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Prognostic value of the CALLY index in De Novo metastatic colorectal cancer: a retrospective study

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ABSTRACT

Aims: The CALLY index, integrating C-reactive protein (CRP), albumin, and lymphocyte count, has been identified as a promising prognostic biomarker in various cancers. The present study aims to evaluate its prognostic significance in De Novo metastatic colorectal cancer (mCRC).

Methods: A retrospective analysis was conducted on 108 patients diagnosed with de novo mCRC at Ankara Etlik City Hospital (2021–2024). The CALLY index was calculated from baseline laboratory values and dichotomized at the median (0.2018). Progression-free survival (PFS) and overall survival (OS) were compared between low and high CALLY groups using the Kaplan–Meier method and log-rank test. The associations between the CALLY index and tumour location, as well as RAS/BRAF mutation status, were evaluated using the chi-square test. Cox regression analyses were also performed to determine independent prognostic factors.

Results: Patients with elevated CALLY scores exhibited significantly prolonged median PFS (24.0 vs. 13.0 months; $p<0.001$) and OS (not reached vs. 15.0 months; $p<0.001$) in comparison to those with low scores. Low CALLY scores were found to be associated with RAS mutations ($p=0.03$) and tumour location ($p=0.04$), but not BRAF mutations ($p=0.37$). In multivariate Cox regression analysis, a high CALLY score remained an independent prognostic factor for both PFS and OS.

Conclusion: A low CALLY index is associated with shorter durations of PFS and OS in patients harboring RAS mutations and right-sided tumour location. Its simplicity and practicality suggest considerable promise for routine clinical use, pending confirmation in large prospective studies.

Keywords: CALLY index, metastatic colorectal cancer, RAS mutation, prognosis

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer worldwide, with approximately 1.9 million new diagnoses recorded in 2020.[1] At the time of diagnosis, approximately 20% of patients present with distant metastases, and 30–40% develop metachronous metastases following primary tumour resection.[2] Despite advances in combined treatment approaches, the 5-year survival rate for metastatic colorectal cancer (mCRC) remains below 20%.[3]

Recent progress in molecular subtyping and targeted therapies has resulted in improved outcomes; however, a significant proportion of patients continue to rely on standard chemotherapy due to limited access to molecular diagnostics or the absence of targetable mutations.[4] This emphasises the necessity for simple, cost-effective prognostic biomarkers to guide treatment.Systemic inflammation has been identified as a significant contributor to tumour progression, angiogenesis and immune evasion.[5] Various indices of inflammation and nutrition, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), have been observed to serve as prognostic markers in various cancer types.[6,7]

The CALLY index, a prognostic tool based on CRP, albumin, and lymphocyte count, has been demonstrated to reflect inflammatory burden and nutritional status. Initially validated in hepatocellular carcinoma, the CALLY index has shown prognostic value in esophageal squamous cell carcinoma and melanoma.[8-10] Low CALLY scores have been shown to correlate with higher inflammation, poor nutritional reserve, and worse survival.[8]

The present study evaluates the prognostic significance of the CALLY index in patients with de novo mCRC, focusing on its association with overall survival (OS), progression-free survival (PFS), primary tumour location, and RAS/BRAF mutation status.

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METHODS

Ethics

The study was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 12.06.2024, Decision No: 462) and was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments.

This retrospective study was conducted at Ankara Etlik City Hospital, Department of Medical Oncology. Patients diagnosed with De Novo mCRC from 2021 onwards were identified through electronic medical records.

Inclusion Criteria

- Diagnosis of de novo mCRC in 2021 or later.
- Complete clinical, pathological, and laboratory data at diagnosis.

Exclusion Criteria

- Non-metastatic disease at diagnosis.
- Prior history of other malignancies.
- Incomplete clinical or laboratory data.

Data Collection

The data collated encompassed demographic particulars (age, gender), tumour characteristics (primary tumour site: right colon, left colon, rectum), comorbidities (hypertension, diabetes, coronary artery disease, cerebrovascular disease, asthma/COPD), molecular mutation profiles (RAS, BRAF), and the locations of metastases (liver, lung, peritoneum).

CALLY Index

The CALLY index was calculated using baseline albumin (g/L), lymphocyte count ($\times 10^9$/L), and CRP (mg/L) values with the formula:

$$\text{CALLY index} = (\text{albumin} \times \text{lymphocyte count}) / (\text{CRP} \times 10^4)$$

The preliminary analyses conducted to determine the optimal cut-off value using Cox regression did not yield statistically significant results due to the limited sample size and the presence of censored data. Therefore, a median-based classification approach, which is commonly used in the literature, was preferred.[11] Patients were stratified into low and high CALLY groups based on the median value (0.2018).

