Original Article

Soluble Triggering Receptor Expressed on Myeloid Cells-1 and Inflammatory Markers in Colorectal Cancer Surgery: A Prospective Cohort Study

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Abstract

Background: Major abdominal surgery, including colorectal cancer (CRC) surgery, leads to systemic inflammatory response syndrome that can be detected and monitored with inflammatory markers testing. The aims of the study were to evaluate the usefulness of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), interleukin-6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) in following the inflammatory response in CRC surgery and postoperative period, as well as to determine if duration of the surgery and the time that the colon has been opened during the surgery (open colon time [OCT]) reflect a larger surgical stress through inflammatory markers rise.
Methods: The study included 20 patients who underwent CRC surgery and 19 healthy volunteers from June 2011 to September 2012. We determined inflammatory markers 1 day before surgery (T0), 24 h (T1), 48 h (T2), and 7 days after the surgery (T3). All statistical analyses were calculated using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium).
Results: Concentrations of CRP, PCT, and IL-6 in all measurement times were statistically different and sTREM-1 did not yield statistical significance. A weak positive correlation was found between IL-6 in T1 and T2 with the duration of the surgery (T1: $r = 0.4060$, $P < 0.0001$; T2: $r = 0.3430$, $P < 0.0001$) and OCT (T1: $r = 0.3640$, $P < 0.0001$, T2: $r = 0.3430$, $P < 0.0001$). A weak positive correlation between CRP in T2 and OCT ($r = 0.4210$, $P < 0.0001$) was also found. The interconnectivity of tested parameters showed a weak positive correlation between CRP and IL-6 in T1 ($r = 0.3680$; $P < 0.0001$), moderate positive correlation in T2 ($r = 0.6770$; $P < 0.0001$), and a strong positive correlation in T3 ($r = 0.8651$; $P < 0.0001$).
Conclusions: CRP, IL-6, and PCT were shown to be reliable for postoperative monitoring. Simultaneous determination of CRP and IL-6 might not be useful as they follow similar kinetics. sTREM-1 might not be useful in CRC postoperative monitoring.
Trial Registration: www.ClinicalTrials.gov, NCT01244022;https://www.clinicaltrials.gov/ct2/show/NCT01244022?term=01244022&rank=1.

Key words: Acute-phase Proteins; Colorectal Cancer; Surgery; Soluble Triggering Receptor Expressed on Myeloid Cells-1

Introduction

Major abdominal surgeries, including colorectal cancer (CRC) surgery, lead to systemic inflammatory response syndrome (SIRS). SIRS could be the consequence of an infection or a different cause like surgical trauma.[1] Laboratory determination of inflammatory markers before and after the surgery were shown to be useful in detecting the cause of SIRS[2] and there is always a need for more specific and reliable inflammatory markers for optimal clinical monitoring.

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is a soluble form of the TREM-1 and is proven as a reliable marker of infection in many different diseases and inflammatory conditions.[3-9] SIRS is very common in critically ill patients, especially in surgical patients, so sTREM-1 has a potential role in postoperative care in distinguishing SIRS from sepsis and indicating bacterial infections in the postoperative period.[10,11]

Interleukin-6 (IL-6) is a proinflammatory cytokine that, among other cytokines, mediates inflammatory response.

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It is commonly used in monitoring the magnitude of inflammatory response in different types of surgeries and everyday clinical practice, particularly in monitoring patients in intensive care units.[12,13]

Procalcitonin (PCT), prohormone of calcitonin, and C-reactive protein (CRP), acute phase protein, are sensitive inflammation markers. PCT showed to be more suitable infection monitoring tool than CRP because it reaches peak levels much earlier than CRP and also has a greater diagnostic accuracy.[14,15] CRP is not a specific marker of infection, but regardless of all its limitations, CRP is the most commonly used inflammatory marker for perioperative monitoring.[16,17]

The aims of this study were to follow the course of the inflammatory response in CRC surgery by following the concentrations of sTREM-1, IL-6, PCT, and CRP as well as to evaluate the usefulness of sTREM-1 in following postoperative CRC surgery period.

Considering that the duration of the surgery, and the time the colon has been opened during the surgery (open colon time [OCT]) define the severity of the procedure, our aim was to investigate if these variables have an effect on concentrations of inflammatory markers during the postoperative period.

