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Integrating inflammation, nutrition, and immunity: the CALLY index as a prognostic tool in digestive system cancers - a systematic review and meta-analysis

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Abstract

Background Digestive system cancers remain a leading cause of cancer-related mortality globally, underscoring the need for reliable prognostic tools. The C-reactive protein-Albumin-Lymphocyte (CALLY) index, which reflects inflammation, nutrition, and immunity, has shown potential in predicting survival. However, comprehensive evaluations of its role in digestive system cancers are still limited.

Methods A meta-analysis of English-language studies from online databases was performed to assess the prognostic value of the CALLY index. Pooled hazard ratios (HRs) were calculated for overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and cancer-specific survival (CSS).

Results A total of eighteen articles (19 studies, encompassing 7,951 patients) were included. A lower CALLY index was significantly associated with poorer outcomes across all survival endpoints. The pooled HR for OS was 1.973 (95% CI: 1.734–2.244), with HRs for DFS, RFS, and CSS being 2.093 (95% CI: 1.682–2.604), 1.462 (95% CI: 1.292–1.654), and 2.456 (95% CI: 1.887–3.221), respectively (all $P < 0.001$). Subgroup analyses for OS demonstrated consistent prognostic significance across various treatment strategies, cancer types, cutoff values, sample sizes, and regions. Notably, the CALLY index was a strong predictor of OS in surgical patients (HR = 2.014, 95% CI: 1.794–2.260, $P < 0.001$). Sensitivity analyses validated the robustness of these findings, with minimal publication bias (Egger's test $P = 0.053$).

Conclusions The CALLY index serves as a cost-effective and reliable biomarker for predicting prognosis in digestive system cancers. Its utility as a pre-treatment risk stratification tool, which integrates key factors of inflammation, nutrition, and immunity, renders it valuable for guiding clinical decision-making.

Keywords CALLY index, Digestive system cancers, Prognostic biomarker, Meta-analysis

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Introduction

Digestive system cancers, including esophageal, gastric, hepatic, colorectal, pancreatic, and gallbladder cancers, represent significant public health challenges due to their high incidence and mortality rates [1]. Addressing the detrimental impact of these cancers requires substantial efforts from healthcare professionals to both prevent and manage their progression. However, this process is frequently slow and resource-intensive, and it is further complicated by the complexity introduced by environmental, genetic, and socioeconomic factors. These factors add complexity to cancer prevention, surgical timing, and postoperative management, posing significant challenges in clinical practice. Identifying effective tumor markers is crucial for recognizing high-risk individuals, optimizing preoperative risk stratification, enhancing prognostic predictability, and informing treatment strategies.

While conventional biomarkers such as carcinoembryonic antigen, cancer antigen 19 – 9, and TNM stage have provided valuable insights to the management of digestive system cancers, emerging blood-derived markers like the pan-immune-inflammation value (PIV) and neutrophil-to-lymphocyte ratio (NLR) are gaining attention for their cost-effectiveness and prognostic reliability [2–4]. However, further research is warranted to identify high-precision biomarkers. It is well established that the host inflammatory response, a hallmark of cancer, plays a critical role in tumor onset, progression, and metastasis [5]. Various inflammatory markers, such as PIV, NLR, and C-reactive protein (CRP), have been shown to predict long-term survival in cancer patients [3, 4, 6].

In this context, the Modified Glasgow Prognostic Score (mGPS), which combines serum CRP and albumin levels, provides a measure of both nutritional status and inflammatory response, demonstrating prognostic value in cancer [7]. Similarly, the Prognostic Nutritional Index (PNI), initially developed to assess preoperative complication risk and optimal surgical timing, is based on factors such as serum albumin and lymphocyte count [8]. Building on these indices, Iida et al. [9] introduced the CRP-Albumin-Lymphocyte (CALLY) index, a non-invasive biomarker that integrates albumin, lymphocyte count, and CRP levels to evaluate liver function, immune status, and inflammation (Supplementary Fig. 1). The CALLY index is calculated as: albumin level (g/dL) × absolute lymphocyte count (cells/μL) / CRP level (mg/dL) × 10^4. Lower CALLY index values have been significantly associated with poorer overall survival (OS) in patients with hepatocellular carcinoma. This low-cost, readily available biomarker has demonstrated substantial prognostic value in various digestive system cancers, including esophageal [10], gastric [11], hepatic [12], and colorectal cancers [13]. However, a study by Shiraishi et al. [14] found no significant association between the CALLY index and prognosis in colorectal cancer patients.

Despite the growing body of research on the CALLY index in digestive system cancers, no comprehensive meta-analysis has been conducted to evaluate its clinical significance. Therefore, this study aims to fill this gap by conducting a systematic meta-analysis to assess the role of the CALLY index in the prognosis of digestive system cancers through a comprehensive review of relevant clinical studies retrieved from online English-language databases.

Materials and methods

Protocol registration

The systematic review protocol was registered on INPLASY (INPLASY202520043) and the full details are available on inplasy.com (https://doi.org/10.37766/inplasy2025.2.0043).

Search strategy

The search strategy was developed collaboratively by all members of the research team, and a comprehensive, systematic search was conducted up to December 31, 2024, across several English-language databases, including PubMed, PMC, Web of Science, Ovid/MEDLINE, and Elsevier/Embase. The following search terms were used: ("C-reactive protein-Albumin-Lymphocyte" OR "CALLY") AND ("cancer" OR "tumor" OR "neoplasm" OR "carcinoma") (Supplementary search strategies). Additionally, references from highly relevant articles were manually reviewed to identify additional studies.