Statistical Analysis

PFS and OS were analyzed using the Kaplan–Meier method, with comparisons via log-rank tests. Associations between CALLY groups and clinical/molecular parameters were assessed using Pearson's Chi-square test. A p-value <0.05 was considered significant. Analyses were performed using IBM SPSS Statistics, Version 26.0 (IBM Corp. Armonk, NY, USA).

RESULTS

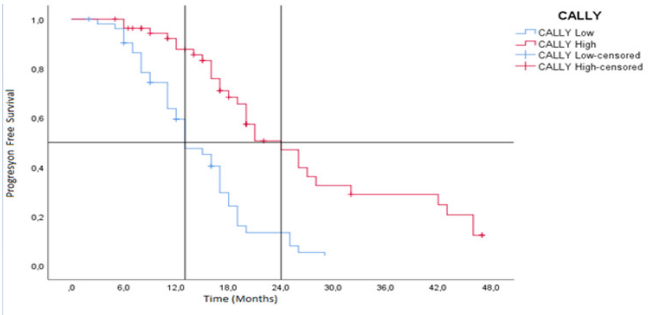
The study population comprised 108 patients with de novo mCRC. The median age recorded was 63.0 years (range: 29.0–82.0), with 60.4% of subjects being male. The most prevalent primary tumour site was the left colon (44.4%), followed by the rectum (33.3%) and the right colon (22.2%). Hypertension (37.0%) and diabetes mellitus (20.4%) were the most prevalent comorbidities. Furthermore, the presence of RAS mutations was detected in 48.1% of patients, while BRAF mutations were identified in 5.6%. The median CALLY index was 0.2018 (range: 0.01–24.8). The most prevalent metastases were those that had spread to the liver (90.7%), followed by those that had spread to the peritoneum (14.8%) and the lungs (9.3%) (**Table 1**).

Table 1. Sociodemographic and clinical characteristics

Age median (range) year	63.0 (29.0-82.0)
Sex	**n (%)**
Male	65 (60.4)
Female	43 (39.6)
Primary tumour location	**n (%)**
Right colon	24 (22.2)
Left colon	48 (44.4)
Rectum	36 (33.4)
Comorbidity	**n (%)**
Hypertension	**40 (37.0)**
Diabetes mellitus	**22 (20.4)**
Coronary artery disease	**17 (15.8)**
Cerebrovascular disease	**11 (10.1)**
Asthma/COPD	**11 (10.1)**
Mutation status	**n (%)**
RAS mutant	52 (48.1)
RAS wild	56 (51.9)
BRAF mutant	6 (5.6)
BRAF wild	102 (94.4)
CALLY index median	0.2018 (0.01-24.8)
Metastatic sites	**n (%)**
Liver	98 (90.7)
Lung	10 (9.3)
Peritoneum	16 (14.8)

COPD: Chronic obstructive pulmonary disease, CALLY: C-reactive protein-albumin-lymphocyte

The analysis of PFS and OS durations was conducted utilising the Kaplan–Meier method, with the study population divided into CALLY score groups. The median PFS in patients with low CALLY scores was 13.0 months (95% CI: 9.96–16.03), while it was 24.0 months (95% CI: 18.40–29.59) in the high CALLY group. The groups exhibited a statistically significant difference according to the log-rank test (χ^2=26.580; p<0.001) (**Figure 1**).



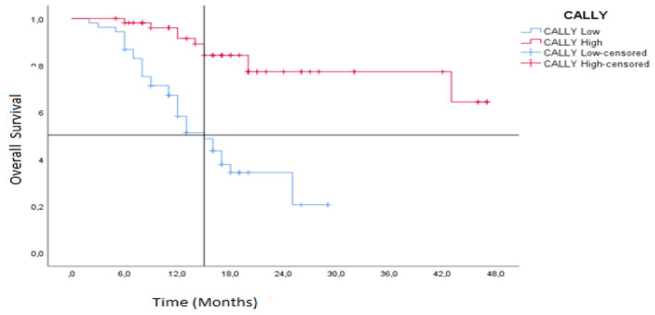
Time (Months)	Low CALLY Group(At Risk)	High CALLY Group(At Risk)
0	53	55
12	30	42
24	5	14
36	–	8
48	–	2

*Number at risk is limited at later time points due to short follow-up durations in some patients.

Figure 1. Kaplan–Meier plot of PFS by CALLY index
PFS: Progression-free survival, CALLY: C-reactive protein-albumin-lymphocyte

The median OS was 15.0 months (95% confidence interval [CI]: 11.1–18.9) in the low CALLY group, whereas the median OS was not reached in the high CALLY group. The log-rank

test revealed a significant difference between the groups (χ^2=25.645, p<0.001), suggesting that patients with higher CALLY scores had significantly longer OS (**Figure 2**).



Time (Months)	Low CALLY Group(At Risk)	High CALLY Group(At Risk)
0	53	55
12	30	42
24	5	16
36	–	9
48	–	3

*Number at risk is limited at later time points due to short follow-up durations in some patients.

