Construction of a novel prediction model based on albumin-hemoglobin score and serum microRNA-497-5p for prognosis of patients with stage II-III colorectal cancer

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Received March 23, 2025; Accepted September 3, 2025

DOI: 10.3892/ol.2025.15432

Abstract. Stage II-III colorectal cancer (CRC) represents the initial phase of tumor invasion and lymph node metastasis. Surgery is the preferred treatment option for patients at this stage, however, due to the complex progression mechanisms of the disease, incomplete tumor resection, postoperative cancer cell metastasis, and the development of drug resistance to chemotherapy often lead to poor prognosis. The present study aimed to investigate the status of poor postoperative prognosis in patients with stage II-III CRC following radical surgery, analyze the impact of preoperative albumin-hemoglobin (ALB-Hb) score and serum microRNA-497-5p (miR-497-5p) levels on adverse outcomes and develop a predictive model for poor prognosis. Baseline data of 154 patients with stage II-III CRC treated at Tianjin Haihe Hospital (Tianjin, China) or Guangzhou First People's Hospital (Guangzhou, China) between December 2021 and December 2024 were retrospectively selected. Patients were stratified into the poor and good prognosis groups based on clinical outcomes. Univariate analysis was performed on baseline characteristics and laboratory parameters. Variables demonstrating notable differences were subsequently evaluated for multicollinearity. Factors without collinearity were incorporated into a Cox proportional hazards regression model to identify determinants of postoperative prognosis in patients treated with radical resection. These predictors were then used to construct a prognostic nomogram, with model accuracy verified through calibration curves. Among the 154 patients with stage II-III CRC, 63 cases (40.91%) had poor prognosis and 91 cases (59.09%) had good prognosis. Univariate and collinearity analyses revealed marked differences in preoperative levels of miR-497-5p, Kallikrein-related peptidase 5 (KLK5), angiopoietin-2 (Ang-2) and ALB-Hb scores, with no collinearity observed ($P<0.05$; variation inflation factor ≤10; tolerance ≥0.1). Cox proportional hazards regression model demonstrated that all these indicators were independent factors influencing poor prognosis following radical surgery in patients with stage II-III CRC (all $P<0.05$). Based on these findings, a nomogram was constructed and calibration curves closely approximated the ideal curve. Preoperative ALB, Hb, miR-497-5p, KLK5, Ang-2 levels and ALB-Hb scores were notable prognostic factors for patients with stage II-III CRC following radical resection, demonstrating high predictive value for poor postoperative outcomes. The present study provided clinically relevant indicators to screen high-risk patients with potential poor prognosis following radical surgery for stages II-III CRC.

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies of the digestive system worldwide. In 2022, it ranked third among all cancers worldwide with >1.9 million new cases reported (1). Although various therapies, including surgery, have markedly improved patient outcomes, the postpertrative survival rat for CRC patients ranges from 30 to 80%, indicating considerable heterogeneity in outcomes among this population. Thus, further clinical research remains necerrssary. Stage II-III CRC represents the initial phase of tumor invasion and lymph node metastasis, for which surgical resection combined with chemotherapy serves as the primary treatment strategy (2). Due to the complex pathological mechanisms, tumor cells exhibit significant heterogeneity. Different subclones show marked variations in treatment sensitivity and microenvironmental adaptability. New blood vessels can supply oxygen and nutrients to cancer cells while secreting factors that promote

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Key words: colorectal cancer, albumin, hemoglobin, serum microRNA

matrix degradation, assisting cancer cells in breaking through physical barriers. Consequently, CRC patients face high rates of postoperative recurrence (30-50%), metastasis (approximately 40%), and mortality (approximately 10.5%) (3). While radical surgery can remove the bulk of tumor, residual cancer cells (undetectable by imaging) retain proliferative capacity and exhibit marked heterogeneity, enabling adaptation to diverse microenvironments, such as inflammatory or hypoxic microenvironments. Furthermore, tumor-induced angiogenesis provides nutrients and oxygen while degrading the extracellular matrix, facilitating vascular and lymphatic invasion, which are key processes driving CRC recurrence and metastasis (4,5). Furthermore, adjuvant chemotherapy often leads to treatment resistance through upregulation of immune checkpoint proteins such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), increased drug efflux pumps and epigenetic modifications in cancer cells, diminishing therapeutic efficacy (6). Investigating prognostic factors following radical resection in patients with stage II-III CRC is essential to prevent adverse outcomes, with particular emphasis on evaluating predictive value.

