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ORIGINAL ARTICLE

# Procalcitonin is One of the Predictive Factors of Dehiscence of the Colorectal Anastomosis

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## Abstract

**Background/Aim:** Dehiscence of the colorectal anastomosis is one of the most serious complications in digestive surgery that is still present in a large percentage today, which significantly increases the cost of treatment and can lead to death. Due to all the above, early detection of anastomotic dehiscence is very important, as well as the decision on surgical treatment. Procalcitonin (PCT) is thought to be an important marker of inflammation and sepsis. Aim of this paper was to confirm PCT as a marker of great sensitivity in early diagnosis of anastomotic leakage.

**Methods:** The study included patients who underwent surgery for colorectal cancer in the period from 2016 to 2020. Patients were operated according to an elective protocol and with an open surgical approach. In patients, PCT values were measured on the 2nd and 4th postoperative day (POD) to determine the association between elevated PCT values and the onset of dehiscence of the colorectal anastomosis.

**Results:** A study was conducted in 118 patients in whom a stapler colorectal anastomosis was created. Colorectal anastomosis dehiscence occurred in 10 patients. In 4 patients with dehiscence, no re-surgical intervention was required, but they were taken care of by conservative methods. Repeated surgery was performed in 6 patients. In all patients with dehiscence, there was a multiple increase in the value of PCT above normal.

**Conclusion:** PCT has high sensitivity and specificity (85 and 74 % respectively) as a marker in dehiscence of colorectal anastomosis. In this study it was found that PCT values were significantly correlated with the dehiscence of anastomosis 2nd POD and especially 4th POD.

**Key words:** Colorectal anastomosis; Anastomotic dehiscence; Procalcitonin.

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## Introduction

Dehiscence of colorectal anastomosis is still one of the most serious complications in colorectal surgery, which significantly worsens the patient's oncological status, prolongs hospitalisation and increases treatment costs and can even lead to death. Even today, the frequency of dehiscence is up to 20 %.[1] The cause of dehiscence itself has not been fully elucidated, but it is believed that several factors may influence its occurrence. These are primarily male sex, high age, duration of surgery and preoperative radiotherapy. Also important are the blood supply to the anastomosis, the tension of the anastomosis, as well as the height of the created anastomoses and the type of surgical technique.[2-4] Diabetes mellitus type II may lead to numerous chronic complications that are mainly caused by pathological influence of hyperglycaemia on blood vessels. Diabetes is also related to high blood lipid levels, hypertension and changes of blood vessel walls.[5] Also, it causes changes



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of blood itself, like increased activation of platelets and blood coagulation disorders. Changes of blood vessels caused by diabetes mellitus may affect small blood vessels (microangiopathy) and large ones (macroangiopathy).[6] Also, body mass index (BMI), due to its metabolic and cardiovascular complications, significantly affects the perfusion in the area of the anastomosis and thus the more frequent occurrence of anastomotic leakage.

Clinical signs of infection are usually manifested in an advanced period, so it is important to have a reliable marker that would be very reliable for early detection of anastomotic leakage and thus to make the right decision on further therapeutic treatment.[7] There are several parameters of inflammation that can be used as indicators of infection, leukocyte count (WBC), C-reactive protein (CRP), Interleukins 6, procalcitonin (PCT) and fever. PCT is a protein made up of 116 amino acids and produced by thyroid C cells. Under normal conditions, PCT values are very low and less than 0.1 ng/mL. It is very significant that the PCT value is multiplied in infections and in septic conditions, so that the monitoring of PCT values can be effectively used as a marker of anastomotic leakage and for the assessment of necessity of surgical reintervention.[8, 9]

