

Evaluation of the Predictive Value of Serum C-Reactive protein and Procalcitonin Levels in Early Detection of Anastomotic Leakage after Gastrointestinal Surgery

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Abstract

Background: Anastomotic leak (AL) after gastrointestinal surgery is a serious postoperative complication that leads to significant morbidity and mortality. **Objective:** To evaluate the role of sequential postoperative serum determinations of C-reactive protein (CRP) and Procalcitonin (PCT) in the identification and prediction of anastomotic leakage after gastrointestinal surgery and to describe the kinetics of PCT and CRP after surgery and their relative usefulness for the early detection of anastomotic leaks after gastrointestinal surgery. **Patients and Methods:** This study is a clinical prospective randomized observational analytical cross sectional study conducted in the elective and emergency surgery theaters of the department of general surgery at Suez Canal university hospital from Jan 2015 to Jan 2016 on 45 patients who underwent small bowel, colonic and rectal surgery with resection and primary anastomosis. The data was collected by using a questionnaire and lab results. **Results:** In our study, 22.2% of study patients developed anastomotic leakage, 48.9% of the studied population was between the ages of (46–60) (range 18-72 years), and 62.2% of the study populations were female. Both biochemical markers were elevated in patients with anastomotic leakage at day2, 3 and 4 and showed slightly similar curves, percentages but the upper hand was for PCT than CRP in the point of early detection and in the much more sensitive and more specific. The Pearson correlation with fistula was more powerful for CRP than for PCT. **Conclusion:** Patients with PCT greater than 0.65mg/dL and CRP greater than 21 mg/dL on Day4, even in the absence of clinical signs, are not permitted to leave the hospital and a diagnostic work-up for sepsis (lung, urinary tract, intra-abdominal, or wound) is actively pursued.

Key words: anastomotic leakage, Procalcitonin, C - reactive protein, gastrointestinal surgery

Introduction

Anastomotic leak (AL) after gastrointestinal surgery is a serious postoperative complication that leads to significant morbidity and mortality. The frequency and consequences of anastomotic failure vary

according to the site of anastomosis within the gastrointestinal tract. It is a serious complication after pancreatic surgery because dehiscence of anastomosis with autodigestion and destruction of surrounding tissue from leaking pancreatic juice is associated with a high mortality rate⁽¹⁾.

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Dehiscence after colorectal anastomosis increases the perioperative mortality rate due to peritonitis and septicemia, and adversely affects the late outcome in survivors because of increased local recurrence of carcinoma. Anastomotic leak may be used as an indicator of the quality of surgical care⁽¹⁻²⁾. Anastomotic leakage is also responsible for delayed resumption of GI transit, pain, prolonged hospital stay and increased costs. On the long term, it worsens functional prognosis after rectal surgery, promotes local recurrence and is a prognostic factor for poor one-year survival in patients undergoing cancer surgery⁽²⁻⁴⁾. According to the report of the French Association of Surgery, elective colorectal surgery in France has a mortality rate of about 4% and an overall morbidity of 35 %⁽⁵⁻⁸⁾. Anastomotic leakage is responsible for many of these complications, and accounts for one third of deaths⁽⁹⁻¹⁰⁾. The anastomotic leak rate varies from 1 to 40% in various reports depending on the definition chosen^(7,8,11). Despite the increased understanding about risk factors for anastomotic leakage and improvement in surgical technique, anastomotic leakage remains an important complication and occurs without obvious cause in some patients⁽¹¹⁾. According to Alves et al, the delayed diagnosis after Post-Operative Day 5 (POD 5) of anastomotic leakage is associated with a mortality rate of 18%, but minimal morbidity if diagnosed and treated before POD 5. Early detection of this complication is essential for timely institution of treatment, making early distinctive markers useful⁽⁵⁾. Early detection allows appropriate treatment and less morbidity with a decreased need for ostomy, and less deterioration in the patients' quality of life. Clinical examination is often nonspecific, and symptoms of anastomotic leakage often develop late^(12,13). Since routine postoperative imaging is not efficient, the use of serum markers of inflammation has been proposed to

