Host-Related Predictive Factors for Anastomotic Leakage Following Large Bowel Resections for Colorectal Cancer*

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Abstract

Aim. To identify the risk, the host-related prognostic factors and their predictive value for anastomotic leakage after colorectal resections following cancer. **Method**. 993 patients who underwent large bowel resection and primary anastomosis above 12 centimeters from the anal verge, without a temporary or permanent stoma at the Surgical Hospital No.3 (Cluj-Napoca, Romania) were retrospectively reviewed. **Results**. 32 (3.22 percent) anastomotic leaks were confirmed. Univariate analysis showed that the preoperative variables significantly associated with anastomotic leakage included: weight loss, smoking, cardiovascular disease, lung disease, hypoproteinemia, diabetes, anemia, leukocytosis, presence of two or more underlying diseases. Alcohol use, cerebrovascular disease, bowel preparation, type of anastomosis, tumor location, stage and histology were not significant variables. Hypoproteinemia (total serum protein level ≤ 6 g/dl) and anemia (serum hemoglobin level ≤ 11 g/dl) remained significant in the logistic regression model. The prognostic role of serum hemoglobin and proteins for the anastomotic leak was assessed using ROC curve analysis. For the cut-off value of serum protein level = 5.5 g/dl, a sensitivity of 61.6 percent and a specificity of 84.2 percent were calculated. The area under the curve was 0.703 (p= 0.0024). The area under the curve for serum hemoglobin was 0.616 (p=0.028). A sensitivity of 64.0 percent and a specificity of 64.7 per cent were obtained for a cut-off value of 9.4 g/dl. **Conclusion**. A serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl could be considered as host-related predictive markers for anastomotic leak in large bowel resections for cancer.

Key words

Anastomotic leak – risk factors – predictive markers.

Introduction

Despite recent advances in colorectal surgery, anastomotic leakage after large bowel resections is still, regrettably, a common surgical experience. Reported failure rates range from 1.5 to 5 percent [1-5] or up to 16 percent in low rectal anastomosis [6, 7]. A leaking anastomosis greatly increases the morbidity and mortality associated with the operation: it doubles the length of the hospital stay and increases the mortality as much as 8 to10 fold [8].

A great number of risk factors are controversially discussed in the literature: general-related to the patient population as well as local-related to the surgical technique. However, there is no consensus regarding the role that each factor plays in anastomosis healing process due to their interdependency [9]. Therefore, better knowledge of risk factors is of decisive importance, especially with regard to the consequences for perioperative management or tactical considerations of surgical procedures.

The aim of this study was to evaluate the possible risk factors for anastomotic leak development after colorectal cancer excision, and also to determine the predictive value of each independent risk factor identified.

Patients and methods

Medical records of 1,199 consecutive patients who underwent colonic or rectal resection for colorectal carcinoma between 2002 and 2006 at the 3rd Surgical Clinic (Cluj-Napoca, Romania) were retrospectively reviewed. Excluded were 206 patients with temporary or permanent stoma, multivisceral resections or patients in whom anastomosis was performed below 12 cm from anal verge (in order to eliminate low distance from anal verge as a possible confounding factor related to the surgical

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technique). All patients were followed until discharge. The anastomoses were hand sewn using single layer interrupted suture, end-to-end, end-to-side, side-to-end, or side-to-side, depending on the surgeon's preference or intraoperative conditions. The operations were performed on an elective basis in 765 patients (77 percent) and with curative intent in 815 patients (82 percent). Those patients undergoing elective surgery benefited from bowel preparation that included mechanical cleaning (polyethylene glycol solution). No mechanical bowel preparation was used in patients with symptoms of obstruction or perforation and in those with emergency surgery. Throughout the study period, the preoperative treatment, including nutrition, intravenous prophylactic antibiotics (ceftriaxone and metronidazole), anticoagulation (low molecular weight heparins) was the same for all patients. The pre-operative blood tests were recorded one day before surgery. Postoperatively, all patients were monitored for symptoms and signs of an anastomotic leak, as abdominal tenderness or peritonism, tachycardia and arrhythmias, presence of abscess or fever.

