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ORIGINAL ARTICLE

Low preoperative serum albumin in colon cancer: a risk factor for poor outcome

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Abstract
Objective The number of colon cancer patients is increasing worldwide. Malnutrition and comorbidities are frequently associated with these patients. The relationships between the preoperative malnutrition and the outcomes of colon cancer patients are unclear; this study aimed to clarify these issues.
Methods A total of 3,849 consecutive colon cancer patients were enrolled in an analysis of short-term outcomes and 2,529 patients were included in an analysis of the long-term outcomes. These patients were divided into the hypoalbuminemic and normal groups according to the definition of hypoalbuminemia (serum albumin<35 g/L).
Results Advanced age, female gender, abnormal CEA levels, right colon or large tumors, mucinous adenocarcinoma, poor differentiation, stage II cancer, TNM advancing T stage, old cardiovascular accident, diabetes, and liver cirrhosis were more likely to be associated with hypoalbuminemia. Hypoalbuminemic patients had a higher rate of postoperative mortality and morbidity, including complications related to wounds, lungs, the urinary system, and anastomosis. The 5-year overall survival rates of patients with normal albumin and hypoalbuminemia were 78.0% and 60.0%, respectively ($P<0.0001$), and the 5-year relapse-free survival rates were 78.9% and 73.5%, respectively ($P=0.0042$). In a multivariate analysis, the albumin level was also significantly correlated with 5-year overall survival (<35 vs. ≥35, HR 1.75; 95% CI 1.49–2.08) and 5-year relapse-free survival (<35 vs. ≥35, HR 1.28; 95% CI 1.04–1.56).
Conclusions Hypoalbuminemia is a predictor of poor surgical outcomes of colon cancer and is a poor prognosis factor for long-term survival of colon cancer after curative operation.

Keywords Hypoalbuminemia · Colon cancer · Outcome · Survival · Comorbidity

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Introduction

The number of cases of colon cancer is increasing in Taiwan and in other developed countries; the number of colectomies performed is also increasing. Malnutrition is a commonly encountered problem when treating colon cancer patients. Serum albumin is closely correlated with the degree of malnutrition and is a regularly used, simple marker of nutrition status [1, 2]. According to some previous studies, patients with hypoalbuminemia who underwent gastrointestinal tract surgery have significantly higher postoperative morbidity and mortality [3, 4]; however, some other studies report no significant differences [5, 6]. Hypoalbuminemia has also been used as a

predictor of the survival of colorectal cancer patients [7–11], although the results are controversial.

Hypoalbuminemia in cancer patients does not only result from the cancer itself, but may also result from associated comorbidities [12, 13]. Furthermore, some comorbidities influence postoperative mortality and morbidity [13–16], as well as the survival of cancer patients [16–18]. There is little information concerning the relationships between hypoalbuminemia, comorbidities, and the outcomes of colon cancer patients. Therefore, this study aimed to clarify these relationships and determine if preoperative hypoalbuminemia might be useful for predicting the postoperative mortality, morbidity, and prognosis of colon cancer patients after receiving an elective and curative surgery.

Patients and methods

From January 1995 to December 2008 inclusive, a total of 3,849 consecutive patients with colon cancer underwent elective and potentially curative surgery at Chang Gung Memorial Hospital. Excluding 117 patients without preoperative serum albumin data (3.0% of colon cancer patients in our hospital), the remaining 3,732 patients were included in the analysis of short-term outcomes in this study. A total of 2,529 patients who received surgery more than 5 years ago and survived for more than 30 days after surgery were included in the analysis of long-term outcomes.

Detailed information regarding patient- and tumor-related variables and follow-up statuses was retrieved from the Colorectal Section Tumor Registry at Chang Gung Memorial Hospital. All data in this registry were collected prospectively. Patient demographic data, tumor characteristics, operative details, and short- and long-term postoperative outcomes were included in the data collection.

Patient-related variables consisted of age, gender, serum albumin level, CEA level, and comorbidities. The patients were divided into two age groups: ≤65 years (young) and >65 years (old). Hypoalbuminemia was defined as serum albumin<35 g/L. CEA levels>5 ng/ml were defined as abnormal. The following comorbidities were recorded: hypertension, cardiac disease, old cardiovascular accident (CVA), asthma, diabetes, hepatitis, liver cirrhosis, thyroid disease, and other comorbidities, such as peptic ulcer disease, urolithiasis, and gall stones.

