Original Article

Risk Factors and Postoperative Morbidities in Colon Cancer Patients with Preoperative Hypoalbuminemia

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Purpose. The aims of this study were to identify the risk factors associated with preoperative hypoalbuminemia in colon cancer patients and to retrospectively determine the relationship between the preoperative hypoalbuminemia and postoperative morbidities of curative colon surgery.

Methods. This study included 2048 consecutive patients who underwent curative surgery for colon cancer between January 1994 and December 2005. These patients were categorized into 2 groups, hypoalbuminemia group (serum albumin level less than 3.5 g/dL) and normal albumin level group.

We analyzed clinicopathologic variables, medical illnesses, and postoperative morbidities in these patients.

Results. Three hundred and ninety five patients (19.3%) had preoperative hypoalbuminemia and 1653 patients had normal albumin level. Preoperative hypoalbuminemia was associated with old age (24.8% vs. 13.1%), right-sided colon cancer (48.1% vs. 36.1%), emergent operation (4.6% vs. 1.1%), poor tumor differentiation (19.8% vs. 13.5%), high preoperative carcinoembryonic antigen levels (46.0% vs. 33.7%), previous cerebrovascular accident (5.8% vs. 3.3%), diabetes mellitus (17.7% vs. 10.7%), and liver cirrhosis (3.3% vs. 0.8%). We identified preoperative hypoalbuminemia as an independent risk factor for postoperative morbidities of wound infection, wound dehiscence (4.6% vs. 1.9%), pneumonia (2.3% vs. 0.1%), bladder dysfunction (5.6% vs. 1.2%), and surgical anastomotic leakage/anastomotic stenosis (1.8% vs. 0.7%). All the above-mentioned associations were statistically significant ($p < 0.05$).

Conclusion. Preoperative hypoalbuminemia is an independent predictor of high postoperative morbidity in colon cancer patients. Further long-term follow-up studies are required for analyzing the long-term outcomes of preoperative hypoalbuminemia.
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Malnutrition is a common problem in colorectal cancer patients, and it can adversely affect treatment outcomes in these patients. Many tools are available for monitoring a patient's nutritional status. Serum albumin level is considered a good indicator of nutritional status.[1] Low levels of circulating albumin –

hypoalbuminemia – reflects poor nutritional status.[2,3] Many factors and medical illnesses, other than the cancer itself, can affect the levels of serum albumin in colon cancer patients. However, these factors are not yet identified. In the literature, several studies have reported hypoalbuminemia to be associated with a poor postoperative outcome and to be strongly associated with postoperative morbidity and mortality.[4-14] On the other hand, several articles report no correlation between low levels of serum albumin and postoperative morbidity.[15-17]

The aims of this study were to identify the risk factors associated with preoperative hypoalbuminemia in colon cancer patients and to determine the relationship between the preoperative hypoalbuminemia and postoperative morbidity of curative surgery in these patients.

Materials and Methods

Between January 1994 and December 2005, 2048 consecutive patients with histologically confirmed colonic adenocarcinoma underwent curative surgeries at the Chang Gung Memorial Hospital. The stage IV colon cancer, non-curative surgeries, rectal cancer and mucinous adenocarcinoma were excluded in this study.

The age, gender, tumor location, operative timing, findings of histology, histologic differentiation, preoperative albumin level, preoperative carcinoembryonic antigen (CEA) level, postoperative morbidity, and underlying medical illnesses were documented for each patient.

Tumor staging was performed according to the TNM classification described in the 6th edition of the cancer staging manual of the American Joint Committee on Cancer.[18] The patients were divided into the following 3 age-groups: young ($\leq$ 40 years), middle (41~75 years), and old (> 75 years). On the basis of the operative timing, the patients were classified into elective and emergent operation groups. Tumor location was categorized as right-sided colon (from the cecum to the distal transverse colon) and left-sided colon (from the splenic flexure to the sigmoid colon). Tumors were classified as low-grade tumors (well or moderately differentiated adenocarcinoma) and high-

grade tumors (poorly differentiated adenocarcinoma). Hypoalbuminemia was defined as serum albumin level lower than 3.5 g/dL, and the patient was said to have abnormal CEA level if CEA level exceeded 5 ng/mL.[19]

Postoperative morbidities were recorded for conditions such as wound infection, wound dehiscence, atelectasis, pneumonia, cardiovascular accident, bladder dysfunction, gastrointestinal obstruction, gastrointestinal bleeding, abdominal abscess, surgical anastomotic leakage, and anastomotic stenosis. The underlying medical illnesses were hypertension, cerebrovascular accidents (CVAs), bronchogenic asthma, diabetes mellitus (DM), peptic ulcer, viral hepatitis, liver cirrhosis, gallstones, and thyroid disorders.

