

## Review Article

# Clinical significance of preoperative albumin and alkaline phosphatase in colorectal cancer: a systematic review and meta-analysis

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**Abstract:** Objective: To investigate the association between preoperative serum levels of albumin (ALB) and alkaline phosphatase (ALP) with postoperative outcome in colorectal cancer (CRC) patients. Methods: A thorough literature search was conducted across Embase, PubMed, and Cochrane Library databases, identifying 20 eligible studies encompassing 61,296 participants. Studies were primarily observational and case-control in nature, with some randomized controlled trials also included. The random effects model was utilized to synthesize the effect sizes, while study quality was appraised using the Newcastle-Ottawa Scale and the Cochrane Risk of Bias Assessment Tool. Results: Findings revealed that CRC patients with preoperative ALB levels below 3.5 g/dl were at an elevated risk for postoperative complications (OR = 2.56, 95% CI: 2.12-3.08), increased mortality (OR = 4.54, 95% CI: 2.02-10.20), and a poorer prognostic survival risk (HR = 2.09, 95% CI: 1.58-2.77). Additionally, elevated ALP levels were associated with a higher risk of poor overall survival (HR = 1.67, 95% CI: 1.44-1.94). However, publication bias was noted in some studies. Conclusion: Preoperative hypoalbuminemia and elevated ALP levels are significantly linked to adverse postoperative events and reduced survival in CRC patients, suggesting their potential as prognostic biomarkers.

**Keywords:** Colorectal cancer (CRC), albumin (ALB), alkaline phosphatase (ALP), prognosis, meta-analysis

## Introduction

Colorectal cancer (CRC) is a prevalent malignancy of the gastrointestinal system. Patients are often in the middle and late stages at the disease diagnosis, resulting in a poor prognosis and low survival rate [1]. According to statistics, by 2020, CRC would rank the third most common cancer and the second most deadly cancer in the world [2, 3]. Early diagnosis and effective treatment are crucial for improving the prognosis of patients with CRC [4]. Colonoscopy is widely regarded as the most effective method of screening for colorectal cancer due to its high sensitivity and specificity [5]. Despite its effectiveness, the procedure can be expensive, requires skilled practitioners, and depends heavily on patient cooperation. Additionally, advancements in molecular technology have underscored the importance of other serological markers such as albumin (ALB) and alkaline phosphatase (ALP) for managing CRC,

alongside the conventional tumor marker carcinoembryonic antigen (CEA) [6-8].

ALB, the predominant protein in plasma, not only reflects the nutritional status of patients but also plays a critical role in inflammatory response, immune mechanism, and the tumor microenvironment [9-11]. ALP, an enzyme present in various tissues of the human body, and is elevated in serum during the occurrence and development of liver diseases, bone diseases, and certain malignant tumors [12, 13]. In patients with CRC, an abnormal increase in ALP level may indicate tumor invasion, metastasis potential [8]. Therefore, both ALB and ALP are crucial markers for diagnosing, evaluating the prognosis, and guiding treatment decisions for CRC.

Previous studies have demonstrated an association between preoperative ALB and ALP levels with clinical characteristics, treatment

response, and prognosis of CRC patients. However, the clinical significance of preoperative levels of ALB and ALP in CRC remains a topic of debate. This is due to the inconsistency in findings across studies, which are often limited by small sample size. As a result, the predictive value of these biomarkers for patient outcome remains unclear and requires further investigation. The objective of this study was to conduct a systematic review and meta-analysis to assess the clinical significance of ALB and ALP in CRC. The goal is to provide clinicians with more accurate biomarkers to guide diagnosis, treatment decision-making, and prognosis evaluation of CRC.

### Methods

This meta-analysis was conducted in accordance with the PRISMA 2009 Checklist.

#### Data source

Two researchers, Dafang Xu and Qun Zhao, independently searched Embase, PubMed, and Cochrane library for relevant observational and case-control studies, as well as key randomized controlled trials (RCTs), according to a pre-designed protocol. The clinical significance of ALB and ALP levels in the severity and prognosis of CRC patients was explored by comparing prognostic data of patients with different levels of ALB and ALP, and by comparing healthy control and CRC groups. The inclusion criteria restricted the selection to English-language articles, and studies involving animal research were excluded.

For the search strategy, both Embase and PubMed, as well as the Cochrane Library, employed a combination of subject words and free words. Some of the search strategies are as follows: #1 "colorectal tumor" exp OR 'colorectal tumor'. #2 "colorectal neoplasm": ab (abstract), ti (title). #3 "neoplasm, colorectal": ab, ti. #4 "neoplasms, colorectal": ab, ti. #5 "tumor, colorectal": ab, ti. #6 "tumors, colorectal": ab, ti. #7 "colorectal cancer": ab, ti. #8 "cancer, colorectal": ab, ti. #9 "colorectal carcinoma": ab, ti. #10 "carcinoma, colorectal": ab, ti. #11 "colorectal carcinomas": ab, ti. #12 "prognosis": ab, ti. #13 "survival": ab, ti. #14 "postoperative": ab, ti. #15 "albumin"/exp OR "albumin". #16 "alkaline phosphatase" exp OR "alkaline phosphatase". #17 #15 OR #16. #18

#12 OR #13 OR #14. #19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR. #20 #17 AND #18 AND #19.