## Methods

This prospective study included 118 patients who were operated at the Clinic of General and Abdominal Surgery of the University Clinical Centre of the Republic of Srpska in Banja Luka. All patients agreed to participate in the study. All study data were used from medical histories, operative protocols and clinical examinations of patients operated at the General Surgery Clinic. In all operated patients, rectal cancer was endoscopically verified and pathohistologically confirmed. All patients underwent preoperative value of tumour markers (C19-9, CEA) and computed tomography (CT) of the abdomen and pelvis. All patients were operated on in an elective protocol when an open laparotomy was performed and a stapler anastomosis was created. The study was conducted in the period from September 2016 to December 2020. The age of the patients included in the study ranged from 53 to 79 years of age. There were 71 male and 47 female patients. All patients who underwent surgery had risk factor I-III according to the American Society of Anaesthesiologist (ASA score). The operation was performed according to all standards of oncological surgery, which included high ligation of the lower mesenteric blood vessels and total or partial mesorectal excision depending on the height of the rectal resection. In all operated patients on the 2nd and 4th postoperative day, patients had blood drawn and measured values of the WBC and PCT. Alinity and the BRAHMS PTC chemiluminescent immunochemical assay processed on an Alinity analyser were used to determine plasma PCT values. In patients with anastomotic leakage, PCT levels were multiplied and dehiscence of the anastomosis was confirmed by the presence of intestinal contents on the drains or on laparotomy and a control finding of CT of the abdomen and pelvis. According to their severity, two types of anastomotic leakage were verified, those that could be solved by conservative methods and those that required surgical reintervention.

## Results

Out of the total number of operated, it was determined that the largest number of operated was over 65 years of age. The number of male patients was 71 (60.2 %) and the Fishers Exact test method determined that there was no statistically significant influence of gender on the development of dehiscence of the anastomosis. Preoperative radiotherapy was performed in 33 (28 %) patients and based on the analysis, it was determined that there was no statistically significant effect of preoperative radiotherapy on the development of dehiscence of the anastomosis. Also, the Fishers Exact test analysis showed that there was no statistically significant effect on the height of the anastomosis and the onset of dehiscence of the anastomosis (Table 1). The total number of dehiscence of the colorectal anastomosis was recorded in 10 (8.47 %) patients. Six (60 %) patients with dehiscence of the anastomosis required re-surgery, while in 4 (40 %) patients with dehiscence conservative treatment was sufficient. Of all operated patients, 1 (0.8 %) was a patient with a fatal outcome, in the group with dehiscence of the anastomosis.

Dehiscence of the anastomosis with anastomotic leakage significantly prolonged hospitalisation

*Table 1: Review of factors that may lead to dehiscence of colorectal anastomosis*

| Dehiscence | | Yes | No | Total |
|---|---|---|---|---|
| **Age** | | | | |
| from 55 to 65 | N | 2 | 33 | 35 |
| | % | 20.0 | 30.6 | 29.7 |
| older then 65 | N | 8 | 75 | 83 |
| | % | 80.0 | 69.4 | 70.3 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Sex** | | | | |
| Male | N | 7 | 64 | 71 |
| | % | 70.0 | 59.3 | 60.2 |
| Female | N | 3 | 44 | 47 |
| | % | 30.0 | 40.7 | 39.8 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Chemoradiotherapy** | | | | |
| Yes | N | 5 | 28 | 33 |
| | % | 50.0 | 25.9 | 28.0 |
| No | N | 5 | 80 | 85 |
| | % | 50.0 | 74.1 | 72.0 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Anastomosis height** | | | | |
| Less than 10 cm | N | 5 | 35 | 40 |
| | % | 50.0 | 32.4 | 33.9 |
| More than 10 cm | N | 5 | 73 | 78 |
| | % | 50.0 | 67.6 | 66.1 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Body mass index (BMI)** | | | | |
| Less than 19 | N | 0 | 8 | 8 |
| | % | 0.0 | 6.8 | 6.3 |
| From 19 to 25 | N | 3 | 60 | 63 |
| | % | 30.0 | 50.8 | 49.2 |
| More than 25 | N | 7 | 50 | 57 |
| | % | 70.0 | 42.4 | 44.5 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Diabetes mellitus** | | | | |
| Yes | N | 4 | 34 | 38 |
| | % | 40.0 | 31.5 | 32.2 |
| No | N | 6 | 74 | 80 |
| | % | 60.0 | 68.5 | 67.8 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |
| **Mortality** | | | | |
| Yes | N | 1 | 0 | 1 |
| | % | 10.0 | 0.0 | 0.8 |
| No | N | 9 | 108 | 118 |
| | % | 90.0 | 100.0 | 99.2 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |

of patients so that in patients without dehiscence the average hospitalisation lasted 8 days, while in patients with dehiscence hospitalization averaged 19.5 days.

*Table 2: Procalcitonin 2nd postoperative day (POD) values in patients with dehiscence and no dehiscence anastomosis*

| Dehiscence | | Yes | No | Total |
|---|---|---|---|---|
| **Prokalcitonin ≥ 2 ng/mL** | | | | |
| Yes | N | 9 | 32 | 41 |
| | % | 90.0 | 29.6 | 34.7 |
| No | N | 1 | 76 | 77 |
| | % | 10.0 | 70.4 | 65.3 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |

*Table 3: Procalcitonin 4th postoperative day (POD) values in patients with dehiscence and no dehiscence anastomosis*

| Dehiscence | | Yes | No | Total |
|---|---|---|---|---|
| **Prokalcitonin ≥ 4 ng/mL** | | | | |
| Yes | N | 10 | 21 | 31 |
| | % | 100.0 | 19.4 | 26.3 |
| No | N | 0 | 87 | 87 |
| | % | 0.0 | 80.6 | 73.7 |
| **Total** | N | 10 | 108 | 118 |
| | % | **100.0** | **100.0** | **100.0** |

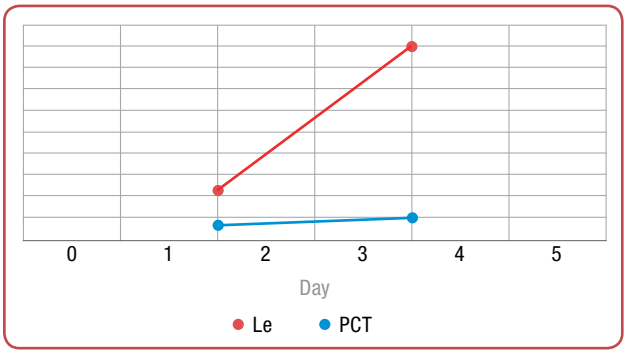


*Figure 1: Correlation of procalcitonin (PTC) and total leucocyte count (Le) values 2nd and 4th postoperative day (POD)*

The Fishers Exact test found that there was a statistically significant correlation between elevated PCT values above 2 ng/mL on the 2nd POD and 4 ng/mL on the 4th POD and dehiscence of the anastomosis. Thus, in patients who had a significantly higher value of PCT on the 2nd and 4th day, this was an important predictive factor in the occurrence of dehiscence of the anastomosis and anastomotic leakage (Tables 2, 3). Additionally, WBC level at the same time points was not markedly or statistically correlated with PCT vales showing different dynamic among the patients (Figure 1).

## Discussion

In this study, patients operated for rectal cancer were followed and it was tried to verify the development of dehiscence of colorectal anastomosis at an early stage by measuring the value of PTC in order to conduct the best possible treatment. There are several parameters such as CRP, interleukin 6 and PCT that are considered important markers for early diagnosis of anastomotic leakage.[10] PCT is a protein that is significantly increased in generalised infections and sepsis when PCT is produced in large quantities by various types of body cells.[9, 11]

