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ORIGINAL ARTICLE

Predictive Factors for Small Intestinal and Colonic Anastomotic Leak: a Multivariate Analysis

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Abstract Anastomotic leak (AL) is a serious complication of intestinal surgery with various predisposing factors. This study aims to assess several risk factors associated with AL after small intestinal and colonic anastomoses through a multivariate analysis. Two hundred twenty-four patients (126 males) with intestinal anastomosis of a median age of 44 years were reviewed. Independent factors associated with AL were male gender (OR = 2.59, P = 0.02), chronic liver disease (CLD) (OR = 8.03, $P < 0.0001$), more than one associated comorbidity (OR = 5.34, P = 0.017), anastomosis conducted as emergency (OR = 2.73, P = 0.012), colonic anastomosis (OR = 2.51, P = 0.017), preoperative leukocytosis (OR = 2.57, P = 0.015), and intraoperative blood transfusion (OR = 2.25, P = 0.037). Predicative factors significantly associated with AL were male gender, CLD, multiple comorbidities, emergent anastomoses, colonic anastomoses, preoperative leukocytosis, and intraoperative blood transfusion.

Keywords Anastomotic leak · Risk factors · Multivariate analysis · Colonic anastomosis

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Introduction

Anastomotic leak (AL) is a serious complication of surgery of the alimentary tract in general, and of intestinal surgery in particular. The gravity of anastomotic disruption extends beyond being an isolated complication to include further life-threatening complications and sometimes mortality.

Leak after intestinal anastomosis varies from 0.5 to 30 %, [1–3], and it can reach up to 39 % according to Buchs and colleagues [4]. Overall incidence of colorectal AL ranges from 1.5 to 16 % globally [5].

Various risk factors are associated with AL which can be subdivided into systemic and local factors; both entities contribute to poor healing and failure of anastomosis [6]. Systemic conditions include anemia, diabetes mellitus (DM), malnutrition, hypoalbuminemia, and prolonged steroid therapy. Local factors comprise local irradiation of bowel, diseased bowel as in Crohn's disease, and intestinal ischemia. In addition, high ligation of inferior mesenteric artery is considered a unique risk factor for disruption of colonic anastomosis [7].

AL varies with regard to the onset of its occurrence. Early leak occurs on the first or second postoperative days, mostly due to technical reasons. Latent leak, which is attributed to failure of the normal healing mechanism, occurs around the end of the first postoperative week.

Clinically, AL has different presentations, when the leak is controlled, it presents as localized intraperitoneal abscess, whereas in cases of uncontrolled leak, frank peritonitis supervenes [8]. Some leaks present in a subtle fashion, often late in the postoperative period [9].

Studying the impact of different risk factors on AL is imperative to know which risk factors are associated with AL significantly higher than other factors. Prevention of AL beforehand is crucial to avoid serious consequences that may cost the patient his life.

Former studies [10, 11] analyzed several risk factors for anastomotic disruption using univariate analyses which identified the overall significance of these factors; nevertheless, the individual contribution and relative weight of each factor were not assessed. Alves and colleagues [2] performed the first multivariate analysis of risk factors for AL. However, they restricted their analysis to colorectal anastomotic leaks only with no parallel analysis of small intestinal AL.

The present study aimed to assess the association of various risk factors with the onset of AL after both small bowel and colonic anastomoses through multivariate analysis of these factors. The objective was to distinguish between factors that significantly predicted anastomotic disruption and leak, and other factors that were considered less relevant. Knowing the most influential factors that predispose to AL help surgeons address these factors properly in attempt to prevent the onset of leak.

Patient and Methods

Study Design and Setting

This retrospective study comprised 224 consecutive patients who underwent intestinal anastomosis in Mansoura University hospitals in the period of January 2010 to January 2016. Ethical approval was obtained from the institutional review board of Mansoura Faculty of Medicine.

