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Prognostic significance of thrombocytosis in metastatic colorectal cancer

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Summary

Objective: Thrombocytosis was frequently observed in patients with malignancies and was associated with reduced overall survival and poor prognosis. The aim of this study was to evaluate the prognostic impact of thrombocytosis on patient survival up to potential progression to metastatic colorectal cancer (CRC), and to analyze the association between thrombocytosis and overall survival in patients with unresected metastases.

Subjects and Methods: This retrospective study was performed at University Hospital Centre Osijek and included patients diagnosed with metastatic CRC. Participants' five-year survival was tracked. Statistical analyses included the χ^2 test, Wilcoxon test for repeated measures, Kaplan–Meier survival analysis, and Cox proportional hazards regression using the Forward method. Analyses were performed in MedCalc software (v18.6.0), with significance defined as $P<0.05$.

Results: A total of 179 patients with metastatic CRC were included in the study. The results showed a statistically significant impact of thrombocytosis on overall survival (P=0.002) and a poorer prognosis, whereas its impact on time to progression to metastatic disease was not statistically significant.

Conclusion: In this study, thrombocytosis was associated with prognosis in patients with metastatic CRC, indicating that elevated platelet counts may help identify patients at higher risk.

KEYWORDS: *carcinoma; colon; metastases; platelets; thrombocytosis*

INTRODUCTION

Platelets, or thrombocytes, are discoid-shaped blood cells formed in the bone marrow by the fragmentation of the cytoplasm of mature megakaryocytes, a process known as thrombocytopoiesis(1,2). Their primary function is participation in primary hemostasis, i.e., the formation of a temporary mechanical plug as part of the hemostatic response to vascular injury. Platelets exert their action through both procoagulant and anticoagulant factors, modulating the vascular microenvironment(3,4). The phenomenon of a *marked increase in platelet count* in cancer patients was first described by Leopold Riess in 1872(1,2). Shortly thereafter, Theodor Billroth expanded on the theory of platelet involvement, linking thrombocytosis to tumor growth and metastatic spread(1,3). He hypothesized that thrombi containing tumor cells could facilitate haematogenous dissemination of

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malignant cells and the formation of metastases, whereby parts of the thrombus embolize distal blood vessels. Thrombocytosis, or elevated platelet count in peripheral blood, has been recognized as a prognostic marker in various types of cancer, including colorectal cancer (CRC). Tumor cells stimulate platelet production via specific molecular mechanisms, while activated platelets further promote tumor growth and metastasis(1,3).

According to the literature data, platelet counts tend to decrease after surgical resection of CRC. This change correlates with disease progression and overall patient survival(1,3). An increasing number of experimental studies suggest that thrombocytosis plays a key role in tumor cell proliferation, angiogenesis, cancer progression, metastasis, and cancer-associated thrombosis. Thrombocytosis is frequently observed in patients with different types of malignancies and is associated with reduced overall survival and poor prognosis. Platelet activation can lead to complex interactions between platelets and tumor cells(1). The pathogenesis of cancer-related thrombocytosis has been supported by findings on the role of interleukin-6 (IL-6)(4). According to research, tumor cells produce IL-6, which stimulates hepatic thrombopoietin synthesis, thereby promoting thrombocytopoiesis by activating megakaryocytes in the bone marrow. In addition to its indirect effects via platelets, IL-6 also plays a direct role in colorectal carcinogenesis and may influence chemotherapy response. However, IL-6 levels are not always correlated with thrombocytosis. Several other factors present in the inflammatory intestinal microenvironment may contribute to its development, which is why results related to thrombocytosis should be interpreted within a broader context(4).

Platelet structure is divided into four zones with distinct functions: the peripheral zone, structural zone, membrane system, and organelle zone, which contains granules and organelles. The organelle zone includes mitochondria, alpha granules, dense granules, lysosomes, and peroxisomes(5). Of these, dense and alpha granules are especially significant because they contain growth factors and bioactive molecules that strongly contribute to metastatic progression. These molecules include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), transforming growth factor beta (TGF-β), sphingosine-1-phosphate (S1P), interleukin-1β (IL-1β), interleukin-8 (IL-8), and lysophosphatidic acid. For example, TGF-β released from platelets promotes epithelial-mesenchymal transition (EMT) in tumor cells. This occurs by activating Smad transcription factors and the NF-κB signaling pathway. EMT causes epithelial cells to acquire a mesenchymal phenotype, which increases their motility and metastatic potential. EMT also provides protection against anoikis, or apoptosis induced by loss of cell adhesion(4). Additionally, IL-6 signaling via STAT3 (signal transducer and activator of transcription 3) can induce VEGF receptor 2 (VEGFR2) in colorectal cancer cells. This completes a pro-carcinogenic loop involving IL-6, platelets, and VEGF within tumor cells(4).

