Risk Factors for Anastomotic Leakage in Open Colorectal Surgery: An Analysis of 558 Patients

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Background: *Anastomotic leakage is one of the major complication after colorectal surgery. Identifying risk factors of anastomotic leakage may prevent anastomotic leakage after colorectal surgery.*

Objective: *To determine the incidence and risk factors for clinical anastomotic leakage after open colorectal surgery.*

Material and Method: *This single-center retrospective study included all patients undergoing colorectal surgery with anastomosis between January 2008 to December 2012. Five hundred fifty-eight patients underwent colorectal surgery during the study period. Patient's demographic data, tumor characteristics, type of surgery, postoperative results and leakage characteristics were collected. Univariate and multivariate analyses were applied to identify risk factors for anastomotic leakage.*

Results: *Five hundred fifty-eight patients were included and 28 (5%) had anastomotic leakage. Most (57.2%) of patients who had anastomotic leakage were diagnosed between three to six days after surgery. After univariate analysis, preoperative radiation (p = 0.023), surgical procedure with low anterior resection (p = 0.037), transverse colectomy (p = 0.022), coloanal anastomosis (p = 0.011), protective stoma (p = 0.006), increased duration of surgery (p = 0.005), and lymph node metastasis (p = 0.001) were selected as seven independent factors with clinical anastomotic leakage. Multivariate analysis revealed four factors associated with anastomotic leakage including low anterior resection (p = 0.042), colo-anal anastomosis (p = 0.002), transverse colectomy (p = 0.005), and increased duration of surgery greater than four hours (p = 0.002). There was no mortality in our study.*

Conclusion: *Based on our evidences, low anterior resection, colo-anal anastomosis, transverse colectomy, increased duration of surgery greater than four hours were found to be independent risk factors with clinical anastomotic leaks in open colorectal surgery.*

Keywords: *Risk factors, Anastomosis leakage, Open colorectal surgery*

J Med Assoc Thai 2017; 100 (Suppl. 9): S47-S54
Full text. e-Journal: *http://www.jmatonline.com*

Anastomotic leakage remains a serious complication after open colorectal surgery[1-3]. The incidence of anastomotic leakage ranges from 3% to 25%[4-6]. This complication can cause significant clinical consequences, increased in-hospital morbidity and mortality[1,5,6]. There also have been some reports of increased risk of local recurrence and decreased long-term survival associated with anastomotic leakage after colorectal cancer surgery[2,3].

Risk factors of anastomotic leakage have been studied, and the most frequent factors included male sex, old age, low anastomosis, cancer, long operation time, emergency surgery, preoperative radiation, and perioperative blood transfusion[7-14].

Identifying risk factors of anastomotic leakage may help to prevent or reduce anastomotic leakage in colorectal surgery. The aim of this study was to determine the incidence and risk factors for clinical anastomotic leakage after open colorectal surgery in our institution.

Material and Method

Between January 2008 to December 2012, 558 patients who underwent open colorectal surgery at department of surgery, Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand were retrospectively reviewed. All patients undergoing procedures with anastomosis for colorectal surgery were included in the study. Patients whose missing data and having procedure without anastomosis including abdominoperineal resection and Hartmann's procedure were excluded from the study.

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Patient characteristics variables included age, sex, tobacco use, body mass index, renal function, history of diabetic, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease, preoperative albumin, anemia (Hct <33%), carcinoembryonic antigen (CEA), steroid use, American Society of Anesthesiologist (ASA) score, and neoadjuvant therapy were collected and analyzed. All operative variables comprised whether the procedure, Anastomosis technique, indication for surgery, type of bowel preparation, protective stoma or placement of drain, surgical duration, blood transfusion, tumor location, and histopathologic details were also collected and analyzed.

Clinical anastomotic leakage was diagnosed if one of the following clinical signs occurred, gas, pus or fecal discharge from drain or drain tract, vagina or incisional wound, peritonitis, and intraabdominal abscess. The imaging study was performed if leakage was suspected.

Various variables of anastomotic leakage included symptoms, timing of leakage, imaging features, and treatment were retrieved and analyzed.

Statistical analysis

The data was collected with epidata program. The univariate relationship was analyzed with Chi-square test. Statistical significance was established at *p*-value of less than 0.05.

