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Original Research Article

Independent perioperative predictive risk factors for the anastomotic leak after emergency bowel resection anastomosis

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ABSTRACT

Background: Anastomotic disruption after bowel resection anastomosis is a devastating and a feared complication, so it is of utmost importance to identify perioperative parameters predisposing to such complication.
Methods: A prospective cohort study was performed in two institutes, and there were 287 patients eligible and included in the study which done from April 2017 to December 2018, 87 patients underwent intervention in the first institute in Zagazig University Hospitals, Egypt. And 200 patients underwent intervention in Riyadh, KSA. Statistical analysis used: Percent of categorical variables were compared using Pearson's Chi-square test or Fisher's exact test when was appropriate. Risk estimation was done by Odds ratio (OR) calculation. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium).
Results: Of the parameters analyzed risk factors for anastomotic leakage that studied in 287 patients, 6 perioperative parameters have significant statistical difference: hypo-albuminaemia (Odd ratio: 6.544 and p-value <0.001), acute intra-abdominal contamination (Odd ratio: 3.921 and P-value <0.004), High WBC'S with high presepsin with p-value <0.001, hyponatremia p<0.004, perioperative blood transfusion and anastomotic tension were found to be independent factors.
Conclusions: Knowledge of independent perioperative predictive factors for leakage is of utmost importance for its early detection, decision making for surgical time, our study concluded the possibility to detect a subgroup of high-risk patients for anastomotic leakage after emergency bowel resection anastomosis.

Keywords: Emergency bowel resection, Intestinal leakage, Risk factors for leakage

INTRODUCTION

Anastomotic disruption is the most devastating complication after intestinal resection anastomosis. Is a dreaded complication.[1-4] Anastomotic leakage can present with various clinical pictures, ranging from asymptomatic patients to life threatening fecal peritonitis.[5] There are dependent and independent factors predispose to such a leak and recognition of these factors is of utmost importance for early detecting and managing this dreaded complication.[6-7]

The primary outcome is recognition of independent perioperative parameters predispose to leakage for early detection and managing dreaded complication.

METHODS

Study approved by the institutional review board and ethical committee of Zagazig University Hospitals.

The study was performed in two institutes, and there were 287 patients were eligible and included in the Zagazig

University Hospitals, Egypt and 200 patients underwent intervention in Riyad, KSA. Study done during the period from April 2017 to December 2018.

All adult patients requiring emergency laparotomy with symptoms and signs of peritonism were considered eligible in the study.

Exclusion criteria

Patients who had undergone upper GIT surgery (gastric or gastro-esophageal) resection anastomosis and patients with a protective stoma proximal to the anastomosis were excluded.

Procedure of assessment

All anastomotic leakage (AL) in our study was clinically symptomatic and defined clinically and with diagnostic imaging or intraoperative findings. We utilized the Imaging techniques for diagnosing some fistulas, and this included, abdomino-pelvic sonography, computed tomographic scans to detect leaks by the presence of contrast extravasations, or an abscess adjacent to a suture/ suture line.

There is no unique or specific definition of a dehiscent bowel anastomosis, which may present as a localized abscess, as a generalized peritonitis, or as faecal discharge from the wound and/or drain. Operative findings of leakage included intra-abdominal contamination with enteric contents, gas, or a visible dehiscence at the site of anastomosis between 2 bowel segments. Peripheral blood samples were collected from patients at the perioperative period. Written informed consent was obtained from all participants according to the local ethics guidelines.

All patients were under complete workup before surgery, nutritional status assessment and patients with albumin less than 3mg/dl and experienced more than 5-6 kg weight loss during the past few months were considered malnourished. Since first day of admission, preoperatively, until 7th day postoperatively, the cut off values of the average serum albumin level, electrolytes, WBC'S and presepsin were monitored and defined according to the median serum levels in our study cohort. Hyponatemia defined as Na less than 130 mEq/L, high WBC's defined as more than 12.000/mm, high presepsin is more than 250 pg/ml. All predictive risk factors are listed in Table 1.

Most of patients didn't receive mechanical preparation as our cases were emergency and urgent cases. All patients didn't receive any oral bowel preparation before surgery. Surgical procedures were classified as clean-contaminated (bowel opened without spillage of contents) or contaminated (gross spillage).

