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Effects of perioperative immunostimulating nutritional therapy on the phagocytic activity of blood platelets in patients with various clinical stages of gastric cancer

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ABSTRACT

Purpose: The aim of this study was to evaluate the total blood platelets count, fraction of phagocytizing thrombocytes (PhT%), and phagocytic index of thrombocytes (PhIT) in gastric cancer considering the stage of the disease, and perioperative immunonutrition support.

Methods: Our study included 44 patients operated for gastric cancer divided into 2 groups depending on the clinical stage, and 40 healthy volunteers –a control group. Group I included 18 patients with stage I-III locoregional malignancies and Group II included 26 patients with stage IV peritoneal dissemination. All patients received immunonutrition during the perioperative period. The phagocytic activity of blood platelets was assessed by measuring PhT% and PhIT prior to and after nutritional therapy.

Results: In Group I, the pre-treatment PhT% and PhIT amounted to 1.08 and 0.99, respectively, and 1.26, and 1.1 after the therapy ($p<0.01$). In Group II, pre-treatment PhT% and PhIT were 1.12 and 0.97, after 1.18 and 1.06, respectively ($p<0.05$). In the controls, PhT% and PhIT were 2.26 and 1.83, respectively, significantly higher comparing to gastric cancer patients ($p<0.01$).

Conclusion: Severe impairment of the thrombocyte phagocytic activity in gastric cancer patients has been found. Phagocytic activity of blood platelets was partially improved as a result of perioperative immunonutrition both in locoregional disease and in peritoneal dissemination.

Key words: : Gastric cancer, blood platelets, immunonutrition, phagocytosis, gastrectomy

INTRODUCTION

Gastric cancer still constitutes a significant clinical problem. Satisfactory, long-term, therapeutic outcomes can be obtained only in early stages of this malignancy. Treatment results for those that are highly-advanced are undeniably non-satisfactory. Approximately 800,000 gastric cancer-related deaths are reported worldwide every year, which places this malignancy in the second position amongst the most frequent reasons for cancer-related mortality [1]. Furthermore, surgical treatment of advanced gastric cancer is associated with high morbidity rates. These unfavorable outcomes are reflected by continuous search for new treatment modalities that could improve the therapeutic outcomes. One such method is the administration of immunostimulating nutritional therapy during perioperative period.

Blood platelets, discovered by Italian histologist Giulio Bizzozero in 1880, play a vital role in hemostasis. These nonnuclear blood cells have the potential for chemotaxis and diapedesis. Due to these characteristics, they can interact with viruses, bacteria and parasites [2]. Furthermore, blood platelets are able to phagocytize viruses, bacteria, antigen-antibody complexes, collagen, and latex particles. This phagocytic potential of thrombocytes was reported by Mustard et al. [3] as early as in 1968. Further studies have revealed that bacteria can be phagocytized, both, by platelet aggregates and by single platelets [4,5]. Upon activation, the thrombocyte changes its shape from discoid to irregular with numerous projections. This morphological change is accompanied by intensification of energetic processes and enhanced protein anabolism inside the activated platelet [6]. The centralization of cellular organelles is also observed along with vacuolization and degranulation. Platelet granules contain peroxidase, acid phosphatase, cationic proteins, and proteolytic enzymes. All of these compounds have strong bactericidal properties [6,7,8]. Additionally, specific receptors are expressed on the surface of blood platelets that are capable of binding and neutralizing bacterial endotoxins. These endotoxins are potent inducers of platelet aggregation [9]. As a result, disseminated intravascular coagulation associated with intravascular formation of thrombocyte aggregates, and thrombocytopenia are reported frequently in the course of bacteremia or endotoxemia [10]. Blood platelets do not form typical phagosomes connected to an external environment via a system of canaliculi. Their phagocytic effect results from the synergistic activity of two peptide compounds: platelet factor 4 (PF4) and connective tissue-activating peptide III (CTAP III). In experimental model, platelets phagocytized 3.5% of inoculated bacteria, and 60% of those bacteria were killed and digested inside the platelets. The process of thrombocyte-mediated phagocytosis was revealed to be fivefold faster as compared to phagocytic activity of granulocytes [11]. Regarding parasitic infections, blood platelets play an important role in destroying parasites. Stimulated thrombocytes reveal cytotoxic activity through release of various inflammatory mediators. They also show phagocytic activity and cooperation with other cell of host immune system. Platelets may have an important role in the pathology of malaria, toxoplasmosis, schistosome infection, echinococcosis, or other parasitic diseases [12].