Tumor-related factors consisted of location, size, morphology, histology, degree of differentiation, and stage. Tumor stages were determined according to the AJCC TNM staging system (sixth edition)[19]. Tumor location was categorized as right colon (from the cecum to transverse colon) or left colon (from the splenic flexure to sigmoid colon). Tumor morphology was divided into polypoid (include flat and polypoid tumors) and non-polypoid (include ulcerative and infiltrative tumors).

According to the definition of hypoalbuminemia, patients were divided into two groups: hypoalbuminemic or normal. Each patient underwent standard oncological resection of colonic tumors and received routine postoperative care.

The short-term outcomes of surgery include postoperative morbidity and mortality. Postoperative morbidities were defined as complications within 30 days of the primary surgery and classified as wounds (infection or dehiscence), and pulmonary (atelectasis or pneumonia), cardiovascular (myocardial infarction, stroke, or embolism), urinary (bladder dysfunction or urinary tract infection), gastrointestinal (obstruction, ileus, or bleeding), anastomotic (leakage, stenosis, abscess formation, or peritonitis), and other conditions. Postoperative mortality was defined as death within 30 days of the primary surgery.

The endpoints of the long-term outcome study were overall survival (OS) and relapse-free survival (RFS). OS was calculated by death from any cause, and RFS was calculated by considering any relapses from the index cancer as the only events for survival analyses. Relapses of cancer were confirmed histologically or radiographically.

Statistical methods

Quantitative data were compared using Pearson's chi-squared and Fisher's exact tests. For multivariate analysis, logistic regression analysis was used to determine any confounding factors of mortality and morbidity; variables where $P<0.05$ in the univariate analyses were used in the multivariate analysis. OS and RFS were calculated by univariate analysis using the Kaplan–Meier method. Survival curves were constructed using the Kaplan–Meier method and were compared using the log-rank test. In order to control for confounding factors, the Cox regression model was used for multivariate analysis in which variables for which $P<0.05$ in the log-rank analyses were used. All P values were two-tailed, and were considered statistically significant if <0.05.

Results

The clinicopathologic characteristics of the patients categorized by serum albumin data are presented in Table 1. The mean ages (standard deviation) of patients in short- and long-term outcome analyses were 63.14 years (13.58) and 62.47 years (13.59), respectively. The proportion of hypoalbuminemia in stage I, II, and III colon cancer patients with elective surgery was 18.6%.

Table 1 Characteristics of patients and tumors in short- and long-term outcome analyses

Variable	Category	Short-term outcome analysis			Long-term outcome analysis		
		No. of cases (*N*=3,732)	Hypoalbuminemic[a] (*N*=693)		No. of cases (*N*=2,529)	Hypoalbuminemic[a] (*N*=480)	
			No. (%)[b]	*P* value		No. (%)[b]	*P* value
Age(years)	≦65	1,930	231 (12.0)	<0.001	1,338	167 (12.5)	<0.001
	>65	1,802	462 (25.6)		1,191	313 (26.3)	
Sex	Male	1,968	341 (17.3)	0.039	1,315	232 (17.6)	0.074
	Female	1,764	352 (20.0)		1,214	248 (20.4)	
Tu location	Right	1,449	337 (23.3)	<0.001	981	237 (24.2)	<0.001
	Left	2,283	356 (15.6)		1,548	243 (15.7)	
Tu morphology	Polypoid	928	189 (20.4)	0.104	657	132 (20.1)	0.398
	Nonpolypoid	2,804	504 (18.0)		1,872	348 (18.6)	
Tu size	≦5 cm	2,354	255 (10.8)	<0.001	1,553	181 (11.7)	<0.001
	>5 cm	1,378	438 (31.8)		976	299 (30.6)	
TNM stage	I	488	48 (9.8)	<0.001	321	36 (11.2)	<0.001
	II	1,731	385 (22.2)		1,206	272 (22.6)	
	III	1,513	260 (17.2)		1,002	172 (17.2)	
TNM T stage	T1	268	24 (9.0)	<0.001	164	15 (9.1)	<0.001
	T2	316	33 (10.4)		217	24 (11.1)	
	T3	1,540	256 (16.6)		773	137 (17.7)	
	T4	1,608	380 (23.6)		1,375	304 (22.1)	
TNM N stage	N0	2,218	433 (19.5)	0.139	1,527	308 (20.2)	0.141
	N1	996	177 (17.8)		643	114 (17.7)	
	N2	518	83 (16.0)		359	58 (16.2)	
Histologic type	Adenocarcinoma	3,394	610 (18.0)	0.011	2,296	422 (18.4)	0.040
	Mucinous	310	77 (24.8)		216	55 (25.5)	
	Signet-ring cell	25	4 (16.0)		17	3 (17.6)	
Histologic grade (differentiation)	Well	659	111 (16.8)	0.001	514	87 (16.9)	0.028
	Moderate	2,802	507 (18.1)		1,865	353 (18.9)	
	Poor	265	74 (27.9)		150	40 (26.7)	
Preoperative CEA	<5	2,307	332 (14.4)	<0.001	1,553	245 (15.8)	<0.001
	≥5	1,313	324 (24.7)		893	212 (23.7)	