aid in early detection of postoperative septic complications^(14,16). Thus, it has been shown that a serum C-reactive protein (CRP) greater than 12.5 mg/dL on the fourth postoperative day is predictive of septic complications. Moreover, fast track surgery and early rehabilitation have become standard in colorectal surgery with hospital discharge by the fifth postoperative day⁽¹⁷⁾. Anastomotic leaks and their consequences can occur well beyond that time, so it is necessary to find a marker of intra-abdominal infection with a high negative predictive value that allows safe hospital discharge with a low risk of re-admission⁽¹⁸⁾. Procalcitonin (PCT) is an inflammatory marker with a short half-life. It is frequently used in the ICU as a prognostic marker for serious infections and has been used to evaluate the response to antibiotic treatment. However, PCT has not been adequately evaluated in the postoperative period⁽¹⁹⁻²³⁾. It is possible that the rise in PCT occurs earlier than that of CRP in bacterial infections⁽²⁴⁻²⁸⁾.

Patients and Methods

Study design

After approval of Ethics Committee of the Faculty of Medicine, Suez Canal University, this clinical prospective randomized study conducted in the elective and emergency surgery theaters of the department of general surgery at Suez Canal university hospital from Jan 2015 to Jan 2016 on 45 patients who underwent small bowel, colonic and rectal surgery with resection and primary anastomosis.

Patients and Methods

All patients were subjected to thorough medical history and physical examination, laboratory investigations to evaluate the patients general condition including; complete blood count, bleeding profile, electrolytes, arterial blood gases, serum albumin random blood sugar, liver and kidney

function tests, Serum CRP and PCT. Pelvi-abdominal ultrasonography, Pelvi-abdominal computerized tomography with double contrast, Other studies as barium meal, enema, upper gastrointestinal endoscopy and colonoscopy if needed.

Pre-operative preparation

This included keeping the patient Nothing Per Oral (NPO), Intravenous fluids, Intravenous antibiotics, Mechanical preparation either polyethylene glycol electrolyte solution, laxatives (mineral oil, agar and phenolphthalein), mannitol, enemas (water, 900 ml; glycerin, 100 ml), sodium picosulphate 10 mg, Bisacodyl (10 mg) + enemas, and diets low and non-residue. For each patient, the following data was recorded: surgical indication, For each intervention data was recorded concerning the surgical approach (laparotomy or laparoscopy), underlying pathology, type of resection (subtotal gastrectomy with gastro-jejunostomy, Roux en Y anastomosis, partial small bowel resection with entero-enteric anastomosis, right hemicolectomy, left hemicolectomy, total colectomy, anterior resection with colorectal anastomosis, proctocolectomy with ileoanal anastomosis, and hepaticojejunostomy anastomosis), characteristics of the anastomosis (mechanical or manual), presence or absence of drain. Patients were examined daily to assess the clinical condition (pain, fever, hemodynamic status, abdominal examination, return of bowel function, and any wound discharge, hemoglobin level). Serum CRP and PCT was measured on the day prior to surgery (Day 0) and on the first, second, third and fourth postoperative days (Day 1, Day 2, Day 3 and Day 4)⁽²⁶⁾. Anastomotic leakage was diagnosed on the clinical signs of peritonitis and/or clinical evidence of free faecal fluid within the abdomen or emerging from the drain site. On clinical suspicion, the diagnosis was confirmed by abdominal and pelvic CT scan, using

intravenous and anorectal contrast. The patients were allocated into two groups according to the presence or absence of anastomotic leakage: with anastomotic leakage, without anastomotic leakage. The two groups were compared according to the following characteristics: gender and average age of patients, underlying pathology, planning of intervention (electives. urgent), surgical approach (laparotomy vs. laparoscopy), type of resection, mean hospital stay, postoperative morbidity and mortality, and mean values of serum CRP and Procalcitonin in the pre-and postoperative period. Serum CRP < 12 mg/L and serum Procalcitonin < 0.05 µg/L were considered normal values^(27,28). *Inclusion criteria:* adults ranging from 18–60 years old, both sexes included, Patients underwent elective or emergency gastrointestinal surgery with resection and primary anastomosis at the same setting while. *Exclusion criteria:* Patients with active infection (respiratory and urinary tract infection) before surgery or an acquired infection in the postoperative period other than leakage (respiratory, urinary tract and surgical wound infection), Patients those received chemotherapy and radiotherapy, Patients on long term corticosteroid therapy, Presence of a defunctioning stoma. After taking the blood samples, chemical analysis for all samples were done at once and value for each sample was recorded. The blood samples (5cc of venous blood from peripheral vein) were collected and the process of serum separation were done by the researcher in the hospital laboratory then coded in the serum form and preserved in the freezer of the blood bank (of the hospital at -80°C temperature) till the time of analysis by the specific kits using ELISA analysis in the hospital laboratory by a fixed laboratory technician. The disposable laboratory materials (e.g. blood sample tubes) used in the research will be brought by the researcher⁽²⁶⁾. CRP was determined

by immunonephelometry automated dimension Vista analyzer (Siemens, Erlangen, Germany). PCT was determined by homogeneous phase sandwich ELISA analysis (Brahms, Hennigsdorf, Germany)⁽²⁶⁾.