There are no studies examining the phagocytic activity of platelets in gastric cancer patients. Furthermore, the potential effects of immunostimulating nutritional treatment on the phagocytic activity of blood platelets in this group of patients during the perioperative period are not understood. Consequently, the aim of this study was to determine the phagocytic activity of blood platelets in relation to clinical stage of gastric cancer. Furthermore, we analyzed the effects of perioperative immunostimulating nutritional therapy on the phagocytic efficiency of thrombocytes as a function of the clinical stage of cancer.

MATERIAL AND METHODS

Qualification of patients

This study included 44 resectable gastric cancer patients (10 women and 34 men, 31 to 84 years of age, mean age 65.9 years). The distribution of gastric cancer clinical stages was as follows: stage I – 4 patients (9.1 %), stage II – 3 patients (6.8%), stage IIIA – 4 patients (9.1%), stage IIIB – 7 patients (15.9%), and stage IV – 26 patients (59.1%). A control group comprised of 40 healthy volunteers. This distribution of clinical stages is presented in *Fig. 1*.

Group I included 18 patients with stage I-III gastric cancers, among them 5 women and 13 men aged from 37 to 84 years of age, mean age 66.7 years. Sixteen complete gastric resections (88.9%) and 2 partial resections of the stomach (11%) were performed in this group; these were all R0 resections. Twenty-six patients with stage IV gastric cancer were enrolled to Group II, among them 5 women and 21 men with age ranging from 31 and 82 years (mean 65 years). Complete gastric resection was performed in 23 (88.5%) subjects, while 3 patients (11.5%) underwent partial resection of the stomach. Procedures performed in this group corresponded to R2 resections, i.e. with macroscopic tumor deposits left in the surgical field.

Exclusion criteria included thrombocytopenia, severe cachexia, and non-resectable gastric malignancy. Clinical stages of gastric malignancies were graded according to the general criteria of TNM classification, approved by the International Union Against Cancer (UICC). Based on the clinical stage of cancer, the patients were qualified into one of two groups. Group I comprised of patients with stage I-III gastric cancer, while Group II included those with stage IV of malignancy.

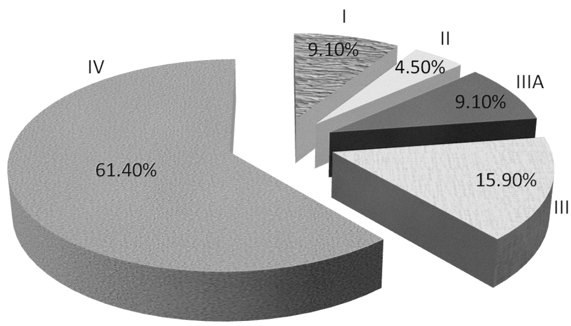
Surgical procedure

Most patients were subjected to complete *en bloc* resection of the stomach, greater omentum and spleen, and D2-D3 resection of the regional lymph nodes. The Flocare naso-intestinal tube for enteral feeding was inserted intraoperatively.

Postoperative feeding

Early postoperative enteral nutrition was started 20 hours post-surgery. Basic commercially available diet was used in the feeding. Its flow rate was began at 8 ml/h and was increased gradually to 100 ml/h. The enteral nutrition was continued for 7 days. During the initial 5 days post-surgery, the patients received additional supplemented parenteral nutrition with the “all-in-one” bags (contents the same as preoperatively). With increasing flow rates of enteral feeding, the volume of intravenous hydration was reduced, but its energetic value and protein content was maintained. Oral nutrition was reinstituted 5 days after surgery, following the assessment of surgical anastomoses for potential leakage.

Figure 1. **The distribution of clinical stages of gastric cancer.**



Nutritional status and biochemical analysis

Nutritional status of all patients was determined preoperatively, and their body mass indices and weight loss percentages were calculated. Additionally, laboratory parameters, such as thrombocyte count, cholesterol and triglyceride concentrations, serum concentrations of total protein and albumins, and total number of lymphocytes were determined. Thrombocyte count and total number of lymphocytes were determined using Advia 120 hematological analyzer.

