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Presepsin (soluble CD14 subtype) as a risk factor for the development of infectious and inflammatory complications in operated colorectal cancer patients

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Purpose: In this pilot study the dynamic of presepsin (soluble CD14 subtype, sCD14-ST) in blood serum was assessed as a possible risk factor for the development of systemic inflammatory response syndrome (SIRS) and infectious and inflammatory complications in operated colorectal cancer patients.
Methods: To determine sCD14-ST by enzyme-linked immunosorbent assay method venous blood was taken 1 hour before surgery and 72 hours after it (3rd day). The presence of SIRS and organ dysfunctions (ODs) according to the Sequential Organ Failure Assessment scale were assessed.
Results: Thiry-six patients with colorectal cancer were enrolled in the study. sCD14-ST level before surgery was 269.8±103.1 pg/mL (interquartile range [IQR], 196.7–327.1 pg/mL). Despite the presepsin level on the 3rd day being higher (291.1±136.5 pg/mL; IQR, 181.2–395.5 pg/mL), there was no statistical significance in its dynamics (P=0.437). sCD14-ST value both before surgery and on the 3rd day after it was significantly higher in patients with bowel obstruction (P=0.038 and P=0.007). sCD14-ST level before surgery above 330 pg/mL showed an increase in the probability of complications, SIRS, and OD (odds ratio [OR], 5.5; 95% confidence interval [CI], 1.1–28.2; OR, 7.0; 95% CI, 1.3–36.7; and OR, 13.0; 95% CI, 1.1–147.8; respectively). Patients with OD had higher levels on the 3rd day after surgery (P=0.049).
Conclusion: sCD14-ST level in operated colorectal cancer patients was much higher if they were admitted with complication like bowel obstruction. Higher preoperative levels of sCD14-ST increase the probability of postoperative complications, SIRS, and OD. Therefore, further studies with large sample size are needed.

Keywords: *sCD14-ST; Colorectal neoplasms; Intestinal obstruction; Systemic inflammatory response syndrome; Complications*

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant disease [1, 2]. According to the World Society of Emergency Surgery, about 1.4 million new cases of CRC have been registered annually in the world; while the number of patients with advanced CRC (stage III–IV) reaches 60% to 70% [2]. In the structure of causes of death from cancer, CRC takes 4th place in the world [1, 3]. Today, more than 66% of patients with CRC are admitted urgently to the hospital due to complications [4]. The most common complication is acute bowel obstruction (ABO), which accounts for 80% to 85% of emergency surgical admissions for this oncopathology [5, 6]. Despite the increase in the efficiency of diagnosis and treatment of ABO over the years, today there are high rates of postoperative complications (46%–50% of cases) and mortality (up to 32% of cases) [7, 8].

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In the pathogenesis of infectious and inflammatory complications and sepsis in acute malignant bowel obstruction, one of the main roles is played by the phenomenon of bacterial translocation (BT), when intestinal bacteria penetrate through the intestinal mucosa into the systemic circulation and then into usually sterile tissues and internal organs [9]. Therefore, for the early diagnosis of such complications, as well as the detection of BT in the blood serum, appropriate markers are determined. Today, one of the reliable BT biomarkers is the soluble CD14 subtype (sCD14-ST; presepsin).

CD14 receptors are present in the body in 2 states; macrophages and monocytes membrane bound (mCD14) and soluble (sCD14) circulating in the systemic circulation [10]. mCD-14 is a membrane glycoprotein that binds to various components of gram-positive and gram-negative bacteria via toll-like receptors (TLR) [11]. The TLR family includes transmembrane receptors with a leucine-rich extracellular domain that interacts with microbial products, defining "pathogen-associated molecular patterns (PAMPs)". Each TLR detects specific PAMPs: for lipopolysaccharide–TLR-4, for bacterial lipoprotein and peptidoglycan–TLR-2, for unmethylated DNA–TLR-9, for double-stranded RNA–TLR-3, and for single-stranded RNA–TLR-7 and -8. Therefore, mCD-14 binds through TLRs to PAMPs and triggers proinflammatory pathways, resulting in the production of cytokines (tumor necrosis factor, interleukin [IL]-1, IL-6, and IL-8) [12], phagocytosis of bacterial pathogens. Then mCD14 undergoes proteolysis by cathepsin D with the formation of sCD14-ST, which is determined in the systemic circulation [13]. An increase in the level of sCD14-ST in the blood can be registered within 1.5 to 2 hours after the onset of infection [14, 15].

