Use of inflammatory markers in the early detection of infectious complications after laparoscopic colorectal cancer surgery with the ERAS protocol

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Abstract

Introduction: *Thanks to laparoscopy and enhanced recovery protocols (ERAS) it is possible to shorten hospitalization. Therefore, it seems reasonable to search for new early markers of infectious complications in order to select patients who are prone to development of complications.*
Aim: *To assess the usefulness of serum levels of C-reactive protein, interleukin-6 and procalcitonin as early indicators of infectious complications in patients after laparoscopic colorectal surgery with ERAS.*
Material and methods: *The prospective analysis included consecutive patients who underwent laparoscopic colorectal cancer resection. The following parameters were included in the analysis: C-reactive protein (CRP), interleukin 6 (IL-6) and procalcitonin measured on postoperative days (PODs) 1, 2, 3. Patients were divided into two groups: uncomplicated (group 1) and complicated (group 2). The difference in levels of the markers and the dynamics of changes observed in both groups were analyzed.*
Results: *Group 1 comprised 34 patients, and group 2 consisted of 17 patients. A significant increase of both absolute values and delta increments on all postoperative days was noted. ROC curve analysis showed that the best cut-off values indicating an infectious process were: CRP 129 mg/l on POD3 (92% sensitivity/80% specificity), IL-6 of 78 pg/ml on POD2 (91% sensitivity/97% specificity) and PCT 0.24 ng/ml on POD3 (93% sensitivity/68% specificity).*
Conclusions: *Our study showed that regular measurement of all analyzed markers in the early postoperative days may be beneficial in the detection of postoperative infectious complications. Further studies are needed to fully assess the role of routine biochemical measurements in the postoperative period after laparoscopic surgery with the ERAS protocol.*

Key words: *complications, laparoscopy, inflammatory markers, procalcitonin, colorectal surgery, enhanced recovery after surgery protocol.*

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Introduction

Colorectal surgical procedures are characterized by a relatively high incidence (up to 15%) of infectious complications [1], which can rise to 30% among patients undergoing surgery for cancer [2]. The most important factors in the reduction of infectious complications, mainly surgical site infections (SSI), are proper, minimally invasive surgical technique and optimal perioperative care. Based on current literature, laparoscopic procedures contribute to a reduction of global risk of postoperative complications [3] and the incidence of SSI [4]. In addition, the use of the perioperative care protocols, based on the Enhanced Recovery After Surgery (ERAS) guidelines, reduces the global postoperative complication rate by up to 40%, shortens length of stay (LOS) and reduces treatment costs [5–7].

However, due to reduced average LOS, the period of close supervisions is also shortened and some complications may develop after discharge from hospital, resulting in subsequent readmission [8]. In fact, most infections are clinically revealed 4–6 days after the operation, which is later than the usual LOS after laparoscopic surgery. Therefore, it has become particularly important to search for specific markers which can be used as surrogates for early detection of infectious complications and, if possible, prediction of their severity during the asymptomatic period [9]. This would allow for screening of patients who should either stay in the hospital longer or be more closely monitored after discharge.

In recent years, many studies have concentrated on several biochemical inflammatory markers such as C-reactive protein (CRP), interleukin-1 (IL-1) and -6 (IL-6), or procalcitonin (PCT). All of them have proven their clinical value in predicting infectious complications [10–13]. However, there are limited data on the use of these markers in surgical patients undergoing minimally invasive procedures with addition of the ERAS protocol [14, 15].

Table I. ERAS protocol used in our unit

1. Preoperative counseling and patient's education
2. No bowel preparation (oral lavage in the case of low rectal resection with total mesorectal excision (TME) and defunctioning loop ileostomy)
3. Pre-operative carbohydrate loading (400 ml of Nutricia preop 2 h prior to surgery)
4. Antithrombotic prophylaxis (Clexane 40 mg *s.c.* starting in the evening prior to surgery)
5. Antibiotic prophylaxis (preoperative cefuroxime 1.5 g + metronidazole 0.5 g *i.v.* 30–60 min prior to surgery)
6. Laparoscopic surgery
7. Balanced intravenous fluid therapy (< 2500 ml intravenous fluids during the day of surgery, less than 150 mmol sodium)
8. No nasogastric tubes postoperatively
9. No drains left routinely for colonic resections, one drain placed for < 24 h in case of TME
10. Transversus abdominis plane (TAP) block, epidural anaesthesia in cases with high risk of conversion
11. Avoiding opioids, multimodal analgesia (oral when possible – paracetamol 4 × 1 g, ibuprofen 2 × 200 mg, metamizole 2 × 2.5 g, or ketoprofen 2 × 100 mg)
12. Prevention of postoperative nausea and vomiting (PONV) (dexamethasone 8 mg *i.v.*, ondansetron 8 mg *i.v.*, metoclopramide 10 mg *i.v.*)
13. Postoperative oxygenation therapy (4–6 l/min)
14. Early oral feeding (oral nutritional supplement 4 h postoperatively, light hospital diet and oral nutritional supplements on the first postoperative day, full hospital diet on the second postoperative day)
15. Urinary catheter removal on the first postoperative day
16. Full mobilization on the first postoperative day (getting out of bed, going to toilet, walking along the corridor, at least 4 h out of bed)

Aim

The aim of the study was to determine the usefulness of CRP, IL-6 and PCT as early indicators of infectious complications among patients undergoing laparoscopic radical resection for colorectal cancer with the perioperative ERAS protocol.