Tumor biomarkers serve as key indicators for cancer detection and diagnosis. Serum microRNA-497-5p (miR-497-5p) acts as a negative regulator, suppressing tumor cell proliferation and promoting apoptosis via protein tyrosine phosphatase 3 inhibition (7). Postoperative nutritional status in patients with stage II-III CRC markedly influences immune-metabolic function and physiological recovery. Albumin (ALB) and hemoglobin (Hb), which are widely used clinical nutrition markers, serve key roles in prognosis (8). A retrospective analysis of the hematological profiles of patients with ovarian cancer identified that ALB levels are associated with tumor matastasis. Furthermore, a validation study in an esophageal cancer cohort demonstrated that ALB could serve as a potential predictor for distant metastasis, highlighting its value in cross-cancer predictive modeling (9). Similarly, a prognostic study in esophageal squamous cell carcinoma demonstrated an association between low pre-treatment Hb levels with poor outcomes (10). The ALB-Hb score, integrating both nutritional markers, provides a comprehensive assessment of patient prognosis, anemia status, inflammatory burden and malignant progression. The Kallikrein family, particularly Kallikrein-related peptidase 5 (KLK5), contributes to CRC cell proliferation, invasion and metastasis by cleaving proteins into bioactive peptides and degrading extracellular matrix (11). A retrospective cohort study of gastric adenocarcinoma biomarkers demonstrated a notable association between elevated KLK5 levels and poor prognosis in patients with esophageal adenocarcinoma (12). Angiopoeitin-2 (Ang-2), a key regulator of angiogenesis, promotes endothelial cell migration and proliferation (13). The levels of Ang-2 fluctuate with tumor aggressiveness and neovascularization. A retrospective cohort study of 52 patients with hepatocellular carcinoma demonstrated an association between high Ang-2 expression and adverse outcomes (14). While miR-497-5p, ALB-Hb score, KLK5 and Ang-2 are mechanistically associated with cancer progression, their combined prognostic potential remains understudied in CRC (15).

A study on factors influencing lymph node metastasis and recurrence in 801 patients with CRC revealed that the lymph node metastasis rate is ~12.5% following surgical resection and CRC lymphadenectomy (16). Existing clinical studies have demonstrated that patients with CRC face risk of local recurrence after surgery and alternative treatment strategies should be considered if pathological specimens indicate lymph node metastasis (17,18). In summary, patients with stage II-III CRC experience slow recovery of physiological function following radical resection, high risk of recurrence and metastasis, and have a postoperative 5-year survival rate ranging from 50 to 70%, with a progression-free survival rate of 45-65% (19). Therefore, clinical attention should be directed toward investigating postoperative prognosis factors and their predictive value. The present study aimed to construct a prognostic nomogram model for patients with stage II-III CRC following radical resection by analyzing retrospective baseline data. Furthermore, the present study aimed to explore the predictive value of biochemical marker levels for poor prognosis. By evaluating preoperative biochemical indicators, the present study aimed to advance research on tumor biomarkers, further refine the precision of individualized postoperative treatment and improve quality of life.

Materials and methods

Study design. The sample size (20) was calculated using the formula $n=(Z_{1-\alpha/2}+Z_{1-\beta})^2 x(\sigma_1^2+\sigma_2^2)/\delta^2$, where n is the sample size, $Z_{\alpha/2}$ denotes the Z value corresponding to the significance level, $Z_{1-\beta}$ is the key value of the standard normal distribution for a power of 1-β, β is the probability of a type II error, σ_1^2 and σ_2^2 represent the variances of each group and δ^2 is the square of the expected effect size. With $\alpha=0.05$, $\beta=0.2$, $\sigma_1=20$, $\sigma_2=25$ and $\delta=7.23$, the required sample size was determined to be 154 cases. A retrospective study was conducted using baseline data from 154 patients with stage II-III CRC treated at Tianjin Haihe Hospital (Tianjin, China) or Guangzhou First People's Hospital (Guangzhou, China) between December 2021 and December 2024. Among them, 83 were male and 71 were female, with ages ranging from 41 to 79 years (median, 58 years). The present study was approved by the Ethics Committee of Tianjin Haihe Hospital [approval no. 2024HHWZ(A)-003; Tianjin, China] and all procedures were performed in accordance with the Declaration of Helsinki.

Inclusion criteria. Inclusion criteria were as follows: i) Patients who met CRC diagnostic standards per Localized colon cancer: European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up (21); ii) patients who fulfilled radical resection criteria outlined in Treatment of Metastatic Colorectal Cancer: American Society of Clinical Oncology Guideline (22); iii) patients who underwent radical CRC surgery at our hospital with postoperative survival >1 year; iv) patients who had complete medical records in our hospital system, including demographic information, diagnosis reports, surgical details and histopathologically confirmed CRC; v) CRC classified as stage II [no lymph node or distant metastasis, but tumor penetration beyond the intestinal wall (potential invasion into pericolic fat, peritoneum or adjacent organs)] or III (metastasis in ≥1 regional lymph node

without distant spread) by the TNM staging system (23) and vi) no history of preoperative chemotherapy.

