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Prognostic and clinicopathological significance of C-reactive protein–albumin–lymphocyte(CALLY) in patients with digestive system neoplasms: a systematic review and meta-analysis

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Abstract

Objective The prognostic significance of the C-reactive protein-albumin-lymphocyte (CALLY) index in digestive system neoplasms (DSNs) has been investigated in several studies, but inconsistencies remain between the results of different studies. Therefore, the aim of this study was to confirm the prognostic significance of CALLY in patients with DSNs and its association with clinicopathological characteristics (CPCs).

Methods The databases PubMed, Cochrane Library, Web of Science, Research Square and Embase were systematically searched for clinical trials with databases up to 1 November 2024. The value of CALLY in predicting overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS) versus cancer-specific survival (CSS) in patients with DSNs was confirmed by calculating the combined hazard ratio (HR) and 95% CI. The combined OR and 95% CI were calculated to assess the association between CALLY and CPCs in patients with DSNs.

Results A total of 18 studies with 7916 patients with DSNs were included in this study. Pooled analysis showed that lower CALLY was associated with poor OS, DFS, RFS and CSS were significantly associated. In addition, low CALLY index was associated with male gender, T3-T4, lymph node metastasis, lymph vessel invasion, complications, stage III-IV and surgical approach were significantly associated. However, there was no association between low CALLY index and histological type, adjuvant chemotherapy, and neoadjuvant chemotherapy.

Conclusions In this meta-analysis, a low CALLY index was significantly associated with poor OS, DFS, RFS and CSS in patients with DSNs and with several CPCs in patients with DSNs.

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Keywords C-reactive protein–albumin–lymphocyte, Digestive system neoplasms, Meta-analysis, Prognosis

Introduction

As a major cause of death worldwide, cancer has become a recognised public health problem [1]. According to the National Center for Health Statistics (NCHS), a total of approximately 590,000 people died from various types of cancer in 2015, with gastrointestinal neoplasms being an important cause of high cancer incidence and mortality [2]. In the GLOBOCAN 2020 report, a total of 3,524,932 deaths were attributed to malignant neoplasms of the digestive system, accounting for 18% of cancer deaths worldwide [3]. In China, which has a high incidence of gastrointestinal neoplasms, gastrointestinal neoplasms accounted for four of the top 10 cancer incidence rankings, including colorectal cancer in 3rd place, stomach cancer in 6th place, liver cancer in 7th place, and oesophageal cancer in 10th place. In addition, four of the top five cancer mortality rankings were for GI malignancies [4]. In addition to the high morbidity and mortality of DSNs, patient prognosis is also an important indicator for assessing the malignancy of a tumour, and according to a public database created by the National Cancer Institute (NCI), the 5-year survival rate for pancreatic cancer was only 12.8%, for liver and intrahepatic cholangiocarcinoma 21.7%, and for gastric cancer 36.4% during the period 2014–2020 [5]. Despite recent advances in various diagnostic modalities, most GI malignancies are still found at advanced stages, and early detection and diagnosis of DSNs remains a challenging process [6–11]. Therefore, the search for personalised prognostic markers with high sensitivity and specificity will help in the early detection and intervention of DSNs, leading to the development of optimal therapeutic regimens and improved patient survival.

The results of several recent studies have shown that inflammatory response and immune function as tumour predisposing factors are highly correlated with tumour development, proliferation, invasion and metastasis [12, 13]. Inflammatory response and immune function have also been shown to play a key role in the prognosis of tumour patients, and several prognostic models have been developed [14–18]. In addition, the role of nutritional status on the therapeutic efficacy and prognosis of cancer patients has been increasingly emphasised, and a large number of clinical studies have been conducted to investigate the causal relationship between the two [19–22]. In recent years, with the depth of research, several studies have established a variety of new personalised prognostic markers based on various laboratory test indicators of inflammation levels and immune function. These include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and the monocyte-to-lymphocyte ratio (MLR), as well as the systemic immune-inflammatory index (SII) and the systemic inflammatory response index (SIRI) based on these three [23–26]. However, some studies have pointed out the limitations of the aforementioned prognostic markers and established a novel scoring method called pan-immunoinflammatory value (PIV) [27]. In addition, various types of prognostic scoring systems based on nutritional status have been shown to be effective predictors [28–30]. However, these prognostic markers and scoring systems are all based on one or two factors and have not yet been combined with inflammation levels, immune function and nutritional status to comprehensively analyse the prognosis of cancer patients. However, the CRP-albumin-lymphocyte (CALLY) index proposed by Hiroya Iida et al. combines inflammation, immunity and nutritional factors simultaneously and is effective in predicting the prognosis of patients with HCC. In his study, the CALLY index was calculated as (Alb[g/dL]×lymphocytes)/(CRP[mg/dL]×104) [31]. In addition, several studies have shown that a lower CALLY index tends to predict worse OS and DFS in gastrointestinal malignancies such as gastric, colorectal, oesophageal and pancreatic cancer [32, 33, 37, 43].

However, the correlation between the prognostic role of the CALLY index in DSNs and CPCs is inconsistent. For example, a low CALLY index was not associated with DFS in tumour patients in the study by Furukawa et al. In other studies, a low CALLY index was associated with worse DFS. In the studies by Takeda et al. [43] and Shiraishi et al. [42], there was no significant correlation between lymph node metastasis and CALLY index. Other studies found the opposite. Furthermore, in the studies by Furukawa et al. [34] and Shiraishi et al. [42], the results showed a strong correlation between postoperative complications and CALLY ($p < 0.05$). On the contrary, in the studies by Aoyama et al. [32] & Fukushima et al. [34], the occurrence of complications was not correlated with the CALLY index. To date, most studies investigating the CALLY index have been single-centre studies with small sample sizes, and no study has yet provided a comprehensive analysis of the predictive role of CALLY in DSNs.

Therefore, considering the strong predictive role of CALLY index in DSNs and the correlation of CPCs. And to further explore the effective predictive role of CALLY index in different DSNs, we conducted a comprehensive systematic review and meta-analysis of the literature related to CALLY index. The aim was to determine the precise role of CALLY index in predicting the prognosis of patients with DSNs and to evaluate the relationship

between CALLY index and CPCs of DSNs, in order to provide a novel and effective prognostic marker for DSNs.

Materials and methods

Study guideline

This trial was conducted according to the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA 2020) guidelines [49] and has been registered on the PROSPERO website (https://www.crd.york.ac.uk/) under the registration number CRD42024622973. In addition, the PRISMA checklist for this study can be found in Table S1 in the appendix.

Search strategy

In this study, two researchers conducted a comprehensive search of five databases, including PubMed, Cochrane Library, Web of Science, Research Square, and Embase, from the time the databases were created until 1 November 2024, to ensure the scientific quality and completeness of the search.To ensure the scientific integrity of the search process, the search terms were limited to "C-reactive protein-albumin-lymphocyte" or "CRP-albumin-lymphocyte" or "CRP-albumin-lymphocyte " or "CALLY" and "gastric cancer" or "colorectal cancer" or "hepatocellular carcinoma" or "pancreatic cancer" or "oesophageal cancer" or "cholangiocarcinoma" or "digestive neoplasms", and the language of the literature is limited to English. Expanded literature retrieval to include Chinese databases such as CNKI, Wanfang, and VIP. No eligible studies meeting inclusion criteria were identified. The search process for this study was conducted independently by two researchers (CDZ and WL). In case of disagreement during the process, a third researcher (LLF) will join in and make a comprehensive selection. The detailed search strategy can be found in the appendix material.

Inclusion and exclusion criteria

All literature included in this review met the following inclusion and exclusion criteria.

Inclusion criteria: (1) The topic of the article was CALLY related to the prognosis of digestive system neoplasms. (2) Pathological or imaging studies diagnosed digestive system neoplasms such as gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer, cholangiocarcinoma, oesophageal cancer, and other digestive system neoplasms. (3) The definition of CALLY was clear and the formula was Alb [g/dL]×lymphocytes)/(CRP [mg/dL]×10^4, and all indicators were the test results of preoperative blood draws. (4) The article clarified the cut-off value of CALLY, and the patients were divided into high group and low group by this cut-off value, and the survival comparison and CPCs were compared between the two groups. (5) Comparative analyses of prognostic indicators (OS, DFS, RFS, CSS) and CPCs were performed by hazard ratio (HR), odds ratio (OR) and its 95% CI. (6) Study types were clinical trials, cross-sectional studies, retrospective studies, and prospective studies.

Exclusion criteria were (1) reviews, case reports, conference abstracts, commentaries and conference reports. (2) Animal studies. (3) Poor study quality, such as overlapping samples or missing data in the included population. (4) Unavailability of full text or missing article content.