Statistical analysis

The process of data analysis was processed and encoded, these codes were entered into the computer through using statistical package for social science SPSS version 16 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as means and standard deviation while qualitative data were expressed as numbers and percentages. Student t test were used to test significance of difference for quantitative variables and Chi square were used to test significance of difference for qualitative variables. p -value < 0.05 was considered statistically significant.

Results

In our study, 48.9% of the studied population was between the ages of (46–60) (range 18-72 years), 62.2% were female, 46.7% of the patients had single co morbidity (table 1). 15.6% of our patients were mechanically prepared, 80% of patients were operated laparotomy and 20% of them were operated laparoscopically, 80% of study patients were manually hand sewn. While 17.7% of the study patients were stapled, 2.2% were mixed, drains were used in whole study patients, 20% of them were re explored, the mean of hospital stay days was 9.2 and the median was 7 days and it was between 3 to 35 days. The mean and the median value of serum albumin level of study patients were 2.9 and it ranged from 2.1 to 3.9, the mean and the median value of serum hemoglobin level of study patients were 11.4 and it ranged from 9 to 14.8 patients were died which represents 17.8% (table 2 and 3). more sensitive and specific, the area under the ROC curve were slightly

similar as at day 2, 3 it was more higher for PCT than CRP 0.820, 0.959 for 0.819, 0.954 and at day 4, it was higher for CRP than PCT 0.979 for 0.959. Also, serum PCT level at day 2 of 0.65 had sensitivity of 80% and specificity of 66%. But serum CRP level at day 2 of 27 had the same sensitivity but more specific 80%. At day 3, 4 and serum PCT levels of 0.7, 0.65 had 100% sensitivity and 95% specificity while that of serum CRP levels 24, 21 had lower sensitivity and specificity than PCT at day 3 as 90%, 89% and equal sensitivity at day 4 as 100% and more specific 98% (Figures 1, 2) In comparison between PCT and CRP in the point of early detection, both markers were elevated in patients with anastomotic leakage at day2, 3 and 4 and showed slightly similar curves, percentages but the upper hand was for PCT than CRP in the point of early detection, higher sensitivity and specificity. The Pearson correlation with fistula was more powerful for CRP than for PCT (Figures 3-6).

Discussion

According to age distribution of the study population, 48.9% of the studied population was between the ages of (46–60) (range 18-72 years), The mean age of our patients was 47.3 with standard deviation 11.02, while 50% of patients developed leakage was between the same age group and it's considered 11.1% of the whole patients. While in a pilot study conducted in France at the Digestive Surgery and Oncology Service, CHU de Dijon by Lagouttea, there were 100 patients with a mean age of 64 and a median age of 63 (range 20—87 years)⁽²⁶⁾ where the median age for the patients in a study in Belgrade at Zvezdara University Clinical Centre by Scepanovic was 65⁽²⁸⁻³⁰⁾. While in a prospective study done in department of surgical oncology and colorectal surgery in Poland and UK by Zawadzki, on 55 patients, the mean age

was $66.1 \pm 11.2^{(30)}$. The mean age of non-leakage group in the study of Almeida, department of general surgery of Centrohospitalar de saojoo, Portugal, was 65.5 years, while in the leakage group was 69.5

Table 1: Demographic data and its relation to the anastomotic leakage

Variables	LEAK		Total	Percent
	No	Yes		
Age groups (Yrs.)				
• 18-30	3	0	3	6.7
• 31-45	12	4	16	35.6
• 46-60	17	5	22	48.9
• > 60	3	1	4	8.9
Gender				
• Male	15	2	17	37.8
• Female	20	8	28	62.2
• Total	35	10	45	100

