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C-Reactive Protein-Albumin-Lymphocyte Index (Cally) As A Prognostic Biomarker in Colorectal Cancer: A Systematic Review

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KEYWORDS
Colorectal cancer; Incidence of cancer; C-reactive protein

ABSTRACT
Globally, colorectal cancer is ranked as the third highest incidence of cancer and the second highest cause of death; therefore, it is in dire need of prognostic markers that can be implemented in health facilities. The *C-reactive protein-albumin-lymphocyte (CALLY) index* is a biomarker that uses the values of CRP, albumin, and lymphocyte counts, which have been utilized to predict the prognosis of various diseases, including colorectal cancer. The research involved a thorough search of several databases, such as PubMed, Science Direct, and Google Scholar, from 2018 to 2025. The journal search strategy began with the determination of research questions using PICO. This study applied inclusion and exclusion criteria to refine the journal searches. A significant increase in the *CALLY* index predicts a reduced risk of death. The *CALLY* index has a higher prognostic value than other prognostic factors for colorectal cancer. Stage II-III colorectal cancer patients with a low pre-operative *CALLY* index have a significantly worse prognosis. Lower *CALLY* values are associated with a poorer prognosis of colorectal cancer. A prospective multicenter study with a larger and more diverse population is needed to validate the findings of this study.

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INTRODUCTION

Research estimates indicate as many as 1.9 million new cases and 935,000 deaths due to colorectal cancer in 2020. Globally, colorectal cancer ranks as the third highest in cancer incidence and the second leading cause of cancer-related death. The increased risk of colorectal cancer is related to changes in dietary habits, notably a shift toward dominant foods from animal sources, sedentary lifestyles, and lack of physical activity, which contribute to excess weight. Additional risk factors include smoking, low fiber consumption, excessive alcohol intake, and consumption of red and processed meats. Key strategies to reduce morbidity and mortality from colorectal cancer include adequate screening and lifestyle modifications (Dekker et al., 2019; Sung et al., 2021).

The risk of developing colorectal cancer increases by approximately 20% with a family history of the disease, particularly among first-degree relatives. Other risk factors include male gender, history of inflammatory bowel disease, prior radiation exposure to the abdominal area, diabetes mellitus, among others (Siegel et al., 2020; Thanikachalam & Khan, 2019).

Dysbiosis, or disruption of the intestinal microbiota balance, has also been recognized as playing a significant role in colorectal cancer progression. Disruption of gut microbiota increases intestinal permeability, which contributes to chronic inflammation. Approximately 20% of malignant colon tumors are initiated by chronic inflammatory processes (Quaglio et al., 2022).

Currently, tumor development can be assessed using various indicators, including those related to systemic inflammatory responses. Cancer is characterized by active inflammation; there for markers of systemic inflammation can provide valuable insights into disease progression (Yamamoto et al., 2021).

The *C-reactive protein-albumin-lymphocyte (CALLY) index* is a biomarker calculated from CRP, albumin, and lymphocyte counts that has been used to predict prognoses across various diseases. The *CALLY* index offers a comprehensive assessment linking inflammatory processes, immune status, and nutritional condition to cancer prognosis (Wu et al., 2025). Studies have shown that a low *CALLY* index correlates with poor outcomes and shorter overall survival (OS) in breast cancer patients. Regarding disease-free survival (DFS), patients with low *CALLY* tend to have longer DFS compared to those with high *CALLY*. Low *CALLY* levels prior to surgery can serve as an independent predictor of poorer prognosis, shortened survival, and tumor progression (Zhuang et al., 2024).

In oral cavity cancer, a low *CALLY* index associates with more advanced disease stages (III–IV), lymph node metastases, deep invasion, extranodal extension, shorter median survival, and the need for adjuvant therapy (Tsai et al., 2022). A study using Cox regression analyses identified the *CALLY* index as an independent prognostic factor for OS and DFS in postoperative epithelial ovarian cancer patients, wherein low *CALLY* indicated worse outcomes and a higher need for adjuvant therapy (Wang et al., 2022).

In hepatocellular carcinoma (HCC), the 5-year survival rate differed significantly based on *CALLY* indices: patients with low *CALLY* had a 5-year OS of 71%, while those with high *CALLY* had only 46%. Similar trends were observed in gastric cancer, where low *CALLY* predicted worse 5-year OS (Hashimoto et al., 2024; Iida et al., 2022). The *CALLY* index combined with tumor stage, nodal involvement, and metastases enables better risk stratification and informed personalized treatment decisions in esophageal cancer patients undergoing esophagectomy (colorectal 13). In renal cancer, the *CALLY* index predicts postoperative recurrence (Meng et al., 2025). A systematic review found that low *CALLY* values correlate with poorer outcomes in digestive system cancers (Wu et al., 2025).