The American Society of Anesthesiologists (ASA) preoperative risk assessment score was used to determine operative risk. The patients with a score of three and four were compared with those with a score one or two.

Table 1: Definition of predictive risk factors.

Factors	Definition
Patient factors	
Medical risk factors and comorbidity	
Old age	Patients above 65 years
Cardiac patients	Congestive heart failure, symptomatic dysrhthmia, valvular diseases
Diabetes	History of type I or II Diabetes mellitus.
Chest diseases	History of COPD or other chronic lung disorder
Renal failure	On hemodialysis or creatinine ≥3
Nutritional and laboratory risk factors	
Malnutrition	Albumin less than 3mg/dl and experience more than 5kg weight loss in the past 5 months.
Obesity	BMI>27
Haematocrite	Less than 28
Hypo-Albuminemia	less than 3mg/dl
Hyponatremia	less than 130 meq/l
High WBC'S	More than 12.000 mm^3
Presepsin	More than 250 pg/ml
Clinical and operative factors	
Prolonged operative time	>3 hours
intra-abdominal infection	Presence of generalized peritonitis or intra-abdominal localized pus.
Chronic inflammation	Presence of Crohns or Ulcerative colitis
Emergent/ Urgent surgery	Urgent due to perforated viscus with generalized peritonitis and possible septicemia or emergency in patients with intestinal obstruction with abdominal distension
ASA (American Society of Anesthesiology): (preoperative assessment of physical status)	I: Normal physical status II: Mild systemic diseases III Moderate systemic diseases IV: Constant threat with life
Multiple blood transfusion	Administration of more than 2 units' blood before, during or after surgery.
Anastomosis under tension	In cases of left sided resection Anastomosis

The ASA score was assigned by the attending anesthesiologist after completing a structured review of

physical status immediately prior to the surgical procedure.

Parameters and data collection

Patient demographics and illness: gender, age, American Society of Anesthesiology (ASA) score, body mass index (BMI), and comorbidity.

Figure 1: Ruptured intestinal lymphoma.

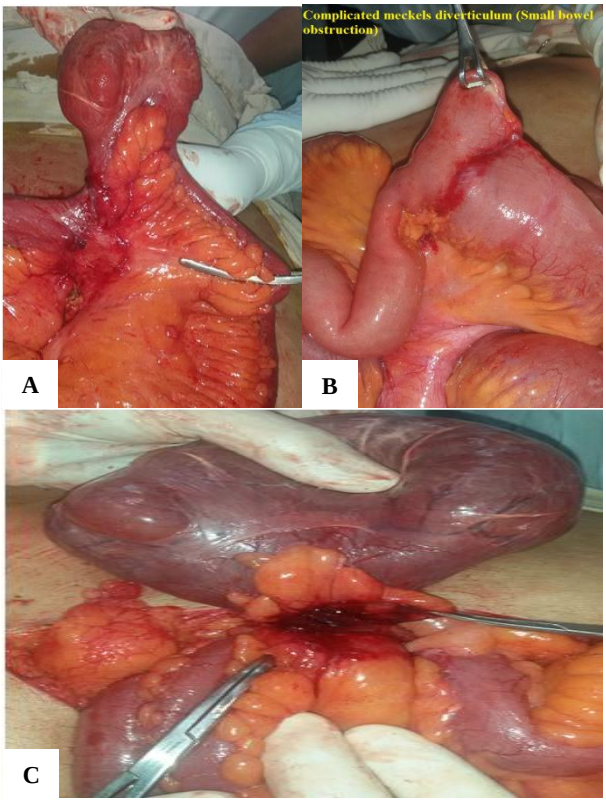

Figure 2: (A) Complicated small bowel diverticulum, (B) complicated meckels diverticulum, (C) strangulated diverticulum.

Type of pathology: Malignancy (Figure 1), complicated diverticulum (Figure 2a-b-c), familial polyposis (Figure 3), band (Figure 4), inflammatory bowel disease with fistula (Figure 5), mesenteric vascular occlusion (Figure 6).

Site of pathology and site of resection anastomosis: (Small bowel resection, right hemicolectomy, left hemicolectomy), and type and location of anastomosis (end-to-end, side-to-end, side-to-side, ileocolic, colocolic or entero-enteric).