Eligibility criteria

The inclusion and exclusion criteria were predefined and applied prior to conducting the search. The inclusion criteria were as follows:

1. Studies involving patients with a clinical diagnosis of digestive system cancers;
2. Studies in which patients had corresponding blood tests and data available for calculating the CALLY index;
3. Studies utilizing the same CALLY index calculation formula, which integrates CRP, albumin levels, and lymphocyte count as described in previous standardized reports, ensuring consistent patient stratification into high and low CALLY index groups;
4. Studies reporting prognostic data for these groups, including hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs).

The exclusion criteria were as follows:

1. Focused on cancer types other than digestive system cancers;
2. Were non-clinical articles, reviews, editorials, or conference abstracts that did not provide original prognostic data;
3. Lacked sufficient information to calculate or extract the CALLY index and corresponding prognostic outcomes.

Selection process

Two independent reviewers conducted the search and screened titles and abstracts based on the predefined eligibility criteria. Full-text articles were subsequently reviewed for eligibility. Any discrepancies between reviewers were resolved through discussion, with a third team member consulted when consensus could not be reached, thereby reducing potential selection and reporting biases. This meta-analysis was conducted in adherence to PRISMA guidelines for systematic reviews and meta-analyses. A PRISMA flow diagram summarizing the study selection process is provided in Fig. 1.

Data extraction

In line with the research objectives, we systematically collected and summarized key characteristics of each study, including author(s), year of publication, cancer type, sample size, cutoff value, analysis methods, and prognostic outcomes. This process was completed through collaborative discussion among research team members.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), a tool commonly used to assess the quality of non-randomized studies. The NOS assigns a maximum of nine points across three categories: selection, comparability, and outcome. Studies scoring 6 or more points were considered high-quality [15]. Studies scoring below 6 were classified as low-quality

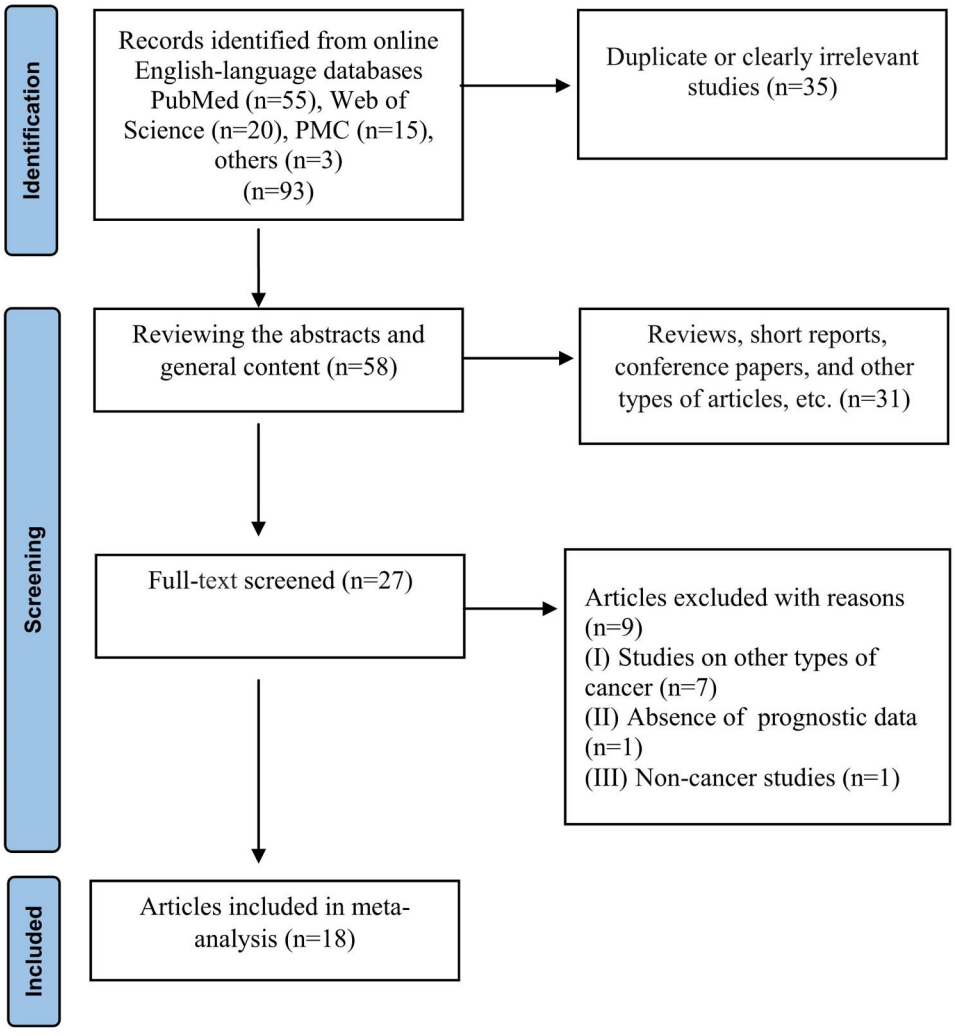

Fig. 1 Flowchart for identifying relevant articles from the literature

and were either excluded from the primary analysis or included in sensitivity analyses to evaluate their impact on the overall findings.

Statistical analysis

Statistical analysis was conducted using STATA version 14.0 (StataCorp, College Station, Texas, USA). The prognostic impact of the CALLY index on survival outcomes was evaluated using pooled HRs with 95% CIs. In accordance with standard practice, HRs derived from multivariable analysis were prioritized for analysis unless only univariate HRs were available. A random-effects model was employed to accommodate anticipated between-study heterogeneity, quantified through the I^2 statistic complemented by Cochran's Q-test, with thresholds set at $I^2 \geq 50\%$ and/or Q-test $P_h < 0.10$ to define substantial heterogeneity. Meta-regression was performed to identify potential sources of heterogeneity, such as sample size, study region, cancer type, cutoff value, analysis method, and treatment strategy. Subgroup analyses were conducted based on these factors, with pooled HRs calculated for each subgroup. Sensitivity analyses were performed by sequentially excluding each study to assess the stability of the pooled HR. Publication bias was evaluated using Egger's test. All statistical tests were two-tailed, with significance set at $P < 0.05$.