Circulating tumor cells may exploit platelets to facilitate their adhesion to endothelial cells at metastatic sites. The significant role of platelets in carcinogenesis is associated with their physiological function in maintaining vascular integrity(1,4). Since tumors often lack a well-developed vascular network, platelets help prevent hemorrhage within tumor lesions(4). Activation of platelets and the coagulation system thus plays a critical role in cancer progression, while tumor angiogenesis is essential for the dissemination of malignant cells throughout the body(1). In oncology patients, components of the extrinsic coagulation pathway, particularly factor VII and tissue factor, are especially activated. Tumor-secreted tissue factor binds to coagulation factor VII, activating factor X and generating thrombin, ultimately contributing to tumor progression. Thrombin not only enables fibrin formation and activates platelet receptors that promote thrombosis, but also directly enhances the tumor's malignant potential. Both tissue factor and thrombin play key roles in tumor growth, angiogenesis, and metastasis(1). In addition to platelets, the tumor microenvironment also contains lymphocytes and macrophages, with varying degrees of infiltration in both primary tumors and metastasis(4).

CRC is a common malignancy of the gastrointestinal tract. It can affect the rectum, colon, or caecum. Despite diagnostic and therapeutic advances, five-year survival rates for patients with CRC remain unsatisfactory. This applies to both

newly diagnosed patients and those with metastases after surgery. Thromboembolic events are common complications in oncology patients, especially with disease progression and metastasis (1). Severe thromboses include disseminated intravascular coagulation (DIC), thrombophlebitis, and pulmonary embolism. These conditions indicate increased platelet activation and aggregation. Such findings may guide future research and the development of new therapeutic strategies for cancer patients(1,3).

Our study aimed to examine how platelet count affects survival until disease progression and overall survival in patients with metastatic CRC whose metastases were not surgically treated. We also analyzed the prognostic value of thrombocytosis in CRC and its metastases.

SUBJECTS AND METHODS

This study is based on a retrospective analysis of data retrieved from the Oncology Clinic medical database at the University Hospital Centre Osijek. The cohort included patients with metastatic CRC diagnosed between 2010 and 2012, with overall survival monitored over a 5-year follow-up period ending in 2017.

ICD-10 diagnoses included were: C18 – colon cancer, C19 – rectosigmoid junction cancer, and C20 – rectal cancer. During the observation, 917 CRC patients were identified: 463 with colon cancer and 454 with rectal cancer. Of these, 203 had metastatic CRC. Due to incomplete data about disease progression, labs, and treatment outcomes, 24 patients were excluded. Thus, 179 patients were included in the study.

All patients signed informed consent for treatment at therapy start, and full anonymity was maintained. Available data included treatment initiation, therapy types, treatment controls, and diagnostic methods. Laboratory results were collected before treatment, during, and at completion. Ethical approval (R2:4754-4>/2017) was obtained from the hospital's Ethics Committee, and the study followed the Declaration of Helsinki and Good Clinical Practice.

The study utilized data from the medical records of treated patients. The variables analyzed included age, sex, site of metastatic disease, date of metastasis detection, and laboratory findings, with a particular focus on platelet count. Platelet values were monitored at each patient visit during treatment. Platelet counts, as well as erythrocyte, leukocyte, and haemoglobin values, were determined using the automated haematology analyzer Sysmex XN-1000. The reference platelet count range at the Laboratory Department of the University Hospital Centre Osijek was 158–424×10⁹/L. The upper limit (424×10⁹/L) was used as the criterion for thrombocytosis in our study.

