

RAPID COMMUNICATION

## Pre-operative hypoalbuminemia is a major risk factor for postoperative complications following rectal cancer surgery

Varut Lohsiriwat, Darin Lohsiriwat, Wiroon Boonnuch, Vitoon Chinswangwatanakul, Thawatchai Akaraviputh, Narong Lert-akayamane

Varut Lohsiriwat, Darin Lohsiriwat, Wiroon Boonnuch, Vitoon Chinswangwatanakul, Thawatchai Akaraviputh, Narong Lert-akayamane, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand  
Author contributions: Lohsiriwat V is the principle investigator who contributed to the acquisition of data and analysis as well as manuscript preparation; Lohsiriwat D, Boonnuch W and Lert-akayamane N conceived the study and critically revised the manuscript; Chinswangwatanakul V and Akaraviputh T participated in the design of the study and data collection.  
Correspondence to: Varut Lohsiriwat, MD, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Prannok Rd, Bangkok Noi, Bangkok 10700, Thailand. [bolloon@hotmail.com](mailto:bolloon@hotmail.com)  
Telephone: +66-2-4198077 Fax: +66-2-4115009  
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### Abstract

**AIM:** To determine the relationship between pre-operative hypoalbuminemia and the development of complications following rectal cancer surgery, as well as postoperative bowel function and hospital stay.

**METHODS:** The medical records of 244 patients undergoing elective oncological resection for rectal adenocarcinoma at Siriraj Hospital during 2003 and 2006 were reviewed. The patients had pre-operative serum albumin assessment. Albumin less than 35 g/L was recognized as hypoalbuminemia. Postoperative outcomes, including mortality, complications, time to first bowel movement, time to first defecation, time to resumption of normal diet and length of hospital stay, were analyzed.

**RESULTS:** The patients were 139 males (57%) and 105 females (43%) with mean age of 62 years. Fifty-six patients (23%) had hypoalbuminemia. Hypoalbuminemic patients had a significantly larger tumor size and lower body mass index compared with non-hypoalbuminemic patients (5.5 vs 4.3 cm;  $P < 0.001$  and 21.9 vs 23.2 kg/m<sup>2</sup>;  $P = 0.02$ , respectively). Thirty day postoperative mortality was 1.2%. Overall complication rate was 25%. Hypoalbuminemic patients had a significantly higher rate of postoperative complications (37.5% vs 21.3%;  $P = 0.014$ ). In univariate analysis, hypoalbuminemia and ASA status were two risk factors for postoperative complications. In multivariate analysis, hypoalbuminemia was the only significant risk factor (odds ratio 2.22,

95% CI 1.17-4.23;  $P < 0.015$ ). Hospitalization in hypoalbuminemic patients was significantly longer than that in non-hypoalbuminemic patients (13 vs 10 d,  $P = 0.034$ ), but the parameters of postoperative bowel function were not significantly different between the two groups.

**CONCLUSION:** Pre-operative hypoalbuminemia is an independent risk factor for postoperative complications following rectal cancer surgery.

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**Key words:** Hypoalbuminemia; Rectal cancer; Outcomes; Morbidity; Postoperative bowel function

**Peer reviewers:** Lars A Pahlman, Professor, Department of Surgery, Colorectal Unit, University Hospital, SE 751 85, Uppsala, Sweden; Walter E Longo, Professor, Department of Surgery, Yale University School of Medicine, 205 Cedar Street, New Haven 06510, United States

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### INTRODUCTION

Malnutrition is a common problem in gastrointestinal cancer patients that adversely affects surgical outcomes<sup>[1-3]</sup>. There are many tools to assess patients' nutritional status. Serum albumin is a good and simple predictor of surgical risk and has a close correlation with the degree of malnutrition<sup>[4]</sup>. Hypoalbuminemia is a predictor of delayed recovery of bowel function and is strongly associated with postoperative complications after right hemicolectomy for right-sided colon cancer<sup>[5]</sup>, or following other major gastrointestinal surgery<sup>[6-8]</sup>. However, there is little information regarding the effect of hypoalbuminemia on the development of postoperative complications after rectal cancer surgery, and the results remain controversial<sup>[9-11]</sup>.

The aims of this study were to determine the relationship between pre-operative hypoalbuminemia and the development of complications following rectal cancer surgery, and to evaluate the effect of hypoalbuminemia on postoperative bowel function and hospital stay.