Material and methods

The study was conducted in a tertiary reference center (university hospital). Data from patients with colon cancer undergoing laparoscopic radical colorectal resection were collected prospectively. Inclusion criteria for the study were: age over 18 years, elective laparoscopic surgery for colorectal adenocarcinoma and use of the ERAS protocol in perioperative care. Exclusion criteria included: patients undergoing open (including conversion from minimally invasive approach) or emergency surgery and those who required multivisceral resection exceeding the large bowel (T4), distant metastases (M1), or rectal cancer treated with transanal endoscopic microsur-

gery (TEM). Also, patients with inflammatory bowel disease, patients with active infection (less than 2 weeks before the procedure) and diagnosed with autoimmune disease and patients among whom implementation of the ERAS protocol was not possible (i.e. due to hospitalization in ICU directly after surgery) were excluded from the study.

Laparoscopic access with four or five trocars and the medial to lateral approach was used as a surgical technique [16]. All patients had the same perioperative care based on the ERAS protocol (Table I), which has been used in this institution for 5 years. Mean compliance with the protocol is over 80% [17].

Blood samples were taken from all patients on the day of surgery (preoperatively) and every morning before the first meal for 3 consecutive postoperative days (POD).

Serum from a blood sample (1 vial of 4.9 ml) was centrifuged for 10 min at 4,000 rpm and then frozen at –80°C until a full set of specimens was collected. Laboratory results for all samples included CRP, IL-6 and PCT levels.

Subsequently, patients were divided into two groups: without perioperative infectious complications (group 1) and with perioperative infectious complications (group 2). European Centre for Disease Prevention and Control (ECDC) guidelines were used for diagnosis and assessment of severity of infectious complications [18].

Statistical analysis

Descriptive statistics for both groups included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, type of surgery, tumor staging, operative time, intraoperative blood loss as well as degree of ERAS implementation. The difference in the concentration of measured markers between the groups was analyzed. The dynamics changes of each analyzed marker concentrations (daily increments analysis) on successive days were also assessed. We performed ROC analysis to determine the optimal POD for obtaining the markers and the cut-off values.

All data were analyzed with StatSoft Statistica v.13. The results are presented as mean ± standard deviation (SD), median and interquartile range (IQR). The study of categorical variables used the χ^2 test of independence. The Shapiro-Wilk test was used to check for a normal distribution of data and Student's *t*-test was used for normally distributed quantitative data. For non-normally distributed quantitative variables, the Mann-Whitney *U* test was used. For dependent variables the Friedman test was used. A receiver operating characteristic (ROC) curve was applied to obtain the area under the curve (AUC) and determine the best cut-off values for each analyzed marker. Results were considered statistically significant when the *p*-value was < 0.05. The study was approved by the local Ethics Review Committee (approval number KBET/211/B/2014). All procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (Fortaleza).

Results

One hundred and four patients underwent colorectal resection between August 2014 and September 2015. Thirty of them were excluded be-

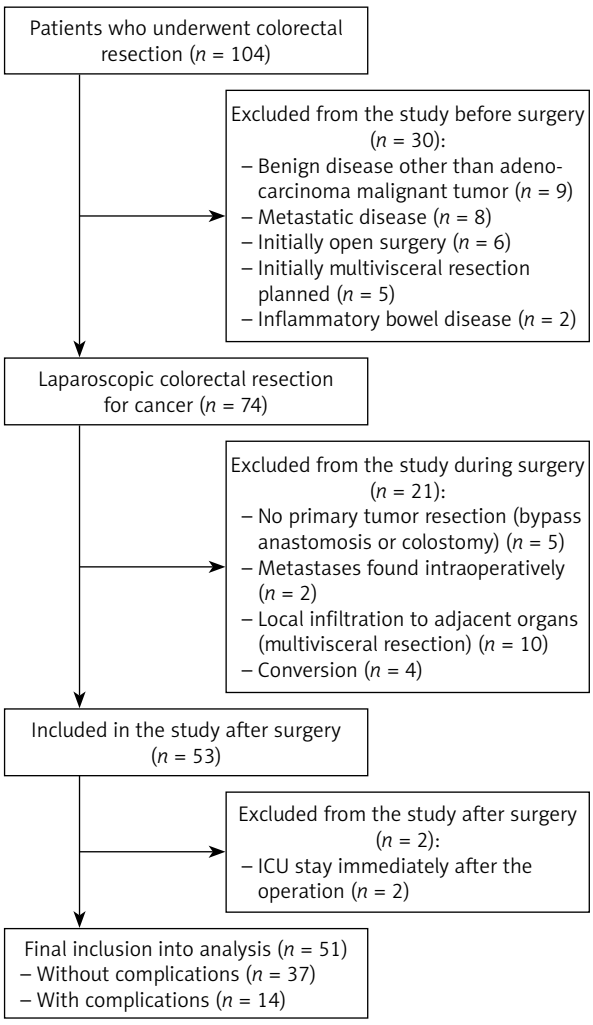

Figure 1. Patients' flow through the study

fore surgery, 21 during surgery. Two patients were excluded because the ERAS protocol was not fully implemented in the postoperative period. Patients' flow through the study and reasons for exclusion are shown in Figure 1.