Figure 2. Kaplan–Meier plot of OS by CALLY index
OS: Overall survival, CALLY: C-reactive protein-albumin-lymphocyte

A statistically significant correlation was observed between the CALLY index and RAS mutation status (p=0.03, Chi-square test). Patients with RAS mutations were identified at a higher frequency in the low CALLY group. Conversely, no substantial discrepancy was observed between the CALLY index and the BRAF mutation status (p=0.37). A significant discrepancy was identified between the CALLY groups with respect to tumour location (p=0.04). Tumours located on the left side were more prevalent in the high CALLY group, while right side tumours were predominantly associated with a low CALLY index. The association of the CALLY index with mutation status and tumour localisation is demonstrated in **Table 2**.

Table 2. Association between CALLY index and tumour location and mutation status

		CALLY low	CALLY high	p value
RAS mutation	Negative	20	32	0.03
	Positive	33	23	
	Total	53	55	
BRAF mutation	Negative	49	53	0.37
	Positive	4	2	
	Total	53	55	
Tumour location	Right	17	7	0.04
	Left	22	26	
	Rectum	14	22	
	Total	53	55	

Pearson Chi-square test, CALLY: C-reactive protein-albumin-lymphocyte

In the univariate PFS, left-sided tumour location (HR: 0.60; 95% CI: 0.38–0.95; p=0.029), RAS mutation (HR: 1.78; 95% CI: 1.21–2.62; p=0.003), and a high CALLY score (HR: 0.35; 95% CI: 0.23–0.53; p<0.001) were identified as significant prognostic factors. In the multivariate analysis, these variables retained their independent significance: left-sided tumour location (HR: 0.65; 95% CI: 0.41–0.99; p=0.045), RAS mutation (HR: 1.65; 95% CI: 1.11–2.45; p=0.013), and a high CALLY score (HR: 0.40; 95% CI: 0.26–0.61; p<0.001) remained significantly associated with PFS (**Table 3**).

OS, univariate analysis showed that left-sided tumour location (HR: 0.55; 95% CI: 0.34–0.89; p=0.015), RAS mutation (HR: 1.85; 95% CI: 1.24–2.76; p=0.002), and a high CALLY score (HR: 0.32; 95% CI: 0.21–0.49; p<0.001) were significant prognostic factors. In multivariate analysis, left-sided tumour location (HR: 0.59; 95% CI: 0.36–0.97; p=0.038), RAS mutation (HR: 1.72; 95% CI: 1.15–2.58; p=0.008), and a high CALLY score (HR: 0.37; 95% CI: 0.24–0.57; p<0.001) remained independently significant (**Table 4**).

Due to the limited number of patients with BRAF mutations (n=6), this variable was not included in multivariate analysis to avoid overfitting and potential model instability.

DISCUSSION

The present findings support the prognostic relevance of the CALLY index in de novo mCRC, reinforcing its role as a surrogate marker of systemic inflammation, nutritional status, and immune competence. These results are in line with previous research conducted in other malignancies, such as hepatocellular carcinoma, esophageal squamous cell carcinoma, and melanoma, where the CALLY index has similarly demonstrated its prognostic value. Such consistency across tumour types highlights the potential of the CALLY index as a broadly applicable tool for outcome prediction in oncology.[8-10]

Systemic inflammation has been demonstrated to promote tumour progression and immune evasion.[6] The CALLY index integrates CRP, albumin, and lymphocyte count, thereby providing a comprehensive measure of these factors. Low CALLY scores, indicative of heightened inflammation and inadequate nutritional reserves, have been associated with unfavourable outcomes, in accordance with previous reports.[8-10]

A salient finding was the observed relationship between low CALLY scores and the presence of RAS mutations. RAS mutations are known to drive more aggressive tumour behavior and confer resistance to anti-EGFR therapies.[12] The association with diminished CALLY values suggests that systemic inflammation may enhance the biological aggressiveness of RAS-mutant tumours, providing a rationale for the consideration of personalized strategies such as anti-inflammatory or intensified therapeutic approaches.[13,14] This observation aligns with previous studies linking inflammatory markers, including the NLR, to molecular alterations in CRC.[15,16] The CALLY index's ability to reflect mutation status may offer added value in guiding molecular stratification, particularly in settings with limited access to advanced genomic testing.