We adopted the following definitions for anastomotic leak: fecal or purulent drainage from the wound or drain, disruption of anastomosis found on reintervention or intra-abdominal collection close to the anastomosis on imaging studies.

Patients' variables such as age, gender, obesity (body mass index > 30 kg/m2), weight loss (> 4 kilograms in the last three months), coexisting medical diseases, alcohol abuse (> 20 g/day over the last three months), smoking history (> 7 pack years), blood tests, tumor location, details of operations, tumor stage (according to the International Union against Cancer, UICC), management of anastomotic leakage, hospital stay, and in-hospital mortality were analyzed from the medical records. Anemia was defined as a hemoglobin value <11 g/dl. Hypoproteinemia was considered when total serum protein level was <6 g/dl. Recorded comorbidities were: diabetes mellitus (if medical treatment was established), cardiovascular disease (hypertension, coronary heart disease, ECG changes and/or angina pectoris in past history and/or specific medical treatment), lung disease (chronic obstructive pulmonary disease, asthma), kidney disease (chronic nephropathies, urolithiasis, obstructive uropathy), cerebrovascular disease (all disorders in which an area of the brain was transiently or permanently affected by ischemia or bleeding).

Statistical analysis was done using the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, Il). Univariate analysis was used to examine the relation between symptomatic anastomotic leak and the variables mentioned above (Tables I, II). Quantitative data were expressed as means ± SD or median (range) accordingly. Comparisons between groups were analyzed by the chi-square test with Yates correction, the Mann-Whitney U-test, or Student's t-test for quantitative and qualitative variables, as appropriate. Variables with a p value < 0.05 in the univariate analysis were subsequently subject to multivariate analysis by logistic regression. Due to the variable number restrictions brought by the small number of anastomotic leakages, three separate multivariate logistic regression models were constructed. For continuous variables, multicollinearity was tested prior to entering the model by means of correlation coefficients matrix (r). Receiver operating characteristic (ROC) curves were calculated, plotting sensitivity to 1–specificity as a measure of predictive performance for anastomotic leak in the study group. The greater the area under the curve (AUC) approaching 1, the greater the predictive performance. Optimum cut-off values, specificity and sensitivity, positive and negative predictive values were obtained for total serum protein and hemoglobin levels.

Table I. Distribution of preoperative variables in patients with anastomotic leakage (AL) and in controls (without AL)

	With AL (n=32)	Without AL (n=961)	Odds Ratio (95% CI)	p value
Gender				
Female	13(40.6%)	470(48.9%)	0.68-2.86	0.478
Male	19(59.4%)	491(51.1%)		
Age (years) (mean (SD)	63.4 (6.3)	64.8 (5.2)		0.10
< 40	2	46	0.30-5.72	0.11
41-60	10	334	0.4-1.82	0.91
61-80	18	545	0.48-2.00	0.83
> 80	2	36	0.39-7.45	0.08
Weight loss (> 4 kg)	11	168	1.31-5.88	0.026
Obesity	9	162	0.63-2.86	0.16
Smoking	15	181	1.69-6.82	0.021
Alcohol	6	97	0.82-5.1	0.98
Cardiovascular disease	22	450	1.17-5.13	0.02
Diabetes	14	139	3.2-14.5	0.016
Lung disease	14	162	1.4-8.99	0.035
Kidney disease	5	67	0.92-6.3	0.07
Cerebrovascular disease	4	47	0.93-8.25	0.13
No. of associated diseases				
None	6	296	0.2-1.25	0.19
One	11	404	0.34-1.51	0.46
Two/More	15	261	1.16-4.18	0.024
Hemoglobin (g/dl) (median/range)	8.9 (9.8)	11.2 (12.7)		0.028
Hemoglobin (<11 g/dl)	18	265	1.65-6.88	0.02
WBC (10^9/l) (median/range)	11.1 (13.2)	7.9 (9.2)		0.049
WBC > 10.000/ mm^3	13	137	2.06-8.84	0.04
Serum protein (g/dl) (mean (SD))	5.3 (6.1)	7.0 (4.6)		0.016
Serum protein <6 g/dl	21	271	2.31-10.21	0.0009

Table II. Distribution of operative variables in patients with anastomotic leakage (AL) and in controls (without AL)

