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PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE COMPUTED HEMATOLOGICAL INFLAMMATORY PARAMETERS IN PATIENTS WITH BREAST CANCER

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Summary

Breast cancer is the most common malignant disease among women, constituting around a quarter of all cancers in women worldwide. This type of cancer is mainly affected by genetic, environmental, and lifestyle factors such as nutrition and physical activity.

A retrospective study including 192 women with breast cancer was performed for six years (from 2015 to 2021). We investigated the relationship between indirect hematological parameters, neutrophil-to-lymphocyte ratio – NLR, platelets-to-lymphocyte ratio – PLR, systemic immune-inflammation index – SII and the treatment outcome. Additionally, we also followed the overall survival (OS) rate.

The obtained results report assessed parameters before and after surgical intervention. Of importance is to emphasize that at a cut-off value of 2.65 ($P = 0.001$) and 3.30 ($P < 0.001$), a decline in the NLR value was noticed after surgical removal of the breast cancer. The same decrease was observed for SII after surgery ($P < 0.001$). Through the study, SII has been shown to be a more relevant parameter compared to NLR and PLR. The study outcome recommends the cut-off value of 2.65 as the optimal for NLR in predicting the effectiveness and successfulness of the surgical procedure.

KEYWORDS: *breast cancer, neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), non-adjuvant treatment*

INTRODUCTION

In the last years, cancer has become a leading public health problem. The incidence of various types of cancer has increased in recent years(1). According to the GLOBOCAN's (online database providing global cancer statistics and estimates of incidence and mortality in 185 countries for 36 types of cancers, and for all cancer sites combined) data, 19.3 million people got diagnosed with cancer in 2020, while almost 10 million people died due to cancer. Breast carcinoma is the most com-

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mon cancer among women, with an estimated 2.26 million cases diagnosed (approximately 24.5% of all cancers in women) and 685 thousand deaths worldwide in 2020(2). Vast majority of breast cancer are carcinomas. According to the data of the Croatian National Cancer Registry in 2019, breast cancer was the most common cancer site among Croatian women (2 999 new cases, 25% of all new caners in women), too(3).

Different stimuli lead a normal physiological healthy and functional cell to transform into a pathologically altered cell. Many genetic factors affect breast cancer, such as mutations in the *BRCA*, *HER2*, *PALB2*, *CHEK2*, *CKD1*, and *STK11* genes(4,5,6,7,8,9). By activation of oncogenes and deactivating tumor-suppressors, there is an uncontrolled growth and division of affected cells, which transfers their DNA defects to the next generation of daughter cells(10). Moreover, breast cancer is also influenced by endogenous and exogenous factors like genetic instability, nutrition, lack of physical activity, use of different medications, and sex hormones(11,12,13,14,15,16,17,18).

Tumor markers are molecules synthesized by tumor cells or by physiologically healthy cells in the presence of cancer. By utilizing different tumor markers, it's possible to identify the presence of cancer and obtain additional information about the cancer itself(1). In breast cancer, the choice of therapy and the overall outcome significantly depend on present tumor markers, such as sex hormone receptors (estrogen and progesterone), HER2/neu receptors, Ki-67 proliferation index, CA 15-3, and CEA(1,19,20,21,22,23,24).

Metastatic breast cancer implies expansion of tumor cells into other parts of the body. Almost every organ in the human body can be affected by metastasis, but in breast cancer, the most common sites of metastasis are bones, lungs, brain, and liver. The metastases can also spread into regional lymph nodes or the contralateral breast(25). Generally, metastatic tumor cells are more aggressive and they are more challenging to treat. They spread through the bloodstream and the lymph system. The occurrence of metastasis is possible months after making the first diagnosis and initiation of therapy. About 30% (20-40%) of women with breast cancer, develop metastasis at some point. In half of the women with breast cancer metastasis develops within the first five years of diagnosis(26). The sole purpose of treating metastatic breast cancer is to maximally preserve patient's quality of life. Despite a good screening program and significant development of diagnostic capabilities, there are still too many women diagnosed with breast cancer at an already advanced stage(27).

Various research in epidemiology and clinical oncology shows a significant impact of the immune system on carcinogenesis. Chronic inflammation processes in the microenvironment of the cancer contribute to the progression, proliferation, invasion, and metastasis of the tumor cells. Research has confirmed how cells involved in inflammation processes and immune response can be detected and monitored using blood count – a cheap, fast, repeatable, and relatively non-invasive method. Consequently, blood count is a favorable search to predict the immune response in cancer patients(28,29,30).

Neutrophils are the largest subgroup of leukocytes in the peripheral bloodstream. They participate in the earliest stages of the immune response (so-called *innate immunity*) while excreting specific granules filled with enzymes and other molecules to defend our organism(31). In carcinogenesis, neutrophils may contribute to the development of tumor mass while supporting migration, invasion, and penetration of tumor cells through the basal membrane(28).

Lymphocytes are unique adaptive immune system cells that synthesize antibodies to defend our body against microorganisms and other harmful substances(31). They have a dual role in carcinogenesis. First, CD8+ cytotoxic T lymphocytes (CTL) have a supervisory function and if they detect some suspicious cells with tumor antigens, they can destroy them immediately(28,32,33). The roles of CD4+ helper lymphocytes are not that clear. Some research assumes that CD4+ lymphocytes help CD8+ lymphocytes differentiate and mature. Other research supposes that CD4+ increase susceptibility to the destruction of the tumor cells by CTL while excreting cytokines(32).

Thrombocytes have a critical role in the initial response to blood vessel damage and maintaining hemostasis. Various signaling molecules (proteins, growth factors, bioactive lipids, reactive oxygen species, magnesium and calcium ions) initiate the coagulation cascade, vasoconstriction, and inflammatory response, which leads to a faster and better repair of the damaged tissue. Tumor cells can secret interleukins, which promote the

synthesis of the thrombopoietin by the liver(34). The increased levels of circulating thrombopoietin can lead to thrombocytosis. Consequently, an increasing number of thrombocytes in the bloodstream can cause disseminated intravascular coagulopathy (DIC)(28). As a result, severe hemodynamic and inflammatory reactions contribute to carcinogenesis and metastasis. Thrombocytes also release different chemokines, cytokines and growth factors which support growth and development of cancers, carry on angiogenesis, and facilitate penetration of the basal membrane(35). Moreover, once tumor cells enter the bloodstream, they are coated with thrombocytes to protect themselves from the CTL and facilitate adhesion on blood vessel walls in distant organs(35,36).

Neutrophil-to-lymphocyte ratio (NLR) is an excellent indicator of the whole immune response of the human body. It unites neutrophils as early reactants of the acute phase and lymphocytes as components of the adaptive immune system specifically directed to destroy cancers. For now, NLR has proved helpful as a prognostic marker in melanoma, nasopharyngeal, gastric, and colorectal cancers. In general, high NLR values before surgery are associated with poor treatment outcomes and higher mortality rates(28,29,37).

Platelet-to-lymphocyte ratio (PLR) is an indirect hematological inflammatory parameter similar to NLR. It shows the organism's immune response to cancer by combining thrombocytes as components of the immune system and bloodstream, that facilitate tumor cell growth, invasion, and metastasis and lymphocytes which seek to destroy tumor cells. Some publicized research asserts NLR as a better prognostic marker to PLR in pancreatic and gastric cancers, while others claim that PLR is better in pancreatic and ovarian cancers. However, high PLR values are generally associated with poor disease outcomes and often indicate the presence of lymph node metastases(28,37).