Tu Tumor

[a] Patients with preoperative hypoalbuminemia

[b] Number of patients (proportion of patients) with preoperative hypoalbuminemia in each caterogy

In short-term outcome analysis, there were no significant differences in tumor morphology and N stage of the TNM system between the normal and hypoalbuminemic groups. Advanced age, females, abnormal CEA levels, right colon tumors, large tumors (tumor size>5 cm), mucinous adenocarcinoma, poor differentiation, stage II cancer, and advancing T stage of the TNM system were more likely to be associated with hypoalbuminemia. Similar results were found in the long-term outcome analysis—except there was no significant difference related to gender.

The comorbidities of patients in the two groups are presented in Table 2. There was no significant difference with respect to associated medical diseases between the two groups (52.9% and 56.4% of normal and hypoalbuminemic patients, respectively; $P=0.098$). There was no significant difference in the occurrence of hypertension, cardiac disease, asthma, hepatitis, and thyroid disease between the two groups. However, CVA ($P<0.001$), diabetes ($P<0.001$), liver cirrhosis ($P<0.001$), other comorbidities ($P<0.001$), and combined comorbidities ($P<0.001$) were significantly more likely to be associated with hypoalbuminemia.

Short-term outcomes

The analysis of postoperative morbidity and mortality in both groups is presented in Table 3. The postoperative mortality rate was 1.2% (45 of 3,732), and the morbidity

Table 2 Associated comorbidities of patients according to preoperative albumin level

Variable	Short-term outcome analysis			Long-term outcome analysis		
	Normal albumin (*N*=3,039) No. (%)	Hypoalbuminemic (*N*=693) No. (%)	*P* value	Normal albumin (*N*=2,049) No. (%)	Hypoalbuminemic (*N*=480) No. (%)	*P* value
No comorbidity	1,430 (47.1)	302 (43.6)	0.098	1,023 (49.9)	221 (46.0)	0.125
Hypertension	821 (27.0)	179 (25.8)	0.525	484 (24.1)	108 (22.5)	0.456
Cardiac disease	262 (8.6)	61 (8.8)	0.882	162 (7.9)	41 (8.5)	0.645
Old CVA	110 (3.6)	46 (6.6)	0.001	71 (3.5)	31 (6.5)	0.003
Asthma	93 (3.1)	26 (3.8)	0.339	70 (3.4)	19 (4.0)	0.562
Diabetes	380 (12.5)	126 (18.2)	<0.001	227 (11.1)	80 (16.7)	0.001
Hepatitis	136 (4.5)	32 (4.6)	0.870	82 (4.0)	21 (4.4)	0.710
Liver cirrhosis	23 (0.8)	25 (3.6)	<0.001	17 (0.8)	15 (3.1)	<0.001
Thyroid disease	57 (1.9)	14 (2.0)	0.759	30 (1.5)	11 (2.3)	0.196
Others	643 (21.2)	190 (27.4)	<0.001	422 (20.6)	127(26.5)	0.005

rate was 11.7% (436 of 3732). Compared to patients with normal serum albumin, hypoalbuminemic patients have a higher rate of postoperative morbidity and mortality, as well as complications related to wounds, lungs, urinary system, and anastomosis. There was no significant difference between the two groups with regard to complications of the cardiovascular or gastrointestinal systems. In these variables, hypoalbuminemia was the only significant factor related to anastomostic complications. In multivariate analysis, TNM stage, age, sex, each category of comorbidity, CEA level, tumor location, tumor morphology, tumor size, histologic type and grade were taken into analysis if it is significant factor in univariate analysis.