Despite these findings, no systematic review has yet focused explicitly on the *CALLY* index as a prognostic biomarker in colorectal cancer. Therefore, this study aims to evaluate the clinical significance of the *CALLY* index in colorectal cancer prognosis.

Several studies have examined systemic inflammation's role in cancer prognosis, especially in colorectal cancer. For instance, Zhang et al. (2020) investigated the *CALLY* index as a prognostic marker across cancers, including colorectal cancer, finding that low *CALLY* correlated with poorer survival and shorter OS in breast cancer patients. However, their study did not fully assess the *CALLY* index's applicability specifically in colorectal cancer nor offer a comprehensive systematic review. Similarly, Li et al. (2021) explored dysbiosis's link to colorectal cancer, emphasizing how gut microbiota disruption can provoke chronic inflammation leading to cancer. Yet, they did not integrate the *CALLY* index as a marker connecting inflammation with colorectal cancer prognosis, leaving a knowledge gap regarding the interaction of these factors.

The objective of this study is to assess the clinical significance of the *CALLY* index in predicting outcomes for colorectal cancer patients. By analyzing relationships between *CALLY* index levels and colorectal cancer prognosis, including OS and DFS, this research aims to provide valuable insights for clinical practice. Potential benefits include offering a useful prognostic tool, facilitating personalized treatment strategies, and improving patient outcomes through enhanced risk stratification. Moreover, this study will help bridge the gap between systemic inflammation, immune response, and colorectal cancer prognosis, potentially leading to improved therapeutic approaches and survival rates.

METHOD

The researchers conducted a thorough search of several databases such as PubMed, Science Direct, and Google Scholar 2018 to 2025. The journal search strategy began with the determination of research questions using PICO, (P) the population in this study was colorectal cancer patients, (I) C-reactive protein-albumin-lymphocyte (CALLY) index, (O) Outcome in this study used CALLY as a prognostic biomarker. This study used inclusion and exclusion criteria to limit journal searches. Inclusion criteria include (1) The study only involves patients with a diagnosis of colorectal cancer, (2) Has laboratory data in the form of CBC, albumin, and CRP, (3) Uses the same CALLY index calculation system. The exclusion criteria in this study are: (1) studies with cancer focus other than colorectal cancer, (2) studies that do not explicitly report CALLY index, (3) studies that do not report OS, DFS, or RFS as results. To ascertain the risk of bias we use the Newcastle Ottawa Score (NOS) by assessing the Selection, Comparability, and Outcome components with a maximum score of 9 points. Journals with a minimum score of 6 are categorized as suitable for use in this systematic review.

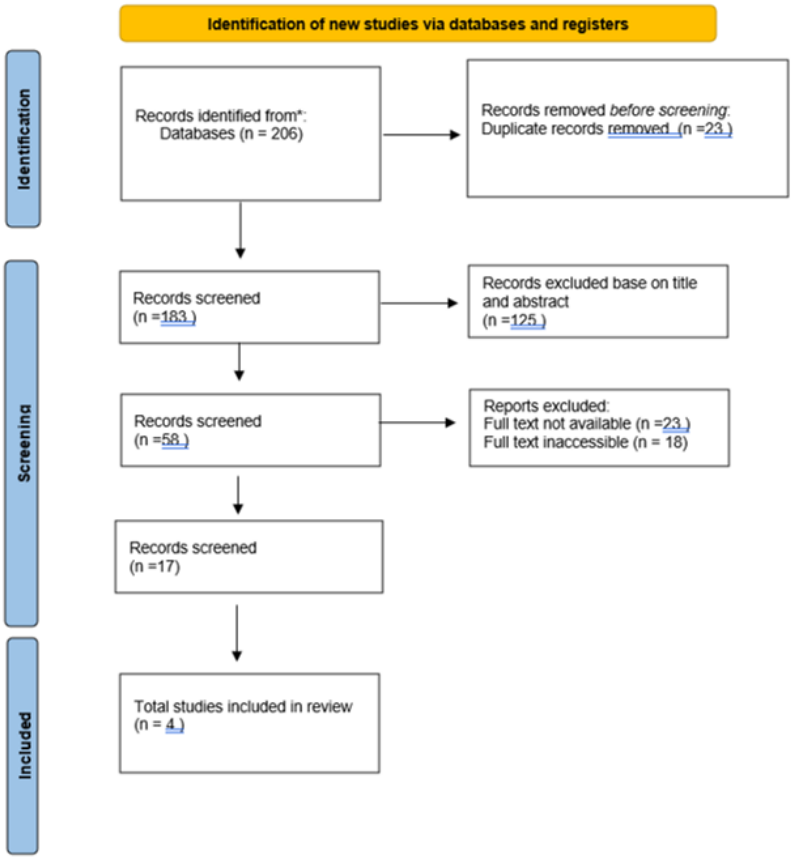

Figure 1. PRISMA FLOWCHART

RESULT AND DISCUSSION

Based on the search strategy, 4 journals were selected with a total of 3720 patients. The retrospective study used was conducted on single and multi-centers. The research was conducted in the period from 2010 to 2020. The CALLY cutoff value was determined in 3 journals using Receiver Operating Characteristic (ROC) analysis while 1 other journal used the median value as the cutoff value. Hazard Ratio (HR) is estimated using univariate and multivariate analysis. Based on the quality and