Systemic immune-inflammation index (SII) is the ratio of the multiplication of neutrophils (N) and thrombocytes (T) to lymphocytes (L) (SII = NxT/L). It unites all three components of the immune response to carcinogenesis: neutrophils, lymphocytes, and thrombocytes. According to recent research, SII is considered a better prognostic marker than all other hematological inflammatory parameters in hepatic, pancreatic, and gastric cancers(38).

Based on these facts, we decided to investigate the relationship between indirect hematological inflammatory parameters (NLR, PLR, SII), and the treatment outcome, as well as the overall survival (OS) of patients with breast cancer after five years.

MATERIALS AND METHODS

This retrospective study was based on clinical, pathohistological and hematological data obtained from 192 women treated for breast cancer at the University Hospital for Tumors, Sestre milosrdnice University Hospital Center (Zagreb, Croatia) during six years, May 2015 – May 2021. All included subjects were female, the median age of patients was 53 (24-84), and all were diagnosed with breast cancer. Within the covered patient group there were different tumor stages: 125 women were diagnosed with breast cancer stage I, 62 women were diagnosed with breast cancer stage II, and five women were diagnosed with breast cancer stage III or IV. There were also different lymph node stages within the covered patient group: 120 women didn´t have lymph node metastases, 42 women had lymph node metastases stage I, 23 women had lymph node metastases stage II, and seven women had lymph node metastases stage III. The most used surgery was breast segmentectomy (131 women), while 41 women underwent ablatio mammae, and 20 women had mastectomy. Only 90 of 192 patients were undergoing chemotherapy – therefore, only 90 patients had values for both time points.

Data was obtained from the hospital information system (IN2 d.o.o., IBIS) and laboratory information system (Samson informatika d.o.o., KLINLAB). EDTA vacuettes of 3mL with the anticoagulant K3EDTA were used for sample collection. Blood parameters were determined on two hematological analyzers in the Department of Medical Biochemistry and Hematology laboratory immediately after blood extraction: Sysmex XN-1000 and Sysmex XN-550 (Sysmex Corporation, Kobe, Japan). Values of leukocytes, lymphocytes, and neutrophils were recorded in two-time points: i) within a month before surgery (N=192) and ii) before the start of chemotherapy, i.e. between two and three months after surgery (N=90). Retrospectively, from the recorded absolute val-

Tablica 1.
Descriptive analysis of the indirect hematological inflammatory parameters (NLR, PLR, SII)

	Median (95% CI)	Min – max	Interquartile range	P-value*
NLR	2.08 (1.97 – 2.28)	0.77 – 7.34	1.64 – 3.00	< 0.001
PLR	134.33 (125.56 – 143.55)	47.21 – 587.5	104.51 – 167.83	0.002
SII	500 (479 – 587)	118 – 2203	374 – 782	< 0.001

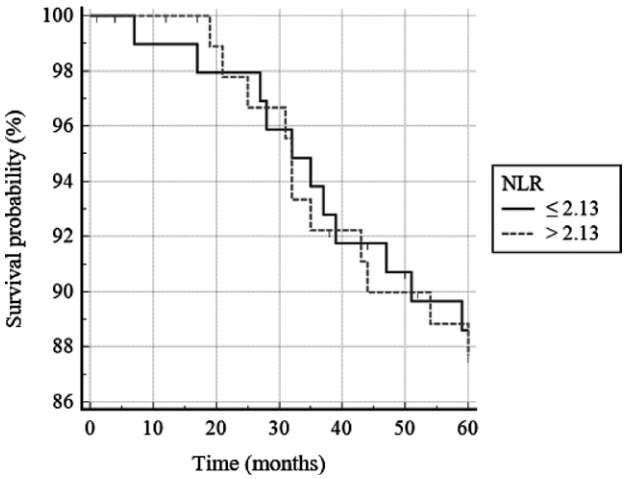

Figure 1. Kaplan-Meier curves of five-year rate OS for patient groups based on low and high NLR values at cut-off value of 2.13

ues, it was possible to calculate NLR, PLR, and SII according to their equations at each time point. Statistical data analysis was done using MedCalc (MedCalc Software, version 19.8, Ostend, Belgium) and Microsoft Excel 2016 (Microsoft Corporation, Redmond, USA).

Cut-off values for NLR (2.13), PLR (88.23), and SII (547) were based on the research study performed by Jiang et al.(38). Five-year OS rate was presented with Kaplan-Meier analysis based on the initial values obtained before surgery. Logrank test was applied to compare the Kaplan-Meier curves of different patient groups (low and high NLR value, low and high PLR value, and low and high SII value). McNemar test was used to determine if there was a significant change in the classification of patients based on NLR, PLR, and SII values after the surgery. Additionally, based on the initial statistical analysis and borderline results for NLR, data was tested with higher cut-off values (2.65 and 3.30) published by Huszno and Kolosza(39), Forget et al.(40), and Hernández et al.(41).

RESULTS

The median age of patients included in the study was 53 (24 – 84). Table 1. shows the descriptive statistics of the indirect hematological inflammatory parameters (NLR, PLR, SII). Kolmogorov-Smirnov test confirmed the data for all of the indirect hematological inflammatory parameters (NLR, PLR, SII) does not follow normal distribution ($P < 0.05$). Total follow-up time ranged from 1 to 60 months, while 4 patients were followed up less than 12 months.

Kaplan-Meier curves for low (N = 41) and high (N = 49) NLR groups based on the cut-off value of 2.13 (Figure 1.) didn't show any difference in the OS of patients after five years (Logrank test: P = 0.855; 57 months mean survival time for both groups).

Kaplan-Meier curves for low (N = 7) and high (N = 83) PLR groups based on the cut-off value of 88.23 (Figure 2.) show differences in the OS of patients after five years. However, the difference in

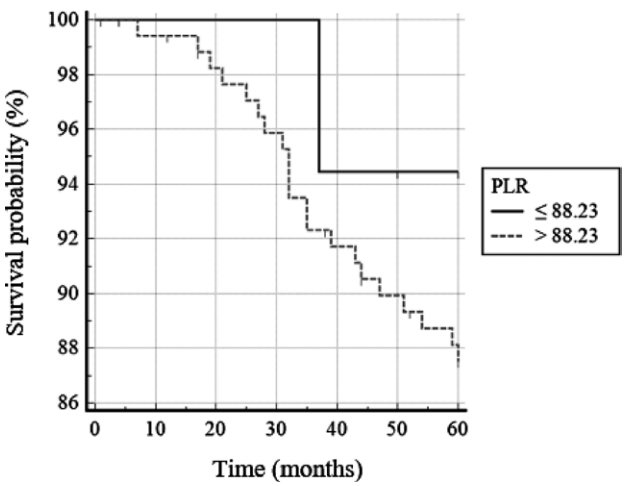

Figure 2. Kaplan-Meier curves of five-year rate OS for patient group based on low and high PLR values at cut-off value of 88.23

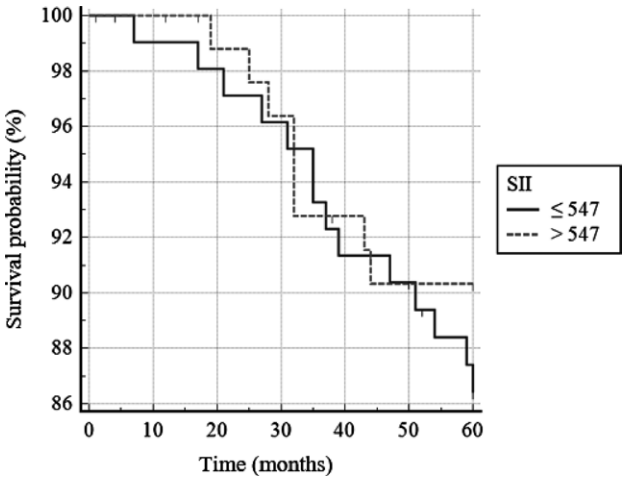

Figure 3. Kaplan-Meier curves of five-year rate OS for patient groups based on low and high SII values at cut-off value of 547

the curves' appearance isn't statistically significant (Logrank test: P = 0.398; 59 months mean survival time for low PLR group and 57 months for high PLR group).