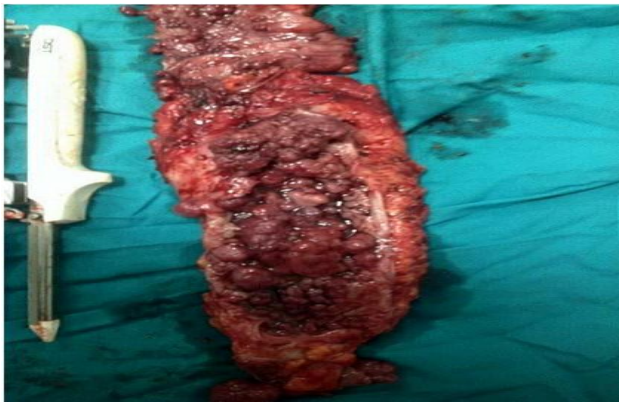

Figure 3: Familial polyposis.

Figure 4: Constricting band.

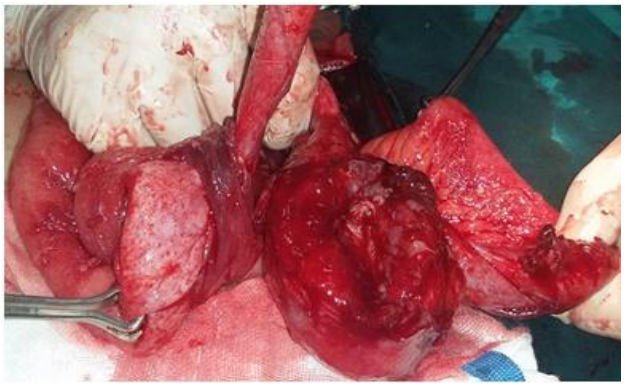

Figure 5: Abscess and fistula.

Technique: conventional or laparoscopy (Figure 7).

All recorded complication mainly leaks was reviewed by both attending and resident doctors on a daily basis or weekly after discharge to assure appropriate standardization of definitions which include early and late leakage.

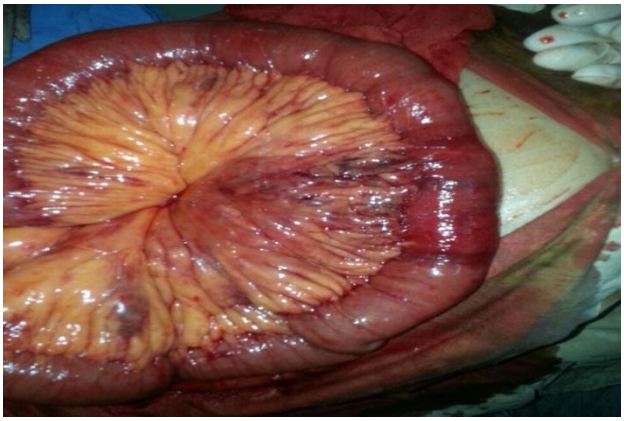

Figure 6: Mesenteric vascular.

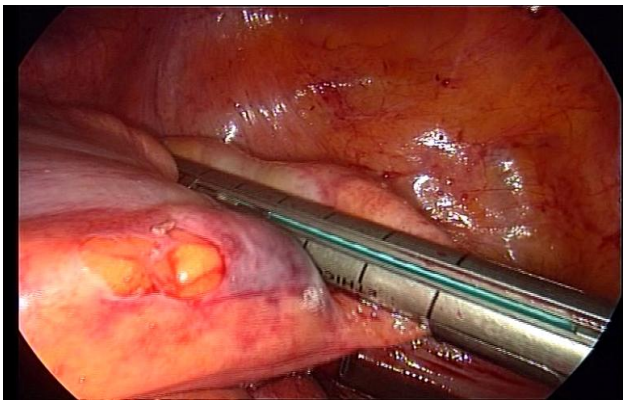

Figure 7: Laparoscopic colectomy.

Statistical analysis

Continuous variables were expressed as the mean ± SD and the categorical variables were expressed as a number (percentage). Percent of categorical variables were compared using Pearson's Chi-square test or Fisher's exact test when was appropriate. Risk estimation was done by Odds ratio (OR) calculation. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium).