Table 4: Distribution of hemoglobin and albumin serum level characteristics

	Albumin	Hemoglobin
Mean	2.913333E0	11.49
Median	2.900000E0	11.00
Std. Deviation	.4424108	1.308
Minimum	2.1000	9
Maximum	3.9000	14

While in the pilot study conducted at the Digestive Surgery and Oncology Service, CHU de Dijon by Lagouttea, 58 were men and 42 were women⁽²⁶⁾. And it was 57.1% males and 42.9% women in Scepanovic study⁽²⁹⁾. While in Zawadzki study, 37 patients were males (67.3%) and 18 patients were females (32.7%)⁽³⁰⁾. In the study of Almeida, 88 (50.8%) of patients were males and 30 (49.2%) were females⁽²⁷⁾. Only 15.6% of our patients were mechanically prepared, 90% of patients developed leakage were not prepared. All patients in Lagouttea study, Scepanovic and Zawadzki study were mechanically prepared as these

years⁽²⁷⁾. In this study, 62.2% of the study populations were female, and 80% of patients who developed leakage were also female (17.7% of the total population).

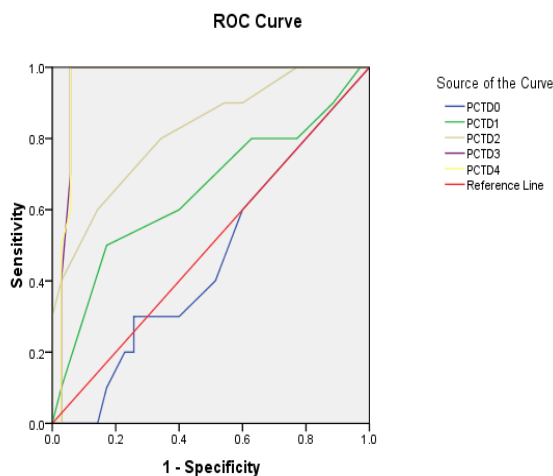
Table 2: Surgical data characteristics and its relation to the anastomotic leakage

Variables	LEAK		Total	Percent
	No	Yes		
Approach				
• Laparoscopic	7	2	9	20
• Laparotomy	28	8	36	80
• Total	35	10	45	100
Repair				
• Mechanical	6	2	8	17.8
• Manual	28	8	36	80
• Both	1	0	1	2.2
• Total	35	10	45	100

studies were on elective cases^(26,29,30). Regarding the surgical technique of the operation, 80% of our patients were operated with laparotomy and 20% were operated laparoscopically, and 80% of patients developed leakages were operated laparotomy. While in the pilot study at Dijon by Lagouttea, there were 65% of patients operated laparotomy and 35% operated laparoscopically⁽²⁶⁾. All patients in the study of Scepanovic were operated with laparotomy⁽²⁹⁾. But at Zawadzki study, 29 patients (52.7%) underwent a robotic surgery while the others (26 patients, 47.3%) underwent open surgery⁽³⁰⁾. In the study of Almeida, there were 31 (17.9%) patients were operated laparoscopically, one of them had developed leakage, while the others (142 (82.1%) patients) were operated laparotomy, 23 patients of them had developed leakage⁽²⁷⁾. In our study, 17.8% of patients suffered from perforated peptic, 15.6% of patients suffered from morbid obesity, 2.2% with esophageal cancer, 6.7% with cancer stomach, 4.4% with periampullary cancer, 6.7% cancer head of pancreas, 2.2%

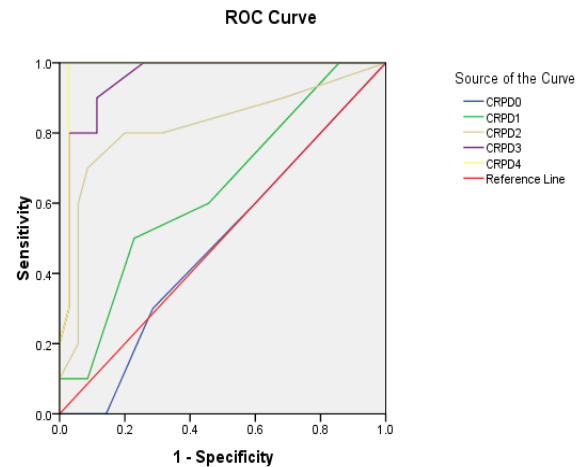
with cholangiocarcinoma, 8.9% with MVO, 4.4% with strangulated small bowel in hernia, 4.4% with cancer caecum, 2.2% with splenic flexure mass, 2.2% with recto sigmoid mass, 4.4% with cancer rectum, 4.4% with closure of colostomy, 2.2% with sigmoid volvulus 8.9% with ligated CBD post cholecystectomy, 2.2% with hepatic flexure mass. while 20% of patients developed leakage accounted for cancer head of pancreas, mesenteric vascular occlusion, morbid obesity and 10% of them accounted for stomach cancer, strangulated small bowel in Para umbilical hernia, cancer caecum, closure of Hartman`s colostomy post recto sigmoid mass. While in the pilot study of