risk assessment of bias 2 journals consisting of Bekki et al (2025) and Yang et al (2023) are very feasible because they have a very low risk of bias and explain the methodology quite clearly. The research by Takeda et al (2024) is also feasible, although it is necessary to pay attention to the location of the study that only uses a single center. Furukawa et al (2025) are still in the feasible category but some things are still a concern such as the lack of multivariate analysis for the main results and the relatively small sample size.

The results of the study from Takeda et al (2024) reported that only 60.7% of patients with CALLY index < 2 had 5-year DFS and 5-year OS (75.9%), while patients with high CALLY index reported 77.8% of them achieving 5-year DFS and 5-year OS (91.6%) with an HR (95%CI) of 1.81(1.31-2.50). Multivariate analysis obtained CALLY index score <2 (p=0.006) as an independent predictor of DFS and OS. The CALLY index score of <2.0 was significantly associated with worse OS and DFS in patients with stage II-III colorectal cancer undergoing resection therapy.

Single and multi center studies conducted by Bekki et al (2025) consistently reported a CALLY index of ≤ 3.35 to be an independent prognostic factor for poor OS (P=0.010) and poor RFS (P=0.045). A low CALLY index is associated with poor OS and RFS (both P<0.001). A low pre-operative CALLY index was independently associated with a poor long-term prognosis in patients with stage I-III colorectal cancer undergoing curative resection.

The study by Furukawa et al (2025) explained that RFS was lower in the low CALLY group compared to high CALLY, but not statistically significant (p=0.062) while OS showed a significant decrease in the low CALLY group compared to high CALLY but remained statistically insignificant (p=0.008).

Multivariate Cox regression analysis by Yang et al (2023) showed that the CALLY index was independently correlated with OS (HR 95%CI 0.91(0.87−0.95), P<0.001). Patients with a high CALLY index had a lower risk of death (HR95%CI 0.45 (0.36−0.56), P<0.001) compared to those with low ones.

Systemic inflammation in cancer causes a decrease in several parameters such as lymphocytes and albumin. Lymphocytes decrease due to pro-inflammatory cytokines and direct or indirect suppression of myeloid cells. Albumin is an acute phase protein that decreases due to the response of pro-inflammatory cytokines such as IL-6 or can also describe a condition of malnutrition caused by cancer. Other inflammatory parameters that tend to increase in cancer are neutrophils, platelets, monocytes, and C-reactive proteins. CRP is significantly increased due to induction of pro-inflammatory cytokines. The combination of both upregulation and downregulation will form various inflammation-related biomarkers such as Glasgow Prognostic Score (GPS), Systemic Inflammatory Score (SIS), Prognostic Nutrition Index (PNI), Neutrophil-Lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), etc (Yamamoto et al., 2021). Other studies combine upregulation and downregulation parameters such as CRP-to-albumin ratio (CAR), lymphocyte-to-CRP ratio (LCR), etc. CRP is a key predictive factor for assessing OS and DFS of stage II/III colon cancer. (colorectal 7) Another study found that the combination of mGPS and NLR was significantly an independent predictor factor in 3-year OS of patients with TNM I-III colon cancer (Golder et al., 2021). CALLY combines a comprehensive assessment that links inflammatory processes, immunology, and nutritional status to cancer prognosis (Wu et al., 2025). A significant increase in the CALLY index predicts a reduced risk of death. The CALLY index has a higher prognostic value than other prognostic factors for colorectal cancer (Yang et al., 2023). Stage II-III colorectal cancer with a low pre-operative CALLY index has a significantly worse prognosis (Bekki et al., 2025; Furukawa et al., 2025; Takeda et al., 2024).

CONCLUSION

The C-Reactive Protein-Albumin-Lymphocyte (CALLY) index has emerged as a significant prognostic biomarker in colorectal cancer, with lower CALLY values linked to poorer outcomes, including higher mortality risk and reduced survival, particularly in stage II-III patients. An analysis of four studies involving 3,720 patients consistently identified low CALLY scores as independent predictors of adverse outcomes such as overall survival (OS) and disease-free survival (DFS). These findings highlight the crucial role of monitoring systemic inflammation and nutritional status in colorectal cancer management. However, to strengthen the clinical application of the CALLY index, future research should focus on large-scale, multicenter studies with more diverse populations to validate and refine its prognostic utility, ultimately aiding in personalized treatment strategies and improving patient care.

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