Data extraction and quality assessment

Data from the included articles were collected independently by two researchers (CDZ and MYL), and disagreements arising during the process were discussed with the participation of a third researcher (LJH) until consensus was reached. All CALLY indices were calculated based on preoperative blood test results, even if patients underwent subsequent surgical or therapeutic interventions. A specially designed data form was used to collect basic information from the included literature, including first author's name, year of publication, country, age, study design, tumour type and stage, duration of follow-up and CALLY cut-off, and to record statistics on primary and secondary survival endpoints (OS, DFS, RFS, CSS) by collecting relevant HRs and their 95% CIs from the included literature. The relationship between CPCs and CALLY was assessed by calculating the OR and 95% CI between each clinicopathological characteristic of the high group and the low group in the included literature. The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which rates studies in terms of selectivity, comparability and outcome [50]. The total score was 9, with 7–9 being considered high quality studies, 4–6 being moderate quality studies, and less than 4 being low quality studies.The included articles in this study all scored greater than 6 and were considered high quality studies.The detailed scoring details can be found in the appendix document.

Statistical analysis

The data in this study were statistically analysed using two software programs, Stata 12.0 (Stata Corporation, College Station, Texas, USA) and Revman 5.3 (Revman, Cochrane Collaboration).The prognostic value of the CALLY index in patients with digestive system neoplasms was assessed by calculating the combined hazard ratio (HR) and 95% CI for each survival endpoint. In addition, the odds ratio (OR) and 95% CI were used to explore the correlation between the CALLY index and CPCs.Cochran's Q statistic and I2 test were used to assess heterogeneity between studies.When $P<0.1$

and $I^2 > 50\%$ indicated significant heterogeneity between studies.When heterogeneity between studies was large ($I^2 > 50\%$, $P < 0.1$), a random-effects model was used; conversely ($I^2 < 50\%$, $P > 0.1$), a fixed-effects model was used. We also performed subgroup analyses to explore potential sources of heterogeneity.Sensitivity analyses were performed by comparing the results of the analyses after excluding the included literature on a case-by-case basis to ensure the overall stability of the study results. Begg's and Egger's tests were used in this study to assess publication bias among the included studies.When the results suggested publication bias among the studies, the trim and fill method was used to fill in the studies with missing estimates to correct for publication bias.In this study, two-sided $P < 0.05$ was considered statistically significant. The rationality of the combined analysis was based on the common inflammatory - immune-trophic axis mechanism of digestive system tumors. The robustness of the results was further verified by subgroup analysis (e.g. gastric cancer, colorectal cancer, esophageal cancer).

Results

Literature search results

According to our search strategy, an initial search of the database yielded 131 documents, and after deleting 36 duplicates, a total of 95 relevant papers were obtained. By reading the titles and abstracts of the articles, we excluded 36 of the literature on animal studies, basic research, case reports and conference proceedings. After reading the full text of the remaining 59 papers, 41 non-compliant papers were excluded, including inability to extract data ($n = 6$), NOS scores lower than 6 ($n = 4$), irrelevant research questions ($n = 19$), and failure to report the required outcome measures ($n = 12$).Finally, 18 studies with a total of 7916 patients with DSNs were included in this meta-analysis.The detailed literature selection process is shown in Fig. 1.

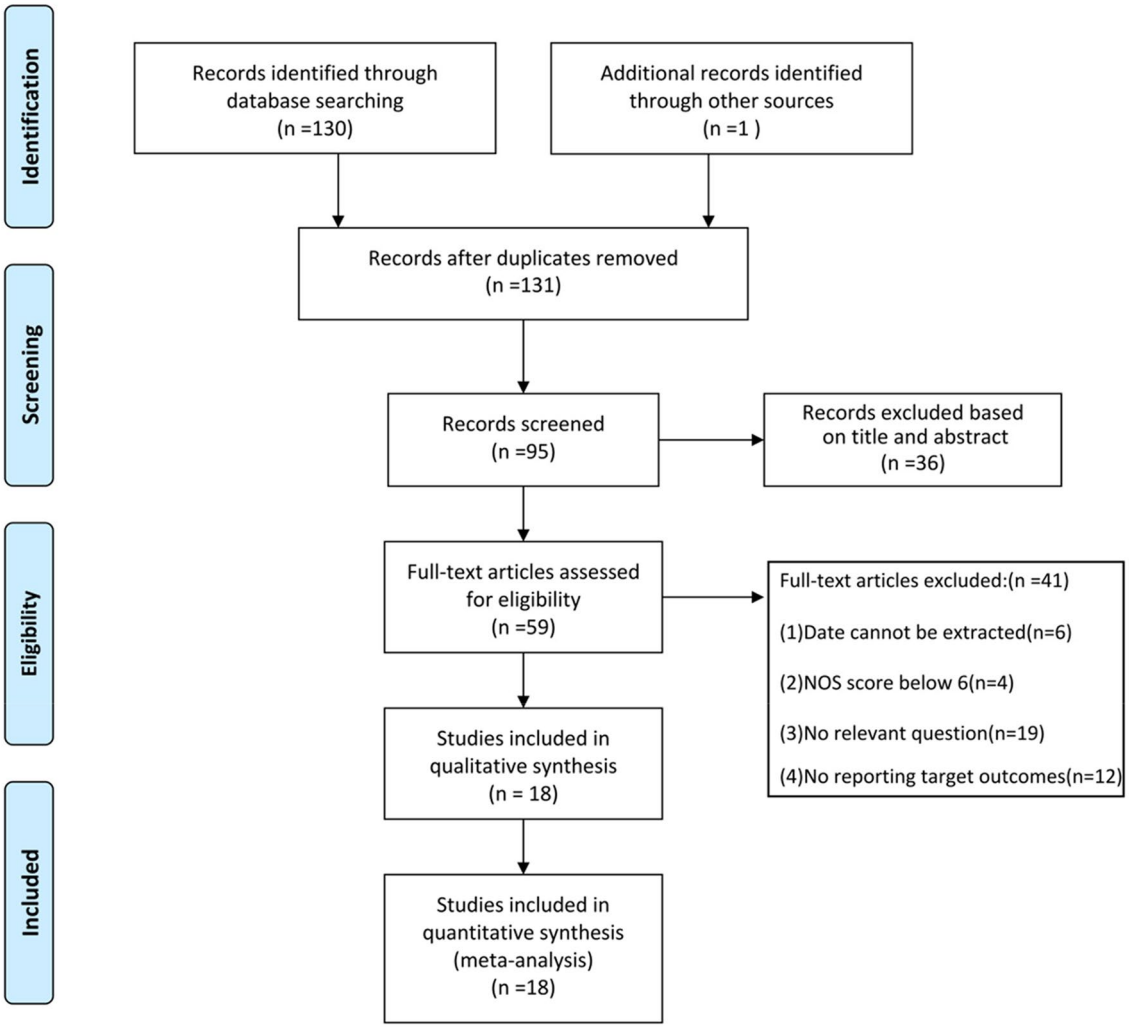

Fig. 1 PRISMA fow diagram for study selection

Characteristics of included studies

The 18 papers included in this review were published between 2021 and 2024, included 6 prospective studies and I^2 retrospective studies.Three of the studies were conducted in China and the remaining 15 studies were conducted in Japan.Among the included studies, 10 studies were single-centre studies and the remaining 8 were multicentre studies, with sample sizes ranging from 143 to 1260. In terms of tumour types in the digestive system, a total of seven studies reported gastric cancer, four reported colorectal cancer, three reported oesophageal cancer, one reported cholangiocarcinoma, one reported pancreatic cancer, one reported hepatocellular carcinoma, and one reported colorectal cancer liver metastasis. The CALLY index in the included studies all used receiver operating characteristic (ROC) curves to determine the optimal threshold. Regarding the significance of the CALLY index for patient prognosis, 16 studies mentioned OS, 7 studies mentioned RFS, 6 studies mentioned DFS and 2 studies mentioned CSS. All used multivariate regression analyses to calculate the corresponding HR with 95% CI.The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS).The 18 included papers were scored between 7 and 9, indicating that they were all of high quality.The detailed basic information is shown in Table 1.

CALLY and OS

In this study, 16 studies with 7335 patients reported the predictive effect of CALLY on OS in patients with DSNs. Since no significant heterogeneity was found ($I^2 = 0\%$, $p = 0.76$), a fixed-effects model was used.The results of the pooled analysis suggested that low CALLY index was significantly associated with worse OS in patients with DSNs (HR = 2.03, 95%CI = 1.83–2.25, $p < 0.00001$) (Fig. 2A). To explore potential heterogeneity, we performed multiple subgroup analyses of the relationship between CALLY index and OS.The results of the subgroup analyses showed that the significance of CALLY index in predicting OS was independent of country, sample size, cut-off value, study design, data source and tumour type ($p < 0.05$).The detailed results of the subgroup analyses are shown in Table 2.