Exclusion criteria. Exclusion criteria were as follows: i) Previously diagnosed CRC; ii) non-primary CRC; iii) previous treatment with radical CRC surgery resection; iv) concurrent malignancies in other organs/sites; v) history of invasive surgical procedures within 1 year prior to enrollment and vi) hematological disease.

Baseline data collection. Baseline data from 154 patients with stage II-III CRC were retrieved from the medical system at Tianjin Haihe Hospital and Guangzhou First People's Hospital, including basic demographics [sex, age, weekly exercise frequency (≥5 or <5 times), BMI and type of surgical treatment (intestinal segment or total rectal resection)], tumor disease status [tumor diameter, pathological type (adenocarcinoma and mucinous adenocarcinoma combined with imprinted cell carcinoma), tumor site (rectum, right or left half colon), tumor classification (ulcer and bulge type), invasion depth (T1-2, T3 and T4) and histological differentiation], biochemical indices (ALB, Hb, miR-497-5p, KLK5 and Ang-2) and nutritional score (ALB-Hb score).

Assessment of poor prognosis in patients with stage II-III CRC. Based on follow-up medical records of patients with stage II-III CRC, recurrence, metastasis (cancer metastasized to tissue and organs such as liver and lungs through blood or lymphatic fluid) or death within 1-year post-radical resection were considered adverse prognostic events for patients with stage II-III CRC.

Preoperative assessment of histological differentiation. Histological differentiation was performed through standardized processing of surgically resected specimens. This included fixation in 10% neutral buffered formalin at room temperature for 24-48 h, paraffin embedding, and sectioning (4 μm), followed by hematoxylin-eosin staining. The hematoxylin staining time was 5-8 min and the eosin staining time was 1-3 min, with all staining steps performed under room temperature conditions. Morphology and arrangement characteristics of glandular structures were observed under laser scanning confocal optical microscope to calculate the proportion of gland formation. Histological differentiation in patients with stage II-III CRC was classified as: Well-(>95% gland formation, low malignancy), medium (50-95% gland formation, intermediate malignancy with malignant potential) or low differentiated (5-50% gland formation, rapid growth rate and high malignancy) (24).

Preoperative assessment of tumor classification. The gross tumor morphology was classified based on preoperative malignant features and invasion patterns as follows: Ulcerative (ulcers penetrating the muscular propria with potential transmural invasion) and protruding/polypoid type (luminal-protruding masses with limited peripheral infiltration) (25).

Preoperative assessment of infiltration depth. The depth of tumor invasion in patients with stage II-III CRC was classified as follows: T1-2, tumor invaded submucosa or muscularis propria; T3, tumor penetrated through muscularis propria into subserosa or non-peritonealized pericolic tissue and T4, tumor invaded beyond visceral peritoneum or adjacent organs/structures (26).

Preoperative assay of miR-497-5p. Morning fasting venous blood samples (3 ml) were collected using anticoagulant tubes [cat. no. RT-cxkng; Bosengtian'ai (Beijing) Technology Co., Ltd.]. The samples were stored at 4˚C for ≤24 h before processing. After centrifugation (483 x g, radius, 13.5 cm; duration, 15 min; temperature, 4˚C), the supernatant was separated and stored at -80˚C. All samples were analyzed within 1 week. Total RNA was extracted using the miRNeasy Mini kit (cat. no. 74104; Qiagen GmbH). RT was performed using the PrimeScript RT Master Mix (Perfect Real Time) kit (cat. No. RR036A; TaKaRa Bio Inc.), follow the manufacturer's instructions. Reverse transcription-quantiative PCR was performed under the following thermocycling conditions: Initial denaturation at 95˚C for 2 min, followed by 35 cycles of denaturation (95˚C; 5 sec), annealing (56˚C; 5 sec) and extension (72˚C; 35 sec). The primers were as follows: miR-497-5p forward (F), 5'-CAGCAGCACACT GTGGTTTGT-3' and reverse (R), 5'-TAGCCTGCAGCA CACTGTGGT-3' and U6 (internal control) F, 5'-ATTGGA ACGATACAGAGA AGATT-3' and R, 5'-GGA ACGCTT CACGA ATTTG-3'. Quantitative detection was performed using a fluorescent dye (Product No. 4913850001; Roche). The relative expression of miR-497-5p calculated using the $2^{-\Delta\Delta Cq}$ method (27).

