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Prognostic significance of the CALLY index in patients with diffuse large B cell lymphoma

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Abstract

The C-reactive protein–Albumin–Lymphocyte (CALLY) index represents a newly introduced biomarker that combines parameters of immune regulation, nutrition, and systemic inflammation and it has been shown to forecast the course of the disease in some malignancies. This research aimed to investigate the prognostic significance of the CALLY index among individuals diagnosed with diffuse large B-cell lymphoma (DLBCL). A cohort of 112 patients diagnosed with DLBCL and managed at the Medical Faculty of Recep Tayyip Erdoğan University between January 2015 and August 2025 was reviewed retrospectively. Based on the determined CALLY index threshold, patients were classified into two distinct categories (<5.93 vs >5.93). A CALLY index below 5.93 was significantly related with the presence of B symptoms, older age, higher disease stage, extranodal involvement, poor Eastern Cooperative Oncology Group performance status (ECOG-PS), higher international prognostic index (IPI) scores, increased lactate dehydrogenase (LDH) levels, and increased mortality. In the univariate analysis performed from an overall survival (OS) perspective, disease stage, IPI score, albumin, C-reactive protein (CRP), ECOG-PS and CALLY index were identified as indicators of prognosis. In multivariate analysis, low CALLY index (<5.93) and ECOG-PS ≥ 2 continued to act as independent factors influencing OS (p=0.001 and p=0.01) Kaplan-Meier analysis revealed that patients exhibiting a CALLY index below 5.93 along with an IPI score of 3 or higher had markedly reduced progression-free survival (PFS) (p=0.049 and p=0.007) and OS (p<0.001 and p=0.005). Low CALLY index independently predicts OS in DLBCL and is linked to decreased PFS and OS durations. It can be considered a potential support tool for clinicians in their decision-making processes and prognosis predictions.

Keywords: CALLY index, diffuse large b-cell lymphoma, prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL), a subtype of non Hodgkin lymphoma, may present with a severe clinical course and is mainly observed in adult patients [1]. International prognostic index (IPI) and related prognostic models are commonly employed for risk stratification [2].

Due to many reasons, including genetic mutation diversity and additional comorbidities, significant differences in survival are observed even among patients in the same risk group [3-5]. Additional prognostic biomarkers based on systemic inflammation and nutrition in DLBCL patients have attracted growing attention in recent years [6-8].

The C-reactive protein–Albumin–Lymphocyte (CALLY) index is an emerging biomarker that combines lymphocyte counts, serum albumin, and C-reactive protein (CRP) levels to reflect immune function, nutritional condition, and systemic inflammatory status. Initially recognized as a predictive indicator in solid tumors, it has been associated to reduced overall survival (OS) and progression-free survival (PFS) across various cancers [9-13]. Current findings indicates that the CALLY index may act as an indicator for prognosis in DLBCL, a disease in which inflammation and immune regulation are central to its pathogenesis [14].

Recent studies have individually examined the association between each component of the CALLY index and prognosis

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in DLBCL. These studies have separately demonstrated that lymphopenia, low serum albumin concentration, or high CRP levels are associated with poor survival outcomes [15-17]. However, because of certain limitations, these factors by themselves may be inadequate for accurately predicting survival, and stronger predictive markers are needed in addition to the IPI score in DLBCL patients.

Although numerous studies have explored the prognostic relevance of inflammation associated indices in DLBCL [6,18], the ability of the CALLY index to serve as a prognostic marker remains largely unexplored. Therefore, evaluating this index in DLBCL patients may contribute to more accurate prediction of disease prognosis and individualization of treatment strategies.

This research aimed to investigate the prognostic significance of the CALLY index among individuals diagnosed with DLBCL.

Material and Methods

A cohort of 112 patients diagnosed with DLBCL and managed at the Medical Faculty of Recep Tayyip Erdoğan University between January 2015 and August 2025 was reviewed retrospectively. Data on clinical characteristics and laboratory results of the patients were found from patient files.