Phagocytic activity of blood platelets

Platelet count and their phagocytic activity were determined twice: on hospital admission and after completing the nutritional therapy.

Phagocytic activity of blood platelets was determined against *Staphylococcus aureus* ATCC 6538P bacterial strain, according to Mantur's et al. method [13]. The bacterial suspension was incubated with previously prepared platelet-rich plasma. Subsequently, the smears were prepared and stained by the Pappenheim method. Microscopic slides were analyzed by light microscopy under 1400-fold magnification. The number of phagocytizing platelets and the phagocytic index (PhIT) were determined as measures of the phagocytic activity of thrombocytes. The fraction of phagocytizing platelets corresponded to the percentage of phagocytizing thrombocytes (PhT%), per 1000 consecutive cells, counted in the specimen. The PhIT was calculated as a mean number of phagocytized bacteria per one out of 100 phagocytic platelets. This index expresses the ratio of phagocytized bacteria to the count of phagocytic platelets.

Nutritional therapy

During preparation for surgery, aside from the hospital oral diet, the patients received parenteral nutrition through the central access. A complete nutritional mixture with total energetic load corresponding to 910 kcal/day was administered for 5 to 7 days prior to the surgery. Commercially available, "all-in-one" bags contained 100 g of glucose, 8 g of nitrogen from standard amino acids, 100 ml of 20% olive oil-based fat emulsion, electrolytes, trace elements and a complete set of vitamins with additional 100 mg of thiamin. Additionally, the bag content was supplemented with glutamine (100 ml of Dipeptiven) and 100 ml of Omegaven fish oil-based fat emulsion. Such solution contained 10 g of ω-3 fatty acids.

Statistical analysis

A given data set has a mean and a standard deviation. The results were subjected to statistical analysis with the Mann-Whitney test, and the statistical significance was defined at $p<0.05$.

RESULTS

Nutritional status of patients from Group I.

In patients from Group I, the mean body mass index (BMI) was 24.7 ± 3.09 kg/m^2. The mean body weight loss was 5.6 ± 5.56%. In this group, the mean total protein was 59.2 ± 7.95 g/l. In 13 patients (72.2%) hypoproteinemia was observed. The mean albumin concentration was 3.29 ± 0.89 g/dl (1.86 g/l – 4.31 g/dl).In 8 patients (44.4%) hypoalbuminemia was observed. The mean cholesterol level was 163.1 ± 33.1 mg/dl. The mean triglyceride concentration in serum was 98.9 ± 38.3 mg/dl. The average number of lymphocytes in peripheral blood was 1,809.0 ± 613.6 cells/μl. Decreased in lymphocytes number below 1,200.0 cells/μl in 3 patients (16.7%) was observed.

Nutritional status of patients from Group II.

In patients from Group II, the mean BMI was 22.7 ± 3.67 kg/m^2. BMI lower than 18.5 kg/m^2 in 5 patients (11.4%) was detected. The mean body weight loss was 15.1 ± 8.35 %.The mean total protein was 60.3 ± 5.65 g/l. In 12 patients (46.1%) hypoproteinemia was observed. The mean albumin concentration was 3.32 ± 0.59 g/dl. In 14 patients (53.8%) hypoalbuminemia was observed. The mean cholesterol level was 150.6 ± 36.4 mg/dl. The mean triglyceride concentration in serum was 83.9 ± 37.9 mg/dl. The average number of lymphocytes in peripheral blood was 1,636.0 $\pm$ 635.8 cells/ul. Decreased in lymphocytes number below 1,200.0 cells/ul in 8 patients (30.%) was observed.

Preoperatively, only the percentage of body weight loss was significantly higher in patients from Group II ($p<0.05$) (*Tab. 1*). Statistical analysis of laboratory data did not show any difference in preoperative nutritional status of patients between Group I and Group II.

Preoperative blood platelets count and their phagocytic activity in patients from Group I vs. Control.

Phagocytic activity of human blood platelets examined by electron microscopy is presented in *Fig. 2*.