Results

Study selection

Based on the search strategy, a total of 93 articles were initially identified in English-language databases. Following a rigorous screening process, 27 articles were selected for full-text assessment. Of these, nine articles were excluded for the following reasons: seven studies focused on other cancer types, one lacked prognostic data, and one was a non-cancer study. Ultimately, 18 articles, encompassing 19 distinct studies, met the inclusion criteria and were incorporated into the final meta-analysis (as illustrated in Fig. 1).

Study characteristics

The included retrospective studies were conducted in Germany, Japan, and China and published between 2021 and 2024, covering seven types of digestive system cancers: colorectal cancer [13, 14, 16], esophageal cancer [10, 17, 18], gastric cancer [6, 19–24], hepatocellular carcinoma [9, 12], cholangiocarcinoma [25], oral cavity squamous cell carcinoma [26], and pancreatic cancer [27]. Collectively, the studies included 7,951 patients who received treatments such as surgery, transarterial chemoembolization, and other synthesized therapies, spanning the period from 2000 to 2023. Sample sizes ranged from 143 to 1,260 patients, and patients were divided into groups based on varying pre-treatment CALLY index cutoff values. Different studies employed a variety of methods to determine the cutoff values, including receiver operating characteristics (ROC) analysis (14 studies), R software (1 study), max-statistics (1 study), restricted cubic spline (RCS) model (1 study), and previously reported thresholds (2 studies). The prognostic data provided by these studies included OS in 18 studies, disease-free survival (DFS) in 6 studies, recurrence-free survival (RFS) in 8 studies, and cancer-specific survival (CSS) in 2 studies. Notably, all studies estimated HRs using univariate analysis, and 18 studies also conducted multivariate analysis. Based on quality assessment, all articles were considered high-quality studies. Detailed information on the included studies is provided in Table 1.

Prognostic value of the CALLY index in predicting survival outcomes in digestive system cancers

The meta-analysis assessed the prognostic impact of the CALLY index on survival outcomes across digestive system cancers. Lower CALLY index values were consistently associated with poorer prognoses. In particular, the OS analysis showed a significant increase in mortality risk, with HRs from 18 studies (7,633 patients) yielding a pooled HR of 1.973 (95% CI: 1.734–2.244) (Fig. 2). This result indicated a nearly twofold increase in the risk of mortality for patients with lower CALLY index values. For DFS, 6 studies (1,747 patients) reported a pooled HR of 2.093 (95% CI: 1.682–2.604) (Fig. 3a), further emphasizing the CALLY index's strong prognostic impact. Additionally, RFS across 8 studies (3,099 patients) showed an HR of 1.462 (95% CI: 1.292–1.654) (Fig. 3b), and CSS, from 2 studies (881 patients), yielded an HR of 2.456 (95% CI: 1.887–3.221) (Fig. 3c). All results demonstrated statistical significance, with P-values < 0.001, affirming the CALLY index's utility in predicting adverse outcomes across digestive system cancers.

For the OS analysis, a mild level of heterogeneity was observed (I^2 = 43.1%, P_h = 0.027). To investigate potential sources of this heterogeneity, a meta-regression analysis was performed on key covariates. The results indicated that none of the assessed variables significantly explained the heterogeneity: sample size ($P = 0.460$), study region ($P = 0.316$), cancer type ($P = 0.139$), cutoff value ($P = 0.973$), analysis method ($P = 0.102$), and treatment strategy ($P = 0.083$). These findings suggested that the mild heterogeneity observed in OS outcomes associated with the CALLY Index was not attributable to these study-level characteristics, supporting the consistency of the CALLY Index as a prognostic factor across various study designs and patient populations within digestive system cancers.