Hypoalbuminemia was an independent factor for postoperative mortality, morbidity, and complications related to wounds, lungs, and the urinary system (Tables 4 and 5). Advanced age, males, asthma, and hypoalbuminemia were significantly associated with morbidity. Advanced age, diabetes, liver cirrhosis, abnormal CEA level, and hypoalbuminemia were significantly associated with mortality. Old CVA and hypoalbuminemia were significantly associated with complications related to wounds. Advanced age, abnormal CEA level, hypoalbuminemia, nonpolypoid tumor, and poorly differentiated tumors were significantly associated with complications of the lungs. Advanced age and hypoalbuminemia were significantly associated with complications of the urinary system. Males, asthma, mucinous adenocarcinoma, and TNM stage II cancer were significantly associated with complications of the gastrointestinal system.

Long-term outcomes

For the 2,529 patients who underwent curative surgery between January 1995 and December 2004 and survived more than 30 days after the operation, the 5-year OS and RFS rates were 74.6% and 77.9%, respectively. When stratified by preoperative serum albumin levels, the 5-year OS rates of patients with normal albumin and hypoalbumi-

Table 3 Postoperative morbidity and mortality according to preoperative albumin level

Category	Normal albumin (*N*=3,039) No. (%)*	Hypoalbuminemic (*N*=693) No. (%)*	*P* value
With any morbidity	287 (9.4)	149 (21.5)	<0.001
Wound-related	57 (1.9)	33 (4.8)	<0.001
Lung	7 (0.2)	22 (3.2)	<0.001
Cardiovascular	4 (0.1)	3 (0.4)	0.124
Urinary	32 (1.1)	27 (3.9)	<0.001
Gastrointestinal	121 (4.0)	27 (3.9)	0.917
Anastomotic	33 (1.1)	15 (2.2)	0.023
Others	33 (1.1)	22 (3.2)	<0.001
Mortality	17 (0.56)	28 (4.0)	<0.001

*Number of patients or tumors (%)

Table 4 Multivariate analysis of mortality and morbidity

	Factors	Univariate		Multivariate	
		RR(95% CI)	*P* value	OR (95% CI)	*P* value
Morbidity	Age (≦65 vs >65)	0.59 (0.49–0.71)	<0.001	0.67 (0.54–0.84)	<0.001
	Sex (female vs male)	0.76 (0.64–0.91)	0.003	0.71 (0.58–0.88)	0.002
	Cardiac disease (yes vs no)	1.40 (1.07–1.83)	0.016	1.34 (0.96–1.86)	0.086
	Old CVA (yes vs no)	1.63 (1.16–2.30)	0.006	1.36 (0.87–2.12)	0.176
	Asthma (yes vs no)	2.00 (1.42–2.83)	<0.001	1.90 (1.18–3.04)	0.008
	Liver cirrhosis (yes vs no)	1.99 (1.17–3.36)	0.015	1.59 (0.76–3.33)	0.222
	Others diseases (yes vs no)	1.25 (1.02–1.52)	0.031	1.24 (0.93–1.65)	0.153
	CEA (<5 vs≥5)	0.77 (0.64–0.92)	0.005	0.84 (0.68–1.04)	0.111
	Albumin (<35 vs≥35)	2.28 (1.90–2.73)	<0.001	2.15 (1.70–2.73)	<0.001
	Histologic type (adenocarcinoma vs mucinous)	0.68 (0.52–0.89)	0.006	0.70 (0.49–0.99)	0.045
	Histologic grade (moderate vs poor)	0.73 (0.54–0.98)	0.038	0.79 (0.53–1.17)	0.231
Mortality	Age (≦65 vs >65)	0.13 (0.05–0.34)	<0.001	0.18 (0.06–0.53)	0.002
	Asthma (yes vs no)	3.37 (1.22–9.32)	0.014	2.51 (0.82–7.71)	0.108
	Diabetes (yes vs no)	3.07 (1.59–5.90)	<0.001	2.32 (1.14–4.73)	0.020
	Liver cirrhosis (yes vs no)	8.52 (3.16–23.00)	<0.001	4.63 (1.23–17.51)	0.024
	CEA (<5 vs≥5)	0.24 (0.12–0.49)	<0.001	0.35 (0.17–0.73)	0.005
	Albumin (<35 vs≥35)	7.32 (3.88–13.80)	<0.001	3.86 (1.94–7.68)	<0.001