Results

Five hundred fifty-eight patients that underwent colorectal surgery with anastomosis were included in our study after excluding patients with missing data and having procedure without anastomosis.

The mean age of patients was 62.28 years at the time of surgery. Most of patients were 60 years or older. Two hundred eighty-five (51.07%) patients were men. Among all operation, right hemicolectomy was performed in 129 (23.11%) and was the most common procedure. The overall clinical anastomotic leakage was 5% (28/558 patients). There was no mortality in our study.

The patient characteristics are listed in Table 1. From univariate analysis, preoperative radiation therapy (p = 0.023) was associated with increased clinical anastomotic leakage. Other risk factors included sex (p = 0.907), age (p = 0.080), obesity (p = 0.837), malnutrition demonstrated by albumin less than 3.5 g/dL (p = 0.324), anemia (p = 0.237), creatinine clearance less than 30 ml/min/1.73 m^2 (p = 0.082), tobacco use (p = 0.546), steroid use (p = 1.000), and ASA score of more than 3 (p = 0.696) were not associated with increased anastomotic leakage.

The operative procedure characteristics are reported in Table 2. From univariate analysis, low anterior resection (p = 0.037), colo-anal anastomosis (p = 0.011), transverse colectomy (p = 0.022), duration of operation (p = 0.005), and protective stoma (p = 0.006) were associated with the development of clinical anastomotic leakage.

The tumor characteristics are detailed in Table 3. Most common tumor site was located at sigmoid (27.95%). From univariate analysis, tumor location and pathological tumor stage were not associated with increased risk of anastomotic leakage. Only regional lymph nodes invasion was an independent factor associated with increased risk of anastomotic leakage (p = 0.001).

Multivariate analysis

After univariate analysis, variables with *p*-value of less than 0.05 were selected for multivariate analysis. The results of multivariate analysis are shown in Table 4. Duration of operation greater than four hours (p<0.002; odds ratio, 4.1; 95% confidence interval, 1.68 to 10.48), low anterior resection (p<0.042; odds ratio, 2.3; 95% confidence interval, 1.03 to 5.13), transverse colectomy (p<0.005; odds ratio, 13.5.1; 95% confidence interval, 2.16 to 84.40), and coloanal anastomosis (p<0.002; odds ratio, 8.9; 95% confidence interval, 2.18 to 36.75) were independently predictive factors of clinical anastomosis leakage.

Characteristic of patients with anastomotic leakage are summarized in Table 5. Most common presenting symptoms of clinical anastomosis leakage were fever (35.7%) followed by abdominal pain (32.1%), pus or feces from drain or anus (14.3%), ileus (10.7%), enterocutaneous fistula (3.6%), and peritonitis (3.6%). Most (57.2%) patients who had anastomotic leakage were diagnosed between three to six days after surgery. Four patients (14.4%) had delayed anastomotic leakage and were diagnosed after postoperative day 14. There was no mortality in our study as a consequence of anastomotic leakage.

Discussion

Anastomotic leakage is one of the most drastic short-term complication after colorectal surgery[1-3]. The incidence of anastomotic leakage is usually underestimated with a range from 3 to 25%[4-6]. This

Table 1. Patient characteristics

Variables	Total patients	Number of leakage (%)	*p*-value
Sex			0.907
Male	285	14 (4.9)	
Female	273	14 (5.1)	
Age			0.080
≤60	236	17 (7.2)	
61 to 70	149	7 (4.7)	
≥71	173	4 (2.3)	
BMI			0.837
<18.5	51	2 (3.9)	
18.5 to 25	350	19 (5.4)	
>25	157	7 (4.5)	
Smoking habits			0.546
Non-smoker	425	20 (4.7)	
Smoker	133	8 (6.0)	
Use of steroids			1.000
Yes	7	0 (0.0)	
No	551	28 (5.1)	
Anemia			0.237
Yes	176	6 (3.4)	
No	382	22 (5.8)	
Albumin (g/dL)			0.324
<3.5	205	14 (6.8)	
≥3.5	294	14 (4.8)	
Creatinine clearance, Ml/min/1.73 m^2			
<30	21	3 (14.3)	
≥30	537	25 (4.7)	0.082
CEA			0.362
<2.5	129	4 (3.1)	
≥2.5	336	17 (5.1)	
ASA score			0.696
1, 2	259	14 (5.4)	
≥3	299	14 (4.7)	
Preoperative radiation			0.023
Yes	13	3 (23.1)	
No	545	25 (4.6)	
Preoperative chemotherapy			0.560
Yes	18	3 (16.7)	
No	540	25 (4.6)	