Patients' Selection

All patients who underwent small intestinal or colonic anastomosis, whether elective or emergent anastomosis, were included. Patients of both genders, all age groups, and patients with associated comorbidities as DM, congestive heart failure, chronic liver, or kidney diseases were included in the study. In order to avoid confounding bias, we excluded patients who had covering (diverting) stoma as a safeguard for the anastomosis.

Process of Data Collection

We searched the archives of Mansoura University principal hospital and emergency hospital for patients who underwent intestinal anastomosis, whether they developed AL or not. Records of these patients were retrieved and reviewed by three of the authors, and the required data were extracted.

Data Collected

- Demographic data of patients including name, age, gender, and comorbid conditions
- Type of admission (elective or emergent)
- Cause of intestinal injury necessitating surgery
- Preoperative leukocytic count
- Operative details including type of intestinal anastomosis (small intestinal or colonic), technique of anastomosis (manual or stapled; single or double layer), experience of the operating surgeon (resident, specialist, consultant), and intraoperative blood transfusion
- Time of presentation and management of AL
- Final outcome of patients with AL

Definitions of Leak

AL was identified by either discharge of intestinal contents through the abdominal wound or drains, or evident signs of peritonitis associated with fever, leukocytosis, or fluid collection in abdominal ultrasonography. Oral contrast studies (gastrografin follow-through), or CT scan of the abdomen and pelvis with oral and intravenous contrasts were used to demonstrate the site of leak. Intestinal fistulas were classified according to standard classification [12] to low output (<200 mL/day), moderate output (200–500 mL), or high output (>500 mL/day).

Data Analysis

Statistical analyses were performed using Excel and SPSS version 23 programs under Microsoft Windows. Fisher's exact and chi-squared tests were used to determine the significance of any differences between patients regarding the different variables. Multivariate analysis of risk factors associated with AL was done using binary logistic regression test. Significance was determined with P value <0.05. The power of this retrospective study was evaluated using post hoc analysis of the results of the primary endpoint (incidence of AL) which revealed a study power of 85 %; also, the 95 % confidence interval (CI) of the incidence of AL was calculated.

Results

Characteristics of Patients and Intestinal Anastomoses

The present study included 224 patients (126 males and 98 females) with intestinal anastomosis. Median age of patients was 44 years (range, 9–80 years). Overall, 66 patients had preoperative comorbidities as follows: 8 patients had history of cardiovascular disease, 33 had history of chronic liver

disease, 16 had type II DM, and 9 patients had more than one comorbidity. Intestinal anastomosis was done on elective or emergent basis in 122 and 102 patients, respectively. Summary of various indications for intestinal anastomosis is illustrated in Table 1.

One hundred twelve small intestinal anastomoses (68 ileal and 44 jejunal), 81 colonic anastomoses, and 31 ileocolic anastomoses were done. Regarding the technique of anastomosis, 216 were manual (35 single-layer and 181 double-layer technique), and eight anastomoses were stapled.

Factors Associated with Anastomotic Leak

Overall, 32 (14.2 %) patients developed AL with 95 % CI = 10.1–19.7. Seven leaks were diagnosed early (within 2–4 days after surgery), whereas 25 leaks were diagnosed six or more days after surgery. Twenty-four (19 %) male patients developed AL, more than twice the incidence of female patients. Around 35 % of patients with comorbid conditions developed AL versus 5.6 % of patients with no associated comorbidities.

Overall, 20.5 % of anastomoses conducted as emergency procedures were complicated with leak versus 9 % of elective anastomoses. Incidences of AL after single-layer manual anastomosis, double-layer manual anastomosis, and stapled anastomosis were 11, 17, and 12.5 %, respectively. Leak was detected after 22.2 % of colonic anastomoses, 9.8 % of small intestinal anastomoses, and 9.6 % of ileocolic anastomoses.

Preoperative leukocytosis was associated with significantly higher rate of AL (22.5 versus 9.7 %). Anemic patients who received intraoperative blood transfusion developed AL significantly higher than patients who did not (22.3 versus 10.8 %). Abdominal drains were inserted in 91 % of cases; however, it has no impact on the incidence of AL. Consultant surgeons, specialized surgeons, and surgical residents conducted 36, 35, and 29 % of anastomoses, respectively. Nevertheless, incidence of AL was comparable among the three groups (Table 2).