Kaplan-Meier analysis for low (N = 44) and high (N = 46) SII groups based on the cut-off value of 547 (Figure 3.) show there is no statistically significant difference between the two groups (Logrank test: P = 0.437; 57 months mean survival time for both groups).

Tables 2. to 4. show the change between patient group classification based on the calculated hematological parameters (NLR, PLR and SII) before (vertical values) and after (horizontal values) surgery. The patients' classification based on NLR and PLR values didn't change due to surgery. However, the change was significant for the patient group with high SII values before surgery since all of them were reclassified into the low SII group after surgery. Likewise, none of the patients that were in the low SII group have been reclassified into the high SII group after the surgery.

Tables 5. and 6. compare the change of NLR classification before and after surgery based on different criteria for cut-off values. Patients' classification before and after surgery changes signifi-

Table 2.

Results of McNemar test for patient distribution according to NLR values before and after surgery at cut-off value of 2.13

	After surgery				Difference (%)	95% CI	P-value*
Before surgery	**NLR**	≤ 2.13	> 2.13	N (%)	- 13.33	- 25.73 – (- 0.94)	0.058
	≤ 2.13	30	11	41 (45.6%)			
	> 2.13	23	26	49 (54.4%)			
	N (%)	53 (58.9%)	37 (41.1%)	N = 90			

Table 3.

Results of McNemar test for patient distribution according to PLR values before and after surgery

	After surgery				Difference (%)	95% CI	P-value*
Before surgery	**PLR**	≤ 88.23	> 88.23	N (%)	- 6.67	- 14.08 – 0.75	0.146
	≤ 88.23	4	3	7 (7.8%)			
	> 88.23	9	74	83 (92.2%)			
	N (%)	13 (14.4%)	77 (85.6%)	N = 90			

Table 4.

Results of McNemar test for patient distribution according to SII values before and after surgery

	After surgery				Difference (%)	95% CI	P-value*
Before surgery	**SII**	≤ 547	> 547	N (%)	- 51.11	- 61.44 – (- 40.78)	< 0.001
	≤ 547	44	0	44 (48.9%)			
	> 547	46	0	46 (51.1%)			
	N (%)	90 (100.0%)	0 (0.0%)	N = 90			

Table 5.
Results of McNemar test for patient distribution according to NLR values before and after surgery at cut-off value of 2.65

	After surgery				Difference (%)	95% CI	P-value*
Before surgery	**NLR**	≤ 2.65	> 2.65	N (%)	- 18.89	- 29.05 – (-8.72)	0.001
	≤ 2.65	50	4	54 (60.0%)			
	> 2.65	21	15	36 (40.0%)			
	N (%)	71 (78.9%)	19 (21.1%)	N = 90			

Table 6.
Results of McNemar test for patient distribution according to NLR values before and after surgery at cut-off value of 3.30

	After surgery				Difference (%)	95% CI	P-value*
Before surgery	**NLR**	≤ 3.30	> 3.30	N (%)	- 17.78	- 26.26 – (-9.30)	< 0.001
	≤ 3.30	67	1	68 (75.6%)			
	> 3.30	17	5	22 (24.4%)			
	N (%)	84 (93.3%)	6 (6.7%)	N =90			

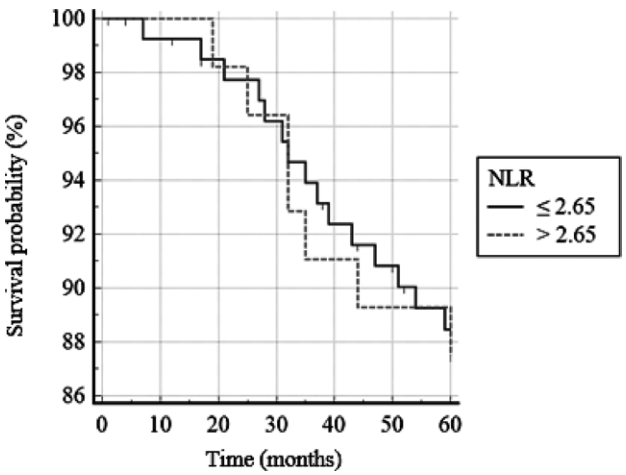

Figure 4. Kaplan-Meier curves of five-year rate OS for patient group based on low and high NLR values at cut-off value of 2.65

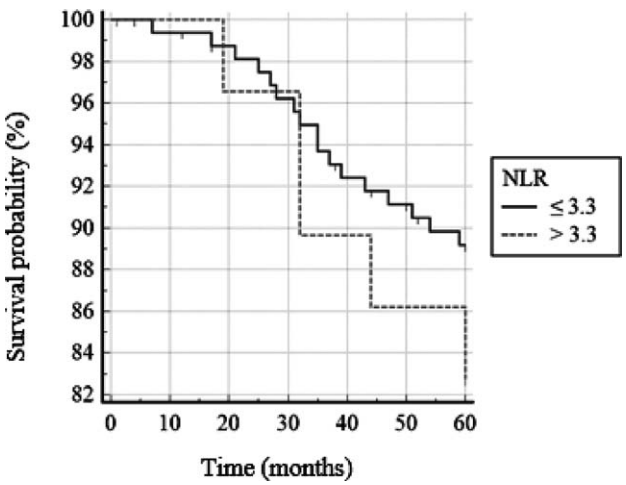

Figure 5. Kaplan-Meier curves of five-year rate OS for patient groups based on low and high NLR values at cut-off value of 3.30

cantly depending on the applied cut-off value. By changing the initial cut-off value from 2.13 to 2.56 and 3.30 significance of McNemar test changed as well.

Additionally, Kaplan-Meier analysis was preformed based on the new cut-off values for NLR (Figures 4. and 5.). However, the statistical significance in both cases did not change since the P-value of Logrank test for 2.65 and 3.30 cut-off were 0.851 and 0.332, respectively.

DISCUSSION

Cancer is often defined as a chronic inflammatory condition of the affected tissue which abounds with immune cells. As in other inflammatory reactions, some factors contribute to the progress and growth of the inflammation, e.g. cancer, as well as other factors that block and prevent the spreading of the pathological changes. Inflammatory cells and mediators are present in

the microenvironment of most, if not all, cancers, irrespective of the trigger for the development(42).

Neutrophils are a subgroup of leukocytes abundant with different granules. The presence and activity of neutrophils lead to the release of enzymes (such as metalloproteinase, elastases, collagenases), growth factors (e.g., vascular endothelial growth factor – VEFG), as well as reactive oxygen species which altogether result in matrix remodeling, growth, and development of the cancer, angiogenesis, and metastasis(43,44,45). On the other hand, some lymphocytes present the tumor-specific immune response(28).

Lymphocytes have several mechanisms of stopping the spreading and destroying the cancer. One way of inducing apoptosis is by secreting interleukins (IL-6, IL-8, and IL-17) which inhibit further growth of tumor cells(46,47). Additionally, other ways of inducing apoptosis are based on CD8+ cytotoxic T lymphocytes (CTL). The first mode of action implies the secretion of proteins called perforins and granzymes by CTLs. Perforins disturb the membrane structure of tumor cells and allow the entry of intercellular fluid into tumor cells. Whilst serin-proteases granzymes split a variety of proteins in tumor cells and can further activate caspases. The second mode of action takes place along the widespread CD95 or Fas receptor. CD95L, the ligand on the CTLs surface, interacts with CD95 receptor on tumor cells and consequently activates caspases again, leading to apoptosis of tumor cells(32).

