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C-reactive protein in drainage fluid as a predictor of anastomotic leakage after elective colorectal resection

C-reaktivni protein u drenažnoj tečnosti kao pokazatelj dehiscencije anastomoze nakon resekcije kolona i rektuma

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Abstract

Background/Aim. C-reactive protein (CRP) is considered to be an indicator of postoperative complications in abdominal surgery. The aim of this study was to determine the significance of serial measurement of CRP in drainage fluid in the detection of anastomotic leakage (AL) in patients with colorectal resection. **Methods.** CRP values in serum and drainage fluid, respectively, were measured on the first, third, fifth, and seventh postoperative day (POD) in 150 patients with colorectal resection and primary anastomosis. The values obtained were compared between the groups of patient without complications of surgical treatment and those with AL. **Results.** Clinically evident AL was observed in 15 patients – in two (4.2%) patients with left colonic surgery, and 13 (12.6%) patients with colorectal anastomosis. Mean values of CRP were higher in the patients with AL than in the patients without complications, both in serum and drainage fluid, with the most significant differences recorded on the PODs 5 and 7 ($p < 0.001$). Correlation analysis showed a positive correlation between serum and drainage fluid CRP levels in both groups of patients. Serum and drainage fluid CRP values on the PODs 5 and 7 are most important in the detection of AL. In 80% of patients with CRP values in the drainage fluid of 53 mg/L for the POD 5 and 42 mg/L for the POD 7 AL was observed. The method specificity was 77% for the POD 5, and 83% for the POD 7. All the patients with CRP values in drainage fluid above 108 mg/L on the POD 5 and 93 mg/L on the POD 7 had AL. **Conclusion.** Serial measurement of CRP in drainage fluid can reliably be used in the detection of AL in patients with colorectal resection. The most significant values obtained on the PODs 5 and 7 were positively correlated with the values registered in serum.

Key words:
c-reactive protein; prognosis; surgical wound dehiscence; surgical procedures, operative; colorectal neoplasms.

Apstrakt

Uvod/Cilj. Smatra se da je C-reaktivni protein (CRP) indikator postoperativnih komplikacija u abdominalnoj hirurgiji. Cilj rada bio je da se utvrdi značaj serijskog merenja vrednosti CRP u drenažnoj tečnosti u detekciji dehiscencije anastomoze kod bolesnika sa resekcijom kolona i rektuma. **Metode.** Vrednosti CRP u serumu i drenažnoj tečnosti kod 150 bolesnika sa kolorektalnom resekcijom i primarnom anastomozom određivane su prvog, trećeg, petog i sedmog postoperativnog dana. Vrednosti CRP u serumu i drenažnoj tečnosti upoređivane su između grupa bolesnika bez komplikacija operativnog lečenja i sa dehiscencijom anastomoze. **Rezultati.** Klinički manifestnu dehiscenciju anastomoze imalo je 15 bolesnika, dva (4,2%) sa kolokoloničnom i 13 (12,6%) sa kolorektalnom anastomozom. Srednje vrednosti CRP su bile veće kod bolesnika sa dehiscencijom anastomoze nego kod bolesnika bez komplikacija i u serumu i u drenažnoj tečnosti, sa statistički najznačajnijim razlikama petog i sedmog postoperativnog dana ($p < 0,001$). Korelaciona analiza pokazala je postojanje pozitivne korelacije između vrednosti CRP u serumu i drenažnoj tečnosti kod obe grupe bolesnika. Najznačajnije vrednosti CRP u detekciji dehiscencije anastomoze dobijene su petog i sedmog postoperativnog dana i za serum i za drenažnu tečnost. Kod 80% bolesnika sa dehiscencijom anastomoze CRP u drenažnoj tečnosti bio je iznad 53 mg/L petog i 42 mg/L sedmog postoperativnog dana. Specifičnost metode bila je 77% za peti i 83% za sedmi postoperativni dan. Kod svih bolesnika sa CRP iznad 108 mg/L petog i 93 mg/L sedmog postoperativnog dana registrovana je dehiscencija anastomoze. **Zaključak.** Serijsko merenje vrednosti CRP u drenažnoj tečnosti pouzdano je u detekciji dehiscencije anastomoze kod obolelih sa kolorektalnom resekcijom. Najznačajnije vrednosti dobijene su petog i sedmog postoperativnog dana i u pozitivnoj su korelaciji sa vrednostima registrovanim u serumu.