Table 1 Main characteristics of studies included in meta-analysis

Author(year)	Study region	Study design	Sample size	Study period	Cancer type	Sampling time	Cutoff values	Cutoff selection	Outcomes, HR estimation	Analysis method	Treatment strategy	Quality score
Müller L (2021)	Germany	retrospective	280	2010–2020	Hepatocellular carcinoma	Before treatment	1	R software	OS, 1.5(1.1–2.1)	U/M	TACE	8
Tsunematsu M (2022)	Japan	retrospective	143	2002–2019	Cholangiocarcinoma	Within 1 week before treatment	3.5	ROC analysis	OS, 2.07 (1.11–3.89) DFS, 2.13 (1.15–3.86)	U/M	Surgery	8
Iida H (2022)	Japan	retrospective	Training cohort, 384	2011–2013	Hepatocellular carcinoma	Before treatment	5	ROC analysis	OS, 1.70 (1.21–2.38) RFS, 1.41 (1.08–1.83)	U/M	Surgery	8
Iida H (2022)	Japan	retrospective	Validation cohort, 267	2011–2013	Hepatocellular carcinoma	Before treatment	5	ROC analysis	OS, 1.81 (1.21–2.71) RFS, 1.56 (1.12–2.15)	U/M	Surgery	8
Tsai YT (2022)	China	retrospective	279	2008–2017	oral cavity squamous cell carcinoma	Within 2 week before treatment	0.65	ROC analysis	OS, 3.816(2.393–6.086) DFS, 2.103(1.451–3.049)	U/M	Surgery	9
Yang M (2023)	China	retrospective	1260	2012–2020	Colorectal cancer	Before treatment	1.47	ROC analysis	OS, 2.22 (1.79–2.78)	U/M	Synthesized treatment	7
Zhang H (2023)	China	retrospective	684	2013–2018	Gastric cancer	Before treatment	1.12	Max-statistics	OS, 1.43(1.11–1.82)	U/M	Synthesized treatment	7
Takeda Y (2024)	Japan	retrospective	578	2010–2017	Colorectal cancer	Within 3 week before treatment	2	ROC analysis	OS, 2.79 (1.32–5.92) DFS, 2.16 (1.25–3.75)	U/M	Surgery	8
Shiraishi T (2024)	Japan	retrospective	263	2016–2023	Colorectal cancer	Before treatment	0.369	ROC analysis	OS, 1.41(0.95–2.10) RFS, 1.01(0.69–1.47)	U	Surgery	7
Aoyama T (2024)	Japan	retrospective	180	2005–2020	Esophageal cancer	Before treatment	5	Previous reports	OS, 2.310(1.416–3.767) RFS, 2.093(1.384–3.165)	U/M	Surgery	8
Ma R (2024)	Japan	retrospective	146	2008–2018	Esophageal cancer	Within 1 week before treatment	2.4	ROC analysis	OS, 3.86 (2.03–7.34) DFS, 2.35(1.28–4.31)	U/M	Surgery	8
Feng J (2024)	China	retrospective	318	2013–2015	Esophageal cancer	Within 1 week before treatment	1.7	RCS model	CSS, 2.72(1.98–3.73)	U/M	Surgery	8
Nakashima K (2024)	Japan	retrospective	175	2011–2019	Gastric cancer	Before treatment	6.96	ROC analysis	OS, 3.00 (1.31–6.93) DFS, 2.18 (1.00-4.76)	U/M	Surgery	8
Fukushima N (2024)	Japan	retrospective	826	2010–2017	Gastric cancer	Before treatment	2	ROC analysis	OS, 2.02 (1.18–3.46) RFS, 1.88 (1.11–3.17)	U/M	Surgery	8
Hashimoto I (2024)	Japan	retrospective	459	2013–2017	Gastric cancer	Before treatment	3.28	ROC analysis	OS, 1.96(1.19–3.23) RFS, 1.69(1.06–2.70)	U/M	Surgery	9
Okugawa Y (2024)	Japan	retrospective	426	2000–2011	Gastric cancer	Within 1 week before treatment	4.93	ROC analysis	OS, 2.57(1.62–4.07) DFS, 1.76(1.01–3.05)	U/M	Surgery	9

Table 1 (continued)

Author(year)	Study region	Study design	Sample size	Study period	Cancer type	Sampling time	Cutoff values	Cutoff selection	Outcomes, HR estimation	Analysis method	Treatment strategy	Quality score
Aoyama T (2024)	Japan	retrospective	259	2005–2020	Gastric cancer	Before treatment	5	Previous reports	OS, 1.791(1.067–3.009) RFS, 1.776(1.102–2.865)	U/M	Surgery	8
Sakurai K (2024)	Japan	retrospective	563	2014–2020	Gastric cancer	The day before treatment	1.19	ROC analysis	OS, 1.82(1.24–2.69) CSS, 1.93(1.19–3.23)	U/M	Surgery	9
Kawahara S (2024)	Japan	retrospective	461	2013–2022	Pancreatic cancer	Within 2 week before treatment	1.9	ROC analysis	OS, 1.772(1.362–2.305) RFS, 1.289(1.006–1.652)	U/M	Surgery	8

HR hazard ration; ROC receiver operating characteristics; RCS restricted cubic spline; OS overall survival; DFS disease-free survival; RFS recurrence-free survival; CSS cancer-specific survival; U univariate analysis; M multivariate analysis

Subgroup analysis of CALLY index and overall survival in patients with digestive system cancers

Given the critical role of OS as a primary endpoint in prognostic evaluations, subgroup analyses were performed to explore the relationship between the CALLY index and OS across different categories (Table 2).

By treatment strategy: Patients undergoing surgery had a stronger association, with a pooled HR of 2.014 (95% CI: 1.794–2.260, $P<0.001$), while those receiving synthesized therapies had a somewhat lower HR of 1.700 (95% CI: 1.260–2.293, $P<0.001$).

By cancer type: Among various digestive system cancer types, gastrointestinal, gastric, colorectal, and esophageal cancers showed the strongest associations, with pooled HRs of 2.009 (95% CI: 1.708–2.364, $P<0.001$), 1.775 (95% CI: 1.517–2.078, $P<0.001$), 1.970 (95% CI: 1.383–2.807, $P<0.001$), and 2.789 (95% CI: 1.890–4.116, $P<0.001$), respectively. In contrast, the hepatobiliary pancreatic cancer subgroup had an HR of 1.712 (95% CI: 1.466-2.000, $P<0.001$).

By CALLY index cutoff values: A cutoff value ≤ 3 showed a pooled HR of 1.977 (95% CI: 1.623–2.409, $P<0.001$), while a cutoff value >3 demonstrated a similar HR of 1.996 (95% CI: 1.688–2.361, $P<0.001$).

By sample size: Studies with fewer than 300 patients had a higher HR of 2.131 (95% CI: 1.657–2.741, $P<0.001$), while studies with larger sample sizes (≥ 300 patients) showed a more moderate HR of 1.871 (95% CI: 1.674–2.091, $P<0.001$).

By study region: Studies conducted in Japan reported an HR of 1.932 (95% CI: 1.715–2.176, $P<0.001$), while those from China had a significantly higher HR of 2.213 (95% CI: 1.392–3.518, $P=0.001$).