Preoperative analysis of ALB and Hb. Plasma was separated by centrifugation (11,180 x g; radius, 10 cm; duration, 10 min; temperature, 4˚C). ALB levels were measured colorimetrically using the bromocresol green method at a wavelength of 628 nm (reaction time 10 min) at room temperature, while Hb levels were determined using the cyanmethemoglobin method at a wavelength of 540 nm (reaction time 5 min). PBS) was used as a blank control. All experiments involving samples and standards were independently repeated three times.

Preoperative analysis of KLK5. Morning fasting venous blood samples (5 ml per patient) were transferred to anticoagulant tubes. The samples were stored at 4˚C for ≤24 h prior to processing. The samples were centrifuged (11,180 x g; radius, 10 cm; duration, 10 min; temperature, 4˚C) to separate the supernatant, which was stored at -80˚C. All analyses were completed within 1 week. KLK5 protein expression in patients with stage II-III CRC was detected using an ELISA kit (cat. no. KLK5; JINGMEI) in strict accordance with the manufacturer's instructions.

Preoperative analysis of Ang-2. Fasting antecubital venous blood samples (5 ml) were transferred to anticoagulant tubes. Following anticoagulation treatment, samples were stored at 4˚C for ≤24 h. The samples were centrifuged (11,180 x g; radius, 10 cm; duration, 10 min; temperature, 4˚C) to separate the supernatant, which was stored at -80˚C. All measurements were completed within 1 week using a commercial Ang-2 ELISA kit (cat. no. EK1215; MultiSciences) accordance with the manufacturer's instructions to determine Ang-2 levels.

Preoperative score of ALB-Hb. The ALB-Hb scoring system was used to assess nutritional status and anemia severity. ALB was scored as follows: 0, ≥35 g/l; 1, 30-35 g/l; 2, 25-30 g/l; 3, 20-24 and 4, <20 g/l. Hb was scored as follows: 0, ≥12 g/dl; 1, 10-12 g/dl; 2, 7-9 g/dl and 3, <7 g/dl. A higher composite total score indicated poorer preoperative nutritional health status, suggesting a negative association between the composite score and health status (28).

Observation indicators. Patients with stage II-III CRC were stratified into poor [experiencing recurrence, metastasis (hematogenous/lymphatic spread to liver/lungs) or death within 1-year post-radical resection] and good prognosis group (no recurrence, metastasis, or death events within 1 year after radical resection, with both the 1-year overall survival rate and progression-free survival rate being 100%). Statistical analysis was performed using 2025 SPSSAU (spssau.com/indexs.html). Significant variables were identified through univariate analysis of baseline characteristics. After multicollinearity testing, a Cox regression model was empoloyed to analyze the hazard ratio (HR), 95% CI and concordance (C)-index. The nomogram function was used to transform the model into a nomogram, and calibration curves were validated using the Bootstrap resampling method with 1,000 repetitions to evaluate the consistency between the predicted probabilities of the nomogram and the actual observed probabilities).

Statistical analysis. Statistical analysis was performed using SPSS (version 27.0; IBM Corp.). This study is based on data from three independent experimental replicates. Categorical data were analyzed by χ^2 test. Measurement data were assessed for normal distribution using the Shapiro-Wilk test, with normally distributed data expressed as mean ± SD and compared using unpaired t-test. Non-normally distributed data were presented as median (25 and 75th percentile) and analyzed using non-parametric Mann Whitney U test (Z-score). Variables demonstrating significant differences were incorporated into a Cox proportional hazards regression model (variables were initially screened using univariate Cox proportional hazards regression, and those with P<0.05 were included in the multivariate Cox proportional hazards regression model), with poor postoperative prognosis following radical resection as the dependent variable and baseline characteristics as independent variables. A stepwise selection method (entry criteria, P=0.05) was used to identify significant prognostic factors. The model evaluated the predictive value of each factor by calculating HRs with corresponding 95% CIs. P<0.05 was considered to indicate a statistically significant difference.

Results

Prognosis of patients with stage II-III CRC following radical surgery. Among 154 patients, 63 patients (40.91%) were classified into the poor prognosis group, while 91 (59.09%) were classified as good prognosis group (data not shown). Within the poor prognosis group, 49 patients (77.78%) demonstrated recurrences, eight (12.70%) demonstrated metastases and six (3.90%) died. These results indicated that ~60% of patients with stage II-III CRC achieved favorable postoperative recovery following radical resection, although a notable proportion experienced a poor prognosis.