Subgroup analyses stratified by tumor type (Table 2) revealed robust prognostic associations of the CALLY index for gastric cancer (HR = 2.01, 95% CI = 1.68–2.41), colorectal cancer (HR = 2.24, 95% CI = 1.84–2.72), and esophageal cancer (HR = 2.79, 95% CI = 1.89–4.12), with low heterogeneity (I^2=0–36%).

CALLY and DFS

In this study, six studies with 1651 patients reported the predictive effect of CALLY on DFS in patients with DSNs.As no significant heterogeneity was found ($I^2 = 0\%$, $p = 0.62$), a fixed-effects model was used.The pooled analysis showed that low CALLY index was significantly associated with worse OS in patients with DSNs (HR = 1.82, 95%CI = 1.46–2.27, $p < 0.00001$) (Fig. 2B). To explore potential heterogeneity, we performed multiple subgroup analyses of the relationship between CALLY index and DFS.The results of the subgroup analyses showed that the significance of CALLY index in predicting OS was independent of sample size, cut-off value and study design ($p < 0.05$).In contrast, there was no significant relationship between CALLY index and Colorectal Liver Metastasis (CRLM) in the cancer staging subgroups.The detailed results of the subgroup analyses are shown in Table 2.

CALLY and RFS

In this study, seven studies with a total of 3177 patients reported the predictive effect of CALLY on RFS in patients with DSNs.As no significant heterogeneity was found ($I^2 = 0\%$, $p = 0.48$), a fixed-effects model was used. The pooled analysis suggested that low CALLY index was significantly associated with worse OS in patients with DSNs (HR = 1.53, 95%CI = 1.33–1.75, $p < 0.00001$) (Fig. 2C). To explore potential heterogeneity, we performed multiple subgroup analyses of the relationship between CALLY index and RFS.The results of the subgroup analyses showed that the significance of CALLY index in predicting RFS was independent of sample size, cut-off value, study design, data source and tumour type ($p < 0.05$).The detailed results of the subgroup analyses are shown in Table 2.

CALLY and CSS

In this study, two studies with a total of 881 patients reported the predictive effect of CALLY on CSS in patients with DSNs. As no significant heterogeneity was found ($I^2 = 26\%$, $p = 0.25$), a fixed effect model was used. The results of the pooled analysis showed that a low CALLY index was significantly associated with worse CSS in DSNs patients (HR = 2.45, 95%CI = 1.88–3.20, $p < 0.00001$) (Fig. 2D). As only two studies reported data on CSS in DSNs patients, further subgroup analysis was not possible.

Relationship between CALLY and CPCs of DSNs

In this study, 15 studies with a total of 6,660 patients reported the relationship between the CALLY index and CPCs in patients with DSNs. The summary analysis shows that the decrease in CALLY index was associated with TNM stage (HR = 0.56, 95%CI = 0.36–0.86, $p = 0.009$), T stage (HR = 0.36, 95%CI = 0.26–0.51, $p < 0.00001$), complications (HR = 1.41, 95%CI = 1.17–1.71, $p = 0.0003$), lymphovascular invasion (HR = 0. 45, 95%CI = 0.29–0.71, $p = 0.0005$), lymph node metastasis

Table 1 Information on the basic characteristics of the included studies

Study (author, years)	C`ountry	Sample size	Gender (M/F)	Age (years) Median(range)	Duration	Study design	Cut-off value	Cancer type	outcome indicator	Survival analysis	NOS score
Aoyama 2024 [32]	Japan	259	183/76	70(32–88)	2005–2020	Prospective study, Single	5.00	GC	OS, RFS, CPCs	Univariate + Multivariate	7
Feng 2024 [33]	China	318	213/105	59(39–76)	2013–2015	Retrospective study, Multiple	3.00	EC	CSS, CPCs	Univariate + Multivariate	8
Fukushima 2024 [34]	Japan	826	594/232	68(60–76)	2010–2017	Retrospective study, Multiple	2.00	GC	OS, RFS, CPCs	Univariate + Multivariate	7
Furukawa 2023 [35]	Japan	183	127/56	65(57–73)	2000–2018	Retrospective study, Single	4.00	CRLM	OS, DFS, CPCs	Univariate + Multivariate	8
Hashimoto 2024 [36]	Japan	459	300/159	65	2013–2017	Prospective study, Single	3.28	GC	OS, RFS, CPCs	Univariate + Multivariate	7
Hiroya 2021 [31]	Japan	384	296/88	69	2011–2013	Retrospective study, Multiple	5.00	HCC	OS, RFS, CPCs	Multivariate	7
Kawahara 2024 [37]	Japan	461	243/218	71(39–88)	2013–2022	Retrospective study, Single	1.90	PC	OS, RFS, CPCs	Univariate + Multivariate	8
Ma 2024 [38]	Japan	146	123/23	69(35–90)	2008–2018	Prospective study, Single	2.40	EC	OS, DFS	Univariate + Multivariate	7
Nakashima 2024 [39]	Japan	175	119/56	70(38–92)	2011–2019	Retrospective study, Single	6.96	GC	OS, DFS, CPCs	Univariate + Multivariate	8
Okugawa 2024 [40]	Japan	426	304/122	66	2000–2011	Prospective study, Single	4.93	GC	OS, DFS	Univariate + Multivariate	7
Sakurai 2024 [41]	Japan	563	343/220	68(57–79)	2014–2020	Retrospective study, Multiple	1.19	GC	OS, CSS, CPCs	Univariate + Multivariate	8
Shiraishi 2024 [42]	Japan	263	149/114	59(24–94)	2016–2023	Retrospective study, Multiple	0.37	CRC	CPCs	Univariate	7
Takeda 2024 [43]	Japan	578	348/230	69(61–76)	2010–2017	Retrospective study, Single	2.00	CRC	OS, DFS, CPCs	Univariate + Multivariate	7
Tomoaki 2024 [44]	Japan	608	371/237	67(61–75)	2010–2018	Retrospective study, Single	3.35	CRC	OS, RFS, CPCs	Univariate + Multivariate	7
Toru 2024 [45]	Japan	180	155/22	69(37–90)	2005–2020	Retrospective study, Multiple	5.00	EC	OS, RFS, CPCs	Univariate + Multivariate	7
Tsunematsu 2022 [46]	Japan	143	66/77	68(60–73)	2002–2019	Retrospective study, Single	3.50	CCA	OS, DFS, CPCs	Univariate + Multivariate	8
Yang 2023 [47]	China	1260	767/493	60(52–67)	2012–2020	Prospective study, Multiple	1.47	CRC	OS	Univariate + Multivariate	8
Zhang 2023 [48]	China	684	479/205	59(52–66)	2013–2018	Prospective study, Multiple	1.12	GC	OS	Univariate + Multivariate	7

Abbreviations: GC, gastric cancer; EC, esophageal cancer; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; CRC, colorectal cancer; PC, pancreatic cancer; CCA, cholangiocarcinoma; M/F, male/female; OS, overall survival; RFS, recurrence-free survival; CPCs, clinicopathological characteristics; NOS, Newcastle-Ottawa Scale