Ključne reči:
c-reaktivni protein; prognoza; rana, hirurška, dehiscencija; hirurgija, operativne procedure; kolorektalne neoplazme.

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Introduction

Anastomotic leakage (AL) is the life-threatening commonest major complication after colorectal cancer surgery. Breakdown of anastomosis results in increased morbidity and mortality [1, 2] and adversely affects quality of life [3], duration of hospital stay, cost [1, 4] and cancer recurrence [5–7]. The reported leak rate varies between 3% and 19% depending on the definition [1, 2, 8–11].

Some studies including our one [12] have shown that elevated serum C-reactive protein (CRP) concentrations in the postoperative period may predict an increased chance of postoperative infection [13] and AL [14]. The fact that CRP begins to increase before the occurrence of postoperative infectious complications, in contrast to clinical signs such as fever, tachycardia, and pain [13], makes it an ideal predictor of postoperative infectious complications. Since this is a nonselective marker of inflammation, before searching for specific, it is necessary to exclude the other infectious complications [13, 14].

According to our knowledge there are no data on the determination of CRP in drainage fluid in the detection of AL in patients with colorectal resection. Peritoneal fluid in its composition is a filtrate of plasma and it is in equilibrium with serum. Our assumption is that the values of CRP in drainage fluid reflect values obtained in serum.

The aim of this study was to determine the sensitivity and specificity of CRP in drainage fluid in the detection of AL in patients with elective colorectal resection.

Methods

Our prospective study enrolled 150 patients with cancer of the left colon and rectum surgically treated at the Clinic for General Surgery, Military Medical Academy, Belgrade in the period from April, 2011 to November, 2012. Characteristics of these patients were given in our previous article [12].

The patients with clinical signs of infection or some other inflammatory condition present preoperatively were excluded from the study. The analysis involved only the patients in whom conventional elective, radical, or palliative surgical intervention was done, with colocolonic or colorectal anasomosis, handsewn or stapled. All the operations were doune by the surgeouns performing at least 30 similar surgical procedures *per* year. Mechanical preoperative large bowel preparation was done only in those with rectal cancers. The patients surgically treated for tumor recurrence were excluded from the study. The creation of diverting ileostomy or transversocolostomy depended on the individual assessment of surgeons. Before the closure of laparotomy incision, abdominal cavity of the patients was routinely drained with at least one drain placed in the area of the pouch of Douglas or in the presacral area, in the region of colorectal anastomosis.

In the immediate postoperative course, within a month of surgery, all remote (pneumonia, urinary infection, infections caused by central venous line) and surgical site (wound infection, AL, intraabdominal abscess collections) infectious complications were registered. Redness, edema, and purulent secretion at the site of laparotomy wound were the clinical criteria establishing the presence of infection in the surgical incision site [16]. Clinical parameters of AL were defined by the presence of purulent or fecal content at the drain site, pelvic abscess, peritonitis, rectovaginal fistula, or the appearance of purulent content from the rectum (*per recti*) [17]. Routine, contrast-enhanced x-ray control of the anastomosis was not implemented, since the patients with asymptomatic leakage, were not relevant for the study. In patients with low colorectal anastomosis, digital rectal examination was an integral part of the examination to detect possible AL. Intraabdominal abscesses were detected by way of the presence of purulent secretion after surgical or percutaneous ultrasound-guided drainage of these collections [16]. Appropriate clinical presentation with a positive x-ray finding in pneumonia, urinary sediment and urine culture in urinary infection, and positive blood culture in infections caused by central venous line, defined the presence of individual remote infections.