Methods

Ethical approval

This study was conducted at the Clinical Department of Laboratory Diagnostics at University Hospital Dubrava and was registered at ClinicalTrials.gov (No. NCT01244022). Informed consent was obtained from all patients. The study was approved by the Ethics Committee of University Hospital Dubrava and was in accordance with the *Helsinki of Declaration* of 1975 as revised in 2000.

Study design

Selection and description of participants

The study included 20 patients who underwent CRC surgery between June 2011 and September 2012 and 19 age- and sex-adjusted healthy volunteers. We estimated that a minimum of five patients per group was required to achieve a statistical power of 80% to detect a statistical difference ($P < 0.05$) in sTREM-1 with an assumed standard deviation of 61 pg/ml (alpha-level of 0.05 and beta-level of 0.20). Results are based on the Rivera-Chavez and Minei study.[11] A larger cohort of 20 patients was selected to exclude patients with possible detection of distant metastasis during surgery or to exclude patients who developed infections or complications such as anastomotic leakage.

The extent of the disease was determined using a standardized protocol that included detection of distant metastasis with computed tomography examination presurgery, and also during the surgery with an examination of intra-abdominal organs. All resected specimens were subjected to pathohistological examination. To obtain more uniform data, inclusion criteria were that we only included patients without distant metastasis, only one surgeon performed resections, and complete local cancer resection (R0 resection) was confirmed in all cases. Exclusion criteria for the study were ongoing infection before surgery, detected distant metastasis as well as admission of neoadjuvant chemotherapy. Different comorbidities were not considered exclusion factors, and for that reason, we included healthy control group to test if the baseline differences in inflammatory markers exist between two groups. All comorbidities and classification of malignant tumors (TNM staging) of CRC patients group are presented in Table 1.

CRC patients underwent radical colorectal surgery as follows: anterior rectosigmoid resection (8/20), left hemicolectomy (1/20), right hemicolectomy (6/20), sigmoid colon resection (2/20), abdominoperineal rectal amputation (1/20), transverse colon resection (1/20), and colectomy (1/20). CRC group included 13 male and 7 female patients, and control group included 11 male and 8 female healthy individuals who were age- and sex-adjusted with CRC group. Median and range of age in CRC group was 72 (52–85) years and in the control group 63 (54–87) years.

For CRC group, blood was drawn in 4 consecutive measurement times: 1 day before the surgery (T0), 24 h (T1) post-surgery, 48 h (T2) post-surgery, and 7 days post-surgery (T3) to detect acute reaction to surgical stress as well as to detect patients who had prolonged surgical stress reaction. The duration of the surgery and the OCT were measured during the surgery.

All patients with CRC received a standardized antibiotic therapy consisting of intravenously applied cefazolin (1 g, 3 times a day) and metronidazole (0.5 g, 3 times a day). Therapy was applied at the beginning of surgery and continued for 3 days after the surgery.

Samples from healthy volunteers were also tested in order to determine baseline concentrations of tested inflammatory markers and to compare the levels in CRC group due to possible changes in concentration of inflammatory markers

Table 1: Comorbidities and classifications of malignant tumors (TNM staging) for colorectal cancer patients group (n = 20)

Characteristics	Ratio
Comorbidity	
Arterial hypertension	9/20
Diabetes mellitus type 2	3/20
Arrhythmia	1/20
Atrial fibrillation	1/20
Osteoporosis	2/20
Prostate adenoma	3/20
No comorbidities	6/20
TNM staging	
T1N0M0	1/20
T2N0M0	6/20
T3N0M0	12/20
T3N1M0	1/20

TNM: Tumor, node, and metastasis.

due to comorbidities and TNM staging. In addition, we tested if there was correlation of inflammatory markers and TNM staging of patients in tested study group. The criteria for the control group consisting of healthy volunteers were that they were judged healthy on the systematic examination and that they had no malignancies. Systematic examination included determination of complete blood count, glucose, urea, creatinine, transaminases, bilirubin, total proteins and CRP, abdominal ultrasound, and complete examination with internal medicine specialist.

Technical information

The concentrations of CRP, IL-6, PCT, and sTREM-1 were measured in sera collected from patients and healthy controls. Sera were obtained following centrifugation at 1370 × *g* for 10 min in a Rotina 35 R Hettich centrifuge (Hettich, Tuttlingen, Germany), and then stored at −80°C until analysis.

sTREM-1 was determined using enzyme-linked immunosorbent assay (ELISA) method (IQ Products, Groningen, Netherlands). The method uses monoclonal primary and secondary antibody. The method also includes calibration in 6 points.[18]

IL-6 was determined using ELISA method (Quantikine, R and D, Minneapolis, USA). The microplate has been precoated with a monoclonal IL-6-specific antibody and the secondary antibody is polyclonal. The method of determination includes calibration in six points.[19] The manufacturer declared intra-assay precision with maximal CV of 4.2% and inter-assay precision with maximal CV of 6.4%.