	With AL	Without AL	Odds ratio (95% CI)	p value
Elective/ emergency operation	25/7	865/96		0.06
Curative/ palliative operation	24/8	791/170		0.9
UICC I	3	109	0.24-2.70	0.41
UICC II	5	174	0.31-2.20	0.65
UICC III	17	435	0.7-2.9	0.67
UICC IV	7	243	0.35-1.93	0.81
Tumor location				
Right colon	10	250	0.60-2.77	0.99
Transverse colon	5	87	0.69-4.59	0.76
Left colon	11	356	0.42-1.87	0.89
Rectum	6	268	0.24-1.46	0.97
Operation type				
Right colectomy	6	270	0.24-1.45	0.96
Transverse colectomy	3	45	0.61-7.18	0.3
Left colectomy	6	121	0.64-3.97	0.85
Sigmoid colectomy	8	236	0.46-2.34	0.69
Subtotal/Total colectomy	3	18	1.56-20.18	0.25
Anterior resection*	6	271	0.23-1.44	0.95
Ileocolic/ colocolic	9/23	273/688	0.45-2.15	0.86

*anastomosis was performed above 12 cm from anal verge

Results

Out of 993 patients, 510 were males and 483 females with a mean age 63.6 years. Indication for surgery was colorectal cancer in all cases. The tumors were mainly located in the rectum in 274 patients (27.6 percent), followed by sigmoid colon in 250 patients, (25.17 percent), ascending colon in 184 patients (18.52 percent), transverse colon in 92 patients (9.26 percent), descending colon in 85 patients (8.56 percent), hepatic flexure in 76 patients (9.26 percent) and splenic flexure in 32 patients (3.22 percent).

Distribution according to the Dukes classification was A class in 25, BI class in 87, BII in 179, CI in 227, CII in 225 and D in 250 patients. The breakdown by TNM classification was: 112 patients in stage I, 179 stage II, 452 stage III and 250 in stage IV disease.

Medical illnesses were present in 697 patients (70.2 percent) (Table I). Cardiovascular disease was the predominant risk factor in more than one half of the patients, followed by obesity, diabetes, lung disease, weight loss and nicotine abuse in almost 20 percent. Other significant risk factors were regular alcohol abuse in 10.37 percent, urinary disorders in 7.25 percent; 276 patients had two or more associated disorders. The types of operation according to the reason for and site of tumor were: right colectomy (276), sigmoid resection (244), left colectomy (127), anterior resection (277), transverse colectomy (48) and subtotal or total colectomy (21). The most common complication was wound infection which occurred in 215 patients (21.65 percent). Other postoperative complications were: prolonged ileus in 44 (4.43 percent), urinary tract infection in 32 (3.22 percent), respiratory complications in 27 (2.71 percent), heart failure in 22 (2.21 percent), septic shock in 19 (1.91 percent), upper gastrointestinal bleeding in 14 (1.4 percent), hemorrhage in 14 (1.4 percent), deep vein thrombosis and pulmonary embolism in 13 (1.3 percent) and intra-abdominal abscess in 11 patients (1.1 percent).

A total of 32 (3.22 percent) patients had anastomotic leaks. There were 19 males and 13 females, mean age 64.08 years (range 53–79). All these patients underwent surgical revision. Overall, leaks were diagnosed at a mean of 10.3 days (range 3–19) postoperatively. The mean postoperative hospitalization was 13.7 days (range 5–74 days). It was significantly longer in the anastomotic leakage group: 38.8 days (range 17–74 days) versus 11.7 days (range 5–46 days), $p < 0.0001$. The overall mortality rate in the anastomotic leakage group was 28.12 percent. Mortality related to anastomotic dehiscence was 21.18 percent.

Univariate analysis revealed no correlation between anastomotic leakage and gender, age, body weight, use of alcohol, emergency operation and tumor histology or tumor stage. The leak rate was similar by surgical site. Only weight loss, smoking, cardiovascular disease, lung disease, diabetes, leukocytosis, two or more underlying diseases, preoperative anemia (serum hemoglobin level ≤11 g/dl) and preoperative hypoproteinemia (total serum protein level ≤6 g/dl) were significantly associated with anastomotic leak occurrence.