On the first, third, fifth, and seventh postoperative day (POD), serum CRP levels were measured, utilizing the method immunonephelometry on a SIEMENS autoanalyzer (DADE Behring BN II). Drain fluid was collected from the intraperitoneal drains placed in the pelvis and CRP levels were measured by the same method at the Institute of Medical Biochemistry, Military Medical Academy, Belgrade.

The usual descriptive statistic parameters were used in statistical analysis of the obtained results (mean value, standard deviation, range, 95% confidence interval, frequency of individual characteristics). Depending on the normality of distribution of the observed parameters and the number of groups among which the statistical significance was sought for, non-parametric tests, the Mann-Whitney *U*-test and Pearson´s correlation test were used. The sensitivity and specificity of relevant biochemical markers were analyzed using the receiver operating characteristic curve (ROC).

Commercially available statistical software package SPSS version 17 (USA) was used for statistical analysis.

Results

We analyzed 150 patients in total, 94 (66.7%) men and 56 (33.3%) women (male-to-female ratio, 1.7 : 1). The youngest operated patient was 33, and the oldest 87 years of age. The average age of the patients was 65 ± 11 years.

The overall morbidity rate associated with surgical treatment was 34%, and mortality rate 4%. Surgical site infections were observed in 41 (27.3%) and remote infections in 10 (6.7%) patients. In 99 surgically treated patients postoperative course was without any complications.

Clinically evident AL was observed in 15 patients – in 2 (4.2%) patients with left colonic surgery, and 13 (12.6%) patients with colorectal anastomosis. The postoperative mortality rate associated with AL was 13%, and out of 6 fatal outcomes, leakage was the immediate cause of death in two of the patients.

Table 1 shows a comparison of the mean values of CRP in serum and drainage fluid for the observed PODs between the group of patients without complications and those with

AL. In all the patients, there was an increase of CRP, with maximum values reported for the POD 3, except for the CRP values in drainage fluid in the group of patients with AL. In those without complications, there was a descending tendency in serum and drainage fluid CRP values, significantly more evident compared to descending CRP values in those with AL. On the POD 1, there was no statistically significant differences in CRP values in the group of patients without complications and those with AL. On the PODs 5 and 7, there was a statistically most significant difference in the values of CRP in serum and drainage fluid between the group of patients without complications and with AL ($p < 0.001$).

Table 2 shows the results of correlation analysis for CRP values in serum and drainage fluid in the group of patients without complications and those with AL for the observed days. Statistically highly significant positive correlation ($p < 0.001$) between the value of CRP in serum and drainage fluid is present for all the observed days in patients without complications, while the highest correlation in the group with AL was observed on the POD 7 (the highest value of the correlation coefficient).

Sensitivity and specificity of serum and drainage fluid CRP measurement in the detection of AL were analyzed using the ROC curve and were shown in Table 3 and Figures 1 and 2.

Table 1

Mean values of C-reactive protein (CRP) in serum and drainage fluid in the patients without complications and those with anastomotic leakage (AL) by postoperative days (POD 1, 3, 5, 7)

Sample	CRP values (mg/L), $\bar{x} \pm SD$			
	Group without complications (n = 99)	AL group (n = 15)		*p*
Serum				
POD 1	95.15 ± 37.97	102.11 ± 39.65	0.532	0.595
POD 3	113.47 ± 40.72	197.25 ± 75.76	3.449	0.001
POD 5	57.10 ± 28.15	175.93 ± 72.51	5.336	< 0.001
POD 7	49.71 ± 29.95	155.61 ± 77.49	5.508	< 0.001
Drainage fluid				
POD 1	21.49 ± 15.61	27.18 ± 23.85	0.666	0.505
POD 3	58.56 ± 17.89	84.20 ± 33.50	3.106	0.002
POD 5	41.87 ± 16.20	84.79 ± 44.01	4.698	< 0.001
POD 7	31.07 ± 15.42	77.75 ± 56.75	4.028	< 0.001