## MATERIALS AND METHODS

### Patients and data collection

After obtaining approval from the Institutional Ethics Committee, we carried out a retrospective analysis of patients undergoing elective oncological resection for rectal adenocarcinoma between January 2003 and December 2006 at the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. Rectal cancer was defined as a tumor with the lower edge located within 15 cm of the anal verge, as measured by rigid sigmoidoscopy. Patients were excluded if they had pelvic exenteration, or had had operations for recurrent tumors or acute complicated conditions such as colonic obstruction.

Each patient had a pre-operative serum albumin assessment. Serum albumin less than 35 g/L was recognized as hypoalbuminemia. Every patient underwent pre-operative mechanical bowel preparation. Standard oncological resection of the rectum was performed by either a laparoscopic or open approach. In case of sphincter-saving operation, colorectal anastomosis was performed without colonic pouch formation or protective stoma. In the case of abdominoperineal resection, primary closure of the perineal wound was performed after a pelvic drain had been placed. A nasogastric tube was inserted at the surgeon's discretion.

Routine postoperative care was provided to each patient. Time to first bowel movement (passing flatus) was recorded by nursing staffs. The patients were allowed to have oral fluid if passing flatus. Resumption of a normal diet was decided by surgeons with patients' compliance. Patients were discharged from the hospital if the drain was removed and they had no fever, good appetite and good ambulation. All patients were scheduled for follow-up at 30 d postoperatively.

Data recorded included patient demographic, tumor characteristics, operative details and postoperative outcomes. Patient-related factors included age, gender, American Society of Anesthesiologist (ASA) status, obesity (body mass index over 30 kg/m<sup>2</sup>), anemia (pre-operative hematocrit less than 30%), hypoalbuminemia and neoadjuvant chemoradiation. Tumor-related factors included location, size and TNM stage. Operation-related factors included the type of operation and requirement of blood transfusion. Postoperative outcomes, including mortality, complications, time to first bowel movement, time to first defecation, time to resumption of normal diet and length of hospital stay, were analyzed.

### Statistical analysis

All data were prepared and analyzed using Statistical Package for the Social Sciences program version 11.0 for Windows (SPSS®, SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to test for a normal pattern of data distribution. Unpaired *t*-tests were used to compare data between the two groups when they showed a normal distribution pattern. The Mann-Whitney *U* test was used when this was not the case. Pearson's Chi-square test and Fisher's exact test were used when the data were quantitative. Stepwise regression analysis was used for multivariate analysis in order to determine any confounding factors. A *P*-value of less than 0.05 was considered statistically significant.

Table 1 Demographic data on non-hypoalbuminemic and hypoalbuminemic patients

	Non-hypoalbuminemic ( <i>n</i> = 188)	Hypoalbuminemic ( <i>n</i> = 56)	<i>P</i> value
Age (yr)	61.4 ± 11.9	64.5 ± 13.5	0.100
Male	111 (59)	28 (50)	0.230
BMI (kg/m <sup>2</sup> )	23.2 ± 3.8	21.9 ± 3.4 <sup>a</sup>	0.021
Tumor size (cm)	4.3 ± 1.7	5.5 ± 2.3 <sup>b</sup>	<0.001
TNM stage			0.310
I	48 (26)	8 (14)	
II	43 (23)	14 (25)	
III	94 (50)	34 (61)	
IV	3 (1)	0 (0)	
Type of anesthesia			0.860
GA alone	73 (39)	21 (38)	
GA + EB	115 (61)	35 (62)	

GA: General anesthesia; EB: Epidural block. Values were given as number (percentage) or mean ± SD. <sup>a</sup>*P* ≤ 0.05, <sup>b</sup>*P* ≤ 0.01 vs Non-hypoalbuminemic.

## RESULTS

Two hundred and forty four patients were studied. There were 139 males (57%) and 105 females (43%) with a mean age of 62 years (range 23-87). Fifty-six patients (23%) had hypoalbuminemia. Patients with hypoalbuminemia had a significantly larger size of the tumors and lower body mass index (BMI), compared with those without hypoalbuminemia (5.5 vs 4.3 cm; *P* < 0.001 and 21.9 vs 23.2 kg/m<sup>2</sup>; *P* = 0.02, respectively). Gender and tumor staging were not statistically different between the two groups (Table 1).