Groups 1 and 2 consisted of 37 (72.5%) and 14 (27.5%) patients, respectively. Table II shows the demographic comparison of both groups and shows no significant differences in terms of age, sex, BMI, ASA scale, type of performed surgery, operative time, intraoperative blood loss or cancer stage. However, there was a significant difference in median LOS (4 vs. 9 days, $p < 0.001$) between the groups. The analysis of infectious complications is presented in Table III and laboratory measurements are displayed in Table IV. Before surgery (POD0 measurement), CRP, IL-6 and PCT levels were comparable. On POD1, levels of all measured markers increased in both groups. In all measurements during the postoperative period, the increase of marker levels was greater in group 2 (Figures 2–4). This observation was applicable to all evaluated markers and differences between the groups were statistically significant ($p < 0.05$).

ROC curve analysis was then performed. For every analyzed marker, curves for successive PODs were compared against each other to find the curve

Table II. Demographic analysis of patient groups

Parameter	Group 1 – not complicated	Group 2 – complicated	Statistical significance
Patients, *n* (%)	37 (72.5)	14 (27.5)	–
Females, *n* (%)	17 (45.9)	7 (50.0)	0.79585
Males, *n* (%)	20 (54.1)	7 (50.0)	
Age, mean ± SD [years]	67.1 ±13.7	63.9 ±10.9	0.449483
BMI, mean ± SD [kg/m^2]	26.7 ±4.8	28.1 ±4.4	0.060147
ASA 2, *n* (%)	23 (62.2)	7 (50.0)	0.43302
ASA 3, *n* (%)	14 (37.8)	7 (50.0)	
AJCC stage I, *n* (%)	18 (48.6)	7 (50.0)	0.99571
AJCC stage II, *n* (%)	8 (21.6)	3 (21.4)	
AJCC stage III, *n* (%)	11 (29.8)	4 (28.6)	
Right hemicolectomy, *n* (%)	12 (32.4)	5 (35.8)	0.87697
Left hemicolectomy, *n* (%)	1 (2.7)	1 (7.1)	
Sigmoid resection, *n* (%)	10 (27.1)	3 (21.4)	
Low anterior resection of the rectum, *n* (%)	13 (35.1)	4 (28.6)	
Abdominoperineal excision, *n* (%)	1 (2.7)	1 (7.1)	
Formation of stoma, *n* (%)	11 (29.7)	3 (21.4)	0.54671
Operative time, mean ± SD [min]	208 ±61.5	193 ±59.6	0.838029
Operative time, median (IQR) [min]	210 (160–240)	180 (160–260)	
Intraoperative blood loss, mean ± SD [ml]	98.2 ±74.6	118.3 ±104.1	0.291479
Intraoperative blood loss, median (IQR) [ml]	50 (50–150)	85 (50–150)	
Length of hospital stay, mean (range) [days]	3.9 ±1.9 (2–8)	9.6 ±6.6	0.000507
Length of hospital stay, median (IQR) [days]	4 (2–5)	9 (4–12)	
Readmission, *n* (%)	4 (10.8)	2 (14.3)	0.73547
Compliance with ERAS protocol	85.7 ±8.6	82.8 ±8.8	0.128201

with the best AUC parameters. Next, the cut-off point for the best curve was established (Figures 5–7). The best day for measurement of CRP and PCT is POD3, while for IL-6 the analysis shows POD2 as being a more effective choice.

In the case of PCT, the cut-off point for POD3 was established at 0.458 ng/l. However, the course of the curve indicated the presence of the second potential cut-off value. Further analysis of the cost-effectiveness of ROC curves at a 10-fold higher incidence of non-recognition of disease than suspected pathology in healthy populations showed that a better cut-off point would be the value of 0.244 ng/l (Figure 7). The same analysis was performed for the other parameters (CRP on POD3 and IL-6 on POD2), but the established cut-off values were similar to those previously calculated.

Finally, a comparison of all obtained curves was performed (Figure 8). Data showed that the best single measurement is IL-6 on POD2.

If all three tests were jointly performed (IL-6 on POD2 and PCT with CRP on POD3, with established cut-off points), that combined test would achieve sensitivity of 100% and 81% specificity if two of those three tests were negative (Figure 9).