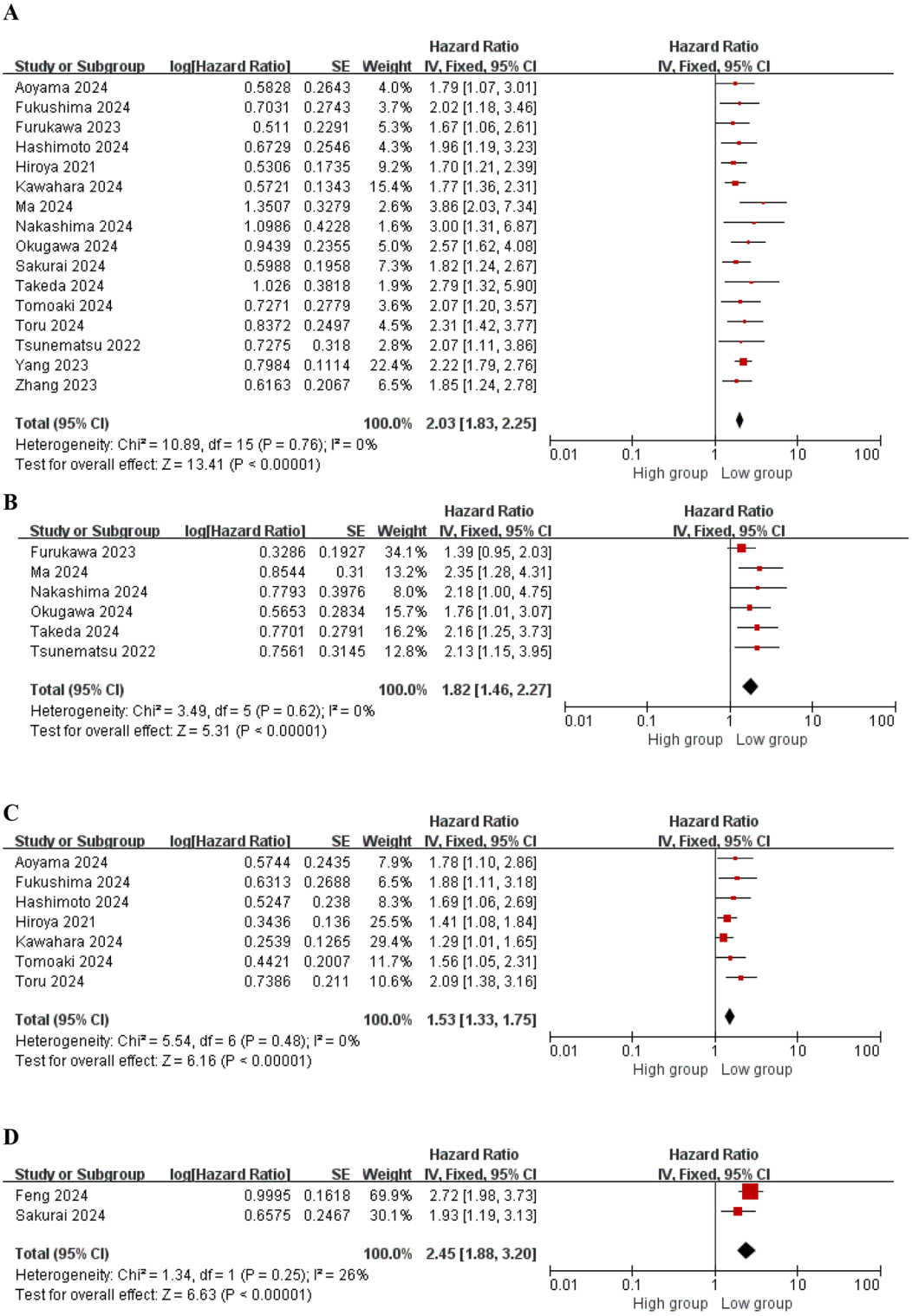

Fig. 2 Forest plot of the meta-analysis of the relationship between CALLY and prognostic indicators in patients with DSNs: (**A**) OS; (**B**) DFS; (**C**) RFS; (**D**) CSS

Table 2 Subgroup analysis of the prognostic value of CALLY in patients with digestive system neoplasms

Subgroups	No. of studies	No. of patients	Effects mode	HR (95%CI)	*p*	Heterogeneity	
						I^2 (%)	Ph
OS							
Total	16	7335	Fixed	2.03(1.83–2.25)	*P* < 0.00001	0	0.76
Country							
China	2	1944	Fixed	2.13(1.76,2.58)	*P* < 0.00001	0	0.44
Japan	14	5391	Fixed	1.99(1.76,2.25)	*P* < 0.00001	0	0.70
Sample size							
≤ 300	6	1086	Fixed	2.17(1.73,2.72)	*P* < 0.00001	11	0.35
> 300	10	6249	Fixed	1.99(1.78,2.24)	*P* < 0.00001	0	0.85
Cut-off value							
≤ 3	7	4518	Fixed	2.06(1.80,2.35)	*P* < 0.00001	10	0.35
> 3	9	2817	Fixed	1.99(1.69,2.34)	*P* < 0.00001	0	0.85
Study design							
Prospective	6	3234	Fixed	2.20(1.89,2.571	*P* < 0.00001	0	0.43
Retrospective	10	4101	Fixed	1.90(1.65,2.18)	*P* < 0.00001	0	0.91
Data sources							
Single	10	3438	Fixed	2.05(1.76,2.38)	*P* < 0.00001	0	0.49
Multiple	6	3897	Fixed	2.01(1.75,2.32)	*P* < 0.00001	0	0.78
Cancer type							
CRC	3	2446	Fixed	2.24(1.84,2.72)	*P* < 0.00001	0	0.81
GC	7	3392	Fixed	2.01(1.68,2.41)	*P* < 0.00001	0	0.86
EC	2	326	Fixed	2.79(1.89,4.12)	*P* < 0.00001	36	0.21
CRLM	1	183	-	1.67(1.06,2.61)	*P* = 0.03	-	-
HCC	1	384	-	1.70(1.21,2.39)	*P* = 0.002	-	-
CCA	1	143	-	2.07(1.11,3.86)	*P* = 0.02	-	-
PC	1	461	-	1.77(1.36,2.31)	*P* < 0.0001	-	-
DFS							
Total	6	1651	Fixed	1.82(1.46,2.27)	*P* < 0.00001	0	0.62
Sample size							
≤ 300	4	647	Fixed	1.76(1.35,2.30)	*P* < 0.0001	1	0.39
> 300	2	1004	Fixed	1.95(1.32,2.88)	*P* < 0.0008	0	0.61
Cut-off value							
≤ 3	2	724	Fixed	2.06(1.80,2.35)	*P* < 0.0001	10	0.35
> 3	4	927	Fixed	1.95(1.32,2.88)	*P* < 0.0008	0	0.61
Study design							
Prospective	2	572	Fixed	2.20(1.89,2.571	*P* < 0.00001	0	0.43
Retrospective	4	1079	Fixed	1.90(1.65,2.18)	*P* < 0.00001	0	0.91
Cancer type							
CRC	1	578	-	2.16(1.25,3.73)	*P* = 0.006	-	-
GC	2	601	Fixed	1.89(1.20,2.97)	*P* = 0.006	0	0.66
EC	1	146	-	2.35(1.28,4.31)	*P* = 0.006	-	-
CRLM	1	183	-	1.39(0.95,2.03)	*P* = 0.09	-	-
CCA	1	143	-	2.13(1.15,3.95)	*P* = 0.02	-	-
RFS							
Total	7	3177	Fixed	1.53(1.33,1.75)	*P* < 0.00001	0	0.48
Sample size							
≤ 300	2	439	Fixed	1.95(1.43,2.67)	*P* < 0.0001	0	0.61
> 300	5	2738	Fixed	1.44(1.24,1.68)	*P* < 0.00001	0	0.67
Cut-off value							
≤ 3	2	1287	Fixed	1.38(1.10,1.73)	*P* = 0.005	38	0.20
> 3	5	1890	Fixed	1.61(1.36,1.91)	*P* < 0.00001	0	0.60
Study design							
Prospective	2	718	Fixed	1.73(1.24,2.42)	*P* = 0.001	0	0.88

Table 2 (continued)

Subgroups	No. of studies	No. of patients	Effects mode	HR (95%CI)	*p*	Heterogeneity	
						I^2 (%)	Ph
Retrospective	5	2459	Fixed	1.49(1.29,1.72)	*P* < 0.00001	18	0.30
Data sources							
Single	4	1787	Fixed	1.46(1.22,1.74)	*P* < 0.0001	0	0.55
Multiple	3	1390	Fixed	1.63(1.32,2.00)	*P* < 0.0001	29	0.24
Cancer type							
CRC	1	608	-	1.56(1.05,2.31)	*P* = 0.03	-	-
GC	3	1544	Fixed	1.77(1.34,2.35)	*P* < 0.0001	0	0.96
EC	1	180	-	2.09(1.38,3.16)	*P* = 0.0005	-	-
HCC	1	384	-	1.41(1.08,1.84)	*P* = 0.01	-	-
PC	1	461	-	1.29(1.01,1.65)	*P* = 0.04	-	-

Abbreviations: HR, hazard ratio; CI, confidence interval; I^2, heterogeneity index (percentage of total variation across studies due to heterogeneity); Ph, P-value for heterogeneity; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; CSS, cancer-specific survival; GC, gastric cancer; EC, esophageal cancer; CRLM, colorectal liver metastasis; CCA, cholangiocarcinoma; PC, pancreatic cancer; HCC, hepatocellular carcinoma

Table 3 The association between CALLY and clinicopathological features in patients with DSNs

