RESEARCH ARTICLE

Serum Procalcitonin Predicts Anastomotic Leaks in Colorectal Surgery

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Abstract

Background: Anastomotic leaks in colorectal surgery results in a high morbidity and mortality rate. Serum procalcitonin levels is known as a sensitive and specific marker of sepsis and could be use as a marker for early detection of a leak allowing early intervention. It may help a clinician decide to perform a CT scan even earlier especially when the diagnosis of a leak is uncertain. The aim of this study is to determine whether serum procalcitonin is a good predictor of anastomotic leak in colorectal surgery. **Methodology:** Between July 2014 until October 2015, 70 patients undergoing colorectal surgery were prospectively analyzed in a single-center tertiary teaching hospital. Demographic and surgical data were obtained. Serum procalcitonin was taken before surgery and at day 3 (72 hours) postoperatively. During the postoperative period, the patients were observed in the ward for features of anastomotic leak and if present, it was managed accordingly. The primary outcome was to prospectively determine an association between serum procalcitonin levels and an anastomotic leak in patients who underwent colorectal surgery with a primary anastomosis. **Result:** The rate of anastomotic leak was 4.5% (3 patients) with a mortality rate of 4.3% (3 patients). A rise in serum procalcitonin was statistically significant among patients with anastomotic leak. The optimal procalcitonin cut-off level at postoperative day 3 was 5.27 ng/mL, resulting in 100% sensitivity, 85% specificity, 23% positive predictive value and 100% negative predictive value. Nevertheless, none of the variables showed statistical significance with an anastomotic leak. **Conclusion:** Procalcitonin is a reliable biochemical marker to help diagnose anastomotic leak in colorectal surgery. Our study has shown that a level of 5 times beyond normal is statistically significant and a value of more than 5.27 ng/mL is confirmatory of a leak.

Keywords: Colon- leak- procalcitonin- rectum- surgery

Asian Pac J Cancer Prev, **18 (7)**, 1821-1825

Introduction

An anastomotic leak is among the most feared complication when operating on the bowel. The rate of anastomotic leaks in colorectal surgery worldwide varies from 6% to 27% with a mortality rate of up to 30% (Teoh et al., 2005; Lagoutte et al., 2012; Matthiessen et al., 2008). Among risk factors for an anastomotic leak are a low anastomosis (<6 cm from the anal verge), preoperative radiation, presence of intraoperative adverse events and male gender (Matthiessen et al., 2008; Matthiessen et al., 2004). Despite advancements in surgical techniques and improved understanding of risk factors, avoiding anastomotic leaks still remains undeniably crucial for a favorable outcome. It increases morbidity and mortality, prolongs hospital stay, increases healthcare costs and contributes to a higher local recurrence rate (Nesbakken et al., 2001; Mirnezami et al., 2011; Frye et al., 2009).

Radiological investigations especially the judicious use of oral contrasted CT scans is the main modality of investigation to detect a leak (Hyman et al., 2007). However, the sensitivity and specificity for a leak is 59% and 88% respectively (Kornmann et al., 2014). Other than the high costs of performing CT scan, exposing a patient to unnecessary radiation can be avoided if a single biochemical marker can be used to reliably prove the presence of a leak. Indeed, if such a test is performed, it could even avoid the need for any radiological imaging

In recent years, C-reactive protein has been used as an early predictor of anastomotic leak after an anterior resectionand infectious postoperative complications in rectal surgery (Nesbakken et al., 2001; Almeida et al., 2012; Welsch et al., 2007). Nevertheless, C-reactive protein lacks sensitivity as well as specificity (Clec'h et al., 2004).

Another biochemical marker is procalcitonin. It has

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been described as an early and sensitive and specific marker of sepsis and maybe utilized in an ICU or emergency department settings (Assicot et al., 1993). Procalcitonin is considered as a prognostic indicator for outcome prediction in septic patients (Clec'h et al., 2004). Other than this, procalcitonin plasmatic concentration has also been used as an early predictor of infection in acute pancreatitis, secondary peritonitis, and infectious complications after thoracic, esophageal, and cardiac surgery (Garcia-Granero et al., 2013).