***Mann-Whitney test; $\bar{x}$ – mean; SD – standard deviaton.**

Table 2

Correlation of C-reactive protein (CRP) values in serum and drainage fluid in the patients without complications and those with anastomotic leakage (AL), by postoperative days (POD 1, 3, 5, 7)

POD	CRP (mg/L), $\bar{x} \pm SD$			
	Serum	Drainage fluid	*r*	*p*
Group without complications (n = 99)				
POD 1	95.15 ± 37.97	21.49 ± 15.61	0.4504	< 0.001
POD 3	113.47 ±40.72	58.56 ± 17.89	0.7275	< 0.001
POD 5	57.10 ± 28.15	41.87 ± 16.20	0.7199	< 0.001
POD 7	49.71 ± 29.95	31.07 ± 15.42	0.6808	< 0.001
AL (n = 15)				
POD 1	102.11 ± 39.65	27.18 ± 23.85	0.6150	0.019
POD 3	197.25 ± 75.76	84.20 ± 33.50	0.5700	0.026
POD 5	175.93 ± 72.51	84.79 ± 44.01	0.5041	0.055
POD 7	155.61 ± 77.49	77.75 ± 56.75	0.9053	< 0.001

***Pearson's test, *r* – correlation coefficient; $\bar{x}$ – mean; SD – standard deviaton.**

Table 3

Sensitivity and specificity of serum and drainage fluid C-reactive protein (CRP) values in the patients with anastomotic leakage by postoperative days (POD 1, 3, 5, 7), expressed as an area under the ROC curve

POD	Cutoff value for CRP (mg/L)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	*p*
Serum (n = 15)					
POD 1	111	54	71	0.538 (0.348–0.729)	0.65
POD 3	140	69	79	0.748 (0.567–0.929)	0.004
POD 5	77	85	77	0.920 (0.849–0.991)	< 0.001
POD 7	90	92	89	0.960 (0.925–0.994)	< 0.001
Drainage fluid (n = 15)					
POD 1	21	53	63	0.552 (0.386–0.719)	0.515
POD 3	77	67	84	0.754 (0.602–0.907)	0.002
POD 5	53	80	77	0.879 (0.770–0.987)	< 0.001
POD 7	42	80	83	0.824 (0.684–0.964)	< 0.001

ROC – receiver operating characteristic; AUC – area under the curve; CI – confidence interval.

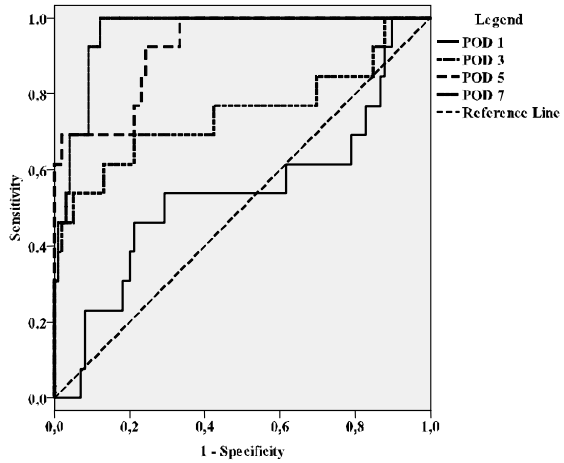

Fig. 1 – Diagnostic accuracy of serum C-reactive protein values in the detection of anastomotic leakage, expressed as a receiver operating characteristic curve; POD – postoperative day