Table 1 Indications for intestinal anastomosis

Indication of intestinal anastomosis		Total number of patients (224)	Number of patients with AL (32)
Emergent (n = 102)	Mechanical small bowel obstruction	18	3
	Mesenteric vascular occlusion	31	8
	Malignant colonic obstruction	7	2
	Traumatic injury of the colon	12	3
	Strangulated hernia	25	4
	Iatrogenic injury of bowel	9	1
Elective (n = 122)	Colon cancer	29	2
	Diverticular disease of the colon	12	2
	Elective closure of ileostomy	25	0
	Elective closure of colostomy	28	1
	Small intestinal tumor	6	0
	Abdominal mass	9	1
	Biliopancreatic diversion	2	0
	Crohn's disease	2	1
	Rectovesical fistula	1	0
	Congenital megacolon	1	1
	Resection rectopexy for rectal prolapse	1	1
	Submucous lipoma in right colon (RT hemicolectomy)	1	1
	Low anterior resection for rectal cancer	3	1
	Colonic stricture	2	0

Multivariate Analysis of Risk Factors

Multivariate analysis (Table 3) of risk factors for AL revealed that the independent factors that were significantly associated with AL were as follows:

- Male gender (OR = 2.59, P = 0.02).
- Chronic liver disease (OR = 8.03, $P < 0.0001$)
- More than one associated comorbidity (OR = 5.34, P = 0.017)
- Anastomosis conducted as emergent procedure (OR = 2.73, P = 0.012)
- Colonic anastomosis (OR = 2.51, P = 0.017)
- Preoperative leukocytic count over 10,000 (OR = 2.57, P = 0.015)
- Intraoperative blood transfusion (OR = 2.25, P = 0.037)

A subgroup analysis (Table 3) was made according to the site of anastomosis, and it revealed that chronic liver disease was the only common factor that contributed significantly to both small intestinal and colonic AL. More than one associated comorbidity significantly predicted small intestinal AL, whereas male gender, emergent anastomosis, preoperative leukocytosis, and intraoperative blood transfusion were significantly associated with colonic AL.

Management and Outcome of AL

Intestinal fistulae that complicated anastomosis were eight low output, two moderate output, and 22 high

Table 2 Risk factors for anastomotic leak

Variable	*N*/total	*P* value[a]	Odds ratio (95 % CI)	*P* value[b]
Age (years)		0.74		
<40	10/90		1	
>40	22/134		1.54 (0.69–3.43)	0.292
Gender		*0.03*		
Female	8/98		1	
Male	24/126		2.59 (1.11–6.06)	*0.028*
Comorbidities		*0.03*		
No comorbidities	9/158		1	
DM	1/16		0.38 (0.5–2.99)	0.358
Cardiac disease	3/8		3.87 (0.88–17.06)	0.074
Chronic liver disease	15/33		8.03 (3.47–18.62)	*<0.0001*
More than one comorbidity	4/9		5.34 (1.35–21.1)	*0.017*
Type of admission		*0.02*		
Elective	11/122		1	
Emergent	21/102		2.73 (1.25–5.98)	*0.012*
Site of anastomosis		*0.03*		
Small intestinal	11/112		1	
Colonic	18/81		2.51 (1.18–5.37)	*0.017*
Ileocolic	3/31		0.58 (0.17–2.03)	0.396
Technique of anastomosis		0.26		
Manual (single layer)	11/100		1	
Manual (double layer)	20/116		1.6 (0.74–3.45)	0.232
Stapled	1/8		0.85 (0.1–7.17)	0.883
Preoperative leukocytic count		*0.01*		
<10,000	14/144		1	
>10,000	18/80		2.57 (1.2–5.5)	*0.015*
Intraoperative blood transfusion		*0.03*		
No	17/157		1	
Yes	15/67		2.25 (1.05–4.83)	*0.037*
Abdominal drainage		1		
Yes	29/204		1	
No	3/20		1.06 (0.29–3.86)	0.924
Surgeon's experience				
Consultant	12/82	0.99	1	
Specialist	11/77		1.02 (0.42–2.49)	0.9
Resident (trainee)	9/65		1.06 (0.41–2.71)	0.89