Variables	No. of studies	No. of patients	Effects model	OR (95% CI)	*p*	Heterogeneity	
						I^2(%)	Ph
TNM stage	8	4324	Random	0.59(0.36,0.86)	0.009	88	*P* < 0.00001
T stage	4	2172	Random	0.36(0.26,0.51)	< 0.00001	64	0.04
Complication	10	3657	Fixed	1.41(1.17,1.71)	0.0003	17	0.29
Adjuvant chemotherapy	8	3247	Random	1.17(0.81,1.69)	0.41	78	*P* < 0.0001
Lymphatic vessel invasion	2	439	Fixed	0.45(0.29,0.71)	0.0005	34	0.22
Lymph node metastasis	11	4555	Random	0.63(0.51,0.79)	< 0.0001	60	0.005
Surgical approach	4	700	Fixed	0.25(0.20,0.29)	< 0.00001	27	0.25
Neoadjuvant chemotherapy	3	824	Random	0.83(0.50,1.39)	0.49	61	0.08
Gender	14	5400	Fixed	1.21(1.07,1.37)	0.002	12	0.33
Histologic type	7	3380	Random	1.07(0.77,1.49)	0.67	68	0.005

Abbreviations: OR, odds ratio; CI, confidence interval; TNM, tumor-node-metastasis staging system; T stage, tumor size/extent classification; I^2, heterogeneity index; Ph, P-value for heterogeneity

(HR = 0.63, 95%CI = 0.51–0.79, $p < 0.0001$), surgical approach (HR = 0.25, 95%CI = 0.20–0.29, $p < 0.00001$) and gender (HR = 1.21, 95%CI = 1.07–1.37, $p = 0.002$) were significantly correlated. However, the decrease in CALLY index was associated with adjuvant chemotherapy (HR = 1.17, 95%CI = 0.81–1.69, $p = 0.41$), neoadjuvant chemotherapy (HR = 0.83, 95%CI = 0.50–1.39, $p = 0.49$) and tissue type (HR = 1.07, 95%CI = 0.77–1.49, $p = 0.67$) showed no significant association (Table 3; Fig. 3).

Publication bias and sensitivity analysis

We used Begg's and Egger's tests to assess potential publication bias.The Begg's and Egger's tests for OS, DFS and RFS all indicated significant publication bias (Fig. 4).We performed the Trim and Fill method for OS, DFS and RFS separately and the results indicated that the results before and after clipping were statistically significant and the results were not reversed (Figs. 5 and S1). This suggests that the results of the study remain robust to publication bias, and detailed results can be seen in Table 4.

In addition, we used the Leave-One-Out method to compare the differences in the respective combined effect values of OS, DFS and RFS to perform a sensitivity analysis.The results indicated that the combined effect values after excluding each study were within the predicted range.Therefore, the results of our study were characterised by stability (Fig. 6).

Discussion

In this systematic review and meta-analysis, we pooled data from 18 studies involving a total of 7916 patients with digestive system neoplasms (DSNs) to comprehensively assess the impact of the C-reactive protein-albumin-lymphocyte (CALLY) index on the prognosis of patients with DSNs. Although previous studies have investigated the potential of the CALLY index in predicting the prognosis of DSNs, the results have not been entirely consistent.Our analysis revealed significant associations between the CALLY index and worse overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS) and cancer-specific survival (CSS) in patients with DSNs. Through in-depth subgroup analyses, we further validated the prognostic predictive power of the CALLY index across sample sizes, cut-off

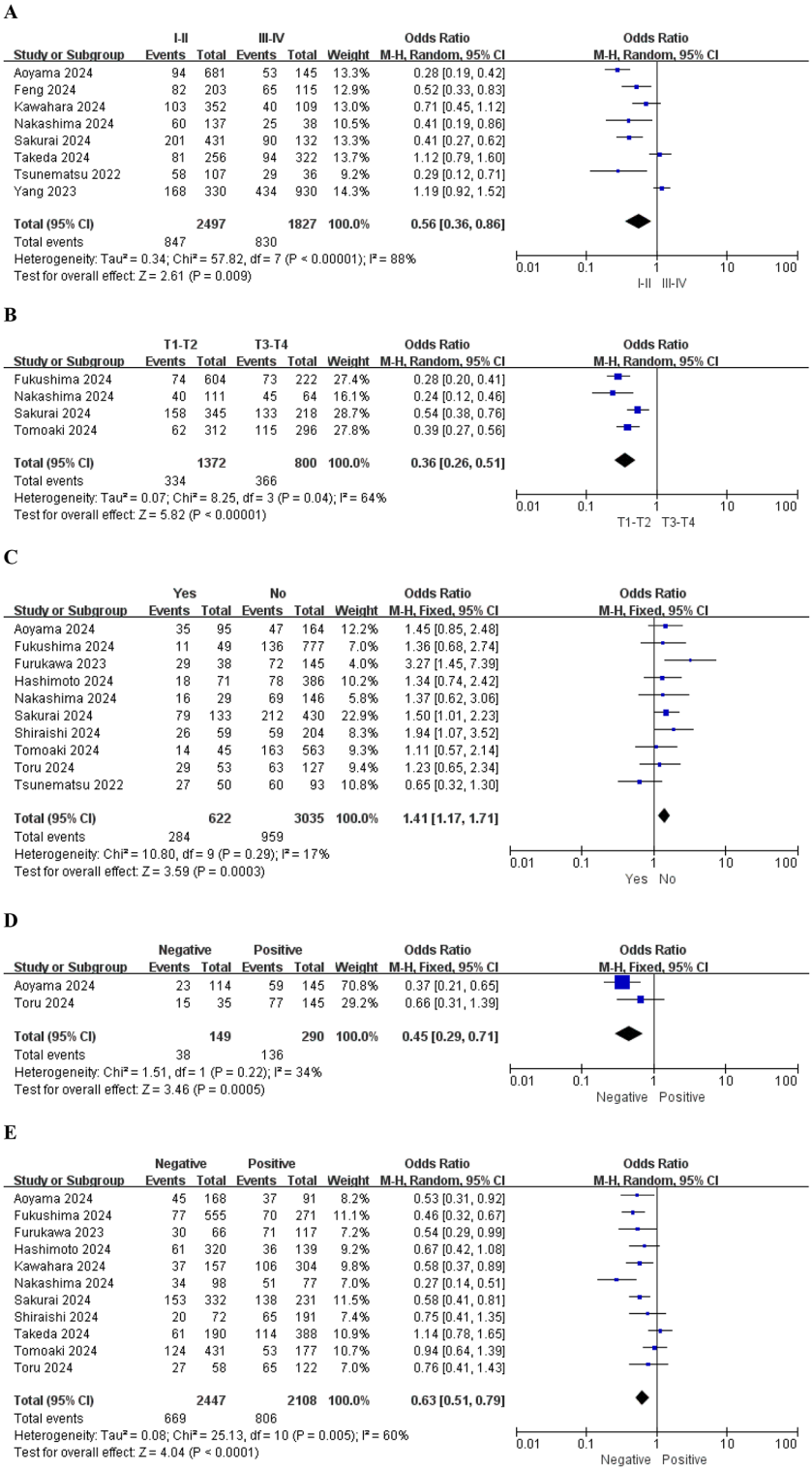

Fig. 3 Forest plot of the meta-analysis of the relationship between CALLY and CPCs in patients with DSNs: (**A**) TNM stage; (**B**) T stage; (**C**) complication; (**D**) lymph vessel invasion; (**E**) lymph node metastasis; (**F**) surgical approach; (**G**) gender; (**H**) adjuvant chemotherapy; (**I**) neoadjuvant chemotherapy; (**J**) histological type

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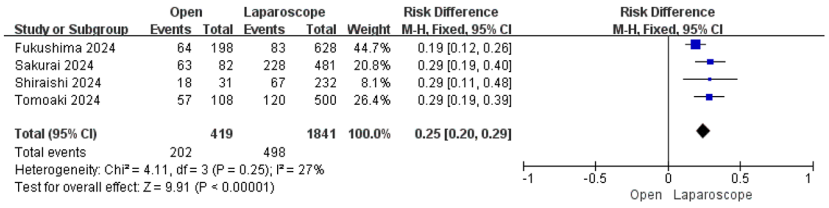

