Original article

Prognostic value of lymphocyte-related systemic inflammatory biomarkers in triple negative breast cancer

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ABSTRACT

The aim was to evaluate inflammatory biomarkers as prognostic factors in patients with triple negative breast cancer. We have collected data from 143 patients and evaluated using Chi-Squared test, Wilcoxon–Mann–Whitney test and Cox regression. We found a relationship between high neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune inflammation index and local advancement features: tumor (T3/T4) (P = 0.0001, P = 0.0198, P = 0.0001), positive regional lymph nodes (P = 0.0014, P = 0.0075, P = 0.0206). In the multivariate analysis metastatic disease, worse performance status and high NLR (hazard ratio: 4.48 [2.05–9.80], P = 0.0002; 2.23 [1.24–4.03], P = 0.0010; 2.23 [1.24–4.03], P = 0.0075) were adverse prognostic factors. High neutrophil-to-lymphocyte ratio with worse performance status turned out an adverse independent prognostic factors.

Key words: triple negative breast cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, the systemic immune inflammation index, prognostic factor

INTRODUCTION

Breast cancer is the most common cancer in women in the world and remains the second cause of cancer deaths in decades [1]. Brest cancer was the first cause of cancer incidence among all oncology patients with estimated 2.3 million new cases (11.7% of all cancers) surpassed lung cancer (2.2 million new cases) and the leading cause of death among women, followed by lung cancer – with 684,996 deaths around the world in 2020 [2]. Triple negative breast cancer (TNBC), which accounts 10–20% of all breast cancer patients, refers to tumors that do not express the estrogen receptor (ER), progesterone receptor (PR) and do not overexpress human epidermal growth factor 2 (HER2) receptor in immunohistochemical staining (IHC). TNBC has been associated with African-American race, deprivation status, younger age at diagnosis, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer and breast cancer type 1 susceptibility protein (BRCA1) mutations [3]. It is assumed that worse results of TNBC treatment are associated with more aggressive malignant behavior and a lack of molecularly targeted therapies [4].

The growing risk of obesity among the societies of highly developed countries and the increase in the percentage of patients with TNBC may suggest certain mechanisms linking obesity and TNBC [5]. The complexity of the pathogenesis of both obesity and TNBC presents a challenge in determining the effect of obesity on TNBC risk. The mechanisms identified in the tumor microenvironment as well as in the obesity microenvironment, such as insulin resistance, inflammatory processes, and survival pathways, that contribute to the development and progression of TNBC are interrelated [5]. In experimental studies, significant differences were observed in the tumor's immune microenvironment depending on the presence of obesity in patients [6]. It was found that with age deterioration of T lymphocyte function is observed, which was exacerbated by obesity and related leptin. Obese patients showed decreased proliferative capacity and increased expression of the exhaustion markers programmed cell death protein 1 (PD-1), lymphocyte activation gene 3 (LAG3), and T-cell immunoglobulin and mucin-domain containing-3 (TIM3) of the CD8+ cytotoxic T-cell compartment [6]. Changes in macrophages in adipose tissue of obese patients with breast cancer was also found. Analysis of macrophages in mammary gland tissue from obesity, cancer-free patients and observed an increase in macrophage density with a M2-biased [7]. In turn the macrophages present in mammary gland tissue from obesity TNBC patients showed that obesity is associated with the presence of pro-inflammatory macrophages M1, which may be protumorogenic [8].

Oncogenic changes in cells lead to the induction of inflammatory pathways in precancerous and malignant cells. Inflammatory cells and their mediators (including chemokines, cytokines and prostaglandins) in the tumor microenvironment influenced on environment of proinflammatory responses that can act in an autocrine and/or paracrine manner on both malignant and non-malignant cells [9]. Thus, inflammation may, on the one hand, stimulate an anti-tumor immune response, but on the other hand induce tumor formation and inhibit immune response [10]. Proinflammatory factors are considered as potential markers for the outcome of patients with cancer because inflammation associated with the tumor has a great influence on the development of cancer, its progression, and its response to the administered therapy [11]. Inflammatory biomarkers as the neutrophil, lymphocyte and platelet count, as well as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) may be prognostic factors in different types of solid tumor [12, 13]. Elevated peripheral indicators of systemic inflammation as NLR, PLR may be associated with poorer outcomes in TNBC [14, 15].

The aim of this study was analysis of the association of NLR, PLR, overweight with survival outcomes in patients with TNBC.

