

## Risk Factors and Diagnostic Criteria for Colorectal Anastomotic Leaks

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**Background:** Anastomotic leakage (AL) after colorectal resection and anastomosis is a major complication with significant morbidity and mortality.

**Objective:** To identify the risk factors for AL and to identify a standardized diagnostic protocol to reduce delay in diagnosis of AL.

**Design:** A Systematic Review.

**Setting:** King Hamad University Hospital, Bahrain.

**Method:** A Systematic Review of English-language studies was performed. An internet search of full-text articles in three different databases: The Cochrane Library (Controlled Trials Register), Medline (PubMed) and EMBASE from 1990 onwards were reviewed.

**Result:** Literature review has produced a varying AL rate of 2% to 22%. The major risk factors isolated were advanced age (>65 years), multiple comorbidities/higher ASA grade, low preoperative serum albumin level, steroid use, longer duration of surgery and contamination of operative field. Delay in diagnosing AL was reduced by use of standardized surveillance protocols postoperatively.

**Conclusion:** Preoperative risk stratification facilitates decision making whether to provide a diverting stoma or not. In addition, a standardized postoperative surveillance decreases delay in the diagnosis of AL, thereby, decreasing morbidity and mortality.

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Surgical resection is the standard treatment for patients with colorectal cancer, complication of diverticular disease, refractory ulcerative colitis and Crohn's disease. Restoration of bowel continuity with a primary anastomosis is undertaken in uncomplicated, elective resections.

Anastomotic leaks (AL) are the leading cause of postoperative death after colorectal surgery and permanent stoma<sup>1,2</sup>. It is a significant complication and has a mortality of 2% to 22%. Several risk factors have been identified in previous research projects that the authors have reviewed, such as male gender, smoking, obesity and alcohol abuse. Factors related to treatment protocols include the use of anti-inflammatory drugs, whether steroids or non-steroids, need for transfusion, procedure duration, timing during duty hour and fecal contamination<sup>3</sup>. Furthermore, American Society of Anesthesiologists (ASA) Grade III/IV patients and prolonged operative times are risk factors for AL after laparoscopic colorectal surgery<sup>4</sup>. Evaluation of preoperative risk by "risk scoring system" helps to identify patients at high probability of an anastomotic leak.

AL risk evaluation by an appropriate scoring system facilitates operative technique selection, such as primary anastomosis, primary anastomosis with diverting stoma or only stoma.

Diagnosis and treatment of AL could similarly be facilitated by a standardized scoring system. Clinical symptoms and signs of fever, abdominal pain and ileus are common, but have low predictive value for AL if observed independently. These signs were combined into a scoring system known as 'The Dutch Leakage Score' (DLS), where patients are scored daily in a systematic manner; points were rendered to predetermined clinical symptoms<sup>5</sup>. It was shown that patients with a higher score were prone to AL and required close clinical observation and/or pre-emptive radiological imaging<sup>6</sup>.

Early detection of AL could reduce the delay in diagnosis and facilitate earlier implementation of definitive treatment whether it is repair and possible preservation of the anastomosis or disconnection of the anastomosis and stoma creation. Suitable preoperative patient selection and vigilant postoperative

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surveillance for AL with appropriate treatment after diagnosis would ensure better outcomes.

Gold standard methods of selecting adequately vascularized bowel ends with no tension at the anastomotic line and appropriate operative sequence could be coupled with innovative anastomotic techniques which result in a favorable outcome, but randomized controlled trials have yet to validate this.

The aim of this systemic review is to identify the risk factors for AL and to identify a standardized diagnostic protocol to reduce delay.

## METHOD

### Search Strategy and Study Selection

Systemic search of the English literature was performed using the following terms:

- Colorectal Anastomosis
- Colorectal Cancer
- Leak
- Risk Factors
- Diagnostic Criteria
- Diagnosis
- Complications
- Surgical Techniques
- Postoperative

The following databases were searched: The Cochrane Library (Controlled Trials Register), Medline (PubMed) and EMBASE. Selected articles, journals and conference highlights were obtained from World Journal of Gastroenterology, Google Scholar and The American Journal of Surgery. Limitations were English language, studies from 1990 onwards and human studies only.

Search results were scanned based on abstracts produced by two reviewers independently and selection was made based on eligibility. The results were cross-checked for any duplications, and the final selection was based on abstract alone.

### Quality of Included Studies

Studies highlighting risk factors were critically appraised based on the methodology quality and the diagnostic tool. The studies were assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool<sup>7</sup>. Studies were evaluated based on selection bias, randomization and publication bias.

The assessment was performed by two reviewers independently, and the consensus was reached; in the event a study was not approved, the main author would be allowed to make the inclusion decision.

