ORIGINAL ARTICLE

# Is preoperative hypoproteinemia associated with colorectal cancer stage and postoperative complications?

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## ABSTRACT

**Aim** To investigate the relationship between preoperative level of serum albumin in patients with colorectal cancer (CRC), stage of CRC and postoperative complications.

**Methods** This cross-sectional retrospective study was conducted at the Clinic for General and Abdominal Surgery of the University Clinical Centre Sarajevo (UCCS). A total of 107 patients surgically treated for CRC in the period between 2013 and 2018 were enrolled in this study and divided into two groups: with hypoalbuminemia (group A) and without hypoalbuminemia (group B).

**Results** The average level of albumin in group A was 29 (25-32) g/L versus 39 (37-41) g/L in group B ($p<0.05$). The average length of hospital stay in group A was 18 (13-25) days, and in group B 14.5 (12-21) days. Patients with hypoalbuminemia (group A) had wound dehiscence more often and more re-interventions compared to group B ($p<0.05$). Binary logistic regression found that serum protein, albumin and globulin levels were not statistically significant in the prediction of CRC stadium or postoperative complications ($p>0.05$).

**Conclusion** Study results show that preoperatively measured levels of serum albumin are not associated with the stage of colorectal cancer and cannot serve as predictors for postoperative complications.

**Key words**: colorectal neoplasms, complications, postoperative period, serum

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**Original submission**:
02 February 2021;
**Revised submission:**
29 March 2021;
**Accepted:**
24 May 2021
doi: 10.17392/1353-21

Med Glas (Zenica) 2021; 18(2):450-455

## INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in both genders and the most common gastrointestinal neoplasm in the world. The reduction of incidence and mortality rates over the last few decades has been associated with the reduction in the incidence of risk factors, the emergence of screening programs, and improved therapeutic protocols (1). Patients who have surgery on colon and rectum often have postoperative complications and thus an increased risk of mortality, poor oncological outcomes, other complications and deterioration of life quality. The potential risks of colorectal surgery are the same as with any other abdominal surgery, and complications most often occur during hospitalization (2).

Albumin has been found to have a protective effect on many biological processes, so low albumin levels are considered markers of disease and malnutrition (3-5). Hypoalbuminemia is associated with higher mortality and morbidity of hospitalized patients, patients with a neoplasm and aging population. Truong et al. have found an increasing trend in both postoperative mortality rate and postoperative complications in patients with preoperative low levels of serum albumin (6).

Lai et al. found that preoperative hypoalbuminemia is a predictor of poor surgical outcome and a factor of poor prognosis in long-term survival of patients with colon cancer after curative surgery (7). In an epidemiological review study related to gastrointestinal and lung cancers, female genital tract cancers, and studies on various cancers, it was concluded that the level of pre-therapy serum albumin may be a useful prognostic factor (8). Study results by Gibbs et al. indicate that decreased concentrations of albumin were a predictor of mortality and morbidity for surgical patients, as well as a good predictor for certain postoperative morbidities such as sepsis and infection; serum albumin is not used often enough in preoperative diagnostics as it represents a good and relatively inexpensive indicator of negative outcomes (9). Preoperative hypoalbuminemia represents an independent risk factor for the development of postoperative surgical wound infection after gastrointestinal surgery, and that the infections were deeper with longer hospital stay (10).

Most studies examine preoperative effects of low albumin; however, albumin tends to decline postoperatively due to a physiological response to trauma and surgical stress at a level of about 33%, and Chinese authors suggest that a decline of more than 15% two days after surgery could be used to identify patients with a high probability of developing postoperative complications and having a poor outcome (11).

Albumin is considered a controversial marker of nutritional status (12). Some studies have proven that preoperative serum albumin is a good predictor of mortality and morbidity after CRC surgery (6,13), as well as a good predictor of surgical outcome after emergency abdominal surgery (14). However, there is no clear relationship of serum proteins to CRC stages and their prognostic value. Similar studies on this subject have not been conducted in our country and the Balkan regions so far.

The aim of this study was to determine whether hypoproteinemia and hypoalbuminemia are associated with the stage of colorectal cancer and whether low level of serum albumin can have an effect on the development and severity of postoperative complications in surgically treated patients with colorectal cancer.

## PATIENTS AND METHODS

### Patients and study design

In this cross-sectional retrospective study 107 patients of both genders, older than 18 years, who were surgically treated for clinically, radiologically, colonoscopically and histopathologically confirmed CRC, in the period from September 2013 to January 2018 at the Clinic for General and Abdominal Surgery, University Clinical Centre Sarajevo (UCCS ) were included.

