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**Authors**

Truong, Adam  
Hanna, Mark H  
Moghadamyeghaneh, Zhubin  
[et al.](#)

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## Implications of preoperative hypoalbuminemia in colorectal surgery

Adam Truong, Mark H Hanna, Zhobin Moghadamyeghaneh, Michael J Stamos

Adam Truong, Mark H Hanna, Zhobin Moghadamyeghaneh, Michael J Stamos, Division of Colon and Rectal Surgery, Department of Surgery, University of California, Irvine Medical Center, Orange, CA 92868, United States

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**Correspondence to:** Michael J Stamos, MD, Division of Colon and Rectal Surgery, Department of Surgery, University of California, Irvine Medical Center, 33 City Blvd West Suite 1600, Orange, CA 92868, United States. [mstamos@uci.edu](mailto:mstamos@uci.edu)  
Telephone: +1-714-4566262

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### Abstract

Serum albumin has traditionally been used as a quantitative measure of a patient's nutritional status because of its availability and low cost. While malnutrition has a clear definition within both the American

and European Societies for Parenteral and Enteral Nutrition clinical guidelines, individual surgeons often determine nutritional status anecdotally. Preoperative albumin level has been shown to be the best predictor of mortality after colorectal cancer surgery. Specifically in colorectal surgical patients, hypoalbuminemia significantly increases the length of hospital stay, rates of surgical site infections, enterocutaneous fistula risk, and deep vein thrombosis formation. The delay of surgical procedures to allow for preoperative correction of albumin levels in hypoalbuminemic patients has been shown to improve the morbidity and mortality in patients with severe nutritional risk. The importance of preoperative albumin levels and the patient's chronic inflammatory state on the postoperative morbidity and mortality has led to the development of a variety of surgical scoring systems to predict outcomes efficiently. This review attempts to provide a systematic overview of albumin and its role and implications in colorectal surgery.

**Key words:** Colorectal surgery; Malnutrition; Albumin; Hypoalbuminemia; Prealbumin; Serum albumin; Nutrition

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**Core tip:** Although albumin remains a flawed marker of nutrition, it offers clear prognostic value in predicting patient outcomes after colorectal surgery. Hypoalbuminemia significantly influences the length of hospital stay, rates of surgical site infections, enterocutaneous fistula risk, and deep vein thrombosis formation. Despite the fact that hypoalbuminemia is classically defined  $< 3.0$  g/dL, clinical judgment must account for albumin levels  $\leq 3.4$  g/dL as even modest hypoalbuminemia can affect outcomes. The subjective global assessment, modified Glasgow Prognostic Score, and Colorectal preoperative Surgical Score scoring systems provide convenient and valuable prognostic information that may help in the

counseling and risk adjustment of patients undergoing colorectal surgery.

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## INTRODUCTION

Albumin is a single polypeptide responsible for five main functions: (1) maintenance of colloid osmotic pressure; (2) binding and transport of solutes; (3) free radical scavenging; (4) platelet function inhibition and antithrombotic effect; and (5) beneficial effects on vascular permeability in the setting of shock and sepsis<sup>[1]</sup>. Albumin is a major source of sulfhydryl groups, which sequester both leukotoxin and nitric oxide, limiting vascular permeability and dilation respectively. Serum albumin has traditionally been used as a quantitative measure of a patient's nutritional status because of its ready availability and low cost. The reliability of albumin as an assessment of malnutrition is controversial because hypoalbuminemia is an acute phase reactant and is affected by systemic inflammation<sup>[2]</sup>. The increased demand for specific amino acids for acute phase protein synthesis degrades available body protein, including albumin<sup>[3-5]</sup>. Therefore, nutritional status is often determined anecdotally by individual care providers based on their own clinical experience and judgment in clinical practice. In this review, we cover in-depth the clinical indications and implications of serum albumin levels in the setting of colorectal surgery. We investigate the correlation between albumin and postoperative complications, inflammatory bowel disease (IBD) treatment, nutritional response, and new prognostic models.