Data collected included patients' age at diagnosis, gender, body mass index, B symptoms (weight loss, fever, night sweats), Eastern Cooperative Oncology Group performance status (ECOG-PS), disease stage, bulky disease, extranodal involvement, and additional comorbidities. Laboratory values (lactate dehydrogenase (LDH) level, albumin level, CRP level, lymphocyte count) were recorded at least 12 hours after fasting on the date of diagnosis. The IPI score and CALLY index were calculated.

The IPI score was calculated on a scale ranging from 0 to 5, based on the following parameters: age, number of extranodal involvement areas, disease stage, LDH levels, ECOG-PS [2].

The CALLY index was calculated using the following formula:

CALLY index = (Lymphocyte count [per μL] × Serum albumin level [g/dL]) / (CRP level [mg/L] × 10^2).

The follow-up period, last check-up date, relapse status, and death status of patients were recorded. Assessment of treatment response was conducted based on the Lugano criteria [19].

OS was defined as the time from diagnosis to death due to any cause or to the last follow-up date, while PFS was defined as the time from diagnosis to disease relapse or progression or to the earliest death.

Study Inclusion Criteria

Patients aged 18 years or older were enrolled in the study with a diagnosis of DLBCL and received rituximab-based chemotherapy, either R CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab) or R mini-CHOP (reduced-dose).

Exclusion Criteria

Patients with active or chronic infection at diagnosis, autoinflammatory disease, prior corticosteroid or immunosuppressive therapy, renal dysfunction or proteinuria, chronic liver disease, a history of malignancy, or previous chemotherapy-radiotherapy were excluded. Additionally, patients with underwent major surgery within the last 4 weeks, DLBCL associated with viral infection, diagnosed with primary central nervous system or testicular DLBCL, receiving treatments other than rituximab-based chemotherapy, and cases with missing information were not included in the study

Based on the CALLY index threshold determined by receiver operating characteristic (ROC) analysis, patients were classified into two distinct categories.

Ethical approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of Recep Tayyip Erdoğan University School of Medicine (No: 2025/175, Date: 25 April 2025).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY). Descriptive data for each group were expressed as frequencies and percentages (n, %). The association between mortality and categorical variables in DLBCL was evaluated using the Chi-square test.

P-values were determined considering the number of patients in each category (using Pearson's Chi-square test /Fisher's exact test, depending on data suitability). ROC analysis was employed to assess the ability of the CALLY index to predict mortality in DLBCL patients. Cut-off values, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) values were calculated. Cox regression analysis was used to evaluate the predictive value of the covariates, with hazard ratios (HR) reported alongside 95% confidence intervals (CI). Variables showing statistical significance in the univariate assessments were subsequently entered into the multivariate model. To examine how these factors influenced mortality, Kaplan-Meier survival curves were generated, and group differences were compared using the log-rank test. Spearman rank correlation method was used to explore the associations among the variables, and the corresponding rho values were reported. A p-value below 0.05 was considered indicative of statistical significance."

Results

The study population consisted of 112 patients, of whom 60 were male and 52 were female, and their mean age was 65 ±

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12.5 years. Among them, 34 were in the early disease stages (1-2), while 78 presented with advanced stages (3-4). The mean body mass index of the study population was calculated as 27±4.1 kg/m². The average follow up period was 48.5 ± 37.4 months, with the longest observation reaching 126 months.

41 patients had an IPI score of 0-2 points (low), while 71 patients had a score between 3-5 points (high).

In terms of comorbidities, 31 patients had diabetes mellitus (DM), 62 patients had hypertension (HT), 14 patients had hyperlipidemia (HL), and 14 patients had coronary artery disease (CAD).

Throughout the follow-up, relapse occurred in 25 patients, and 57 patients died.

The optimal cut-off value for the CALLY index was determined as 5.93 based on ROC curve analysis using the Youden Index, which identified the threshold with the highest combined sensitivity and specificity for predicting survival outcomes. (AUC:63.2% p:0.016 (95% CI: 52.9-73.4) Sensitivity:43.9% Specifity:81.8%) (Figure 1). The CALLY index was found to be low (<5.93) in 35 patients and high (>5.93) in 77 patients.