Thrombocytes are also important components of the immune response to cancers. Affected by different signal molecules from tumor cells, thrombopoiesis is increased in the bone marrow, which leads to thrombocythemia in the peripheral blood stream. The risk of DIC is increased due to the increased number of circulating thrombocytes. Through their physiological function of repairing damaged endothelial blood vessel tissue, thrombocytes have a dual role: to stop and assist the spread of tumor cells. Vasoconstriction, clotting, and inflammatory response stimulation oppose carcinogenesis. Meanwhile, matrix remodeling, amplified expression of adhesion receptors and excretion of chemokines as well as cytokines, contribute to easier penetration of tumor cells into the intracellular space and blood stream. Therefore, they benefit carcinogenesis and metastasis. Moreover, clots between tumor cells and thrombocytes are formed which facilitate the survival of tumor cells in the blood stream(36).

NLR has been shown as a cheap, easily available, and useful prognostic marker in various inflammatory diseases and cancers of different tissues and organs. NLR encompasses the two most significant groups of leukocytes that participate in carcinogenesis as well as in immune response against carcinogenesis. In 2019 the Zagreb score was developed and investigated at the University Hospital for Tumors in patients with colorectal cancer (CRC). The potential Zagreb score was calculated by adding 1 point for elevated NLR for more than 75%, minimally three consecutively elevated percentage of immature granulocytes (%IG), doubling of immature granulocytes relative value to absolute neutrophils count ratio (IG ratio) and immature granulocytes relative value to leucocytes count ratio (IT ratio) at three consecutive time points. The study showed Zagreb score has the potential to predict the need for re-operation in time(48). Due to its prognostic significance for post-surgery complications in CRC patients and very short turnaround time (TAT), for more than two years, NLR has been routinely used at the University Hospital for Tumors in agreement with the anesthesiology, resuscitation and intensive care specialists. Multiple times thanks to, among other parameters, the increase in NLR value it was possible to respond in time and initiate a necessary re-operation or change the antibiotic therapy to prevent further life-threatening complications. Based on the experience gained from the implementation of NLR in CRC patients, our goal was to evaluate its potential or patients with breast cancer. After reviewing the professional literature, it has been found that most research considers NLR as a predictive prognostic marker just before chemotherapy in breast cancer patients. In this research, the predictive value of NLR has been investigated in patients with breast cancer before and after surgery.

The predictive value of NLR has been proven in patients with hepatocellular carcinoma (HCC) (49) and lung cancer(50,51). Mouchli et al. investigated the prognostic value of NLR in post-therapeutic recurrence and survival of patients with HCC. In their research they concluded that pretreatment NLR is of great prognostic value for survival outcome and cancer recurrence in patients with HCC(49). Cedres et al. demonstrated

that patients with non-small cell lung cancer (NSCLC) and NLR values < 5 have twice longer survival than patients with NLR values ≥ 5 (median survival 11.1 months vs. 5.6 months, P = 0.017)(51). Ozyurek et al. came to similar conclusions but via lower cut-off values: patients with NSCLC and NLR < 3 had a median survival of 31.1 months, while patients with NLR ≥ 3 had a median survival of 18 months (P = 0.003)(50).

Based on the similar inclusion criteria with our study design, the research from Jiang et al. has been chosen as the source of cut-off values. Even though our study included a smaller number of participants (N = 192 vs. N = 249), its novelty lies in the examination of the prognostic value of these parameters before surgery in contrast to their research which examined their prognostic value before chemotherapy. The study by Jiang et al. determined SII as the only factor independently associated with survival (P = 0.017) – high SII is related to the shorter mean OS time compared to low SII (65 vs. 41 months, P ≤ 0.001)(38). Our study results didn't confirm that. Moreover, the five-year OS rate for patient groups at the University Hospital for Tumors based on low and high SII values didn't show any statistically significant difference (P = 0.437). Jiang et al. also related low NLR and low PLR values with better mean OS time (64 vs. 50 months, P ≤ 0.001; 61 vs. 59 months, P = 0.007)(38). In the current study, high and low values in relation to cut-off values for NLR and PLR didn't show statistically significant differences in the OS time (P = 0.855 and P = 0.398). However, Jiang et al. didn't identify a significant independent association between NLR or PLR and OS time upon multivariable analysis (P > 0.05) and therefore concluded that pretreatment SII is of superior prognostic value than NLR and PLR in breast cancer(38). By comparing the results from Table 2., 3. and 4. in the current study, we could make similar conclusion: SII values before and after surgery (P < 0.001) have been a more relevant parameter than NLR (P = 0.058) and PLR (P = 0.146).

Guo et al. conducted a meta-analysis of 17079 individuals to investigate the prognostic value of NLR and PLR for breast cancer patients. Pooled results have shown that patients with high NLR values before treatment were associated with worse OS and poor disease-free survival (DFS) compared to those with low NLR values (OS: P < 0.001 and DFS: P < 0.001)(52). Liu et al. came to similar conclusions in their meta-analysis which involved eighteen eligible studies. The combined results demonstrated that patients with high NLR values before treatment had poorer outcome in DFS (HR = 1.87, 95% CI = 1.41 – 2.48) as well as a decreased OS (HR = 1.72, 95% CI = 1.30 – 2.27)(53). Contrary to this meta-analysis, our study did not show any association between NLR values before treatment and OS (P = 0.855). This might be due to several reasons. First, this was a retrospective designed study with a smaller sample size (N = 192). Second, the current study used cut-off values from another, previous study done by Jiang et al.(38) and didn't investigate own values based on the included patients. Third, there wasn't enough data for patient exclusion due to other potential causes of elevated NLR, PLR and SII values such as an acute infection or chronical inflammatory disease. Finally, the determination period before and after surgery for obtaining NLR, PLR and SII values wasn't strictly uniform. The median time for measurements in the current study was 12 days before surgery (minimum 0 days, on the day of surgery and maximum 59 days before) and 53 days after surgery (minimum 21 and maximum 122 day after).

Since our results did not confer with the majority of literature, the study was expanded by examining different cut-off values for NLR classification to see if the initial cut-off was too low. By looking for similar study designs, we decided to use the cut-off values from the studies by Huszno and Kolosza(39) as well as Forget et al.(40) and Hernández et al.(41). Huszno and Kolosza carried out a retrospective analysis of 436 breast cancer patients and found that five-year OS was lower in the group with NLR > 2.65 compared to the group with NLR ≤ 2.65 (82.5 vs. 89.6%, P = 0.053)(39). Based on that, in the current study an additional Kaplan-Meier curve of OS in patients with breast cancer based on low or high NLR values was made using a NLR cut-off value of 2.65. Still, no statistically significant difference was found (P = 0.851). By applying the new cut-off value of 2.65 in Table 5., i.e. in comparison of NLR values before and after surgery, a statistically significant difference was found (P = 0.001). It is worth mentioning that twenty-one out of thirty-six patients with high NLR values (NLR > 2.65) before surgery had a decline in NLR values after surgery and were included in the group with low NLR values (NLR ≤ 2.65) afterward. Forget et

al. primarily investigated the association between intraoperative NSAIDs use in conservative breast cancer surgery and breast cancer DFS. Similarly, they also evaluated the association between breast cancer DFS and preoperative NLR and determined that an NLR > 3.3 before surgery was associated with a shorter DFS (P = 0.01) and OS (P = 0.046)(40). Meanwhile, Hernández et al. analyzed the prognostic value of NLR in breast cancer patients treated with neoadjuvant chemotherapy. Retrospective research of 150 breast cancer patients showed that low NLR values (< 3.33) were associated with a better survival (P = 0.024)(41). Consequently, another Kaplan-Meier analysis was done, using an NLR cut-off value of 3.30 according to the study by Forget et al.(40) and Hernandez et al.(41). However, this cut-off value also did not show a statistical difference in the OS between low and high NLR patient' groups (P = 0.332). By applying the new cut-off value of 3.30 in Table 6., i.e. in comparison of NLR values before and after surgery, a statistically significant difference was found (P < 0.001). Finally, seventeen out of twenty-two patients with high NLR values (NLR > 3.30) before surgery had a decline in NLR values after surgery and were included in the group with low NLR values (NLR ≤ 3.30) afterward.