As is known, with CRC, disorders of the immune system and imbalance of normal intestinal microbiota occur, as well as a violation of the intestinal barrier, which occurs at the site of the tumor growth, because the tumor causes dysplasia of the epithelium. In the case of ABO, microcirculation disorders occur in the area of obstruction, and subsequent ischemia and hypoxia of the intestinal wall. Increased BT in patients with CRC, especially complicated by ABO, may lead to postoperative infectious and inflammatory complications. Therefore, this pilot study sought to analyze the course of sCD14-ST in blood serum and to assess its possible risk factor for the development of systemic inflammatory response syndrome (SIRS) and infectious and inflammatory complications in operated CRC patients.

METHODS

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Bioethics Committee of the NJSC "Karaganda Medical University" (assigned No. 30). Informed consent was obtained from all individual participants included in the study.

Patient characteristics

Thirty-six patients with CRC were included in this study. Fifteen patients were male and 21 were female. The age ranged from 38 to 89 years with the median age of 65.1 ± 12.2 years (interquartile range [IQR], 60–73 years). All characteristics of patients are shown in Table 1. In addition to patients with CRC, the study included patients admitted to the hospital with ABO as a complication of CRC. The diagnosis of ABO was based on clinical data (abdominal pain, stool, and gas retention), as well as based on an X-ray examination of the abdominal organs (the presence of arches and Kloiber's cups). The study group included only patients who underwent open surgery (laparotomy). Pregnant women, patients under the age of 18 years, with human immunodeficiency virus infection, liver cirrhosis, and benign ABO were excluded. The clinical diagnosis was made after surgery and on the basis of histological results.

All patients underwent clinical, instrumental, and laboratory research methods in hospitals in accordance with clinical protocol No. 60 of the Ministry of Health of the Republic of Kazakhstan "Acute bowel obstruction". Laboratory tests included a complete blood count (including levels of leukocytes, platelets, and erythrocyte sedimentation rate), a biochemical blood test (including levels of urea, creatinine, and total bilirubin), which were used to assess the presence of SIRS and organ dysfunctions on the Sequential Organ Failure Assessment (SOFA) scale. Since C-reactive protein (CRP) is not included in the standard analysis of the treatment protocol, it was measured only in 4 patients with organ dysfunctions in the intensive care unit (ICU).

To determine sCD14-ST, venous blood was taken 1 hour before surgery and 72 hours after it (3rd day). To evaluate the association of sCD14-ST plasma levels with the presence of ABO, SIRS and organ dysfunctions, all available samples were stratified by the presence or absence of ABO, SIRS or no-SIRS, and by the presence or absence of organ dysfunctions by SOFA scale. The severity of postoperative complications was assessed by the Clavien-Dindo classification. Grade II complications were in 1 patient, grade IIIb in 5 patients, grade IVb in 1 patient, and grade V in 2 patients.

Methods of collection, transportation, and storage of venous blood and enzyme-linked immunosorbent assay diagnostics of the sCD14-ST

Venous blood sampling was taken 1 hour before surgery and on the 3rd day after it. Venous blood was collected in 5 mL vacutainers with a coagulation activator and a serum gel separator. Vacutainers with blood were placed in a rack in a refrigerator (4°C–8°C) until transportation. Transportation was carried out strictly vertically in a thermos with ice at a temperature of 2°C to 8°C. The delivered samples were centrifuged for 20 minutes at 1,000 ×*g*, after which the gel completely separated the serum from the