### Data Extraction

The study details regarding sample size, methodology, presentation of results and analysis were extracted and carefully analyzed. Risk factors were interpreted based on their statistical significance. Diagnostic tools were also recognized

through the statistical presentation of the data collected. Only simple mathematical calculations were used to present data in percentages.

## Data Analysis

Data selected was reviewed using a theoretical approach. No database was applied.

## RESULT

Anastomotic leakage (AL) rate from various national audits, large retrospective and prospective studies varied from 2% to 22%. There were 20,441 participants amongst the studies selected, out of which only 1,431 (7%) were diagnosed with an anastomotic leak.

Definition of a leakage was practically similar amongst all studies selected, which reflected only primary anastomosis; this similarity removed any confounding factors. The definition of leakage was either clinical or radiological; data relevant to clinical was taken into consideration only as it is more applicable to the aim of our study.

Only one of the selected studies considered other colonic pathologies (inflammatory, infectious and malignancy) in an anastomosis; however, 90% of the cases were secondary to a malignant pathology.

### Patient Factors for AL

The majority of the studies showed that male patients above the age of sixty had the highest incidence of AL evidenced by the 20,441 participants studied across the United States and Dutch database<sup>8,9</sup>. Those with an ASA score of more than one are associated with co-morbidities were also at higher risk of developing AL. Amongst the modifiable risk factors, Body Mass Index of greater than 30 increases the risk of leakage by 40%, and nicotine abuse increased the risk of a leakage by at least 30%, while those with both factors were at a cumulative risk for leakage<sup>10</sup>. Nicotine abuse had a higher rate of mortality attributable to a cardiovascular event. Steroid use amongst patients preoperatively was shown to have a higher risk of AL attributable to delayed healing<sup>4</sup>.

### Laboratory Factors for AL

Preoperative steroids and patients with albumin levels less than 3.5g/dL were at a significant high-risk of developing AL<sup>4,8</sup>. Patients with Hemoglobin levels of less than 12 g/dl and those who required a blood transfusion either preoperatively, intraoperatively or postoperatively were at a higher risk of developing a leak<sup>11</sup>. C-reactive protein (CRP) level measured post-operatively were an indicator for diagnosis of AL but not directly studied to be a predictor of AL, according to a study performed by medical university school in Portugal; an early persistent increase in CRP after colorectal anastomosis was a marker of anastomotic leakage<sup>10</sup>. A value exceeding 140mg/L on postoperative day three is significantly associated with anastomotic leakage if other sources of infection (wound, chest and urinary) are ruled out.

### Operative Factors for AL

There was no difference in AL between patients with and without a defunctioning stoma in the Dutch surgical colorectal audit<sup>9</sup>. Resections performed were right hemicolectomy, extended right hemicolectomy, left hemicolectomy, transverse colectomy, sigmoid colectomy, anterior resections, total or subtotal resections and other colectomies. There was no significant difference in AL regarding the procedures. Some studies mentioned a higher rate of leaks in anterior and low anterior resections (colo-rectal and colo-anal anastomosis). There was no significant difference in the leak rates after left or right sided resection and anastomosis. Surgery in the emergency setting, such as obstructed or perforated tumor was associated with a higher risk of AL. Emergency surgery is most often performed outside normal working hours (evening and night shifts) from different specialties have reported worse postoperative outcome<sup>12</sup>. Increased duration of surgery and spillage or fecal contamination were also associated with increased risk of AL<sup>8</sup>. Surgical procedures requiring urological or gynecological interventions are independent predictors of leak<sup>11</sup>.

Several large studies and national audits have revealed that there is no association between preoperative bowel preparation and leak rates. However, some recently published data suggesting that bowel preparation may reduce surgical site infection<sup>13</sup>.

### Tumor Factors Affecting AL

Complicated tumors with either perforation or obstruction have a higher risk for AL due to the emergency condition of the surgery<sup>14</sup>. Location of the tumor (distal < 10 cm from the anal verge) was shown to be at 3.5 times higher risk for AL, especially in patients with comorbidities or a male gender<sup>15</sup>.

Tumors at TNM Stage II to IV were 2.3 times more likely to develop an AL compared to stage I. Histological type (adenocarcinoma versus mucinous versus signet) or histological grade was not a statistically significant risk factor<sup>11</sup>. Radiotherapy or chemotherapy prior to elective surgical procedure was cumulative factors in increasing the risk of AL.

### Colon Leakage Score Pre and Intraoperative

Colon leakage score (CLS) is clinically relevant scoring system predictive of AL preoperatively, see table 1. The system is based on patient and preoperative variables<sup>16</sup>. The study was based on systematic review of the literature and the selection of salient risk factors. The CLS was tested in a retrospective cohort of consecutive patients who had a left-sided colorectal resection and anastomosis. Anastomotic leakage was defined by a set of clinical and radiological findings.