## LITERATURE RESEARCH

We performed a systematic literature review through an electronic search of MEDLINE from PubMed and the Cochrane Library until May 2015. We used the following search terms and associations: Albumin, hypoalbuminemia, serum protein, nutrition, malnutrition, colorectal surgery, gastrointestinal (GI) surgery, complications, and mortality. Articles were assessed in a tiered fashion. We first screened the titles, assessed abstracts for relevance, then analyzed the entire text of the papers. Only papers in the English language were included. After removing duplicates, 379 total records were found, 339 of which were in English. Thirty-five articles remained after screening and their full texts were analyzed. We completed our search by visiting the bibliographies of relevant articles.

## HYPOALBUMINEMIA IN SURGICAL PATIENTS

In the early 1950's, hypoalbuminemia was noted to negatively influence postoperative recovery<sup>[6,7]</sup>. This finding was followed by work from Harvey who reported that a low serum albumin was the best indicator of concurrent sepsis<sup>[8]</sup>. A high incidence of malnutrition in the hospital setting was only first described in 1974 by Banh<sup>[9]</sup> and Butterworth<sup>[10]</sup>. Contemporary data currently shows that malnutrition has a prevalence of 30% to 50% in hospitalized patients, and is one of the most important patient outcome determinants, affecting length of hospitalization, cost, morbidity, and ultimately mortality<sup>[11,12]</sup>. Most notably, hypoalbuminemia is associated with poor tissue healing, decreased collagen synthesis, and granuloma formation in surgical wounds, ultimately delaying wound healing<sup>[13-17]</sup>. Serum albumin levels have traditionally been used as a biochemical marker of individual nutritional status prior to surgery. It is regarded as an accurate preoperative prognostic indicator in a variety of surgical procedures including cardiac<sup>[18]</sup>, trauma<sup>[19]</sup>, and general surgery<sup>[6,20-22]</sup>. This was perhaps best illustrated in a large-scale non-randomized retrospective study using the National Veteran's Affairs Surgical Database of 54215 patients from 44 tertiary care centers by Gibbs *et al.*<sup>[23]</sup> on major non-cardiac surgeries. Thirty-day morbidity and mortality were measured by C-index (C) where a value of 0.0-0.5 indicates any association between variables are likely due to chance, and C of 0.5-1.0 indicates a strong predictive value or correlation<sup>[24]</sup>. Univariate analysis revealed that albumin < 3.5 g/dL was the strongest preoperative predictor of both 30-d morbidity (C = 0.68) and mortality (C = 0.78), just ahead of American Society of Anesthesiology class. Furthermore, multivariate analysis showed that albumin levels were the strongest predictor of both morbidity [odds ratio (OR) = 0.68; 95%CI: 0.56-0.60] and mortality (OR = 0.44; 95%CI: 0.41-0.48). Albumin levels also independently predicted complication rates of systemic sepsis, acute renal failure, coma, failure to wean from ventilation, and bleeding/transfusions amongst 16 other complications (C = 0.78, 0.76, 0.76, 0.75, 0.72 respectively; all *P* < 0.001). Additionally, analysis of preoperative albumin and major post operative complications in 2003 by Kudsk *et al.*<sup>[25]</sup> identified clinical hypoalbuminemia as an independent determinant of hospital stay, serious postoperative complications (albumin < 4.25 g/dL), and mortality (albumin < 3.25 g/dL).

On the other hand, an ongoing debate continues to exist regarding the value of albumin as a clinical marker of malnutrition. There is no clear consensus amongst healthcare professionals about the definition of malnutrition. Suggested markers include albumin and prealbumin, which are widely used today, and transferrin and retinol binding protein, which are newer evolving

nutritional markers<sup>[9]</sup>. Recent studies have attempted to dispel several myths regarding malnutrition. Albumin and prealbumin have historically been touted as indicators of nutritional risk in the hospital setting, however early literature was based off subjective data and the underlying assumption that albumin and prealbumin accurately reflected nutritional status<sup>[26-28]</sup>. Golden previously showed that kwashiorkor was caused by lack of antioxidants, not dietary proteins<sup>[29]</sup> and in a small study by Carlson *et al.*<sup>[30]</sup> of 10 military burn patients, no correlation was found between nitrogen balance and albumin level, further dispelling serum protein beliefs. A retrospective study of all nutrition consults within 2 years totaling 528 patients suggested that patients' underlying acute or chronic conditions, not nourishment, was responsible for the changes in perioperative albumin<sup>[8]</sup>. Despite this mounting evidence, consensus exists that although albumin may be a poor marker of nutrition, hypoalbuminemia offers clear prognostic value in predicting surgical outcomes<sup>[26,31]</sup>.