Table 1. Baseline characteristics of the study cohort

Characteristic	Data
No. of patients	36
Age (yr)	65.1 ± 12.2 (60–73)
Sex	
Male	15 (41.7)
Female	21 (58.3)
Tumor localization	
Rectum	6 (16.7)
Rectosigmoid junction	3 (8.3)
Sigmoid colon	15 (41.7)
Colon	9 (25.0)
Cecum	3 (8.3)
Cancer staging	
I	5 (13.9)
II	16 (44.4)
III	8 (22.2)
IV	7 (19.4)
With bowel obstruction on admission	
Presence	14 (38.9)
Absence	22 (61.1)
Complication	
Presence	9 (25.0)
Absence	27 (75.0)
Wound suppuration	1
Anastomotic leak	5
Abdominal abscess	4
Peritonitis	4
Sepsis	3
SIRS	
Presence	12 (33.3)
Absence	24 (66.7)
SOFA score	
0	32 (88.9)
1–6	1 (2.8)
7–9	3 (8.3)
≥10	0 (0)

Values are presented as number only, mean ± standard deviation (interquartile range), or number (%).
SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment scale.

clot, forming a tight barrier. The obtained sample of freshly prepared serum was stored at –20°C to –80°C for up to 2 months, to avoid loss of biological activity and contamination. Repeated freeze/thaw cycles were not allowed.

Commercial enzyme-linked immunosorbent assay (ELISA) kit for presepsin (sCD14-ST, human) from Cloud-Clone Corp. (Katy, TX, USA) was used to determine sCD14-ST. The analysis was performed according to the manufacturer's instructions on an ELISA robotic system Evolis from BioRad (Hercules, CA, USA). The microplate provided in this kit was precoated with biotinylated antibodies specific for sCD14-ST. Standards and patient serum samples were added to each well of the microplate and incubated at 37°C for 1 hour. Then avidin conjugated with horseradish peroxidase was added to each well and incubated at 37°C. After the addition of the tetramethylbenzidine substrate solution, only those wells containing sCD14-ST changed color, these changes were measured spectrophotometrically at a wavelength of 450 ± 10 nm. The level of sCD14-ST in the samples was then determined by comparing the absorbance of the samples with a standard calibration sample.

Statistical analysis

STATISTICA ver. 8.0. (StatSoft Inc., Tulsa, OK, USA) was used for statistical analysis. Data are presented as mean, standard deviation, and IQR. Wilcoxon nonparametric test was used to compare the marker values before and on the 3rd day after surgery. Comparison between the 2 independent groups was performed using the Mann-Whitney U-test. In this case, $\alpha = 0.05$, $1 - \beta = 80\%$. The results were considered statistically significant at $P < 0.05$.

RESULTS

Measurement of the sCD14-ST level in dynamics

The presepsin values were measured 1 hour before the operation and on the 3rd day after it. The sCD14-ST level before surgery was 269.8 ± 103.1 pg/mL (IQR, 196.7–327.1 pg/mL); despite presepsin level on the 3rd day being higher (291.1 ± 136.5 pg/mL; IQR, 181.2–395.5 pg/mL), there was no statistically significance in its dynamics ($P = 0.437$).

Association sCD14-ST with the presence or absence of acute bowel obstruction

In patients with ABO, the mean presepsin value before surgery was 322.9 ± 123.9 pg/mL (IQR, 194.4–393.3 pg/mL); on the 3rd day, it was 373.4 ± 151.7 pg/mL (IQR, 229.8–499.4 pg/mL). In patients without ABO, sCD14-ST level before surgery was 236.0 ± 71.6 pg/mL (IQR, 198.9–265.2 pg/mL); on the 3rd day, it was 238.6 ± 97.0 pg/mL (IQR, 167.9–269.6 pg/mL). Differentiation of patients with or without ABO showed that the presepsin level was much higher in patients with ABO both before and on the 3rd day after surgery ($P = 0.038$ and $P = 0.007$).

Association sCD14-ST with the development of postoperative complications

In patients with postoperative complications, sCD14-ST level before surgery was 286.4 ± 121.1 pg/mL (IQR, 198.9–375.6 pg/mL);

on the 3rd day, it was 324.8 ± 159.8 pg/mL (IQR, 225.4–371.2 pg/mL). In patients without complications, presepsin value before surgery was 263.5 ± 97.1 pg/mL (IQR, 194.4–296.1 pg/mL); on the 3rd day, it was 278.1 ± 127.5 pg/mL (IQR, 176.8–419.8 pg/mL). It was found that sCD14-ST level before surgery above 330 pg/mL increases the probability of complications in patients with CRC (odds ratio [OR], 5.5; 95% confidence interval [CI], 1.1–28.2) (Table 2, Fig. 1).