Sensitivity and publication bias analysis

A sensitivity analysis was performed to assess the stability of the association between the CALLY index and OS. The results confirmed the robustness of the findings, with each predictive point remaining within the 95% CI (Fig. 4). To assess publication bias, Egger's test was performed, yielding a P-value of 0.053 (Fig. 5). Although this value was slightly above the conventional threshold for statistical significance, it suggested minimal publication bias, thereby supporting the validity of the findings. Overall, these analyses underscored the consistent association between a lower CALLY index and poorer OS in the included studies.

Discussion

The treatment of cancer remains a complex process. Despite significant advancements in surgical techniques and multidisciplinary treatments in recent years, not all patients benefit equally, primarily due to variations in their baseline health status. Therefore, assessing patients'

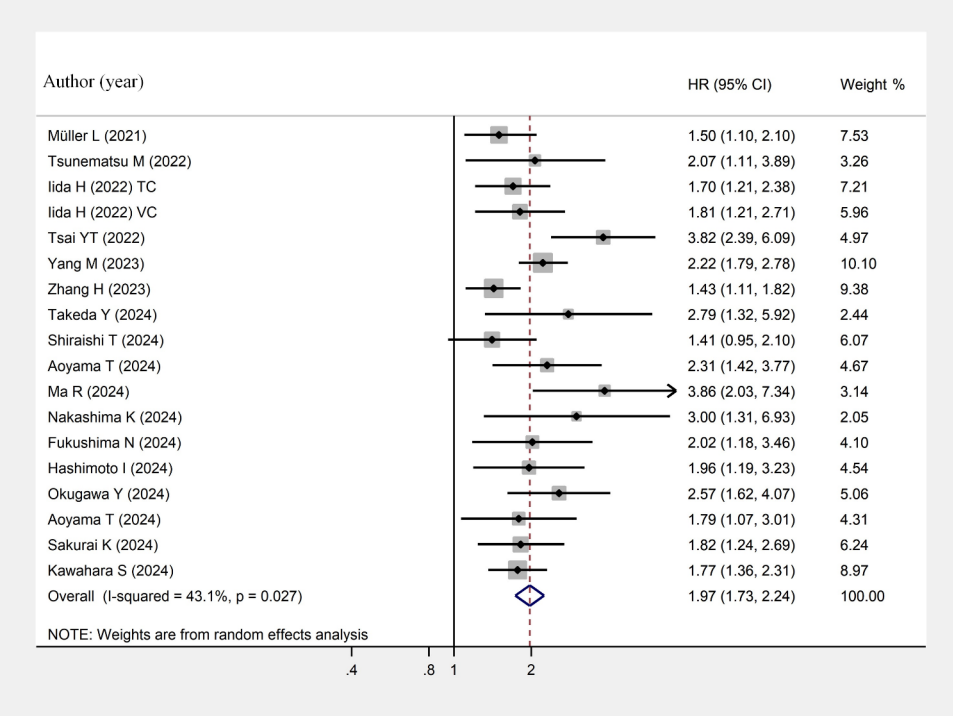

Fig. 2 Forest plots of overall survival in patients with digestive system cancers stratified by CALLY index levels

pre-treatment conditions is crucial. Evaluation systems such as PNI, the Charlson comorbidity index, and the mGPS have been shown to assist clinicians in optimizing treatment plans and improving patient outcomes [7, 8, 28]. Unlike these traditional indices, the CALLY index provides a more comprehensive reflection of a patient's inflammatory, nutritional, and immune status, offering unique advantages in prognostic evaluation. As an accessible, simple, and cost-effective marker derived from blood tests, preliminary evidence supports the potential clinical utility of the CALLY index.

The CALLY index, by integrating serum albumin, lymphocyte count, and CRP, provides a comprehensive assessment of a patient's physiological state, linking inflammation, nutritional status, and immune function with cancer progression and prognosis. Specifically, albumin is a widely recognized marker of nutritional status, synthesized in the liver and crucial for maintaining protein reserves necessary for physiological resilience, particularly under stress. Low albumin levels, often resulting from inflammation-induced liver dysfunction or malnutrition, are associated with poorer outcomes in cancer patients [29]. CRP serves as a marker of systemic inflammation, typically elevated in cancer patients due to cytokines like interleukin-6 and tumor necrosis factor-alpha produced by both tumor and immune cells. Elevated CRP levels are associated with increased tumor aggressiveness, as chronic inflammation supports a tumor-promoting microenvironment [30]. Lymphocytes, essential to adaptive immunity, play a vital role in tumor surveillance, with low lymphocyte counts indicating a weakened immune defense [31]. Together, these components within the CALLY index offer a holistic assessment of a patient's ability to manage tumor growth and recovery. A higher CALLY index indicates a favorable balance across nutritional, immune, and inflammatory domains—factors linked to improved survival outcomes. Conversely, a low CALLY index may be associated with increased postoperative complications, delayed initiation of adjuvant therapy, and ultimately compromise survival.

In this meta-analysis, we included 7,951 patients with digestive system cancers from 19 studies. Our results confirmed that a lower pre-treatment CALLY index was significantly associated with worse prognosis, showing consistent predictive value across OS, DFS, RFS, and CSS. These findings suggested that the patient status reflected by the CALLY index was both scientifically sound and accurate, supporting its potential as an important component of pre-treatment evaluation systems for digestive system cancers.