## HYPOALBUMINEMIA AND COLORECTAL SURGERY

Despite the growing fund of research surrounding albumin status in general surgery patients, colorectal surgery maintains a unique relationship with nutritional status and albumin level. Colorectal surgery patients are often malnourished due to advanced malignancy or inflammatory bowel disease that results in poor oral intake, intestinal blockages, intestinal fistulas, poor absorptive capacity, and large volume losses from the GI tract<sup>[32]</sup>. Kudsk *et al.*<sup>[25]</sup> emphasized the potential for bias if the surgical site is not considered. Malnutrition is observed in up to 80% of patients with advanced colorectal cancer putting them at increased risk for postoperative complications<sup>[33-35]</sup>. Burden *et al.*<sup>[36]</sup> showed that 1 in 5 pre-operative colorectal cancer patients undergoing surgery were malnourished when measuring body weight (weight loss > 10%) and had a significantly lower handgrip strength ( $P = 0.013$ ), a measure of nutritional status<sup>[37]</sup>. Hypoalbuminemia has also been associated with delayed recovery of postoperative bowel function, further worsening postoperative nutritional recovery<sup>[38]</sup>. Preoperative albumin levels have been shown to be the best predictor of mortality after colorectal cancer surgery<sup>[12,39]</sup>. It is important to concede that the current research surrounding albumin levels is limited and heterogeneous; each study uses different qualifications and methods. Below is a review of the current literature surrounding hypoalbuminemia and its relationship to colorectal surgery.

## COMPLICATIONS

Although the classic definition for hypoalbuminemia is < 3.0 g/dL, studies' definitions vary widely from < 2.7 in some studies to < 3.5 g/dL in others<sup>[12,40,41]</sup>. Using

the American College of Surgeons National Quality Improvement Program (NSQIP) database to measure 30-d postoperative surgical outcomes, Moghadamyeghaneh *et al.*<sup>[12]</sup> emphasized the effect of modest hypoalbuminemia as defined by serum albumin levels between 3.0 and 3.4 g/dL. The mortality rate in patients with modest hypoalbuminemia and without hypoalbuminemia was 6% and 1.7% respectively, and the morbidity risk was greater as well [adjusted odds ratio (AOR) = 1.876; 95%CI: 1.51-2.05;  $P < 0.01$ ]. Not surprisingly, the highest morbidity (60.4%) and mortality (26.2%) rates occurred at serum albumin levels lower than 2 g/dL. Additionally, this study showed a linear correlation between albumin level and postoperative mortality, meaning any decrease in serum albumin level from the normal value (> 4 g/dL) had serious effects on the outcomes following colorectal resections. The rate of increase in mortality and morbidity was estimated to be approximately 49% and 24% respectively for each 1 g/dL decrease in albumin level ( $P < 0.05$ ). Colon cancer patients had a higher rate of modest hypoalbuminemia compared to rectal cancer patients (AOR = 1.55;  $P < 0.01$ ).

## HOSPITAL STAY

Two studies published in 2010 evaluated the association between albumin level and length of hospital stay. Using a cohort of 95 patients admitted for either upper GI surgery or colorectal surgery over a 19-mo period in Australia, Garth *et al.*<sup>[11]</sup> showed that preoperative albumin level was linear and inversely related to the length of hospital stay ( $R = -0.325$ ;  $P < 0.01$ ). Interestingly, grouped analysis revealed upper GI patients presented with significantly lower albumin than colorectal patients. Thirty-one percent of the upper GI group had albumin levels < 3.5 g/dL vs 14% of the colorectal group ( $P < 0.05$ ). Hennessey *et al.*<sup>[16]</sup> showed that an albumin level < 3.0 g/dL was associated with prolonged inpatient stay with a negative linear relationship (19.5 d vs 12 d;  $P < 0.001$ ;  $R^2 = -0.319$ ;  $P < 0.001$ ). Additionally, in 2014 a compilation of 108,898 patients, the largest sample to date of hypoalbuminemic colorectal surgery patients by Moghadamyeghaneh *et al.*<sup>[12]</sup> showed that the median length of stay after surgery was an average of 2 d longer in patients with even modest hypoalbuminemia (albumin 3.0-3.4 g/dL) compared to patients with serum albumin > 3.4 g/dL (95%CI: 1.83-2.34;  $P < 0.01$ ). A study from Thailand showed that an albumin level < 3.5 g/dL increased the length of hospital stay from  $6.8 \pm 2.6$  to  $9.6 \pm 4.7$  d ( $P = 0.001$ )<sup>[38]</sup>.