Table III. Types of complications

Complications	*N* (%)
Anastomotic leakage	4 (7.8)
Surgical site infection – deep or superficial form	4 (7.8)
Intraperitoneal abscess	2 (3.9)
Urinary tract infection	2 (3.9)
Pneumonia	1 (1.9)
Infectious diarrhea (*C. difficile*)	1 (1.9)

Discussion

This study showed that in all patients, regardless of complications, all parameters increased after the operation as compared to preoperative values. This rise was more pronounced among patients with infectious complications. Moreover, we observed that among uncomplicated cases, levels of CRP, IL-6 and PCT – after an initial rapid increase on POD1 – remained stable or even decreased over the following days. That dynamic was not observed among patients who developed complications. We noted that the most specific single marker is IL-6 measured on POD2. However, consecutive measurements of IL-6

Table IV. Analysis of biochemical parameters

Parameter	Group 1 – not complicated	Group 2 – complicated	Statistical significance
CRP, mean ± SD (median):			
Pre	14.33 ±39.22 (3.30)	18.96 ±30.39 (5.70)	0.118844
1	75.65 ±36.78 (81.30)	102.71 ±50.18 (109.82)	0.039516
2	111.67 ±62.10 (109.69)	220.81 ±69.68 (250.10)	0.000006
3	88.83 ±85.08 (57.35)	230.25 ±91.60 (240.55)	0.000154
IL-6, mean ± SD (median):			
Pre	23.96 ±50.91 (5.11)	17.77 ±31.42 (10.10)	0.359943
1	78.14 ±68.23 (58.34)	345.63 ±402.98 (147.00)	0.002355
2	34.34 ±22.84 (25.62)	763.49 ±1906.56 (121.80)	0.000004
3	17.99 ±11.80 (12.71)	206.26 ±332.67 (50.71)	0.000224
PCT, mean ± SD (median):			
Pre	0.10 ±0.20 (0.04)	0.30 ±0.85 (0.04)	0.701681
1	0.52 ±0.71 (0.21)	1.12 ±1.49 (0.46)	0.042699
2	0.63 ±1.27 (0.20)	1.41 ±1.33 (1.27)	0.004723
3	0.68 ±2.14 (0.13)	1.24 ±1.39 (0.90)	0.001502

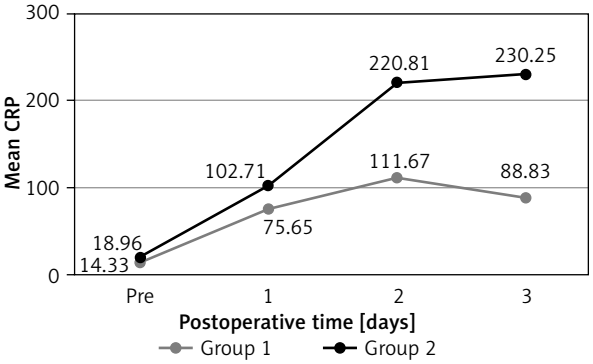

Figure 2. Mean CRP levels measured during consecutive PODs in both groups

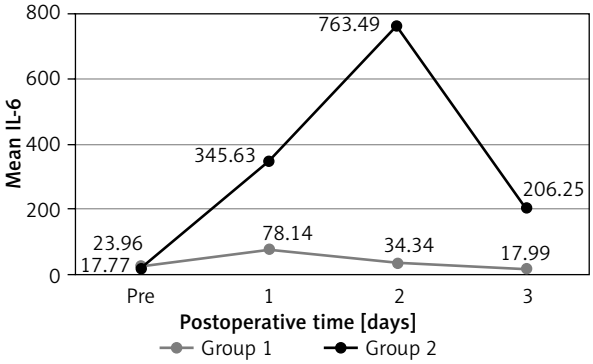

Figure 3. Mean results of IL-6 measurements on successive PODs in both groups

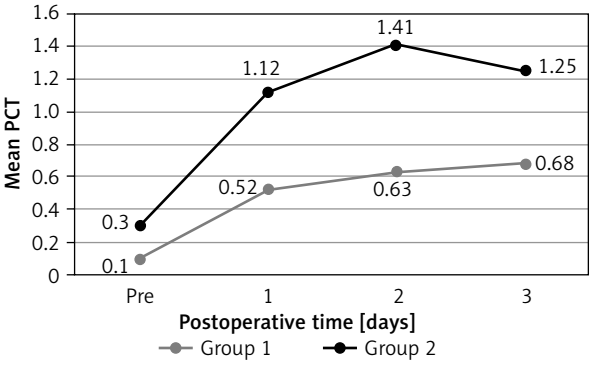

Figure 4. Mean PCT levels in both groups, measured on consecutive PODs

on POD2 combined with CRP and PCT on POD3 may give more reliable information for decision-making about safe discharge of patients from hospital after laparoscopic colorectal surgery.