#### Inclusion criteria and exclusion criteria of study subjects

Inclusion criteria: (1) Published observational studies, case-control studies and randomized controlled studies on ALB and ALP levels related to the treatment of CRC; (2) Patients with CRC diagnosed by colonoscopy and pathological examination; (3) Studies with definite ALB or ALP levels reported; (4) Studies with complete data.

Exclusion criteria: (1) Research on incomplete data and inability to obtain relevant information; (2) In vitro cell experiments, animal experiments; (3) Lack of original data, such as reviews, meeting abstracts, case reports, letters, and expert consensus; (4) Repetitively published literature.

#### Extraction of the main indicators of the study

The ALB level was classified into two groups: hypoproteinemia (< 3.5 g/dl) and non-hypoproteinemia ( $\geq$  3.5 g/dl). The incidence of postoperative complications, survival rate, mortality, and hazard ratio (HR) of hypoproteinemia on the prognosis of patients with CRC were extracted. ALP levels in both CRC patients and healthy individuals, as well as the HR of elevated ALP levels on the prognosis and survival of CRC patients were also extracted.

#### Extraction of other general data for the study

The literature was screened by Dafang Xu and Qun Zhao to extract the data. Any large differences in the screening process were resolved through discussion and negotiation within the research group. The extracted data included the country, first author, publication time, study time, study type, number of patients, patient characteristics, age, gender, and ALB/ALP level grouping.

#### Quality evaluation of included studies

The study quality evaluation was conducted using the Newcastle-Ottawa Scale (NOS) [14], which is primarily used for assessing the quality of observational studies. The quality of the

included RCTs was evaluated using the Cochrane risk bias assessment tool [15]. The evaluation includes multiple indicators, such as random sequence generation, allocation concealment, blinding, result data integrity, selective reporting, and other sources of bias. This comprehensive evaluation helps to reduce the impact of bias. Each indicator was assessed as “low risk”, “uncertain risk”, or “high risk”. The two researchers jointly conducted a summary of the bias evaluation of all included RCTs.

### *Statistical analysis*

Statistical analysis was conducted using R 4.3.0 software with the programs of “meta” and “ggstatsplot”. Continuous variables were expressed as weighted mean difference (SMD) and 95% confidence interval (95% CI), and categorical variables, including dichotomous or polytomous variables, were represented by odds ratio (OR) and its 95% CI. The hypothesis test used was the H test, expressed as Z value and P value. A significance level (alpha) of 0.05 was set for hypothesis tests. If the P-value was less than 0.05, it indicated a significant difference between groups. The results were presented using a forest plot.

### *Heterogeneity analysis*

The Q test was used to analyze heterogeneity, and the results were expressed as the  $I^2$  value. A  $P > 0.10$  and  $I^2 < 50\%$  indicates small heterogeneity, and either the fixed effect model (FEM) or random effect model (REM) can be used to combine the effect amount. A  $P < 0.10$  and  $I^2 > 50\%$  suggests heterogeneity, and a REM should be selected.

### *Sensitivity analysis*

Sensitivity analysis was conducted to evaluate the stability and reliability of the combined effect size derived from the meta-analysis.

By systematically removing one study at a time and recalculating the meta-analytic summary measure, the influence of each individual study on the overall result was assessed. If the recalculated effects did not significantly deviate from the original results, the meta-analysis was considered stable and reliable. Significant changes upon exclusion of a study indicate potential issues with robustness, suggesting the results should be interpreted with caution.

### *Publication bias*

Publication bias occurs when the likelihood of publishing research findings is influenced by the nature and direction of results. Studies showing significant results are often more likely to be published than those showing non-significant results [16]. To visually assess symmetry of the studies, a funnel plot was drawn using the ‘meta’ package of R 4.3.0 software.

## Results

### *Overview of literature retrieval*

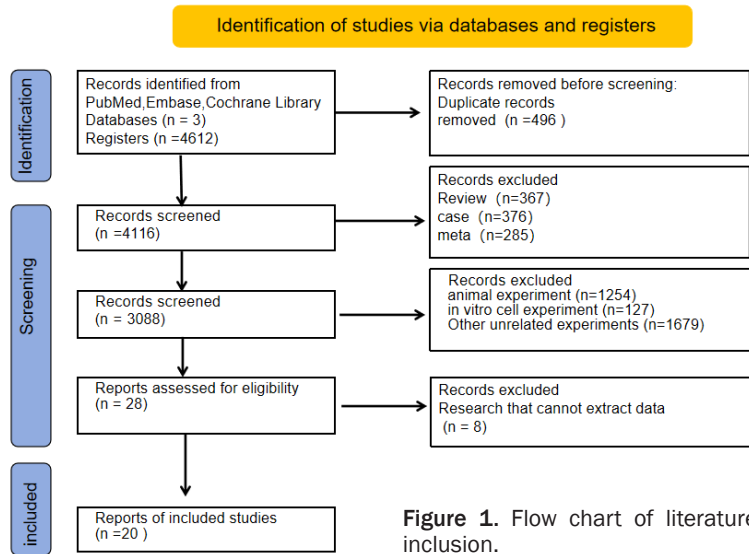
A search of the Embase database (2,551 articles), PubMed database (1,920 articles), and Cochrane Library (141 articles) using the search strategy of “subject words plus free words” retrieved a total of 4,612 articles. 496 duplicate studies were identified and removed using the EndNote software. The initial step involved removing review articles and case reports (1,028 articles) as well as irrelevant studies such as animal experiments and in vitro cell experiments. This left 28 related studies, which were then screened again to exclude articles from which data could not be extracted. Ultimately, 20 studies were included for this meta-analysis, involving a total of 61296 samples (**Figure 1**).

