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**ADMINISTRATIVE INFORMATION****Support - No.****Review Stage at time of this submission - Completed but not published.****Conflicts of interest - None declared.****INPLASY registration number:** INPLASY202520043**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 February 2025 and was last updated on 8 February 2025.**INTRODUCTION**

**Review question / Objective** Digestive system cancers are a leading cause of cancer-related mortality worldwide. Effective prognostic tools are essential for guiding treatment strategies and improving patient outcomes. The C-reactive protein-Albumin-Lymphocyte (CALLY) index, a blood-derived biomarker reflecting inflammation, nutrition, and immunity, has shown potential as a predictor of survival. However, comprehensive analyses of its role in digestive system cancers were still lacking.

**Condition being studied** Digestive system cancers are major contributors to public health challenges, with cancers such as esophageal, gastric, hepatic, and colorectal cancers ranking among the highest in incidence and mortality rates. Additionally, pancreatic and gallbladder cancers also represent significant causes of cancer-related mortality [1]. Addressing the extensive harm

caused by these cancers requires substantial effort from healthcare professionals to mitigate their development and progression. However, achieving such changes is often a slow, difficult, and inefficient process, requiring considerable time and resources. The complexity introduced by environmental, genetic, and socioeconomic factors further complicates cancer prevention, surgical timing, and postoperative management, presenting new issues for clinical practice. Identifying effective tumor markers can aid in recognizing high-risk individuals, optimizing preoperative risk stratification, enhancing prognostic predictability, and informing treatment strategies.

**METHODS**

**Search strategy** The following search terms were used: ("C-reactive protein-Albumin-Lymphocyte" OR "CALLY") AND ("cancer" OR "tumor" OR "neoplasm" OR "carcinoma").

**Participant or population** Patients with a clinical diagnosis of digestive system cancers.

**Intervention** Studies applying the same CALLY index calculation formula, with patients divided into high and low CALLY index groups.

**Comparator** Studies applying the same CALLY index calculation formula, with patients divided into high and low CALLY index groups.

**Study designs to be included** Non-randomized study will be included.

**Eligibility criteria** (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 applying the same CALLY index calculation formula, with patients divided 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). Exclusion criteria included studies focusing on other types of cancers, non-clinical articles, reviews, and similar types of studies.

**Information sources** The search strategy was developed collaboratively by all members of the research team. A comprehensive, systematic search was conducted across several English-language databases, including PubMed, PMC, Web of Science, Ovid/MEDLINE, and Elsevier/Embase.

**Main outcome(s)** Eighteen articles (19 distinct studies, 7,951 patients) were included. Lower CALLY index levels were significantly associated with poorer outcomes across endpoints. The pooled HR for OS was 1.973 (95% CI: 1.734–2.244).

**Additional outcome(s)** Subgroup analyses focusing on OS confirmed consistent prognostic significance across treatment strategies, cancer types, cutoff values, sample sizes, and regions. Notably, the CALLY index was significantly associated with OS in surgical patients (HR = 2.014,  $P < 0.001$ ).

**Data management** 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.

**Quality assessment / Risk of bias analysis** The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), with studies scoring 6 or more points considered high-quality. Publication bias was evaluated using Egger's test.

**Strategy of data synthesis** The prognostic impact of the CALLY Index on survival outcomes was evaluated using pooled HRs with 95% CIs. A random-effects model was chosen to account for expected heterogeneity among studies. Heterogeneity was assessed using the  $I^2$  statistic and Q-test, with  $I^2 \geq 50\%$  or  $Ph < 0.01$  indicating substantial heterogeneity.

**Subgroup analysis** 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 analysis** Sensitivity analyses were conducted by sequentially excluding each study to assess the stability of the pooled HR.

**Language restriction** English.

**Country(ies) involved** China.

**Keywords** CALLY index, digestive system cancers, prognostic biomarker, meta-analysis.

#### **Contributions of each author**

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