



DIAGNOSTIC ACCURACY OF C-REACTIVE PROTEIN IN THE EARLY DETECTION OF INFECTION AFTER ELECTIVE COLORECTAL SURGERY

Sadyojata Murugesan	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India. - Corresponding Author
Chabungbam Gyan Singh	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India. - Corresponding Author
Sowdin Reddy Chittvolu	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India.
Lalhruaitluanga Puia	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India.
Yibenthung S Ezung	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India.
Haobam Manihar Singh	Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur, India.

ABSTRACT Elective colorectal surgery is associated with postoperative infectious complications in upto 40% of the cases. In different infections and clinical settings, the course of relative CRP variations and the CRP ratio, can discriminate early in the clinical course, survivors from non survivors. We conducted a prospective cross sectional study in Department of Surgery, RIMS, Manipur, India from October 2014 to August 2016. Out of the 77 patients who underwent colorectal surgery 12 sustained postoperative complications in which surgical site infection was the most common 58.3% followed by pleural effusion 33.3%, with one death from abdominoperineal resection. ROC curve analysis showed that early post-operative CRP concentrations on POD 3 had significant predictive values for the development of post-operative infectious complications. The study showed an increase in CRP in the early post-operative days with a significant difference between patients with and without complications.

KEYWORDS : CRP , postoperative infection, colorectal surgery

INTRODUCTION : C-reactive protein (CRP), an acute-phase protein, is an acknowledged marker of infections and has been linked to the development of systemic inflammatory response syndrome. The measurement of serum CRP levels is an available test and has been widely used in clinical practice to detect infections and monitor their treatment.^{1,3} CRP as an indicator of postoperative septic and surgical complications has been assessed in abdominal surgery^{4,5} and CRP has also been assessed as an early predictor of anastomotic leakage in rectal surgery.^{3,6,7} Elective colorectal surgery is associated with postoperative infectious complications in upto 40% of the cases.^{8,9} Despite recent advances in both surgical technique and perioperative care, infectious complications remain a major clinical problem in colorectal surgery, contributing to significant postoperative morbidity, increased mortality, prolonged hospital stay and additional costs.¹⁰⁻¹³ As a result, early diagnosis of the infectious complications is a crucial step in order to initiate treatment as soon as possible.¹⁴ Nonetheless, the diagnosis of infectious complications after elective colorectal surgery is frequently misleading, delaying its resolution. Consequently the availability of an early sensitive and specific marker of postoperative infectious complications would be of great interest.¹⁵ Several biomarkers of infection, namely C reactive protein and Procalcitonin, have been shown to be useful in the diagnosis of infection in different clinical settings as well as in the assessment of its response to antibiotic therapy.¹⁶⁻¹⁸ C reactive protein has been studied by several authors as an early predictor of abdominal septic complications after esophageal, pancreatic and rectal resection with sensitivities and specificities between 65% and 80%.¹⁹⁻²² C reactive protein is one of these biomarkers and probably the most widely used. In different infections and clinical settings, the course of relative CRP variations and the CRP ratio, can discriminate early in the clinical course, survivors from non survivors.²³⁻²⁵ This study is being done to diagnose post colorectal surgical sepsis at the earliest with a cheaper and reliable lab test , to avoid unwanted expensive antibiotics, to cut short length of hospital stay and more importantly to think of other complications which mimics sepsis in this modern era of evidence based medicine.

1. To test the diagnostic accuracy of C-reactive protein in the early detection of infection after elective colorectal surgery.
2. To determine the sensitivity, specificity, positive predictive value, negative predictive value and cut-off of CRP as a diagnostic precursor to infection after elective colorectal surgery

