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Pre-operative Hypoalbuminemia in Colorectal Cancer Patients Undergoing Elective Surgery – A Major Risk Factor for Postoperative Outcome

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Rezumat

Hipoalbuminemia preoperatorie la pacienții cu cancer colorectal supuși chirurgiei elective - factor major de risc pentru evoluția postoperatorie

Background: Incidența hipoalbuminemiei la pacienții chirurgicali variază în diversele studii publicate pe această temă cu vârsta, stadiul tumorii, intervalul de timp de la apariția simptomelor până la prezentarea la medic, simptomele bolii și obiceiurile nutriționale ale pacienților. Obiectivul principal al studiului a fost evaluarea incidenței hipoalbuminemiei la pacienții cu cancer colorectal supuși intervențiilor elective într-un spital universitar din România și a impactului hipoalbuminemiei asupra evoluției postoperatorii a pacienților. Obiectivul secundar al studiului a fost acela de a identifica și alți posibili factori de risc pentru evoluția postoperatorie a acestor pacienți.
Pacienți și metodă: Studiul a înrolat 252 de pacienți supuși chirurgiei colorectale de elecție în care s-a practicat o anastomoză. S-au evaluat incidența hipoalbuminemiei (albuminele serice 3,5 < g/dL), a fistulelor, precum și a altor complicații postoperatorii (de ex. infecțiile postoperatorii). S-au evaluat, comparativ, durata spitalizării și mortalitatea la 30 de zile la pacienții cu albumine serice normale și scăzute.
Rezultate: 28,9% din pacienții înrolați în studiu au fost hipoalbuminemici. Incidența fistulelor în grupul de studiu a fost de 5,5%. Această incidență a fost de 2,3% și de 13,3% la pacienții cu albumine serice normale și, respectiv, cu hipoalbuminemie (p=0.001). La analiza multivariată, OR a fost de 6.65 [95% CI:2.01-21.96] la pacienții cu hipoalbuminemie moderată și de 24.75 [95% CI: 6.75-90.67] la pacienții cu hipoalbuminemie severă. Asocierea dintre fumat și consumul de alcool a crescut factorul de risc pentru complicații postoperatorii la 1,96 [95% CI: 0.51-7.46].
Concluzii: Incidența mare a hipoalbuminemiei la pacienții din grupul nostru de studiu, justifică atât intervenții nutriționale preoperatorii, cât și protocoale chirurgicale specifice în cazurile operate în urgență. Studii ulterioare pe grupuri mari populaționale sunt necesare pentru a cuantifica exact impactul fumatului și a consumului de alcool asupra evoluției postoperatorii acestor pacienți.

Cuvinte cheie: cancer colorectal, hipoalbuminemie, chirurgie, fistule

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Abstract

Background: The incidence of hypoalbuminemia in surgical patients varies in different studies with age, tumor stage, time interval to the first referral to a doctor, symptoms of disease and nutritional habits of the population. The main objective of this study was to evaluate the incidence of hypoalbuminemia in

colorectal cancer patients undergoing scheduled surgery in an academic hospital in Romania and the impact of hypoalbuminemia on perioperative outcome. The secondary objective was to identify other possible risk factors for the postoperative outcome.
Material and Methods: 252 patients undergoing scheduled colorectal surgery with anastomosis have been enrolled in the study. Incidence of hypoalbuminemia (serum albumin 3.5 < g/dL), fistulas and other postoperative complications (e.g. infections) has been evaluated. LOS and 30-days mortality have also been evaluated comparatively in patients with normal and low serum albumin.
Results: 28.9% of our patients were hypoalbuminemic. The incidence of fistulas was 5.5 % in the study group and 2.3% and 13.3% in patients with normal serum albumin and hypoalbuminemic patients, respectively (p=0.001). Multivariate analysis showed that the OR was 6.65 [95% CI:2.01-21.96] in patients with moderate hypoalbuminemia and 24.75 [95% CI: 6.75-90.67] in patients with severe hypoalbuminemia. Association between alcohol consumption and smoking increased risk ratio to 1.96 [95% CI: 0.51-7.46].
Conclusion: The high incidence of hypoalbuminemia in our patients justifies preoperative nutritional interventions and specific surgical protocols in emergency cases. Further studies are needed to exactly quantify the impact of smoking and alcohol consumption on postoperative outcome.