Association sCD14-ST with the clinical presence of systemic inflammatory response syndrome

In SIRS group, the presepsin value before surgery was 282.5 ± 115.3 pg/mL (IQR, 190.1–360.1 pg/mL); on the 3rd day, it was 335.9 ± 147.7 pg/mL (IQR, 227.6–399.9 pg/mL). In no-SIRS group, before surgery was 263.5 ± 98.3 pg/mL (IQR, 198.9–287.3 pg/mL) and on the 3rd day was 268.7 ± 127.9 pg/mL (IQR, 170.2–380.1 pg/mL). It was also found that sCD14-ST level before surgery more than 330 pg/mL increases the probability of SIRS (OR 7.0, 95% CI: 1.3–36.7; Table 2, Fig. 2).

Table 2. Distribution of patients depending on sCD14-ST level before surgery and the presence of SIRS and complications

Variable	sCD14-ST level	
	≥ 330 pg/mL	< 330 pg/mL
SIRS		
Presence	6	6
Absence	3	21
Complication		
Presence	5	5
Absence	4	22

Values are presented as no. of patients.
sCD14-ST, soluble CD14-ST; SIRS, systemic inflammatory response syndrome.

Association sCD14-ST with the Sequential Organ Failure Assessment scores and organ dysfunctions

Differentiation of patients with or without organ dysfunctions depending on the SOFA score showed statistical difference in presepsin level on the 3rd day after surgery (P = 0.049). In patients without organ dysfunction (SOFA score, 0), presepsin value was 260.6 ± 100.3 pg/mL (IQR, 194.4–298.3 pg/mL) before surgery and 271.5 ± 118.5 pg/mL (IQR, 176.8–360.1 pg/mL) on the 3rd day from it. In patients with organ dysfunctions, 343.6 ± 108.7 pg/mL (IQR, 269.6–417.6 pg/mL) and 447.5 ± 189.1 pg/mL (IQR, 298.3–596.6 pg/mL), respectively.

DISCUSSION

This study was aimed at analyzing the dynamics of sCD14-ST level as a biomarker of BT and a possible risk factor for the development of SIRS and infectious and inflammatory complications in patients with CRC. Despite modern methods of diagnosis and treatment, this group of patients in the postoperative period remains at high risk of complications and organ dysfunctions. In this study, infectious and inflammatory complications, including sepsis, occurred in 9 patients (25.0%), and organ dysfunctions occurred in 4 patients (11.1%), which is quite a high rate.

In CRC patients, the permeability of the intestinal mucosa increases, which can be explained by the disruption of the bowel architecture by malignant tissue. In case of malignant bowel obstruction, this is all aggravated by intestinal hypoperfusion, in which a large number of proinflammatory mediators are produced. A cascade of immune reactions is activated: activation of

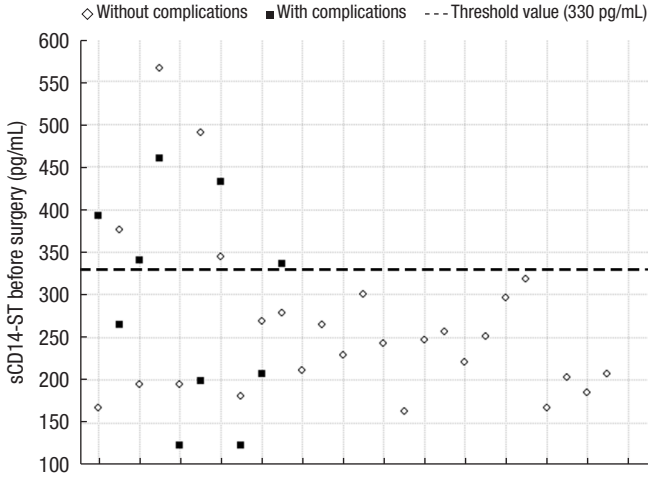

Fig. 1. Soluble CD14-ST (sCD14-ST) levels before surgery in patients with and without postoperative infectious and inflammatory complications.