## ILEUS

Postoperative bowel function is a major determinant of the length of hospital stay and nutritional recovery of a patient. A key retrospective study of 80 patients undergoing right hemicolectomy by Lohsiriwat *et al.*<sup>[38]</sup> showed that an albumin level < 3.5 g/dL compared to

an albumin > 3.5 g/dL was associated with increased postoperative complications (0 and 14 respectively;  $P < 0.001$ ), time to first bowel movement (55.3 and 69.5 h respectively;  $P = 0.018$ ), and time to resume a normal diet (4.0 to 4.9 d respectively;  $P < 0.001$ ). In multivariate analysis, only delayed time to first bowel movement was associated with preoperative hypoalbuminemia. Similarly, Millan *et al.*<sup>[42]</sup> showed that albumin levels < 35 mg/dL were significantly associated with postoperative ileus ( $P = 0.042$ ) in a retrospective study of 773 patients. Kronberg *et al.*<sup>[43]</sup> also showed in a study of 413 patients that preoperative serum albumin concentration was lower in patients who developed postoperative ileus (3.83 mg/dL vs 4.09 mg/dL;  $P = 0.039$ ; OR = 0.90). Prolonged postoperative ileus symptoms include nausea and vomiting, inability to tolerate an oral diet, abdominal distention, and delayed passage of flatus and stool<sup>[44,45]</sup>. Decreasing preoperative albumin was a predictor for prolonged postoperative ileus (OR = 1.11 per gram per litre unit change; 95%CI: 1.02-1.22;  $P = 0.047$ )<sup>[46]</sup>.

## SURGICAL SITE INFECTION

A study of 524 patients undergoing GI surgery [of which 339 (64%) underwent colorectal surgery] in 4 institutions in Ireland showed that patients who developed a surgical site infection had a lower median preoperative serum albumin than those who did not develop an infection, 3.0 g/dL and 3.6 g/dL respectively ( $P < 0.001$ )<sup>[16]</sup>. One hundred and thirty-eight patients (26.3%) had a low pre-operative albumin level (< 3.0 g/dL) and were found to be at increased risk for severe surgical site infections. Of the patients developing a superficial wound infection, 46.4% had a low albumin level ( $P = 0.001$ ). In those with deep wound infections, 80% had low albumin levels ( $P = 0.004$ ), and in those with organ space infection, 83.3% had low albumin levels ( $P = 0.397$ ).

## FISTULAS

Enteric or enterocutaneous fistulas are abnormal communications between the gastrointestinal tract to another cavity or through the skin respectively. Although uncommon, they are a significant concern within colorectal surgery due to their relatively high incidence and considerable morbidity and mortality, first described in a classic case study of 157 patients in 1960<sup>[47-49]</sup>. An estimated 75%-85% of enterocutaneous fistulas are postoperative complications following bowel injury *via* inadvertent enterotomy and/or anastomotic leakage<sup>[50]</sup> and 30%-80% eventually require surgical treatment despite advances in medical treatment<sup>[51-53]</sup>.