RESULTS

Over one and a half-year study period, 287 patients undergoing intestinal anastomosis without faecal diversion met inclusion criteria for the study.

Table 2: Demographic data.

Variables	Number of patients (n=287)	
	No.	%
Age (years)		
<65	150	52.26%
>65	137	47.74%
Sex		
Male	130	45.30%
Female	157	54.70%

Categorical variables were expressed as number (percentage).

Patient demographic information is outlined in (Table 2). 29 patients (10.1 %) developed an anastomotic leak. A study including 130 males and 157 females. There were 150 patients below 65 years and 137 patients more than 65 years; the mean age of patients with a leak below 65 years old was ±57 years and ±69 years for patients above 65 years**.** Overall mortality was 5.9% (17/287) patients. The findings from the analysis showed no statistical difference between patients with and without leaks in terms of demographics and mortality.

Six parameters: hypoalbuminaemia, acute intra-abdominal contamination, perioperative blood transfusions, anastomotic tension or anastomosis of left side, hyponatremia and high WBC'S with high presepsin level in serum were found to be independent predictive parameters for anastomotic leakage in the early postoperative period (Table 3).

Patients in the leakage group were more often hypoalbuminemia and malnourished (26/29) than the patients with good nutritional status (3/29 patients, P 0.001 and odd ratio 6.544 and CI 95% was (1.932-22.172). Malnutrition recorded as one of the most important independent risk factor for leakage.

Table 3: Predictive risk factors for leakage.

	All (N=287)		Leakage (N=29)		No leakage (N=258)		OR	(95%CI)	P value‡
	No.	%	No.	%	No.	%			
Age (years)									
<65	132	45.99	12	9.09	120	90.91	0.812	(0.373– 1.768)	0.599
>65	155	54.01	17	10.97	138	89.03	Reference		
Comorbidity									
One diseases	143	49.83	13	9.09	130	90.91	0.800	(0.370–1.730)	0.570
More than one	144	50.17	16	11.11	128	88.89	Reference		
Hypoalbuminema and nutrition status									
Albumin <3 md/dl	173	60.28	26	15.03	147	84.97	6.544	(1.932–22.172)	0.001
Albumin >3 md/dl	114	39.72	3	2.63	111	97.37			

Continued.

	All (N=287)		Leakage (N=29)		No leakage (N=258)		OR	(95%CI)	P value‡
	No.	%	No.	%	No.	%			
BMI									
<33 kg/m^2	171	59.58	10	5.84	161	94.16	0.396	(0.178– 0.881)	0.090
>33 kg/m^2	115	40.07	19	16.58	96	83.42	Reference		
WBC and presepsin									
WBC >12000 mm^3 and prespsin >250 pg/ml	157	54.37	24	14.64	133	92.39.03	5.527	(2.692–13.283)	0.001
WBC <12000 mm^3 and prespsin <250 pg/ml	130	45.62	5	4.13	125	87.35.72	Reference		
Anastomotic method									
Single layer	145	50.52	11	7.59	134	92.41	0.566	(0.257–1.245)	0.153
Two layer	142	49.48	18	12.68	124	87.32	Reference		
Bowel distension									
Marked distension	132	45.99	17	12.88	115	87.12	1.762	(0.809–3.838)	0.150
No distension	155	54.01	12	7.74	143	92.26	Reference		
Peritonitis and contamination									
Contamination	166	57.84	24	14.46	142	85.54	3.921	(1.451–10.598)	0.004
Clean	121	42.16	5	4.13	116	95.87	Reference		
Anastomosis under tension									
Present	156	54.36	23	17.56	108	82.44	5.324	(2.097-13.520)	<0.001
Absent	131	45.64	6	3.85	150	96.15	Reference		
Pathology									
Malignant	143	49.83	13	9.09	130	90.91	0.800	(0.370– 1.730)	0.570
Non malignant	144	50.17	16	11.11	128	88.89	Reference		
Hyponatremia									
<130 Meq/L	166	57.84	24	14.46	142	85.54	3.921	(1.451– 10.598)	0.004
>130 Meq/L	121	42.16	5	4.13	116	95.87	Reference		
Blood loss									
Marked with transfusion	130	45.30	24	18.46	106	81.54	6.883	(2.545– 18.616)	<0.001
No blood transfusion	157	54.70	5	3.18	152	96.82	Reference		
Surgery									
Emergency	132	45.99	13	9.85	119	90.15	0.949	(0.439– 2.053)	0.894‡
Urgent	155	54.01	16	10.32	139	89.68	Reference		
Technique									
Open	133	46.34%	17	12.78%	116	87.22%	1.734	(0.796– 3.778)	0.162
Laparoscopic	154	53.66%	12	7.79%	142	92.21%	Reference		
Drain									
Yes	155	54.01%	15	9.68%	140	90.32%	0.903	(0.419–1.947)	0.795
No	132	45.99%	14	10.61%	118	89.39%	Reference		
ASA									
I	96	33.45%	5	5.21%	91	94.79%	0.150	(0.044–0.510)	0.001
II	83	28.92%	6	7.23%	77	92.77%	0.213	(0.072–0.626)	
III	67	23.34%	7	10.45%	60	89.55%	0.318	(0.112–0.904)	
IV	41	14.29%	11	26.83%	30	73.17%	Reference		
Operative time									
<2 hours	118	41.11%	7	5.93%	111	94.07%	0.270	(0.103–0.706)	0.012
2-3 hours	95	33.10%	8	8.42%	87	91.58%	0.394	(0.156–0.998)	
>3 hours	74	25.78%	14	18.92%	60	81.08%	Reference		
Hospital stay									
4-5 days	80	27.87%	0	0%	80	100%	0.011	(0.001–0.184)	<0.001
5-6 days	153	53.31%	0	0%	153	100%	0.005	(0.001–0.096)	
>6 days	81	28.22%	29	35.80%	52	64.20%	Reference		