The majority of previous studies which analyzed inflammatory markers were based on populations treated with a classical surgical approach without the perioperative ERAS protocol [12, 14, 19]. Both laparoscopic surgery and the ERAS protocol have been shown to diminish the inflammatory response after surgical trauma [20–22]. It may be expected that the impact of the surgery itself on the inflam-

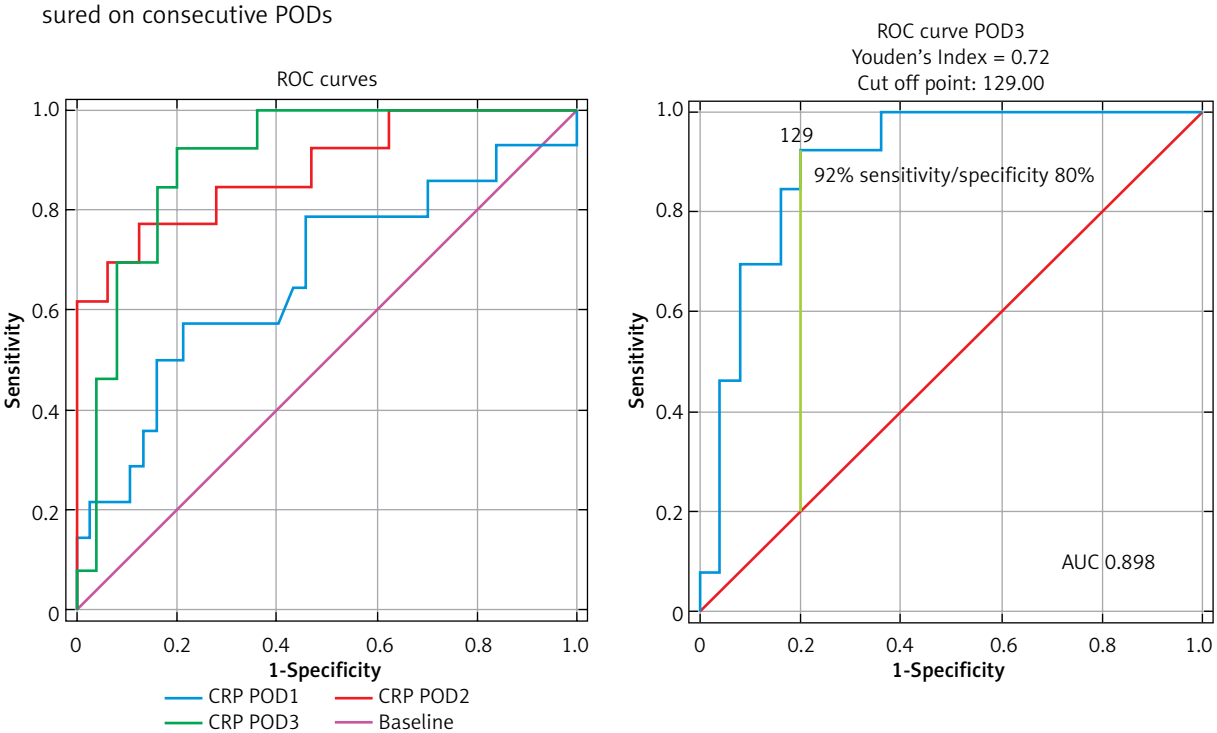

Figure 5. ROC curve analysis for CRP on successive PODs. AUC analysis revealed that the best parameters are achieved on POD3. Established cut-off point is 129 mg/l