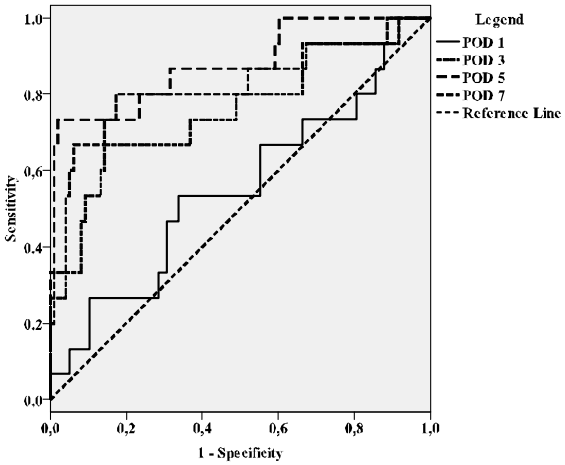

Fig. 2 – Diagnostic accuracy of C-reactive protein values in drainage fluid in the detection of anastomotic leakage expressed as a receiver operating characteristic curve; POD –postoperative day.

Discussion

Despite many advances in surgery, the quest for uneventful healing of the intestinal anastomosis remains a challenge after colon and rectal resections. AL is the most serious complication of surgical treatment and a significant obstacle to the successful treatment of patients with colorectal resection [18]. It is more common after rectal surgery, between 8% and 14% [2, 10, 19], compared to the colon, ranging from 3% to 7% [20, 21].

Differences in the frequency of, among other things, are due to different criteria used for the diagnosis of leakage. In order to better define, a new grading system was proposed by the International Study Group of Rectal Cancer (ISGRC) [22]. In analysis of our patients, we used exclusively the clinical criteria to establish AL [22, 23], and it was reported in 15 patients, in two (4.2%) patients with left colonic surgery, and 13 (12.6%) patients with colorectal anastomosis. The rates of morbidity and mortality significantly increase after AL, with mortality reported between 12% and 27% [1, 24, 25]. Postoperative mortality rate with AL in our study was 13%, and out of six deaths, leakage was the immediate cause of death in two. Early detection of this, potentially most dangerous complication, in the absence of clear clinical manifestations, would make possible an early introduction of appropriate therapeutic measures intended to alleviate or eliminate adverse effects.

CRP is the most popular and most widely available marker of the acute inflammatory response [26]. 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-β originating at the site of inflammation. It is a pentameric protein with various molecular functions including complement activation and opsonization [27]. Within 6 h after stimulation, CRP serum levels exceed normal values and peak after about 48 h. 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 [28]. In numerous studies, the significance of the serial measurement of CRP in serum in detecting infectious complications of surgical treatment and/or AL was shown [29–32].

According to the available literature, we found no data on whether someone is determined CRP levels in drainage fluid. While some advocates [8], and others do not find justification [33], a routine approach in our institution involves mandatory drainage of the abdominal cavity after colorectal resection by placing at least one drain that runs through a separate incision in the skin. A few years ago another option proved to be interesting in patients with drainage done and refers to the ability to analyze the drainage of fluid in the purpose of early detection of AL [34]. Some biomarkers have been proposed as objective diagnostic parameters [35] and are collected from the fluid through the drain located near the site of interest. Potential biomarkers include immune (IL-1, IL-6 and IL-10, tumor necrosis factor alpha) parameters, tissue repair (matrix metalloproteinase-1, 2, 9 and 13) parameters, parameters of ischemia (glucose, lactate, glycerol), and microbiological (lipopolysaccharides, pH, pCO2, and pO2) parameters [35].