Key words: colorectal cancer, hypoalbuminemia, surgery, fistulas

Introduction

The number of patients with colorectal cancer undergoing surgery has been increasing over last years in Romania and the newly introduced screening programs will contribute to early detection of an increased number of these patients.

Similar to patients from other countries, most of our patients present to a medical examination and further investigation when symptoms of this disease are prominent and approximately 30% as an emergency examination (1-2). Thus, there is usually a certain time interval between the onset of the disease and referral to a doctor, in which symptoms persist and the effects of colorectal cancer become more prominent.

Malnutrition is one of these effects commonly encountered in colorectal cancer patients that affects postoperative outcome, its most reported incidence varying between 30-60% (3-4). The incidence varies with the instrument used for nutritional screening, stage of disease, characteristics of health systems (colorectal cancer screening programs) and with other factors. This is why numerous studies have focused on the best tools to assess malnutrition in colorectal cancer patients (5-6).

From these numerous tools, it is important to choose those most related to surgical outcome (5-8).

Although in some studies still correlated with nutritional status in surgical patients, serum albumin levels are especially well correlated with surgical outcome and postoperative complications (9-11). The correlation with nutritional status is relatively poor due to numerous factors that may influence serum albumin in cancer patients, including metabolic changes, an increased protein turnover and especially cancer associated inflammation (9,12,13).

As a consequence, different studies were focused on evaluating preoperative hypoalbuminemia and its impact on patients' perioperative outcome (11,14-18).

The primary objective of our prospective study was to evaluate the incidence of hypoalbuminemia in our colorectal cancer patients undergoing scheduled surgery and to correlate this parameter with postoperative complications and length of hospital stay. We have also intended to investigate if there are additional risk factors for postoperative outcome in our patients.

Material and Methods

After obtaining the approval of the Ethics Committee of the Regional Institute of Gastroenterology and Hepatology - Cluj-Napoca (nr. 9422/10 nov.2011), all consecutive patients undergoing surgery for colorectal cancer in our institute between November 2011 - July 2012 (9 months) have been included in this prospective study. Taking into consideration that one of our purposes was to investigate the effect of hypoalbuminemia on postoperative fistulas, only cases where anastomosis has been practiced were included into the study (*Fig. 1*). All patients have been operated under general inhalation anesthesia following the same protocol.

Rectal cancer was defined as a tumor with the lower edge located within 15 cm of the anal verge, as measured by rigid sigmoidoscopy.

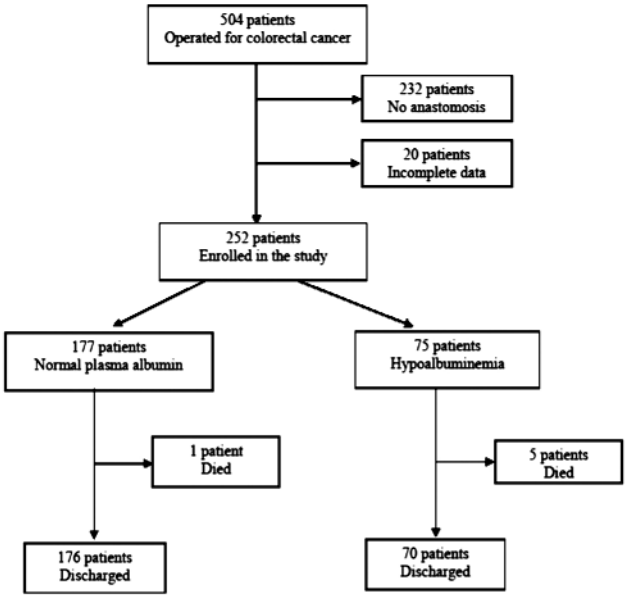


Figure 1. *Patients' flow chart*

Exclusion criteria were emergency cases, laparotomies, and interventions without anastomosis.