### *General characteristics of the included studies*

Among the 20 studies that fulfilled the inclusion criteria, most were observational studies, with a few RCTs. A total of 61,296 samples were involved. Among them, 11 articles [17-27] reported ALB level, and 9 articles [28-36] reported ALP level. All the 11 articles [17-27] reported the prognostic value of preoperative ALB level in patients with CRC. Three out of the 9 articles [31, 33, 35] compared the ALP levels between healthy people and CRC patients, and the remaining 6 articles [28-30, 32, 34, 36] reported the effect of different levels of ALP on the postoperative survival of CRC patients. **Tables 1** and **2** present the main features of the studies included.

### *Quality evaluation of the included studies*

The quality of observational studies was evaluated using the NOS scale. There were no studies with a score  $\leq 3$  points, 9 studies [18, 21-23, 27, 29, 31, 34, 35] were of moderate quality



with a score of 4-6 points, and 8 studies [17, 19, 20, 24-26, 33, 36] were of high quality with a score of  $\geq 7$  points (Tables 1, 2). The Cochrane risk bias assessment tool was used to evaluate the quality of the RCTs involved. Three studies [28, 30, 32] described a random sequence generation method with low risk. However, the specific methods of allocation concealment and allocation blindness were not clearly described, and data integrity was also deemed to be at low risk. Other potential bias factors were also low, meeting the requirements of this article. The two authors had no disagreement on the eligibility of the full-text article (Cohen kappa = 1).

#### Meta-analysis results

**Comparison of postoperative complications among patients with CRC with different preoperative ALB levels:** Five studies [19, 22-25] reported differences in postoperative complications between CRC patients with ALB levels below and above 3.5 g/dl. The results showed moderate heterogeneity ( $I^2 = 31\%$ ,  $P = 0.21$ ) among the included literature, and a random effect model was applied. After removing the literature of Lohsiriwat et al. [24], the overall  $I^2$  value was 0, indicating no heterogeneity. Therefore, Lohsiriwat et al. [24] was identified as the source of heterogeneity. The meta-analysis results indicated that CRC patients with  $ALB < 3.5$  g/dl were at higher risk of postoperative complications compared to those with  $ALB \geq 3.5$  g/dl (OR = 2.56, 95% CI = 2.12-3.08, Z =

9.85,  $P < 0.01$ ), as illustrated in Figure 2.

**Comparison of postoperative mortality in CRC patients with different preoperative ALB levels:** Four studies [20-23] reported the difference in mortality rate in CRC patients with ALB levels below and above 3.5 g/dl. The results showed high heterogeneity among the included literature ( $I^2 = 94\%$ ,  $P < 0.01$ ), suggesting high heterogeneity, and thus a random model was applied. To identify the source of heterogeneity, literature was eliminated one by one for sensitivity analysis. The results indicated that ex-

cluding the publication of Hu et al. [21] eliminated heterogeneity ( $I^2 = 0$ ), thus it was identified as the source of heterogeneity. The meta-analysis results suggested that CRC patients with ALB level below 3.5 g/dl had a higher mortality rate compared to those with ALB levels higher than 3.5 g/dl (OR = 4.54, 95% CI = 2.02-10.20, Z = 3.66,  $P < 0.01$ ), as illustrated in Figure 3.

**Prognosis for survival in CRC patients with hypoproteinemia:** Five studies [17, 18, 23, 26, 27] investigated the relationship between hypoproteinemia (generally defined as  $ALB < 3.5$  g/dl) and the prognosis and survival of CRC patients. The results showed moderate heterogeneity among the included literature ( $I^2 = 67\%$ ,  $P = 0.02$ ) among the included studies, thus a random model was chosen. The results indicated that the elimination of Wang's literature [27] resulted in an overall  $I^2$  of 0, indicating no heterogeneity. Therefore, Wang's literature [27] was identified as the source of heterogeneity. The meta-analysis results indicated that CRC patients with hypoproteinemia ( $ALB < 3.5$  g/dl) had a poor prognosis, with a combined effect size HR of 2.09 (95% CI: 1.58-2.77), as shown in Figure 4.