All patients had a preoperative analysis of serum proteins, and possible postoperative complications were recorded. Patients with a neoplasm of different organs were excluded from the study.

Patients were divided into two groups: the patients with preoperative hypoproteinemia (group A; 75 patients), and the patients with preoperative reference values of serum proteins (group B; 32 patients).

The research was accepted and approved by the Department of Science and Education of the Clinical Centre of the University of Sarajevo and completed in compliance with the Helsinki Declaration.

## Methods

An analysis of preoperative serum total protein and albumin levels was determined at the Clinical Chemistry and Biochemistry Clinic at UCCS on a Dimension®Clinical Chemistry System (Siemens, Germany) apparatus using Flex® reagents from Siemens Healthcare Diagnostics (Newark, DE, USA). Referent values for total proteins were 62.0–82.0 g/L, and the referent values for albumins were 35.0–50.0 g/L. All values below the set referent values were considered as hypoproteinemia and hypoalbuminemia.

The principle of oncological surgery with "en bloc" organ resection and associated lymphatic and vascular arcade was followed during operative treatment. Pathohistological analysis of the biopsy material was performed by a pathologist as part of the standard diagnostic procedure, while microbiological tests were performed by the Hospital's microbiological laboratory.

TNM classification of the American Committee for cancer of 2010 was used for classification of colorectal cancer stages (15): the stage of colorectal cancer was marked from I to IV. The values of serum proteins were observed in relation to the stage of the disease.

The occurrence of early postoperative complications such as surgical wound dehiscence, anastomotic dehiscence, abscess development, bacteremia, ileus, and the need for early reintervention were analysed in monitored patients.

## Statistical analysis

Kolmogorov-Smirnov test or Shapiro-Wilk test was used to examine normal distribution of data. Variables with normal distribution were presented as mean±standard deviation (SD) and compared by the parametric tests (t-test, ANOVA). Variables not displaying normal distribution were presented as median and interquartile range and compared by nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test). The ANOVA multiple comparison test was used to examine differences in serum protein values with respect to TNM classification and stage of colorectal cancer. Nominal and ordinal variables in the study were analysed using the $\chi 2$ test. Regression analysis examined the predictor value of serum proteins in assessing the stage of colorectal cancer and the occurrence of postoperative complications. Accepted statistical significance was at the level of $p<0.05$.

## RESULTS

The age of the patients of both groups did not differ statistically significantly: 71 (62-76) vs. 68 (62-75.8) years (p=0.552). There was also no statistically significant difference in the gender distribution of the patients in both groups: 36 (48%) vs. 13 (40.6%) males, and 39 (52%) vs. 19 (59.4%) females, respectively (p=0.483).

Stage III CRC was the most common in both groups: in 37 (49.3%) patients of group A and 20 (62.5%) of group B. The most common localization of cancer in both groups was in the rectum and sigmoid area: 32 (42.7%) in group A, 25 (78.1%) in group B.

Preoperative hypoproteinemia was verified in 75 (70%) patients with CRC (Figure 1).

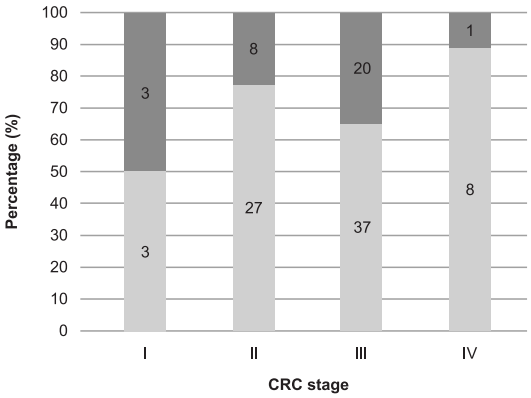


**Figure 1. Presence of hypoproteinemia (lighter coloured) in individual stages of colorectal cancer (CRC)**

Statistically significant differences in the mean values of total serum proteins (p=0.276), serum albumins (p=0.739) or serum globulins (p=0.081) in relation to CRC stage were not confirmed in the patients with hypoproteinemia (group A) (Table 1).