Postoperative fever, sepsis (localized or generalized peritonitis) and feculent discharge from operative wound or drains were deemed signs of AL similar to the diagnostic criteria of AL used to assess risk factors in multiple studies. Leaks detected only on radiological imaging and not clinically relevant were not considered to have an AL relevant to its applicability to the aim of this review. In this study CLS accurately predicted the risk of AL following left-sided colorectal surgery. It facilitated the selection of patients for primary anastomosis or proximal defunctioning stoma based on CLS scoring. Two factors were included in the system: intraoperative, such as the amount of blood loss (directly related to the need for blood transfusion)

and the length of the surgery. These two factors are incorporated into the score intraoperatively.

There is no difference in the association between CLS and the site of anastomosis (rectal or colon) based on data from a small sample size of 121 left-sided colorectal surgery cases without any stoma; 10 cases had a clinical diagnosis of AL<sup>16</sup>. The mean CLS score of these cases was 15.7, whereas the mean CLS score was 7.6 for those that didn't develop a clinical AL<sup>16</sup>. In facilitating surgical decisions of either a stoma versus an anastomosis, a cut-off score of 11 has been suggested with a risk of AL of less than 3%. Any patient with a score of CLS of more than 11 is considered to be high-risk for leakage<sup>16</sup>.

**Table 1: Colon Leakage Score (CLS) and its Variables<sup>16</sup>**

Colon Leakage Score (CLS) and Points Per Variable		Score
<b>Age</b>	<60	0
	60-69	1
	70-79	2
	>80	4
<b>Gender</b>	Female	0
	Male	1
<b>ASA</b>	I	0
	II	1
	III	3
	IV	6
<b>BMI</b>	19-24	0
	25-30	1
	>30/<19 or wt loss (>5kg/6 mo)	3
<b>Intoxication</b>	No	0
	Smoking	1
	Alcohol (>3 U/d)	1
	Steroids (present use excluding inhalers)	4
<b>Neoadjuvant therapy</b>	No	0
	Radiotherapy	1
	Chemoradiation	2
<b>Emergency surgery</b>	No	0
	Bleeding	2
	Obstruction	3
	Perforation	4
<b>Distance of anastomosis to anal verge (cm)</b>	>10	0
	5-10	3
	<5	6
<b>Additional procedures</b>	No	0
	Yes	1
<b>Blood loss (cc), Blood transfusion</b>	<500	0
	500-1000	1
	1001-2000	3
	>2000	6
<b>Duration of operation (h:min)</b>	<2:00	0
	2:00-2:59	1
	3:00-3:59	2
	>4:00	4

## Dutch Leakage Score Postoperative

Standardized postoperative surveillance has been shown to decrease significantly the delay in diagnosis of AL thereby preventing morbidity and mortality. The delay in diagnosis of AL was defined as the period from the first signs of clinical deterioration to confirmation of diagnosis. A standardized "Leakage Score" based on certain general observations (temperature, heart rate, respiratory rate, urine output, mental status and improving or deteriorating clinical condition), local examination findings (ileus, gastric retention, wound fascial dehiscence, abdominal or wound pain), laboratory data (Increasing WBC count, increasing CRP and renal function – S. creatinine) and dietary status (normal diet or tube feeding) was able to predict AL<sup>5</sup>.

Retrospective application of the score proved to be significantly accurate in predicting leakage and prompting specific tests and imaging studies (CT with contrast enema). The retrospective analysis was applied to patient records from three teaching hospitals in the Netherlands (total of 1,066 resections between 1996 and 1999).

In a prospective study, the score was applied to 224 consecutive resections from August 2004 to 2006. The Leakage Score was determined daily for all patients. A significantly higher score for patients with AL was found from day 5 to day nine postoperatively. Standardized surveillance was shown to facilitate earlier diagnosis during the treatment period. Also, a decrease in mortality rate was demonstrated when patients were monitored with Standardized surveillance such as application of leakage score, see table 2.

**Table 2: Leakage Score<sup>5</sup>**

Item	Normal Value	Score	Abnormal Value	Score
<b>General</b>				
Fever	≤38.0 °C	0	>38.0 °C	1
Heart Rate	≤100/min	0	>100/min	1
Respiratory Rate	≤30/min	0	>30/min	1
Urinary Production	≥30ml/hr or 700 mls/day	0	<30ml/h or 700mls/day	1
Mental Status	Normal status	0	Agitation or Lethargy	2
Clinical Condition	Stable or improving	0	Deterioration	2
<b>Local Physical Examination</b>				
Signs of ileus	No ileus	0	Ileus	2
Gastric retention	No gastric retention	0	Gastric Retention	2
Fascial Dehiscence	None	0	Fascial Dehiscence	2
Abdominal pain, other than wound pain	No pain other than wound pain	0	Pain other than wound pain	2
<b>Laboratory Investigations</b>				
Signs of infection	No increase in leukocyte number or CRP	0	Increase of ≥5% in leukocytes or CRP	1
Kidney Function	No increase in urea or creatinine	0	Increase of ≥5% in urea or creatinine	1
<b>Diet</b>				
Nutritional Status	Normal diet	0	Tube Feeding/ TPN	1/2