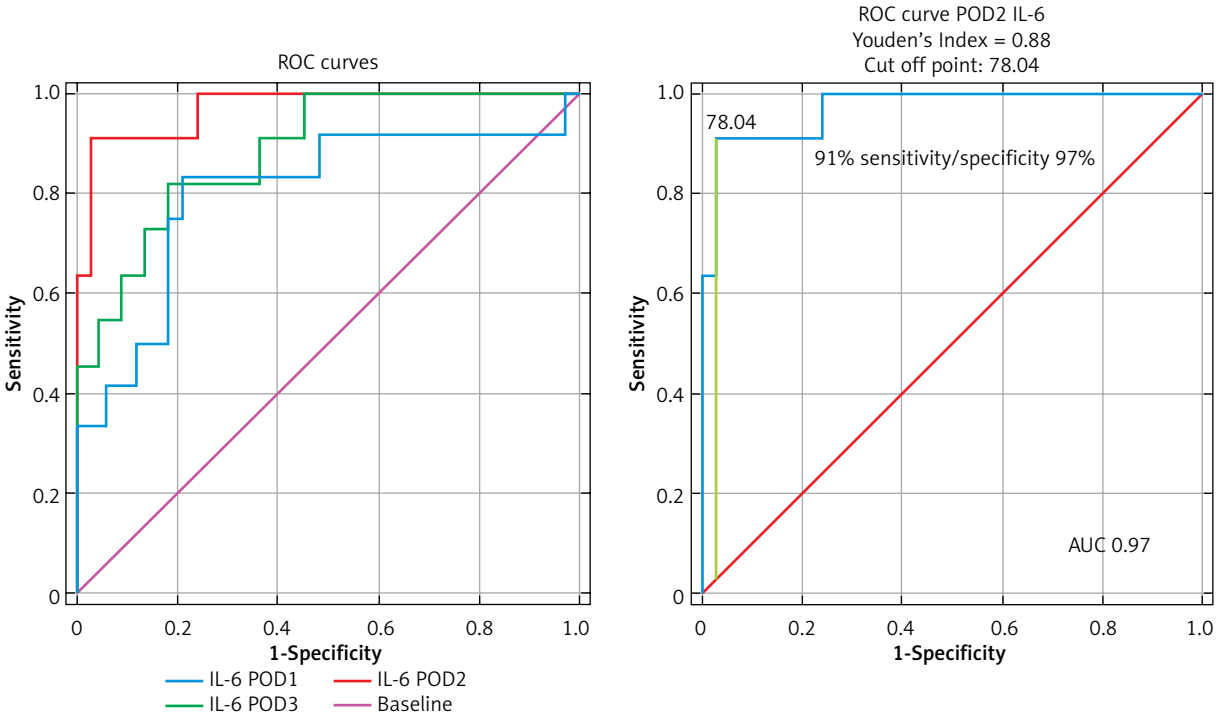

Figure 6. ROC curve analysis for IL-6 on successive PODs. AUC analysis showed the best parameters on POD2. Established cut-off point is 78.04 pg/l

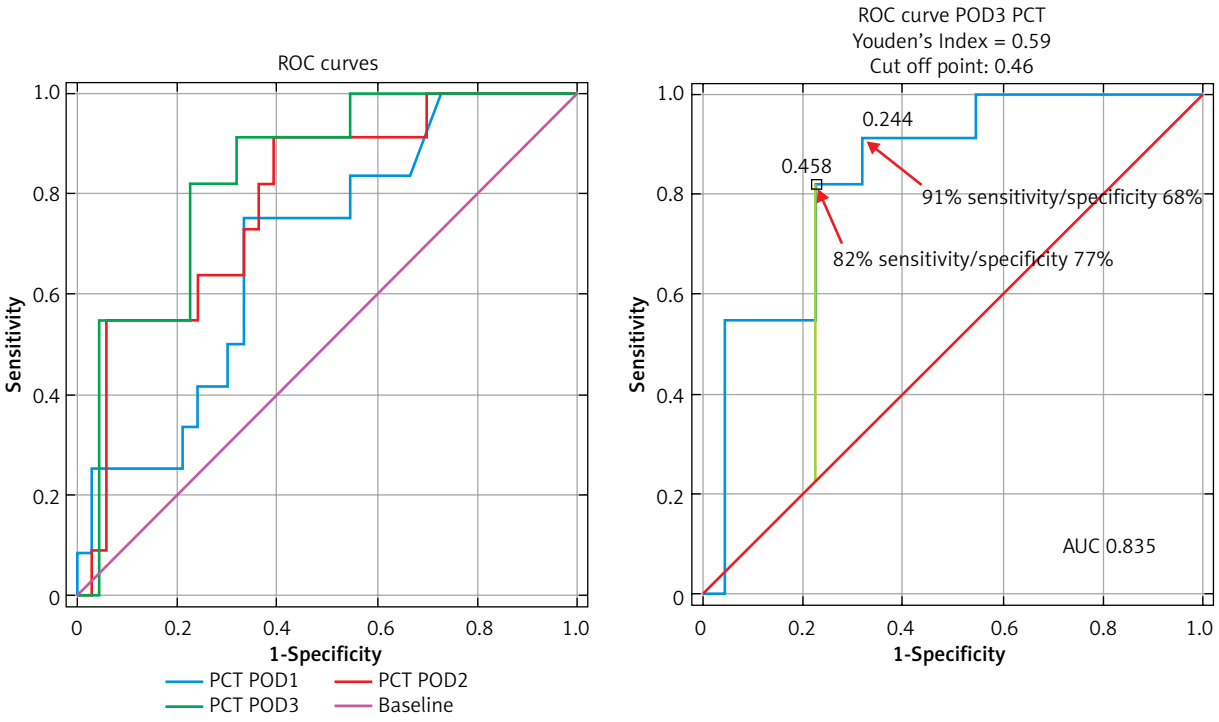

Figure 7. ROC curve analysis for PCT on successive PODs. POD3 was observed to achieve the best parameters in AUC evaluation. Established cut-off point is 0.244 ng/l (see text description)