**Table 1. Comparison of differences in the values of serum proteins according to the stage of colorectal cancer (CRC) in patients with hypoproteinemia**

| Variable | CRC stage | No of patients | Mean±SD | p |
|---|---|---|---|---|
| **Total proteins** (g/L) | I | 3 | 63.00±8.30 | 0.276 |
| | II | 27 | 60.85±9.21 | |
| | III | 37 | 62.29±7.86 | |
| | IV | 8 | 59.00±4,24 | |
| **Albumins** (g/L) | I | 3 | 25.50±2.12 | 0.739 |
| | II | 27 | 28.56±4.78 | |
| | III | 37 | 27.47±5.76 | |
| | IV | 8 | 27.50±4.95 | |
| **Globulins** (g/L) | I | 3 | 27.50±7.78 | 0.081 |
| | II | 27 | 32.61±5.96 | |
| | III | 37 | 36.76±8.40 | |
| | IV | 8 | 31.50±0.71 | |

The frequency of postoperative complications (infection, anastomosis dehiscence, abscess and ileus) did not statistically significantly differ between the observed groups. Wound dehiscence occurred statistically more frequently in group A

**Table 2. Postoperative complications of patients with or without hypoproteinemia**

| Postoperative complication | No (%) of patients | | p |
|---|---|---|---|
| | With hypoproteinemia (n=75) | Without hypoproteinemia (n=32) | |
| **Infection** | **13 (17.3)** | **7 (21.9)** | **0.587** |
| Surgical wound dehiscence | 10 (13.3) | 0 | 0.024 |
| Anastomosis dehiscence | 7 (9.3) | 2 (6.3) | 0.460 |
| Abscess | 4 (5.3) | 0 | 0.236 |
| Ileus | 3 (4.0) | 0 | 0.340 |
| Early reintervention | 17 (22.7) | 2 (6.3) | 0.033 |
| **Reinterventions** | | | 0.038 |
| Without | 58 (77.3) | 30 (93.8) | |
| One | 13 (17.3) | 2 (6.3) | |
| Two | 4 (5.3) | 0 | |

compared to group B (p=0.024). A need for early reintervention was noticed in 17 (22.7%) patients with hypoproteinemia, and in only two (6.3%) patients without hypoproteinemia. Thus, in the patients with preoperative hypoproteinemia (group A) surgical reinterventions were significantly more often performed (p=0.038).

However, the average length of hospitalization did not statistically differ between the two observed groups of patients (p=0.113). The average length of hospital stay in patients with hypoproteinemia (group A) was 18 days (ranging from 13 to 25 days), while the average length of hospital stay in group B with normal values of serum protein was 14.5 days, ranging from 12 to 21 days.

Values of total serum proteins, albumins and globulins were not statistically significant in the prediction of CRC stage (Table 3). The values of serum total proteins, albumins and globulins were not statistically significant in the prediction of postoperative complications (Table 4).

**Table 3. Prognostic value of serum proteins in the assessment of colorectal cancer (CRC) stage***

| Variable | **Median** (IR 25-75) | B | Beta | p |
|---|---|---|---|---|
| Total proteins | 67.8 (62.5-73.4) | 0.071 | -0.459 | 0.647 |
| Albumins | 34.0 (31-36.5) | 0.080 | 0.065 | 0.948 |
| Globulins | 34.0 (29.7-37.9) | 0.081 | 0.666 | 0.507 |

*The dependent variable: the stage of CRC; IR, interquartile range; B, regression coefficient; beta, ratio probability

## DISCUSSION

Numerous studies have been conducted in order to find factors with favourable effects, i.e. factors that have adverse effects on the survival of cancer patients, and on mortality and morbidity of surgical patients (16,17). In this regard the significance of serum albumin values has also been investigated (18,19).

In our study we used preoperative serum levels of total proteins, albumins and globulins, as it is known that there is a relationship between nutritional status and albumin levels in patients with CRC (20,21); these patients, due to advanced disease, are often in malnutrition, which results in poor oral food intake, intestinal obstruction, fistula formation, poor absorption capacity and large volume loses from the gastrointestinal tract (22).

In this regard, Gupta and Lis in their review study of the epidemiological literature found in 26 (from 29) studies better survival of patients with gastrointestinal cancer if they had serum albumin >35 g/L (8). Worryingly, in our study, the group of patients with hypoalbuminemia had significantly lower mean serum albumin value (29 g/L) than the indicated cut off value for better survival.