Lagouttea, there was Cancer (52 patients): 2 rectum, 14 left colon, 16 right colon, 1 transverse colon. Diverticulitis (17 patients). Benign colon tumor (3 patients). Re-anastomosis (8 patients). Others: polyps unresectable by endoscopy (7 patients), solitary ulcer (1 patient), rectal villous adenoma (1 patient), ileo-cecal stricture (2 patients), familial adenomatous polyposis (2 patients), anastomotic stricture (3 patients), migration of prosthetic material into the rectum (2 patients), ischemic stricture (1 patient), colonic metastasis from melanoma (1 patient)⁽²⁶⁾. While it was 96.8% carcinoma in the study of Belgrade and was 3.2% IBD⁽²⁹⁾.



Area Under the Curve				
Test Result Variable(s)	Area	Cutoff	Sensitivity	Specificity
PCTD0	.461	0.02	40	49
PCTD1	.651	0.65	60	60
PCTD2	.820	0.65	80	66
PCTD3	.959	0.7	100	95
PCTD4	.959	0.65	100	95

Figure 1: serum PCT level and characteristics for prediction of anastomotic leakage.



Area Under the Curve				
Test Result Variable(s)	Area	Cutoff	Sensitivity	Specificity
CRPD0	.483	3	60	40
CRPD1	.640	21	60	55
CRPD2	.819	27	80	80
CRPD3	.954	24	90	89
CRPD4	.979	21	100	98

Figure 2: Serum CRP levels and characteristics for prediction of anastomotic leakage.

All patients in Zawadzki study were cancer colon⁽³⁰⁾. In the study of Almeida, there were 129 (74.5%) patients had cancer colon, 17 patients of them developed leakage, 8

(4.6%) patients had IBD, 2 patients of them developed leakage, 4 (2.3%) patients had diverticular disease, 32 (18.4%) patients had other pathologies, 5 patients of them

developed leakage⁽²⁷⁾. In our study, 80% of our patients were manually hand sewn, 10% developed leakage. While 17.7% of our patients were stapled, 25% of them developed leakage and one patient with esophageal cancer was repaired mechanically for construction of gastric tube and manually for esophagogastric anastomosis. While Lagouttea and Belgrade there were 16% protective ileostomy (in our study there were on protective stoma), 57% stapled anastomoses, and 43% hand-sewn

anastomoses⁽²⁶⁾. And it was 75% hand sewn versus 25% mechanical in the study of Scepanovic⁽²⁹⁾. While in Zawadzki study, 29 patients (52.7%) were stapled and 26 patients (47.3%) were hand sewn⁽³⁰⁾. Drains were used in whole study patients while it was 62% in the pilot study of Lagouttea⁽²⁶⁾. We found that 22.2% of our patients developed anastomotic leakage, 20% of them were re-explored. While it was 13% of patients included in pilot study done at Dijon by Lagouttea⁽²⁶⁾.

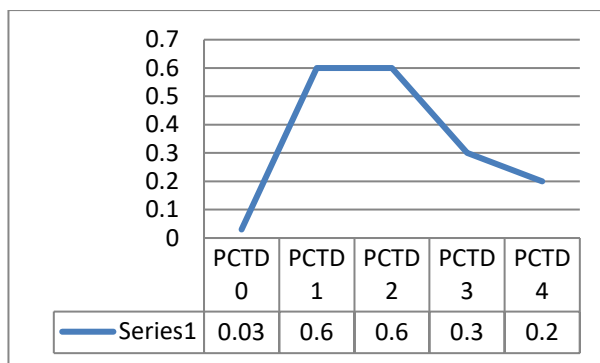


Figure 3: Median serum PCT levels at Do, D1, D2, D3, and D4 characteristics in non-anastomotic leak