Statistical Analysis

Results are presented in tabular form. Categorical data are presented as absolute and relative frequencies, while numerical data are described by the mean and standard deviation, and, where applicable, the median and interquartile range. The nonparametric χ^2 (Chi-square) test was used to compare two or more independent samples (qualitative categorical data). Statistical analysis was performed using MedCalc (version 18.6.0; MedCalc Software bvba, Ostend, Belgium), with a significance level of $P<0.05$. The Wilcoxon test was used to compare repeated numerical measurements. The influence of platelet count on survival was analyzed using the Kaplan-Meier method, and Cox proportional hazards regression with Forward variable selection was used to identify prognostic factors.

RESULTS

A total of 179 patients with metastatic CRC with complete data on disease progression and laboratory findings were included in the study. The average age of participants was 61.1±10.9 years, ranging from 26 to 86 years. The results of the analysis are presented in Table 1, showing the number of patients by sex, diagnostic method, type of diagnosis, and sites of metastases. There were significantly more male patients (61.4%) diagnosed with CRC than female patients (38.6%) (Chi-square test, $P=0.03$). At initial diagnosis, 59.2% of patients had C18 – malignant neoplasm of the colon, 39.1% C20 – malignant neoplasm of the rectum, while the fewest diagnoses (1.7%) were recorded for C19 – malignant neoplasm of the rectosigmoid junction (Chi-square test, $P<0.001$). A statistically significant difference was observed between patients whose diagnosis was

confirmed by colonoscopy (Chi-square test, P<0.001) and those diagnosed by surgery or a combination of surgery and colonoscopy. A statistically significant difference was also noted between metastases present at the time of CRC diagnosis and those that developed during the disease course (Chi-square test, P=0.04). The most common site of metastasis was the liver (60.9%) (Table 1).

Analysis of blood count parameters showed a statistically significant difference in erythrocyte (Wilcoxon test, P<0.001) and platelet (Wilcoxon test, P=0.001) counts before therapy initiation and after a certain treatment period. Thus, erythrocyte and platelet counts were significantly lower after therapy (Table 2). We have divided patients into two groups based on platelet count: normal (158–424×10⁹/L) and higher than normal (>424×10⁹/L). Based on the results, a statistically significant association between platelet count and patient survival was identified (Kaplan-Meier survival test, P=0.002), whereas no significant impact on time to metastasis was observed (Table 3).

Table 1.

The distributions of demographic and clinical variables

Characteristic	Categories	Number (%) of patients	P-value*
Patient sex	Male	110 (61.4)	**0,03**
	Female	69 (38.6)	
Diagnoses † (ICD-10)	C18 – Malignant neoplasm of colon	106 (59.2)	**<0,001**
	C19 – Malignant neoplasm of rectosigmoid junction	3 (1.7)	
	C20 – Malignant neoplasm of rectum	70 (39.1)	
Method of diagnosis	Colonoscopy	23 (14.5)	**<0,001**
	Surgery	78 (43.6)	
	Colonoscopy and surgery	78 (41.9)	
Metastases	Present at time of colorectal cancer diagnosis	108 (60.3)	**0,04**
	Developed during disease	71 (39.7)	
Sites of metastases	Liver	109 (60.9)	0,06
	Other (lungs, peritoneum, lymph nodes)	70 (39.1)	
Total		179 (100.0)	

** Chi-square test*
† ICD-10; International classification of diseases and related health problems

Table 2.

Comparison of blood count parameters before and after therapy

Blood Count Parameter (units)	**Median (IQR) Before Therapy**	**Median (IQR) After Therapy**	**P-value***
Leukocytes (x10⁹/L)	7.95 (6.95 – 10.3)	8.15 (6.5 – 10.2)	0.89
Erythrocytes (x10¹²/L)	4.3 (4.0 – 4.7)	4.0 (3.5 – 4.5)	**<0.001**
Hemoglobin (g/L)	119.5 (107.5 – 128.5)	120.5 (107.0 – 135.0)	0.13
Platelets (x10⁹/L)	330.5 (258.5 – 419.0)	288.0 (207.5 – 385.5)	**0.001**

**Wilcoxon test*

Table 3.