PCT was determined using electrochemiluminescence immunoassay method on Cobas e411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).[20] The method uses biotinylated monoclonal PCT-specific antibody and a monoclonal PCT-specific antibody labeled with a ruthenium complex. The manufacturer declared intra-assay precision with maximum CV of 8.8% and inter-assay precision of 16.3%.

CRP was determined using an immunoturbidimetric method on AU 2700 plus analyzer (Beckman Coulter, Tokyo, Japan). The values of CRP calibrators follow the IFCC standard CRM 470.[21] Laboratory data for overall precision is 2.27%.

Statistical analysis

The Kolmogorov-Smirnov test was used to test for a normal distribution of the data. The Friedman test was used for repeated measures comparisons and Mann-Whitney test was used to test the statistical difference between sTREM-1, IL-6, PCT, and CRP of CRC patients before the surgery and healthy control group. Correlation analysis with Kendall correlation coefficient was used to test the correlation of inflammatory marker concentration in T1 with the duration of the surgery and the OCT as well as correlation between inflammatory marker concentration before surgery with TNM staging of CRC patients. A value of $P < 0.05$ was considered statistically significant. MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

Results

We compared the concentrations of CRP, IL-6, PCT, and sTREM-1 of the control group and CRC group before the surgery (in T0 monitoring time) to test the base values of tested parameters. The results of the Mann-Whitney test are presented in Table 2.

We found no statistically significant correlation between concentrations of inflammatory markers before the surgery and TNM staging of CRC patients (CRP, $P = 0.3127$; IL-6, $P = 0.5650$; sTREM-1, $P = 0.076$; PCT, $P = 0.0566$).

Changes in concentrations of tested inflammatory markers in T0, T1, T2, and T3 were tested with Friedman test and the results are shown in Table 3. *Post hoc* analysis showed statistically significant difference between all measured times (T0–T2) for CRP, IL-6, and PCT. sTREM-1 did not yield a statistical significance in any measurement point. Time-course of the changes in CRP, IL-6, PCT, and sTREM-1 concentrations is shown in Figure 1.

We also tested the correlation of concentrations of inflammatory markers with the duration of the surgery (median and range, 131 min [100–275 min]) and OCT (median and range, 12.5 min [0–70.0 min]) using correlation analysis with Kendall correlation coefficient.

We found weak positive correlation between IL-6 measured 24 h after the surgery (T1) with the duration of the surgery ($r = 0.4060$, $P < 0.0001$) and OCT ($r = 0.3640$, $P < 0.0001$), as well as a weak positive correlation between IL-6 measured 48 h after the surgery (T2) with the duration of the surgery ($r = 0.3430$, $P < 0.0001$) and OCT ($r = 0.3430$, $P < 0.0001$). We also found a weak positive correlation between CRP measured 48 h after the surgery (T2) with OCT ($r = 0.4210$, $P < 0.0001$).

The interconnectivity of CRP, IL-6, PCT, and sTREM-1 was tested with correlation test and showed a weak positive

Table 2: Comparison between CRP, IL-6, PCT, and sTREM-1 concentrations in control group and colorectal cancer group of patients

Parameter	Control group ($n = 19$)	Colorectal cancer group ($n = 20$)	*U*	*P*
CRP (mg/L)	1.60 (1.18–2.19)	2.85 (1.82–5.52)	85.50	0.0033
IL-6 (pg/ml)	1.70 (1.18–2.20)	3.75 (2.74–5.23)	45.00	<0.0001
PCT (ng/ml)	<0.020*	0.039 (0.020–1.940)	35.00	0.0001
sTREM-1 (pg/ml)	2.43 (1.58–5.01)	5.79 (0.30–16.92)	124.00	0.1016

Data are presented as median (interquartile range). *PCT concentration in the control group were all <0.020 ng/ml. In order to calculate Mann-Whitney test we used value 0.020 ng/ml. CRP: C-reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; sTREM-1: Soluble triggering receptor expressed on myeloid cells-1.