Table 5 Multivariate analysis of each type of morbidity

Morbidity	Factors	Univariate		Multivariate	
		RR(95% CI)	*P* value	OR (95% CI)	*P* value
Wound	Old CVA (yes vs no)	2.55 (1.30–4.97)	0.005	2.41 (1.18–4.92)	0.016
	Albumin (<35 vs≥35)	2.54 (1.67–3.87)	<0.001	2.26 (1.43–3.59)	0.001
	Tumor size (≦5 vs>5)	0.59 (0.39–0.88)	0.009	0.70 (0.45–1.09)	0.118
Lung	Age (≦65 vs >65)	0.04 (0.01–0.27)	<0.001	0.12 (0.03–0.54)	0.005
	Asthma (yes vs no)	3.50 (1.07–11.40)	0.028	2.31 (0.61–8.79)	0.218
	Liver cirrhosis (yes vs no)	8.85 (2.77–28.25)	0.006	4.22 (0.82–21.71)	0.085
	CEA (<5 vs≥5)	0.25 (0.11–0.58)	<0.001	0.32 (0.13–0.77)	0.011
	Albumin (<35 vs≥35)	13.79 (5.92–32.16)	<0.001	8.40 (3.27–21.54)	<0.001
	Tumor morphology (polypoid vs nonpolypoid)	2.28 (1.37–5.82)	0.003	3.15 (1.39–7.16)	0.006
	Histologic grade (moderate vs poor)	0.32 (0.12–0.87)	0.018	0.28 (0.10–0.82)	0.021
Urinary	Age (≦65 vs >65)	0.32 (0.18–0.57)	<0.001	0.38 (0.21–0.69)	0.002
	Sex (female vs male)	1.75 (1.04–2.93)	0.033	1.72 (1.01–2.91)	0.045
	Albumin (<35 vs≥35)	3.70 (2.23–6.14)	<0.001	3.06 (1.80–5.21)	<0.001
Gastrointestinal	Age (≦65 vs >65)	0.67 (0.49–0.93)	0.015	0.74 (0.53–1.05)	0.088
	Sex (female vs male)	0.57 (0.41–0.80)	0.001	0.56 (0.39–0.80)	0.001
	Cardiac disease (yes vs no)	1.65 (1.04–2.60)	0.032	1.56 (0.95–2.57)	0.080
	Asthma (yes vs no)	3.42 (2.07–5.65)	<0.001	3.37 (1.89–6.02)	0.000
	Histologic type (adenocarcinoma vs mucinous)	0.54 (0.35–0.85)	0.008	0.51 (0.31–0.83)	0.006
	TNM stage (II vs III)	1.56 (1.09–2.22)	0.013	1.57 (1.08–2.28)	0.018
Anastomosis	Albumin (<35 vs≥35)	2.00 (1.09–3.65)	0.023		

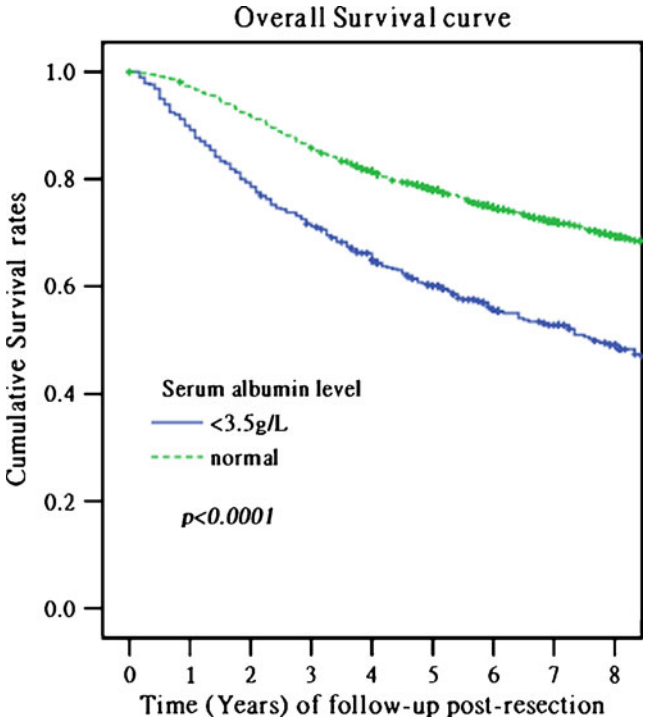

Fig. 1 Kaplan–Meier overall survival curves of colon cancer patients with curative resection stratified by albumin level

nemia were 78.0% and 60.0%, respectively ($P<0.0001$), and the 5-year RFS rates were 78.9% and 73.5%, respectively ($P=0.0042$). Hypoalbuminemic patients had significantly poorer OS (Fig. 1) and RFS rates (Fig. 2) compared to patients with normal serum albumin.