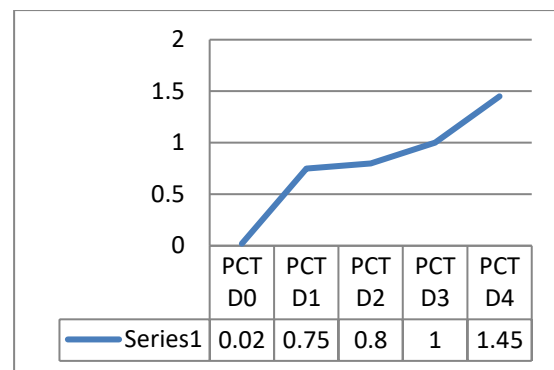


Figure 4: median serum PCT levels at Do, D1, D2, D3, and D4 characteristics in anastomotic leak

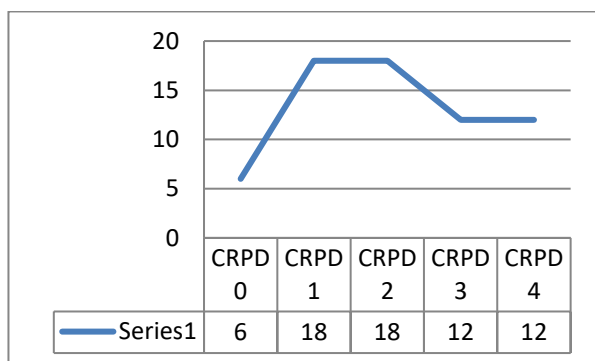


Figure 5: median serum CRP levels at Do, D1, D2, D3, and D4 characteristics in non-anastomotic leak

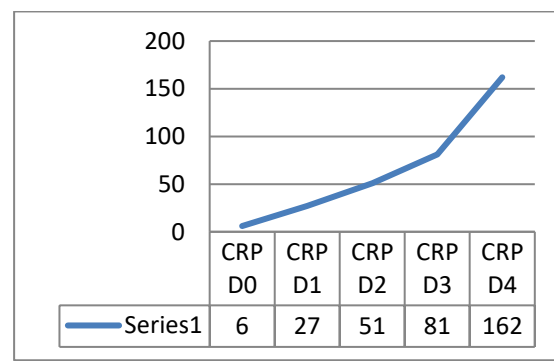


Figure 6: median serum CRP levels at Do, D1, D2, D3, and D4 characteristics in anastomotic leak

And it was 9.6% at the study done in Belgrade at Zvezdara University Clinical Centre by Scepanovic⁽²⁹⁾. Also, it was 9.1% (5 patients) at the study of Zawadzki and all of them were reexplored⁽³⁰⁾. In the study of Almeida, there were 24 (13.8) patients developed leakage, 21 of them had been reexplored⁽²⁷⁾. The mean of hospital stay days was 9.2 and the median was 7 days and it was between 3 to 35 days. At

Lagouttea study, the average length of stay was 12.5 ± 9.8 days (range: 4-55 days)⁽²⁶⁾. While at Zawadzki study, the mean hospital stays in non AL was 5.9 ± 1.6 , but in AL patients were 6.7 ± 3.2 days⁽³⁰⁾. In the study of Almeida, the mean hospital stay in non AL was 11.7 days, but in AL patients was 29.5 days⁽²⁷⁾. The mean and the median value of serum albumin level of study patients were 2.9 and it ranged from