Multivariate analysis showed that serum hemoglobin level less than 11 g/dl and serum protein level less than 6 g/dl were independent risk factors for anastomotic leakage (Table III).

Receiver operating characteristic (ROC) curves were plotted to assess the value of preoperative serum protein level (Fig.1) as a predictive marker for anastomotic leak. A cut-off point of 5.5 g/dl was determined by using the ROC method, giving serum protein measurement an AUC of 0.703 (0.616-0.781) - p=0.0024; sensitivity 61.6 percent (31.6-86); specificity 84.2 percent (76.2-90.4); positive likelihood ratio 3.9 and a negative likelihood ratio of 0.46.

The ROC analysis also revealed the moderate prediction power of serum hemoglobin level for anastomotic leak occurrence (Fig. 2). AUC for serum hemoglobin level was 0.616 (0.573-657) (p=0.028). A sensitivity of 64.0 percent (42.5-82.0) and a specificity of 64.7 percent (60.4-68.9) were obtained for a cut off value ≤ 9.4 g/dl. The positive and negative likelihood ratios for the cut-off value were 1.81 and 0.56 respectively.

Discussion

Suture dehiscence has been associated with one fifth

Table III. Multivariate analysis of the variables related to anastomotic leakage

Parameter	OR	95% CI	p
Weight loss (>4 kg)	1.01	0.95-1.05	0.674
Obesity	1.16	0.74-1.53	0.527
Smoking	1.08	0.39-1.89	0.329
Alcohol	1.10	0.54-1.34	0.493
Cardiovascular disease	1.21	0.97-1.54	0.126
Diabetes	1.28	0.87-1.63	0.101
Lung disease	1.01	0.65-1.02	0.875
Hemoglobin (<11 g/dl)	2.28	1.21-2.87	0.004
WBC >10.000/mm^3	1.07	0.89-1.21	0.216
Serum proteins <60g/l	1.97	1.10-2.01	0.028

Three separate logistic regression models were constructed, including:
Model 1: weight loss (>4 kg), smoking and use of alcohol.
Model 2: obesity, diabetes, cardiovascular disease, lung disease.
Model 3: hemoglobin, WBC, S-Protein (as continuous variables).

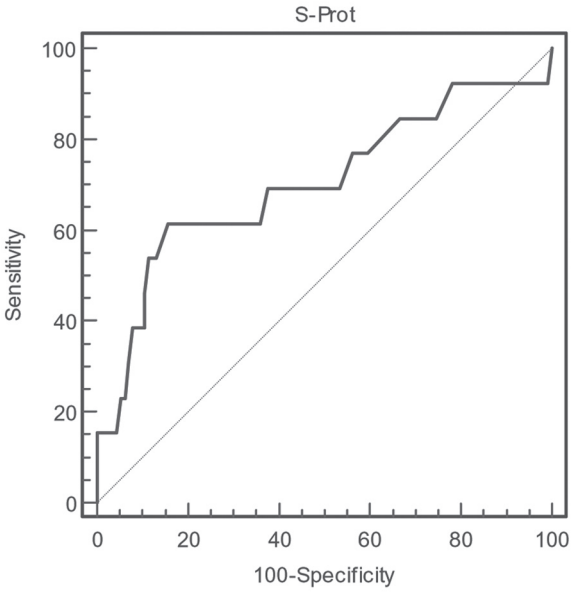

Fig 1. ROC curve of serum protein levels

to one third of all postoperative deaths in patients who underwent an intestinal anastomosis [10].

Several studies regarding factors that contribute to failure of large bowel anastomosis have been published. The majority of these studies had focused on the anastomosis after rectal cancer resections. Furthermore, there are no reports examining the predictive value of each independent factor for anastomotic leak development.

In our study, the analyzed variables were subdivided into general - related to the patient's characteristics and local - related to the surgical technique and tumor characteristics. Most of the variables cited in the literature as potential risk factors for anastomotic leakage were reviewed.