MATERIALS AND METHODS : We conducted a prospective cross sectional study on 77 patients who underwent elective colorectal surgery in the Department of Surgery at Regional Cancer Centre, RIMS, Manipur, India from October 2014 to August 2016. 5 ml of whole blood was collected from the patients using sterile 5ml disposable syringes after cleaning the cubital surface with cotton and spirit. The blood samples collected in sterile plain vials and allowed to clot so that the blood serum can be separated and CRP estimation was done by immunoturbidimetric CRP analyser. Descriptive statistical analysis will be carried out using mean and percentages and chi square test will be employed for test of significance. Informed written consent will be taken from all patients. Privacy and confidentiality will be maintained in all cases by coding the patients. Data collected were checked for consistency and completeness. T test was used to compare the means of variables like age, body weight, CRP values, etc., between the groups with infection and those without infection. Chi-square test of independence was used to test the association between categorical dependent variables like sex, indication for surgery, disease location etc between the two groups. P-value of less than 0.05 was considered to be statistically significant.

INCUSION CRITERIA :

Patients undergoing elective colorectal surgery

EXCLUSION CRITERIA :

- Patients on systemic antibiotics at the time of surgery.
- Patients not willing to participate in the study.
- Emergency surgery.
- Infection prior to surgery.

ETHICAL ISSUES: Ethical approval was obtained from the

Institutional Ethics Committee, RIMS, Imphal before the beginning of the study.

CONFLICT OF INTEREST : The study investigator and his guiding mentors declare no conflict of interest.

RESULTS: The mean age of the respondents was 58.3 years. Majority of the patients in this study were in the age group of 41-60 years (55.8%) while the least were in the below 40 years age group (14.4%) (n=77). Baseline characteristics of the patients who underwent Colorectal surgery are described in Table 1. Out of 77 patients, 12 patients sustained postoperative infection, surgical site infection (n=7) 58.3% was the most common, followed by pleural effusion (n=4) 33.3%, with one death from abdominoperineal resection 1 (8.4%). The mean C-reactive protein levels between infection and non-infection groups following colorectal surgery taken at different points in time beginning from preoperative value. There is a steady increase in CRP levels in the infection group till the 3rd postoperative day, followed by a decline thereafter. In contrast, the CRP levels in the no infection group rises till the 2nd postoperative day and then sharply falls to a very low level (Figure 1). The CRP levels are elevated to a statistically significant level in patients with infection, in concordance with the advent of infection in these patients. There was a statistically significant difference in CRP values between the two groups till the 5th postoperative day (Table 2).

In the preoperative period, there was no significant difference in the CRP levels between the groups, and the area under the ROC curve (AUC=649) was not statistically significant (p=0.103) (Table 3). In the 1st postoperative day too, there was no significant difference in the CRP levels between the groups, and the area under the ROC curve (AUC=0.629) was not statistically significant. (p=0.158). There is a statistically significant elevation of the CRP levels in the patients with infectious complications compared to those without infection (AUC=0.923; p<0.001) in the 2nd postoperative period (Table 4) (Figure 2). From the above ROC curves, it can be inferred that C-reactive protein levels are most useful in the detection of infection following elective colorectal surgery as early as the 3rd postoperative day (Table 5) (Figure 3). The cut off level of CRP to identify patients at risk of developing infection is found to be 175.5 mg/dl, and the corresponding sensitivity and specificity are 91.67% and 83.33% respectively.

Table 1: Baseline characteristics of the patients who underwent Colorectal surgery (n=77)

Characteristics	Infection (n=12)	No Infection (n=65)	p value
Age (years)	58.5 ± 10.9	58.2 ± 11.6	0.968
Sex (M:F)	8:4	41:24	0.812
Weight (kg)	67.1 ± 7.3	64.7 ± 8.0	0.305
Average hospital stay	18.1	8.8	<0.001
Postoperative mortality (%)	8.3	0	0.019
Indication for surgery			
Interval Appendectomy	4	25	
Cancer	7	19	0.250
Hemorrhoids	0	13	
Colostomy closure	1	6	
Rectal polyp	0	2	
Location of the disease			
Ascending colon	5	31	0.316
Descending colon	3	7	
Sigmoid & rectum	4	27	
Surgical intervention			
Appendectomy	4	25	
Right hemicolectomy	3	4	0.342
Left hemicolectomy	2	10	
Colostomy closure	1	6	
Hemorrhoidectomy	0	13	
Sigmoidectomy	1	5	
Polypectomy	0	2	
Abdominoperineal resection	1	0	