2.1 to 3.9. The mean and the median value of serum hemoglobin level of study patients were 11.4 and it ranged from 9 to 14. In this study 8 patients were died which represents 17.8%, 50% of them had developed anastomotic leakage. At Lagouttea study, 2 patients died which represents 2%⁽²⁶⁾. While 3 patients died in the study of Scepanovic Belgrade which represents 1.9%⁽²⁹⁾. And no one died in Zawadzki study⁽³⁰⁾. According to the values of serum PCT levels, the median of Do, D1, D2, D3, and D4 were 0.3, 0.6, 0.6, 0.3 and 0.2 accordingly in the patients whom didn't develop anastomotic leakage. While those who develop anastomotic leakage were 10 (22.2%) patients as follow 0.2, 0.75, 0.8, 1 and 1.45. At Lagouttea study, the values of serum PCT levels, the median of Do, D1, D2, D3, and D4 were 0.007, 0.062, 0.081, 0.063 and 0.045 in the patients whom didn't develop anastomotic leakage. While those who develop anastomotic leakage were 13 (13%) patients as follow 0.013, 0.163, 0.134, 0.111 and 0.026⁽²⁶⁾. At Zawadzki study, serum PCT were measured prior to surgery, 8 h after the incision, on the first and third postoperative day (0, +8 h, POD 1, POD 3) and the values of median serum PCT levels were 0.05, 0.07, 0.72 and 0.22 in the patients whom didn't develop anastomotic leakage. While those who develop anastomotic leakage were 5 (9.1%) patients as follow 0.05, 0.05, 3.3 and 4.88⁽³⁰⁾. This study showed that serum PCT level of 0.02 at day 0 has no much significance in prediction of anastomotic leakage, sensitivity 40% and specificity 49% as well the serum PCT level of 0.65 at day 1 has no much significance, sensitivity 60% and specificity 60%. This differs from day 2 as the sensitivity increased up to 80% with specificity 66% at the serum PCT level value of 0.65, also at value of 0.75 sensitivity was 60% and specificity was 31% as the area under ROC curve increased 0.820 which showed a high significance for prediction of anastomotic leakage. While

at day 3 and day 4 at the serum PCT level values of 0.7, 0.65, the sensitivity was 100% with specificity 95% and the area under ROC curve increased up to 0.959 which showed a very high significance for prediction of anastomotic leakage. The mean values of serum PCT levels increased on POD 1 and 3 in all patients, but the rise of PCT was significantly higher among the patients with AL only on POD 3. The mean PCT on POD 1 was 2.0 ng/ml in non-AL and 3.8 ng/ml in AL patients, whereas on POD 3 it was 0.56 ng/ml and 10.4 ng/ml, respectively⁽³⁰⁾. Analysis of ROC curves showed that PCT on POD 3 had AUC of 0.30. A cut-off value for PCT on POD 3 was calculated at the level of 3.26 ng/ml with 75% sensitivity and 100% specificity for AL⁽³⁰⁾. According to the values of serum CRP levels, the median of Do, D1, D2, D3, and D4 were 6, 18, 18, 12 and 12 in the patients whom didn't develop anastomotic leakage. While those who develop anastomotic leakage were 10 (22.2%) patients as follow 6, 27, 51, 81 and 162. At Lagouttea study, the values of serum CRP levels, the median of Do, D1, D2, D3, and D4 were 0.47, 12.4, 15.2, 11.30 and 8.5 in the patients whom didn't develop anastomotic leakage. While those who develop anastomotic leakage were 13 (13%) patients as follow 2.33, 15.5, 22.1, 23.05 and 20.8⁽²⁶⁾. At Zawadzki study, serum CRP were measured prior to surgery, 8 h after the incision, on the first and third postoperative day (0, +8 h, POD 1, POD 3) and the values of median serum CRP levels were 4.3, 6.14, 108.31 and 105.26 in the patients whom did not develop anastomotic leakage. While those who develop anastomotic leakage were 5 (9.1%) patients as follow 1.69, 4.4, 133.5 and 299.61⁽³⁰⁾. In the study of Almeida, serum CRP were measured preoperative and post-operative up to the 9th day post-surgery. The values of mean serum CRP levels were 15, 98, 132, 105, 69, 40, 40, 29, 49 and 36 in the patients whom didn't had leakage. While those who