The 3.2 percent rate of anastomotic leakage found in our series is within the range reported in the literature - 1.5 to 10 percent and is an acceptable rate [11-13]. The leakage

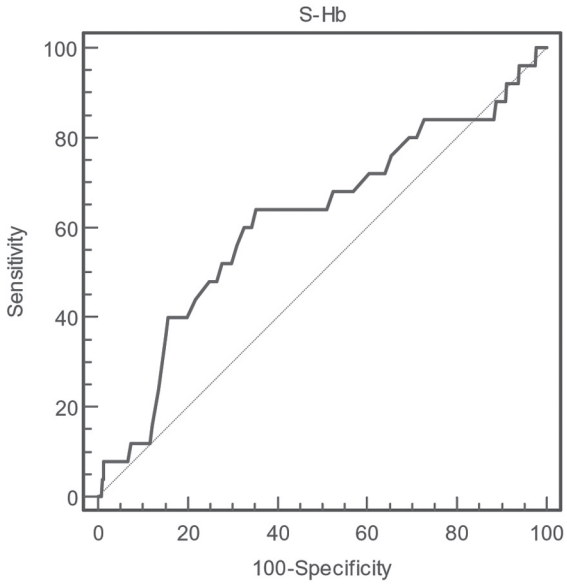

Fig 2. ROC curve for serum hemoglobin levels

related mortality rate ranged from 10 to 15 percent in various publications [12, 13] and it was 21.87 percent (7 patients) in our study. The overall mortality of 28.12 percent (9 patients) was similar to that found by other authors [15].

Premorbid medical conditions reflect patient's general status and add to the surgical risk, affecting anastomotic healing [16, 17]. The association of anastomotic leak with several clinical and biologic findings has been established [3, 16, 19-22]. Male gender [3, 19], ASA grade > 3, leukocytosis [21], systemic hypertension, tobacco and alcohol use [7, 20], age, previous abdominal surgery, malnutrition, metabolic disorders, weight loss, obesity, cardiovascular disease [16, 21], diabetes mellitus and multiple blood transfusions [16, 22] have been associated with anastomotic dehiscence.

In our study, among the clinical and biological factors analyzed, weight loss, smoking, cardiovascular disease, lung disease, hypoproteinemia, diabetes, anemia, leukocytosis, two or more underlying diseases were significantly associated with anastomotic leakage in the univariate analysis.

A great number of studies describe surgical related variables as risk factors for the development of leakage [3, 17-22]. In contrast, therapeutic parameters were not identified as risk factor in our cohort. We recruited only patients with cancer who underwent hand sewn anastomosis, performed by senior surgeons. Moreover, since many studies [6, 9] proved that very low rectal anastomosis has a high risk of dehiscence due to anatomical conditions, in order to exclude this bias we analyzed only patients in whom anastomosis was performed above 12 cm from the anal verge. The ROC analysis indicated that low values of serum proteins (<5.5 g/dl) and serum hemoglobin (<9.4 g/dl) were predictive for the patients with an anastomotic leak; serum protein value seemed to be the most sensitive and specific host predictor for the development of anastomotic dehiscence.

Why do low values of serum proteins and hemoglobin

predict an unfavorable outcome from the anastomosis point of view? The reasons for which the two factors predispose to anastomotic leakage were clearly stated. Hypoproteinemia affects anastomotic healing through either lack of essential amino acids for collagen synthesis or deterioration of patients' immunocompetence [22]. Hemoglobin is related to perfusion and oxygenation of the anastomotic margins (an essential factor for anastomotic healing). All other risk factors are probably directly or indirectly related to these fundamental phases of the healing process [22, 23]. Few reports have been dedicated to study the predictive value of various factors for anastomotic leakage following colorectal resections. The majority of these studies were focused on local factors [17]. To the best of our knowledge, no study has tested the predictive role of preoperative serum proteins and serum hemoglobin levels for large bowel anastomotic leak by means of ROC analysis.

Conclusion

Low values of serum proteins or serum hemoglobin are significantly associated with anastomotic leakage both in univariate and multivariate analysis: patients with serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl are at a high risk of anastomotic leak. Thus, the risk of dehiscence can be more accurately predicted and used as an indicator for the need of preoperative correction of anemia and hypoproteinemia to improve the viability of the anastomosis.

Conflicts of interest

None to declare.

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