complication can cause considerable morbidity and mortality[1,5,6]. One of the most mentioned oncological impact include the increased risk of local recurrence and decreased long-term survival associated with anastomotic leakage after colorectal cancer surgery[2,3].

Significant number of risk factors for anastomotic leakage have been extensively studied including male sex, old age, low anastomosis, cancer, long operation time, emergency surgery, preoperative radiation, and perioperative blood transfusion[7-14].

This rate of anastomotic leakage varies in many studies. The overall leak rate of 5% reported in our study compares with the results of other reporting leak rates of 3 to 25%[4-6]. There was no mortality in our study where other reported 12 to 27%[4-6].

In our study, most presenting symptom of anastomotic leakage was fever (35.7%). Highest leakage rate was diagnosed clinically at six days postoperatively (range 1 to 17 days). Various presenting symptom of clinical anastomotic leakage were fever (35.7%), abdominal pain (32.1%), pus or feces from drain or anus (14.3%), Ileus (10.7%), enterocutaneous fistula, and

Table 2. Operative procedure characteristics

Variables	Total, n	Leakage, n (%)	*p*-value
Elective	467	23 (4.9)	
Emergency	91	5 (5.5)	0.794
Bowel preparation			0.545
Yes	411	22 (5.4)	
No	147	6 (4.1)	
Operation			
Ileocecectomy	6	0 (0.0)	1.000
Right hemicolectomy	129	3 (2.3)	0.110
Right extended hemicolectomy	66	1 (1.5)	0.233
Left hemicolectomy	28	2 (7.1)	0.645
Left extended hemicolectomy	5	1 (20.0)	0.228
Transverse colectomy	5	2 (40.0)	0.022
Sigmoidectomy	107	4 (3.7)	0.500
Anterior resection	75	1 (1.3)	0.156
Low anterior resection	113	10 (8.8)	0.037
Colo-anal anastomosis	10	3 (30.0)	0.011
Subtotal colectomy	14	1 (7.1)	0.518
Surgical drains used			0.330
Yes	176	14 (8.0)	
No	379	14 (3.7)	
Stoma			0.006
Yes	25	5 (20.0)	
No	530	23 (4.3)	
Anastomosis technique			0.281
Hand sewn <one layer>	285	12 (4.2)	
Hand sewn <two layer>	48	1 (2.1)	
Stapled	225	15 (6.7)	
Blood transfusion			0.175
Yes	86	7 (8.1)	
No	472	21 (4.4)	
Duration of operation(h)			0.005
<4	512	21 (4.1)	
≥4	46	7 (15.2)	

peritonitis (3.6%). Hyman N et al reported that overall leaks were diagnosed at a mean of 12.7 days postoperatively, which is the time after hospital discharge and recommended CT scan as preferred diagnostic modality[15].

Among the preoperative risk factors, preoperative radiation was significantly associated with anastomotic leakage in univariate analysis in our study. Suding P et al[16] reported that low serum albumin level, male sex, and steroid use were associated with increased risk of anastomotic leakage. Konishi et al[12] reported that preoperative long-term steroid use was also an independent risk factor for anastomotic leakage. Other preoperative risk factors mentioned in previous studies included smoking, diabetes mellitus, and ASA classification of 3 or greater[9,17,18].

From our study, there seemed to be higher anastomotic leakage in left-sided colon resection and rectal resection (7 to 40%). From univariate analysis, low anterior resection, colo-anal anastomosis, transverse colectomy, longer duration of operation, and protective stoma were significantly associated with anastomotic leakage. Veyrie N et al reported leakage rates for Right colectomies of 1.35% versus 5.20% for left colon resections[19]. Hyman et al also found the higher rate of anastomotic leak after ileorectal anastomosis[15].