Significant *P* value (<0.05) is written in italics

[a] *P* value calculated by chi-squared test

[b] *P* value calculated by binary logistic regression analysis

output fistulae. Conservative management was sufficient in 14 AL, whereas 18 leaks required surgical intervention in the form of diversion, re-anastomosis or abdominal drainage (Table 4). Eleven (4.9 %) mortalities were recorded after AL, nine of them were due to high output intestinal fistula. Table 5 shows that patients' demographics, type of intestinal fistula, and management of AL did not significantly influence the outcome of patients with AL.

Discussion

AL is the most serious complication of intestinal anastomosis owing to its high morbidity and mortality rates. AL may present in an insidious manner with low-grade fever and prolonged ileus, or present classically with severe abdominal pain, tachycardia, high-grade fever, and acute abdomen. Serious consequences of intestinal AL include peritonitis, localized intra-abdominal

Table 3 Subgroup analysis of risk factors for AL according to site of anastomosis

Item		Small bowel anastomosis	Colonic anastomosis	Ileocolic anastomosis
Leak/total number		11/112	18/81	3/31
Age >40	Leak/total number	6/47	15/65	1/22
	Odds ratio (*P* value)	1.69 (0.41)	1.18 (0.82)	0.17 (0.16)
Male gender	Leak/total number	5/47	18/69	1/10
	Odds ratio (*P* value)	1.27 (0.708)	*2.96 (0.04)*	1.06 (0.96)
Chronic liver disease	Leak/total number	5/14	9/16	1/3
	Odds ratio (*P* value)	*8.52 (0.002)*	*8 (0.001)*	6.5 (0.18)
More than one co-morbidity	Leak/total number	3/5	1/3	0/1
	Odds ratio (*P* value)	*18.5 (0.003)*	1.79 (0.64)	2.6 (0.57)
Emergent anastomosis	Leak/total number	8/57	12/33	1/12
	Odds ratio (*P* value)	2.61 (0.17)	*3.73 (0.02)*	0.77 (0.84)
Preoperative leukocytosis	Leak/total number	4/23	14/43	0/14
	Odds ratio (*P* value)	2.31 (0.21)	*3.85 (0.03)*	0.14 (0.21)
Intraoperative blood transfusion	Leak/total number	3/28	12/35	0/4
	Odds ratio (*P* value)	1.08 (0.91)	*3.25 (0.03)*	0.77 (0.87)

Significant *P* value (<0.05) is written in italics

collection (abscess), septicemia, and ultimately septic shock, multiorgan failure (MOF), and death.

Several risk factors contribute to the onset of leak; these factors can be classified as patient-related and technical factors. Patient-related factors comprise age, gender, and systemic illness as chronic liver disease, hypoalbuminemia, cardiac diseases, DM, and cancer [6, 7]. Technical factors are related to the technique and site of anastomosis, surgeon's experience, use of abdominal drains, and intraoperative blood transfusion.

The overall incidence of AL in our study was 14.2 % which is within the range of 0.5–39 % reported by former studies [1–4]. On the other hand, colonic AL occurred in 22 % of patients in the present study, again within the reported range of 1–24 % [13]. This wide variability in the incidence of AL can be attributed to different baseline characteristics of patients and technical variations among the different studies.

Our analysis of various risk factors for AL showed that patients' gender and associated comorbidities significantly predicted the onset of AL, yet the age of patients did not have any significant relation with AL. Type of admission, site of anastomosis, preoperative leukocytic count, and intraoperative blood transfusion were associated with significantly higher rates of leak. Conversely, technique of anastomosis, experience of the operating surgeon, and use of abdominal drains did not substantially factor in the incidence of leak.