In a univariate analysis of OS and RFS rates, the following factors were examined: TNM stage, age, sex, each category of comorbidity, CEA level, occurrence of morbidity, tumor location, morphology, size, histologic type, and grade. TNM stage ($P<0.0001$), age ($P<0.0001$), sex ($P=0.0466$), hypertension ($P=0.0028$), cardiac disease ($P=0.0336$), old CVA ($P<0.0001$), diabetes ($P<0.0001$), liver cirrhosis ($P=0.0097$), other medical diseases ($P=0.0012$), CEA level ($P<0.0001$), occurrence of morbidity ($P<0.0001$), tumor morphology ($P=0.0003$), histologic type ($P=0.0024$), and histologic grade ($P=0.0019$) were significant predictors of OS. TNM stage ($P<0.0001$), hypertension ($P=0.0236$), cardiac disease ($P=0.0366$), CEA level ($P<0.0001$), tumor morphology ($P<0.0001$), histologic type ($P=0.0001$), and histologic grade ($P<0.0001$) were significant predictors of RFS.

For multivariate analysis, the significant predictors from univariate analysis were introduced into the Cox regression model; the results are shown in Table 6 (OS) and Table 7 (RFS). For the OS rate, the remaining significant predictors were TNM stage (stage III vs. I—HR 2.11, 95% CI 1.57–2.83), age (>65 vs. ≤65—HR 1.92, 95% CI 1.65–2.23), sex (male vs. female—HR 1.16, 95% CI 1.01–1.33), old CVA (yes vs. no—HR 1.76, 95% CI 1.32–2.36), diabetes (yes vs. no—HR 1.23, 95% CI 1.01–1.49), CEA level (≥5 vs <5—HR 1.64, 95% CI 1.42–1.89), albumin level (<35 vs. ≥35—HR 1.75, 95% CI 1.49–2.08), and histologic type (signet-ring cell vs. adenocarcinoma—HR 2.26, 95% CI 1.16–4.38). For the RFS, the remaining significant predictors were TNM stage (stage II vs. I—HR 1.81, 95% CI 1.11–2.96; stage III vs. I—HR 4.21, 95% CI 2.59–6.85), CEA level (≥5 vs. <5—HR 2.04, 95% CI 1.72–2.43), albumin level (<35 vs. ≥35—HR 1.28, 95% CI 1.04–1.56), tumor morphology (nonpolypoid vs. polypoid—HR 1.53, 95% CI 1.20–1.96), and histologic type (signet-ring cell vs. adenocarcinoma—HR 2.53, 95% CI 1.27–5.06).

In both the uni- and multivariate analyses, hypoalbuminemia was a significant predictor of poorer OS and RFS.

Discussion

Malnutrition is a common problem that debilitates cancer patients—including those with colon cancer [12, 20, 21]. Malnutrition in colon cancer patients may result from higher metabolism rates induced by cancer, reduction of food intake, impairment of hepatic protein synthesis, or blood loss, etc. [12, 20, 21]. Although it cannot comprehensively represent the nutritional status of patients [12], serum albumin level is extensively used. Hypoalbuminemia is widely accepted to be a good indicator of malnutrition

