

# Research Progress of Albumin-Based Composite Markers in Prognosis Evaluation of Patients with Colorectal Cancer

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**How to cite this paper:** Lei, X. and Yu, J. (2025) Research Progress of Albumin-Based Composite Markers in Prognosis Evaluation of Patients with Colorectal Cancer. *Journal of Biosciences and Medicines*, 13, 24-36. <https://doi.org/10.4236/jbm.2025.139003>

**Received:** July 25, 2025

**Accepted:** August 30, 2025

**Published:** September 2, 2025

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## Abstract

In recent years, the relevant components in the blood of cancer patients have been confirmed to be related to the progression of the disease, and the value of serum albumin in predicting the efficacy of colorectal cancer patients has been widely studied. In addition, with the understanding of different degrees of nutritional risk in cancer patients due to various reasons and the acceleration of disease progression, more and more studies have explored the prognostic value of nutrition-related markers in cancer patients. This article reviews the research literature on the role of albumin-related composite indicators in the prognosis of patients with colorectal cancer at home and abroad in recent years, and deeply discusses the key role of relevant composite indicators in predicting tumor prognosis and guiding clinical intervention, aiming to promote the optimization of colorectal cancer treatment programs and the improvement of patients' prognosis.

## Keywords

Colorectal Cancer, Prognosis, Albumin Related Composite Index

## 1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death worldwide [1]. In recent years, the age of onset of CRC has shown a trend of younger age, and most patients have been in local advanced stage at the first visit, with poor prognosis, which poses a serious threat to human health and quality of life [2].

Malnutrition is a common perioperative complication in patients with digestive

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tract tumors due to digestive and absorption disorders, and affects the prognosis [3]. Albumin (Alb) is the most commonly used indicator to evaluate the nutritional status of cancer patients. It is mainly synthesized by hepatocytes and is the highest protein in human plasma, accounting for more than 50% [4]. It not only maintains plasma colloid osmotic pressure, nutrient transport, metabolism of harmful substances and other physiological processes, but also plays an important role in the body's anti-infection. The level of Alb decreases in acute inflammation, reflecting the severity of the body's damage. In addition, studies have found that Alb may have important prognostic value in CRC patients [5]. The most commonly used staging method for CRC is tumor, node, metastasis (TNM) staging. TNM staging is a scoring system for assessing tumor invasion of the colon, the number of lymph node metastasis in the relevant colon segment, and whether there is distant organ metastasis [6]. The stage of the disease is still the most important prognostic factor for CRC.

How to improve the efficacy of CRC, prolong the survival time of patients and improve the prognosis has become a research hotspot. In recent years, many studies have pointed out that Alb has a significant impact on the prognosis of patients with colorectal cancer, but Alb, a single indicator, cannot better represent the prognosis of patients with colorectal cancer. Many studies have combined albumin with human inflammatory indicators, nutritional indicators and other body components, suggesting that albumin-based composite markers are of great value for the clinical prognosis of patients with gastrointestinal tumors. Therefore, it is of great clinical significance to develop the best markers for postoperative complications, recurrence and prognosis evaluation of CRC patients.

## 2. Albumin and Inflammation-Related Composite Indicators

### 2.1. Neutrophil Count and Albumin-Related Composite Markers

Neutrophils play a vital role in the human body, especially the cytokines and chemokines they secrete. High levels of neutrophil counts are considered to be closely related to the poor prognosis of malignant tumors [7] [8].

Neutrophil-albumin ratio (NAR) is an emerging prognostic marker that combines inflammation and nutritional status assessment. High NAR is an independent risk factor for postoperative complications and long-term prognosis in CRC patients [9]. Tawfik *et al.* [10] analyzed 98 patients with CRC who underwent total mesorectal excision (TME) after standard neoadjuvant chemoradiotherapy (nCRT), and found that NAR before nCRT was an independent predictor of pathological complete response (pCR), and high NAR indicated poor response to nCRT. The NAR-based study can provide a reference for the prognosis and clinical decision-making of CRC patients.

Liang *et al.* [11] constructed a new prognostic marker LANR, defined as lymphocyte  $\times$  albumin/neutrophil, based on preoperative lymphocyte, albumin and neutrophil. LANR is a valuable new prognostic indicator in overall survival (OS) and progression-free survival (PFS). It can provide a reference for patients with re-

sectable colorectal cancer and help clinicians and patients choose treatment options.