In patients from Group I, the average number of platelets was 232,588 ± 69,464.1/μl. Before the immunonutrition, no significant differences in the number of platelets in patients

Table 1. **Body mass index, percentage of body weight loss and biochemical data of patients with gastric cancer in stage I-III (Group I) and stage IV (Group II).**

	Group I	Group II	Statistical significance of difference (p)
BMI (kg/m^2)	24.7 ± 3.09	22.7 ± 3.67	NS
Body weight loss (%)	5.6 ± 5.56	15.1 ± 8.35	<0.05
Total protein (g/l)	59.2 ± 7.95	60.3 ± 5.65	NS
Albumin (g/dl)	3.29 ± 0.89	3.32 ± 0.59	NS
Cholesterol (mg/dl)	163.1 ± 33.1	150.6 ± 36.4	NS
Triglyceride (mg/dl)	98.9 ± 38.3	83.9 ± 37.9	NS
Total lymphocyte count (cells//ml)	1809.0 ± 613.6	1636.0 ± 635.8	NS

Table 2. **Number of blood platelets, percentage of phagocyting platelets (PhT%) and phagocytic index (PhIT) in patients from Group I before the immunonutrition (GI1) and after (GI2) and in normal donors (Control).**

	Group I 1 n = 18	Group I 2 n = 18	Control n = 40	Statistical significance of difference (p)		
				GI1/GI2	GI1/Control	GI2/Control
Blood platelets (/ml)	232,588.0 ± 69,464.0	798,923.0 ± 280,536.0	229,150.0 ± 52,505.0	<0.01	NS	<0.01
PhT%	1.08 ± 0.07	1.26 ± 0.08	2.26 ± 0.576	<0.01	<0.01	<0.01
PhIT	0.99 ± 0.1	1.1 ± 0.08	1.83 ± 0.37	<0.01	<0.01	<0.01

Table 3. **Number of blood platelets, percentage of phagocyting platelets (PhT%) and phagocytic index (PhIT) in patients from Group II before immunonutrition (GII1) and after (GII2) and in normal donors (Control).**

	Group II 1 n = 26	Group II 2 n = 26	Control n = 40	Statistical significance of difference (p)		
				GII1/GII2	GII1/Control	GII2/Control
Blood platelets (/ml)	283,250.0 ± 93,803.0	522,563.0 ± 233,595.0	229,150.0 ± 52,505.0	<0.01	<0.05	<0.01
PhT%	1.123 ± 0.01	1.176 ± 0.18	2.259 ± 0.57	<0.05	<0.01	<0.01
PhIT	0.973 ± 0.1	1.065 ± 0.11	1.83 ± 0.37	<0.01	<0.01	<0.01

with gastric cancer (Group I) and normal donors were observed. In control group, the average number of platelets was 229,150 ± 52,505.7/µl (*Tab. 2).*

Before the immunonutrition, the average percentage of PhT% was 1.08 ± 0.07%. It was significantly lower comparing to the normal donors 2.26 ± 0.32%, p<0.01 (*Tab. 2*).

The average PhIT was 0.99 ± 0.1. It was significantly lower comparing to the normal donors 1.83 ± 0.37, p<0.01.

Preoperative blood platelets count and their phagocytic activity in patients from Group II vs. Control.

In patients with advanced gastric cancer from Group II, the average number of platelets was 283,250.0 ± 93,803.8/µl (*Tab. 3*). It was significantly higher comparing to the number of blood platelets in patients from Group II and normal donors, p<0.05.

In this group of patients, the average PhT% was 1.12 ± 0.09%. It was significantly lower comparing to the normal donor, p<0.01.

The average PhIT was 0.97 ± 0.1 (*Tab. 3*). It was significantly lower comparing to the normal donors, p<0.01.

Figure 2. **Bacilli *Staphylococcus aureus ATCC 6538P* with electron-dense elementary bodies (→) within platelet (thrombocyte cytoplasm) and close to the platelet. ME Magn. x 12 000.**