About protective stoma, Konishi et al reported that although there were no statistical differences in leakage rates between patients with and without

Table 3. Tumor characteristics

Variables	Total patients	Number of leakage (%)	*p*-value
Indication for surgery			0.343
Cancer	481	25 (5.2)	
Benign colonic neoplasm	26	1 (3.8)	
Diverticulitis	18	2 (11.1)	
Other	28	0 (0.0)	
Tumor location			0.389
Small bowel	14	0 (0.0)	
Appendix	13	0 (0.0)	
Cecum	52	2 (3.8)	
Ascending colon	50	2 (4.0)	
Hepatic flexure	30	1 (3.3)	
Transverse colon	47	3 (6.4)	
Splenic flexure	14	1 (7.1)	
Descending colon	24	1 (4.2)	
Sigmoid	156	5 (3.2)	
Rectum	136	13 (9.6)	
Rectosigmoid	22	0 (0.0)	
pT stage			0.588
T1	13	0 (0.0)	
T2	83	4 (4.8)	
T3	329	17 (5.2)	
T4	41	4 (9.8)	
pN stage			0.001
N0	230	7 (3.0)	
N1	136	5 (3.7)	
N2	104	13 (12.5)	

Table 4. Multivariate analysis

Variables	Odds ratio	95% Cl	*p*-value
Duration of operation ≥4 h	4.1	1.68 to 10.48	0.002
Low anterior resection	2.3	1.03 to 5.13	0.042
Transverse colectomy	13.5	2.16 to 84.40	0.005
Colo-anal anastomosis	8.9	2.18 to 36.75	0.002

covering stoma, surgeons should be aware of high-risk patients and decide whether to create a diversion stoma during surgery[12]. In our study, the creation of protective stoma was a risk factor for anastomotic leakage. Theoretically protective stoma can decrease some, even not all severe consequences of an anastomosis leakage.

Previous studies on effect of mechanical bowel preparation on anastomotic leakage rate showed conflicting results. Scarborough JF et al showed that preoperative combined mechanical bowel preparation and oral antibiotics resulted in a reduced anastomotic leakage rate[20]. In contrast to this study, our study did not reveal the association between mechanical bowel preparation and anastomotic leakage rate. Also, recent systematic review by McDermott FD et al reported that mechanical bowel preparation did not reduce anastomotic leakage either in colonic or in rectal operation[17] and therefore can be avoided[21].

Tumor location and tumor invasion were not risk factor for anastomotic leakage, but regional lymph node invasion was risk factor for anastomotic leakage. In contrast to our study, Eberl T et al reported that tumor localization, tumor diameter were independent

Table 5. Characteristics of anastomotic leakage

Variables	Number of patients	Percent (%)
Symptoms		
Fever	10	35.7
Abdominal pain	9	32.1
Ileus	3	10.7
Pus from drain or anus	4	14.3
Enterocutaneus fistula	1	3.6
Peritonitis	1	3.6
Timing of leaks <days>		
1	0	0
2	0	0
3	1	3.6
4	2	7.1
5	5	17.9
6	8	28.6
7	3	10.7
8	1	3.6
9	1	3.6
10	1	3.6
11	1	3.6
12	1	3.6
13	0	0
14	1	3.6
15	1	3.6
16	1	3.6
17	1	3.6
Imaging features		
Fluid and air collection	14	56
Contrast leak	7	28
Anastomotic disruption	1	4
Free air	3	12

factors associated with anastomotic dehiscence in multivariate analysis[22].

Our study has its limitation included the heterogeneity of patients, the difficulty in medical record retrieval and the underestimation of leakage. Because our study included only clinical-leakage patient and we did not performed routine imaging to detect leakage in all suspicious patients, we may find higher leakage rate from radiologic imaging. However, one of the strengths of our study is that our study included consecutive patients of two surgeons and is limited to single center.

Conclusion

In summary, duration of the operation longer than four hours, low anterior resection, transverse colectomy, and colo-anal anastomosis were independent risk factors identified for developing clinical anastomotic leakage. Knowing of these risk factors will help surgeons be aware and have low clinical threshold for early diagnosis of anastomotic leakage of these high-risk patients after open colorectal cancer surgery.

What is already known on this topic?