Procalcitonin is produced exclusively in the thyroid C cells. It is extremely low in healthy individuals (Gendrel et al., 2000). In septicemia, alternative pathway inclusive of activated procalcitonin is released by multiple non-thyroidal tissue types which include white blood cells, spleen, kidney, pancreas, colon, adipocytes and the brain (Müller et al., 2001).

The presence of bacterial endotoxins stimulates synthesis of procalcitonin and it is rapidly released into the circulation after 3-4 hours and peaks after 8-24 hours. The main aim of the study was to determine the role of serum procalcitonin as an early and reliable biochemical marker for sepsis associated with anastomotic leaks.

Materials and Methods

This was a prospective observational study carried out over a period of one year and 2 months from 1st of July 2014 to 30th of October 2015. Approval was obtained from UKM MC Ethical Committee before embarking into this study.

The study population comprised patients who were surgically managed by Colorectal Unit, Department of Surgery, Hospital Canselor Tuanku Mukhriz. Those patients who had undergone colorectal surgery with primary anastomosis were included in this study. Patients excluded from this study were those who were less than 18 years old, not consented for enrollment, presented with perforated tumour and those with obvious active infection prior to surgery.

A written consent was achieved from all the participants. All patients had undergone standardized anesthetic protocol prior to the operation. Bowel preparation with oral fleet was given. Prior to the incision, prophylactic antibiotics mainly parenteral cephalosporin group and metronidazole were administered. All patients were managed according to fast-tract surgery protocols. During postoperative period, patients underwent routine hematological and biochemical profile. Procalcitonin was taken a day prior to operation as a baseline and at day 3 (72 hours) postoperatively.

Procalcitonin is measured by electrochemiluminescence immunoassay Elecsys BRAHMS PCT (Roche Diahnostics GmbH, D-68298 Mannheim, Germany). The functional assay sensitivity of Elecsys BRAHMS PCT is 0.06 ng/mL; a value of <0.5 ng/mL indicates a low risk of severe or septic shock, and a value of >2 ng/mL represents a high risk of severe sepsis or septic shock.

The patients were observed in the ward for features of anastomotic leak. In the case of positive anastomotic leak, further treatment will be managed according to the grades based on definition of anastomotic leak. According to Clavien-Dindo grades, anastomotic leak is classified either minor or major types. Minor anastomotic leak (Clavien-Dindo grades I and II) needs conservative medical treatment whereby major type (Clavien-Dindo grades III and IV) needs percutaneous radiological drainage or exploratory laparatomy (Dindo et al., 2004).

Anastomotic leak is defined clinically by peritonitis, pus or faecal discharge from the pelvic drain, pelvic abscess, or rectovaginal fistula (Frye et al., 2009). Diagnosis of anastomotic leak can be confirmed by one or more of the following which include clinically by presence of peritonitis or frank pus or fecal discharge from the drain, or radiologically by computed topography scan with contrast enema or intraoperative findings (Garcia-Granero et al., 2013).

Other septic complications might be involved are wound infection, pneumonia, and urinary tract infection. Wound infection is diagnosed in the presence of obvious signs of inflammation or pus discharge from the surgical site. Pneumonia is defined clinically and confirmed by presence of pulmonary haziness from chest radiograph. Urinary tract infection is detected by presence of leukocytes and nitrite in urine sediment test and confirmed by urine culture and sensitivity test.

Those patients were followed up until discharge which fulfilling all the following criteria: presence of bowel movement, absence of features suggesting sepsis, ability to take orally and ambulate well. This study was complete the moment patient could be discharged from the ward with any septic complications.

Continuous variables were reported as mean and SD, meanwhile categorical variables were expressed as number of patients and percentage. Statistical difference between categorical groups was completed by Chi-square test meanwhile Fisher's exact test was used instead if the expected frequency is too small. For the continuous group,statistical analysis was performed by independent student t test. In order to generate accuracy of procalcitonin, receiving operating characteristic (ROC) curve was utilized statistically, hence creating area under the curve, sensitivity, and specificity. In order to determine the optimal cut-off point, Youden's index was performed (Youden et al., 1950). The new cut-off point was used as the baseline and was categorized into 2 groups. Both were compared with a gold standard, which is CT scan and intraoperative findings. From this Fischer exact test, a new sensitivity, specificity, negative predictive value and positive predictive value were determined.