Univariate analysis of factors affecting the prognosis of patients with stage II-III CRC. Preoperative levels of ALB (27.26±3.58 vs. 30.61±3.74 g/l), Hb [5.94 (4.80, 7.60) vs. 9.23 (8.20, 10.40) g/dl] and miR-497-5p (0.35±0.04 vs. 0.41±0.02; all P<0.001) were significantly lower in the poor compared with the good prognosis group (Table I). By contrast, KLK5 (3.82±1.41 vs. 3.28±1.33 ng/ml), Ang-2 [3.32 (3.20, 3.60) vs. 3.19 (3.00, 3.40) g/l] and ALB-Hb score [5.00 (4.00, 5.00) vs. 3.00 (2.00, 4.00); all P<0.001] were significantly higher in the poor prognosis group. All comparisons were significant (ALB, t=5.561; Hb, Z=-7.742; miR-497-5p, t=12.275; KLK5, t=2.417; Ang-2, Z=-4.236; ALB-Hb, Z=-7.727), which suggested these biomarkers may influence the prognosis in patients with stage II-III CRC.

Dependent and independent variable assignment and multicollinearity analysis. Postoperative prognosis in patients with stage II-III CRC was set as the dependent variable (0 for good prognosis and 1 for poor prognosis; Table II). Preoperative ALB, Hb, miR-497-5p, KLK5 and Ang-2 levels and ALB-Hb score were assigned as independent variables (actual measured values). The collinear analysis revealed that there was no multicollinearity between levels of preoperative ALB, Hb, miR-497-5p, KLK5 and Ang-2 and ALB-Hb scores (variation inflation factor ≤10 and tolerance ≥0.1), which indicated their suitability for inclusion in the Cox proportional hazards regression model.

Cox proportional risk regression analysis of factors affecting the prognosis of patients with stage II-III CRC. Multivariate Cox proportional hazards regression analysis of significant univariate variables revealed that preoperative ALB, Hb, miR-497-5p, KLK5 and Ang-2 levels and ALB-Hb score were factors influencing the prognosis for patients with stage II-III CRC following radical resection (all P<0.05; Table III). These parameters were incorporated into the prognosis model development for patients with stage II-III CRC.

Nomogram, calibration curves for predicting the prognosis of patients with stage II-III CRC. A nomogram and calibration curve were constructed based on the aforementioned analysis (Fig. 1). The calibration curve closely approximated the ideal curve, with a C-index of 0.803 (95% CI, 0.802-0.804). The nomogram demonstrated good accuracy and predictive performance, indicating high accuracy of the Cox proportional hazards prediction model. These results suggested that preoperative ALB, Hb, miR-497-5p, KLK5 and Ang-2 levels and ALB-Hb score have significant predictive value for poor prognosis in patients with stage II-III CRC.

Discussion

For patients with stage I CRC, the 5-year survival rate after surgery is >90%, indicating a high surgical success rate, while patients with stage IV CRC (with distant metastasis) who undergo palliative surgery, the 5-year survival rate is less than 10%. However, stage II-III CRC constitutes the predominant

Table I. Univariate analysis of factors affecting prognosis of patients with stage II-III CRC.

A, Demography

Characteristic	n	Poor prognosis group (n=63)	Good prognosis group (n=91)	χ^2/t/Z-score	P-value
Sex				0.117	0.732
Male	83	35	48		
Female	71	28	43		
Mean age, years		59.25±6.32	57.96±7.93	1.076	0.284
Weekly exercise frequency				1.922	0.166
≥5	54	19	35		
<5	100	44	56		
Median BMI, kg/m^2	-	18.51 (17.00, 19.50)	18.05 (17.30, 19.60)	-0.404	0.686
Type of resection				0.154	0.695
Intestinal segment	64	25	39		
Total rectal	90	38	52		

B, Tumor disease status

Characteristic	n	Poor prognosis group (n=63)	Good prognosis group (n=91)	χ^2/t/Z-score	P-value
Median tumor diameter, cm		5.54 (4.20, 6.80)	4.96 (4.20, 6.90)	-0.382	0.702
Pathological type				0.059	0.808
Adenocarcinoma	138	56	82		
Mucinous adenocarcinoma + signet ring cell carcinoma	16	7	9		
Tumor site				0.192	0.908
Rectum	63	27	36		
Right half colon	37	15	22		
Left half colon	54	21	33		
Tumor classification				0.283	0.595
Ulcer	24	11	13		
Bulge	130	52	78		
Invasion depth				3.616	0.164
T_{1-2}	33	12	21		
T_3	82	30	52		
T_4	39	21	18		
Histological differentiation				1.467	0.226
Well-medium	92	34	58		
Low	62	29	33		