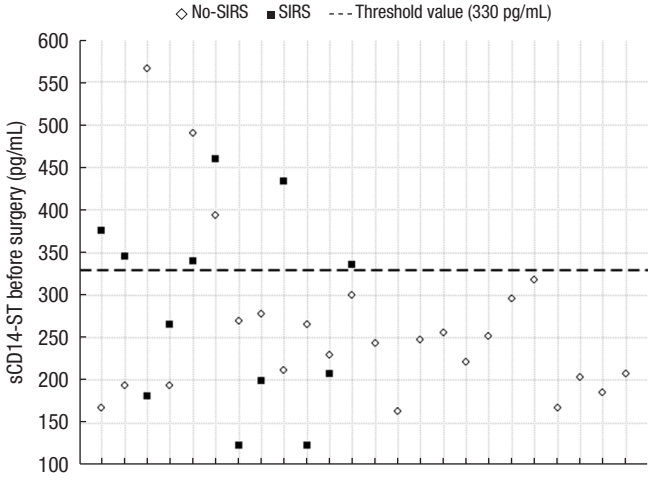

Fig. 2. Soluble CD14-ST (sCD14-ST) levels before surgery in systemic inflammatory response syndrome (SIRS) and no-SIRS groups.

the complement system, chemotaxis, migration of neutrophils, macrophages, lymphocytes to the intestinal ischemia areas. These reactions contribute to the aggravation of microcirculation disorders and increase intestinal mucosa ischemia and hypoxia. Hypoperfusion, ischemia, and subsequent reperfusion of damaged intestine areas enhance the inflammatory response and lead to oxidative stress. The death of enterocytes, disruption of intercellular tight junctions, increased intestinal wall permeability and disruption of the intestinal barrier function occurs. Bacteria or their endotoxins penetrate the damaged mucous barrier, where they are recognized by innate immune cells (macrophages, dendritic cells), fibroblasts, and epithelial cells. This all enhances the immune response, which becomes systemic and can lead to sepsis and even death [16]. Giunco et al. [17] in their work investigated sCD14-ST as a marker of BT in elderly patients with CRC. They discovered that high levels of sCD14-ST correlated with a higher percentage of CD8 activated cells in patients who had disease relapse or progression. The authors attributed the damage of the gut mucosa with the release of microbial products that trigger immune activation and proinflammatory responses that negatively affected disease outcome.

Several studies have shown that there are significant differences in sCD14-ST levels in patients with SIRS and sepsis. Vodnik et al. [18] determined that presepsin level in patients with SIRS and abdominal sepsis was significantly different. In patients with SIRS, the mean sCD14-ST value was 430.0 ± 141 pg/mL (range, 170–689 pg/mL), in the sepsis group these values were 1,508.3 ± 866 pg/mL (range, 639–4,223 pg/mL) ($P < 0.0001$). Juroš et al. [19] found that sCD14-ST has the highest diagnostic accuracy in abdominal sepsis. The mean sCD14-ST value in the group without sepsis was 525.5 pg/mL (IQR, 269.8–696.0 pg/mL) and with sepsis 1,121.5 pg/mL (IQR, 462.5–2,265.0 pg/mL) ($P < 0.0001$). In addition, Zhang et al. [20] identified sCD14-ST as an effective biomarker of sepsis in meta-analysis. Among the 11 included studies, the sCD14-ST threshold ranged from 317 to 729 pg/mL, the sensitivity was 0.70 to 1.00, and the specificity was from 0.62 to 0.93. Again in a study by Carpio et al. [21], sCD14-ST has been shown to be an accurate diagnostic marker for differentiating between SIRS and sepsis, and as a predictor of outcome and risk of death. In this study, the median and CI of presepsin levels on the 3rd day in intensive care patients with SIRS and sepsis, including abdominal sepsis, were 244 pg/mL (range, 158–830 pg/mL) and 472 pg/mL (range, 391–596 pg/mL), respectively.