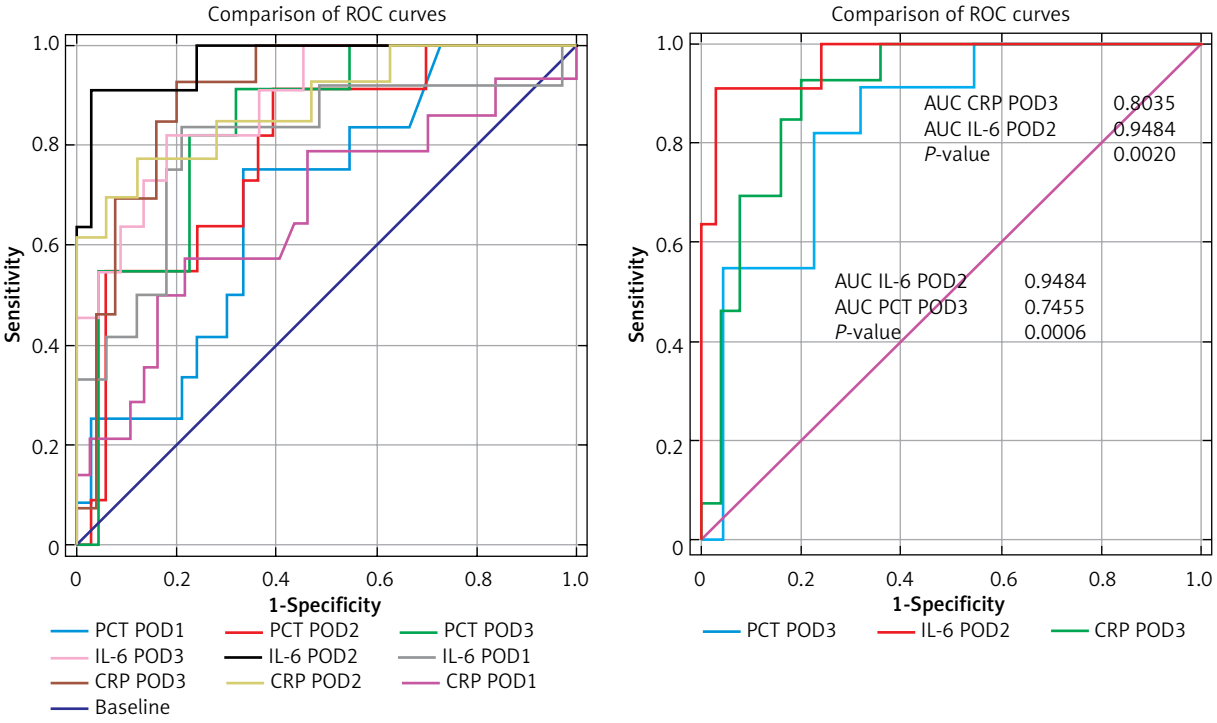

Figure 8. ROC curve analysis for all analyzed parameters. AUC computation revealed the best parameters for the test based on IL-6 measured on POD2

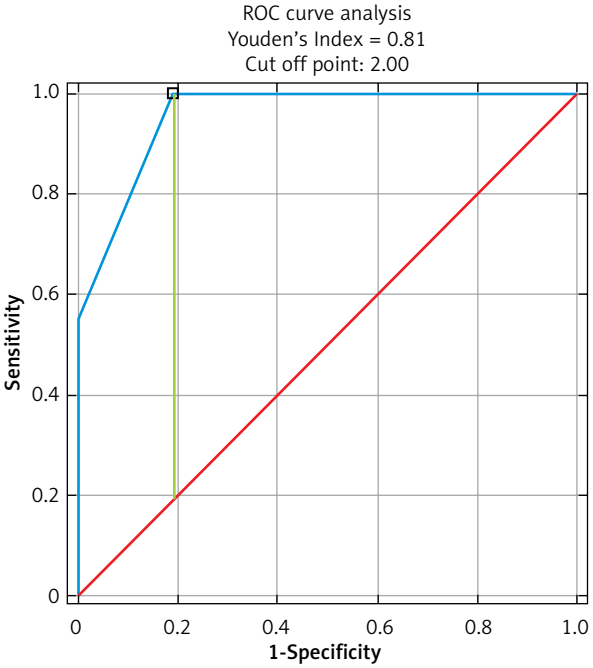

Figure 9. ROC curve analysis for the combined test based on measurements of 3 successive values (IL-6 on POD2 and PCT with CRP on POD3 with previously established cut-off points). When 2 of the 3 values are "negative", the test predicts an uncomplicated postoperative period with sensitivity of 100% and specificity of 81%

matory response will be minor in this case. Several studies have unequivocally shown that this thesis has been confirmed in clinical observations [20, 23–25]. It could be expected that the concentrations, as well as the cut-off values, of analyzed inflammatory markers will vary significantly in our population when compared to the classical approach. In the case of ultra-short postoperative stays, early detection of infectious complications is crucial due to the short supervision of these patients. This study showed that inflammatory markers can be used as a surrogate for determining the high-risk group for infectious complications.

C-reactive protein is a well-studied plasma marker for anastomotic leak or other infectious complications after colorectal surgery. However, similarly, most of the studies were based on patients operated on in a classical approach without the ERAS protocol, and the authors define a cut-off value for postoperative day 4 or 5 [26–29]. Also, established cut-off points were designed to be as specific as possible in detecting specific septic complications (usually anastomosis leak), and are much higher than values occurring in the course of the infectious process without sepsis.

Our study was designed not to detect a specific complication, but to identify a group at high risk of

infectious complications in order to consider longer hospital stay or closer surveillance during follow-up. The cut-off values were established at very low levels to ensure that almost no infectious complication was missed, accepting the fact that a meaningful number of patients who will not develop infectious complications will still be included in the high risk group.

To achieve this goal we performed cost-effectiveness analysis of ROC curves where we established that the "cost" of a patient missed by a test and who develops complications is ten times greater than the "cost" of a patient who is assigned to the high-risk group and yet does not develop any infectious complications.