C, Biochemical indices

Characteristic	n	Poor prognosis group (n=63)	Good prognosis group (n=91)	χ^2/t/Z-score	P-value
Mean ALB, g/l		27.26±3.58	30.61±3.74	5.561	<0.001
Median Hb, g/dl		5.94 (4.80,7.60)	9.23 (8.20,10.40)	-7.742	<0.001
Mean miR-497-5p		0.35±0.04	0.41±0.02	12.275	<0.001
Mean KLK5, ng/ml		3.82±1.41	3.28±1.33	2.417	0.017
Median Ang-2, g/l		3.32 (3.20,3.60)	3.19 (3.00,3.40)	-4.236	<0.001

Table I. Continued

D, Nutritional scores

Characteristic	n	Poor prognosis group (n=63)	Good prognosis group (n=91)	χ^2/t/Z-score	P-value
Median ALB-Hb score		5.00 (4.00,5.00)	3.00 (2.00,4.00)	-7.727	<0.001

CRC, colorectal cancer; ALB, albumin; Hb, hemoglobin; miR, microRNA; KLK5, Kallikrein-related peptidase 5; Ang-2, angiopoeitin-2.

Table II. Dependent and independent variable assignment and multicollinearity analysis.

Factor	VIF value	Tolerance
ALB levels	4.059	0.246
Hb levels	4.005	0.250
ALB-Hb score	8.753	8.753
miR-497-5p levels	1.069	0.936
KLK5 levels	1.040	0.962
Ang-2 levels	1.167	0.857

VIF, variation inflation factor; ALB, albumin; Hb, hemoglobin; miR, microRNA; KLK5, Kallikrein-related peptidase 5; Ang-2, angiopoeitin-2.

clinical cohort, which makes their postoperative outcomes relevant for clinical practice. Investigating prognostic factors and their predictive value in these patients may directly guide post-resection intervention strategies and prolong survival (29). In the present study, 154 patients with stage II-III CRC were stratified by postoperative outcomes (63 in the poor and 91 in the good prognosis group). Preoperative ALB, Hb, miR-497-5p, KLK5 and Ang-2 levels and ALB-Hb score were significant prognostic factors with high predictive value for adverse outcomes.

miR-497-5p, a recognized tumor suppressor, is frequently downregulated in patients with CRC (30). Long non-coding RNA (lncRNA) AC009022.1 exacerbates CRC progression by inhibiting miR-497-5p expression, thereby enhancing cancer cell proliferation, migration and invasion (31). Elevated AC009022.1 levels are associated with poor patient prognosis, a finding consistent with existing research on lncRNAs in CRC advancement (27). A previous study confirmed that the B cell lymphoma-2/miR-497 values are associated with cancer metastasis and shorter survival in patients with CRC (32). The poor prognosis group exhibited significantly lower preoperative miR-497-5p levels compared with the good prognosis group. Located on human chromosome 17p13.1, miR-497-5p serves as a molecular sponge to upregulate solute carrier family 7 member 5, a transporter of large neutral amino acids associated with tumor proliferation and invasiveness. This mechanism modulates cell cycle progression, apoptosis and other oncogenic processes (33). Furthermore, miR-497-5p targets multiple oncogenes (for example, 26S proteasome non-ATPase regulatory subunit 7, a putative CRC target) by binding their 3'-untranslated regions, suppressing gene expression and promoting cancer cell apoptosis (34,35). In patients with stage II-III CRC with limited lymph node/metastasis spread, post-resection residual cancer cells may disseminate via hematogenous/lymphatic routes. In this process, miR-497-5p slows disease progression by decreasing the resistance to chemotherapeutic drugs such as oxaliplatin, irinotecan or 5-fluorouracil and affecting cell function. By contrast, patients with lower miR-497-5p levels demonstrate no inhibition of malignant biological behaviors such as invasion, metastasis, and proliferation in CRC cells. Therefore, patients with stage II-III CRC with low preoperative miR-497-5p levels demonstrate more severe malignant disease after surgery, resulting in a higher incidence of adverse prognosis.