The increase in PCT concentrations reaches its maximum in 6-8 hours and in the case of sepsis values can reach up to 1000 ng/mL.[12] Dehiscence of the colorectal anastomosis is still one of the most difficult complications of colorectal surgery that occurs in a high percentage, which significantly increases the cost of treatment and can be fatal.[13, 14] Mortality in dehiscence of the colorectal anastomoses ranges up to 30 %.[15] Because of all this, early diagnosis of dehiscence of the anastomosis is very important to reduce treatment costs and mortality.[16] Some studies have shown that PCT is one of the best markers for distinguishing sepsis from non-infectious inflammatory reactions, even more so in intra-abdominal infections and especially anastomotic leakage, the increase in PCT is much higher than in extra abdominal infections.[17-19]

In their study, Meisner et al found that in the first days after colorectal surgery there was a physiological increase in PCT as a result of contamination when working with the intestines as well as due to the preparation with the intestines.[20, 21] Giaccaglia et al also confirmed in their experiences that measuring PCT values on the first postoperative day was not necessary, so they measured PCT values on the third and fifth POD in their study. PCT values were significantly higher on the third and fifth postoperative day in patients with anastomotic leakage than in patients without anastomotic leakage.[7]

In this study, PCT values were measured on the 2nd and 4th POD in all patients operated on for rectal cancer. PCT values on the 2nd day were significantly increased in all patients with anastomotic leakage. By nine patients with anastomotic dehiscence, PTC values were greater than 3 ng/mL, while in only one patient with anastomotic dehiscence, PTC values were less than 3 ng/mL. Fourth POD value of PTC by all ten patients with dehiscence anastomosis was higher than 7 ng/mL and in one patient the values reached 19 ng/mL.

In their study, Sarbinowski et al examined PCT, CRP, WBC and interleukin 6 in patients operated on for colorectal cancer. In the study, they determined the importance of these markers for the assessment of the occurrence of anastomotic leakage and for the development of systemic inflammatory syndrome. They found that only an increase in PCT concentration was statistically significant in patients with anastomotic leakage and systemic inflammatory syndrome.[22] In their study of 100 patients operated on for colorectal cancer on the first, second, third and fourth postoperative days, Lagoutte et al found that CRP was a more appropriate marker of anastomotic leakage than PCT, with a specificity of 87 % to 75 %.[23] Elevated PCT values were found to have much higher specificity than CRP values as a marker of anastomotic leakage. In their study of 154 patients, Tatsuoka et al found that PCT 4th POD has higher specificity and sensitivity than CRP values in patients with dehiscence of colorectal anastomosis.[24]

Besides, Takakura et al in their study confirmed PCT as an important prognostic marker of anastomotic leakage in patients operated on for colorectal cancer.[25] In this study, which included 118 patients operated on colorectal cancer, it was found that all patients with anastomotic leakage had a significant increase in PCT values on the second and fourth day compared to patients without anastomotic leakage. Biomarker for acute infection and inflammation such as WBC was insignificantly correlated with PCT level confirming their less sensitivity for dehiscence. Therefore, monitoring of WBC is not considered as a relevant biomarker for dehiscence although they are commonly measured in our centre. Also, a certain number of observed patients without anastomotic leakage showed an increase in PCT values, but these values were elevated in less than 30 % of patients, unlike patients with anastomotic leakage where PTC was elevated in 100 % of patients. Significantly, PCT 4th POD values in patients without anastomotic leakage were always significantly lower than in patients with anastomotic leakage. In a patient without anastomotic leakage, PCT was elevated in patients with pneumonia, urinary tract infection and local operative wound infection. In his study of 100 patients after colorectal surgery, Elyazed found that PCT was elevated in patients with pneumonia, which was a postoperative complication. PCT was elevated at 2nd, 3rd and 5th POD in nearly 84 % of patients with pneumonia.[26]

## Conclusion

PCT value is an important predictor of anastomotic dehiscence and anastomotic leakage in colorectal surgery. An increase in PCT on the 2nd and especially on the 4th POD is one of the safest indicators of anastomotic leakage, which requires additional diagnosis and adequate therapy.

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## Conflict of interest

None.

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