Notably, this meta-analysis underscored the CALLY index's potential as an effective preoperative risk stratification tool for patients with digestive system cancers. Importantly, the CALLY index could be practically applied in surgical settings by guiding personalized modifications in perioperative nutritional support, the timing of adjuvant therapies, and the intensity of follow-up, ultimately optimizing postoperative outcomes. By capturing

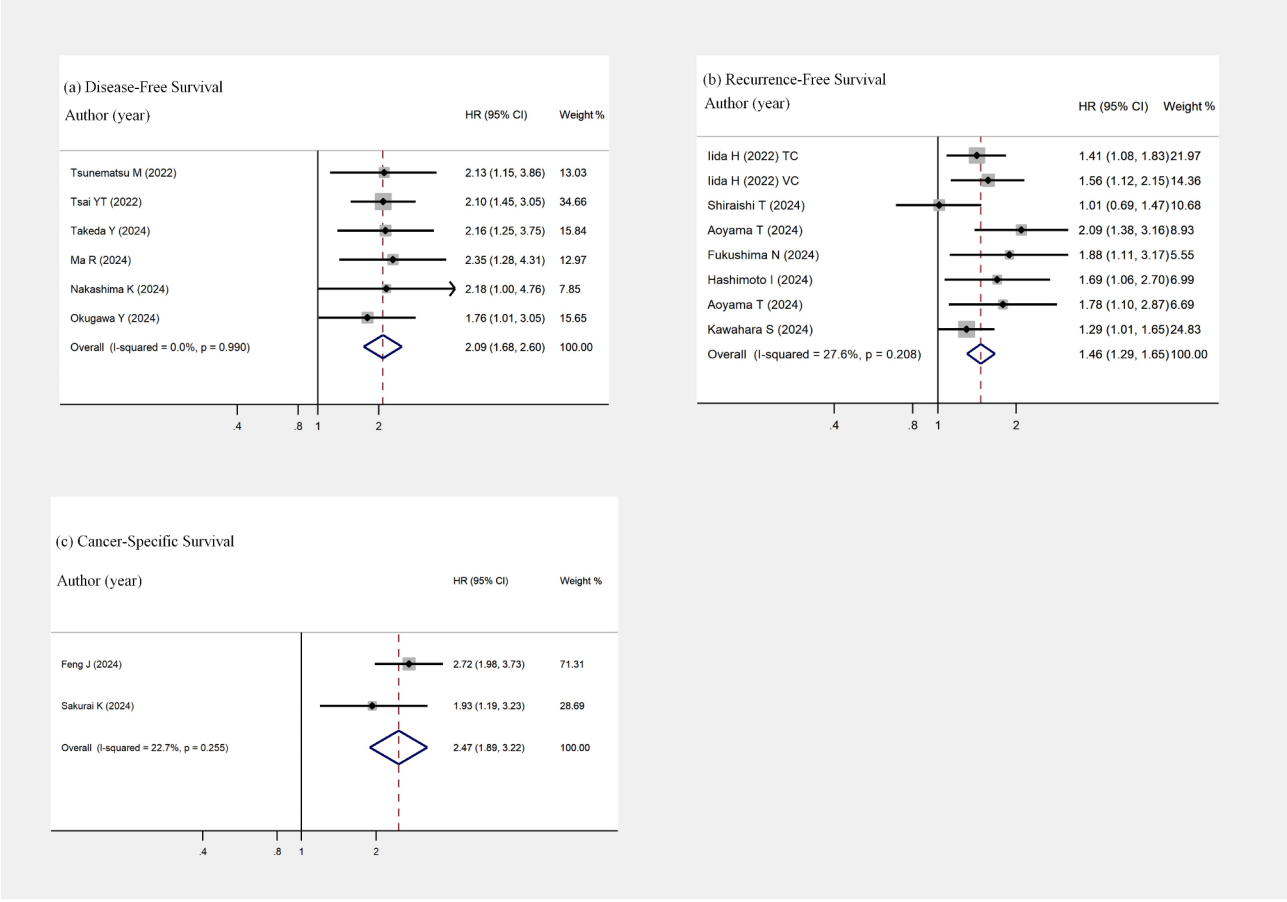

Fig. 3 Forest plots of survival outcomes in patients with digestive system cancers: (**a**) Disease-Free Survival, (**b**) Recurrence-Free Survival, and (**c**) Cancer-Specific Survival Stratified by CALLY Index Levels

Table 2 Subgroup analyses of CALLY index and OS in digestive system cancers

Categories		Studies (patients)	HR (95% CI)	I^2 (%)*	P_h*	Z	*P*
Treatment strategy	Surgery	15(5409)	2.014(1.794–2.260)	29.5	0.135	11.90	< 0.001
	Synthesized treatment	3(2224)	1.700(1.260–2.293)	74.8	0.019	3.48	< 0.001
Cancer type	Gastrointestinal cancer	12(5819)	2.009(1.708–2.364)	39.8	0.076	8.41	< 0.001
	Gastric cancer	7(3392)	1.775(1.517–2.078)	18.2	0.291	7.15	< 0.001
	Colorectal cancer	3(2101)	1.970(1.383–2.807)	56.2	0.102	3.75	< 0.001
	Esophageal cancer	2(326)	2.789(1.890–4.116)	35.6	0.213	5.16	< 0.001
	Hepatobiliary pancreatic cancer	5(1535)	1.712(1.466-2.000)	0.0	0.889	6.78	< 0.001
Cutoff value	≤ 3	10(5340)	1.977(1.623–2.409)	65.1	0.002	6.76	< 0.001
	> 3	8(2293)	1.996(1.688–2.361)	0.0	0.814	8.07	< 0.001
Sample size	< 300	9(1992)	2.131(1.657–2.741)	58.0	0.014	5.89	< 0.001
	≥ 300	9(5641)	1.871(1.674–2.091)	22.9	0.240	11.03	< 0.001
Study region	Japan	14(5130)	1.932(1.715–2.176)	0.0	0.514	10.85	< 0.001
	China	3(2223)	2.213(1.392–3.518)	86.9	< 0.001	3.36	0.001