Table 2: Mean CRP levels between the study arms of colorectal surgery (n=77)

CRP values(mg/dl)	Infection (n=12)	No infection (n=65)	p value
Pre-op	24	19	0.55
POD1	119	101	0.13
POD2	181	135	<0.001
POD3	202	106	<0.001
POD4	187	76	<0.001
POD5	166	44	<0.001

Table 3: Diagnostic accuracy of CRP levels in predicting the onset of infection in the preoperative period (n=77)

CRP values	Sensitivity	1-specificity
13	100%	100%
14.5	91.7%	95.4%
15.5	83.3%	69.2%
16.5	75%	60%
17	75%	47.7%
18.5	50%	38.5%
19.5	41.7%	30.8%
24.5	41.7%	13.8%
26.5	33.3%	6.2%
32	25%	0.0%

Table 4: Diagnostic accuracy of CRP levels in predicting the onset of infection in the 2nd postoperative period (n=77)

CRP values	Sensitivity	1-specificity
130	100%	100%
131.5	100%	83.1%
133	100%	73.8%
134.5	100%	58.5%
135.5	100%	40%
137	100%	29.2%
176.5	91.7%	16.7%
181.5	83.3%	6.2%
184.5	66.7%	0%

Table 5 : Diagnostic accuracy of CRP levels in predicting the onset of infection in the 3rd postoperative period (n=77)

CRP values	Sensitivity	1-specificity
136	100%	100%
137	100%	83.1%
175.5	100%	73.8%
180.5	83.3%	52.3%
185	73.8%	0%

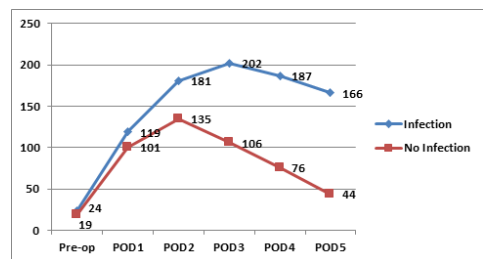


Figure 1: Mean CRP values of elective colorectal surgery patients (n=77)

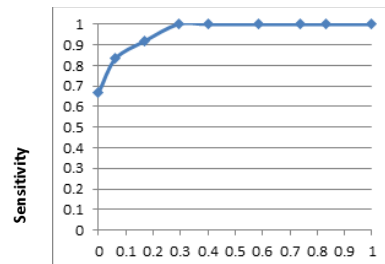


Figure 2: Receiver operator characteristics curve of mean 2nd postoperative day C-reactive protein values of patients undergoing elective colorectal surgery (n=77) Area under the curve=0.929. P value=<0.001.

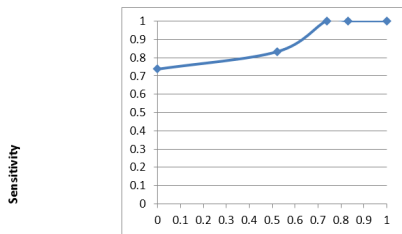


Figure 3: Receiver operator characteristics curve of mean 3rd postoperative day C-reactive protein values of patients undergoing elective colorectal surgery (n=77). Area under the curve=0.914 (Pvalue=<0.001)