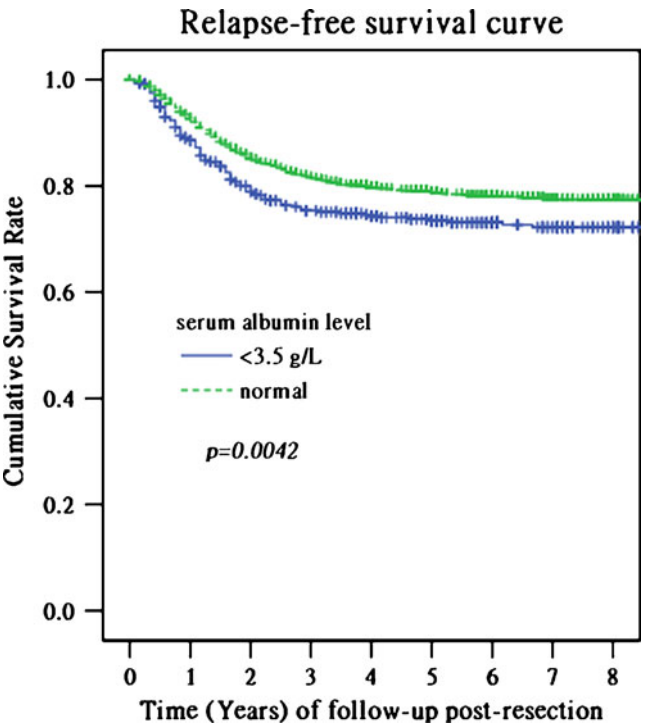

Fig. 2 Kaplan–Meier relapse-free survival curves of colon cancer patients with curative resection stratified by albumin level

Table 6 Significant variables from univariate analyses for overall survival, and statistics of univariate and multivariate analyses

Variable	category	Univariate		Multivariate	
		5-year SR (%)	*P* value	HR (95% CI)	***P* value**
TNM stage	I	88.3	<0.0001	1.00	
	II	80.1		1.13 (0.84–1.52)	0.419
	III	63.6		2.11 (1.57–2.83)	<0.001
Age	≦65	81.3	<0.0001	1.00	<0.001
	>65	67.0		1.92 (1.65–2.23)	<0.001
SEX	Female	75.9	0.0466	1.00	
	Male	73.4		1.16 (1.01–1.33)	0.041
Hypertension	No	75.1	0.0028	1.00	
	Yes	73.0		0.97 (0.82–1.15)	0.746
Cardiac disease	No	74.9	0.0336	1.00	
	Yes	71.2		1.09 (0.86–1.38)	0.495
Old CVA	No	75.4	<0.0001	1.00	
	Yes	52.8		1.76 (1.32–2.36)	<0.001
Diabetes	No	75.5	<0.0001	1.00	
	Yes	68.2		1.23 (1.01–1.49)	0.043
Liver cirrhosis	No	74.7	0.0097	1.00	
	Yes	58.9		1.63 (0.99–2.69)	0.056
Other diseases	No	76.0	0.0012	1.00	
	Yes	69.6		1.14 (0.97–1.34)	0.122
CEA level	<5	81.1	<0.0001	1.00	
	≥5	63.8		1.64 (1.42–1.89)	<0.001
Albumin level	≥35	78.0	<0.0001	1.00	
	<35	60.0		1.75 (1.49–2.08)	<0.001
Morbidity	No	75.7	<0.0001	1.00	
	Yes	65.6		1.21 (0.99–1.47)	0.064
Tu Morphology	Polypoid	80.9	0.0003	1.00	
	nonpolypoid	72.4		1.15 (0.96–1.38)	0.127
Histologic type	Adenocarcinoma	75.3	0.0024	1.00	
	Mucinous	69.5		1.11 (0.87–1.42)	0.406
	Signet-ring cell	39.7		2.26 (1.16–4.38)	0.016
Histologic grade (differentiation)	Well	79.4	0.0019	1.00	
	Moderate	73.9		1.05 (0.87–1.29)	0.550
	Poor	66.2		1.26 (0.90–1.75)	0.181

SR: survival rate, HR: hazard ratio, 95% CI: 95% confidence interval, Tu: tumor

[1–4, 22]. In the present study, 18.6% of colon cancer patients were hypoalbuminemic. In reality, the proportion of hypoalbuminemic colon cancer patients may be higher than in the present study because stage IV patients were excluded.

The association between hypoalbuminemia and adverse outcomes of elective [23], cardiac [24], and gastrointestinal surgery [3, 4, 25] has been known for many years. However, hypoalbuminemia is not an independent condition of surgical patients; certain types of diseases and characteristics of colon cancer patients also contribute to hypoalbuminemic status [12, 13]. However, previous studies have not explored the association of hypoalbuminemia with conditions such as diseases related to old CVA, diabetes mellitus, or liver cirrhosis, as well as cancer patient characteristics of advanced age, males, right side colon cancer, tumor size, depth of tumor invasion, mucinous type, poor differentiation, and abnormal CEA revealing in this study. These kinds of diseases and characteristics of colon cancer patients were also associated with adverse surgical outcomes; different factors may be associated with different postoperative complications. The confounding influences of hypoalbuminemia, characteristics of colon cancer patients, and diseases on surgical outcomes are seldom discussed in previous studies—the present study aimed to elucidate these issues. The results of this study show that hypoalbuminemia is an independent risk factor for postoperative mortality, morbidity, as well as complications related to wounds, lungs, the urinary system, and anastomosis, but