develop anastomotic leakage were 24 (13.8%) patients as follow 22, 116, 187, 201, 129, 162, 178, 201, 209 and 174 respectively⁽²⁷⁾. This study showed that serum CRP level of 3 at day 0 has no much significance in prediction of anastomotic leakage, sensitivity 60% and specificity 40% as well the serum CRP level of 21 at day 1 has no much significance, sensitivity 60% and specificity 55%. This differs from day 2 as the sensitivity increased up to 80% with specificity 80% at the serum CRP level value of 27 as the area under ROC curve increased 0.819 which showed a high significance for prediction of anastomotic leakage. While at day 3 and day 4 at the serum CRP level values of 24, 21 the sensitivity was 90%, 100% with specificity 89%, 98% and the area under ROC curve increased up to 0.954, 0.979 which showed a very high significance for prediction of anastomotic leakage. In the study of Belgrade by Scepanovic, POD 2, mean serum CRP was 187 mg/L in leak group and 132 mg/L in non leak group. On POD 3, those values were 201 mg/L in leak group and 105 mg/L in non-leak group. Based on the evaluation of the ROC curves, a cut-off value of 140 mg/L on POD 3 maximized the sensitivity (78%) and specificity (31%) of serum CRP in predicting the risk of leakage⁽²⁹⁾. The mean value of CRP increased on POD 1 and POD 3 in all patients. The peak of CRP was significantly higher in the AL group only on POD 3. On the third postoperative day the mean values of CRP were 114 mg/l in non-AL patients and 321 mg/L in AL patients⁽³⁰⁾. Analysis of ROC curves showed that CRP on POD 3 had AUC of 0.996. A cut-off value for CRP on POD 3 was calculated at the level of 245.64 mg/l, which resulted in 100% sensitivity and 98% specificity of AL⁽³⁰⁾. There was no statistically significant difference in preoperative CRP between the non leakage and leakage group. In the postoperative period, however, it was clearly observed that from POD 2 onwards, the values of serum CRP were

significantly higher in leakage group. In non-leakage group, mean serum CRP reached a peak on POD 2, followed by a rapid decline thereafter. On POD 2, mean serum CRP was 187 mg/L in leakage group and 132 mg/L in non leakage group. On POD 3, those values were 201 mg/L in leakage group and 105 mg/L in non leakage group. Based on the evaluation of the ROC curves a cut-off value of 140 mg/L on POD 3 maximized the sensitivity (78%) and specificity (31%) of serum CRP in predicting the risk of leakage⁽²⁷⁾. In comparison between PCT and CRP in the point of early detection and the much more sensitive and specific, the area under the ROC curve were slightly similar as at day 2, 3 it was more higher for PCT than CRP 0.820, 0.959 for 0.819, 0.954 and at day 4, it was higher for CRP than PCT 0.979 for 0.959. Also, serum PCT level at day 2 of 0.65 had sensitivity of 80% and specificity of 66%. But serum CRP level at day 2 of 27 had the same sensitivity but more specific 80%. At day 3, 4 and serum PCT levels of 0.7, 0.65 had 100% sensitivity and 95% specificity while that of serum CRP levels 24, 21 had lower sensitivity and specificity than PCT at day 3 as 90%, 89% and equal sensitivity at day 4 as 100% and more specific 98%. Indeed, both of the biochemical markers were elevated in patients with anastomotic leakage at day 2, 3 and 4 and showed slightly similar curves, percentages but the upper hand is for PCT than CRP in the point of early detection and in the much more sensitive and more specific. At Lagouttea study, the area under the ROC curve for CRP was higher than that for PCT on Days 2, 3, and 4 as follow 0.711, 0.801 and 0.319 for 0.659, .674 and 0.750. By analysis of ROC curves for each marker on each day, sensitivity thresholds were established. At a threshold of 13.0 mg/dL, CRP had sensitivity and specificity of 80%. With a threshold of 0.068 mg/dL, PCT had a sensitivity and specificity of 70% (maximum sensitivity obtained with

the PCT)⁽²⁶⁾. Comparison of ROC curves for Belgrade patients was Day 3, Day 5, and Day 7 with respective area under the curve values of 0.738, 0.756 and 0.827⁽²⁹⁾. The Pearson correlation with fistula was more powerful for CRP than for PCT in our study and in the study of Dijon. Thus, a patient with a PCT greater than 0.65mg/dL and CRP greater than 21 mg/dL on Day4, even in the absence of clinical signs, is not permitted to leave the service and a diagnostic work-up for sepsis (lung, urinary tract, intraabdominal, or wound) is actively pursued. While in Lagouttea study it was PCT greater than 0.1 mg/dL and CRP greater than 12.5 mg/dL. And it was on day 3, a cut-off value of CRP 135 mg/l was associated with the development of AL, providing a sensitivity of 73 % and specificity of 73 %.on Day 7, a cutoff value of CRP 30 mg/l was associated with development of AL, providing a sensitivity of 80 % and specificity of 90 %, and a high diagnostic accuracy⁽²⁶⁾.

Conclusion

Patients with PCT greater than 0.65mg/dL and CRP greater than 21 mg/dL on day4, even in the absence of clinical signs, should not leave the hospital and a diagnostic work-up for sepsis (lung, urinary tract, intra-abdominal, or wound) should be actively pursued.

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