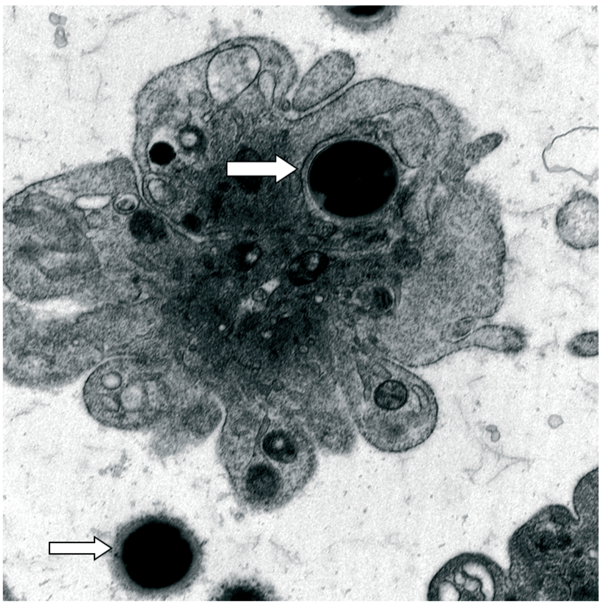


Figure 3. **The preoperative blood platelet counts in patients from Group I (GI PTL1) and Group II (GII PTL1).**
Mann-Whitney Test p < 0.05.

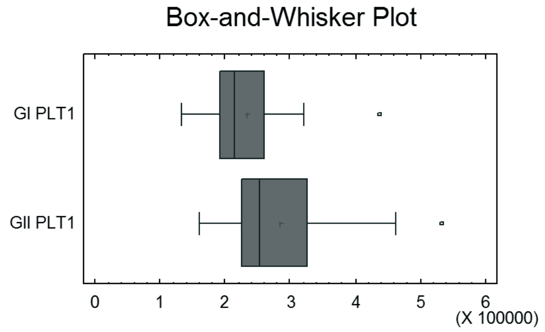
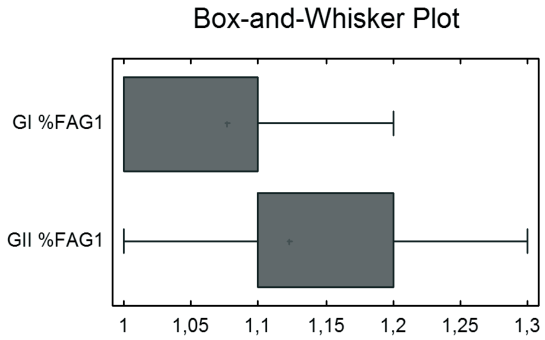


Figure 4. **The preoperative percentage of phagocyting platelets in patients from Group I (GI %FAG) and from Group II (GII %FAG).**
Mann-Whitney Test p = NS.



Preoperative blood platelets count and their phagocytic activity in patients from Group I vs. Group II.

Patients from Group II had significantly higher preoperative platelet counts than patients in Group I, p<0.05 (*Fig. 3*).

There was no difference in the preoperative PhT% between patients from Group I and Group II, p=NS (*Fig. 4*).

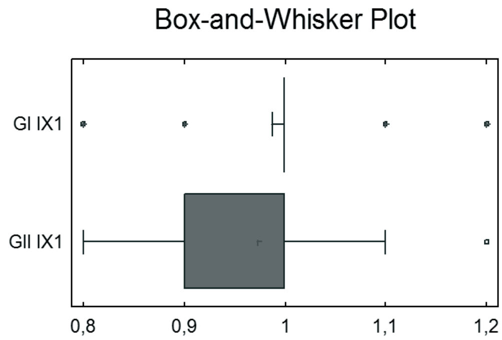
There was no difference in the preoperative PhIT of blood platelets between patients from Group I and Group II, p=NS (*Fig. 5*).

Postoperative blood platelets count and their phagocytic activity in patients from Group I vs. preoperative values, and Control.

Tab. 2 shows the average number of platelets, PhT% and PhIT in gastric cancer patients from Group I before the immunonutrition (GI1) and after the immunonutrition (GI2) and in normal donors (Control).

After the immunonutrition the increase in platelets was observed, in the average of 798,923.0 ± 280,536.0/µl, p<0.01. It was significantly higher comparing to Control Group, p<0.01.

Figure 5. **The preoperative phagocytic index of blood platelets in patients from Group I (GI IX1) and Group II (GII IX1).**
Mann-Whitney Test p = NS.



Also, the increase in the PhT% was observed, in the average of 1.26 ± 0.08%, p<0.01. It was still significantly lower comparing to the normal donors (*Tab. 2*).

After the immunonutrition, the PhIT increased significantly, in the average of1.1 ± 0.08, p<0.01. It was still significantly lower comparing to the normal donors (*Tab. 2*).

Postoperative blood platelets count and their phagocytic activity in patients from Group II versus preoperative values, and Control.