Compared to the values observed in previous studies, this study showed that preoperative sCD14-ST level in operated CRC patients was 269.8 ± 103.1 pg/mL (IQR, 196.7-327.1 pg/mL); despite the presepsin level on the 3rd day being higher (291.1 ± 136.5 pg/mL; IQR, 181.2–395.5 pg/mL), there was no statistical significance in its dynamics ($P = 0.437$). Previously, in patients with CRC, sCD14-ST was not studied in dynamics, depending on the presence of ABO upon admission or the occurrence of infectious and inflammatory complications. This study revealed that in patients with CRC admitted with ABO, the level of sCD14-ST both before surgery and on the 3rd day after it was significantly higher in the group with ABO ($P = 0.038$ and $P = 0.007$). It can be assumed that the presence of ABO aggravates the disturbances in gut permeability and causes the penetration of bacteria and their endotoxins into the systemic circulation, causing SIRS.

sCD14-ST level before surgery more than 330 pg/mL showed an increase in the probability of developing postoperative infectious and inflammatory complications in CRC (OR, 5.5; 95% CI, 1.1–28.2). Moreover, the most frequent postoperative complication was anastomotic leakage (5 patients, 13.9%). Four patients had a combination of several complications. And only sepsis occurred in 8.3% of cases (3 patients). The sCD14-ST value before surgery in patients with complications ranged from 123.7 to 459.6 pg/mL, and on the 3rd day from 167.9 to 658.5 pg/mL, which was the highest level in the total patients' cohort.

It was found that presepsin level before surgery above 330 pg/mL increases the probability of SIRS (OR, 7.0; 95% CI, 1.3–36.7). Accordingly, it can be assumed that an increase in sCD14-ST, as a marker of BT, indicates an increase in the immune response and SIRS, which occur in response to an increase in the systemic circulation of bacteria or their endotoxins.

Moreover, sCD14-ST levels on the 3rd day after surgery significantly differed depending on the organ dysfunctions, according to the SOFA scale ($P = 0.049$). Patients with higher levels of sCD14-ST had organ dysfunctions, most often acute renal failure and acute cardiovascular failure. Of the 4 patients with SOFA scores of more than 1 point, 3 had sepsis (7–9 points); their presepsin levels on the 3rd day ranged were 225.4 and 658.5 pg/mL. In 1 patient with less organ dysfunctions (1–6 points), septic complications did not occur; the presepsin level on the 3rd day was 534.7 pg/mL.

Today, CRP is also considered one of the markers of the systemic inflammatory response. Shibutani et al. [22] in their study mentioned that preoperative serum CRP level is a convenient biomarker and predictor of poor prognosis after surgery for CRC [22]. In our study, it was not possible to assess the prognostic significance of CRP, since it was measured only in patients with organ dysfunctions in ICU (4 patients). From routine analyzes, the researchers also noted that high erythrocyte sedimentation rate (ESR) levels are a risk of postoperative complications. Lee et al. [23] in their study analyzed ESR as a factor affecting postoperative morbidity, overall survival, and oncologic outcomes in patients with CRC. They reported that ESR of > 27 mm/hr ($P = 0.014$) was an independent risk predictor for morbidity and higher risk of postoperative complications. In our study, the mean ESR value before surgery was 24 mm/hr (increased value was in 52% of patients), on the third day after surgery 36 mm/hr (increased value was in 89% of patients). However, there was no statistical difference in ESR in dynamics, as well as depending on the presence of SIRS and complications.

This is the pilot study and so it has some limitations. With the participation of only 36 patients, the statistical power of the study

is limited, but nevertheless, as far as we know, this is the first study that assesses the dynamics of sCD14-ST levels in operated CRC patients, depending on the presence of ABO upon admission and the occurrence of postoperative infection and inflammatory complications. Further studies with more patients are needed to clarify the usefulness of sCD14-ST in this context.

This study demonstrated that sCD14-ST level in operated CRC patients was much higher if they were admitted with complication like ABO. Higher preoperative levels of sCD14-ST increase the probability of postoperative complications, SIRS, and organ dysfunction. Therefore, further studies with a large sample size are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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