Impact of Platelet Count on Metastasis Occurrence and Survival Time

Survival Time in months (no. of patients)	**Median (95% CI) Platelets ≤424 x10⁹/L**	**Median (95% CI) Platelets >424 x10⁹/L**	**P-value***
After diagnosis (n=170)	36.0 (29.0 – 41.0)	21.0 (17.0 – 29.0)	**0.002**
Time to metastasis occurrence (n=75)	15.0 (12.0 – 25.0)	16.0 (4.0 – 20.0)	0.10

**Kaplan-Meier survival test*

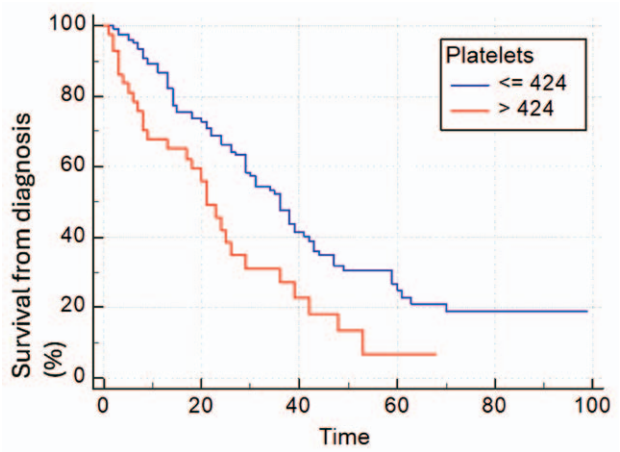

Figure 1. Platelets and survival time in months from diagnosis to death (Kaplan-Meier curve)

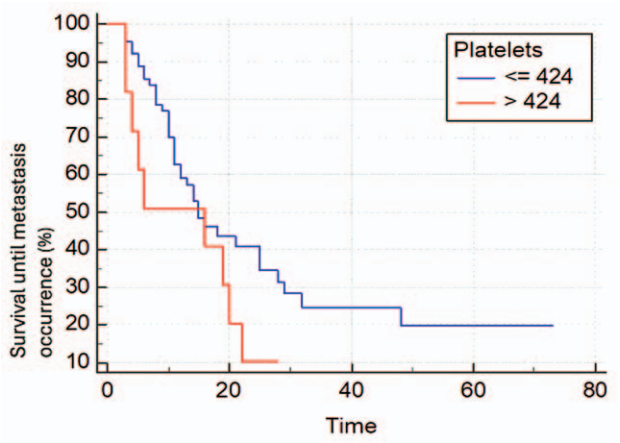

Figure 2. Platelets and survival time in months from diagnosis to the occurrence of metastasis (Kaplan-Meier curve)

Table 4.

Impact of observed parameters/predictors (leukocytes) on survival time

Leukocytes / no. of patients	**B**	**Exp(b)**	**95% CI**	**P-value***
After diagnosis / n=170	0.17	1.18	1.10 – 1.27	**<0.001**
Time to metastasis occurrence / n=75	0.17	1.19	1.06 – 1.33	**0.003**

**Cox proportional hazards regression (Forward method)*

The Kaplan-Meier curve illustrates the effect of baseline platelet levels on patient survival time from diagnosis to death (Figure 1), while Figure 2 depicts the influence of baseline platelet levels on time to metastasis occurrence.

Data analysis employed the Cox regression model, including the following parameters: patient age and initial values of erythrocytes, leukocytes, platelets, and haemoglobin. Leukocyte count was identified as the only statistically significant predictor in both the patient survival analysis and the time-to-metastasis analysis in patients without metastases at diagnosis. The beta regression coefficient (b=0.17) for survival time and time to metastasis occurrence, along with the odds ratios and corresponding 95% confidence intervals, were presented using the Forward method in the Cox regression model (Table 4).

DISCUSSION

According to the data from the World Health Organization and its International Agency for Research on Cancer from 2025, CRC is the third most common cancer worldwide, after breast and lung cancer, with an estimated 1.9 million new cases annually. It ranks as the second leading cause of cancer-related mortality, with over 900,000 deaths per year(6).

In Croatia, data from the Cancer Registry of the Croatian Institute of Public Health for 2021 indicate the following: among men, prostate cancer is the most common, followed by cancers of the trachea, bronchus, and lung, while CRC ranks third (16%); among women, breast cancer is the most prevalent, followed by CRC (13%) and respiratory tract cancers(7).