Detailed information regarding anamnesis and symptoms of admission for surgery has been collected. Patient demographic data, comorbidities, site and stage of tumor, operative protocol and short-term outcome including postoperative complications were also included in the database. As comorbidities we recorded cardio-vascular diseases (myocardial ischemia, arrhythmias, cardiac failure, hypertension, strokes), respiratory diseases (asthma, COPD), liver diseases (viral hepatitis, steatosis, cirrhosis), diabetes, renal failure, and other significant comorbidities that may influence postoperative outcome. We have also recorded alcohol consumption and smoking.

In terms of alcohol consumption we recorded as moderate those patients admitting to drinking less than 1-2 drinks/day, while as severe alcohol consumption we considered patients drinking more than 2 drinks/day. We have also recorded patients in connection to smoking. Heavy smokers were considered those patients smoking more than 20 cigarettes/day.

Bowel preparation was ensured in all patients. Anastomoses were manually sutured in the vast majority of cases (95% of all cases). All patients were operated on by senior surgeons.

During the postoperative period, patients were provided routine postoperative care with antibiotic prophylaxis, multimodal analgesia, DVT prophylaxis and early mobilization.

All patients received prophylactic antibiotics using third generation cephalosporin and metronidazole started 30 min before incision and continued 24 h postoperatively. Multimodal analgesia included non-steroidal agents and paracetamol unless contraindicated and opioids (morphine) at patient's request.

Nasogastric tubes were at the choice of the surgeon, only if patients had severe PONV, not responsive to treatment.

Postoperative recorded data included infections, fistulas, thrombosis, and other complications. Patients were discharged from the hospital when postoperative drains were removed, with no fever, able to eat and drink and to ambulate.

Postoperative outcome, including mortality, 30 days after operation was also monitored and recorded.

According to the definition in the literature (13), hypoalbuminemia was defined as a serum level $<$ 3.5 g/dL while a serum level $<$ 2.5 g/dL was defined as severe hypoalbuminemia.

Surgical site infections (SSI) were defined and registered according to CDC definition (19). Tumor stages were determined according to AJCC tumor staging (20).

Preoperative evaluation also included basic laboratory tests including serum albumin, hemoglobin, glycemia, creatinine and blood urea nitrogen, and hepatic evaluation where the case required it.

Carcinoembryonic antigen (CEA) has been determined only in 183 patients because of financial reasons by ELISA technique. Normal values for this method as given by our laboratory were 0-5.8 ng/ml.

Statistical analysis

Statistical calculation was done by using statistical package SPSS 16.0 (Chicago, Illinois, USA). Sample size was calculated assuming that the percentage of patients with hypoalbuminemia is 20% as reported in the literature. A sample size of 245 patients was able to detect a 20% incidence of hypoalbuminemic patients with a study power of 80%, and an α coefficient of 0.05 and a β of 0.20.

Chi square, T-student or Fisher's Exact Test were used according to standard application criteria. A p 0.05 was considered significant.

A generalized linear model was used for univariate analysis of the influence of risk factors on the presence of fistulas. We have also done a multivariate analysis of the influence of risk factors on the incidence of fistulas and statistical significance for OR was calculated using Maentel-Haenszel test, considering a 0.05 level of risk.

Results

From 504 patients scheduled for colorectal cancer surgery, a total number of 252 patients in which resection and anastomosis has been practiced completed the study (*Fig. 1*). In 232 patients anastomoses have not been practiced and were excluded from the study. Patients' demographic data are shown in *Table 1*. As can be seen the mean age of the study groups was 63.46 $\pm$ 11.26 years, and 161 (63.88%) of patients were males.

As can be seen in *Table 1* mean body mass index (BMI) in the study group was 25.569$\pm$4.502 kg/m^2, at the limit between normoponderal and obese.