Not surprisingly, serum albumin level has been shown to be a vital prognostic factor of healing enteric fistulas<sup>[49,54]</sup>. In a retrospective chart review of 53 GI cancer patients with postoperative enteric fistula complications, Lu *et al.*<sup>[49]</sup> showed a significant corre-

lation between enteric fistula healing/recovery and an increased serum albumin level ( $P = 0.029$ ) and lower fistula drainage amount (< 500 mL/d) ( $P = 0.013$ ) after multivariate analysis. Additionally, amongst patients with both increasing albumin levels and < 500 mL/d of fistula drainage, over 90% of fistulas fully resolved with conservative therapy after total parenteral nutrition (TPN)<sup>[49,55]</sup>. However, although TPN nutritional support has been shown to aid recovery, careful monitoring for underlying or uncontrolled sepsis is required as patients are prone to rapidly deteriorate<sup>[52]</sup>.

Once it is obvious that operative repair is unavoidable, the decision between early surgical fistula treatment vs initial nutritional support with delayed surgery is a difficult one. In a report of 135 consecutive patients with enterocutaneous fistulas by Visschers *et al.*<sup>[53,56]</sup> hypoalbuminemic patients failed to recover well after restorative surgery. Patients with an albumin level below 2.5 g/dL continued to show signs of inflammation postoperatively despite being treated for infection, which lead to eventual deterioration and death in the majority (17/25; 68%) of patients while those who had albumin > 2.5 g/dL had lower mortality (8/25; 32%). Operative fistula repair in hypoalbuminemic patients is therefore recommended only after a nutritive recovery period of at least 6 wk.

## DEEP VEIN THROMBOSIS/PULMONARY EMBOLISM

There is limited data regarding the predictive factors of postoperative venous thromboembolism in patients undergoing colorectal resection. Using data from the large national NSQIP database from 2005 to 2011, Moghadamyeghaneh *et al.*<sup>[41]</sup> showed that a serum albumin < 3.5 mg/dL significantly increased the risk of developing a postoperative deep vein thrombosis (DVT) (AOR = 1.69; 95%CI: 1.49-1.93;  $P < 0.01$ ). Additionally, hypoalbuminemia was also associated with an increased risk of pulmonary embolism (PE) (AOR = 1.21; 95%CI: 1.02-1.42;  $P < 0.02$ ) although the strongest risk factor for PE was not surprisingly a DVT.

## INFLAMMATORY BOWEL DISEASE AND HYPOALBUMINEMIA

Inflammatory bowel disease is broadly classified into two variants, ulcerative colitis (UC) and Crohn's disease (CD). The mainstay of UC and CD therapy is medical management, however up to 1/3 of Crohn's patients will undergo abdominal surgery within the first 5 years of diagnosis<sup>[57]</sup>. In CD, hypoalbuminemia has been shown to be a predictor of intraabdominal septic complications after intestinal anastomosis by Yamamoto *et al.*<sup>[58]</sup> in a retrospective chart review of 343 patients undergoing 1008 intestinal anastomoses between 1980 and 1997. In this study, albumin levels < 3.0 g/dL were considered hypoalbuminemic and significantly affected

the incidence of intra-abdominal sepsis in univariate and multivariate analysis with *P* values of 0.01 and 0.04 respectively. Intraabdominal sepsis occurred in 21% of patients with hypoalbuminemia in contrast to 12% in those without. If all significant risk factors in this study (hypoalbuminemia, steroid use at least one month immediately before surgery, and abscess or fistula at the time of laparotomy) were present, the incidence of sepsis reached 50%. Because reoperations for early postoperative complications were not included in this study, the impact of serious postoperative or refractory hypoalbuminemia could not be assessed.

Intraabdominal sepsis and delayed wound healing are significant consequences of hypoalbuminemia in IBD patients<sup>[59]</sup>. For these reasons, ileal pouch anal anastomosis (IPAA), the treatment of choice for UC, has traditionally been avoided due to the large number of suture or staple lines and wide pelvic dissection in malnourished patients<sup>[60,61]</sup>. An 8-year single-institution prospective study identifying 405 patients showed that an albumin level < 3.5 g/dL was significantly associated with IPAA pouch failure within 30 d to 10 years, development of anastomotic leak, postoperative transfusion, and prolonged inpatient stay using univariate analysis<sup>[62]</sup>. Multivariate analysis revealed preoperative hypoalbuminemia as a strong predictor for anastomotic leak and prolonged median length of stay after pouch surgery, which was 60% longer than in patients with normal albumin levels.