Categorical variables were expressed as number (percentage); OR: Odds Ratio; 95%CI: 95% Confidence Interval; ‡ Chi-square test; p<0.05 is significant.

Preoperative serum albumin levels in leakage group (L) (median, 3.6 g/dL; range, 3.0-4.1 g/dL) were not lower than in non-leakage (NL) (median, 4.2 g/dL; range, 3.0-5.2 g/dL; p=0.474). In the meanwhile, postoperative serum albumin levels in leakage group were significantly lower than in NL on postoperative day (postoperative) day 0 (L: median, 2.6 g/dL and range, 2.3-3.5 g/dL; NL: median, 3.1 g/dL and range, 1.6-4.0 g/dL; p=0.0003), postoperative day 1 (L: median, 2.7 g/dL and range, 2.4-3.1 g/dL; NL: median, 3.3 g/dL and range, 2.3-4.3 g/dL; p=0.0002), postoperative day 3 (L: median, 2.9 g/dL and range, 2.4-3.2 g/dL; NL: median, 3.3 g/dL and range, 2.2-4.1 g/dL; p=0.0003), and postoperative day 7 (leakage: median, 3.1 g/dL and range, 2.4-3.6 g/dL; NL: median, 3.6 g/dL and range, 2.5-4.3 g/dL; p=0.0024).

Serum Na, showed no difference and no significance in the preoperative period but was significantly different in the postoperative period, 24 patients from 29 patients with leakage showed hyponatremia with Odd Ratio 3.921, serum sodium levels in L group were significantly lower than in NL on postoperative day (postoperative) 1 (AL: median, 130 MEQ/L and range, 130-139 Meq/l; non leakage one: median, 134 Meq/l and range, 132-141 Meq/l p=0.0001), POD3 (Leakage group: median, 124 Meq/l and range, 121-129 Meq/; NL: median, 134 MEQ/L and range, 130-139 Meq/l; p=0.0003).

The mean body mass index was ≥ 37 kg/m^2 in the leakage group and ≤ 37 kg/m^2 in the other group. 20 patients from 29 patients with leakage has BMI more than 37 with P value 0.090.

Serum WBC levels in (L) group were significantly higher than in (NL group), from postoperative day 2 till postoperative day 7 with presepsin level become higher and significant from day 3 till day 7. Postoperative day 3 (L: median WBC'S, 12700/mm^3 and range, 10,200-14,740/ mm^3; NL: median, 700 mm^3 and range, 4200-11,830/ mm^3; p=0.003). In the meanwhile, serum WBC levels between L group and NL did not show statistical difference in the preoperative period. Postoperative day 7 (L: median, 12,790/mm^3 and range, 9340-18,00 mm^3; NL: median/mm$_3$ and range, 6900-14,500/mm^3; p=0.006). Presepsin level became higher from day 3 with median 580 pg/ml and range 320-730 pg/l and p=0.004.