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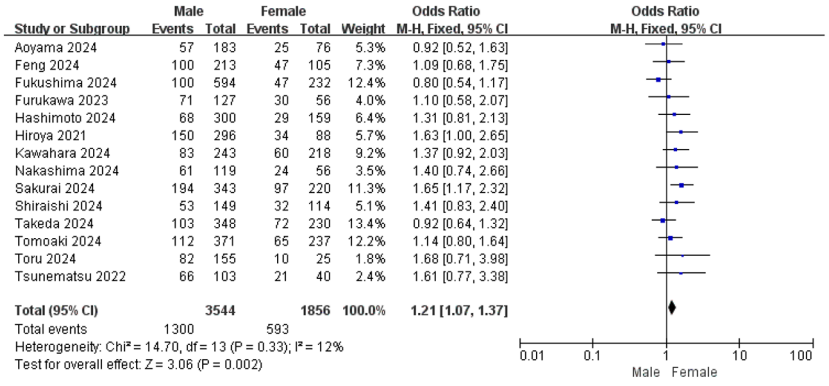

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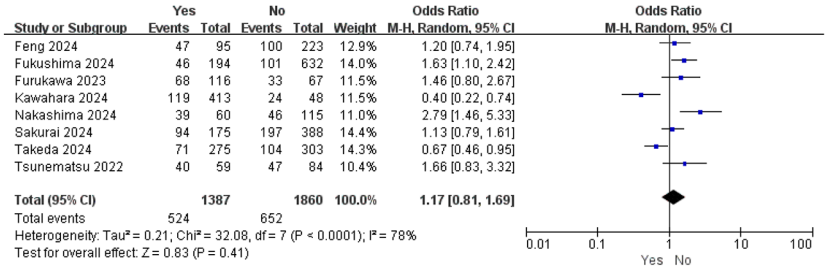

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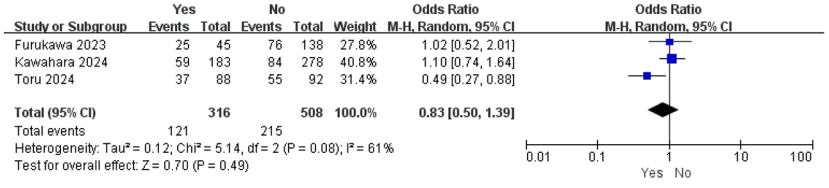

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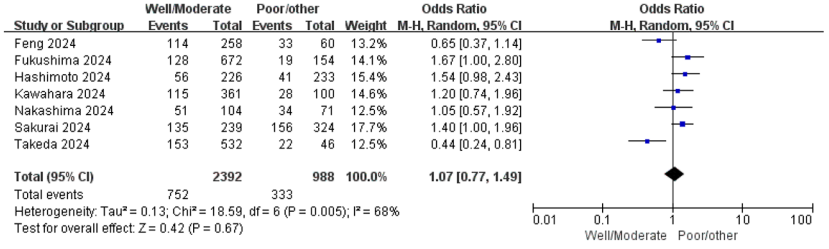

Fig. 3 (continued)

values, study designs and tumour types, and found that decreased CALLY index was associated with multiple CPCs of patients with DSNs, including TNM stage, T stage, comorbidities, lymphovascular invasion, lymph node metastasis, surgical approach and gender, suggesting that patients with low CALLY index may be at higher risk of tumour aggressiveness and disease progression. Overall, this study provides strong evidence for the

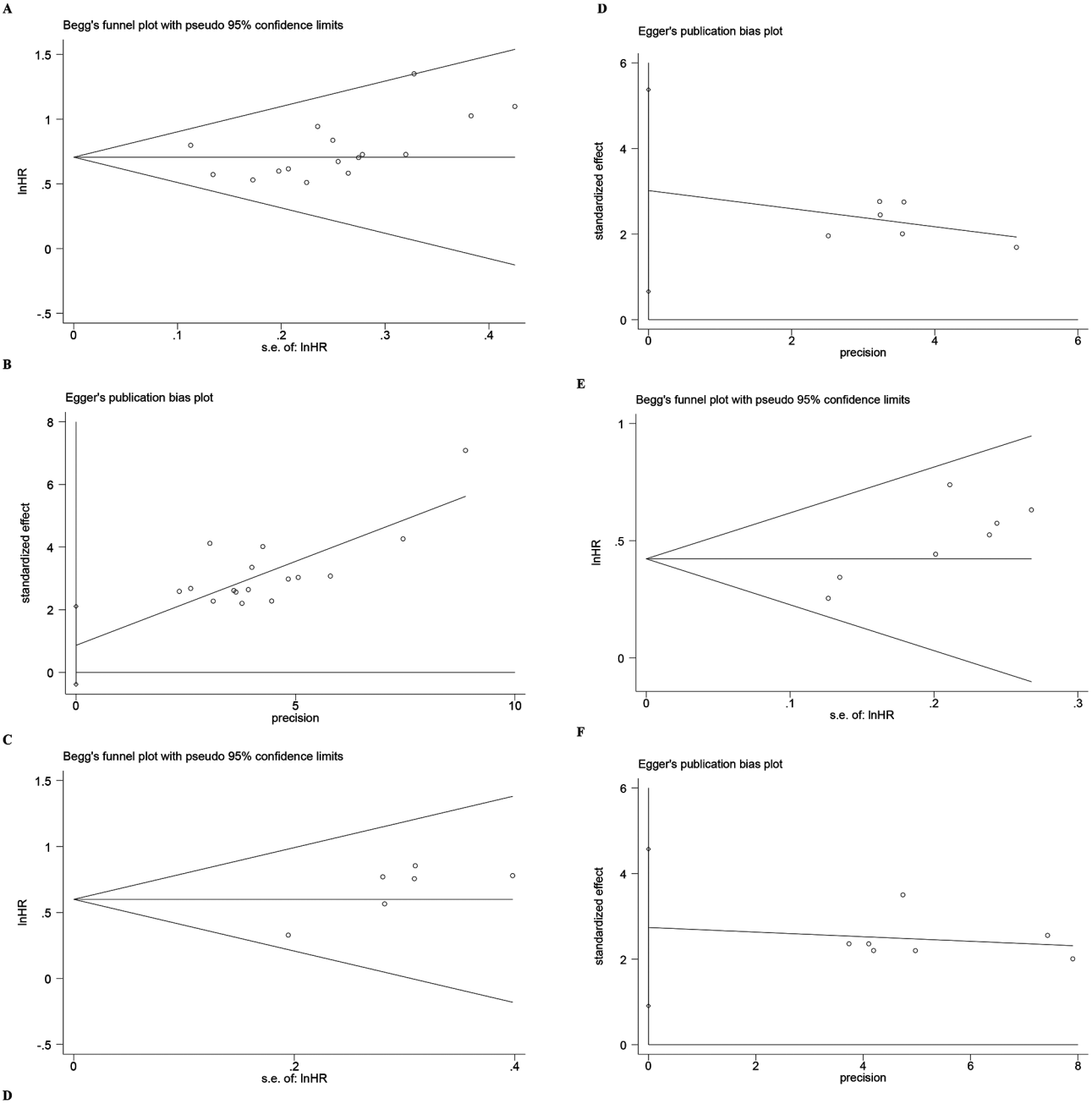

Fig. 4 Publication bias tested by Begg's test and Egger's test: (**A**) Begg's test for OS; (**B**) Egger's test for OS; (**C**) Begg's test for DFS; (**D**) Egger's test for DFS; (**E**) Begg's test for RFS; (**F**) Egger's test for RFS

CALLY index as a valuable biomarker in the prognostic assessment of patients with DSNs, and we recommend the CALLY index as a reliable and cost-effective prognostic indicator.

Inflammation, immune function and albumin levels are three key factors that influence changes in the CALLY index, and they interact through different mechanisms to affect the prognosis of tumour patients.First, inflammation plays a complex role in tumour development. The inflammatory microenvironment can promote tumour cell growth, invasion and metastasis [51–53].Inflammatory cells, such as tumour-associated macrophages (TAMs) and tumour-associated neutrophils (TANs), promote tumour progression by releasing pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and chemokines that not only act directly on tumour cells, but also affect the function of immune cells, e.g., These cytokines not only act directly on tumour cells, but also affect the function of immune cells, for example by inhibiting the activation and proliferation of T cells, thereby weakening the