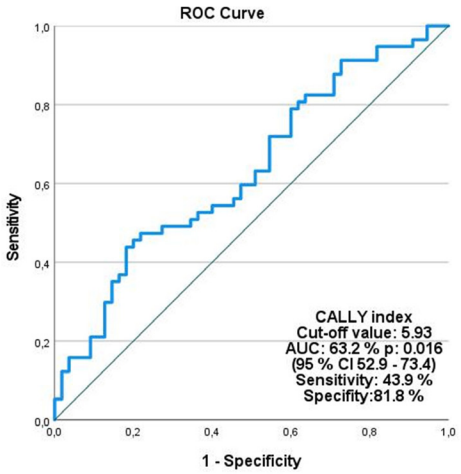

Figure 1. ROC analysis of the CALLY index

A CALLY index below 5.93 was significantly related with the presence of B symptoms (p<0.001), older age (p=0.036), higher disease stage (P<0.001), extranodal involvement (p=0.003), poor ECOG-PS (p=0.001), higher IPI score (p<0.001), increased LDH levels (p=0.026), and increased mortality (p=0.003) (Table 1).

Table 1. Comparison of demographic and clinical characteristics according to CALLY index groups

Variables		CALLY index		p
		< 5.93	> 5.93	
		N (%)	N (%)	
Age (years)	**<60**	7 (20)	31 (40.3)	**0.036**
	≥ 60	28 (80)	46 (59.7)	
Gender	**Female**	12 (34.3)	40 (51.9)	0.082
	Male	23 (65.7)	37 (48.1)	
B symptoms	**Negative**	17 (48.6)	63 (81.8)	**<0.001**
	Positive	18 (51.4)	14 (18.2)	
Stage	**1-2**	3 (8.6)	31 (40.3)	**<0.001**
	3-4	32 (91.4)	46 (59.7)	
ECOG-PS	**0-1**	24 (68.6)	71 (92.2)	**0.001**
	2-4	11 (31.4)	6 (7.8)	
Bulky disease	**No**	27 (77.1)	64 (83.1)	0.453
	Yes	8 (22.9)	13 (16.9)	
IPI score	**0-2**	3 (8.6)	38 (49.4)	**<0.001**
	3-5	32 (91.4)	39 (50.6)	
Extranodal involvement	**No**	3 (8.6)	27 (35.1)	**0.003**
	Yes	32 (91.4)	50 (64.9)	
LDH (U/L)	**< 240**	9 (25.7)	37 (48.1)	**0.026**
	≥ 240	26 (74.3)	40 (51.9)	
Relapse	**No**	25 (71.4)	62 (80.5)	0.284
	Yes	10 (28.6)	15 (19.5)	
Exitus	**No**	10 (28.6)	45 (58.4)	**0.003**
	Yes	25 (71.4)	32 (41.6)	

ECOG-PS: Eastern Cooperative Oncology Group performance status, IPI: International prognostic index, LDH: Lactate dehydrogenase

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In the correlation analysis, a moderate negative correlation was observed between the CALLY index and the IPI score (p<0.001, rho=-0.410).

In the univariate analysis for PFS, disease stage, bulky disease, IPI score, ECOG-PS, and extranodal disease were each linked to PFS. In the multivariate model, advanced stage and bulky disease continued to act as independent factors influencing PFS (p=0.012 and p=0.004) (Table 2).

In the univariate analysis performed from an OS perspective, disease stage, IPI score, albumin, CRP, ECOG-PS and CALLY index were identified as indicators of prognosis. In multivariate analysis, low CALLY index (<5.93) and ECOG-PS ≥ 2 continued to act as independent factors influencing OS (p=0.001 and p=0.01) (Table 3).