Table 3: Changes in CRP, IL-6, PCT, and sTREM-1 concentrations in four consecutive measurement time points ($n=20$)

Time	CRP (mg/ml)	IL-6 (pg/ml)	PCT (ng/ml)	sTREM (pg/ml)
T0	2.85 (1.10–78.10)	3.75 (0.90–15.80)	0.039 (0.020–1.940)	5.79 (0.30-16.92)
T1	74.10 (26.60–118.10)	70.15 (11.80–6520.10)	0.480 (0.089–4.000)	9.04 (0.56–18.32)
T2	121.85 (69.70–218.50)	36.60 (7.40–162.70)	0.440 (0.020–9.370)	8.63 (1.36–23.70)
T3	13.95 (5.00–337.20)	7.30 (0.90–3157.60)	0.130 (0.026–2.270)	8.90 (1.09–23.70)
F	96.152	65.821	14.576	2.363
P	<0.001	<0.001	<0.001	0.081

Data are presented as median (interquartile range). CRP: C-reactive protein; IL-6: Interleukin 6; PCT: Procalcitonin; sTREM-1: Soluble triggering receptor expressed on myeloid cells-1.

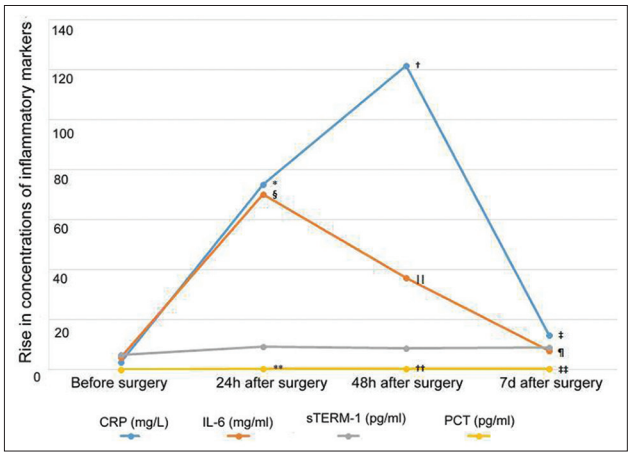

Figure 1: Time-course of the changes in CRP, IL-6, procalcitonin and soluble triggering receptor expressed on myeloid cells-1 concentrations in four consecutive measurement time points. *$P < 0.05$, CRP before surgery versus 24 h after surgery; †$P < 0.05$, CRP 24 h after surgery versus 48 h after surgery; ‡$P < 0.05$, CRP 48 h after surgery versus 7 days after surgery. §$P < 0.05$, IL-6 before surgery versus 24 h after surgery; ‖$P < 0.05$, IL-6 24 h after surgery versus 48 h after surgery; ¶$P < 0.05$, IL-6 48 h after surgery versus 7 days after surgery. **$P < 0.05$, PCT before surgery versus 24 h after surgery; ††$P < 0.05$, PCT 24 h after surgery versus 48 h after surgery; ‡‡$P < 0.05$, PCT 48 h after surgery versus 7 days after surgery. CRP: C-reactive protein; IL-6: Interleukin 6; sTREM-1: Soluble triggering receptor expressed on myeloid cells-1; PCT: Procalcitonin.

correlation between CRP and IL-6 24 h after the surgery (T1, $r = 0.3680$, $P < 0.0001$), moderate correlation 48 h after the surgery (T2, $r = 0.6770$, $P < 0.0001$), and 7 days after the surgery (T3, $r = 0.8651$, $P < 0.0001$).

Discussion

Recent publications continue to search for new and specific inflammatory markers that are most suitable for diagnosis and prognosis for specific diseases and types of surgeries.[22,23] It is well known that chronic inflammation is a key feature of many cancers including CRC.[24] We tested baseline levels of inflammatory markers and showed that all tested inflammatory markers (CRP, IL-6, and PCT) except sTREM-1 were significantly higher in the CRC group prior the surgery (T0) than that in our healthy control, although all inflammatory markers except CRP were within reference ranges before the surgery. Wider 95% confidence interval for CRP in T0 is due to one patient who had subclinical raise in CRP concentration probably because of bacterial translocation that is often present in CRC patients. Basic difference between inflammatory markers in our tested groups supports the thesis that local SIRS plays an important role in the progression of carcinoma.[24,25] Furthermore, the preliminary results also suggest that sTREM-1 is not suitable for detecting chronic inflammation considering that the difference between the tested groups was not statistically different.