**Comparison of ALP levels between healthy people and CRC patients:** Three studies [31, 33, 35] compared the ALP levels between CRC patients and healthy controls, involving a total of 297 patients with CRC and 169 healthy controls. The studies showed low heterogeneity ( $I^2$

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**Table 1.** Basic information of the included literature on the relationship between ALB level and prognosis of CRC patients

| Country  | First author    | Year of publication | Type of research                  | Research time                | Number of patients | Patient characteristics   | Gender (male/female)    | Age (year)    | Proportion of patients with hypoalbuminaemia | NOS grade |
|----------|-----------------|---------------------|-----------------------------------|------------------------------|--------------------|---|-------------------------|---------------|--|-----------|
| USA      | Hu [20]         | 2016                | Retrospective, multi-center study | 2009-2012                    | 18,532             | Patients undergoing surgery for colorectal cancer                               | Not described           | Not described | 27.8%  | 7         |
| China    | Wang [27]       | 2015                | Retrospective                     | February 2005-November 2007  | 340                | Patients with stage II or III colorectal cancer who underwent radical resection | 192 (56.5%)/148 (43.5%) | 59.6 (26-84)  | Not described                                | 6         |
| Thailand | Lohsiriwat [24] | 2007                | Retrospective study               | January 2004-December 2005   | 84                 | Patients undergoing right colon cancer resection                                | 40 (48%)/44 (52%)       | 64 (27-89)    | 57%  | 7         |
| China    | Lai [23]        | 2010                | Retrospective study               | 1995-2008                    | 6,378              | Patients undergoing surgery for colon cancer                                    | Not described           | Not described | Not described                                | 4         |
| Romania  | Ionescu [22]    | 2013                | Perspective study                 | November 2011-July 2012      | 252                | Patients undergoing colorectal cancer anastomosis                               | Not described           | Not described | 28.9%  | 6         |
| England  | Egenvall [18]   | 2018                | Retrospective study               | 2007-2010                    | 417                | Patients undergoing radical surgery for stage I to III colorectal cancer        | Not described           | 69            | Not described                                | 5         |
| Germany  | Hardt [19]      | 2017                | Perspective study                 | September 2009-December 2014 | 370                | Patients who underwent resection of the rectal adenocarcinoma                   | Not described           | Not described | 18%  | 7         |
| Thailand | Lohsiriwat [25] | 2008                | Retrospective study               | 2003-2006                    | 244                | Patients undergoing resection of rectal adenocarcinoma                          | 139 (57%)/105 (43%)     | 62            | 23%  | 8         |
| China    | Sun [26]        | 2009                | Retrospective study               | January 1996-December 2006   | 1367               | Patients undergoing surgical treatment for colorectal cancer                    | 757 (55.4%)/610 (44.6%) | 66            | 28.7%  | 8         |
| USA      | Hu [21]         | 2019                | Retrospective study               | 2009-2013                    | 30676              | Patients undergoing surgery for colorectal cancer                               | Not described           | Not described | 17%  | 6         |
| USA      | Cengiz [17]     | 2006                | Retrospective study               | 1994-2003                    | 99                 | Patients undergoing surgery for colorectal cancer                               | 62 (62.6%)/37 (37.4%)   | 57.15         | Not described                                | 7         |

Note: CRC, Colorectal Cancer; ALB, Albumin.

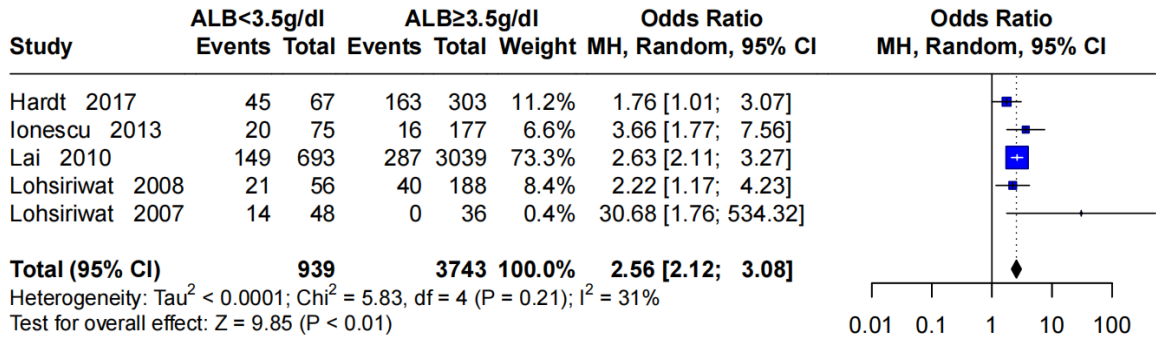
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**Table 2.** Basic information of the included literature on the relationship between ALP level and prognosis of CRC patients