The mean albumin plasma level in the study group was 3.65 $\pm$ 0.62 g/dL. 75 patients (29.8%) did have albumin plasma level $\leq$ 3.4 g/dL, while 14 (5.6%) of these patients were severe hypoalbuminemic (albumin plasma level $\leq$ 2.5g/dL).

Mean hemoglobin level in our study group was 12. 29 $\pm$ 2.29 g/dL. However, 38% of patients were admitted for surgery with a hemoglobin level of 9.0 g/dL.

82 patients (32.5 %) were heavy smokers and 48 patients (19%) admitted to drinking alcohol.

The incidence of postoperative fistulas in the study group was 5.55 % (*Table 2*), while in patients with severe hypo-albuminemia this incidence was of 42.9% (p=0.001). From all 14 patients with postoperative infections in the study group, 10 cases (71.4%) were registered in patients with hypo-albuminemia (p= 0.055) (*Table 3*).

Among the 14 patients who developed fistulas, 4 declared severe alcohol consumption and 3 were heavy smokers. This is why we have preceded to a univariate analysis on the impact of these risk factors on postoperative fistulas. A multivariate analysis was also done to assess the impact of different combinations of factors on the incidence of postoperative fistulas.

This analysis showed that the incidence of anastomotic leaks was significantly higher in hypoalbuminemic patients (p=0.001), (OR=6.65, CI95%=1.9-18.2) as compared with alcohol consumption and smoking with an OR=1.96 (0.51-

Table 1. *Demographic data of the study group*

Age (years)*	63.46 ±11.27
Gender (male/female)	161/ 91 (63.89/ 36.11%)
Weight (Kg)*	74.17 ±14.15
BMI (Kg/m²)*	25.57 ± 4.50
Tumor location (no patients/%)	
Right colon	53 (21.03)
Left colon	21 (8.33)
Transverse colon	14 (5.55)
Sigmoid colon	76 (30.15)
Rectum	88 (34.92)
Tumor stage (no. of patients /%)	
Stage 0	3 (1.19)
Stage I	31 (12.30)
Stage II	99 (39.28)
Stage III	108 (42.85)
Stage IV	11 (4.36)
Hemoglobin level (g/dL)*	12.29 ± 2.29
Co-morbidities (no. of patients /%)	
cardiac diseases	139 (55.16)
respiratory	24 (9.52)
diabetes mellitus	28 (11.11)
cirrhosis	1 (0.39)
Surgical intervention (no patients/%)	
Right hemicolectomy	53 (21.03)
Left hemicolectomy	21 (8.33)
Sigmoid resection	76 (30.15)
Segmental transverse resection	14 (5.55)
Anterior rectal resection	88 (34.92)
Carcinoembryonic antigen (CEA) (ng/mL)	11.05±33.7
Surgical time (min)	121.74±48.64
Intraoperative blood loss (ml)	159.45±149.03

* Data are expressed as mean ± SD

Table 2. *Postoperative complications*

Complication	No. of patients (%)
Anastomotic fistulas	14 (5.55%)
Infections*	19 (7.53%)
Wound-SSI	6 (2.38)
Urinary	13 (5.15%)
Cardiac complications	
Acute myocardial ischemia/infarction	0
Arrhythmias	4 (1.58)
Respiratory complications bronchopneumonia	3 (1.19)
Thrombosis	0
Pulmonary embolism	1(0.39)
Hemorrhage	2 (0.79)
Acute renal failure	2 (0.79)
Bowel obstruction	5 (1.98)
Deceased	6 (2.38)

* 2 patients had neither fistulas nor infections

7.46) (*Table 4*). By comparison OR for severe hypoalbuminemia was 24.75 (6.75-90.67) ($p < 0.05$). Despite not being significant, the combination of alcohol and smoking had an increased OR as compared with each of the factors considered separately.