Statistical analysis was carried out using IBM SPSS statistical package, version 22.0.

Results

A total of 70 patients were recruited into this study from 1st of July 2014 to 30th of October 2015. Among them, 71.4% (n = 50) were male and 28.6% (n = 20) were female. The mean age was 61.6 ± SD 12.7 years.

A total of 62 patients had either a primary or recurrent colorectal malignancy while the remainder 8 patients had benign disease. The most common surgery

Table 1. Details of Surgery

	Number of patients, n	Percentage, %
Type of surgery		
Right hemicolectomy	10	14.3
Left hemicolectomy	4	5.7
Sigmoid colectomy	6	8.6
Anterior resection	22	31.4
Hartman reversal	8	11.4
Stoma closure	11	15.7
Others	9	12.9
Type of anastomosis		
Stapler	64	91.4
Hand-sewn	6	8.6
Anastomotic leak		
Anastomotic leak	3	4.3
No leak	67	95.7
Mortality		
Mortality	3	4.3
Alive	67	95.7

performed was an anterior resection, which accounted for 31.4% of all procedures (Table 1). Overall, 28% of the patients underwent a minimally invasive technique and anastomosis were performed by staplers in 91.4% of cases with 61% having an end-to-end configuration while the remaining 39% of patients had a side-to-side technique (Table 1). A covering ileostomy was performed in 27.1% of cases.

Anastomotic leak was detected in 3 patients, two of which were diagnosed by CT scan while the other required a laparotomy (Table 1). Mortality occurred in 4.3% of which 2 cases were due to anastomotic leaks and the other of an acute coronary event (Table 1). Univariate analysis was performed on demographic data and the risk of an anastomotic leak. None of the parameters were statistically significant (Table 2).

Serum procalcitonin (PCT) levels and leucocyte counts (TWC) were analyzed whether they could predict complications at day 3 after surgery. Both did not reveal any statistically significant results (Table 3).

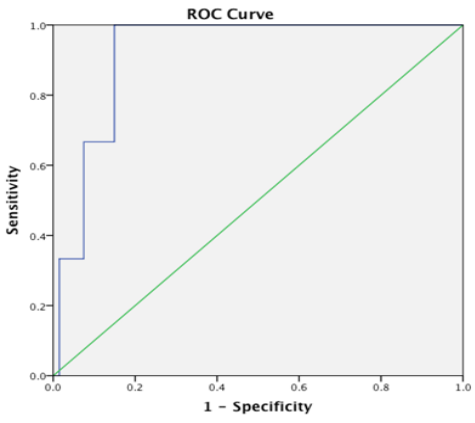

Figure 1. ROC Curve for PCT at Day 3

Table 2. Anastomotic Leak after Surgery – Univariate Analysis

Categorical data	Overall population (n = 70)		
	AL, n (%)	No AL, n (%)	P-value*
Gender			
Male	2 (2.9)	48 (68.6)	1
Female	1 (1.4)	19 (27.1)	
Ethnic group			
Chinese	3 (4.3)	35 (50)	0.451
Malay	0 (0)	30 (42.9)	
Indian	0 (0)	1 (1.4)	
Others	0 (0)	1 (1.4)	
Diagnosis			
Cancer	3 (4.3)	59 (84.3)	1
No cancer	0 (0)	8 (11.4)	
Type of surgery			
Right hemicolectomy	2 (2.9)	8 (11.4)	Invalid
Left hemicolectomy	0 (0)	4 (57.1)	
Sigmoid colectomy	0 (0)	6 (8.6)	
Anterior resection	1 (1.4)	21 (30)	
Hartman reversal	0 (0)	8 (11.4)	
Stoma closure	0 /(0)	11 (15.7)	
Others	0 (0)	9 (12.9)	
Surgical approach			
Open	3 (4.3)	47 (67.1)	0.552
Laparoscopy	0 (0)	20 (28.6)	
Type of anastomosis			
Stapler	3 (4.3)	61 (87.1)	1
Hand-sewn	0 (0)	6 (8.6)	
Anastomotic technique			
End-to-end	1 (1.4)	42 (60)	0.555
Side-to-side	2 (2.9)	25 (35.7)	
Covering ileostomy			
Yes	1 (1.4)	18 (25.7)	1
No	2 (2.9)	49 (70)	
Age, years old			P-value**
Mean (SD)	68.67 (9)	61.27 (12.8)	0.327
Duration of surgery, minutes			
Mean (SD)	176.7 (49.3)	206.1 (91.11)	0.582