Because of the high complication rate of pouch creation in IBD patients, a staged operation is favored. Nisar *et al*<sup>[62]</sup> showed that hypoalbuminemic patients with IBD who underwent a single-stage total proctocolectomy (TPC) with concurrent pouch creation had a significantly longer inpatient stay and increased postoperative transfusion requirements compared to two-stage subtotal colectomy (STC) with subsequent completion proctocolectomy and IPAA. A higher risk of anastomotic leak in hypoalbuminemic patients was found in single-stage TPC and IPAA (22%) compared to initial STC with follow-up completion proctectomy and IPAA (11%). However, the sample only comprised 24 TPC patients and 10 with STC. Interestingly, this study was one of very few which analyzed serum albumin levels as a continuous variable and thus found that the improvement in albumin between the time of STC and IPAA correlated significantly with the baseline albumin ( $R^2 = 0.814$ ), ( $P < 0.0001$ ).

In a retrospective case series of 78 patients with CD but without hypoalbuminemia, Zerbib *et al*<sup>[63]</sup> showed that weaning steroids and applying enteral nutrition at > 30 kcal/kg ideal body weight/day in intestinal non-occluded patients or TPN in patients with intestinal occlusion together with abscess drainage and antibiotic therapy for 2-3 wk preoperatively minimized the usage of a temporary diverting stoma [7.7% (6/78) of patients] while achieving uneventful operative outcomes in 58% of the total patients. This rate of diverting stoma utilization was significantly lower than a previously

reported series for penetrating CD by Goyer *et al*<sup>[64]</sup> who reported a rate of 39%. This suggests a strong correlation between preoperative nutrition and Crohn's disease surgical outcomes.

## PREOPERATIVE TREATMENT OF HYPOALBUMINEMIA

While the deleterious effects of hypoalbuminemia on the rate of postoperative complications have been well established, pre-surgical correction of hypoalbuminemia remains a subject of debate. While some believe a low albumin level indicates malnutrition, others postulate that the hypoalbuminemia stems from the chronic disease state and resultant inflammation and is not due to malnutrition, thus hindering any beneficial effects of nutritional therapy<sup>[3]</sup>. Although enteral and parenteral nutrition have been shown to improve outcomes in malnourished patients undergoing major elective surgery<sup>[65]</sup>, preoperative nutrition not been well studied in populations undergoing colorectal surgery. The consensus is to stabilize baseline nutritional status and to administer enteral or parenteral nutrition to severely hypoalbuminemic patients preoperatively, even if a delay in surgery is necessary.

In 1982, a study by Rombeau *et al*<sup>[66]</sup> of 33 consecutive IBD patients demonstrated that preoperative TPN given for at least 5 d resulted in significantly fewer postoperative complications ( $P < 0.05$ ). All patients had an albumin < 3.5 g/dL or a transferrin level < 150 mg/dL. In a case series by Jacobson, 15 consecutive CD patients given preoperative TPN were compared to 105 control patients matched for known postoperative complication factors<sup>[67]</sup>. TPN was given between 18 and 90 (avg = 46) d preoperatively before undergoing intestinal resection with primary hand-sewn anastomoses. In this study the average albumin level was significantly increased from 3.4 to 3.9 g/dL ( $P < 0.01$ ) through TPN. There was a significantly higher rate of complications in the non-TPN group (29/105) compared to the TPN group (0/15) ( $P < 0.05$ ). Although the TPN group was without postoperative complications, the risk of preoperative complications should be recognized. In the TPN group, repeated central venous catheter thromboses requiring up to 5 replacements occurred in 4 patients and a pneumothorax which resolved after 5 d of evacuation occurred in one other patient.