In aim to verify the results obtained in drainage fluid in our patients, we compared them with the serum CRP values, between the group of patients without complications of surgical treatment and those with AL. The mean values of CRP in drainage fluid were lower compared with the values the serum for both groups of observed patients (without complications and with AL). The highest CRP levels were registered on the POD 3, except for the values in drainage fluid in the group of patients with AL with the highest CRP registered on the POD 5. In patients without complications, after an initial rise of CRP values, there was a gradual decline of CRP on days to follow. In those with AL, high CRP values persisted on the PODs 5 and 7 (Table 1). Similar trends in changes of CRP in serum is found in the papers of other authors [13, 29, 30]. On the POD 1, there was no statistically significant difference in the values of CRP in serum and drainage

fluid between patients without complications and with AL. Statistically, the most significant difference occurred on the fifth and seventh POD (Table 1).

Correlation analysis showed a highly statistically significant positive correlation between the measured values of CRP in serum between the groups of patients without complications and those with AL for all the observed days. In the group of patients with AL statistically significant positive correlation was found on the PODs 1, 3 and 7, while on the POD 5 positive correlation was at the border of statistical significance ($p = 0.055$) (Table 2). We can conclude that changes in serum CRP values were accompanied by appropriate changes in the values of CRP in drainage fluid.

Serum and drainage fluid CRP values on the PODs 5 and 7 are most important in the detection of AL. The area under the ROC curve on the POD 5 was 0.920 and 0.960 on the POD 7 for serum CRP, and 0.879 and 0.824 for CRP values in drainage fluid. AL was observed in 85% of the patients on the POD 5 and in 92% on the POD 7, with serum CRP values of 77 mg/L and 90 mg/L. The method specificity was 77% for the POD 5, and 88% for the POD 7. All the patients with AL had serum CRP values above 139 mg/L on the POD 5 and 150 mg/L on the POD 7. In 80% of patients with CRP values in the drainage fluid of 53 mg/L for the POD 5 and 42 mg/L for the POD 7 AL was observed. The method specificity was 77% for the POD 5, and 83% for the POD 7. All the patients with CRP values in drainage fluid above 108 mg/L on the POD 5 and 93 mg/L on the POD 7 had AL.

However, as a nonselective marker of inflammation and is not a completely reliable indicator of infection, CRP could be taken into consideration only within the clinical presentation context [36].

Conclusion

Our results indicate that measurement of CRP in drainage fluid can be reliably used in early detection of anastomotic leakage as the most serious infectious complication after colorectal resection. These values were positively correlated with CRP in serum, especially on the fifth and seventh day, when the risk from the appearance of this complication is greatest. Whether measurement of C-reactive protein in common with other biomarkers, in drainage fluid, contributes to more accurate early detection of patients at risk of developing anastomotic leakage after colorectal resection remains to be confirmed in future studies. Anastomotic leakage is inevitable companion of colorectal resection in a certain number of patients, and hence, its detection is of crucial importance because it allows early implementation of therapeutic measures to reduce the adverse effects.

REFERENCES

1. *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.
2. *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.
3. *Nesbakken A, Nygaard K, Lunde OC.* Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br J Surg 2001; 88(3): 400−4.
4. *Koperna T.* Cost-effectiveness of Defunctioning Stomas in Low Anterior Resections for Rectal Cancer. Arch Surg 2003; 138(12): 1334−8.
5. *Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH,* et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004; 240(2): 255−9.
6. *Ptok H, Marusch F, Meyer F, Schubert D, Gastinger I, Lippert H.* Impact of anastomotic leakage on oncological outcome after rectal cancer resection. Br J Surg 2007; 94(12): 1548−54.
7. *Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P.* Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011; 253(5): 890−9.
8. *Peeters KC, Tollenaar RA, Marijnen CA, Klein KE, Steup WH, Wiggers T*, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005; 92(2): 211−6.
9. *Jestin P, Påhlman L, Gunnarsson U.* Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study. Colorectal Dis 2008; 10(7): 715−21.
10. *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.
11. *Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R.* Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246(2): 207−14.
12. *Kostić Z, Panišić M, Milev B, Mijušković Z, Slavković D, Ignjatović M.* Diagnostic value of serial measurement of C-reactive protein in serum and matrix metalloproteinase-9 in drainage fluid in the detection of infectious complications and anastomotic leakage in patients with colorectal resection. Vojnosanit Pregl 2015; 72(10): 889–98.
13. *Welsch T, Müller SA, Ulrich A, Kischlat A, Hinz U, Kienle P,* et al. C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. Int J Colorectal Dis 2007; 22(12): 1499−507.
14. *Matthiessen P, Henriksson M, Hallböök O, Grunditz E, Norén B, Arbman G.* Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection. Colorectal Dis 2008; 10(1): 75−80.
15. *Miki C, Mohri Y, Toiyama Y, Araki T, Tanaka K, Inoue Y,* et al. Glasgow Prognostic Score as a predictive factor differentiating surgical site infection and remote infection following colorectal cancer surgery. Br J Cancer 2009; 101(9): 1648−9.
16. *Moyes LH, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC.* Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer. Br J Cancer 2009; 100(8): 1236−9.
17. *Cong Z, Fu C, Wang H, Liu L, Zhang W, Wang H.* Influencing factors of symptomatic anastomotic leakage after anterior resection of the rectum for cancer. World J Surg 2009; 33(6): 1292−7.