The role of preoperative serum albumin as a prognostic tool in survival of colorectal cancer patients was demonstrated by many studies (23,24), but investigations of association of hypoproteinemia with the different stages of CRC are very limited. In a Turkish study, albumin levels among patients with preoperative metastatic disease were lower compared to those who were metastasis-free as a part of a systemic inflammatory response. Among patients with advanced disease, albumin levels were more reflective of tumour size, respectively the depth of the CR-wall invasion rather than the specific tumour stage, with larger tumours having lower serum albumin levels. The authors suggested that the larger volume of tumour cells translates into a higher production of proinflammatory cytokines, which in turn suppress albumin hepatic production (25).

Our study has shown that values of total serum proteins, albumin, and globulin did not prove statistically significant in the prediction of colorectal carcinoma stage. Such finding suggests that preoperative hypoproteinemia and hypoalbuminemia are most likely related to some other factors such

**Table 4. Statistical significance of serum proteins in the prediction of postoperative complications occurrence**

| Variable | Statistical significance | | | | | |
|---|---|---|---|---|---|---|
| | Infection (n=20) | Surgical reintervention (n=19) | Surgical wound dehiscence (n=10) | Anastomosis dehiscence (n=9) | Abscess (n=4) | Ileus (n=3) |
| Total proteins | 0.967 | 0.996 | 0.817 | 0.492 | 0.937 | 0.805 |
| Albumins | 0.840 | 0.996 | 0.201 | 0.474 | 0.097 | 0.223 |
| Globulins | 0.628 | 0.996 | 0.201 | 0.468 | 0.506 | 0.597 |

as continuous systemic inflammatory response to a malignant tumour that causes loss of body protein in these patients (26).

Recently, there has been a hypothesis that the albumin-globulin (AGR) ratio could have greater clinical significance and may be used as an index of disease-status, but since it does not indicate specific proteins that have been altered in the ratio, it cannot be used as a specific marker. Generally, normal AGR is 0.8-2.0, and lower values could indicate long-term mortality increase in cancer patients (27). In our study this ratio in both groups relative to mean values was in the normal range (0.9 and 1.1, respectively).

In our study, the average length of hospital stay of patients with hypoproteinemia was shorter by 3.5 days (19.4%) comparing to the group without hypoproteinemia. Lohsiriwat et al. showed that albumin level of <35 g/L statistically significantly prolonged hospitalization from 6.8±2.6 days to 9.6±4.7 days (28). Our results were similar to the results of this study in relation to the absolute number of additional days of hospital stay (3.5 vs. 2.8 days). However, the total length of hospital stay of our patients was longer, which could be due to significantly more pronounced hypoalbuminemia and its possible impact on the delayed recovery of our patients.

Investigating the relationship between hypoalbuminemia and the occurrence of postoperative complications in patients with CRC we did not find differences between the groups in case of wound infection, anastomosis dehiscence, abscess and ileus.

Abdominal wound dehiscence is a serious postoperative complication with a mortality rate of up to 45%, and reported prevalence of 0.4%-3.5% (29,30). Important risk factors for wound dehiscence include age, gender, chronic pulmonary disease, ascites, jaundice, anaemia, emergency operations, type of surgery, cough and wound infection (31). Wound dehiscence as a postoperative complication in our study occurred in 13.3% patients with hypoproteinemia, while in the group with referent levels of serum proteins it did not occur. Low preoperative level of albumin might be a risk factor for wound dehiscence. Aksamija et al. have found in a study on 3504 patients operative wound dehiscence after laparotomy in 1.25 patients, of whom 50% had hypoalbuminemia (32). In a prospective study on 50 patients with wound dehiscence in India, 76% patients had an albumin level of 30-36 g/L (33).

In our study, however, we found a link between the need for surgical reintervention and preoperative hypoalbuminemia. An investigation of the effects of preoperative hypoalbuminemia and the outcome of open abdominal aortic aneurysm surgery (OAR) and endovascular surgery of abdominal aortic aneurysm (EVAR) found a strong correlation of significant hypoalbuminemia with postoperative complications and the need for reoperation within 30 days (34).

The main limitation of the study was that it was a retrospective study in a single institution based on data obtained from patients' medical histories. More recent data could not be included in the study because this research was completed as a part of the graduate thesis of the first author at the School of Medicine, University of Sarajevo, in mid-2018. However, this is the first study in Bosnia and Herzegovina examining the association between preoperative albumin, a stage of colorectal cancer and postoperative complications in patients undergoing surgery for primary operable colorectal cancer.

In conclusion, the obtained results show that preoperatively measured concentrations of total proteins and albumins in the serum of patients with colorectal cancer are not predictors for colorectal cancer stage.

## FUNDING

No specific funding was received for this study.

## TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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