Wang *et al.* [12] added albumin on the basis of neutrophil-to-lymphocyte ratio (NLR), and the results showed that albumin-NLR was a useful inflammatory marker, which was superior to systemic inflammation score (SIS) and modified Glasgow prognostic score (mGPS) in predicting OS of CRC patients undergoing radical resection.

The above neutrophil-albumin related composite indicators have important predictive value for the prognosis of CRC patients, but further prospective studies are still needed to verify these results.

## 2.2. Lymphocyte Count and Albumin-Related Composite Markers

The level of lymphocyte count is related to the immune function of the body. Related studies have shown that low lymphocyte count is associated with lower anti-tumor immune response, which may lead to tumor growth and disease progression, thereby shortening survival time [13].

The product of lymphocyte count and Alb level (lymphocyte  $\times$  albumin, LA) was first proposed by Yamamoto [14]. A total of 448 patients with clinical stage II/III rectal cancer were included in this study. Studies have shown that LA is a new prognostic biomarker that can be used to evaluate the prognosis of patients with stage II/III rectal cancer; low LA value was associated with poor OS and PFS.

Prognostic nutritional index (PNI) is calculated as: Alb level + 0.005  $\times$  peripheral blood lymphocyte count, which combines the nutritional status of the whole body and inflammatory response factors, and can reflect the immune function of patients to a certain extent [15]. Li *et al.* [16] included 221 CRC patients and used PNI to construct a prognostic prediction model. The results showed that PNI was an independent risk factor for postoperative complications in CRC patients and a powerful tool for predicting the survival outcome of CRC patients.

Takamizawa *et al.* [17] constructed the COUNT scoring system using Alb, total cholesterol and lymphocyte count, and found that the CONUT score was an independent prognostic factor for OS in patients with stage IV CRC. A meta-analysis also showed that the CONUT score was an actual prognostic factor associated with CRC prognosis. The COUNT scoring system indicates that nutritional and inflammatory status are useful prognostic indicators in CRC patients [18].

Çağlıyan *et al.* [19] composed albumin, lymphocyte, hemoglobin and platelet into a new composite index, which was calculated by hemoglobin level (g/L)  $\times$  albumin level (g/L)  $\times$  lymphocyte count (/L)/platelet count (/L) (HALP), namely HALP score. In this study, 103 patients who underwent CRC surgery were divided into two groups according to the HALP score. The results showed that low HALP score was significantly correlated with the poor prognosis of CRC patients and could be used as an important prognostic marker in the clinical management of CRC patients.

Miyata *et al.* [20] introduced a new prognostic scoring system, the albumin-total lymphocyte count-RAS index (ALRI), which divided 445 patients with stage

I-III CRC who underwent radical resection into high and low groups according to the best cut-off value of ALRI. The results showed that ALRI was an independent prognostic factor for 5-year RFS and OS. The composite index can comprehensively reflect inflammation, nutrition and genetic information, and provide a comprehensive assessment for the prognosis of CRC patients.

### 2.3. C-Reactive Protein and Albumin-Related Composite Markers

C-reactive protein (CRP) is one of the most commonly used indicators to evaluate the inflammatory state of cancer patients before or after surgery, and it also has certain predictive value for the prognosis of malignant tumors. In a large representative study of American adults, a strong dose-response correlation between CRP levels and colorectal cancer mortality was observed [21].

According to the different combinations of serum CRP and Alb values, Forrest *et al.* first reported the value of Glasgow prognostic score (GPS) in the prognosis evaluation of patients with lung cancer [22]. Based on previous studies, McMillan *et al.* [23] proposed the modified Glasgow prognostic score (mGPS) and found that it was more accurate in predicting the prognosis of CRC patients. A retrospective study of 996 patients with stage IV CRC showed that mGPS was an independent prognostic factor for OS in patients with stage IV CRC [17].

C-reactive protein/albumin ratio (CAR) is also an important indicator to evaluate the prognosis of CRC patients. Preoperative CAR is a risk factor for OS in patients undergoing CRC surgery [24]. Son *et al.* [25] combined mGPS and CAR, and the results showed that the two had a synergistic effect and had higher prognostic accuracy in CRC patients than mGPS or CAR alone.

Yang *et al.* [26] combined C-reactive protein, albumin and lymphocyte count into the CALLY index. By collecting the clinicopathological and laboratory characteristics data of 1260 CRC patients, multivariate Cox regression analysis was performed. It was concluded that the CALLY index was independently associated with the OS of CRC patients and had higher prognostic value than classical CRC prognostic factors. The nomogram based on gender, age, CALLY index and TNM stage can provide more accurate prognostic prediction than TNM stage.