Statistical methods

Pearson's chi-square test was performed for comparing 2 subgroups within a group. A Cox proportional-hazards model with step-wise variable selection was used for multivariate analysis to assess the effects of multiple factors. All statistical tests were 2-tailed, and p values less than 0.05 were considered statistically significant.

Results

The patients' characteristics, clinicopathologic variables related to preoperative albumin level were shown in Table 1. Of the 2,048 patients enrolled in the study, 395 (19.3%) had preoperative hypoalbuminemia. Preoperative hypoalbuminemia was associated with old age (24.8% vs. 13.1%, $p < 0.001$). Tumors located in the right-sided colon were associated with a higher risk of preoperative hypoalbuminemia (48.1% vs. 36.1%, $p < 0.001$). Of the 395 patients with preoperative hypoalbuminemia, 18 (4.6%) received emergent operation; on the other hand, 19 of the 1635 patients (1.1%) in the normal albumin group received emergent operation ($p < 0.001$). High-grade tumor differentiation ($p = 0.002$) and preoperative CEA levels exceeding 5 ng/mL[19] ($p < 0.001$) were more likely to be associated with preoperative hypoalbuminemia.

Table 2 demonstrated medical co-morbidity in

Table 1. Clinicopathologic variables and medical illnesses in patients with hypoalbuminemia and in patients with normal albumin levels

Variable	Parameter	Hypoalbuminemia group (N = 395) (number, %)	Normal albumin level group (N = 1653) (number, %)	*p* value
Age (years)	< 40	16 (4.1)	139 (8.4)	< 0.001
	40~75	281 (71.1)	1297 (78.5)	
	> 75	98 (24.8)	217 (13.1)	
Sex	Male	191 (48.4)	868 (52.5)	0.138
	Female	204 (51.9)	785 (47.5)	
Tumor location	Right sided	190 (48.1)	596 (36.1)	< 0.001
	Left sided	205 (51.9)	1057 (63.9)	
Operative timing	Elective	377 (95.4)	1634 (98.9)	< 0.001
	Emergent	18 (4.6)	19 (1.1)	
Preoperative CEA	< 5 ng/dL	202 (54.0)	1064 (66.3)	< 0.001
	> 5 ng/dL	172 (46.0)	540 (33.7)	
Histologic differentiation	Low-grade	318 (80.5)	1430 (86.5)	0.002
	High-grade	77 (19.8)	223 (13.5)	

CEA: carcinoembryonic antigen

Table 2. Medical co-morbidity in patients with hypoalbuminemia and in patients with normal albumin levels

Variable	Parameter	Hypoalbuminemia group (N = 395) (number, %)	Normal albumin level group (N = 1653) (number, %)	*p* value
Hypertension	Yes	88 (22.3)	79 (22.9)	0.420
	No	307 (77.7)	1274 (77.1)	
Cardiac disease	Yes	28 (7.1)	134 (8.1)	0.405
	No	367 (92.9)	1518 (91.8)	
Cerebrovascular accident	Yes	23 (5.8)	55 (3.3)	0.018
	No	372 (94.2)	1598 (96.7)	
Asthma	Yes	18 (4.6)	53 (3.2)	0.124
	No	337 (95.4)	1600 (96.8)	
Diabetes mellitus	Yes	70 (17.7)	181 (10.1)	< 0.001
	No	325 (82.3)	1472 (89.9)	
Viral hepatitis	Yes	19 (4.8)	59 (3.6)	0.156
	No	376 (95.2)	1594 (96.4)	
Liver cirrhosis	Yes	13 (3.3)	13 (0.8)	< 0.001
	No	382 (96.7)	1640 (99.2)	

patients with hypoalbuminemia and normal albumin levels. The patients having medical illness such as CVA, DM, and liver cirrhosis were prone to be associated with preoperative hypoalbuminemia (*p* < 0.05).

Table 3 showed postoperative morbidities for both groups. The incidence of postoperative morbidities in patients with preoperative hypoalbuminemia was significantly higher than that in patients with normal albumin levels (24.8% vs. 10.6%, *p* < 0.001). Higher morbidity rates were observed for wound infection, wound dehiscence, pneumonia, bladder dysfunction, anastomotic leakage and anastomotic stenosis (*p* < 0.05).

Tables 4 and 5 showed different risk factors for postoperative morbidity determined by univariate and multivariate analyses. The results of the univariate analysis showed that age over 75 years, co-morbidities with hypertension, CVA, asthma, DM, liver cirrhosis and preoperative hypoalbuminemia significantly increased the risk of postoperative morbidities. The different risk factors were pooled for multivariate analysis. The preoperative hypoalbuminemia was an independent risk factor (*p* < 0.05) of postoperative morbidities.