* The random effect model was used, when the $I^2 > 50\%$ or $P_h < 0.10$, otherwise the fixed effect model was applied; CALLY C-reactive protein-albumin-lymphocyte; OS overall survival; HR hazard ration; CI confidence interval; P_h P-value for heterogeneity based on Q test; P P-value for statistical significance based on Z test

critical physiological indicators—nutritional status, immune function, and inflammation—that influence cancer prognosis, the CALLY index provides a balanced assessment of a patient's recovery potential. Analysis of 5,409 surgical patients from 15 studies revealed that patients with higher CALLY index had improved post-operative survival, indicating that those with stronger nutritional and immune profiles and lower inflammation levels tend to achieve more favorable post-surgical outcomes. Moreover, previous studies have shown that

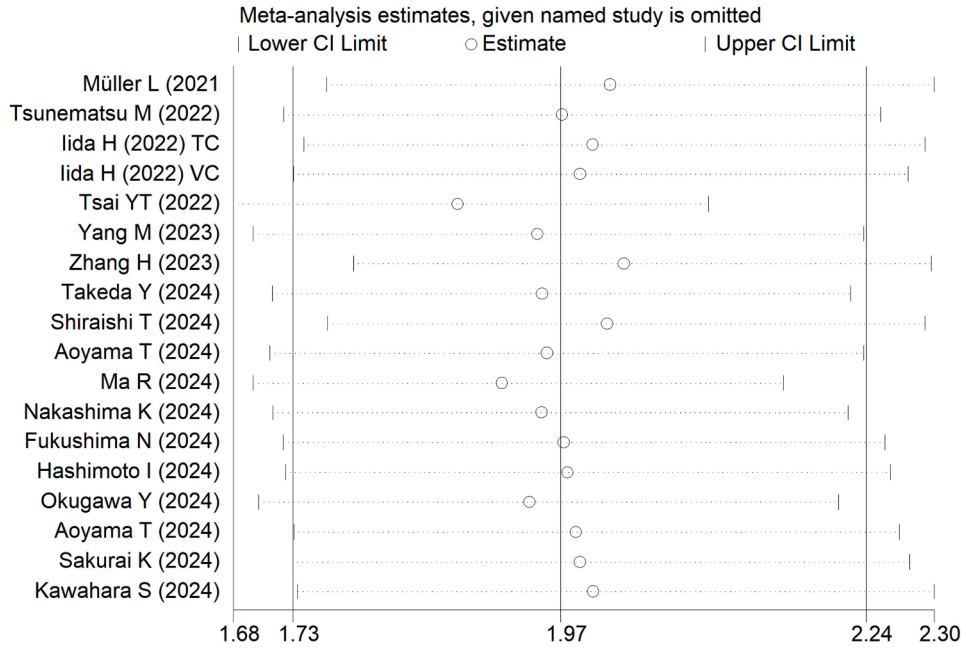

Fig. 4 Sensitivity analysis of overall survival in patients with digestive system cancers

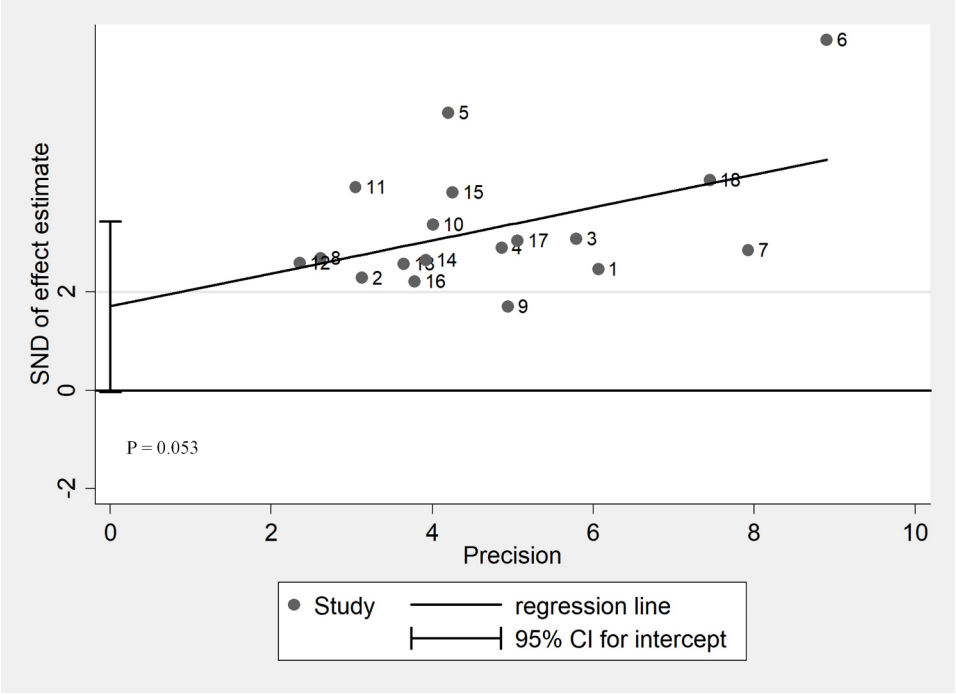

Fig. 5 Assessment of publication bias in the included studies using Egger's test

preoperative nutritional support and anti-inflammatory treatments can improve postoperative recovery, further supporting the rationale for CALLY index-guided interventions [7, 8, 28]. In line with these findings, prospective interventional studies such as those by Schuetz et al. [32] and the ESPEN guidelines by Arends et al. [33] underscored that individualized nutritional strategies and tailored perioperative treatment could significantly enhance recovery, thereby lending support to the feasibility of establishing the CALLY index as a clinically actionable biomarker for perioperative risk stratification. Additionally, subgroup analyses in this meta-analysis demonstrated the CALLY index's effectiveness across various digestive system cancer types, with the strongest

associations observed in gastrointestinal cancers—specifically esophageal, colorectal, and gastric cancers—while a comparatively weaker association was noted in the hepatobiliary pancreatic cancer subgroup. These findings reinforced its suitability as a tool for personalized risk management, enabling tailored treatment strategies that aligned with each patient's unique physiological profile.