Patients with more than one comorbid diseases have a high incidence of leakage than patients with one comorbidity, comorbid diseases were an insignificant risk factor for anastomotic leakage.

We recorded high incidence of leakage in patients with gross intraabdominal contamination and fecal peritonitis (24/29 patients), (p=0.004, odd ratio 3.921 and CI 95% was (1.451-10.598) also patients with marked bowel distension are associated with considerable percent of leakage but was an insignificant risk factor.

The site of anastomosis and anastomosis under tension, revealed a significant difference in the study results, patients with left-sided anastomosis has leakage (19/23) more than that of the right side (4/23 patients), (p value <0.001, odd ratio 5.324 and CI 95% was (2.097-3.520). So we find anastomosis under tension is a significant risk factor.

In the leakage group, 11 patients (37.9%) with single layer anastomosis showed leakage while 18 patients (62.1%) with two layer anastomosis showed leakage, P value 0.153 (no significant difference). Also, there is no significant difference between laparoscopic and open technique regarding leakage.

Patients having many blood transfusions are more associated with leakage with p<0.001, odd ratio 6.883 and CI 95% was 2.545-18.616.

Duration of operation was ranging from <2 hours to >3 hours, in the leakage group, 14 patients 18.92% took more than 3 hours and 60 patients 81.08% in the other group (P=0.012), prolonged procedures associated with an incidence of leakage more than short procedures but of insignificant values.

The ASA classification of a preoperative physical condition, which accounts for these patient factors, was not statistically significant in our study.

In the leakage group, all the 29 patients (100% from leakage group) stayed more than 6 days, with no patient stayed less than these days, while in non-leakage group, only 64.20% of patients stayed more than 6 days. (P value was significant <0.001) odd ratio ranged from 0.011 to 0.005.

The predicting factors for leakage are the same in both institutes. Outpatient follow-up complication data were available in 86% of discharged patients.

DISCUSSION

The crackle and impact on patients when dehiscence does occur is disastrous, leading to prolonged intensive care unit (ICU) and hospital stays, with subsequent increased morbidity and mortality. This study is a thorough evaluation of 287 intestinal anastomoses that is intended to study all risk factors for leakage.

Depending on patient factors like age, sex, comorbid diseases or depending on clinical factors (ASA), or the type of pathology, leaks do occur but shows no significant statistical analysis as clarified from our study and these makes investigating the issue challenging. The findings from the analysis showed no statistical difference between patients with and without leaks in terms of demographics and mortality. To address this, many authors have focused on narrow aspects of anastomotic leaks, frequently examining one particular factor in a specific operation or multiple factors in a specific disease.[8] On the other hand, Yi-Wei Li.[9]

Demonstrated risk factors for AL including male sex, high American Society of Anesthesiologists (ASA) fitness grade, emergency surgery, gender is not with statistical significance in our study.

Our study showed that patients with malnutrition and low albumin level had a significant leak rate. A study that is completely compatible with our study showed that significant effects of malnutrition on colonic anastomotic leak (AL), also surgical site infection (SSI) can occur with marked malnutrition and may be explained by the adverse effect on tissue healing processes, such as collagen synthesis or synthesis of sulfated mucopolysaccharides or affecting fibroblast proliferation.[10,11] Another study also compatible with us have shown a relationship between preoperative serum albumin level and the occurrence of anastomotic fistulas and the reduction of the value of serum albumin in the 5th postoperative day were the factors that were associated significantly with the development of clinical AL.[12] serum albumin level often decreases after moderate to major gastrointestinal surgery because of increased vascular permeability, third space albumin loss with surgical stress, and perioperative fluid overload.[13]

There was no significant difference of preoperative serum albumin level between the anastomotic leakage group (L) and the nonanastomotic leakage group (NL). Postoperative serum albumin levels in L group were significantly lower than in NL group.

Serum albumin is considered the most important parameter in correlation with the degree of malnutrition that can contribute to the development of postoperative complications.