* using Fischer exact test; ** using independent t-test

Further analysis was then performed to analyze interactions between biochemical markers and infection. Nevertheless, both markers did not show any statistical difference as both showed p-value of more than 0.05 (Table 4).

Both the mean value of PCT and TWC showed a statistically significant difference at day 3 in determining an anastomotic leak. PCT mean value in the anastomotic leak group was 25.48 ng/mL and the mean value in the no anastomotic leak group was 4.71 ng/mL (Table 4), where as the mean value for TWC was 16.17 in the anastomotic group and 10.2 for no anastomotic leak group (Table 4). Both parameters were then tested by ROC curve analysis.

From the ROC curve, only PCT had a statistically significant difference with p value of 0.014, resulting in

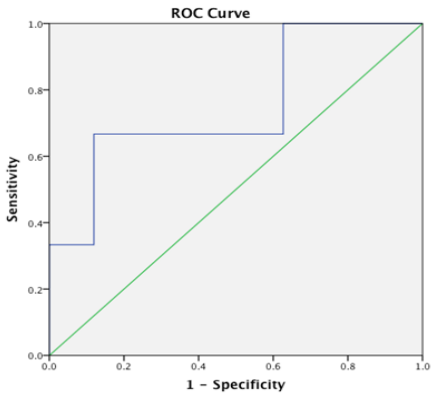

Figure 2. ROC Curve for TWC at Day 3

Table 3. PCT and TWC Mean Values between No Complication and Complication Group

	POD	No Complication Group (n = 53)	Complication Group (n = 17)	P value*
PCT, ng/mL	0	2.56 (5.32)	5.47 (6.85)	0.072
	3	4.63 (15.61)	8.6 (14.12)	0.354
TWC, x10^3/µL	0	10.21 (4.21)	9.9 (4.79)	0.802
	3	10.2 (3.55)	11.5 (4.7)	0.231

* using independent t test. Data are expressed as mean (SD); PCT, procalcitonin; TWC, total white cell

AUC of more than 0.8 compared to TWC with only 0.71 (Table 4). As shown in the ROC curve, procalcitonin had an enticing curve, which it skewed nearer to the top left in comparison to the total white cell, indicating that it has a better graph (Figure 1 and 2). The best cut-off point for PCT and TWC were selected by the use of Youden index according to sensitivity and specificity19. When the PCT was 5.27 ng/mL, Youden index resulted in sensitivity of 100% and specificity of 85% (Table 4). In comparison, total leucocyte counts resulted in a cut-off point of 8.65 x10^3/µL, producing 67% sensitivity and 37% specificity (Table 4).

The PCT level of 5.27 ng/mL was taken as the baseline

Table 4. PCT and TWC Mean Values Between No Infection and Infection Group

	POD	No Infection Group (n = 61)	Infection Group (n = 9)	P-value*
PCT, ng/mL	0	2.86 (5.52)	6.05 (7.26)	0.125
	3	4.63 (14.62)	12.18 (18.63)	0.167
TWC, x10^3/µL	0	10.07 (4.26)	10.58 (5.0)	0.746
	3	10.2 (3.57)	12.6 (5.31)	0.089
	POD	No AL Group (n = 67)	AL Group (n = 3)	P value*
PCT, ng/mL	0	3.27 (5.92)	3.123 (2.75)	0.965
	3	4.71 (14.05)	25.48 (29.9)	0.02
TWC, x10^3/µL	0	10.13 (4.27)	10.23 (6.65)	0.969
	3	10.26 (3.47)	16.17(8.27)	0.009