Nutritional CRP ratio (NCR) is a new inflammation and nutrition-related blood marker. Stephan *et al.* [27] adopted a two-stage design, including a discovery cohort and an external validation cohort, involving a total of 212 untreated CRC patients; it was found that NCR can be used as an independent prognostic predictor to predict the overall survival of patients with colon cancer. It can also be used as a supplement to the TNM staging system to optimize the risk stratification of colon cancer patients.

### 2.4. Fibrinogen and Albumin-Related Composite Markers

Fibrinogen (Fib) is a protein synthesized by the liver that plays a key role in blood coagulation. When blood vessels are damaged, coagulation factors are activated, and Fib is converted into fibrin to form a blood clot, thereby preventing blood loss

and promoting wound healing. Fib is not only abnormally expressed in coagulation-related diseases, but also increased in varying degrees in cases of surgery, infection, trauma and tumor. Fib is a key inflammatory regulatory factor, which is related to the proliferation, angiogenesis, invasion and metastasis of malignant tumor cells, the formation of inflammatory microenvironment and the level of inflammation [28].

A total of 17 articles were included in a meta-analysis involving 6863 CRC patients. High plasma fibrinogen levels before treatment were significantly associated with poor survival outcomes in CRC patients [29]. In recent years, many studies have found that the ratio of plasma Fib level to serum Alb level (fibrinogen-albumin ratio, FARI) can comprehensively reflect the nutrition, coagulation and inflammation of tumor patients, and can be used as a predictor of survival in cancer patients. In a retrospective study of 604 CRC patients, it was found that CRC patients with high FARI may have shorter disease-free survival (DFS) and OS, which may be related to the poor prognosis of CRC patients [30]. An *et al.* [31] integrated Fib level and serum Alb level into FA scoring system. This study showed that preoperative FA score was an independent prognostic factor for CRC patients undergoing radical resection, which may help to predict the response to chemotherapy in clinical practice. It can also be used as a supplement to the TNM staging system to identify high-risk patients.

### 3. Albumin and Nutrition-Related Composite Indicators

#### 3.1. Advanced Lung Cancer Inflammation Index

Advanced lung cancer inflammation index (ALI) is a marker based on Alb and body mass index (BMI), which was first proposed by Jafri *et al.* [32]. It was originally used for nutritional screening in patients with non-small cell lung cancer. In recent years, studies have found that ALI is also associated with the prognosis of lung cancer, colorectal cancer, gastric cancer and other malignant tumors.

A retrospective study of 662 CRC patients who underwent surgery by Xie *et al.* [33] showed that ALI was an independent predictor of short-term and long-term prognosis in CRC patients, especially in the advanced tumor stage; aLI-based nomogram can provide accurate and individualized prediction of postoperative complication risk and survival rate for CRC patients. Zhang *et al.* [34] analyzed 4010 patients undergoing radical CRC surgery and found that lower ALI was associated with more postoperative complications, worse OS and DFS, and ALI was an independent risk factor for overall complications, OS and DFS.

#### 3.2. Geriatric Nutrition Risk Index

The geriatric nutrition risk index (GNRI) is designed by Bouillanne *et al.* [35] to predict the nutrition-related morbidity and mortality of elderly inpatients by combining Alb level and weight change rate. Low GNRI indicates moderate to severe malnutrition risk, and high GNRI indicates no or low risk malnutrition.

Hayama *et al.* [36] analyzed 259 patients with stage I-III CRC who underwent

radical surgery over 65 years old. The patients were divided into low GNRI (RFS:  $\leq 90.5$ , OS  $\leq 101.1$ ) group and high GNRI (RFS:  $>90.5$ , OS  $> 101.1$ ) group. Multivariate analysis showed that low GNRI group was an independent risk factor for 3-year RFS ( $P = 0.006$ ) and OS ( $P = 0.001$ ) in CRC patients. Kaplan-Meier analysis showed that the 3-year RFS and 3-year OS of the low GNRI group were significantly worse than those of the high GNRI group ( $P = 0.001, 0.0037$ ). Preoperative low GNRI was significantly associated with poor prognosis in elderly CRC patients.