Azab et al. in their research examined the usefulness of NLR in predicting short- and long-term mortality in breast cancer patients more than 10 years ago. This research was the source and motivation to investigate NLR in breast cancer and many other cancers worldwide. A large study sample allowed them a statistical division into quartiles based on NLR values(54). Different cut-off values based on various quartiles matched with different cut-off values presented in the Tables 2., 5. and 6. of our study: 1st NLR = 2.13; 2nd NLR = 2.65 and 3rd NLR = 3.30. Azab et al. determined a shorter one-, two- and five-year survival in patients in the 4th quartile (NLR ≥ 3.33) compared to the patients in the lower three quartiles (NLR < 3.33) (P < 0.001). However, the lower three quartiles of NLR values (1st quartile NLR < 1.80; 2nd quartile 1.80 ≤ NLR < 2.45; 3rd quartile 2.45 ≤ NLR < 3.33) didn't show a statistically significant difference between each other based on the OS(54). Opposite to them, in the current study the results for NLR at all three cut-off values (2.13, 2.65 and 3.30) didn´t show any statistically significant difference in the OS time of patients after five years (P = 0.855, P = 0.851 and P = 0.332). But similar to the results of Azab et al., we found out that NLR classification before and after surgery changed based on different criteria for cut-off values. The patients' classification based on NLR values at cut-off value of 2.13 didn't change due to surgery (P = 0.058). By changing the initial cut-off value from 2.13 to 2.56 and 3.30 the patients' classification before and after surgery changes significantly (P = 0.001 and P < 0.001).

PLR also proved as a cheap, easily available, and useful prognostic marker in various inflammatory diseases and cancers of different tissues and organs. PLR includes thrombocytes which have a dual role in carcinogenesis and metastasis as well as lymphocytes which are aimed at the destruction of tumor cells. While monitoring treatment outcomes of patients with breast cancer undergoing neoadjuvant chemotherapy, PLR proved to be a useful marker(55). Moreover, other studies on patients with breast cancer confirmed a relationship between PLR and immune response – higher PLR values indicated a stronger immune reaction and worse treatment outcome(56,57,58).

While the research by Azab et al. considered NLR as a better marker in predicting long-term survival in breast cancer patients, with an explanation that neutrophils contribute more to carcinogenesis than thrombocytes(37), the research by Cho et al. pointed out that PLR is a superior prognostic marker than NLR in monitoring treatment outcome in breast cancer patients(59). Azab et al. found out that both NLR and PLR were significant predictors of mortality in the multivariant analysis (P < 0.001 for both). But in case of the lymphocyte subsets analyses – evaluation of the contribution of low lymphocyte counts alone in the predictive ability of PLR and NLR, NLR remained a significant predictor of mortality (P < 0.001 for HR 4.80 and P = 0.025 for HR 3.59), while PLR was no longer statistically significant (P = 0.220 for HR 1.83 and P = 0.070 for HR 2.69). Therefore, NLR is significantly better than PLR and lymphocyte count alone in predicting five-year mortality in breast cancer patients, according to Azab et al.(37). Moreover, Liu et al. investigated NLR and PLR values in 318 nonmetastatic breast cancer patients. Univariate analysis indicated that both elevated parameters (P < 0.001 for both) were associated with poor OS. In high NLR group, the estimated median OS was 42.3 months, while contrary, in

low NLR group, the estimated median OS was 78.2 months (P < 0.001). Similar results were found for PLR. In high PLR group, the estimated median OS was 51.5 months, while in low PLR group, the estimated median OS was 79.3 months (P < 0.001). The predictive value of elevated NLR remained in the multivariable analysis (P < 0.001), but not for PLR (P = 0.104). The analysis results for DFS were almost the same as for the OS. Univariate analysis revealed a significant association between increased NLR and PLR (P < 0.001 for both), but in the multivariable analysis only elevated NLR remained its predictive value (NLR: P < 0.001 and PLR: P =0.229). Therefore, they concluded that both increased NLR and PLR are associated with poor survival, but only NLR is independently correlated with OS and DFS(57). On the other hand, Cho et al. for the first time simultaneously compared the relationship between NLR, derived neutrophil-to-lymphocyte ratio (dNLR), PLR, lymphocyte-to-monocyte ratio (LMR) and clinicopathologic variables, disease-specific survival (DSS), and DFS in 661 breast cancer patients. The results showed that a high PLR value was the only inflammatory marker that was independently associated with worse DSS (mean survival duration, 133.3 vs. 172.2 months, P < 0.001) and DFS (mean survival duration, 92.1 vs. 137.6 months, P < 0.001) in the all-patient group(59). In addition, Huszno and Kolosza presented NLR and PLR as equally good prognostic markers in evaluating the OS of patients with breast cancer. Based on their results, the five-year OS was lower in patients with high PLR values compared to patients with low PLR values (78.7% vs. 89.4%, P = 0.020)(39).

A retrospective study done in Graz on patients treated between 1999 and 2004 identified the preoperative PLR as an independent prognostic marker for survival in breast cancer patients. Multivariable analysis on a cohort of 793 women identified PLR as an independent prognostic factor of poor outcome for patients' cancer-specific survival (CSS) (P = 0.042) as well as an independent prognostic factor for poor survival (P = 0.047). Univariable analysis also showed a significant association between increased PLR and the occurrence of distant metastases (P = 0.010)(58).

Contrary to the study conducted by Jiang et al. which showed the mean OS time in patients with low PLR values was significantly longer than in those with high PLR values (61 vs. 59 months, P = 0.007)(38), our study didn't confirm these results (P = 0.398). However, Jiang et al. didn't identify a significant independent association between PLR and the OS time upon multivariable analysis (P > 0.05)(38).

An updated meta-analysis done by Guo et al. involved twelve studies with 6930 patients and explored the prognostic role of PLR in predicting OS of patients with breast cancer. The combined results demonstrated that patients with higher PLR values were associated with a significantly poor prognosis (P = 0.002). Their subgroup analysis suggested that a cut-off value of 185 was better for PLR in predicting prognosis of breast cancer patients (P < 0.001)(52). This could be a possible explanation why our results with a lower cut-off of 88.23 (Figure 2.) didn´t show any differences in the OS between low and high PLR patient groups (P = 0.398).

Research by Ma et al. collected data of 203 breast cancer patients who underwent surgery after receiving standard neoadjuvant therapy and analyzed the effects of NLR, PLR and LMR on the DFS. They detected a statistically significant difference in the duration of the remission period to the onset of relapse between different patient groups based on PLR values. Patients with breast cancer and high PLR values (PLR > 135) had a shorter remission period than patients with breast cancer and low PLR values (PLR ≤ 135; P < 0.001). However, multivariate analysis revealed that PLR was not a prognostic indicator of DFS in neoadjuvant chemotherapy patients. Ma et al. concluded similarly to us, that this might be because of the included study population and the sample size(60).