Table 3. Postoperative morbidities for patients in the hypoalbuminemia group and the normal albumin level group

Morbidity	Hypoalbuminemia group (N = 395) (number, %)	Normal albumin level group (N = 1653) (number, %)	p value
With morbidity	98 (24.8)	175 (10.6)	< 0.001
Wound infection/dehiscence	18 (4.6)	32 (1.9)	< 0.001
Pneumonia	9 (2.3)	1 (0.1)	< 0.001
Cardiovascular accident	1 (0.3)	3 (0.2)	0.772
Bladder dysfunction	22 (5.6)	20 (1.2)	< 0.001
Gastrointestinal obstruction/bleeding	23 (5.8)	83 (5.0)	0.510
Abdomen abscess/peritonitis	3 (0.8)	10 (0.6)	0.728
Anastomotic leakage/stenosis	7 (1.8)	11 (0.7)	0.034

Table 4. Univariate analysis of risk factors associated with postoperative morbidity

Factors	Morbidity (%)	p value
TNM stage (I/III)	14.6/12.3	0.334
TNM stage (II/III)	16.1/12.3	0.361
Age (< 40/> 75)	12.3/19.4	0.067
Age (40~75/> 75)	12.2/19.4	0.001
Hypertension (Yes/No)	16.3/12.5	0.036
Cardiac disease (Yes/No)	17.3/13.0	0.147
Cerebral vascular disease (Yes/No)	24.4/12.9	0.006
Asthma (Yes/No)	28.2/12.8	0.001
Diabetic mellitus (Yes/No)	18.7/12.6	0.01
Viral hepatitis (Yes/No)	13.9/13.3	0.866
Liver cirrhosis (Yes/No)	26.2/13.2	0.032
Pre-OP CEA (< 5 ng/dL/> 5 ng/dL)	12.2/14.7	0.110
Albumin (< 3.5 g/dL/> 3.5 g/dL)	24.8/10.6	< 0.001
Tumor location (Right sided/Left sided)	11.8/14.3	0.124
Tumor grading (Low-grade/High-grade)	12.8/16.3	0.099
Operative timing (Elective/Emergent)	13.6/24.3	0.086

Pre-OP CEA: preoperative carcinoembryonic antigen.

Table 5. Multivariate analysis of risk factors associated with postoperative morbidity

Factors	Morbidity Odds ratio (95% Confidence interval)	p value
Age (≤ 40 vs. > 75)	0.87 (0.45-1.70)	0.69
Age (41~75 vs. > 75)	0.72 (0.50-1.04)	0.08
Hypertension (Yes vs. No)	0.87 (0.50-1.50)	0.62
Cerebrovascular disease (Yes vs. No)	0.80 (0.40-1.61)	0.53
Asthma (Yes vs. No)	0.47 (0.23-0.98)	0.045
Diabetes mellitus (Yes vs. No)	0.82 (0.48-1.42)	0.49
Albumin (< 3.5 g/dL vs. > 3.5 g/dL)	2.50 (1.75-3.55)	< 0.001

Discussion

Patients with colon cancer are at a risk of malnutrition with cachexia. Cancer-related malnutrition can occur due to reduced food intake, altered tissue wasting, and several pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), produced by tumors.[20,21] Serum albumin level has been linked to nutritional status[22] and considered as an indicator of nutritional status.[5] Albumin has a long half-life (21 days), and low albumin concentration reflects prolonged malnourishment.[8] In this study,

the cut-off value used for hypoalbuminemia (less than 3.5 g/dL of albumin) was the same as the previously reported cut-off value.[5]

Valberg et al.[2] reported that loss of albumin in colon cancer patients is related to several factors, such as tumor size, tumor location, non-epithelial tumor surface, and tumor inflammation. We found that old age, right-sided colon tumor, emergent operation, high-grade tumor differentiation, and abnormal preoperative CEA levels (> 5 ng/dL) were significantly associated with hypoalbuminemia. In patients with right-sided colon cancer the tumor size (29.51 cm^2, SD 24.46) was significantly larger than that in patients with left-sided colon cancer (19.14 cm^2, SD 17.57), ($p < 0.001$). Right-sided colon tumors are associated with less severe clinical symptoms and signs such as tenesmus, bloody stools, and small caliber stools. Meanwhile, cecum and ascending colon form the widest part of the large bowel. Also, right-sided colon cancer cannot be detected earlier than left-sided colon cancer. Thus, by the time patients with right-sided colon cancer presented clinical symptoms, the tumor is reasonably big. Valberg[2] has reported that bigger tumors cause more epithelial loss and intestinal protein loss. This may explain why right-sided colon cancer was a significant risk factor for hypoalbuminemia ($p < 0.001$) in this study.

