Clinical Nutrition xxx (2016) 1–6

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients

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ARTICLE INFO

Article history:
Received 23 May 2016
Accepted 23 August 2016

Keywords:
Albumin
Colectomy
Colon cancer
Malignancy
Nutrition

SUMMARY

Background & aims: The National Veterans' Affairs Surgical Risk Study identified preoperative hypoalbuminemia as an independent risk factor for postoperative morbidity and mortality. Since that time, few studies have investigated the use of preoperative markers as tools to risk stratify colon cancer patients. The purpose of our study is to determine if there is an association between preoperative hypoalbuminemia and 30-day patient morbidity and mortality in colon cancer patients using the Targeted-Colectomy American College of Surgeons National Surgery Quality Improvement Program (ACS-NSQIP).
Methods: Stage I, II, and III elective colon resections with ileocolostomy or colocolostomy were identified within the ACS-NSQIP targeted colectomy database from 2012 through 2013. Hypoalbuminemia was defined as albumin <3.5 g/dL. Patients with hypoalbuminemia were compared to those with a normal albumin level in terms of 30-day morbidity and mortality. The albumin level at which point 30-day morbidity and mortality increased was identified.
Results: A total of 5143 patients met inclusion criteria; 4397 (85.5%) patients had a normal albumin level while 746 (14.5%) had hypoalbuminemia. Preoperative hypoalbuminemia significantly increased the risk of 30-day mortality ($p < 0.0001$). The association of hypoalbuminemia with 30-day outcomes was more significant in patients who underwent open surgery and had an intra-abdominal anastomosis. The risk of an adverse event was observed to increase at an albumin level $\leq$3.1 g/dL.
Conclusions: Preoperative hypoalbuminemia is associated with an increased risk of early patient morbidity and mortality in patients undergoing surgery for colon cancer. Preoperative optimization of this patient population warrants further investigation in order to prevent delay from surgical intervention to adjuvant therapy.

1. Introduction

Surgical resection with curative intent remains the mainstay of treatment for colon cancer [1,2]. Nevertheless, previous studies have shown that adjuvant chemotherapy leads to an improved disease-free and overall survival rate in all patients with stage III colon cancer and some patients with stage II colon cancer [3]. However, this benefit is lost if initiation of adjuvant therapy is started more than eight weeks postoperatively [4,5]. One risk factor that might lead to a delay in adjuvant therapy is postoperative surgical morbidity.

In 1999, Gibbs et al. published the results of 54,215 patients who underwent non-cardiac surgery at Veterans Affairs medical centers throughout the United States and found that preoperative hypoalbuminemia was an independent risk factor for increased perioperative morbidity and mortality [6]. This finding is particularly important for patients with colon cancer. Not only is colon cancer the second most common cause of death in the United States, but these patients inherently have an impaired nutrition status due the underlying malignant process [6–10]. Indeed, previous studies have shown that tumor-related cachexia has a negative impact on anastomotic healing [7–10].

Colon cancer patients are typically screened for malnutrition risk once they are admitted to the hospital following surgical intervention. Unfortunately, the effect of malignancy on a patient's nutritional status has already manifested at this point. Furthermore, nutrition assessment parameters, including serum albumin levels, have limited usefulness in the postoperative setting as they

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http://dx.doi.org/10.1016/j.clnu.2016.08.023
0261-5614/

transition from a proxy for nutritional status to the dynamic and catabolic response to stress, injury, and infection [11]. Therefore, accurate identification of at-risk patients must occur in the preoperative setting. The purpose of our study is to investigate the effect of preoperative hypoalbuminemia on 30-day morbidity and mortality in patients undergoing elective colon resection for colon cancer using the Targeted-Colectomy National Surgical Quality Improvement Program (NSQIP) database. We hypothesize that patients with hypoalbuminemia will experience increased 30-day morbidity and mortality compared to patients with a normal albumin level.

2. Materials & methods

All patients undergoing elective colon resection from 2012 through 2013 with primary anastomosis were identified within the main NSQIP database using Current Procedural Terminology (CPT) codes. Specifically, those patients undergoing open partial colectomy with an intra-abdominal anastomosis were identified by CPT codes 44140 and 44160. Patients undergoing laparoscopic partial colectomy with an intra-abdominal anastomosis were identified by CPT codes 44204 and 44205. Patients undergoing an open partial colectomy with a pelvic anastomosis were identified by CPT code 44145. Finally, patients undergoing a laparoscopic partial colectomy with pelvic anastomosis were identified by CPT code 44207.

All operative cases identified within the main NSQIP database with the aforementioned CPT codes were merged with the NSQIP targeted colectomy database. Within the targeted colectomy database is a 'col-indication' variable which describes the primary indication for surgery. Only patients with the primary indication for surgery of colon cancer were included in our analysis. Patients with disseminated/stage IV colon cancer, chemotherapy within 30 days of surgery, radiation therapy within 90 days of surgery, positive margins, non-elective cases, and those pregnant at the time of surgery were excluded from our analysis.