SII is a newer marker in the clinical-oncological world and is yet to be proven as a good or even better prognostic marker than NLR and PLR. A big difference compared to NLR and PLR is that SII includes all three blood parameters connected to the immune response of the human body to carcinogenesis: neutrophils, thrombocytes and lymphocytes. Therefore, SII unites NLR and PLR into one comprehensive derived hematological parameter. Since it has only been in use for a few years, it isn't surprising that there are only small number of studies on the use of SII in patients with breast cancer available.

Liu et al. compared NLR, PLR and SII in patients with metastatic NSCLC. By applying 603.5 as a cut-off value it was determined that patients

with low SII values priori to treatment with nivolumab have a significantly longer OS and progression free survival (PFS) that patients with high SII values (median OS 19.8 months vs. 8.9 months (P = 0.005); median PFS 6.9 months vs. 2.4 months (P = 0.006)). Moreover, they concluded that SII is a better prognostic marker than NLR and PLR (61). Bartl et al. studied SII as a prognostic marker in vulvae cancer. They had been monitoring 130 patients with vulvae cancer over a period of almost 20 years in Vienna. Patients with high SII values before starting treatment had a shorter OS rate in comparison with patients with low SII values before starting treatment: 54.1% vs. 71.1% (P = 0.001)(62). Matsubara et al. pointed out that SII is superior to NLR and PLR as a prognostic marker for predicting the PFS and OS in patients with endometrial cancer. Furthermore, the PFS and OS in patients with high SII values was considerably shorter than in patients with low SII values (PFS: P = 0.014 and OS: P = 0.011)(63).

Jiang et al. came to the same conclusion about the superiority and advantages of SII in addition to NLR and PLR for patients with breast cancer. They determined a statistically significant difference in the OS of patients based on their SII values: mean OS time of 65 months in patients with low SII values vs. 41 months in patients with high SII values (P ≤ 0.001). Median OS time was only reached in the high SII and high NLR groups (39 months and 48 months). Moreover, in univariate analysis SII, NLR and PLR were significantly associated with differential OS. However, in case of multivariable analysis only SII was identified as independently associated with OS – patients with low SII values had prolonged OS time (P = 0.017)(38).

Contrary to other studies, our results showed there was no difference in the OS between patients with low and high SII values (Logrank test: P = 0.437). Chen et al. demonstrated that patients with breast cancer and low SII values before starting neoadjuvant chemotherapy had significantly lower risks of disease progression compared to patients with high SII values. Besides, patients with low SII values were related to prolonged DFS (P = 0.006) and OS (P = 0.005). The mean DFS for all enrolled cases with low SII was 40.76 months and the mean DFS for all patients with high SII was 31.11 months. Similarly, results were found for OS: the mean OS for all enrolled cases with low SII was 53.68 months, while the mean OS for all enrolled cases with high SII was 44.47 months. Moreover, the DFS rates at 3-, 5- and 10-year in low SII group were 35.9%, 21.2% and 5.1%, while the DFS rates at 3-, 5- and 10-year in high SII group were 25.5%, 11.3% and 3.8%. Similar results were reported for the OS rate at 3-, 5- and 10-year: in low SII group 47.4%, 33.3% and 8.3% vs. in high SII group 35.8%, 20.8% and 6.6%(64).

Another research by Wanga et al. in patients with triple-negative breast cancer also reported worse outcomes in patients with high SII values. Median OS in patients with high SII values was about 40 months while median OS in patients with low SII values was about 61 months (P < 0.001). Besides OS, the median DFS was also different based on SII values: 14.4 months in patients with high SII values vs. 22.4 months in patients with low SII values (P < 0.001). Multivariable analysis showed that elevated SII was an independent risks factor for poor OS (P < 0.001) as well as poor DFS (P = 0.005)(65).

Ji and Wang conducted a meta-analysis about prognostic prediction of SII for patients with gynecological and breast cancer in 2020. They involved nine articles with a cohort of 2724 patients. The pooled results indicated that high SII values were significantly associated with shorter OS (P < 0.001). Likewise, the meta-analysis revealed that high SII values were significantly associated with poor DFS (P < 0.001). Ji and Wang concluded that high SII may be a promising indicator for the prediction of poor prognosis in patients with gynecological and breast cancer(66).

Considering all of the available literature, our study was the first one to examine follow-up value of NLR, PLR and SII after surgery (before chemotherapy) to see if there is a difference in the stratification of patients according to their inflammation response. Searching on PubMed, only 6 studies investigated all three parameters (NLR, PLR and SII) simultaneously in breast cancer patients, while none of them as follow-up parameters in different time points like in our study (before and after surgery). McNemar test for NLR values at a cut-off value of 2.13 (P = 0.058) and PLR values at a cut-off value of 88.23 (P = 0.146) didn't show any statistically significant difference in patient stratification before and after surgery. However, NLR values at a cut-off value of 2.65 (P = 0.001) and 3.30 (P < 0.001), as well as SII values at cut-off value of 547 (P < 0.001) showed a statistically significant

change after surgery. Twenty-one patients out of the total thirty-six patients (58.3%) had a decrease in NLR values below the cut-off value of 2.65 after surgery, while seventeen out of total twenty-two patients (77.3%) had a decrease in NLR values below the cut-off value of 3.30 after surgery. In the case of SII, all forty-six patients with high SII values had a significant decrease below the cut-off value after surgery. This could be due to the successful removal of cancer and reduction of local inflammatory reaction. Therefore, a decrease in SII below the cut-off value measured at the second time point, i.e. after surgery, could be considered as an indirect marker of a successful and comprehensive surgery.

However, this study has several limitations which must be considered when interpreting the results. First, the present study was done at a single hospital and relatively small-sized sample. Second, there was no examination for other inflammation processes in patients with breast cancer included in our research which might have elevated NLR, PLR and SII values in some time point. In this case, data on other inflammation parameters, such as CRP and PCT might have been helpful to exclude these patients. Another option could have been to study the anamnesis of each patient in detail before including them into the study. This way possible infection, medication, malnutrition, severe stress, and non-malignant inflammatory diseases could have been detected. Third, we didn´t use a uniform measurement period before and after surgery to determine NLR, PLR and SII values. The median time for measurements in our study was 12 days before surgery (minimum 0 days, right before the surgery and maximum 59 days before the surgery) and 53 after surgery (minimum 21 and maximum 122 days after the surgery). Finally, our study didn't use population specific cut-off values but rather predetermined cut-off values from Jiang et al.(38).

CONCLUSIONS

Based on the six-year study data on 192 women diagnosed with invasive breast cancer, we observed the potential of neutrophil-to-lymphocyte ratio – NLR, platelets-to-lymphocyte ratio – PLR, and systemic immune-inflammation index – SII as available, ready-to-use parameters and their importance to the multidisciplinary team of experts and patient outcome. The main conclusions of our retrospective study can be summarized in the following statements:

Pretreatment NLR, PLR and SII values did not have a significant prognostic value for overall survival in patients with invasive breast cancer.

Significant decline in the NLR value was noticed after surgical removal of the breast cancer at the cut-off value of 2.65 ($P = 0.001$) and 3.30 ($P < 0.001$).

The study outcome recommends the cut-off value of 2.65 as the optimal for NLR in predicting the effectiveness and successfulness of the surgical procedure.

The decline in SII values is an even better predictor for the successfulness of the surgery ($P < 0.001$).