Although no significant difference in incidence of leak was observed among different age groups, more than two thirds of leaks in our study were in patients above 40 years. Gluszek

Table 4 Management of anastomotic leak

Type of intestinal fistula	Number	Conservative management	Surgical management		
			Diversion	Reanastomosis	Drainage
High output	22	6	13	3	0
Moderate output	2	1	1	0	0
Low output (8)	8	7	0	0	1
Total	32	14	14	3	1

Table 5 Outcome of patients with anastomotic leak

Variable		Number	Survived	Died	*P* value
Age	<20	1	1	0	0.64
	20–40	9	7	2	
	40–60	12	8	4	
	>60	10	5	5	
Gender	Male	24	14	10	0.2
	Female	8	7	1	
Comorbidities	No comorbidities (9)	9	7	2	0.83
	DM	1	1	0	
	Cardiac disease	3	2	1	
	Chronic liver disease	15	9	6	
	More than one	4	2	2	
Output of fistula	Low and moderate	10	8	2	0.42
	High	22	13	9	
Management	Conservative	14	11	3	0.26
	Surgical	18	10	8	

and his colleagues [14] have mentioned that older patients are more liable to AL due to the associated comorbidities, and atherosclerosis compromising blood supply of the anastomosis.

Male patients in our report developed AL more than twice female patients. Male gender was associated with significantly higher incidence of colonic AL concordant with Quan et al. [15] who identified male gender as a risk factor for colorectal AL due to narrow male pelvis, and hormonal differences that affect intestinal microcirculation contributing to higher risk of anastomotic failure. On the other hand, male gender was not associated with higher rates of small intestinal AL.

Associated comorbidities, particularly multiple comorbidities, were associated with higher incidence of anastomotic disruption, coping with Alves and colleagues [2] who found ASA >II to be a significant independent contributing factor to colorectal AL. Chronic liver diseases constituted half of the associated comorbidities in the present report which is logical due to high prevalence of hepatitis C virus infection, and schistosomal hepatic affection in our community [16]. Neither DM nor cardiovascular diseases were observed as important predictors for AL, in contrast to another study [17] that recognized cardiovascular diseases and DM as significant factors associated with occurrence of AL.

In agreement with Choy and colleagues [18] who considered emergent intestinal anastomosis a significant risk factor for AL, the present study reported higher incidence of anastomotic disruption in patients operated on emergent basis (20 %) versus patients operated as elective cases (5 %). Emergent intervention is more frequently associated with AL due to lack of adequate preoperative preparation and stabilization of debilitated patients who usually present with hemodynamic instability, in addition to the considerable effect of fecal contamination that often exists in these cases.

Large bowel anastomoses exhibited significantly higher rates of AL than small intestinal anastomoses; this can be attributed to higher intra-luminal pressure, poorer vascularity, and higher load of bacterial flora of the large intestine compared to small bowel. Ileal anastomoses and low pelvic anastomoses were the most common sites for AL in our study, concordant with Kumar et al. [19] who reported that ileal anastomoses were the most prone for anastomotic failure.

Chronic liver disease and multiple associated comorbidities significantly predicted small intestinal AL; on the other hand, preoperative leukocytosis and intraoperative blood transfusion were highly associated with colonic AL. It was notable that chronic liver disease was the only common factor that was significantly associated with both small and large bowel AL which makes sense as chronic liver disease is usually associated with hypoalbuminemia that compromises healing by impairing collagen synthesis and reducing the host immune competence, thus predisposing to AL [20].

We could not detect remarkable difference between stapled and manual anastomoses regarding incidence of leak which copes with what Lustosa and colleagues [21] reported; however, they also noticed that stapled technique attained shorter time for anastomosis, yet higher risk for stricture. Conversely, another study [18] found stapled anastomoses safer and associated with lower rates of AL than manual anastomoses.