Based on these data, approximately 3,600 individuals are diagnosed with CRC annually in Croatia, of which 60% are men. Earlier registry data from 2011 similarly reported the incidence of CRC at 15% in men and 13% in women. Regarding mortality, the trend in CRC mortality has remained stable over the past 10 years, though the number of new cases has increased by about 1% annually over the past 20 years(7).

CRC is more common among older adults, although approximately 20% of cases are diagnosed

in individuals younger than 60 years. Most patients are between 65 and 75 years old(7). In our study, the mean age of patients was 61 years, slightly younger than the average reported in the literature. This may be explained by the age range targeted by the National Program for Early Detection of CRC, which focuses on individuals aged 50 to 75 years, aligning with the average age of our cohort.

The development of CRC is most often associated with prolonged exposure to risk factors. The risk significantly increases with age. Additional risk factors include family history, polyps, and certain genetic predispositions. Common lifestyle-related risk factors include: a diet high in processed meat and low in fruits and vegetables; a sedentary lifestyle; smoking; excessive alcohol consumption(8). Obesity is considered a significant risk factor for CRC development. Notably, Croatian men rank highest in Europe in obesity prevalence, with nearly two-thirds of the adult population classified as overweight or obese(9).

Our study included 179 patients diagnosed with CRC, comprising 110 men (61.4%) and 69 women (38.6%). Analysis revealed a statistically significant difference in disease occurrence by sex, with a higher proportion of affected men (P=0.03). These findings align with cancer registry data indicating a higher incidence in males.

Regarding the primary tumor site, the distribution was as follows: C18 in 106 patients (59.2%), C19 in 3 patients (1.7%), and C20 in 70 patients (39.1%). Statistical analysis demonstrated that diagnosis C19 was significantly less frequent (P<0.001) than C18 and C20, which were the predominant localizations in this cohort. These findings are consistent with national cancer registry data indicating that the colon is the most common site for CRC(7).

In daily clinical practice, colonoscopy is considered the *gold standard* for CRC diagnosis(10). This method enables earlier detection of mucosal changes, often allowing for complete cure. Additionally, polyps, present in nearly 50% of CRC patients, can be removed during the procedure(10). Our data on diagnostic methods revealed a significant difference between patients diagnosed by colonoscopy only (23 patients, 14.5%), surgery only (78 patients, 43.6%), or combined surgery and colonoscopy (78 patients, 41.9%) (P<0.001). This can be explained by the fact that many patients present with pronounced symptoms, increasing the likelihood of cancer detection and the necessity of surgical intervention, which remains the primary treatment. Literature reports that 30–40% of patients have advanced disease at diagnosis, highlighting the high frequency of metastases(11). Some patients are asymptomatic, while others exhibit one or more symptoms indicative of disease presence, such as gastrointestinal bleeding, abdominal pain, constipation, or diarrhea(12). Symptomatic patients have a shorter 5-year survival than asymptomatic patients, indicating the prognostic value of symptom presence(11).

Our results show a statistically significant difference between metastases present at diagnosis and those developed during disease progression (P=0.04). At diagnosis, metastases were detected in 108 (60.3%) patients, while 71 (39.7%) developed metastases later. No significant difference was found in metastatic sites (P=0.06), with the liver as the leading site (109 patients, 60.9%), followed by the lungs, peritoneum, and lymph nodes (39.1%). Other studies similarly report liver metastases as the most frequent initial metastatic site(13).

Our results demonstrate that thrombocytosis impacts both patient survival from diagnosis to death and the time to metastasis. Platelet counts were monitored before therapy initiation and after a defined treatment period. A statistically significant decrease in platelet (P=0.001) and erythrocyte counts (P<0.001) was observed after treatment, suggesting a therapeutic effect on haematological parameters. Thrombocytosis showed a significant effect on patient survival (P=0.002), whereas its impact on time to metastasis was not statistically significant.