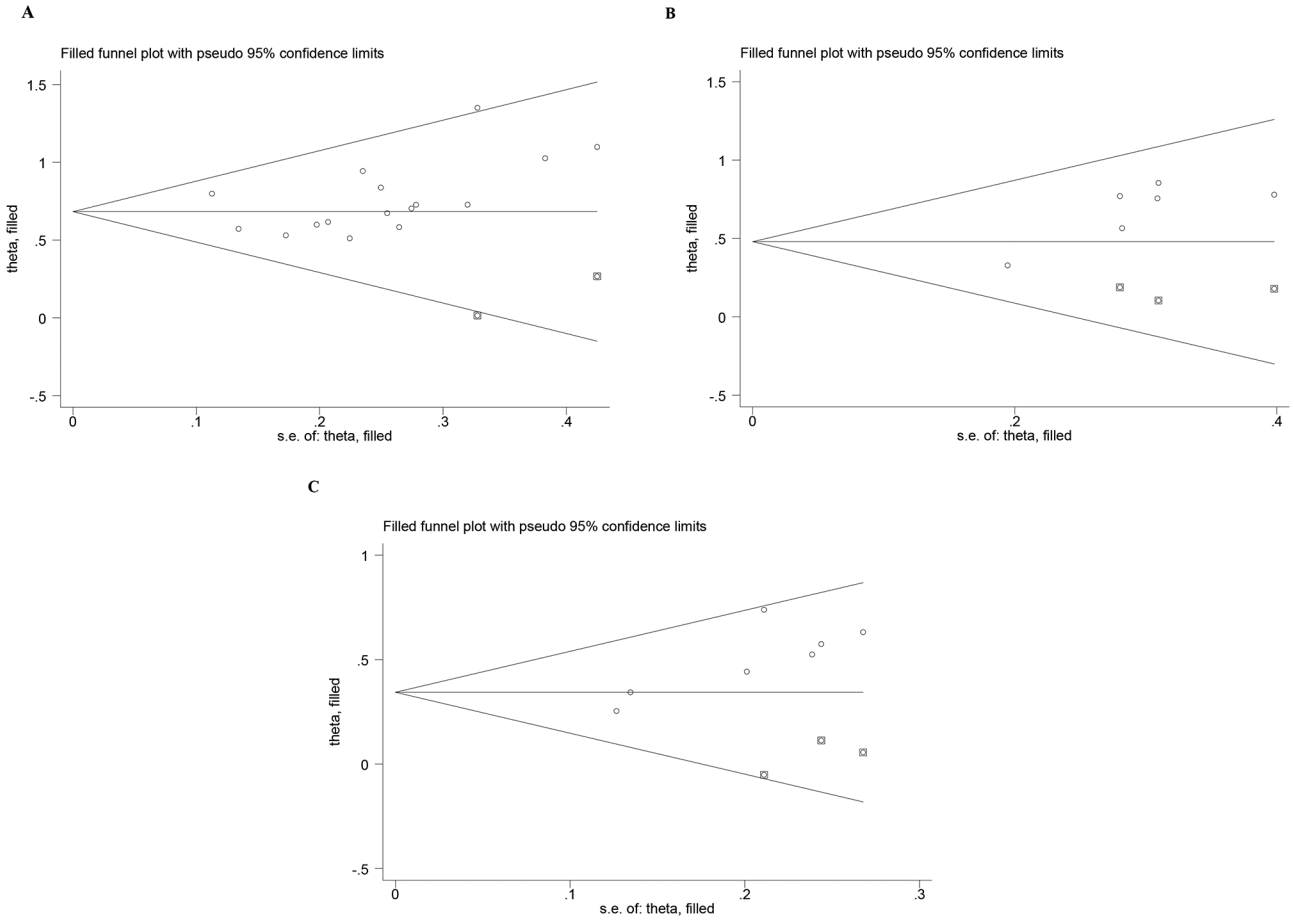

Fig. 5 Publication bias tested by Trim and Fill method: (**A**) OS; (**B**) DFS; (**C**) RFS

Table 4 The results of publication bias and trim and fill method

Prognostic indicator	Begg's *p*-Value	Egger's *p*-Value	OR (95% CI)		*p*-Value	
			pre-correction	post-correction	pre-correction	post-correction
OS	0.013	0.158	0.707(0.603,0.810)	0.683(0.581,0.784)	< 0.001	< 0.001
DFS	0.452	0.024	0.600(0.379,0.820)	0.479(0.291,0.668)	< 0.001	< 0.001
RFS	0.035	0.012	0.422(0.288,0.557)	0.344(0.224,0.464)	< 0.001	< 0.001

Abbreviations: Begg's test, rank correlation method for publication bias; Egger's test, linear regression method for publication bias; OR, odds ratio; CI, confidence interval; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival

anti-tumour immune response [54].In addition, inflammation is associated with impaired nutrient metabolism in the tumour microenvironment, leading to nutrient deficiencies that further affect immune cell function [55]. Second, immune function plays a critical role in tumour prognosis.Immune cells, particularly T cells and NK cells, exert anti-tumour effects by recognising and killing tumour cells. However, tumour cells can use various mechanisms to evade immune surveillance, including reducing the expression of MHC molecules and inducing the production of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which inhibit effective immune responses [56–59].In addition, a state of nutrient deprivation in the tumour microenvironment, particularly glucose and amino acid deficiency, affects the metabolism and function of immune cells, leading to immunosuppression [60]. Finally, albumin levels are an important indicator of the nutritional status of tumour patients.Decreased albumin levels are usually associated with malnutrition, inflammation and hepatic insufficiency.Hypoalbuminemia is associated with poor prognosis in tumour patients because it reflects the body's physiological stress response to tumour burden.Albumin is also a key protein in the maintenance of plasma colloid osmotic pressure and in the transport of a variety of substances, and reduced levels may affect drug distribution and metabolism and thus therapeutic efficacy. In summary, inflammation, immune function and albumin

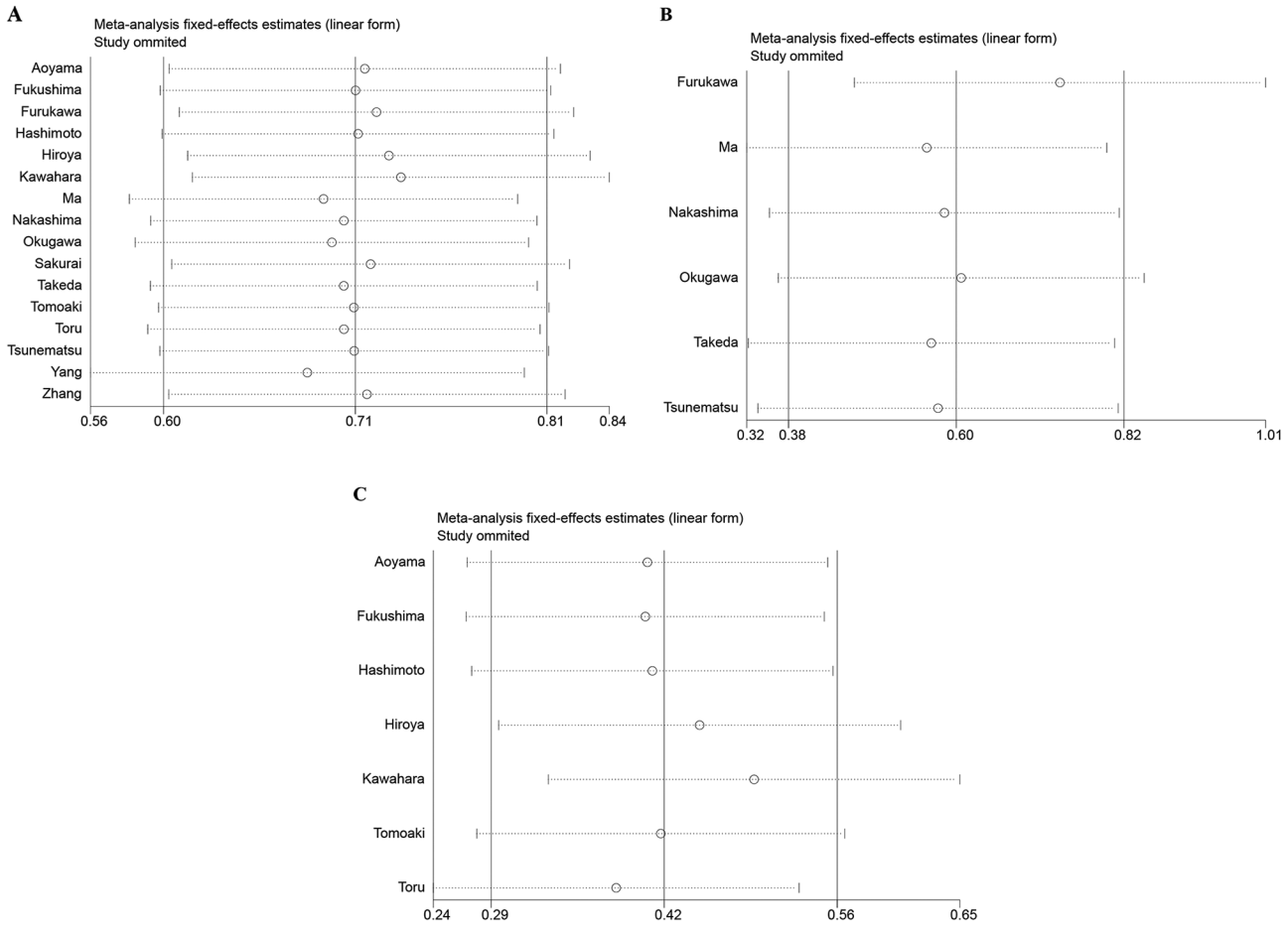

Fig. 6 Sensitivity analyses of outcomes. (**A**) OS; (**B**) DFS; (**C**) RFS

levels work together to cause changes in the CALLY index by influencing the tumour microenvironment, immune cell function and nutritional status.The interaction and balance of these factors determine the prognosis of tumour patients and provide potential therapeutic targets for tumour therapy.By modulating these factors, it may be possible to improve the immune status of patients and enhance the anti-tumour immune response, thereby improving treatment efficacy and patient survival. Compared to existing prognostic markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI), CALLY provides a more comprehensive view of patient prognosis by innovatively integrating nutritional, immune and inflammatory dimensions, demonstrating its unique advantages.