Despite its prognostic utility, the clinical application of the CALLY index requires careful consideration. Variations in cutoff values, sample sizes, and geographic regions did not significantly alter its prognostic value in this meta-analysis, suggesting its robustness across diverse clinical settings. However, the absence of standardized cutoff points remains a limitation, potentially affecting reliability and cross-study comparability. Standardization of cutoff values or demographic-specific adjustments, particularly accounting for regional variations, may enhance its clinical utility. Additionally, variations in baseline characteristics, particularly in populations with comorbid inflammatory or hepatic conditions, may compromise the index's specificity. For instance, in regions with prevalent chronic liver diseases, elevated CRP levels may reflect hepatic inflammation rather than tumor biology, complicating prognostic interpretation. Future research should stratify populations based on inflammatory and liver disease status or develop correction models to mitigate confounding factors, while also conducting further multicenter studies that account for geographic and population-based differences to validate and potentially calibrate the index, ultimately optimizing its role as a pre-treatment risk assessment tool.

Based on the results of this meta-analysis, we believe that the CALLY index holds significant promise as an easily accessible and cost-effective prognostic tool for patients with digestive system cancers. Compared with traditional indexes such as PNI and mGPS, the CALLY index can provide valuable information for clinicians to guide pre-treatment evaluation and personalize treatment strategies by assessing patients' nutritional status, immune function, and inflammatory state. Incorporating the CALLY index into clinical practice can improve decision-making processes, especially in preoperative risk stratification, and facilitate more tailored interventions to optimize patient outcomes. For instance, patients with low CALLY index scores might benefit from preoperative nutritional support, anti-inflammatory treatments, and immunomodulatory therapies. It is important to note that the cutoff values used across included studies were derived using diverse methods (e.g., ROC analysis, R software, max-statistics, RCS model, or based on previous reports, as summarized in Table 1), and no universally accepted threshold exists in the current clinical setting. To address this issue, further prospective studies, particularly those with diverse populations and large sample sizes, will be essential to establish more robust and standardized cutoff values for clinical application. Moreover, explicit evaluation of potential regional influences—such as differences in genetic backgrounds, dietary habits, and tumor biology—should be undertaken to clarify whether these factors modify the CALLY index's prognostic performance. These studies can further explore the roles of this index and other traditional ones in different cancer types, along with their potential for patient monitoring during the entire treatment. This will offer more comprehensive prognostic insights.

Several limitations should be noted. In summary, our study was limited by three key factors: the retrospective nature of the included studies, the lack of universally standardized cutoff values for the CALLY index, and the potential confounding effects of comorbidities on index levels. First, the analysis primarily included retrospective studies, which were inherently subject to potential biases in patient selection, data collection, and reporting. Moreover, although studies from multiple geographic regions were included, the sample predominantly consisted of studies from East Asia. This geographic concentration may reflect underlying differences in genetic predisposition, dietary factors, and tumor biology that could affect the CALLY index's performance, underscoring the need for external validation in more diverse populations. Additionally, a lack of universally standardized CALLY index cutoff values across studies also presented a limitation, potentially impacting the reliability and cross-study comparability of results. Furthermore, the adjustment for various prognostic factors in the multivariate analyses differed among studies, which may affect the stability of the CALLY index as an independent prognostic marker. Lastly, due to the inability to further explore diseases that might affect CALLY index levels in cancer patients within this meta-analysis, determining whether the CALLY index accurately reflected tumor-specific conditions remained a challenge.

Conclusion

This meta-analysis supports the CALLY index as a robust prognostic tool for digestive system cancers, with lower levels linked to poorer outcomes. Subgroup analyses further highlight its utility in pre-treatment risk stratification, especially among surgical patients. Future prospective multicenter studies should adopt a registry-based design, validate findings in geographically diverse populations, and explore correlations with nutritional and inflammatory markers, alongside standardizing cutoff values and evaluating CALLY-based interventions.

Abbreviations

PIV	Pan-Immune-Inflammation Value
NLR	Neutrophil-to-Lymphocyte Ratio

CRP	C-Reactive Protein
mGPS	Modified Glasgow Prognostic Score
PNI	Prognostic Nutritional Index
CALLY	CRP-Albumin-Lymphocyte Index
OS	Overall Survival
HR	Hazard Ratio
CI	Confidence Interval
DFS	Disease-Free Survival
RFS	Recurrence-Free Survival
CSS	Cancer-Specific Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle-Ottawa Scale
ROC	Receiver operating characteristics
RCS	Restricted cubic spline

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

Author contributions
Study conception and design: B W and JH L; Material preparation, data retrieval, and analysis: JT L, CD S, and DL Y; Interpretation of the results: JT L, DL Y, and JH L; Paper writing: B W and JH L. All authors read and approved the final manuscript.

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Data availability
All data are available from the corresponding author.

Declarations

Ethics approval and consent to participate
As the data utilized in this study were derived exclusively from publicly available databases, ethical approval and informed consent were not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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