Table 2. Cox regression analysis of factors independently predicting progression-free survival (PFS)

Scale and Subdimensions	Univariate analysis				Multivariate analysis			
	p	HR	95 % CI for HR		p	HR	95 % CI for HR	
			Lower	Upper			Lower	Upper
Age	0.469	0.747	0.339	1.646				
Gender	0.901	0.952	0.434	2.088				
B symptoms	0.052	2.195	0.994	4.847				
Stage	**0.010**	13.842	1.868	102.549	**0.012**	13.191	1.777	97.904
ECOG-PS	**0.004**	4.110	1.570	10.758				
Bulky Disease	**0.002**	3.504	1.567	7.839	**0.004**	3.271	1.454	7.360
IPI score	**0.013**	3.922	1.342	11.463				
Extranodal involvement	**0.032**	4.875	1.149	20.691				
LDH (U/L)	0.233	1.670	0.720	3.876				
Lymphocyte (/µl)	0.575	1.000	0.999	1.000				
Albumin (g/dL)	0.103	0.566	0.285	1.123				
CRP (mg/L)	0.091	1.017	0.997	1.038				
CALLY index	0.058	0.458	0.204	1.027				

B symptoms, Stage, ECOG-PS, Bulky Disease, Extranodal involvement, CALLY index selected as covariate. ECOG-PS: Eastern Cooperative Oncology Group performance status, IPI: International prognostic index, LDH: Lactate dehydrogenase, CRP: C-reactive protein

Table 3. Cox regression analysis of factors independently predicting overall survival (OS)

Scale and Subdimensions	Univariate analysis				Multivariate analysis			
	p	HR	95% CI for HR		p	HR	95 % CI for HR	
			Lower	Upper			Lower	Upper
Age	0.052	1.820	0.995	3.329				
Gender	0.214	1.400	0.824	2.381				
B symptoms	0.408	1.276	0.716	2.275				
Stage	**0.002**	3.124	1.527	6.390	0.067	2.035	0.951	4.357
ECOG-PS	**<0.001**	4.548	2.462	8.401	**0.001**	2.879	1.506	5.507
Bulky Disease	0.164	1.557	0.835	2.906				
IPI score	**0.007**	2.308	1.258	4.233				
Extranodal involvement	0.058	1.941	0.979	3.849				
LDH (U/L)	0.055	1.745	0.987	3.083				
Lymphocyte (/µl)	0.059	1.000	0.999	1.000				
Albumin (g/dL)	**<0.001**	0.442	0.281	0.695				
CRP (mg/L)	**0.020**	1.017	1.003	1.032				
CALLY index	**<0.001**	0.299	0.169	0.528	**0.01**	0.449	0.244	0.826

Age, Stage, ECOG-PS, Extranodal involvement, LDH, Lymphocyte, Albumin, CRP, CALLY index selected as covariate. ECOG-PS: Eastern Cooperative Oncology Group performance status, IPI: International prognostic index, LDH: Lactate dehydrogenase, CRP: C-reactive protein

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Kaplan-Meier analysis revealed that patients with lower CALLY index values had shorter PFS and OS (P=0.049, P<0.001) (Figure 2 and Figure 3). In addition, patients presenting with higher IPI scores (3-5) had notably shorter PFS and OS (p=0.007, p=0.005) (Figure 4 and Figure 5).

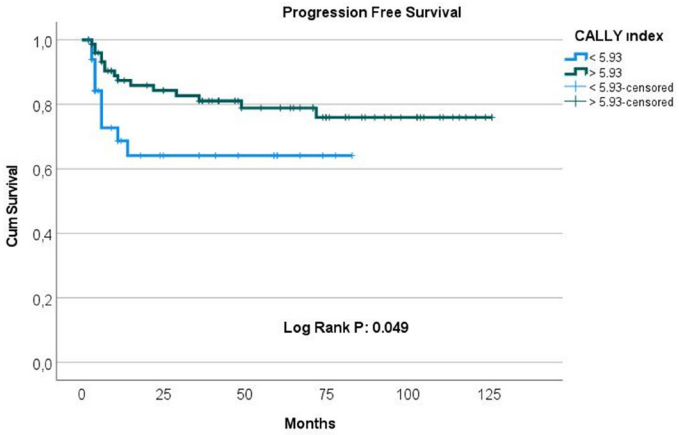

Figure 2. Kaplan–Meier survival curves for progression free survival (PFS) according to CALLY index