Previous studies revealed that risk factors for anastomotic leakage including low anastomosis in rectum (<6 cm), male sex, and preoperative radiation. Leakage of colorectal anastomosis is usually associated with short-term and long-term morbidity.

What this study adds?

The study revealed some risk factors of anastomotic leakage that were not often mentioned in the literatures including transverse colectomy and the longer operative time of more than four hours. Knowing of these risk factors will assist surgeons to realize and be aware so they will have early recognition of these complication in high-risk patients.

Potential conflicts of interest

None.

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ปัจจัยเสี่ยงสำหรับการรั่วของรอยต่อในการผ่าตัดลำไส้ใหญ่และทวารหนักแบบเปิด: การวิเคราะห์ในผู้ป่วย 558 ราย

จุไรรัตน์ ทุมนันท์, วีรพัฒน์ สุวรรณธรรมา, จักรพันธ์ เอื้อนรเศรษฐ์

ภูมิหลัง: การรั่วของรอยต่อเป็นหนึ่งในภาวะแทรกซ้อนที่สำคัญหลังการผ่าตัดลำไส้ใหญ่และทวารหนัก การทราบปัจจัยเสี่ยงของการรั่วของรอยต่ออาจช่วยป้องกันการรั่วของรอยต่อหลังผ่าตัดลำไส้ใหญ่และทวารหนักได้

วัตถุประสงค์: เพื่อประเมินอุบัติการณ์และปัจจัยเสี่ยงต่อการเกิดการรั่วของรอยต่อหลังการผ่าตัดลำไส้ใหญ่และทวารหนัก

วัสดุและวิธีการ: ทำการศึกษาโดยเก็บข้อมูลย้อนหลังในสถาบันเดียว โดยรวบรวมผู้ป่วยที่มาผ่าตัดลำไส้ใหญ่และทวารหนัก และมีการต่อลำไส้ใหญ่ในช่วงเดือนมกราคม พ.ศ. 2551 ถึงเดือนธันวาคม พ.ศ. 2555 พบว่ามีผู้ป่วยจำนวน 558 รายได้รับการผ่าตัดลำไส้ใหญ่และทวารหนักในช่วงเวลาดังกล่าว มีการจัดเก็บข้อมูลพื้นฐานของผู้ป่วยลักษณะของก้อนมะเร็ง ชนิดการผ่าตัด ผลการผ่าตัดและลักษณะของการรั่วของรอยต่อการวิเคราะห์ทางสถิติแบบ univariate ถูกใช้เพื่อประเมินปัจจัยเสี่ยงของการรั่วของรอยต่อ

ผลการศึกษา: ผู้ป่วยจำนวนทั้งสิ้น 558 ราย และพบว่ามีจำนวน 28 ราย (5%) มีการรั่วของรอยต่อ ผู้ป่วยส่วนใหญ่ได้รับการวินิจฉัยการรั่วของรอยต่อประมาณ 6 วันหลังผ่าตัด หลังจากการวิเคราะห์แบบ univariate พบว่าการฉายรังสีก่อนผ่าตัด ($p = 0.023$) การผ่าตัดแบบ low anterior resection ($p = 0.037$) การผ่าตัดแบบ transverse colectomy ($p = 0.022$) การผ่าตัดแบบ colo-anal anastomosis ($p = 0.011$) การมี protective stoma ($p = 0.006$) และการผ่าตัดที่ใช้ระยะเวลานาน ($p = 0.005$) และการมีการแพร่กระจายไปยังต่อมน้ำเหลือง ($p = 0.001$) จัดว่าเป็นปัจจัยเสี่ยงที่สัมพันธ์กับการเกิดการรั่วของรอยต่อ ไม่พบมีผู้ป่วยเสียชีวิตในการศึกษานี้

สรุป: จากข้อมูลของการศึกษานี้พบว่าการผ่าตัดแบบ low anterior resection, colo-anal anastomosis transverse colectomy และการผ่าตัดที่ใช้เวลานานกว่า 4 ชั่วโมง เป็นปัจจัยเสี่ยงสำคัญต่อการเกิดการรั่วของรอยต่อในการผ่าตัดลำไส้ใหญ่และทวารหนักแบบเปิด