### 3.3. Albumin-to-Globulin Ratio

Albumin-to-globulin ratio (AGR) is a widely available nutritional and inflammatory marker that can be used as a prognostic factor for a variety of malignant tumors. Li *et al.* [37] included a total of 511 CRC patients who underwent radical surgery in two hospitals. Among them, the data of 396 patients were used to train the cohort to explore prognostic factors and construct nomograms; the data of another 115 patients were used to validate the cohort to verify the performance of the nomogram. The results showed that preoperative AGR and PNI were effective immunonutrition indicators for evaluating the prognosis of patients with colorectal cancer. Li *et al.* [38] analyzed the dynamic changes of AGR in cancer patients before and after surgery. In 2844 CRC patients, 2267 non-small cell lung cancer (NSCLC) patients and 507 hepatocellular carcinoma (HCC) patients, the dynamic changes of AGR after surgery, including perioperative change patterns and longitudinal trajectories, are independent prognostic factors for pan-cancer patients.

### 3.4. Hemoglobin to Albumin Ratio

Lv *et al.* [39] combined preoperative hemoglobin and albumin, namely hemoglobin to albumin ratio (HAR), using Cox regression analysis to determine whether HAR is an independent prognostic factor, and verified the survival difference of different TNM stages by Kaplan-Meier curve. The results showed that HAR was an independent predictor of postoperative complications and long-term prognosis in CRC patients, and low HAR was associated with worse survival outcomes, especially in stage III patients.

### 3.5. Albumin-Muscle Fatty Degeneration Scale

Cancer cachexia (characterized by muscle atrophy and muscle fat infiltration) is associated with poor prognosis, but the prognostic value of muscle mass (SMI) and muscle density (SMD) is controversial. Yerim *et al.* [40] proposed albumin-muscle fat mass index (AMG, formula = albumin  $\times$  SMD) to integrate muscle mass and inflammatory nutritional status. The study included 906 patients with stage I-III CRC. Kaplan-Meier survival analysis, multivariate Cox regression, and iAUC (integrated area under the ROC curve) were used to compare the predictive efficacy of AMG with SMI, SMD, and albumin. The results showed that AMG is a new independent prognostic indicator for CRC patients, which integrates muscle mass and inflammatory nutritional status, and is superior to traditional single

indicators.

## 4. Albumin and Other Body Composition-Related Composite Indicators

### 4.1. Albumin-Bilirubin Index

Albumin-bilirubin index (ALBI) is an objective indicator for evaluating liver function and has been used to predict the prognosis of various cancers (such as hepatocellular carcinoma, gastric cancer, and colorectal cancer). Shi *et al.* [41] divided the preoperative ALBI data of 1506 CRC patients into high-value group and low-value group, and compared the clinicopathological characteristics of the two groups. The results showed that ALBI score  $\geq -2.4$  was an independent risk factor for distant metastasis after CRC surgery. Kim *et al.* [42] added the significance of postoperative ALBI score changes on the prognosis of CRC in previous studies; a total of 723 patients with CRC who underwent surgery were included, and interference factors such as preoperative chemoradiotherapy and emergency surgery were excluded. The results showed that the combination of preoperative and postoperative ALBI was an independent prognostic factor for OS in CRC patients, and the predictive efficacy was better than that of single ALBI score. This study confirmed for the first time the independent predictive value of ALBI-trend for the prognosis of CRC, and provided a more accurate prognostic assessment tool for clinical practice.

### 4.2. Preoperative Albumin-to-Alkaline Phosphatase Ratio

Preoperative albumin-to-alkaline phosphatase ratio (AAPR) has shown prognostic value in hepatocellular carcinoma, gastric cancer and other tumors. Mehmet *et al.* [43] included 358 CRC patients who underwent surgery for data analysis. The results showed that low AAPR was associated with a poor survival trend, but it did not reach statistical significance. AAPR failed to be an independent prognostic factor for CRC. Jiang *et al.* [44] retrospectively analyzed the clinical data of 221 patients with stage I-III CRC, performed a series of survival analysis to evaluate the prognostic value of AAPR, and performed univariate and multivariate Cox analysis to determine independent risk factors. The results showed that preoperative AAPR level was a good predictor of postoperative survival in patients undergoing laparoscopic radical CRC surgery, and AAPR  $< 0.495$  was an independent risk factor for postoperative OS reduction.