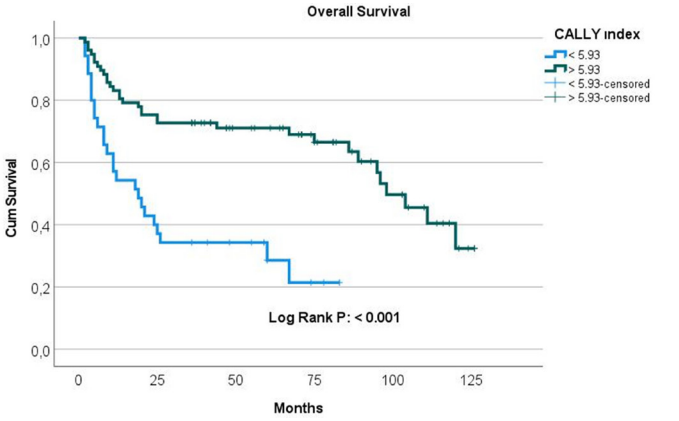

Figure 3. Kaplan–Meier survival curves for overall survival (OS) according to CALLY index

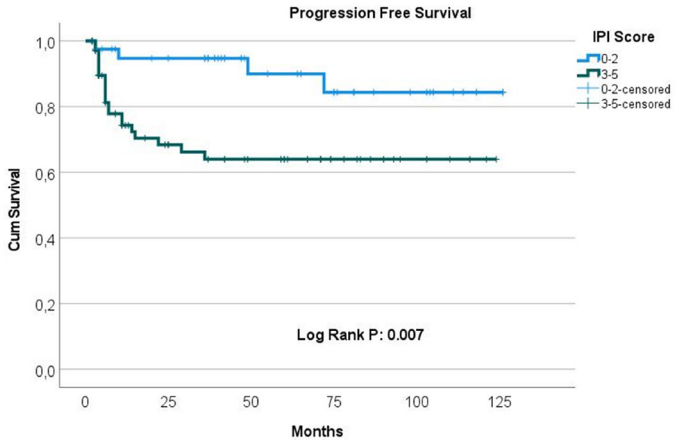

Figure 4. Kaplan–Meier survival curves for progression free survival (PFS) according to IPI score

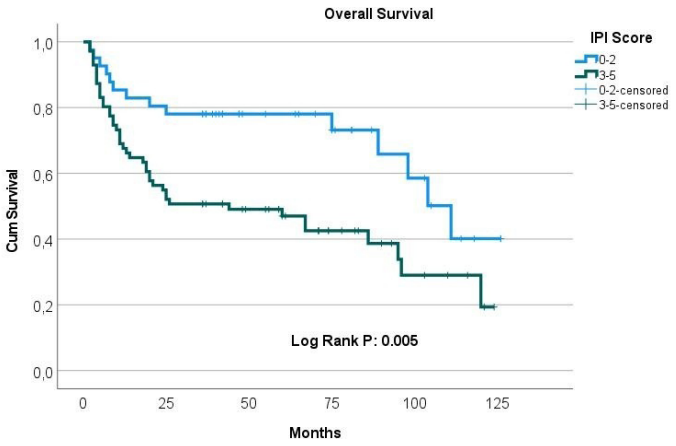

Figure 5. Kaplan–Meier survival curves for overall survival (OS) according to IPI score

Among patients with a CALLY index <5.93, median OS was 33.1 months (95% CI: 22.4-44), while median PFS reached 55.56 months (95% CI: 41.7-69.5). In contrast, those with a CALLY index >5.93 had a median OS of 83.1 months (95% CI: 71.8-94.4) and a median PFS of 101.3 months (95% CI: 90.3-112.4).

Discussion

To our knowledge, this is the first study to comprehensively investigate the association between pre-treatment CALLY index level and disease course in DLBCL. Low CALLY index and poor performance status emerged as independent determinants of overall survival. Additionally, patients with a low CALLY index tended to experience shorter PFS and OS. Furthermore, a moderate and negative correlation was detected between the CALLY index versus IPI score.