## DISCUSSION

AL following surgical intervention is serious complication which, even after revision surgery, leads to prolonged convalescence, associated morbidities or lead to death due to 'Multi-Organ Dysfunction'. Leakage of large bowel contents is also associated with other complications, such as wound infection, DVT, pulmonary embolism, chest infections and CVA<sup>17</sup>. Established AL requires surgical treatment and defunctioning stoma in most cases. The presence of a stoma does cause undesirable effects on patient's quality of life. Additionally, patients might suffer complications of the stoma, such as, parastomal hernia, skin irritation, retraction or prolapse of the stoma.

Appropriate patient selection based on preoperative and intraoperative risk factors should aid in decision making on whether to construct a defunctioning stoma. Similarly standardized post-operative surveillance parameters aid in the diagnosis of AL earlier.

The analyzed variables were associated with the patient, tumor and operative parameters. The risk factors cited in literature were identified and studied. The CLS, which is based on a list of previously defined variable factors was applied to a retrospective cohort of patients and studied. It was found to predict accurately the risk of AL following colorectal resections. Other surgical risk scores have been developed in the past, but they do not give guidance on intraoperative decision making and instead focus on mortality and morbidity. In the study by Dekker et al a cutoff value of 11 on CLS is cited to distinguish between low and high-risk patients, such as patients with scores higher than 11 should be considered for a defunctioning stoma. Individual surgeons can decide on specific cut-off values based on their experience and whether they wish to avoid unnecessary stoma creation.

CLS is usually calculated preoperatively, but intraoperative blood loss and duration of surgery are important predictive factors. They are indirectly indicative of technical difficulties during the procedure and further refine the decision making.

The Leakage score was developed to standardize postoperative surveillance and reduce variability. Postoperative variables observed in AL's were selected by focused literature search. The surgical Infection Study Group described the clinical signs of AL which included fever, raised WBC and increased CRP level<sup>18</sup>. It is well documented in the literature that delays in diagnosis of AL results in increased mortality<sup>19</sup>. The Leakage Score if studied retrospectively and applied prospectively was able to reduce the delay in diagnosis of AL and thereby reduce the associated mortality. In a retrospective study by Dulk et al, the mortality rate was 39% while in the prospective standardized surveillance group the mortality rate was 24%. Therefore it was feasible to introduce a protocol for standardized surveillance for AL after colorectal surgery. The strength of the variables was based on clinical relevance by the authors as no literature was available documenting pertinent variables. In the past, various studies have described varying postoperative parameters that are linked to AL but no standardized scoring system could be applied in the clinical setting was tested. The variables in the Leakage score can be easily documented on history taking and physical examination. Without standardized monitoring, patients may be subjected to non-indicated tests which may not help the diagnosis. Currently, the leakage score is being optimized through a registration project involving several Dutch centers, where various parameters will be collected.

Limitations and robustness of the study: There have been no RCTs for determining the risk factors and diagnostic criteria for diagnosing colorectal AL's. Currently historical data and small series of retrospective studies and prospective trials is the best available evidence.

Possible limitations in the development of CLS study by Dekker et al is the involvement of nine surgeons with no technical details. In addition, 139 patients represent a small sample. The strength given to various variables could be questioned but there seemed to be a consensus on the important risk factors across several studies.

To validate the Leakage score a larger group of patients will be required. Several variables should be considered and the validity of the cutoff values to diagnose AL could be questioned. In addition, there was difference in data collection of variables between the historical control and prospective study. Further validation of the Leakage score by way of a national registration project in several Dutch centers is continuing and may lead to a modified DUTch LeaKage (DULK) scoring list.

The strengths and weaknesses of review methods: Only English language publications were included in the systematic review and therefore we could have missed informative data in other languages. Also the sample size of patients in some of the studies included was small and could affect the accuracy of the conclusion.

## CONCLUSION

**The standardized postoperative surveillance (Dutch leakage score) after colorectal surgery could provide valuable guidance on diagnostic options to diagnose AL for surgical residents who are developing their clinical diagnostic skills. The routine implementation of a standardized surveillance system will lead to better postoperative care.**

**The CLS and the Dutch Leakage score both conform to currently available evidence in the literature and have demonstrated the ease of implementation.**

**Further validation of both the CLS and the Leakage score in a large multicenter study should solve this difficult clinical situation.**

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