Tadanobu et al, in his study, preoperative serum albumin levels between leakage and NL group were not statistically different (although serum levels in L group were slightly lower than that in NAL, p=0.474).[14] A possible explanation for this finding may be that our cohort was not afflicted with advanced CRC with distant metastasis or cancer cachexia, which result in hypoalbuminemia. The majority of our patients had tumors at earlier stages (over 70% of patients in this cohort were node negative). In his study, intraoperative blood loss, intraoperative fluid overload, and lower perioperative urine output did not affect postoperative hypoalbuminemia. It has been reported that the distribution of albumin from intravascular to extravascular space is remarkably increased during stress, such as in severe sepsis. In other words, inflammation secondary to leaked digestive fluid might accelerate extravascular albumin permeability into the nearby leakage site in the abdominal cavity.

Author**,** in his study, found the leak rate in anastomoses of the rectum was 9.0%, while the leak rate of the other anastomoses was 5.4 %.[15] Mean serum sodium level was 138.8 mmol/l in the group with an anastomotic leak and 140.5 mmol/l in the group without. Hyponatremia (<136 mmol/l) was present in 23% of patients in the group with an anastomotic leak and in 15 % in the group without (p<0.001). In multivariate analysis, leukocytes and serum sodium level remained as significant markers of an anastomotic leak. As a marker of an anastomotic leak, hyponatremia had a specificity of 93% and a sensitivity of 23%, while the presence of either leukocytosis or hyponatremia had a sensitivity of 68%, a specificity of 75%, a positive predictive value of 18%, and a negative predictive value of 97% and this is totally compatible with our study.

Presepsin, a new sCD14-subtype biomarker, a soluble N-terminal fragment of the cluster of differentiation (CD) marker protein CD14. Released into the circulation during activation of monocytes upon recognition of lipopolysaccharide from infectious agents, so has a role in the diagnosis of sepsis. In recent years, a number of studies have investigated the potential of presepsin in the diagnosis of sepsis, and have reached conflicting conclusions about whether presepsin can provide adequate differentiating power.[16] In our study, presepsin was found as one of the most independent parameters predispose to leakage. Of the different parameters variables analyzed in this prospective study, Anastomotic tension associated with increased the leak rate. This is compatible with authors who shown higher rates of dehiscence in left side colonic anastomosis compared with other anatomic sites.[17,18]

From our parameters, the study also showed that perioperative blood transfusion is an independent risk factor for increased anastomotic leakage (95% CI, 2,545 to 18.616). And this is compatible with other reports who have also shown an increased rate of leaks related to perioperative blood transfusions.[15] These findings were attributed to the immunosuppressive effect of allogenic transfusions, also compatible with Qu et al, who detected that intra-operative transfusions/ blood loss >100 ml (OR 3.79, 95% CI 2.48-5.49, P<0.001).[19]

There is no significant difference between laparoscopic and open technique regarding leakage but there is a considerable advantage of laparoscopy, rapid recovery, early regain of intestinal function, no early or late postoperative complication of conventional surgery.

The presence of intraabdominal infection with fecal or purulent contamination also considered strong independent risk factors and correlated with leak formation. This compatible with the fact that, it is not the timing of an operation but rather the patient's nutritional and physiologic compromise and, specifically, the condition of the bowel that determines the anastomotic breakdown, this was compatible with Arnaud et al.

Finally, we reported an incidence of leakage (10.1%) as a general and from the parameters analyzed risk factors,

only 6 parameters: Decreased albumin with malnutrition, perioperative factors (acute intra-abdominal contamination, perioperative blood transfusions, hyponatremia, high WBC'S with high presepsin and Anastomotic tension or left-sided anastomosis) was associated with anastomotic leak, this was compatible with several international series who and not may be skewed from other studies because they enrolled patients with upper gastrointestinal surgery and patients with stoma.

CONCLUSION

Knowledge of independent predictive factors for leakage is of utmost importance for its early detection, decision making for surgical time, managing postoperative complications. Our study concluded and showed that it is possible to detect a subgroup of high- risk patients for anastomotic leakage after emergency bowel resection anastomosis, a temporary stoma can be done and proposed for these high risk patients, especially for those with two or more risk factors among the independent parameters for AL from our analysis.

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