REFERENCES

1. Šupe-Domić D, Petrić Miše B. Onkološke bolesti. In: Medicinska biokemija i laboratorijska medicina u kliničkoj praksi. Topić E, Primorac D, Janković S, Štefanović M, (ed.). Zagreb: Medicinska naklada, 2018, p 624-637.
2. GLOBOCAN 2020: New Global Cancer Data, 2020, www.uicc.org/news/globocan-2020-new-global-cancer-data, access 28.02.2021.
3. Incidencija raka u Hrvatskoj 2019., Registar za rak Republike Hrvatske, 2021, https://www.hzjz.hr/wp-content/uploads/2021/12/Bilten44_2019.pdf, access 15.03. 2022.
4. National Cancer Institute (NIH): BRCA Gene Mutations, 2020, https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet, access 04. 12.2020.
5. HER2 Status, 2020, https://www.breastcancer.org/symptoms/diagnosis/her2, access 18.12.2020
6. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014; 371(6):497-506. doi: 10.1056/NEJMoa1400382.
7. Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol. 2008;26(4):542-548. doi: 10.1200/JCO. 2007.12.5922.
8. Izadi S, Nikkhoo A, Hojjat-Farsangi M, Namdar A, Azizi G, Mohammadi H, et al. CDK1 in Breast Cancer: Implications for Theranostic Potential. Anticancer Agents Med Chem. 2020;20(7):758-767. doi: 10.2174/18 71520620666200203125712.

9. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209-3215. doi: 10.1158/1078-0432.CCR-06-0083.
10. Patophysiology of Breast Cancer, 2013, http://cancer-world.info/pathophysiology-of-breast-cancer/, access 04.12.2020.
11. Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect. 2003;111(4):389-394. doi: 10.1289/ehp.5686.
12. Russo J, Hu YF, Silva IDCG, Russo IH. Cancer risk related to mammary gland structure and development. Microsc Res and Tech. 2001;52:204-223. doi: 10.1002/1097-0029(20010115)52:2<204::AID-JEMT1006>3.0.CO;2-F.
13. Friedenreich CM. Review of anthropometric factors and breast cancer risk. Eur J Cancer Prev. 2001;10(1):15-32. doi: 10.1097/00008469-200102000-00003.
14. Hulka BS, Stark AT. Breast cancer: cause and prevention. Lancet. 1995;346(8979):883-887. doi: 10.1016/s0140-6736(95)92713-1.
15. Breast cancer and combined oral contraceptives: results from a multinational study. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Br J Cancer. 1990;61(1):110-119. doi: 10.1038/bjc.1990.23.
16. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ. 2000;321(7261):624-628. doi: 10.1136/bmj.321.7261.624.
17. Rock CL, Lampe JW, Patterson RE. Nutrition, genetics, and risks of cancer. Annu Rev Public Health. 2000;21:47-64. doi: 10.1146/annurev.publhealth.21.1.47.
18. Kelsey JL. Breast cancer epidemiology: summary and future directions. Epidemiol Rev. 1993;15(1):256-263. doi: 10.1093/oxfordjournals.epirev.a036112.
19. Fuqua SA, Cui Y, Lee AV, Osborne CK, Horwitz KB. Insights into the role of progesterone receptors in breast cancer. J Clin Oncol. 2005;23(4):931-932. doi: 10.1200/JCO.2005.05.152.
20. Kaptain S, Tan LK, Chen B. Her-2/neu and breast cancer. Diagn Mol Pathol: 2001;10(3):139-152. doi: 10.1097/00019606-200109000-00001.
21. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med: 2001;344(11):783-792. doi: 10.1056/NEJM200103153441101.
22. Vrodljak E, Šamija M, Kusić Z, Petković M, Gugić D, Krajina Z. Klinička onkologija. Zagreb: Medicinska naklada, 2013. str. 44-45.
23. Duffy MJ. CA 15-3 and related mucins as circulating markers in breast cancer. Ann Clin Biochem. 1999;36(Pt5):579-586. doi: 10.1177/000456329903600503.
24. Vrdoljak E, Šamija M, Kusić Z, Petković M, Gugić D, Krajina Z. Klinička onkologija. Zagreb: Medicinska naklada, 2013. str. 37.
25. Metastatic Breast Cancer, 2021, https://www.breastcancer.org/symptoms/types/recur_metast, access 16.02.2021.
26. Brustkrebs-Metastasen, 2020, https://www.gynecology-guide.com/brustkrebs/brustkrebs-metastasen/, access 31.12.2020.
27. Vrdoljak E,Šamija M, Kusić Z, Petković M, Gugić D, Krajina Z. Klinička onkologija. Zagreb: Medicinska naklada, 2013. str. 201.
28. Chen L, Kong X, Yan C, Fang Y, Wang J. The Research Progress on the Prognostic Value of the Common Hematological Parameters in Peripheral Venous Blood in Breast Cancer. Onco Targets Ther. 2020;13:1397-1412. doi: 10.2147/OTT.S227171.
29. Shilpa M., Kalyani R., Sreeramulu PN. Prognostic value of pre-treatment routine hematological parameters in breast carcinoma: Advantageous or deleterious?. Biomedical Research and Therapy. 2020;7(8):3916-3920. doi: 10.15419/bmrat.v7i8.621.
30. Lee KH, Kim EY, Yun JS, Park YL, Do SI, Chae SW, et al. The prognostic and predictive value of tumor-infiltrating lymphocytes and hematologic parameters in patients with breast cancer. BMC Cancer. 2018;18(1):938. doi: 10.1186/s12885-018-4832-5.
31. Abbas AK, Lichtman AH, Pillai S. Stanična i molekularna imunologija. Zagreb: Medicinska naklada, 2018. str. 14-18.
32. Abbas AK, Lichtman AH, Pillai S. Stanična i molekularna imunologija. Zagreb: Medicinska naklada, 2018. str. 388-391.
33. Lee KH, Kim EY, Yun JS, Park YL, Do SI, Chae SW, et al. The prognostic and predictive value of tumor-infiltrating lymphocytes and hematologic parameters in patients with breast cancer. BMC Cancer. 2018;18(1):938. doi: 10.1186/s12885-018-4832-5.
34. Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P, et al. Platelet "first responders" in wound response, cancer, and metastasis. Cancer Metastasis Rev. 2017;36(2):199-213. doi: 10.1007/s10555-017-9682-0.
35. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. Blood. 2015;126(5):582-588. doi: 10.1182/blood-2014-08-531582.
36. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-458. doi: 10.1038/nrc1098.
37. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol. 2013;30(1):432. doi: 10.1007/s12032-012-0432-4.
38. Jiang C, Lu Y, Zhang S, Huang Y. Systemic Immune-Inflammation Index Is Superior to Neutrophil to Lymphocyte Ratio in Prognostic Assessment of Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy. Biomed Res Int. 2020;2020:ArtID7961568. doi: 10.1155/2020/7961568.