Table 7 Significant variables from univariate analyses for relapse-free survival, and statistics of univariate and multivariate analyses

Variable	Category	Univariate		Multivariate	
		5-year SR (%)	*P* value	HR (95% CI)	*P* value
TNM stage	I	94.9	<0.0001	1.00	0.018
	II	84.5		1.81 (1.11–2.96)	<0.001
	III	64.1		4.21 (2.59–6.85)	<0.001
Hypertension	No	76.7	0.0236	1.00	
	Yes	81.8		0.83 (0.67–1.02)	0.077
Cardiac disease	No	77.4	0.0366	1.00	
	Yes	83.4		0.76 (0.53–1.09)	0.137
CEA	<5	85.0	<0.0001	1.00	
	≥5	65.6		2.04 (1.72–2.43)	<0.001
Albumin	≥35	78.9	0.0042	1.00	
	<35	73.5		1.28 (1.04–1.56)	0.020
Tu Morphology	Polypoid	87.5	<0.0001	1.00	
	nonpolypoid	74.5		1.53 (1.20–1.96)	0.001
Histologic type	Adenocarcinoma	78.4	0.0001	1.00	
	Mucinous	75.0		1.03 (0.76–1.39)	0.859
	Signet-ring cell	41.1		2.53 (1.27–5.06)	0.008
Histologic grade (differentiation)	Well	84.9	<0.0001	1.00	
	Moderate	76.3		1.10 (0.86–1.42)	0.442
	Poor	72.7		1.11 (0.73–1.69)	0.633

SR, survival rate; *HR*, hazard ratio; *95% CI*, 95% confidence interval; *Tu*, tumor

not the gastrointestinal system or other complications. Although some previous studies suggest that hypoalbuminemia is significantly associated with postoperative ileus [26], this can be neither proved nor disproved by this study since postoperative ileus was not isolated from complications of the gastrointestinal system. The results of this study show that other kinds of adverse outcomes are associated with certain organ diseases. Old CVA patients are significantly associated with postoperative complications of wounds. Asthma patients have higher rate of complications of gastrointestinal system. Diabetes mellitus was a risk factor of postoperative mortality.

It is still controversial whether preoperative hypoalbuminemia influences the long-term outcomes of colon cancer patients. Some studies report that by itself, hypoalbuminemia is not an independent factor of survival [9, 10]. However, in conjunction with other factors, such as CRP [9] and CEA [10], they can significantly alter survival rates. Few studies report that hypoalbuminemia is an independent factor for poor survival [7, 11]. However, the analyses used in past survival studies have included overall, disease-free, cancer-specific, and relapse-free survival rates; the results of survival studies vary according to the definition of survival used. It has previously been reported that non-surgical patients with hypoalbuminemia exhibit poor long-term survival [27, 28]. It is reasonable to suggest that hypoalbuminemic colon cancer patients have poor long-term survival rates because they tend to be older and exhibit comorbidities. Whether preoperative hypoalbuminemia influences the further metastasis of colon cancer is not known. In this study, both overall and relapse-free survival rates—representing the possibility of further metastasis—were analyzed. The results revealed that by itself, preoperative hypoalbuminemia in colon cancer patients is an independent factor for poor long-term outcomes, including overall and relapse-free survival—this holds true even according to multivariate analysis, which included the variances in patient and cancer characteristics, and comorbidities. That is to say, colon cancer patients with preoperative hypoalbuminemia have poorer postoperative OS rates and a higher possibility of further cancer metastasis.

Although hypoalbuminemia is a well-known predictor of poor surgical outcomes, pre- or perioperative administration of albumin does not decrease the occurrence of complications [6, 12, 29, 30]. Recent studies revealed that pre- or perioperative nutritional supplements may improve surgical outcomes [31–33]. Whether the administration of albumin or nutritional supplements can improve long-term outcomes or diminish further metastasis remains unknown; further studies are needed.

Conclusion

Hypoalbuminemia is a predictor of poor surgical outcomes of colon cancer patients. It is also a poor prognosis factor

for long-term survival of colon cancer patients after curative operation.

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