Tab. 3 shows the average number of platelets, PhT% and PhIT in gastric cancer patients from Group II before the imunonutrition (GII1) and after the immunonutrition (GII2) and in normal donors (Control).

After the immunonutrition the increased number of platelets was observed. An average one was 522,563.0 ± 233,595.0/µl, p<0.01 (*Tab. 3*).

Also, the increase in the PhT% was observed, in the average of 1.1 ± 0.18%, p<0.05. It was still significantly lower comparing to the normal donors, p<0.01.

After the immunonutrition, the PhIT increased significantly, in the average of 1.06 ± 0.11, p<0.01. It was still significantly lower comparing to the normal donors (p<0.01).

DISCUSSION

In this study, the phagocytic activity of blood platelets from gastric cancer patients was markedly impaired as compared to healthy individuals. Both, the fraction of phagocytic platelets and the phagocytic index of patients, were significantly lower than in the controls. It is currently not known if this considerable impairment of phagocytic activity of the platelets results from malignancy-associated immunosuppression or it is a consequence of accompanying nutritional status impairment. In the present study, patients and controls did not differ significantly in terms of laboratory parameters of protein and lipid metabolism. However, patients with disseminated cancer showed considerable loss of weight, clearly indicating their impaired nutritional status. Our results suggest, that the phagocytic activity of blood platelets in gastric cancer patients can be associated with the stage of the disease. An increase in platelet count was observed in patients with the dissemination of cancer into the abdominal cavity. In spite of this, the percentage of phagocytizing blood platelets did not rise. Additionally, a tendency for the lower phagocytic index was noted in this group. This observation suggests that phagocytic potential of blood platelets decreases gradually in higher stages of neoplastic process. This reduction seems to result from the effect of platelets exhaustion on formation of gastric cancer metastases. Our previous studies have revealed a marked impairment of bactericidal activity of blood platelets in gastric cancer patients [14]. Furthermore, thrombocytes were deficient in bactericidal properties in cases of non-resectable gastric malignancies.

Furthermore, there is no evidence in regards to the effects of immunostimulating nutritional therapy on phagocytic efficiency of blood platelets. Another objective of this study was to assess the effects exerted by perioperative immunostimulating nutritional therapy on the phagocytic activity of blood platelets. We observed a significant improvement in the phagocytic activity of blood platelets resulting from nutritional therapy implementation. However, in spite of a rise in phagocytic activity, the platelets' ability to phagocyte bacteria did not reach the levels observed in healthy individuals. Another important finding pertained to the differences in the degree of phagocytic activity improvement in thrombocytes from patients with various clinical stages of gastric cancer. At the end of immunostimulating therapy, an improvement in the platelet phagocytic activity documented in subjects with disseminated cancer was less pronounced than in individuals who underwent radical gastric resection.

The role that blood platelets play in carcinogenesis and formation of metastases in neoplastic disease is well known [15,16]. In contrast, little is known about the phagocytic activity of thrombocytes in this setting as available literature lacks reports about the phagocytic activity of thrombocytes in gastric cancer cases and in patients with other malignancies. High count, distribution in the circulation, and discoid shape make the platelets play an important role in protective mechanisms of a body. Interaction between antibodies and specific Fc receptors on the surface of platelets constitutes a signal that stimulates thrombocyte cytotoxicity [17,18]. Potential targets of cytotoxic attack include also neoplastic cells. The renal artery embolization in patients with renal cancer led to increase in blood platelets count and decrease of phagocytic index [19]. Preoperative platelets count significantly associated with metastasis of lymph nodes in non-small cell lung cancer [20]. It is an independent prognostic factor of overall patients survival. Moreover, platelets linoleic acid can be used as a biomarker of advanced non-small cell lung cancer [21]. The platelet-lymphocyte ratio is an independent prognostic factor of overall survival in patients with resectable colorectal cancer [22].

CONCLUSIONS

The phagocytic activity of thrombocytes was severely impaired in gastric cancer patients. The disturbances in phagocytic function of thrombocytes could play a role in pathogenesis and may be prognosis of gastric cancer. Their function could be partially improved by perioperative immunostimulating nutritional therapy. This improvement offers an additional argument for perioperative immunonutrition support in gastric cancer patients.

Conflict of interest

The authors report no potential conflict of interest.

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