Technique of hand-sewn anastomosis, whether single or double layer, did not affect the outcome of the present study. This observation was formerly reported by Khan et al. [22] who concluded that single-layer intestinal anastomosis does not carry any increased risk of complications, whereas it took significantly lesser time for construction and also costs lower

than double-layer anastomosis. Similarly, a meta-analysis of randomized trials [23] found no evidence supporting that double-layer anastomosis yielded lower incidence of leak than single-layer anastomosis.

Preoperative leukocytosis and intraoperative blood transfusion were associated with higher risk of anastomotic disruption, similar to what other multivariate analysis has observed [2]. Leukocytosis indicates active inflammatory process induced by intestinal leak and secondary peritonitis; thus, it can be a marker of considerable fecal contamination of the peritoneal cavity that compromise healing of the anastomosis and eventually leading to anastomotic disruption and leak [24]. The need for intraoperative blood transfusion implies to low hemoglobin levels of patients and, thus, relative ischemia of the anastomosis that can compromise its vitality and healing. Kirchhoff and colleagues [25] found intraoperative blood transfusion a well-established independent risk factor for complications in colorectal surgery, particularly AL.

Experience of the operating surgeon did not affect the incidence of AL, which disagrees with former studies [26] that recognized this factor as important predictor of AL. Since junior surgeons who performed intestinal anastomosis in our study were carefully supervised by more senior colleagues, the incidence of AL did not show remarkable differences between experienced surgeons and trainees. Additionally, experienced surgeons performed more difficult and complicated cases whereas junior surgeons carried out the relatively simple and easy procedures; therefore, the different type and level of difficulty of surgery can account for the nonsignificant difference in AL between consultant surgeons and residents.

A meta-analysis [27] concluded no significant benefit of abdominal drainage after intestinal anastomosis in reducing the incidence of AL or other complications. Similarly, rates of AL in drained and nondrained patients in our report were almost the same, denoting the questionable utility of abdominal drains. We inserted drains in more than 90 % of patients with intestinal anastomosis, not as a prophylactic measure against leak, but for early detection of the onset of AL.

Although Draus and colleagues [28] reported high rates of spontaneous closure of high output fistulae, most patients in our report with this type of fistula were managed surgically. We initially managed patients with high output fistulae in a conservative manner to improve their nutritional status and optimize them for surgery, in agreement with Haffejee [29] who described conservative treatment as a bridge to formal surgical resection in these situations.

The overall mortality rate in our study was less than 5 % which is within the range of 2.2 to 22 % reported by previous studies [2, 14]. Mortality of AL is attributed to multiple collaborative factors as bad general condition of most patients, associated comorbidities, nutritional and electrolyte disturbance, and septic shock. Our study observed higher mortality rates among male patients, patients above 60 years, patients with multiple associated comorbidities, and high output fistula, confirming the results of Tan and colleagues [30]. However, neither patients' characteristics nor type of intestinal fistula had significant impact on incidence of mortality of AL.

Limitations of the Study

Certain issues about the present study should be recognized. Being a retrospective study, this report carries some risk of bias. In addition, we did not address some important factors for AL as operative time, steroid intake by the patients, degree of intraoperative septic contamination, and irradiation therapy because the relevant data for these factors were not complete in our records.

Finally, this report studied risk factors for AL after both small intestinal and colonic anastomoses, which can be confounding as each of them can be recognized as a separate entity. However, we tried to determine the common risk factors for AL in both groups and the risk factors specific for each group separately to be properly addressed.

Conclusion

The most significant independent factors associated with the onset of AL were male gender, chronic liver diseases, more than one associated comorbidity, anastomoses performed as emergency, colonic anastomoses, preoperative leukocytosis, and intraoperative blood transfusion. Chronic liver disease was the only common risk factor for both small intestinal and colonic AL.

Patients' age, DM, technique of anastomosis, use of abdominal drain, and surgeon's experience had no significant influence on the incidence of AL. Neither the age and gender of patients nor the type of intestinal fistula had significant impact on incidence of AL mortality.

Compliance with Ethical Standards Ethical approval was obtained from the institutional review board of Mansoura Faculty of Medicine.

Conflict of Interest The authors declare that they have no conflict of interest.

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