The prognostic role of thrombocytosis prior to CRC treatment has been analyzed by Long et al.(14) through a meta-analysis of studies identified in PubMed, EMBASE, and the Cochrane Library. Elevated platelet counts before treatment were associated with poorer overall and disease-free survival, confirming thrombocytosis as an independent prognostic factor in CRC(14). Similarly, Bailey et al. in primary care settings found that thrombocytosis (>400×10^9/L) was linked with increased CRC risk, highlighting its stratification value and the need for further evaluation of its diagnostic and prognostic relevance(15). A cohort study performed at the Sidney Kimmel Cancer

Centre at the Thomas Jefferson University Hospital examined preoperative platelet counts in 1,513 surgically resected CRC patients. Results showed that thrombocytosis correlated with poorer overall survival, higher recurrence rates, and increased distant metastasis incidence, persisting for 5 years post-surgery. Platelet count, as a routine and cost-effective marker, was proposed as a valuable marker for recurrence risk assessment and metastasis prediction(16). Retrospective research by Lin et al. involving 150 surgically treated CRC patients reported significantly worse 5-year survival in patients with thrombocytosis (13.3%) compared with those with normal platelet counts (56.3%) (17). These findings support our study's results and further confirm the prognostic importance of thrombocytosis in metastatic CRC.

Baseline erythrocyte, leukocyte, platelet, and haemoglobin values, alongside patient age, were included in a Cox regression model. Leukocyte count emerged as a statistically significant predictor of both survival and time to metastasis in patients without metastases at diagnosis. The Forward selection method yielded identical beta coefficients (b=0.17) for survival time and metastasis-free time. Odds ratios and 95% confidence intervals were similar, indicating that each unit increase in leukocyte count increases metastasis risk by 1.19-fold and death risk by 1.18-fold. Although not the primary focus of our study, findings on erythrocytes, haemoglobin, and leukocytes offer valuable insights for future research. The role of platelets in CRC pathogenesis is complex, involving bidirectional interactions among platelets, tumor cells, leukocytes, stromal, and endothelial cells. Many clinical questions remain unresolved, and well-designed clinical trials are needed to elucidate these mechanisms.

CONCLUSION

Our results indicate that thrombocytosis is a significant prognostic marker in patients with metastatic colorectal cancer. However, these findings should be interpreted within the context of the inherent limitations of the retrospective study design and the lack of clinical data (e.g., comorbidities, symptoms indicative of disease presence, overall metastatic burden, and concomitant anticoagulation therapy). Therefore, further prospective, multicenter investigations are warranted to establish the definitive prognostic utility of platelet counts for patient outcomes in this clinical setting.

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Sažetak

Prognostički značaj trombocitoze kod metastatskog kolorektalnog karcinoma

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Cilj: Trombocitoza je često uočena kod pacijenata s malignim bolestima i povezana je sa smanjenim ukupnim preživljenjem i lošom prognozom. Cilj ove studije bio je prikazati utjecaj trombocitoze kao prognostičkog markera na preživljenje pacijenata do potencijalne progresije bolesti u metastatski karcinom debelog crijeva, uz analizu povezanosti trombocitoze s ukupnim preživljenjem kod pacijenata s neoperiranim metastazama.

Ispitanici i metode: Retrospektivno istraživanje provedeno na Klinici za onkologiju Kliničkog bolničkog centra Osijek uključilo je pacijente s dijagnozom metastatskog karcinoma debelog crijeva. Pacijenti su praćeni tijekom petogodišnjeg razdoblja preživljenja. Za statističku obradu korišteni su χ^2-test, Wilcoxon test za usporedbu ponovljenih mjerenja, Kaplan-Meier analiza preživljenja i Cox proporcionalna regresija s Forward metodom. Sve analize provedene su korištenjem MedCalc softvera (v18.6.0) pri razini značajnosti $P < 0,05$.

Rezultati: U studiju je uključeno ukupno 179 pacijenata s dijagnozom metastatskog karcinoma debelog crijeva. Rezultati su pokazali statistički značajan utjecaj trombocitoze na preživljenje ($P = 0,002$) i njezinu povezanost s lošijom prognozom kod pacijenata, dok utjecaj trombocitoze na vrijeme do progresije u metastatsku bolest nije bio statistički značajan.

Zaključak: Trombocitoza se u ovom istraživanju pokazala kao vrijedan prognostički čimbenik kod pacijenata s metastatskim karcinomom debelog crijeva.

KLJUČNE RIJEČI: *debelo crijevo; karcinom; metastaze; trombociti; trombocitoza*