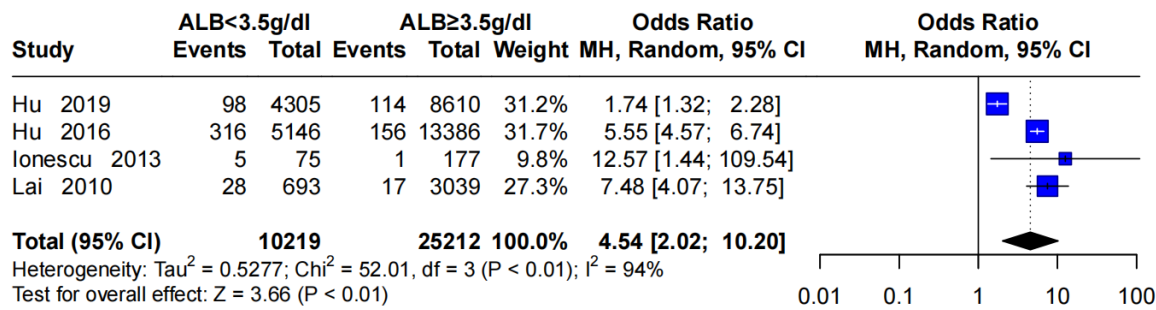
| Country     | First author  | Year of publication | Type of research   | Research time                     | Number of patients | Patient characteristics   | Gender (male/female)    | Age (year)       | ALP group   | NOS grade |
|-------------|---------------|---------------------|--|-----------------------------------|--------------------|---|-------------------------|------------------|---|-----------|
| Switzerland | Walach [35]   | 1991                | Case control study                                       | Not described                     | 122                | Patients with colorectal cancer, classified as Dukes' A, B1, B2, C and D            | Not described           | Not described    | Not described   | 4         |
| France      | Mitry [32]    | 2004                | Analysis of individual data in phase III clinical trials | Not described                     | 602                | Patients with advanced colorectal cancer treated with irinotecan                    | 358 (59.5%)/244 (40.5%) | 50 (24-75)       | ALP does not exceed twice the normal range (< 2 N)        | /         |
| Canada      | Asmis [28]    | 2011                | Phase III clinical trial (NCIC CTG CO.17)                | Not described                     | 572                | Patients with advanced colorectal cancer (ACRC) received cetuximab treatment        | 203 (62.1%)/132 (37.9%) | Not described    | The ALP is below or above the upper limit of normal (UNL) | /         |
| USA         | Bruckner [29] | 2022                | Clinical Research  | Not described                     | 205                | Patients with advanced gastrointestinal cancer                                      | 110 (54%)/95 (46%)      | Not described    | ALP > 135 IU/L  | 4         |
| Spain       | Suárez [34]   | 2015                | Retrospective study                                      | February 2003 to December 2012    | 125                | Synchronous stage IV colorectal cancer patients                                     | 89 (71.2%)/36 (28.8%)   | 64.9 (33-84)     | ALP levels were normal and elevated                       | 6         |
| China       | Zeng [36]     | 2023                | Retrospective study                                      | January 1, 2010 to April 30, 2022 | 85                 | High grade rectal neuroendocrine neoplasms patients who underwent radical resection | 50 (58.8%)/35 (41.2%)   | 57.0 (52.0-66.0) | ALP > 100.0 U/L   | 7         |
| Turkey      | Gür [31]      | 2011                | Case control study                                       | 2008-2009                         | 69                 | Forty colon cancer patients and 29 healthy volunteers                               | Not described           | Not described    | Health and CRC  | 6         |
| Belgium     | Efficace [30] | 2006                | Prospective Multicenter Randomized Controlled Trial      | Not described                     | 299                | Patients with advanced metastatic colorectal cancer                                 | 180 (60.2%)/119 (39.8%) | 61.2 (23.6-76.1) | ALP > 300.0 U/L   | /         |
| Iraq        | Qader [33]    | 2021                | Case control study                                       | Not described                     | 458                | Patients with, colorectal cancer, prostate cancer, and myocardial infarction        | Not described           | Not described    | Not described   | 7         |

Note: CRC, Colorectal Cancer; ALP, Alkaline phospholipase.

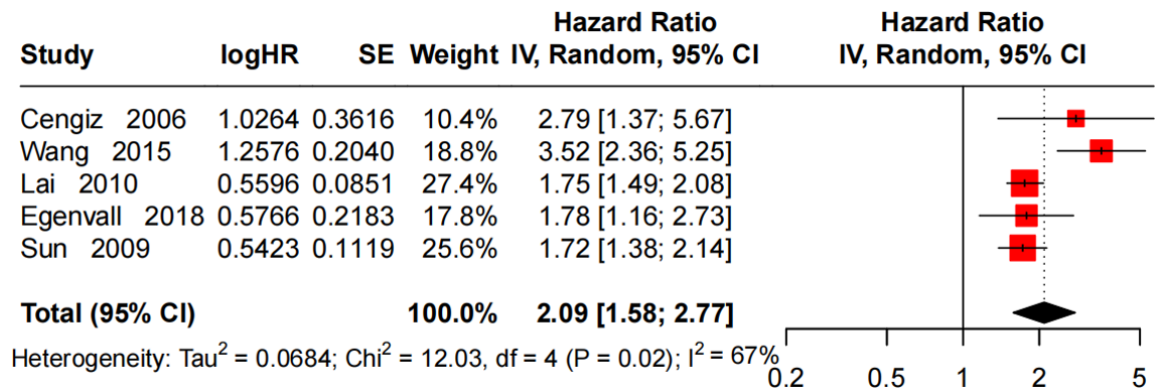
## Albumin and alkaline phosphatase in colorectal cancer



**Figure 2.** Forest plot of postoperative complications in CRC patients with different preoperative ALB levels. Note: CRC, Colorectal Cancer; ALB, Albumin.



**Figure 3.** Forest plot of postoperative mortality in CRC patients with different preoperative ALB levels. Note: CRC, Colorectal Cancer; ALB, Albumin.