In this systematic review and meta-analysis, the combined results indicate a strong association between the CALLY index and poor prognosis in patients with digestive system neoplasms, despite differences in the setting of the cut-off value of the CALLY index between studies. This variability in the setting of cut-off values may have had some impact on the interpretation of the results of individual studies, but overall our analysis demonstrates the general applicability of the CALLY index in predicting patient survival. CALLY cutoff values, population characteristics, and combined HR for different tumor types are shown in Appendix Table S3. This observation underscores the robustness of the CALLY index as a prognostic marker, suggesting that a low CALLY index can serve as a strong indicator of poor patient prognosis regardless of the cut-off value used.Thus, although the choice of cut-off value may influence the specific findings of individual studies, the overall trend suggests that the CALLY index retains its consistency in prognostic prediction across different settings, providing strong support for its widespread clinical use. In addition, the CALLY index integrates inflammation (CRP), nutritional status (albumin), and immune function (lymphocytes) - pathophysiological pathways shared by digestive system tumors (DSNs). Despite differences in the biological characteristics of different tumor types, subgroup analysis showed that CALLY index had consistent prognostic value in gastric cancer (HR = 2.01), colorectal cancer (HR = 2.24), and esophageal cancer (HR = 2.79) (Table 2)

with low heterogeneity (I^2 = 0–36%). Support the rationality of the merge analysis (Appendix Figure S2).

In this meta-analysis, we identified potential publication bias using Begg's and Egger's tests, which may affect the generalisability of the results. However, after correcting for potentially missing studies using the trim-and-fill method, we found that the association between a low CALLY index and poor prognosis in patients with digestive system neoplasms remained intact, suggesting that the prognostic value of the CALLY index remains robust even in the presence of publication bias, further validating its reliability as a prognostic biomarker. Thus, although the presence of publication bias may have affected the visibility of some studies, our findings still support the validity of the CALLY index in predicting patient survival, highlighting its potential for important applications in clinical practice.

This study covers a wide range of gastrointestinal malignancies, including gastric, colorectal and hepatocellular carcinoma, and this diversity of tumour types provides a unique perspective for assessing the generalisability of the CALLY index. Despite possible differences in biological characteristics and treatment response between tumour types, the results of our analyses consistently showed that a low CALLY index was associated with poor prognosis for these tumour types.This consistency across tumour types suggests that the CALLY index may serve as a generalised prognostic indicator that is not limited to specific tumour types. However, tumour heterogeneity also suggests the need to consider tumour type-specific effects when interpreting the results, which may represent a potential variability factor in the accuracy of prognostic assessment.Therefore, future studies need to further explore the specific application of the CALLY index in different tumour types and how to optimise the prognostic assessment model by incorporating tumour-specific biomarkers.Despite the diversity of tumour types, our findings still emphasise the broad applicability and importance of the CALLY index as a powerful prognostic tool in the management of digestive system neoplasms.

In addition, we observed relatively low heterogeneity between the included studies, which may be due to consistency between studies in terms of patient populations, methods of calculating the CALLY index and reporting of results.Although low heterogeneity facilitated our ability to draw more consistent conclusions, it may also have masked potential clinical and methodological differences between studies. This consistency may limit our in-depth understanding of the application of the CALLY index in different clinical contexts, especially when dealing with different tumour types or treatment strategies. Thus, although low heterogeneity seems to increase the robustness of our findings, we must also be careful not to overstate these results, as they may not be fully applicable to all patient populations or clinical practice settings.Future studies need to further explore and explain the reasons for this low heterogeneity and its potential impact on the prognostic value of the CALLY index.

The CALLY index, a biomarker that integrates inflammatory, immune and nutritional status, is demonstrating its prognostic value in several medical fields. In digestive malignancies, the CALLY index has shown predictive utility, while in patients with non-metastatic nasopharyngeal carcinoma, the CALLY-EBV DNA index, which combines the CALLY score and EBV DNA levels, provides a new perspective on patient prognostic stratification and helps to construct prognostic models that are more predictive than the traditional TNM staging system [61]. In breast cancer, the CALLY index is strongly correlated with overall survival (OS) and disease-free survival (DFS), providing an independent indicator for prognostic assessment of postoperative patients, and a low CALLY index is strongly correlated with tumour progression and shortened survival [62]. Similarly, in ovarian cancer patients, the CALLY index shows potential as a prognostic biomarker and is an effective and efficient predictive biomarker of postoperative prognosis in ovarian cancer patients [63].Furthermore, in the cardiovascular field, the CALLY index was negatively correlated with the risk of cardiorenal syndrome (CRS), suggesting that the CALLY index may be a powerful and independent predictor of CRS, superior to traditional inflammatory markers [64]. Finally, the CALLY index was associated with the risk of sarcopenia in community-dwelling and hospitalised patients, and high CALLY index values were independently associated with a lower risk of sarcopenia, providing a convenient measure of nutritional and inflammatory risk factors for sarcopenia [65].These findings suggest that the CALLY index is not only prognostic in gastrointestinal malignancies, but also demonstrates its potential as a predictive tool in other medical fields. Although esophageal cancer had a higher CALLY truncation value (2.40-5.00 vs. Gastric cancer 1.12–6.96) may reflect a more aggressive biology, but the consistency of prognostic associations supports its generalization. Future studies need to optimize thresholds in conjunction with tumor-specific biological markers (Appendix Table S3).

Although the results of this paper provide strong evidence for the application of the CALLY index in the prognostic assessment of patients with digestive system neoplasms, there are still several limitations that limit its direct application and generalisability in clinical practice. First, further empirical support is needed for the clinical application of the findings, especially for the adaptation and optimisation of the CALLY index in different clinical settings and treatment strategies. In addition, although

this study has demonstrated the association between the CALLY index and patient prognosis, the underlying biological mechanisms and molecular pathways have not been fully elucidated, which is crucial for understanding how the CALLY index affects tumour progression and treatment response. Finally, the diversity of treatments and interventions in the included studies may have affected the true assessment of the relationship between the CALLY index and prognosis, suggesting that future studies need to consider the impact of these variables in different patient populations. Therefore, future studies should aim to explore the biological basis of the CALLY index, validate its applicability in different clinical settings and populations, and assess the performance of the CALLY index in different treatment contexts to improve its utility and validity in clinical practice.

Conclusion

In conclusion, this meta-analysis revealed a strong association between the C-reactive protein-albumin-lymphocyte (CALLY) index and prognosis in patients with digestive system neoplasms (DSNs).A low CALLY index was significantly associated with poor patient outcomes in terms of overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) and cancer-specific survival (CSS). Given its cost-effectiveness and stability, the CALLY index is a reliable prognostic biomarker.

Abbreviations

CALLY	C-reactive protein–albumin–lymphocyte
DSNs	Digestive system neoplasms
CPCs	Clinicopathological characteristics
OS	Overall survival
DFS	Disease-free survival
RFS	Recurrence-free survival
CSS	Cancer-specific survival
HR	Hazard ratio
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03779-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions

Conception/design: CDZ, JL, CH, JW, and XY. Provision of study material or patients: CDZ, JL, YM, LW, and GZ. Data collection and/or assembly: JL, YM, LW, and GZ. Data analysis and interpretation: CDZ, JL, YM, LW, GZ, CH, JW, and YX. Manuscript writing: CDZ, JL, YM, LW, GZ, CH, JW, and YX. Final approval of the manuscript: CDZ, JL, YM, LW, GZ, CH, JW, and YX.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Our study does not require approval since it is a meta-analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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