The time-course analysis of this study showed an increase in CRP, IL-6, and PCT in early postoperative period after CRC surgery. CRP reaches its peak 48 h after the surgery and PCT 24 after surgery (T1) that is in accordance with literature data that confirm that PCT reaches peak levels before CRP.[2,26] PCT concentrations were in the range of low risk for sepsis and septic shock in all 4 points of measurement and in comparison to literature data, suggested that no complications were developing.[27] Considering IL-6 concentrations, the rise in T1 measuring point follows the early raise of PCT, but has the faster fall in concentrations and almost reaches preoperative concentration on day 7 (T3) that is also in compliance with literature data.[26] There is a research that suggests that a rise in postoperative IL-6 concentrations could lead to early detection of anastomotic leakage,[28] but considering that we had no complications in our studied group, we could not confirm that conclusion. Some literature sources showed a similar raise in IL-6 concentration in postoperative period in peritoneal lavage emphasizing that studies did not show any significant difference in cytokines levels between patient with and without anastomotic leakage.[28,29] Considering that current study did not include participants with that kind of complications, the results could suggest that the time-course raise and lowering of IL-6 concentrations is a consequence of surgical stress.

According to our results, every tested inflammatory marker except sTREM-1 shows a trend in a postoperative period. sTREM-1 concentrations showed no statistically significant changes in postoperative period. This might be due to not only very good inflammation suppression using optimal antimicrobial treatment[18,30] but also the fact that sTREM-1 is susceptible to many serum components such as complement that interfere and lead to big variability between results among different manufacturers.[18] Considering previously mentioned limitations of sTREM-1 detection methods, sTREM-1 ELISA test has to be improved to be suitable for

clinical application[31] to be sure that the problem does not lie in variability of the tests. In addition, some studies showed that measurement of sTREM-1 at the site of the infection (such as cerebrospinal fluid and bronchoalveolar lavage) appears to have higher clinical significance than serum or plasma measurements.[32,33]

One of the reasons for this inconsistency could lie in the previously mentioned fact that commercially available ELISA tests for sTREM-1 are very susceptible to endogenous and exogenous interferences that can be seen from variability between different kits.[18]

There are studies that define sTREM-1 as a good and reliable inflammation and sepsis marker,[16,34] but the present study is in accordance with publications that show this marker to be unreliable in detecting inflammation process in specific diseases[5,10] possibly due to previously mentioned reasons.

Considering that this study showed no raise in sTREM-1 concentrations in tested sampling times, it supports the premise that in the study SIRS was a consequence of surgical trauma. As a result of a surgical trauma, SIRS can conceal postoperative infections.[35] Results of time-course analysis showed that sTREM-1 concentrations show no significant increase in surgical stress; therefore, there is a possibility that sTREM-1 could differentiate between infectious and noninfectious SIRS. The limitations of this study are that it did not include patients who developed infectious complications and the study cohort was not compared to septic or polytrauma group of patients, so future studies with a larger cohort should answer that dilemma. In addition, it would be interesting to test the influence of TNM stages on inflammatory markers on a larger cohort with more diverse TNM stages than our study group.

To the best of our knowledge, few studies tested the effect of the duration of the surgery and the time that the colon has been opened (OCT) on inflammatory parameters. We wanted to test these parameters considering that patients endured more extensive surgical stress and were exposed to intestinal microflora if the surgery lasted longer and the procedure included longer OCT. The results showed weak positive correlation for IL-6 and CRP with the duration of the surgery and OCT at the first 2 days after the surgery suggesting that the increase of those two markers reflects more extensive surgical stress. Considering we only found a weak correlation, further studies considering the impact of the duration of the surgery as well as OCT could test this on a larger cohort. Weak and moderate correlations also revealed interconnectivity of CRP and IL-6 that follow the similar postoperative kinetics that is also visible from time-course analysis. PCT and sTREM-1 did not show correlation with any tested inflammatory markers. These results suggest that there might be meaningless in following both CRP and IL-6 concentrations in postoperative follow-up of patients who underwent CRC surgery so the decision to follow one of these markers should be made based on method verification data, standardization, automatization, time of analysis, and cost.

In conclusion, results of this study showed that acute phase proteins such as CRP, IL-6, and PCT might be reliable tools for monitoring postoperative period in CRC surgery. The results also suggested that simultaneous determination of CRP and IL-6 might not be necessary, and sTREM-1 might not be useful in postoperative follow-up of CRC patients.

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Conflicts of interest

There are no conflicts of interest.

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