* using independent t test; Data are expressed as mean (SD); PCT, procalcitonin; TWC, total white cell; Al, anastomotic leak

Table 5. Participants with Anastomotic Leak of PCT and TWC on Postoperative Day 0 and 3

	POD	Sensitivity (%)	Specificity (%)	pAUC	AUC	Cut-off
PCT, ng/mL	0	67	72	0.07	0.716	1.83
	3	100	85	0.014	0.92	5.27
TWC, x10^3/µL	0	67	73	0.862	0.53	12.6
	3	100	37	0.143	0.751	8.55

PCT, procalcitonin; TWC, total white cell; AUC, area under the curve; p, p-value

Table 6. Cross-Tabulation between New PCT and Gold Standard

	Gold Standard		Total	P value
	AL	No AL		
PCT > 5.27	3	10	13	0.005*
PCT < 5.26	0	57	57	
Total	3	67	70	

*, using Fisher's exact test; PCT in ng/mL

and a cross-tabulation table was created between new PCT levels and the gold standard of determining anastomotic leaks (Table 4). A Fisher exact test was then made resulting in a p-value of 0.05. Based on the cross-tabulation table, the sensitivity of PCT at day 3 after surgery was 100%, specificity was 85%, positive predictive value was 23% and negative predictive value was 100% (Table 5 and 6).

Discussion

Leak after bowel anastomosis is the most dreaded complication for a surgeon. The rate of anastomotic leak varies in different centers from 6% to 27% with a mortality rate of up to 30% (Teoh et al., 2005; Lagoutte et al., 2012; Matthiessen et al., 2008). The overall incidence of anastomotic leak in this study was relatively lower at 4.3% and mortality rate of 4.3%. This is probably due to the fact then the study was done in a specialized colorectal unit.

In recent years, a raised C-reactive protein level has proven to be a reliable early predictor of anastomotic leak after anterior resectionand infectious postoperative complications in rectal surgery (Lagoutte et al., 2012; Kornmann et al., 2014; Welsch et al., 2007). However, Clec'h et al concluded that C-reactive protein lacks specificity and sensitivity to determine diagnosis and prognosis after surgery and fail to identify between patients with and without sepsis (Welsch et al., 2007).

Several studies have shown that PCT can be useful in detection of postoperative infections after cardiac, thoracic and orthopaedic surgery (Falcoz et al., 2005; Jebali et al., 2007; Hunziker et al., 2010). However, the pathophysiology and the microbials in these procedures are dissimilar to those in colorectal surgery. An anastomotic leak will create a septic environment caused by transient bacterial contamination or translocation of bacteriae during malperfusion of the bowel. Gram-negative, gram-positive, as well as anaerobic bacteria, including common gut flora, such as Escherichia coli, Klebsiella pneumoniae,

Streptococcus species and Bacteroides fragilis enter the peritoneal cavity causing intraabdominal sepsis (Hunziker et al., 2010).

The relevance of our study is the usefulness of PCT in predicting an anastomotic leak, which lessens the morbidity and mortality of a delayed diagnosis. Increased PCT despite any clinical signs will further warrant diagnostic imaging to confirm an anastomotic leak. It could also help in the early initiation of antibiotics. In the era of modern fast-track protocol in colorectal surgery, looking for a reliable marker is crucial, thus allowing safe and early discharge of patient. The negative predictive value of 100% in our study proves that in a patient with a normal PCT value at day 3 post-surgery, any suspicion of an anastomotic leak can be safely ruled out.

The limitation of this study is the relatively small number of patients with anastomotic leaks. A larger sample size is definitely needed in future studies to increase the statistical power of the study.

In conclusion, the present study has proven the role of procalcitonin as a biochemical marker for anastomotic leak. A level of 5 times beyond normal is significant. We recommend the investigation to be executed upon clinical suspicion just before a radiological confirmatory test is performed. A serum procalcitonin lesser than 5.27 ng/mL is proof of an absence of a leak.

Funding

This study received funding from research grant of Universiti Kebangsaan Malaysia.

Declaration of Interests

The author and co-authors have no conflicts of interest to declare.

Acknowledgments

This study was approved by the Ethical Committee of Universiti Kebangsaan Malaysia.

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