### 4.3. D-Dimer to Albumin Ratio

D-dimer reflects hypercoagulable state and is associated with tumor metastasis and survival. Wei *et al.* [45] incorporated the preoperative plasma D-dimer to albumin ratio (DAR). A total of 1339 CRC patients were included, excluding interference factors such as neoadjuvant therapy and thrombotic diseases. The results showed that preoperative DAR was an independent predictor of PFS and OS in CRC patients. High DAR indicated poor prognosis and could assist clinical risk stratification.

#### 4.4. Albumin to Carcinoembryonic Antigen Ratio

Carcinoembryonic antigen (CEA) is a traditional prognostic marker for CRC, but the predictive efficacy of CEA alone is limited. Xu *et al.* [46] included 156 patients with stage I-IV CRC who underwent radical surgery. The optimal cut-off value of ALB to CEA ratio (ACR) was determined according to the ROC curve. Kaplan-Meier survival analysis and Cox regression model were used to evaluate the prognostic value. The results showed that ACR was a strong prognostic factor for CRC, and low ACR was significantly associated with worse survival, and the predictive efficacy was better than the traditional single marker.

#### 4.5. Lactate Dehydrogenase to Albumin Ratio

As a key enzyme in the glycolysis pathway, lactate dehydrogenase (LDH) can support the growth of tumor cells. Hu *et al.* [47] combined LDH with albumin to obtain lactate dehydrogenase/albumin ratio (LAR). The study included 1334 CRC patients. The relationship between LAR and OS and DFS was evaluated by using restricted cubic spline (RCS) combined with Cox regression model. A survival nomogram based on LAR and other clinical features was constructed, and its efficacy was evaluated by ROC curve, calibration curve and decision curve analysis (DCA). The results showed that LAR was a reliable prognostic marker for OS and DFS in CRC patients, and its predictive efficacy was better than that of the traditional TNM staging system. LAR-based nomogram can provide more accurate survival prediction for CRC patients. Shu *et al.* [48] included 3868 CRC patients for statistical analysis. The results also showed that LAR was not only an independent predictor of overall complications and major complications in CRC patients, but also an independent predictor of OS and DFS. Wu *et al.* [49] included 382 CRC patients for statistical analysis, and also concluded that LAR is a potential prognostic marker for CRC patients, which is related to tumor stage, but not to tumor differentiation.

### 5. Conclusion

#### 5.1. The Value of Albumin-Related Composite Indicators and Improvement Measures

TNM staging is currently the most commonly used cancer prognosis evaluation system, but the prognosis of patients with the same TNM staging is also quite different, so it is difficult to predict the prognosis of individual TNM staging. In recent years, studies have shown that inflammatory response is involved in the occurrence and development of malignant tumors, and the increase of some inflammatory response indicators suggests that patients have the risk of poor prognosis. Nutritional status is the core variable of the prognosis of cancer patients. Early screening, accurate assessment and individualized nutritional intervention should be the key links of multidisciplinary comprehensive treatment. A number of clinical studies have explored the application value of albumin-related composite markers in postoperative complications, recurrence and prognosis evaluation

of CRC patients, but there are still some shortcomings. First of all, most studies are single-center studies with a small number of samples, and it is difficult to provide sufficient evidence for clinical efficacy. Secondly, because some markers in the blood will change dynamically before, during and after treatment, as Kim *et al.* [42] added postoperative ALBI score changes in previous studies, its predictive efficacy is better than a single ALBI score. Li *et al.* [37] analyzed the dynamic changes of AGR in cancer patients before and after surgery, and the results were also better than a single preoperative indicator. However, most studies only use pre-treatment data. At present, there is a lack of relevant studies showing that biomarkers at a certain time node have more predictive value, and more studies are needed to explore.

## 5.2. Future Prospects

Based on the current research, in the future, machine learning and artificial intelligence algorithms can be used to integrate a large amount of data such as patient body composition and clinical characteristics to build a more accurate risk prediction model. Predict the risk of poor prognosis such as postoperative complications in patients with colorectal cancer in advance, and provide strong support for personalized treatment. A large-scale, long-term follow-up study was conducted to explore the effect of changes in blood components on the long-term quality of life of patients with colorectal cancer, covering multiple dimensions such as physical function, psychological status, and social activities. Through more high-quality randomized controlled trials and multi-center studies, the effectiveness and safety of various composite indicators are verified to provide more reliable evidence for clinical practice. Continuous high-quality research will promote the development of personalized and efficient treatment of colorectal cancer, and improve the survival rate and long-term quality of life of patients.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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