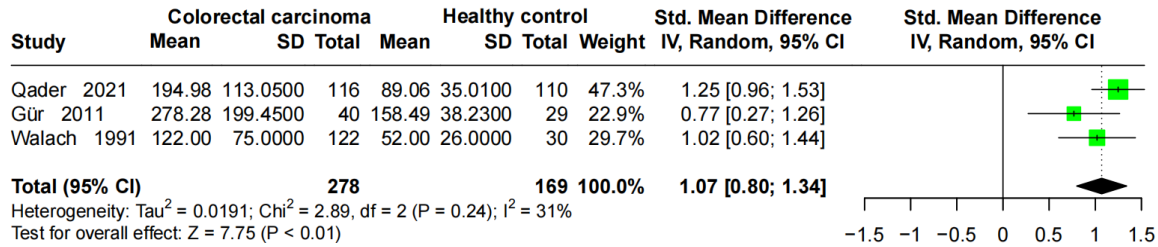
**Figure 4.** Forest plot of the prognostic survival of CRC patients with or without hypoproteinemia. Note: CRC, Colorectal Cancer.

= 31%,  $P = 0.24$ ), and a REM was used for analysis. Sensitivity analysis showed that removing either Qader et al. [33] or Gür et al. [31] eliminated heterogeneity, identifying these as potential sources. The meta-analysis results indicated that the ALP level in the CRC group was significantly lower than that in the healthy control group, with a significant combined effect size of  $\text{SMD} = 1.07$ , 95% CI: 0.80-1.34

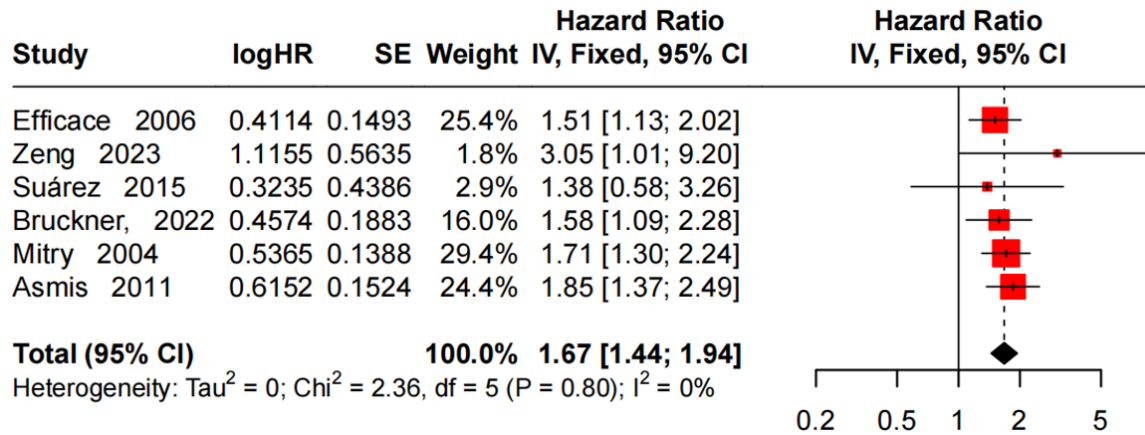
and a test statistic ( $Z = 7.75$ ,  $P < 0.01$ ), as shown in **Figure 5**.

*Risk of different degrees of elevated ALP for the overall survival of patients with CRC:* Six studies [28-30, 32, 34, 36] reported the impact of different elevated ALP on the prognosis and survival of CRC patients. The results showed no heterogeneity among studies ( $I^2 = 0\%$ ,  $P =$

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**Figure 5.** Forest plot of ALP levels in healthy individuals and CRC patients. Note: CRC, Colorectal Cancer; ALP, Alkaline phospholipase.



**Figure 6.** Forest plot of different levels of elevated ALP for overall survival of CRC patients. Note: CRC, Colorectal Cancer; ALP, Alkaline phospholipase.

0.80), and thus a fixed model was used for the analysis. The meta-analysis results indicated a significantly increased risk of poorer overall survival for CRC patients with elevated ALP levels, with a combined effect size of  $HR = 1.67$ , 95% CI: 1.44-1.94, as shown in **Figure 6**.