The absence of a significant association between the CALLY index and BRAF mutation status may reflect the limited biological interaction between BRAF-driven oncogenesis and systemic inflammatory or nutritional pathways captured by this index. Additionally, the underrepresentation of BRAF-mutant cases in the study cohort may have constrained the

Table 3. Cox regression analysis for progression-free survival PFS

Variable	Univariable HR (95% CI)	p-value (univariable)	Multivariable HR (95% CI)	p-value (multivariable)
Tumour location-left colon	0.60 (0.38–0.95)	0.029	0.65 (0.41–0.99)	0.045
Tumour location-rectum	0.75 (0.47–1.20)	0.231	0.80 (0.50–1.28)	0.354
RAS mutation (positive vs. negative)	1.78 (1.21–2.62)	0.003	1.65 (1.11–2.45)	0.013
BRAF mutation (positive vs. negative)	-	-	-	-
CALLY index (high vs. low)	0.35 (0.23–0.53)	<0.001	0.40 (0.26–0.61)	<0.001

PFS: Progression-free survival, HR: Hazard ratio, CI: Confidence interval, CALLY: C-reactive protein-albumin-lymphocyte

Table 4. Cox regression analysis for OS

Variable	Univariable HR (95% CI)	p-value (univariable)	Multivariable HR (95% CI)	p-value (multivariable)
Tumour location-left colon	0.55 (0.34–0.89)	0.015	0.59 (0.36–0.97)	0.038
Tumour location-rectum	0.70 (0.43–1.14)	0.152	0.74 (0.45–1.22)	0.241
RAS mutation (positive vs. negative)	1.85 (1.24–2.76)	0.002	1.72 (1.15–2.58)	0.008
BRAF mutation (positive vs. negative)	-	-	-	-
CALLY index (high vs. low)	0.32 (0.21–0.49)	<0.001	0.37 (0.24–0.57)	<0.001

OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, CALLY: C-reactive protein-albumin-lymphocyte

statistical power to detect such a relationship. These findings are concordant with previous studies suggesting that BRAF mutations exert minimal influence on inflammation-based prognostic models, thereby underscoring the specificity of the CALLY index for certain molecular subtypes, particularly those involving RAS-driven tumour biology.[10]

The distribution of CALLY index levels across tumour locations may reflect underlying biological patterns observed in CRC. Left-sided tumours tended to align with higher CALLY scores, which may correspond to a more favorable inflammatory and nutritional profile. In contrast, right-sided tumours appeared more frequently in the lower CALLY group, supporting their association with adverse systemic conditions and less favorable clinical behavior. These patterns are consistent with existing evidence on the prognostic implications of tumour sidedness in CRC.[17-19]

The CALLY index's reliance on routine laboratory tests renders it both cost-effective and practical, especially in settings with limited resources. It has the capacity to guide treatment decisions, such as identifying patients with low CALLY scores and RAS mutations for the purpose of intensified therapies or clinical trials. In a study conducted by Acar et al.[10] in 2025, a CALLY-based nomogram was proposed for melanoma risk stratification, and a similar approach is considered to be potentially applicable in mCRC.

A high CALLY score has been associated with longer PFS and OS across various malignancies in the literature. Consistent with previous findings, our study also demonstrated that patients with a high CALLY index had significantly longer PFS and OS durations.[8-10]

Moreover, the presence of RAS mutation and right-sided tumour location were associated with shorter PFS and OS in our study, in line with the existing literature. These findings are consistent with prior studies indicating that RAS mutations and right-sided tumour location are linked to a more aggressive disease course in CRC.[20]

Limitations

This study has several limitations. First, the retrospective and single-center design may lead to selection bias and restrict the generalizability of the findings to broader populations. Second, the relatively small sample size, particularly in certain molecular subgroups, may have reduced the power to detect associations between the CALLY index and specific clinical or genetic variables. Third, no statistically significant cut-off point could be determined in the ROC analysis for the CALLY index; therefore, patients were classified based on the median CALLY score (0.2018). Although this approach is commonly used in similar retrospective prognostic studies, it may limit the external applicability and clinical interpretability of the findings. Moreover, the CALLY index does not include critical clinical parameters such as tumour burden, performance status, or patterns of metastatic spread, all of which can impact survival outcomes.

Additionally, the follow-up durations for a significant portion of the patients were relatively short due to the recent establishment of our hospital. This resulted in a limited number of patients at risk in long-term follow-up points in the Kaplan–Meier analyses, particularly in the Low CALLY group (the risk tables displayed below **Figure 1, 2**). This stems from the lack of long-term follow-up data for newly diagnosed patients. Prospective multicenter studies with longer and more homogeneous follow-up durations may overcome this limitation and more accurately confirm the prognostic value of the CALLY index. Finally, the integration of complementary biomarkers such as circulating tumour DNA or molecular signatures may further enhance the clinical utility of this scoring system.[18]

CONCLUSION

The CALLY index is a simple, cost-effective prognostic biomarker in De Novo mCRC. Low CALLY scores are associated with RAS mutations, right-sided tumour location, and significantly shorter durations of PFS and OS. These

findings highlight the index's potential utility in routine clinical decision-making, warranting validation in large-scale prospective cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 12.06.2024, Decision No: 462).

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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