Our analysis has shown that CRP level measurements well differentiates patients into two groups as early as on POD1. Evaluation of ROC curves showed that the best sensitivity and specificity are achieved on POD3. The proposed cut-off values used in our research are much lower than previously mentioned in other studies involving open resections [27, 29], but are similar to those performed on laparoscopic groups [30, 31].

Only a few studies have examined the utility of IL-6 as a marker of anastomosis leak, SSI or other infectious complications in colorectal surgery [32, 33]. This might be due to the difficulty in determining the exact value of this marker in plasma samples gathered from operated patients, due to a relatively short half-life of IL-6 [34]. Zielinska-Borkowska *et al.* did not confirm the usefulness of IL-6 in prediction of anastomotic leak [32]. Having said that, their analysis was based only on preoperative and POD1 measurements. Moreover, the studied population was much more heterogeneous then the one investigated in our study. Bilgin *et al.* analyzed IL-6 in fluid derived from drains on POD3 and POD5 after low anterior resections and did not find significant differences between groups [33]. That analysis did not measure the systemic response but only local IL-6 production. Moreover, it is obvious that the peritoneum secretes more fluid during peritonitis, which could cause dilution of the analyzed marker. This could explain why this test did not reveal differences. Our study demonstrated the value of this marker for the differentiation of uncomplicated patients and those who develop infectious complications. The levels of IL-6 significantly varied, even on POD1, between the two groups. The analysis based on the ROC curve showed that the most clinically significant values are obtained on POD2. It seems that, despite the difficulty of determining the exact value for this parameter and its variability across measurements, the differences between the analyzed groups are of such a large magnitude that the pre-laboratory bias is minimized.

Procalcitonin is considered a very good marker of the systemic inflammatory response to infections, especially caused by Gram-negative bacteria. It is more specific than CRP, particularly in systemic infections such as pneumonia, infectious endocarditis or sepsis [35]. Also, because of the shorter half-life, it is considered to be a more useful indicator for monitoring the response to treatment in the case of an ongoing infection, compared to CRP. The literature indicates its significance in detecting anastomotic leaks and other SSI in colorectal surgery [36–38]. Our analysis confirmed this observation. Statistically significant differences in obtained values of procalcitonin for both groups were seen as early as POD1 and the analysis of ROC curves showed the greatest usefulness of determining this parameter on POD3.

Our study shows that we can effectively predict an uncomplicated (due to infections) postoperative course in patients in whom IL-6 on POD2 and CRP and PCT on POD3 are below defined cut-off values. The sensitivity of combined measurements was 100% (even if only 2 out of 3 tests were negative), and it may by a clinical criterion for safe early discharge in patients undergoing laparoscopic colorectal operations, managed perioperatively according to the ERAS protocol.

Based on the above data, we have tried to establish a preliminary diagnostic algorithm for asymptomatic patients. The data suggest that measuring the IL-6 serum level on POD2 can help in the decision-making process regarding further hospitalization. Only 3% of patients with a negative IL-6 on POD2 are at risk of developing an infectious complication, so in the absence of symptoms, the patient can be safely discharged from hospital, when all other discharge criteria according to the ERAS protocol have been fulfilled. On the other hand, if the patient has a higher value than the cut-off point proposed in this research (even if the patient is asymptomatic), it would be advisable to keep the patient in the hospital on POD3 and measure levels of CRP and PCT. If both tests are negative on POD3, the patient is safe to discharge. For patients with nonspecific symp-

toms and a positive test on POD3, the proposed sequence of tests may facilitate the decision to perform further diagnostic tests, including invasive procedures, or prolonging patient hospitalization for further observation.

Our study has certain limitations which are typical for a single-centre pilot study. The study sample is relatively small, especially in the group of patients with complications, which is a common problem in this type of research [13, 39]. Therefore, our analyses should be repeated in larger cohorts. On the other hand, all patients were selected cases, undergoing a similar type of the minimally invasive colorectal procedure. The baseline characteristics of groups of patients with and without complications, as well as the adherence to the protocol, were comparable. That allows us to draw the conclusion that the differences are closely related to occurring complications. As a pilot study, it was merely aimed at analyzing the usefulness of those measurements in diagnostics of infectious complications in the early postoperative period, and to predict the best time for measurement of each parameter. That is the reason why established values of the cut-off points, as well as the sensitivity and specificity of the tests, can significantly differ from the real optimal values. Our team is now conducting further research.

Conclusions

Our study showed that regular measurements of all analyzed markers in the early postoperative days may be beneficial in the detection of postoperative infectious complications. Although changes are observed early after surgery in all parameters, the most specific single marker is IL-6 measured on POD2. However, consecutive measurements of IL-6 on POD2 combined with CRP and PCT on POD3 may give more reliable information and provide a useful tool for decision-making about safe discharge of patients from hospital after laparoscopic colorectal surgery with the ERAS protocol.

Conflict of interest

The authors declare no conflict of interest.

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