Thirty day postoperative mortality was 1.2% (3 patients died; one massive pelvic hemorrhage, one perioperative myocardial infarction, and one anastomotic leakage with respiratory failure). Overall complication rate was 25%. Infectious complications were diagnosed in 59 patients (24%); 42 surgical site infections, 13 anastomotic leakage, 2 urinary tract infection and 2 pneumonia. Two patients (1%) developed noninfectious complications during hospitalization (one acute respiratory failure and one perioperative myocardial infarction). Hypoalbuminemic patients had a significantly higher rate of postoperative complication (37.5% vs 21.3%, *P* = 0.014).

Univariate analysis revealed hypoalbuminemia and ASA status as two risk factors for the development of postoperative complications (Table 2). In multivariate analysis, hypoalbuminemia was the only significant risk factor for postoperative complications (odds ratio 2.22, 95% CI 1.17-4.23; *P* < 0.015). Length of hospital stay in hypoalbuminemic patients was significantly longer than that in non-hypoalbuminemic patients (13.0 vs 10.4 d, *P* = 0.034), but time to first bowel movement, time to first defecation and time to resumption of normal diet were not significantly different between the two groups (Table 3).

## DISCUSSION

Patients with rectal cancer are at risk of malnutrition due to cancer-induced higher metabolism, dietary intake reduction, and cancer cachexia<sup>[12-14]</sup>. Tumor necrosis factor-alpha is considered to be the main mediator of cancer cachexia

**Table 2** The relationship between the clinical characteristics of the patients and the development of postoperative complications analyzed using a univariate model

Variables	Category	n	Complication rate, n (%)	P value
Age	≥ 60	102	26 (25.5)	0.880
	< 60	142	35 (24.6)	
Gender	Male	139	38 (27.3)	0.330
	Female	105	23 (21.9)	
Obesity	Yes	10	3 (30.0)	0.710
	No	234	58 (24.8)	
ASA status	I	65	11 (16.9)	0.041
	II	162	42 (25.9)	
	III	17	8 (47.1) <sup>a</sup>	
Anemia	Yes	18	6 (33.3)	0.390
	No	226	55 (24.3)	
Hypoalbuminemia	Yes	56	21 (37.5)	0.014
	No	188	40 (21.3) <sup>a</sup>	
Neoadjuvant therapy	Yes	23	5 (21.7)	0.900
	No	221	56 (25.3)	
Tumor size	≥ 5 cm	105	27 (25.7)	0.820
	< 5 cm	139	34 (24.4)	
Rectal tumor location	Upper	56	14 (25.0)	0.430
	Middle	134	30 (22.3)	
	Lower	54	17 (31.4)	
Sphincter-saving procedure	Yes	179	44 (24.6)	0.800
	No	65	17 (26.2)	
Operation time	> 4 h	87	24 (27.6)	0.490
	< 4 h	157	37 (23.6)	
Blood transfusion	Yes	32	9 (28.1)	0.660
	No	212	52 (24.5)	

<sup>a</sup>P ≤ 0.05.

as it is responsible for different metabolic alterations and leads to impairment of hepatic protein synthesis<sup>[15]</sup>. Cancer patients also have increased whole protein turnover and subsequent body nitrogen loss<sup>[16]</sup>. Albumin has a long half-life of 20 d, so that metabolic effects on its concentration reflect prolonged malnourishment, as in cancer patients. Hypoalbuminemia is widely accepted to be a good indicator for malnutrition in many national cancer studies<sup>[7,11,17]</sup>. It is remarkable that tumor size, but not the stage, is relevant to hypoalbuminemia. The clear explanation of this association remains unknown. It is possible that large tumors cause more gastrointestinal symptoms, leading to poor intake and partial gut obstruction.