Lashner *et al*<sup>[68]</sup> further quantified the significance of preoperative TPN. In a retrospective single-center/single-surgical team study of 103 CD patients, preoperative TPN was only beneficial to CD patients by reducing the length of bowel resection during small bowel resection by more than 20 cm ( $P < 0.04$ ). There was no difference in complication rates. During ileocectomy, TPN patients had a shorter resection by approximately 11 cm when compared to non-TPN patients ( $P < 0.02$ ). However, it appears that the cost of shorter bowel resections in TPN patients was longer hospital stays (12 d;  $P < 0.001$ ). Although this study included patients undergoing

large bowel resection, none of them received preoperative TPN. In this study, TPN was given between 5-7 d and administration > 10 d was not recommended. In contrast, the European Society for Clinical Nutrition and Metabolism guidelines state that if a severe nutritional risk is present, preoperative nutrition therapy, if possible, by enteral route for 10-14 d before surgery is recommended even if the surgery has to be delayed<sup>[69]</sup>. Additionally, Visschers *et al.*<sup>[53]</sup> recommended delaying enterocutaneous fistula repair at least 6 wk to stabilize baseline nutritional status in severely malnourished patients.

## NEW COLORECTAL SURGERY SCORING SYSTEMS

Broad efforts have been made to use albumin levels together with other clinical markers to create a scoring system predicting postoperative morbidity or mortality. The Subjective Global Assessment (SGA) scale combines both subjective aspects of the patient's history such as gastrointestinal symptoms and dietary change and objective aspects such as ankle edema, albumin levels, and tumor grade<sup>[70]</sup>. The SGA stratifies patients into A, B and C categories yielding significant differences in median survival in their cohort of 235 patients (log rank 13.36;  $P = 0.0013$ ). The SGA provides useful prognostic information in patients with advanced colorectal cancer and may identify malnourished patients quickly but suffers due to the inclusion of subjective measures exposing it to observer bias.

The modified Glasgow Prognostic Score (mGPS) ranges from 0-2 and is composed of C-reactive protein (CRP) and albumin levels. mGPS was shown by Park *et al.*<sup>[71]</sup> in a retrospective single-center study to tightly correlate with overall survival (OS) in patients undergoing elective resection of colon cancer ( $P < 0.001$ ). When mGPS and tumor-node-metastasis (TNM) staging were combined, they effectively stratified outcomes of patients undergoing potentially curative resection of colorectal cancer. A TNM stage I /mGPS = 0 yielded a 5-year cancer specific survival (CSS) and overall survival of 97% and 87% respectively; whereas a TNM stage III /mGPS = 2 exhibited a 5-year CSS and OS of 32% and 26% respectively ( $P < 0.001$ ). Additionally, the mGPS stratified the survival of patients who received adjuvant chemotherapy after resection of stage III colon cancer. Patients with mGPS = 0 had a 50% relative increase in survival at 5 years with adjuvant therapy, whereas those with mGPS = 1-2 received no benefit ( $P = 0.003$ ). The mGPS provides important prognostic information in patients undergoing colorectal resections and can help guide adjuvant therapy, especially when combined together with TNM staging.

The Colorectal preoperative Surgical Score (CrOSS) was proposed by Kong *et al.*<sup>[39]</sup> in 2015 as a response to other scoring systems, which require postoperative variables or may be too complex or difficult to assess

at the patient's bedside. Their multivariate logistic regression analysis of 46 variables yielded 4 independent predictors for mortality following colorectal surgery: Age  $\geq 70$ , urgent surgery, albumin level  $\leq 3.0$  g/dL, and congestive heart failure, together composing the CrOSS score. CrOSS accurately predicted mortality with a receiver operating characteristic (ROC) of 0.870 and calibration  $P$ -value of 0.937. The score was internally and externally validated to the Portsmouth and Colorectal Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity and the 2012 Barwon Health model (ROC = 0.788,  $P = 0.24$ ). CrOSS offers a simple yet robust preoperative risk stratification model, specifically tested in colorectal surgery.

## NEW MARKERS FOR MALNUTRITION AND INFLAMMATION

Although albumin remains the widest studied marker for malnutrition, several other markers have been proposed to aid perioperative assessment of a colorectal surgery patient. Prealbumin, transferrin and retinol binding protein are considered traditional markers of nutrition; however, recent data demonstrates their poor relationship to nutrition status<sup>[9]</sup>. Because the markers for a patient's nutrition status are often negative acute-phase reactants, efforts have been made to quantify a patient's inflammatory status as an indirect measure of nutrition and postoperative morbidity and mortality.