The mean length of hospital stay (LOS) in the study group was 12.42±5.04 days; LOS in hypoalbuminemic patients was 12.99±5.31 days in patients with hypoalbuminemia and 15.43 ± 6.04 days in severe hypoalbuminemic patients, respectively ($p=0.032$). As can be seen in *Table 3*, the LOS was significantly longer in patients with severe and prolonged hypoalbuminemia without statistical significance in patients with moderate hypoalbuminemia ($p=0.251$).

As can be seen in *Table 3* the number of wound infections was significantly increased in hypoalbuminemic patients ($p < 0.05$).

Overall 30-day mortality was 2.38 % (6 patients). Mortality in non-hypoalbuminemic patients was 0.6%, and of 6.7% in hypoalbuminemic patients ($p=0.01$). Causes of death were sepsis due to fistulas in 4 cases, liver failure in 1 case and cardiac complications in 1 case.

Discussion

Malnutrition is a significant finding in cancer patients; its prevalence varies between 30-60% according to geographical distribution, tumor location and cancer stage (3,4) and between 20-27% in colorectal cancer (3,4).

There are numerous reasons for developing malnutrition

Table 3. *Comparative results on clinical outcome in the study group*

	Non-hypoalbuminemic patients (n= 177)	Hypoalbuminemic patients† (n= 75)	p
Postoperative infections (no. of patients /%)	12 (6.76%)	10 (13.33%)	0.093
- SSI	0	6 (8%)	<0.001
- respiratory	1 (0.5%)	2 (2.6%)	0.16
- urinary	11 (6.2%)	2 (2.6%)	0.245
Fistulas (no. of patients /%)	4 (2.3%)	10 (13.3%)	0.001
Length of hospital stay (d)	12.21±4.9	12.99±5.31	0.251
		15.43±6.04*	0.032*
Death (no. of patients /%)	1(0.6)	5 (6.7)	0.01

*Serum albumin < 2.5 g/dL, † Serum albumin < 3.4 g/dL

Table 4. *Serum albumin, alcohol consumption and smoking and the risk of fistulas*

Factors	Multivariate analysis	
	OR (95% CI)	P value*
Smoking	0.51 (0.2-3.7)	0.137
Moderate alcohol consumption	0.5 (0.168-1.18)	0.476
Severe alcohol consumption	0.3 (0.03-2.38)	0.397
Alcohol consumption & Smoking	1.96 (0.51-7.46)	0.55
Moderate hypoalbuminemia	6.65 (2.01-21.96)	0.001
Severe hypoalbuminemia	24.75 (6.75-90.67)	<< 0.001

(*) Maentel-Haenszel test

in colorectal cancer patients: reduced dietary intake, increased metabolism and protein turnover, cancer cachexia and increased digestive losses (10,11).

Serum albumin was one of the tools used to evaluate nutrition in surgical patients due to its correlation with nutrition (10-12). However, recent studies have shown that serum albumin has a poor correlation with nutritional status due to numerous factors that may alter serum albumin: liver and renal disease, insulin level, zinc deficiency, fluid shift, thyroid metabolism and hydration state, long standing malnutrition and inflammation (12,18).

Inflammatory mediators, especially increased levels of IL-6 and TNF-alpha, released due to an augmented inflammatory response, may increase acute phase protein synthesis at the expenses of albumin synthesis (15,22).

Despite those recent findings, albumin level was proved to have a major impact on surgical outcome, length of hospital stay and postoperative complications: fistulas, infections, wound healing and other morbidities (10-13,21, 23-25). This is why albumin screening has an important role in the context of preoperative evaluation in patients undergoing surgery.

The incidence of hypoalbuminemia varies in different reports with the location and stage of disease, tumor size, age and co-morbidities (10,11). Lai et al. and Lohsiriwat et al. reported incidences between 18.6%-23% in patients with colorectal cancer (10,11), while this incidence was of 82% in critically ill patients with cancer as recently reported by Ñamendys-Silva et al (26). The incidence of hypoalbuminemia in our patients with colorectal cancer was of 28.9%, higher than those reported by Lai and Lohsiriwat (10,11). This increased incidence justifies implementation of preoperative nutritional screening and interventions whenever patient's state allows these interventions.