39. Huszno J, Kolosza Z. Prognostic value of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratio in breast cancer patients. Oncol Lett. 2019 Dec;18(6):6275-6283. doi: 10.3892/ol.2019.10966.
40. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth. 2014 Jul;113(Suppl1):i82-7. doi: 10.1093/bja/aet464.
41. Marín Hernández C, Piñero Madrona A, Gil Vázquez PJ, Galindo Fernández PJ, Ruiz Merino G, Alonso Romero JL, et al. Usefulness of lymphocyte-to-monocyte, neutrophil-to-monocyte and neutrophil-to-lymphocyte ratios as prognostic markers in breast cancer patients treated with neoadjuvant chemotherapy. Clin Transl Oncol. 2018 Apr;20(4):476-483. doi: 10.1007/s12094-017-1732-0.
42. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-444. doi: 10.1038/nature07205.
43. Walz W, Cayabyab FS. Neutrophil Infiltration and Matrix Metalloproteinase-9 in Lacunar Infarction. Neurochem Res. 2017;42(9):2560-2565. doi: 10.1007/s11064-017-2265-1.
44. Tan KW, Chong SZ, Wong FH, Evrard M, Tan SM, Keeble J, et al. Neutrophils contribute to inflammatory lymphangiogenesis by increasing VEGF-A bioavailability and secreting VEGF-D. Blood. 2013;122(22):3666-3677. doi: 10.1182/blood-2012-11-466532.
45. Queen MM, Ryan RE, Holzer RG, Keller-Peck CR, Jorcyk CL. Breast cancer cells stimulate neutrophils to produce oncostatin M: potential implications for tumor progression. Cancer Res. 2005;65(19):8896-8904. doi: 10.1158/0008-5472.CAN-05-1734.
46. Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, et al. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol. 2011;54(5):948-955. doi: 10.1016/j.jhep.2010.08.041.
47. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res. 2008;14(21):6735-6741. doi: 10.1158/1078-0432.CCR-07-4843.
48. Mayer Lj, Langer S, Gaće M, Hrabač P, Šostarić M, Fijan I, et al. Prediction score for complications after colorectal cancer surgery based on neutrophils/lymphocytes ratio, percentage of immature granulocytes, IG and IT ratios. Libri Oncologici. 2019;47(1):1-5. doi: 10.20471/LO.2019.47.01.01.
49. Mouchli M, Reddy S, Gerrard M, Boardman L, Rubio M. Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma." Review article. Ann Hepatol. 2021;22:100249. doi: 10.1016/j.aohep.2020.08.067.
50. Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. Prognostic Value of the Neutrophil to Lymphocyte Ratio (NLR) in Lung Cancer Cases. Asian Pac J Cancer Prev. 2017;18(5):1417-1421. doi: 10.22034/APJCP.2017.18.5.1417.
51. Cedrés S, Torrejon D, Martínez A, Martinez P, Navarro A, Zamora E, et al. Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol. 2012;14(11):864-869. doi: 10.1007/s12094-012-0872-5.
52. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W, et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: An updated meta-analysis of 17079 individuals. Cancer Med. 2019 Aug;8(9):4135-4148. doi: 10.1002/cam4.2281.
53. Liu X, Qu JK, Zhang J, Yan Y, Zhao XX, Wang JZ, et al. Prognostic role of pretreatment neutrophil to lymphocyte ratio in breast cancer patients: A meta-analysis. Medicine (Baltimore). 2017 Nov;96(45):e8101. doi: 10.1097/MD.0000000000008101.
54. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol. 2012;19(1):217-224 doi: 10.1245/s10434-011-1814-0.
55. Cuello-López J, Fidalgo-Zapata A, López-Agudelo L, Vásquez-Trespalacios E. Platelet-to-lymphocyte ratio as a predictive factor of complete pathologic response to neoadjuvant chemotherapy in breast cancer. PLoS One. 2018;13(11):e0207224. doi: 10.1371/journal.pone.0207224.
56. Durhan A, Durhan G, Eroğlu A. Regression in local recurrence in the contralateral breast following mastectomy in bilateral locally advanced breast cancer: A comparison of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios. Turk J Surg. 2018;34(2):140-142. doi: 10.5152/UCD.2016.3214.
57. Liu C, Huang Z, Wang Q, Sun B, Ding L, Meng X, et al. Usefulness of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in hormone-receptor-negative breast cancer. Onco Targets Ther. 2016;9:4653-4660. doi: 10.2147/OTT.S106017.
58. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;110(10):2524-2530. doi: 10.1038/bjc.2014.163.
59. Cho U, Park HS, Im SY, Yoo CY, Jung JH, Suh YJ, et al. Prognostic value of systemic inflammatory markers and development of a nomogram in breast cancer. PLoS One. 2018;13(7):e0200936. doi: 10.1371/journal.pone.0200936.
60. Ma Y, Zhang J, Chen X. Lymphocyte-to-Monocyte Ratio is Associated with the Poor Prognosis of Breast Cancer Patients Receiving Neoadjuvant Chemotherapy. Cancer Manag Res. 2021;13:1571-1580. doi: 10.2147/CMAR.S292048.

61. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal. 2019;33(8):e22964. doi: 10.1002/jcla.22964.
62. Bartl T, Bekos C, Postl M, Alexander R, Polterauer S, Stefanie A, et al. The systemic immune-inflammation index (SII) is an independent prognostic parameter of survival in patients with invasive vulvar cancer. J Gynecol Oncol. 2021;32(1):e1. doi: 10.3802/jgo.2021.32.e1.
63. Matsubara S, Mabuchi S, Takeda Y, Kawahara N, Kobayashi H. Prognostic value of pre-treatment systemic immune-inflammation index in patients with endometrial cancer. PLoS One., 2021;16(5):e0248871. doi: 10.1371/journal.pone.0248871.
64. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pretreatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med. 2020;24(5):2993-3021. doi: 10.1111/jcmm.14934.
65. Wang P, Yue W, Li W, Luo Y, Li Z, Shao Y, et al. Systemic immune-inflammation index and ultrasonographic classification of breast imaging-reporting and data system predict outcomes of triple-negative breast cancer. Cancer Manag Res. 2019;11:813-819. doi: 10.2147/CMAR.S185890.
66. Ji Y, Wang H. Prognostic prediction of systemic immune-inflammation index for patients with gynecological and breast cancers: a meta-analysis. World J Surg Oncol. 2020 Aug 7;18(1):197. doi: 10.1186/s12957-020-01974-w.

Sažetak

PROGNOSTIČKI ZNAČAJ PREDOPERATIVNIH RAČUNSKIH HEMATOLOŠKIH UPALNIH PARAMETARA KOD PACIJENTICA S KARCINOMOM DOJKE

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Karcinom dojke je najčešća zloćudna bolest među ženama i čini oko četvrtinu svih karcinoma u žena na svjetskoj razini. Na ovu vrstu neplastične bolesti, raka, uglavnom utječu genetski, okolišni i životni čimbenici poput prehrane i tjelesne aktivnosti.

U ovom radu riječ je o retrospektivnom istraživanju koje je uključivalo 192 žene s rakom dojke, a obuhvaća podatke prikupljene tijekom šest godina (od 2015. do 2021.). Istraživan je međusobni odnos između neizravnih hematoloških parametara, omjera neutrofila i limfocita – NLR, omjera trombocita i limfocita – PLR, indeksa sistemske imunološke upale – SII te ishoda liječenja. Osim toga, praćena je ukupna stopa preživljavanja (OS).

Dobiveni rezultati prikazuju odnos praćenih parametara prije i nakon kirurške intervencije te je važno naglasiti da je kod graničnih vrijednosti od 2,65 ($P = 0,001$) i 3,30 ($P < 0,001$) uočen pad vrijednosti NLR nakon kirurškog uklanjanja tkiva karcinoma dojke. Isti pad zabilježen je za SII nakon operacije ($P < 0,001$). Kroz provedenu studiju, pokazalo se da je SII relevantniji parametar u usporedbi s NLR i PLR.

U konačnici, možemo zaključiti iz istraživanja, da se granična vrijednost od 2,65 preporučuje kao optimalna za praćenje vrijednosti NLR u predviđanju učinkovitosti i uspješnosti kirurškog zahvata.

KLJUČNE RIJEČI: *karcinom dojke, omjer neutrofila i limfocita (NLR), omjer trombocita i limfocita (PLR), indeks sistemske imunološke upale (SII), neadjuvantno liječenje*