In this present study, univariate analysis showed that hypoalbuminemia and ASA status were significant risk factors for postoperative complications following rectal cancer surgery. However, hypoalbuminemia was the only independent factor for postoperative morbidity after multivariate analysis. Our finding is consistent with those of two large population-based prospective studies in France<sup>[7]</sup> and the United States<sup>[11]</sup>. Gibbs *et al*<sup>[11]</sup> reported that a decrease in serum albumin from concentrations greater than 46 g/L to less than 21 g/L was associated with an exponential increase in mortality rates from less than 1% to 29% and in morbidity rates from 10% to 65% following non-cardiac surgery. Moreover, hypoalbuminemia was a better predictor of some types of morbidity, especially sepsis and major infections. Ryan *et al*<sup>[18]</sup> showed decreased serum albumin concentration on the first postoperative day was also an independent predictor of poor surgical outcome

**Table 3** Univariate analysis of clinical outcomes (mean ± SD)

	Non-hypoalbuminemic (n = 188)	Hypoalbuminemic (n = 56)	P value
Postoperative complication (%)	21.3	37.5 <sup>a</sup>	0.014
Time to first bowel movement (h)	2.3 ± 1.4	2.7 ± 1.6	0.090
Time to first defecation (d)	4.5 ± 1.7	4.6 ± 2.5	0.730
Time to resumption of normal diet (d)	4.8 ± 2.7	5.4 ± 2.9	0.180
Length of hospital stay (d)	10.4 ± 8.0	13.0 ± 8.9 <sup>a</sup>	0.034

<sup>a</sup>P ≤ 0.05.

following gastrointestinal cancer surgery.

Hypoalbuminemia was associated with poor tissue healing, decreased collagen synthesis in the surgical wounds or at the anastomosis<sup>[19-21]</sup>, and impairment of immune responses, such as macrophage activation and granuloma formation<sup>[22,23]</sup>. Therefore, in hypoalbuminemic patients, wound infection, remote infections such as pneumonia, and anastomotic leakage, were commonly found.

According to the present study, a tendency towards delayed recovery of postoperative bowel function has also been found in hypoalbuminemic patients, although this effect did not reach statistical significance. This may be because such patients develop more complications, including intra-abdominal sepsis, and because lower serum albumin causes swelling and edema of the intestine<sup>[24]</sup>, resulting in paralytic ileus. Clearly, there would be other factors contributing to postoperative bowel function, such as narcotics administration and electrolyte status<sup>[25-27]</sup>. Prolonged hospitalization in hypoalbuminemic patients may be the result of higher rates of postoperative complication and delayed bowel recovery.

With regard to the treatment of pre-existing hypoalbuminemia, no published studies have been able to demonstrate any advantage of albumin infusion on morbidity and mortality<sup>[28,29]</sup>. This may be because of insufficient albumin replacement or increased leakage of synthetic albumin into the extravascular spaces. However, a recent prospective randomized study reported the administration of a supplemented diet before and after surgery was beneficial to outcomes in malnourished patients with gastrointestinal cancer<sup>[30]</sup>.

In conclusion, pre-operative hypoalbuminemia is an independent risk factor for postoperative complications following rectal cancer surgery. Hypoalbuminemic patients also have a nonstatistically significant tendency to delayed recovery of postoperative bowel function. Low serum albumin may be used as a simple and low-cost prognostic tool to predict the risk of adverse surgical outcomes.

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## COMMENTS

### Background

Malnutrition is a common problem in gastrointestinal cancer patients that adversely affects surgical outcomes. There are many tools to assess patients' nutritional status. Serum albumin is a good and simple predictor of surgical risk and has a close correlation with the degree of malnutrition. Hypoalbuminemia is a predictor of delayed recovery of bowel function and is strongly associated with postoperative complications in colon cancer surgery.

### Research frontiers

There is little information regarding the effect of hypoalbuminemia on the development of postoperative complications after rectal cancer surgery, and the results remain controversial.

### Innovations and breakthroughs

The present study clearly demonstrates hypoalbuminemia is associated with an increased rate of complications, and has a negative impact on postoperative recovery following rectal cancer surgery.

### Applications

Pre-operative assessment of patients with rectal cancer may routinely include serum albumin levels. Patients with pre-operative hypoalbuminemia should be informed about the higher rate of complications after rectal cancer surgery. Every effort to improve patients' pre-operative malnourishment without delayed surgical treatment should be encouraged. Further research might focus on the effect of hypoalbuminemia on long-term surgical outcomes and cancer survival.

### Terminology

Pre-operative hypoalbuminemia is an independent risk factor for postoperative complications following rectal cancer surgery.

### Peer review

This is an interesting paper showing that hypoalbuminemia will have an impact on postoperative recovery and complication. It is well known that malnourished patients do worse than those with a good nutrition status in the postoperative course. It is well written, the data is excellent and references timely.

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