ECOG PS is an important clinical indicator in determining the treatment strategy for DLBCL patients and constitutes one of the fundamental components of the IPI score [2]. Additionally, it is accepted as a prognostic marker in predicting survival outcomes. A previous study indicated that ECOG-PS served as an independent determinant of survival in DLBCL [5]. Similarly, another study demonstrated that low pre-treatment albumin levels and high ECOG-PS values predicted poorer outcomes [20]. In this study, a high ECOG-PS emerged as an independent predictor of poorer OS. This finding supports the notion that performance status is an important clinical parameter to be considered in predicting survival in DLBCL.

The IPI score and its derivatives have been shown to be strong indicators of prognosis in DLBCL and remain the most widely used prognostic marker [2,21]. Recent studies have reported that the IPI retains its validity in predicting prognosis after R-CHOP treatment, but its predictive power may be enhanced when used in combination with biological and inflammatory markers in certain subgroups [22,23]. Furthermore, it has been noted that IPI derivatives demonstrate higher sensitivity in predicting survival compared to the classic IPI, particularly in elderly or high-risk patients [23,24]. These findings have once again demonstrated

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that the IPI score forms the basis of clinical risk classification in DLBCL and suggest that its integration with new biomarkers may improve prognostic accuracy. In this cohort, higher IPI scores were associated with reduced progression-free and overall survival, while the CALLY index showed a negative correlation with the IPI score, indicating that poorer immunonutritional status is linked to higher clinical risk categories in DLBCL. Therefore, incorporating the CALLY index into existing prognostic frameworks may enhance risk stratification by identifying patients with diminished immunonutritional reserve who may be at higher risk despite having similar IPI scores. These findings underscore the complementary prognostic value of the CALLY index and indicate that its integration with the IPI score may enhance the accuracy and comprehensiveness of clinical risk assessment.

Lymphocytes serve as a major measure of the body's immune functionality [25]. In recent years, they have emerged as important indicators of prognosis in DLBCL. In a study by Watanabe et al., low pre-treatment lymphocyte count in DLBCL independently predicted poorer PFS and OS [15]. Another study demonstrated that low CD4+ T lymphocytes are associated with low PFS, independent of age and IPI [26]. Similarly, lymphopenia was shown to anticipate relapse prior to clinical manifestation in DLBCL patients [27]. In our study, lymphopenia emerged as a borderline significant prognostic factor for OS. Therefore, the presence of lymphopenia prior to treatment may positively contribute to clinical decision-making processes as an important indicator of both immune deficiency and disease aggressiveness.

Albumin level is an important biomarker, reflecting both inflammation throughout the body and the patient's nutritional status, and overall disease burden in malignency. Reduced serum albumin commonly indicates a worse clinical course, advanced disease stage, and high IPI scores in DLBCL patients [28,29]. Low albumin levels may arise as a result of elevated levels of inflammatory mediators, including interleukin-6 and tumor necrosis factor-alpha (TNF-α), in the tumour microenvironment and the liver's negative acute phase response. This mechanism has an adverse effect on survival by reflecting both systemic inflammation and malnutrition [30]. Recent research indicates that reduced pre-treatment albumin levels independently predict OS and PFS in DLBCL. As reported by Zhao et al., low albumin levels independently predicted reduced PFS and OS in 403 DLBCL cases [31]. Similarly, another study demonstrated that low serum albumin levels among DLBCL patients who were treated with R-CHOP weakened the immune response, leading to treatment resistance, shorter OS, and poorer prognosis [16]. Current findings support that albumin levels are not only a nutritional marker but also a reflection of tumour-related inflammatory processes. In this study, reduced serum albumin emerged as an predictor of OS. This finding suggests that serum albumin levels may be clinically useful in predicting disease prognosis in DLBCL.