Colon cancer patients who received emergent surgeries at our institute had cancer obstruction or perforation with peritoneal sign. In patients with obstructions, the proximal colonic lumen was always dilated with diffuse edema and inflammation of the colonic wall; thereby affecting protein absorption. Hence, emergent operation was a risk factor for hypoalbuminemia ($p < 0.001$).

Preoperative CEA levels more than 5 ng/mL was a risk factor for hypoalbuminemia.[19] In previous investigations,[7,14,23] colorectal cancer patients with preoperative CEA levels more than 5 ng/mL and albumin levels less than 3.5 g/dL had a poor prognosis. We did not analyze the overall survival time for our patients. A close follow-up study of patients with preoperative hypoalbuminemia and high CEA levels is needed.

The co-morbidities of liver cirrhosis, DM, and CVA were correlated with hypoalbuminemia. Univariate analysis indicated that co-morbidity of any of the above-mentioned conditions with hypoalbuminemia was also a risk factor for postoperative morbidity. Cirrhosis of the liver reduces the production of albumin in the liver, thus causing hypoalbuminemia. Microalbuminuria (excretion of albumin in urine) and microvascular albumin leakage were common syndromes in patients with severe DM.[24,25] Excessive loss of protein through the urinary system can lead to hypoalbuminemia.

Low level of serum albumin indicates malnutrition and is associated with morbidity and adverse outcomes after an operation.[6,8,9,22,26-28] We found that several risk factors such as the patient's age, right-sided colon cancer, emergent operation, high-grade tumor differentiation, preoperative CEA levels > 5 ng/dL, CVA, DM, and liver cirrhosis are related to preoperative hypoalbuminemia. The results of multivariate analysis showed that hypoalbuminemia is an independent predictor of postoperative morbidity. Preoperative investigation of medical illnesses and patients' characteristics is useful for predicting the risk of hypoalbuminemia and of postoperative morbidity. Surgeons must be aware and careful while treating colon cancer patients with the above-mentioned risk factors.

Conclusion

In this study, we found several risk factors associated with preoperative hypoalbuminemia in colon cancer patients. On the other hand, preoperative hypoalbuminemia was identified as an independent predictor of postoperative morbidity. Further long-term follow-up studies are required for analyzing the long-term outcomes of preoperative hypoalbuminemia in colon cancer patients.

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原　　著

手術前低血漿白蛋白的結腸癌患者之
相關危險因子與併發症分析

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目的　本研究的目的是藉由病例回溯的方法，鑑別手術前低血漿白蛋白的結腸癌患者之相關危險因子，和手術前低血漿白蛋白症與手術後併發症得關係加以分析探討。

方法　本研究收集自 1994 年 1 月至 2005 年 12 月結腸癌接受根治性手術切除的病例，共有 2048 例患者。這些患者根據手術前血漿白蛋白濃度被分成兩組，分別為低血漿白蛋白組 (血清白蛋白低於 3.5 克/分升) 和正常血漿白蛋白組。
我們分析兩組病人臨床病理上、內科方面相關生理疾病、及手術後併發症上的差異性。

結果　手術前低血漿白蛋白組的病患共 395 人 (19.3%)；正常血漿白蛋白組的病患共 1653 人。手術前低血漿白蛋白組與高年紀 (24.8% 比 13.1%)，右側結腸癌 (48.1% 比 36.1%)，急診緊急手術 (4.6% 比 1.1%)，腫瘤分化度較差者 (19.8% 比 13.5%)，術前高腫瘤胚胎抗原指數 (46.0% 比 33.7%)，先前的腦血管病變 (5.8% 比 3.3%)，糖尿病患者 (17.7% 比 10.7%) 和肝硬化患者 (3.3% 比 0.8%) 等等有相關連性。在手術前低血漿白蛋白組中，我們分析出傷口感染，傷口癒合不全 (4.6% 比 1.9%)，肺炎 (2.3% 比 0.1%)，膀胱機能障礙 (5.6% 比 1.2%)，手術吻合處滲漏，或手術吻合處狹窄 (1.8% 比 0.7%) 為手術後併發症的獨立危險因子，有達到統計學上的意義 ($p < 0.05$)。在多重變異分析中，我們也發現手術前低血漿白蛋白為手術後併發症的一個獨立的獨立危險因子。

結論　在結腸癌患者中，有關於手術後併發症而言，手術前低血漿白蛋白是一個獨立的預測因子。　在未來中,更進一步長期研究及長期預後分析研究也是有必要的。

關鍵詞　結腸腫瘤、低血漿白蛋白、營養不良、併發症。