high-intermediate)	7.69 (2.14-27.59)	0.002	0.54 (0.25-1.17)	0.118
IPI (high)	14.02 (4.08-48.26)	<0.001	0.07 (0.02-0.26)	<0.001
Beta-2-microglobulin (high)	1.85 (0.94-3.61)	0.073	0.59 (0.28-1.23)	0.156

HRs and 95% CIs were calculated using Cox proportional hazards regression. Univariable and multivariable analyses were performed to assess the prognostic significance of the CALLY score, IPI categories, and beta-2 microglobulin levels. In the multivariable model, both low CALLY score and higher IPI category remained independent predictors of poor overall survival. A low CALLY score was defined as ≤ 0.78 . IPI categories were referenced against the low-risk group.

DLBCL: Diffuse large B-cell lymphoma, HR: Hazard ratio, CI: Confidence interval, CALLY: C-reactive Protein-Albumin-Lymphocyte Index, IPI: International Prognostic Index

In the multivariable Cox model adjusting for IPI risk categories and beta-2-microglobulin, low CALLY remained independently associated with increased mortality (HR: 3.42, 95% CI: 1.16-10.08; $p=0.025$) (Table 2). Notably, the inclusion of the CALLY Index in the multivariable model did not attenuate the prognostic impact of the IPI, indicating that both metrics offer complementary prognostic information.

The sustained statistical significance of the CALLY Index in multivariable Cox analysis, even after adjusting for IPI risk categories, underscores its ability to capture prognostic dimensions not fully addressed by the IPI. The study highlights the potential of the CALLY Index as a clinically applicable, cost-efficient, and non-invasive biomarker for improving risk categorization and tailoring prognostic assessment in DLBCL patients.

DISCUSSION

This work constitutes the initial attempt to explore the prognostic implications of the CALLY Index in DLBCL. The present analysis indicates that a low baseline CALLY Index independently correlates with inferior OS, even when adjusted for established clinical prognostic tools such as the IPI and the NCCN-IPI. These results are consistent with previously reported associations between systemic inflammatory/nutritional biomarkers and outcomes in both solid tumors and lymphomas.^{8,23}

Conventional prognostic models such as the IPI and NCCN-IPI exhibit limited capacity to capture the biological heterogeneity of DLBCL, particularly among patients classified within intermediate-risk categories.²⁴ This limitation has driven the development of complementary or alternative strategies incorporating immune-nutritional biomarkers-such as the PNI, Systemic Immune-Inflammation Index (SII), and Advanced Lung Cancer Inflammation Index-each of which contributes to a more nuanced risk stratification framework. In recent years, growing attention has increasingly focused on the intricate interplay of systemic inflammation, nutritional state, and tumor progression as a critical determinant of cancer prognosis. Within the context of DLBCL, biomarkers such as the NLR, SII, PLR, and PNI have been independently associated with prognostic outcomes.^{10,25-27} Among these, the CALLY Index-comprising serum albumin, absolute lymphocyte count, and CRP-offers a unified reflection of immunonutritional status and systemic inflammation, thus capturing a more integrative measure of tumor-host interactions.²⁸

Moreover, dynamic biomarkers such as circulating tumor deoxyribonucleic acid (ctDNA) provide real-time insights into disease burden and therapeutic response. Studies have shown that early ctDNA clearance after treatment initiation predicts better survival, even before radiologic response is evident.^{29,30} However, ctDNA measurement is limited by cost and availability, making readily accessible laboratory indices such as CALLY a more practical option for most institutions. In line with this, our prior investigations in DLBCL and primary CNS lymphoma have underscored the clinical utility of easily obtainable laboratory markers for real-world prognostic assessment.^{14,31,32}

In our study, the CALLY Index maintained its prognostic significance across clinically relevant subgroups, including patients stratified by age, stage, extranodal involvement, and LDH levels. Its reliance on routine laboratory values makes it highly feasible for use in real-world settings. Importantly, the CALLY Index was independently predictive of OS in multivariate Cox models, reinforcing its potential as a robust prognostic biomarker.

Limitations

Among the study's limitations, its retrospective and monocentric design stands out as a major factor limiting external generalizability. Moreover, dynamic alterations in the CALLY Index and their association with therapeutic response were not investigated. External validation across independent patient cohorts remains essential to confirm the prognostic robustness of the CALLY Index in DLBCL.

Future investigations should prioritize prospective, multicenter cohorts to confirm the prognostic significance of the CALLY Index. Additionally, integrating CALLY with imaging-based response assessments, molecular biomarkers, and measurable residual disease markers may enhance precision prognostication. Investigating how changes in the CALLY Index during therapy correlate with therapeutic response or relapse could also provide clinically actionable insights. Finally, studies exploring the prognostic impact of the CALLY Index in novel therapeutic settings, including immunotherapy or bispecific antibody-based regimens, would further expand its applicability.

CONCLUSION

In summary, the CALLY Index serves as an independent and readily applicable prognostic indicator of OS in DLBCL. By incorporating markers of systemic inflammation and nutritional status, it provides added value to traditional clinical models such as IPI. Its simplicity, cost-effectiveness, and widespread availability render it a practical tool in routine practice. Well-designed prospective trials are warranted to substantiate its prognostic utility and to clarify its role in shaping personalized management strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Bursa Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Decision No: 2021-7/30, Date: 02.06.2021).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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