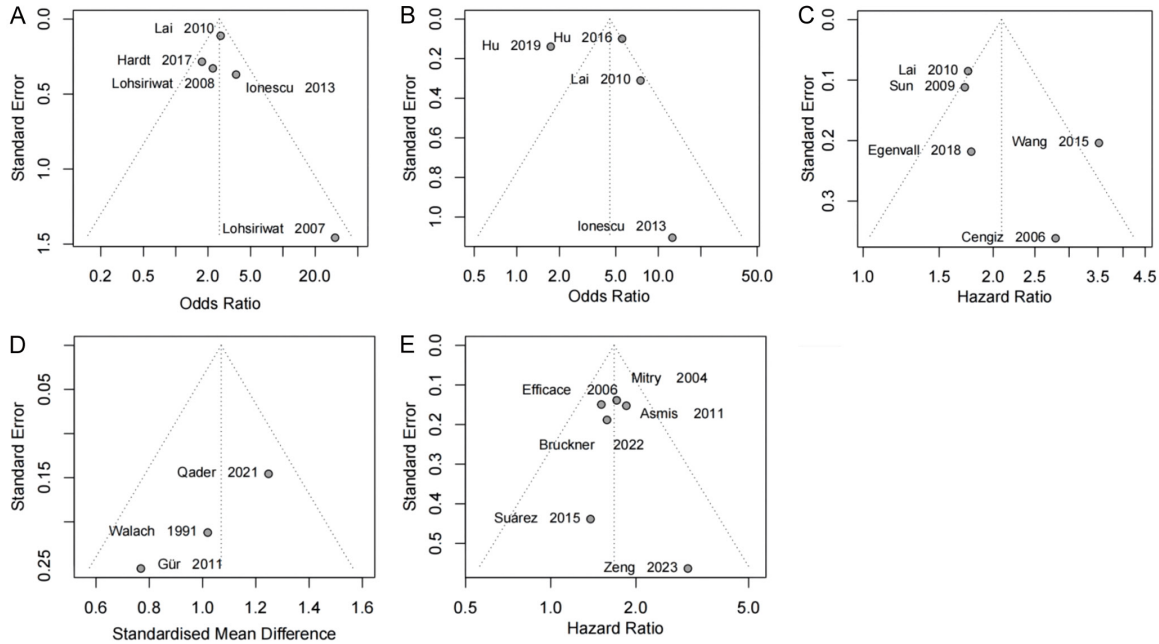
### Literature publication bias

A funnel plot was used to qualitatively evaluate the publication bias of the included 20 studies. Ideally, a funnel plot should display a symmetrical funnel shape, with more studies centered and fewer studies evenly distributed on both sides. As the size of the study increases, the standard error decreases, leading to a tighter clustering of larger study points around the true effect size estimate at the bottom of the funnel plot. The data revealed significant asymmetry in the funnel plot of publications involving post-operative complications in CRC patients with  $ALB < 3.5$  g/dl versus those  $\geq 3.5$  g/dl (**Figure 7A**), suggesting potential publication bias in the

five studies [19, 22-25]. Similarly, significant asymmetry was observed in the funnel plot of publications analyzing post-treatment mortality in CRC patients with  $ALB < 3.5$  g/dl versus those  $\geq 3.5$  g/dl, indicating publication bias in the four included studies [20-23] (**Figure 7B**). However, the funnel plot of publications on hypoalbuminemia ( $ALB < 3.5$  g/dl) and the prognosis of CRC patients (**Figure 7C**) did not exhibit significant asymmetry, suggesting an absence of publication bias in the five studies [17, 18, 23, 26, 27] analyzed. Conversely, the funnel plot of publications comparing ALP levels between healthy individuals and CRC patients (**Figure 7D**) showed significant asymmetry, indicating publication bias in the three included studies [31, 33, 35]. No significant asymmetry was detected in the funnel plot of publications on overall survival in CRC patients with varying levels of elevated ALP (**Figure 7E**), leading to the conclusion that there was no publication bias in the six studies [28-30, 32, 34, 36] evaluated.



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**Figure 7.** Publication bias was assessed by funnel plot. A: Funnel plot of publications reporting postoperative complications in CRC patients with different preoperative ALB levels; B: Funnel plot of publications reporting postoperative mortality in CRC patients with different preoperative ALB levels; C: Funnel plot of publications reporting prognostic survival of CRC patients with different preoperative ALB levels; D: Funnel plot of publications reporting ALP levels in healthy people and CRC patients; E: Funnel plot of publications reporting different elevated ALP on the overall survival of CRC patients. Note: CRC, Colorectal Cancer; ALB, Albumin; ALP, Alkaline phospholipase.

### Discussion

The objective of this systematic review and meta-analysis is to examine the clinical importance of preoperative levels of ALB and ALP in patients with CRC. Our analysis of the included studies indicates that preoperative hypoalbuminemia (ALB < 3.5 g/dl) is linked to a poor prognosis in patients with CRC, and elevated ALP levels are associated with an increased risk of mortality. These findings offer new biomarkers for the clinical management of CRC and could significantly impact treatment decision-making and prognosis evaluation for patients.

#### *Preoperative ALB levels and prognosis in CRC patients*

ALB level is a crucial nutritional indicator. Tumor cells often require increased ALB uptake to maintain their metabolism, leading to a decrease in ALB retention capacity and hypoalbuminemia. This study found that CRC patients with preoperative ALB levels below 3.5 g/dl had significantly higher rates of postoperative complications and mortality compared to those

with normal ALB levels. This finding aligns with a meta-analysis of the prognostic significance of the C-reactive protein to albumin ratio (CAR) in patients with CRC [37]. Both studies agree that low ALB level is a risk factor for poor prognosis in patients with CRC. However, in a systematic review and meta-analysis conducted by Christina et al. [38] involving seven observational studies with a total of 236,480 individuals, they demonstrated that preoperative hypoalbuminemia was not associated with 30-day mortality; this discrepancy could be attributed to differences in sample size and the duration of follow-up. In our study, only four articles were included, with a sample size of 25,431 cases. The smaller sample size in our study may have an impact on the statistical power of detecting significant associations. Furthermore, it is important to consider the follow-up period. Christina et al. concentrated on short-term outcome (30-day mortality), whereas our study assessed long-term outcome. The effect of hypoalbuminemia on mortality may become more pronounced over time, which may explain the differences in findings. Hypoalbuminemia usually indicates poor nutritional status, which can