DISCUSSION : Despite many advances in surgery, the quest for uneventful healing of the intestinal anastomosis remains a challenge after colorectal surgeries. Anastomotic leak is the most dreaded complication of surgical treatment and a significant obstacle to the successful treatment of patients with colorectal surgeries. It is more common after rectal surgery, between 8 percent and 14 percent,²⁶⁻²⁸ compared to the colon ranging from 3 to 7 percent.^{29,30} It has been shown that at about 40 percent of clinically significant leaks are diagnosed after discharge from the hospital and require readmission for abdominal symptoms.^{31,32} This rate is certainly increasing in the era of fast track colorectal surgery with earlier discharges from the hospital [usually as early as the POD 4]. In our study majority of patients were in the age group of 41-60 years and mean age at presentation was 58.3 years. The anastomotic leakage is a serious complication which should be diagnosed as early as possible to reduce the associated morbidity and mortality. Thus the need for an early diagnosis of serious complications becomes clear. However, this diagnosis is not always easy in the early postoperative period because of the few clinical manifestations present at that time which contributes to increased morbidity and mortality. According to Alves et al³¹, the delayed diagnosis [after POD 5] of serious complications is associated with a mortality rate of 18 percent, 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. CRP is the most popular and widely available marker of the acute inflammatory response,³³ the production of CRP occurs almost exclusively in the liver by hepatocytes as part of the acute-phase response upon stimulation by interleukin[IL]-6, tumor necrosis factor- α and IL-1-B originating at the site of inflammation. It is a pentameric protein with various molecular functions including complement activation and opsonisation.³⁴ Within 6 hours after stimulation CRP serum levels exceed normal values and peak after about 48 hours. CRP has a nearly constant serum half-life of about 19 hours. Therefore the CRP serum concentration is determined by its synthesis rate and reflects the intensity of the stimulus for acute inflammatory responses.³⁵ In numerous studies, the significance of the serial measurement of CRP in serum in detecting infectious complications of surgical treatment was shown.³⁶⁻³⁸

For academic and research purpose cases of appendectomy and haemorrhoidectomy/pexy were included in the study apart from classic colorectal surgeries. The mean age of respondents was 58.3%. In our study majority were cases of resolved appendicitis for elective appendectomy [n=29], followed by cancer[n=26]. Other cases included haemorrhoids (n=13), colostomy closure (n=7) and rectal polyp (n=2). Cancers included Carcinoma of cecum and ascending colon (n=7), Carcinoma descending colon (n=12), Carcinoma sigmoid (n=6) and Carcinoma rectum (n=1). All of them underwent elective surgeries(open appendectomy, hemicolectomies, colostomy closure, haemorrhoidectomy, stapled haemorrhoidectomy, sigmoidectomy, polypectomy, abdominoperineal resection respectively) out of which twelve of them had septic complications. Out of the twelve patients who developed post operative complications (p=0.3) SSI (surgical site infection), (n=7), was the most common, followed by pleural effusion(n=4), with one death from abdominoperineal resection. Out of the twenty nine appendectomy cases four developed surgical site infections, three out of seven right hemicolectomies developed pleural effusion, two out of twelve cases of left hemicolectomies developed surgical site infections. One case of sigmoidectomy, out of the six cases developed surgical site infection. Thus surgical site infections were the most common form of septic complication [n=7], 58.3 percent, pleural effusion developed in 3 cases of right hemicolectomies and 1

abdominoperineal resection, accounting for 33.3 percent. None of the haemorrhoidectomy or polypectomy patients developed infection. This suggests that more distal the pathology in intestines more are the chances of infective complications. In total seventy seven colonic procedures 12 developed complications, which is not statistically significant, probably as they are all elective surgeries.