There is an association between metastasis and recurrence of cancer following radical CRC surgery with the weakening of the immune response and delayed wound healing (36). Proteins are key for synthesis and secretion of immune cells; insufficient protein levels may impair the production and function of immune cells, leading to a decrease in immune cell count and further weakening the immune response capacity (37). The tissue wound healing process requires a large amount of protein, iron and other nutrients to support the synthesis of collagen for repair. Furthermore, a regression cohort study of patients with hepatocellular carcinoma reported that nutritional status-associated scores helped predict the prognosis of patients treated with anti-hepatocellular carcinoma therapy (38). The present study revealed that the poor prognosis group had significantly lower ALB and Hb levels but higher ALB-Hb scores compared with the good prognosis group. These results suggested that nutritional status notably impacted postoperative recovery in patients with stage II-III CRC after radical resection, which aligns with previous research (39). ALB and Hb are key elements in the assessment of nutritional status and immune function. ALB is synthesized by liver with a normal range of 40-55 g/l; low expression is common in malnourished individuals (40). Hb is a key indicator for the assessment of anemia, with a normal range of 120-160 g/l in male and 110-150 g/l in female patients; low expression commonly presents in anemic individuals with insufficient oxygen supply (41). Patients with cancer exhibit a high metabolic state because the consumption of large amounts of nutrient energy required for growth of malignant tumors weakens the immune system and recovery ability of body (42). Certain patients with stage II-III CRC demonstrate metastasis to neighboring tissue and organs before surgery and incomplete surgical removal leads to continuous consumption of energy, which triggers malnutrition. Furthermore, postoperative chemotherapeutic drugs damage healthy cells, leading to

Table III. Multivariate Cox proportional risk regression analysis of factors affecting the prognosis of patients with stage II-III CRC.

Factors	β	SE	Z-score	P-value	OR	HR 95%CI
ALB levels	-0.271	0.039	-6.892	<0.001	0.763	0.706-0.824
Hb levels	-0.161	0.059	-2.703	0.007	0.851	0.758-0.957
ALB-Hb score	1.353	0.147	9.215	<0.001	3.868	2.901-5.157
miR-497-5p levels	-6.518	1.414	-4.610	<0.001	0.001	0.000-0.024
KLK5 levels	0.214	0.089	2.403	0.016	1.238	1.040-1.474
Ang-2 levels	1.353	0.147	9.215	<0.001	3.868	2.901-5.157

CRC, colorectal cancer; ALB, albumin; Hb, hemoglobin; miR, microRNA; KLK5, Kallikrein-related peptidase 5; Ang-2, angiopoeitin-2; HR, hazard ratio; OR, odds ratio; SE, standard Error.