Correction of severe hypoalbuminemia may also be necessary during postoperative management (13), according to current guidelines. This increased incidence of hypoalbuminemia also justifies including protective diverting colostomy/ileostomy in our patients requiring colonic resection, similar to other surgical protocols (23).

The incidence of postoperative fistulas in our study was of 5.55% similar to other studies (10,27) and greater than in other studies (23,28-30). In hypoalbuminemic patients the incidence of fistulas was 13.3%. As compared with our results, Richardson et al. found an incidence of 21% in patients with an albumin level of less than 3 g/dL, while in patients with albumin level over 3 g/dL this incidence was of only 3.4% (23). Richardson's overall incidence of fistulas was of 6.8%, slightly higher than ours.

Apart from hypoalbuminemia, other major patient related risk factors for anastomotic leaks have been identified in different studies. It has been demonstrated that smoking and alcohol are significant risk factors for anastomotic leaks (31,32). In our study we did not find a significant correlation between alcohol consumption or smoking analysed separately and fistulas. However, a combination of these two factors increased odds ratio, similar to other studies (31). Moreover nearly 30% of patients developing fistulas in our study were heavy drinkers (describing more than 4 drinks/day) and 3 of them were heavy smokers (more than 20 cigarettes/day). Nicotine - induced vasoconstriction, carbon monoxide-induced hypoxia and increased platelet adhesiveness with consecutive microthrombosis at anastomosis site are potential mechanisms explaining the influence of smoking on the anastomosis healing process (31). Likewise an impaired healing process due to nutritional deficiencies in alcoholic patients may be responsible for anastomotic fistulas (31).

Similar to other studies (10,11), we did find a significantly increased incidence of surgical site infections in patients with hypoalbuminemia.

The length of hospital stay was significantly longer in severe hypoalbuminemic patients in our study populations as compared with non-hypoalbuminemic patients ($p=0.01$), result that is similar to others (10). In patients with moderate hypoalbuminemia although LOS was longer as compared with patients with normal albumins, the difference did not reach statistical significance. This prolonged hospitalization may be the final result of a higher incidence of postoperative complications (anastomotic leaks, infections) and perhaps of a delayed bowel function as reported by others, even if this was not proved to be significant (10).

Overall mortality in our study group was of 2.38%; 5 patients (6.7%) have died in the group with low serum albumins ($p=0.01$). Mortality in our study is similar to that of some hospitals in Denmark (33) and higher than the overall mortality reported by Lohsiriwat et al and Lai et al (10,11). However our mortality in patients with normal serum albumin is similar to others (11). Others have recently reported slightly

higher rates on larger group of patients (34-36).

Our study has a few limitations. One of these may be the selection of only those patients in which resection and anastomosis has been done and this may have changed the postoperative infection rate that could otherwise appear also in those patients without anastomosis. We did not monitor time to resumption of bowel function in neither non- nor and hypo-albuminemic patients that may have been another potential explanation for the differences in LOS between these categories of patients. We did not study the correlation between the quantity of alcohol consumption and number of cigarettes/day and the risk for developing fistulas.

In conclusion in our study the incidence of hypo-albuminemia in patients undergoing colorectal surgery for cancer was greater than the average reported in the literature. The clinical implication of this high incidence of hypo-albuminemia consists in the need for implementation of both surgical and nutritional screening protocols in our colorectal cancer patients. Advising patients to stop drinking and smoking before surgery, preoperative nutritional interventions and correcting hypoalbuminemia whenever necessary during preoperative and postoperative period must be included in these protocols that may improve postoperative results. Further studies are needed to evaluate more accurately the implication of lifestyle habits like smoking and alcohol consumption on the risk to develop fistulas taking in consideration that a great percentage of our patients have these habits.

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Conflict of interest

Nothing to declare.

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