CRP is an indicator of the systemic inflammatory response and reflects the immune status in the tumor-associated microenvironment, influencing the progression and prognosis of malignant diseases, including DLBCL [32,33]. High CRP levels may contribute to reduced survival through several biological mechanisms. Firstly, cytokines and chemokines secreted by tumour cells may stimulate hepatic CRP synthesis, reflecting the aggressive biological behaviour of the tumour. Furthermore, elevated CRP levels may indicate the severity of the inflammatory response in the tumour microenvironment and the role of this inflammation in supporting tumour progression. In addition, high CRP concentration may also be considered an indicator of a weakened T-lymphocyte-mediated immune response against the tumour [34,35]. When these mechanisms are considered together, it is suggested that elevated CRP could indicate worse outcomes in DLBCL. Troppan et al. reported that CRP emerged as a prognostic indicator for 5-year OS and PFS in individuals with DLBCL [36]. Another meta-analysis evaluated the predictive role of CRP and reported that elevated pre-treatment CRP levels predicted poorer overall and progression-free survival in individuals with DLBCL [17]. Similarly, in our study, elevated CRP emerged as an predictor of overall survival. The findings indicate that CRP may be considered a potential marker for predicting the biological behaviour of the disease.

Various indices indicating nutrition or inflammation levels have attracted attention as potential indicators that may help estimate the clinical course of cancer [37,38]. The CALLY index, which represents the combination of nutritional status, immune dysfunction, and systemic inflammation that significantly contribute to tumor development and progression, has recently emerged as an indicator related to patient prognosis in several cancers. One study has demonstrated that patients with cholangiocarcinoma who have a low CALLY index (<3.5) have significantly shorter PFS and OS durations, and this index has emerged as an independent factor associated with outcome patterns in cancer. [39]. Similarly, an investigation conducted on a cohort of 174 individuals with breast malignancy reported that the CALLY index served as an independent determinant of both overall survival and recurrence-free survival after surgical treatment [10]. Another study by Feng et al. found that individuals with a lower CALLY index had a substantially lower 5 year cancer-specific survival probability [11]. Another investigation in lung cancer reported that patients with reduced CALLY index values exhibited poorer overall survival, and that this parameter showed notable sensitivity and accuracy in estimating 3- and 5-year survival outcomes [13]. The consistent results obtained in different organ cancers imply that the CALLY index functions as a meaningful prognostic marker, irrespective of cancer type

In the current study, lower CALLY index independently predicted overall survival and showed a significant relationship with shorter OS and PFS durations. In malignancies such as DLBCL, where a compromised immune response is evident, low CALLY

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levels may reflect an increased systemic inflammatory response and malnutrition. This situation may contribute to a shorter survival period by reducing both the host's immune response capacity and the response to treatment. Therefore, low CALLY index can be considered a clinically helpful prognostic parameter for closer clinical monitoring, individualization of treatment, and timely planning of supportive interventions, allowing for early prediction of the risk of adverse prognosis in DLBCL.

Study Strengths and Limitations

To the best of our knowledge, this study provides early independent evidence supporting the prognostic utility of the CALLY index in DLBCL. Additionally, the use of a homogeneous, single-center cohort managed under standardized diagnostic and therapeutic protocols reduces clinical variability and enhances the internal validity of the findings. However, several limitations should be acknowledged. The retrospective design and single-center setting may limit causal inference and reduce the generalizability of the results. Although the sample size reflects the available patient population, larger multicenter prospective studies are required to confirm these observations and improve their applicability.

Conclusion

Low CALLY index independently predicts OS in DLBCL and is linked to decreased PFS and OS durations. The CALLY index, which integrates three fundamental biological processes (inflammation, immune regulation, and nutrition) that play a important role in the course of DLBCL, may be considered a potential support tool for clinicians in their decision-making processes and prognosis prediction. It should be investigated more comprehensively in prospective studies as a marker that can contribute to risk-based, individualized approaches in patient follow-up.

Ethical Approval
Approved by the Non-Interventional Clinical Research Ethics Committee of Recep Tayyip Erdoğan University School of Medicine (No: 2025/175, Date: 25 April 2025).

Patient Consent
Informed consent was waived due to the retrospective design.

Conflict of Interest
The authors declare no conflict of interest.

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