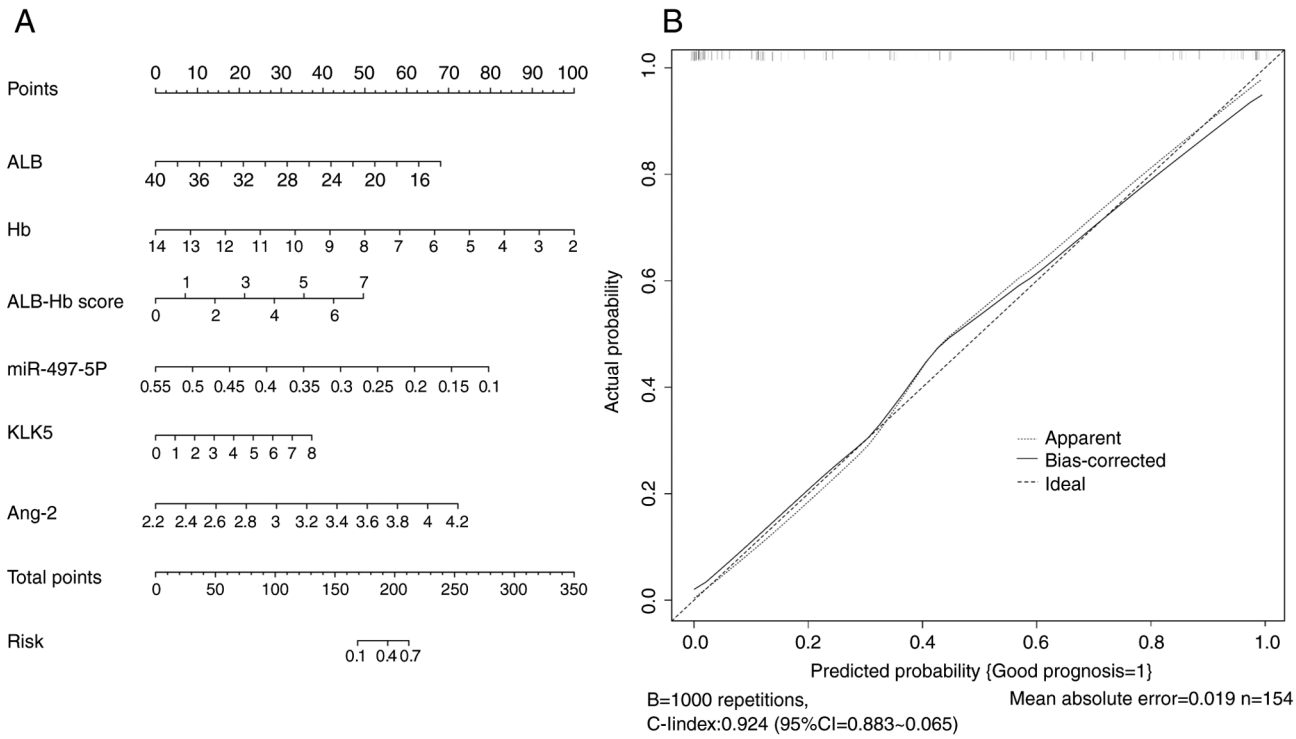

Figure 1. Nomogram and calibration curves to predict the prognosis of patients with stage II-III colorectal cancer. (A) Nomogram; (B) Calibration curve. ALB, albumin; Hb, hemoglobin; miR, microRNA; KLK5, Kallikrein-related peptidase 5; Ang-2, angiopoeitin-2.

gastrointestinal dysfunction and affecting nutrient absorption, thus aggravating malnutrition (43). Therefore, nutrition-associated indicators such as preoperative levels of ALB, Hb and ALB-Hb scores boast predictive value for prognostic outcomes in patients undergoing radical surgery for stage II-III CRC.

Inflammation is a key factor in the development, metastasis and drug resistance formation of various types of cancer (44), including colorectal, liver, pancreatic cancer, gastric cancer, and non-small cell lung cancer. The inflammatory response activates KLK5, which exacerbates the systemic inflammatory response via the secretion of pro-inflammatory factors such as Tumor Necrosis Factor-α, Interleukin-1β (IL-1β), and Interleukin-6 (IL-6), providing a chronic inflammatory environment for tumor growth and accelerating tumor progression (45). KLK5 participates in tumor neovascularization by cleaving extracellular matrix components such as laminin, fibronectin, and type IV collagen, facilitating tumor cell penetration through the basement membrane. Furthermore, KLK5 increases intratumoral vascular permeability, enhancing tumor cell transmigration across vascular walls and lymphatic vessels (46). Ang-2 is associated with intratumoral angiogenesis, tumor invasiveness and metastatic potential (47). Ang-2 is also involved in tumor angiogenesis, growth and metastasis by increasing vascular permeability and reducing the ability of the immune system to identify and remove tumor cells (48). Thus, the incidence of poor prognosis in patients with cancer increases with Ang-2 levels (49). The present study demonstrated that preoperative Ang-2 levels in the poor prognosis group were higher compared with those in the good prognosis group,

indicating that aberrantly high Ang-2 may predict adverse outcomes following radical resection in stage II-III CRC. Furthermore, patients with stage II-III CRC with elevated preoperative KLK5/Ang-2 levels demonstrated significantly higher postoperative inflammation risks. Within the chronic inflammatory microenvironment, sustained KLK5 activation promotes tumor angiogenesis and vascular permeability, facilitating nutrient supply for cancer progression. This cascade further elevates Ang-2 levels, exacerbating vascular leakage and causing uneven chemotherapeutic distribution while enhancing circulating tumor cell invasiveness and distant metastasis potential, collectively contributing to treatment resistance and poor prognosis, thereby establishing preoperative Ang-2 as a predictive biomarker for adverse outcomes post-radical resection (50,51).

CRC is characterized by high postoperative recurrence rates, which makes long-term prognostic monitoring clinically key. However, the present study had limitations. The present study only investigated 1-year postoperative outcomes in patients with stage II-III CRC, representing a relatively short follow-up period. As a two-center retrospective analysis, the present study did not directly predict the long-term prognosis. Furthermore, the results may be influenced by the accuracy of original data. Future research should focus on long-term outcomes post-radical resection by integrationg more clinicopathological features (such as perineural invasion, lymphovascular invasion, and number of lymph nodes examined), imaging characteristics, and nutritional indicators (weight change, dietary habits, physical activity levels) to develop a more comprehensive predictive model.

In summary, ~60% of patients with stage II-III CRC achieved favorable recovery within 1 year of radical tumor resection, while a subset experienced poor postoperative outcomes. Preoperative levels of ALB, Hb, miR-497-5p, KLK5 and Ang-2, along with ALB-Hb score, were identified as notable prognostic factors with high predictive value and clinical relevance. These biomarkers should be incorporated into clinical screening protocols to guide targeted interventions to potentially improve patient prognosis in future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QW, HW and LL conceived and designed the present study. QW and HW confirm the authenticity of all the data in the present study. ZW contributed to data collection and analysis. HW wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tianjin Haihe Hospital (Tianjin, China) [approval no. 2024HHWZ(A)-003] and all procedures were performed in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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