impair postoperative immune function and increase the risk of complications including postoperative infection, anastomotic leakage, and intestinal obstruction [39-41]. Furthermore, hypoalbuminemia may be associated with the invasiveness and metastatic potential of tumors, promoting tumor spread and increasing the likelihood of recurrence [42]. The study found that patients with hypoalbuminemia had significantly shorter prognostic survival, which may be attributed to the more malignant biological behavior of tumors. Therefore, the preoperative albumin level may serve as a useful indicator for evaluating the prognosis of patients with CRC. This information can help clinicians better assess the risk to patients before surgery and make personalized treatment decisions.

### *Association between ALP levels and CRC*

ALP is an enzyme found in various human tissues, especially in the liver and bones [43]. Raised ALP levels may be seen in liver diseases such as gallstones, primary liver or bile duct tumors and metastatic liver tumors [44, 45]. Recent studies suggest that ALP can halt inflammatory signal transduction and induce inhibitory immune response by regulating purine signaling [46]. ALP is implicated in the regulation of tumor growth [47]. However, there is a limited number of studies comparing ALP levels between healthy individuals and CRC patients, which restricts a full understanding of ALP's role in CRC. In studies where comparisons exist, ALP levels were found to be significantly elevated in patients with CRC compared to healthy controls. This aligns with ALP's involvement in bone metastasis and liver dysfunction, both of which affect the prognosis of CRC patients. Elevated ALP levels may indicate liver dysfunction and possibly be related to liver metastases, serving as a significant prognostic factor in CRC patients.

A previous study analyzed 2,790 CRC patients and found that ALP, CEA, and CA125 were independent risk factors for CRC bone metastasis [48]. A retrospective study [49] analyzed 10,800 CRC patients with TNM stage I-IV who underwent surgical treatment and found that patients with elevated ALP levels had a lower 5-year OS rate than those with normal preoperative ALP levels. This suggests that ALP may

be a risk prognostic factor for CRC. A study of 239 patients with metastatic CRC found that ALP was a prognostic factor for overall survival and a predictor of progression-free survival in patients receiving first-line chemotherapy [50]. In a retrospective study of 105 CRC patients [51], elevated ALP levels were associated with higher TNM staging, especially in patients with liver metastases; those with elevated ALP levels during their last visit had a 5.7 times higher likelihood of poor outcome than those with normal ALP levels. In our study, elevated ALP levels were consistently associated with poorer outcome in CRC, highlighting its use as a biomarker for evaluating prognosis, particularly in the context of liver and bone metastasis.

### *Study heterogeneity*

In assessing the heterogeneity of studies comparing alkaline phosphatase (ALP) levels between healthy individuals and colorectal cancer (CRC) patients, several factors contributed to the variability and potential biases observed. First, it is necessary to note that different studies may use varied techniques for measuring ALP levels, leading to potential inconsistencies. Variations in sample handling, processing, and the specific protocols followed by different laboratories may have introduced discrepancies in the results. Second, the selection criteria for research subjects differed between studies. For instance, Qader et al. [33] reported that ALP level was significantly higher in patients with CRC and prostate cancer (PCa) than in the control population. However, the study involved multiple cancer types, which may have affected the interpretation of the data and the comparison of ALP levels. It is beyond dispute that ALP levels may be influenced by a plethora of factors, including liver and bone diseases, which are more prevalent in CRC patients. Furthermore, it is noteworthy that the study of Gür et al. [31] compared only the ALP levels of 40 CRC patients and 29 healthy volunteers. The sample size was relatively small, which may have introduced some bias, potentially affecting the stability and generalizability of the results. Consequently, these findings must be meticulously elucidated, and the relationship between ALP levels and CRC may be more intricate than currently perceived. As ALB and ALP levels may be influenced by various factors, multivariate analysis should be considered in

future research to control potential confounding factors and provide more accurate risk assessment. Consequently, further studies are required to substantiate its clinical significance and to elucidate the biological mechanism before ALP can be employed as a prognostic biomarker for CRC.

### Limitations of the study

While this study presents compelling evidence for the clinical relevance of preoperative ALB and ALP levels in CRC, there are still some limitations. First, the included studies vary in design, sample size, and patient selection criteria, which may impact the stability and generalizability of the findings. Second, publication bias may have led to the exclusion of studies with negative or unpublished results. Furthermore, the analysis may be affected by potential confounding factors due to the lack of raw data.

To improve accuracy, future studies should consider using a larger sample size and a prospective study design to assess the relationship between preoperative ALB and ALP levels with the prognosis of CRC.

### Conclusion

Preoperative ALB and ALP levels have important clinical significance in the prognosis evaluation for patients with CRC. Hypoalbuminemia and elevated ALP levels are linked to a poor prognosis in CRC patients. The evaluation of these biomarkers may help clinicians better assess the risk of patients before surgery and guide personalized treatment decisions. However, further high-quality studies are required to confirm these findings and to explore their clinical application.

### Disclosure of conflict of interest

None.

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