Preoperative patient variables, intraoperative patient variables, and 30-day morbidity and mortality outcomes, as limited by the NSQIP database, were investigated. Chi-square, Fisher's exact test, and between groups t-test were used to examine differences in patient demographics, intraoperative variables, and postoperative outcomes between those patients with a normal preoperative albumin level and those with preoperative hypoalbuminemia.

Composite binary outcome variables were created in order to improve the ability to determine an association between hypoalbuminemia and early patient morbidity and mortality. These outcomes included cardiac (myocardial infarction or cardiac arrest requiring cardiopulmonary resuscitation), pulmonary (prolonged intubation, reintubation, or pneumonia), wound events (superficial surgical site infection, deep wound infection, organ space infection, or wound dehiscence), septic events (sepsis or septic shock), renal events (acute kidney injury or postoperative renal failure requiring dialysis), clotting events (deep venous thrombosis or pulmonary embolism), and a grand composite outcome which included all of the binary outcomes in addition to the incidence of 30-day mortality and return to the operating room. For 30-day postoperative outcomes that had significant univariate associations with hypoalbuminemia, multivariate logistic regression was used to examine the independent association of hypoalbuminemia with 30-day morbidity and mortality outcomes, controlling for any covariates that might act as confounders (based on having an association of $p \leq 0.10$ with preoperative albumin level). A backward-elimination approach was used in which predictors with $p > 0.10$ were dropped at each step.

The association of hypoalbuminemia with early patient morbidity and mortality was further investigated based on the type of surgical approach (open vs. laparoscopic) and location of the anastomosis (intra-abdominal vs. pelvic). A surgical approach−hypoalbuminemia interaction term and anastomotic location−hypoalbuminemia interaction term were incorporated into the regression model. When this interaction was significant, it meant that the association of hypoalbuminemia with 30-day morbidity and mortality differed between patients who underwent an open versus a laparoscopic procedure or those who had an intra-abdominal versus a pelvic anastomosis, respectively.

Despite the fact that an albumin level of 3.5 g/dL or greater is considered 'normal,' previous studies have found differing albumin values at which point patient morbidity and mortality is increases [5]. For patients with colon cancer undergoing an elective colectomy, we were interested in further delineating low albumin levels associated with an increased risk of 30-day morbidity and mortality. Therefore, various cut points from 2.5 g/dL to 4.4 g/dL were used to determine the binary albumin indicator which had the best sensitivity, specificity, positive predictive value, and negative predictive value for the grand composite 30-day outcome. This albumin level was combined with the albumin level that maximized the diagnostic information available for the 30-day grand composite outcome using positive and negative likelihood ratios. The likelihood ratio can be used to update the odds of an event based on the test result. If the test is negative, the pre-test odds of having the event are updated using the negative likelihood ratio. If the test is positive, the pre-test odds of having the event are updated using the positive likelihood ratio. The difference between the pre-test odds of having the event and the post-test odds of having the event tells us whether the test provided any new information. Tests that provide more information are more useful, while a test that provides no information is of questionable value. At each albumin level, we subtracted the post-test odds of a negative test from the post-test odds of a positive test in order to calculate the expected information we might obtain from the test. The significant albumin level is the value that maximizes the information obtained from these tests while also achieving reasonable sensitivity and specificity.

Statistical analysis was done using SAS version 9.3 and $p < 0.05$ was considered statistically significant.

3. Results

A total of 5143 patients met inclusion criteria; 4397 (85.5%) patients had a normal preoperative albumin level and 746 (14.5%) patients had preoperative hypoalbuminemia. The average albumin level for patients in the normal range was 4.10 g/dL while the average albumin level for those patients with hypoalbuminemia was 3.07 g/dL. Patients with preoperative hypoalbuminemia were older ($p < 0.0001$), more likely to be female ($p < 0.02$), and had more comorbidities than those patients who had a normal preoperative albumin level (Table 1). In terms of preoperative objective measures of nutritional status, hypoalbuminemia patients had a significantly lower body mass index (BMI) ($p = 0.01$) and were more likely to have lost > 10% of their total body weight within the six months prior to surgery ($p < 0.0001$). Additional patient demographics are detailed in Table 1.

Operative variables are displayed in Table 2. Patients with preoperative hypoalbuminemia were more likely to have an open procedure and were more likely to undergo colectomy with an intra-abdominal anastomosis compared to patients with a normal preoperative albumin level ($p < 0.0001$ for both outcomes).

As previously described, all demographic variables that were statistically significant at $p \leq 0.10$ were included in a multivariate regression model to determine the independent association of hypoalbuminemia with 30-day morbidity and mortality outcomes.

Please cite this article in press as: Haskins IN, et al., Preoperative hypoalbuminemia is associated with worse outcomes in colon cancer patients, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.08.023