In our study after elective colorectal surgery, surgical site infection (n=7) was 58.3 percent, pleural effusion (n=4) was 33.3 percent and mortality occurred in one patient i.e. 8.4 percent. Similar results were observed in other studies with elective surgeries in their study group.³⁹ Among various risk factors involved in postoperative complications, in our study we studied the location of the disease, the pre-op TLC, pre-op CRP level, pre-op hypoalbuminemia, etc which had significant impact on post operative outcome which has similar observations in other studies.⁴⁰ This study showed an increase in CRP in the early postoperative period after colorectal surgery with a significant difference between patients with and without complications. ROC curve analysis showed that early postoperative CRP concentrations on POD 2 and POD 3 had significant predictive values for the development of post operative infectious complications. The diagnostic accuracy of CRP on POD 2 and POD 3 as a predictor of septic complications after elective colorectal surgery[areas under the curve of 0.929 and 0.914 respectively] were only similar to those obtained by Welsch et al^{21,7} [0.80 and 0.88, respectively] and Francois Radais et al [0.706 and 0.804, respectively]. CRP kinetics has been recently described by several authors like Welsch et al and Woeste G et al,^{7,41} as a predictor of infectious postoperative complications. Two recent studies reported that persistently increased CRP levels after POD 2-4 were associated to a later diagnosis of abdominal leak[AL].^{21,22} These authors found that prolonged elevation and/or a absence of decline in CRP levels were associated with more infectious complications and poorer outcome. More recently Warschkowet al⁴² demonstrated that CRP values exceeding 123 mg/l on POD 4 were associated with a higher risk of infectious complications. These authors found that CRP level above 143 mg/l had a good diagnostic accuracy to detect infectious complications with an AUC ROC 0.76. Ortega Deballon et al⁴⁴ demonstrated that serum levels of CRP on the POD 4 are a good predictor of AL in colorectal surgery for a cut – off point of 125 mg/l, sensitivity 81.8 %and specificity of sixty four percent. Gracia-Graneroetal⁴³ obtained similar results for the values on third, fourth and fifth PODs.

Our study showed CRP level, reached maximum on POD 3 and has maximum sensitivity of 91.67% and a specificity of 83.33%. The mean cut of value of CRP in our study was 175.5 mg/l. Komeret al⁴⁵ have published a work similar to the present one, the study material including all types of colorectal surgery. Their methods and results are similar to the present study, they showed that CRP at POD 3 had 82% accuracy. They had a higher cut off than the present study [190 vs 175.5mg/l]. They also obtained a slightly lower sensitivity [82% vs 9.67%]. In our study the CRP value peaked on the POD 3, [as is well known that CRP values peak at forty eight hours and then decline] but did not decline on other post operative days. CRP decreased persistently in patients with an uneventful post operative course and reached the basal level. This tallying with above works is a strong argument in favour of the usefulness of the CRP in this setting. This seems to suggest that the early and sustained elevation of post operative serum CRP may be used as a predictor of post operative complications [Anastomotic leak if other complications are excluded].The present work was done in order to define the accuracy of CRP in early detection of infection with a cheaper and reliable test, and to reduce hospital stay and use of unwarranted and prolonged antibiotics. The mean cut-off value of CRP level reached maximum on POD-3, with a maximum predictive sensitivity of 91.67% and specificity of 83.33% and a positive predictive value of 71.43% in the prediction of postoperative septic complications. Warschkow et al⁴² demonstrated that CRP values exceeding 123 mg/l on day four post operatively was associated with a higher risk of complications. These authors found that CRP level above 143mg/l had a good diagnostic accuracy to detect complications. The total leucocyte count was significantly higher in patients with septic complications but its accuracy was much lower than for CRP, so the total leucocyte count is not as useful as the serum CRP, which rises earlier. Combination of CRP and total leucocyte count may be accurate in detecting the post operative complications.⁴² This study shows that the post operative complications was significant on POD 3. CRP is a non-specific, systemic, manifestation of an active inflammatory process and that CRP detects as early as the POD 3. The

limitations of the study are, since the number of cases are small, it limits the statistical power of the analysis; also it's a single center study; also recently other biomarkers like LBP (Lipopolysaccharide binding protein), procalcitonin, matrix metalloproteinase have been used as a screening tool for abdominal leak and complications and increased concentrations of LBP in drain fluid were associated with a higher chance of early detection. Although our study lacks statistical power a major and persistent CRP cut-off value on the POD 3 and thereof with significance level $p = <0.001$, adds to the validity of the data.

CONCLUSION : The study showed an increase in CRP in the early post-operative days with a significant difference between patients with and without complications. ROC curve analysis showed that early post-operative CRP concentrations on POD 3 had significant predictive values for the development of post-operative infectious complications. Developing postoperative complications can be detected early by monitoring CRP concentration levels serially on PODs 1 to 5, which is very important in early detection of postoperative complications.