18. *Daams F, Luyer M, Lange JF.* Colorectal anastomotic leakage: aspects of prevention, detection and treatment. World J Gastroenterol 2013; 19(15): 2293−7.
19. *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.
20. *Rickert A, Willeke F, Kienle P, Post S.* Management and outcome of anastomotic leakage after colonic surgery. Colorectal Dis 2009; 12(10): 216−23.
21. *Krarup PM, Jorgensen LN, Andreasen AH, Harling H.* A nationwide study on anastomotic leakage after colonic cancer surgery. Colorectal Dis 2012; 14(10): 661−7.
22. *Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A,* et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010; 147(3): 339−51.
23. *Kingham TP, Pachter PL.* Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 2009; 208(2): 268−78.
24. *Alves A, Panis Y, Trancart D, Regimbeau J, Pocard M, Valleur P.* Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002; 26(4): 499−502.
25. *Thornton M, Joshi H, Vimalachandran C, Heath R, Carter P, Gur U,* et al. Management and outcome of colorectal anastomotic leaks. Int J Colorectal Dis 2011; 26(3): 313−20.
26. *Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J.* Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004; 39(2): 206−17.
27. *Gabay C, Kushner I.* Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340(6): 448−54.
28. *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.
29. *Kørner H, Nielsen HJ, Søreide JA, Nedrebø BS, Søreide K, Knapp JC.* Diagnostic accuracy of C-reactive protein for intraabdominal infections after colorectal resections. J Gastrointest Surg 2009; 13(9): 1599−606.
30. *Woeste G, Müller C, Bechstein WO, Wullstein C.* Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery. World J Surg 2010; 34(1): 140−6.
31. *MacKay GJ, Molloy RG, O'Dwyer PJ.* C-reactive protein as a predictor of postoperative infective complications following elective colorectal resection. Colorectal Dis 2011; 13(5): 583−7.
32. *Ortega-Deballon P, Radais F, Facy O, D'Athis P, Masson D, Charles PE,* et al. C-reactive protein is an early predictor of septic complications after elective colorectal surgery. World J Surg 2010; 34(4): 808−14.
33. *Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T.* Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. Colorectal Dis 2006; 8(4): 259−65.
34. *Tsujinaka S, Konishi F.* Drain vs No Drain After Colorectal Surgery. Indian J Surg Oncol 2011; 2(1): 3−8.
35. *Komen N, de Bruin RW, Kleinrensink GJ, Jeekel J, Lange JF.* Anastomotic leakage, the search for a reliable biomarker. A review of the literature. Colorectal Dis 2008; 10(2): 109−15.
36. *Warschkow R, Tarantino I, Torzewski M, Näf 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 patients. Int J Colorectal Dis 2011; 26(11): 1405−13.

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