In 2012, Oberhofer *et al.*<sup>[72]</sup> showed an increase in CRP in the early postoperative period after colorectal surgery was correlated with a significant increase in complication rates ( $P < 0.001$ ), which agreed with Welsch *et al.*<sup>[73]</sup> who demonstrated that CRP values greater than 140 mg/L on postoperative day 3 or 4 predicted infectious complications and anastomotic leaks after colorectal surgery. Conversely, preoperative CRP levels were not correlated with postoperative complication incidence. Oberhofer *et al.*<sup>[72]</sup> also concluded that postoperative procalcitonin increased significantly more in patients with postoperative complications than those patients without complications, with the highest predictive value on postoperative day 5 ( $P < 0.001$ ). Procalcitonin is also a reliable laboratory marker for early diagnosis of surgical site infection and sepsis after colorectal cancer surgery ( $P < 0.001$ )<sup>[74,75]</sup>.

Prealbumin (PAB), also known as transthyretin, is a visceral protein and a negative acute phase reactant similar to albumin. PAB's advantage over albumin is its shorter half-life (2-3 d), thus it may be more useful for detecting acute changes in nutritional status. However, similar to albumin, PAB has been shown to be a poor marker of nutritional status as evidenced by studies of extreme cases of starvation, which fail to show consistent or reversible decreases in PAB levels<sup>[9,76,77]</sup>. In addition, PAB has been shown to be inferior to albumin as a predictor of colon cancer recurrence. A study of 158 patients with operable colorectal carcinoma in Japan,

56 patients (35.4%) with decreased preoperative PAB and 15 patients (9.5%) with decreased preoperative albumin levels, showed that both a low preoperative serum PAB and albumin were associated with early disease recurrence ( $P = 0.0005$  and  $P = 0.0002$  respectively)<sup>[78]</sup>. However, only albumin maintained its significance in multivariate analysis ( $P = 0.048$ ) while PAB lost significance, indicating that only albumin is an independent predictor of early colorectal carcinoma recurrence.

Additionally, interleukin-6 has recently been shown to correlate with more advanced colorectal cancer<sup>[79]</sup> and was found to cause reactive thrombocytosis, upregulation of CRP, and downregulation of albumin production by the liver, all processes of acute inflammation<sup>[80]</sup>. Preoperative thrombocytosis with a platelet count greater than  $300 \times 10^9/L$  was related to overall survival in multivariate analysis ( $P = 0.039$ ; OR = 1.642; 95%CI: 1.025-2.629)<sup>[81]</sup>.

Recent studies demonstrate positive survival outcomes after colorectal surgery by targeting the systemic inflammatory response with anti-inflammatory agents such as broad-spectrum nonsteroidal anti-inflammatory drugs or aspirin<sup>[82,83]</sup>. Adequate dietary habits are also associated with both decreased colorectal cancer risk and postoperative outcomes. Increased marine n-3 polyunsaturated fatty acids consumption was protective against postoperative complications after colorectal cancer surgery<sup>[84-86]</sup>.

## CONCLUSION

Although albumin remains a flawed marker of nutrition, it offers clear prognostic value in predicting patient outcomes after colorectal surgery. Hypoalbuminemia significantly influences the length of hospital stay and complication rates, specifically surgical site infection, enterocutaneous fistula, and DVT formation. However, these studies are mostly small-cohort non-randomized retrospective studies or large scale studies using national data bases and this topic would benefit from further study. Although clinical hypoalbuminemia is classically defined as serum concentrations  $< 3.0$  g/dL, clinical judgment must account for albumin levels  $\leq 3.4$  g/dL as even modest hypoalbuminemia can affect outcomes. Surgical delay for preoperative nutrition has been shown to improve the morbidity and mortality in patients with severe nutritional risk. Hypoalbuminemic patients may benefit from a staged colorectal resection vs a single operation, especially in the setting of IBD. Efforts to quantify a patient's nutritional status indirectly with inflammatory markers show promise, but the data is superficial and overall inferior to albumin. However, addressing systemic inflammation with anti-inflammatory agents has demonstrated positive survival outcomes in pilot studies. How these developing new markers will be used in combination with albumin is an interesting frontier, meanwhile the SGA, mGPS, and cROSS scoring systems provide convenient and valuable

prognostic information that may help in the counseling and risk adjustment of patients undergoing colorectal surgery.

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