REFERENCES :

- Gupta R, Singh R, Soni M. C-reactive protein as an indicator of sepsis in orthopaedic trauma. *Indian J Med Sci* 2002; 56:501-7.
- Mehra A, Langkamer VG, Day A, Harris S, Spencer RF. C-reactive protein and skin temperature post knee replacement. *Knee* 2005; 12:297-300.
- Korner H, Nielsen HJ, Soreide JA, Nedrebo BS, Soreide K, Knapp JC. Diagnostic accuracy of C reactive protein for intraabdominal infections after colorectal resections. *J Gas-trointest Surg* 2009; 13:1599-1606.
- Mustard RA, Bohnen JM, Haseeb S, Kasina R. C-reactive protein levels predict postoperative septic complications. *Arch Surg* 1987; 122:69-73.
- Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumor necrosis factor-alpha and C-reactive protein in patients undergoing major operations. *Eur J Surg* 1995; 161:17-22.
- Matthiessen P, Henriksson M, Hallbook O, Grundtitz E, Noren B, Arbmán G. Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection. *Colorectal Dis* 2008; 10:75-80.
- Welsh T, Muller SA, Ulrich A, Kischlat A, Hinz U, Kienle P, et al. C reactive protein an early predictor for infectious postoperative complications in rectal surgery. *Int J Colorectal Dis* 2007; 22:1944-7.
- Nakamura T, Mitomi H, Ihara A, Onozato W, Sato T, Ozawa H, et al. Risk factors for wound infections after surgery for colorectal cancer. *World J Surg* 2008; 32(6):1138-41.
- Rovera F, Dionigi G, Boni L, Piscopo C, Massiuchi P, Alberio MG, et al. Infectious complications in colorectal surgery. *Surg Oncol* 2007; 16(3):121-4.
- Alves A, Panis Y, Tranacart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. *World J Surg* 2002; 26(4):499-502.
- Buchs NC, Gervaz P, Secic M, Bucher P, Mugnier-konrad B, Morel P. Incidence, consequences and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. *Int J Colorectal Dis* 2008; 23(3):265-70.
- Makela JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. *Dis Colon Rectum* 2003; 46(5): 653-60.
- Veyrie N, Ata T, Muscari F, Couchard AC, Msika S, Hay JM, Fingerhut A, Dziri C. Anastomotic leakage after elective right versus left colectomy for cancer: prevalence and independent risk factors. *J Am Coll Surg* 2007; 205(6):785-93.
- Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34(6):1589-96.
- MacKay GJ, Malloy RG, Dwyer PJ. C-reactive protein as a predictor of postoperative infective complications following elective colorectal resection. *Colorectal Dis* 2007; 13(5):583-7.
- Fujii T, Tabe Y, Yajima R, Tsutsumi S, Asao T, Kuwano H. Relationship between C-reactive protein levels and wound infections as a predictor for incisional SSI. *Hepatogastroenterology* 2011; 58:752-5.
- Novotny A, Emmanuel K, Bartels H, Siewert JR, Holzmann B. Indicators for early prediction of outcome in sepsis. *Chirurg* 2005; 76(9):837-44.
- Simon I, Gaubin F, Amre DK, Louis P, Lacroix J. Serum procalcitonin and C-reactive protein level as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; 39(2):206-17.
- Preas HL, Nysten ES, Snider RH, Becker KL, White JC, Agosti JM, et al. Effects of anti-inflammatory agents on serum levels of calcitonin precursors during human experimental endotoxemia. *J Infect Dis* 2001; 184(3):373-6.
- Deitmar S, Anthoni C, Palmes D, Haier J, Senninger N, Bruwer M. Are leucocytes and CRP early indicators of anastomotic leakage after esophageal resection? *Zentralblchir* 2009; 134(1):83-9.
- Welsch T, Frommhold K, Hinz U, Weigand MA, Kleeff J, Friess H, et al. Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications. *Surgery* 2008; 143(1):20-8.
- Cruikshank AM, Hansell DT, Burns HJ, Shenkin A. Effect of nutritional status on acute phase protein response to elective surgery. *Br J Surg* 1989; 76(2):165-8.
- Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care* 2010; 14(1):15-9.
- Povoa P. C-reactive protein: available marker of sepsis. *Intensive Care Med* 2002; 28(3):235-43.
- Ranzani OT, Prada LF, Zampieri FG, Battalini LC, Pinaffi JV, Setogute YC, et al. Failure to reduce C-reactive protein levels more than 25% in the last 24 hours before intensive care unit discharge predicts higher in-hospital mortality: a cohort study. *J Crit Care* 2013; 27(5):529-15.
- Trencheva K, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T et al. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. *Ann Surg* 2013; 257(1):108-13.
- Komen N, Dijk J, Lalmahomed Z, Klop K, Hop W, Kleinrensink G et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. *Int J Colorectal Dis*. 2009; 24(7):789-95.
- Shiomi A, Ito M, Saito N, Hirai T, Ohue M, Kubo Y et al. The indications for a diverting stoma in low anterior resection for rectal cancer: a prospective multicentre study of 222 patients from Japanese cancer centers. *Colorectal Dis* 2011; 13(12):1384-9.
- Rickert A, Willeke F, Kienle P, Post S. Management and outcome of anastomotic leakage after colonic surgery. *Colorectal Dis* 2009; 12(10):216-23.
- Krurup PM, Jorgensen LN, Andreasen AH, Harling H. A nationwide study on anastomotic leakage after colonic cancer surgery. *Colorectal Dis* 2012; 14(10):661-7.
- Mokart M, Merlin A, Sannini JP, Brun JR, Delpero G, Houvenaeghel P. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of post-operative sepsis after major surgery. *Br J Anaesth* 2005; 94:767-73.
- Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg* 2007; 245:254-8.
- Kopterides I, Siempos I, Tsangaris A, Tsantes A, Armaganidis I. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2010; 38:2229-41.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; 340:6.
- Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J Clin Invest*. 1993; 91(4):1351-7.
- Carsin H, Assicot M, Feger F, Roy O, Pennacino I, Bever H. Evolution and significance of circulating procalcitonin levels compared with IL-6, TNF[alpha] and endotoxin levels early after thermal injury. *Burns* 1997; 23:218-24.
- Schuetz P, Crain M, Thomann R, Falconier C, Wolbers M, Widmer I. Effect of procalcitonin based guidelines versus standard guidelines on antibiotic use in lower respiratory tract infections. *JAMA* 2009; 302:1059-66.
- Falcoz PE, Laluc F, Toubin MM, Puyraveau M, Clement F, Mercier M. Usefulness of procalcitonin in the early detection of infection after thoracic surgery. *Eur J Cardiothorac Surg* 2005; 27:1074-8.
- Sharath Chandra BJ, Kumar S, and Girish S. Evaluation of C-reactive protein as an early predictor of septic complications after elective colorectal Surgery. *International Journal of Applied Research* 2015; 1(13):28-37.
- Almeida AB, Faria G, Moreira H, Sousa J, Silva P, Maia JC. Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery. *Int J Surg* 2012; 10(2):87-91.
- Woeste G, Müller C, Bechstein WO, and Wullstein C. Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery. *World J Surg* 2010; 34(1):140-6.
- Warschke R, Tarantino I, Torzewski M, Naff F, Lange J, Steffen T. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 pa-tients. *International Journal of Colorectal Disease*. 2011; 26(11):1405-13.
- Garcia-Granero A, Frasson M, Flor-Lorente B, Blanco F, Puga R, Carratalá A, et al. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: A prospective observational study. *Dis Colon Rectum* 2013; 56(4): 475-83.
- Ortega-Deballon P, Radais F, Facy O, D'Athis P, Masson D, and Pierre EC. C-reactive protein is an early predictor of septic complications after elective colorectal surgery. *World J Surg* 2010; 34(4):808-14.