MATERIALS AND METHODS

Study population

This study included 143 subsequent histologically confirmed invasive TNBC cases, out of group of 854 patients with invasive breast cancer which were diagnosed and qualified for chemotherapy in Department of Oncology and Immuno-Oncology, Warmian-Masurian Cancer Center of The Ministry of The Interior and Administration's Hospital, Affiliated to University of Warmia and Mazury in Olsztyn, Poland between January 2015, and December 2017. Eligible criteria were aged ≥18 years with cytologically or pathologically confirmed diagnosis of TNBC, as defined by ER < 1% and PR < 1% expression at IHC analysis and an IHC score for HER2 of 0, 1+, or 2+ with negative in situ hybridization (ISH). All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0–2 and availability of pre-treatment absolute peripheral blood neutrophil, lymphocyte and platelet counts; height, weight, creatinine blood serum level. Patients with incomplete follow-up data or active concurrent infection were excluded. At recruitment, personal data of each participant regarding clinical characters and survival information were collected from clinical records or family contacts. As the factors related to systemic inflammatory may be related to

both the tumor profile and the patient's profile, the results of the blood count before chemotherapy reflecting the patient's status, regardless of the anatomical advancement of the disease, have been analyzed. The overall survival (OS) was defined as time from the data of administration of first dose of chemotherapy to the data of death or status check in the National Health Fund register on 02.2021 for censored observations. Until that day, 49 patients had died while 94 were censored observations.

The study was approved by the Regional Ethical Review Board at the Warmian-Masurian Medical Chamber, Olsztyn, Poland. The Institutional Review Board (IRB) number of this study is WMIL-KB/345/2019. The requirement for written informed consent was waived according to the decision of IRB due to the retrospective nature of this study.

Data collection

Clinical characteristics including age, gender, height, weight, type of treatment, surgery, chemotherapy, radiotherapy, creatinine blood serum level, total blood count, histological subtype of cancer and grade, clinical TNM stage, pathologic type as well as outcomes were collected. The tumors were staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC 7th ed., 2010). For the purpose of this study, we chosen the earliest available data about eligible patients before first cycle of chemotherapy.

The blood cell counts including neutrophil, platelets, and lymphocyte before treatment were extracted from the medical records. NLR has been calculated from total neutrophil number (10^3/μl) divided by total leukocyte number (10^3/μl). PLR has been counted similarly, by dividing total platelet count ($\times 10^3$/μl) by total leukocyte number ($\times 10^3$/μl).

SII defined as follows: SII = P × N/L, where P, N and L were the peripheral platelet, neutrophil and lymphocyte counts. We calculated Body Mass Index (BMI) from height and body mass from the first, closest to and before administration of first chemotherapy cycle. As for glomerular filtration rate (GFR), we have used the Cockcroft–Gault equation, calculated from sex, creatinine blood serum level, body weight and height.

Statistical analysis

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. The differences between the two assessed groups were evaluated using the Pearson Chi Square test for categorical variables and the U Mann-Whitney test for continuous variables. Median survival and life tables were computed using the product-limit estimate by the Kaplan-Meier method. Binary variables were converted from continuous or ordinal variables using following rules:

- ECOG: 0–1 versus 2
- age: <70 years versus ≥ 70 years
- BMI: cut points were taken from the literature for overweight and obesity (25 kg/m^2 and 30 kg/m^2, respectively) [16]
- NLR and PLR: cut points were taken from the literature (3.0 for NLR; 185 for PLR) [17]
- SII: cut point was taken from the literature as 600 [18].

Univariate analyses of variables influencing OS were performed by log rank test, which identified a preliminary list of significant factors. All variables with P value less than 0.1 were thereafter included in a multivariate analysis that was performed by Cox proportional-hazard regression with the forward stepwise method for variable selection. P values less than 0.05 (two-sided) were considered to indicate statistical significance.

Statistical analyses were performed using the statistical package Statistica 12.5 (Dell Software, Round Rock, TX, USA).

RESULTS

Patient characteristics

Overall, 143 patients were eligible for the analysis. The median follow-up was 53.3 months (95% CI: 50.9–78.9). The detailed characteristics of patients at the start of the first cycle of chemotherapy are presented in table 1.

Table 1. Patients' baseline demographic and clinical characteristics.

Parameter	Number of patients (%)
Age, median, range (in years)	58 (29–85)
Gender	
• male	0
• female	143 (100)
Race	
• Caucasian	143 (100)
ECOG PS	
• 0	108 (75)
• 1	34 (24)
• 2	1 (1)
Tumour stage:	
• T1	21 (15)
• T2	67 (47)
• T3	31 (22)
• T4	24 (17)

Lymph node status	
• N0	69 (48)
• N1	53 (37)
• N2	15 (10)
• N3	6 (4)
Metastases	
• M0	131 (92)
• M1	12 (8)
AJCC stage	
• I	13 (9)
• II	74 (52)
• III	44 (31)
• IV	12 (8)
Chemotherapy	
• NAC	78 (55)
• AC	53 (37)
• PC	12 (8)
ALC median, (95% CI), $\times 10^9$/l	4.30 (2.10–13.80)
Platelets, median (95% CI), $\times 10^9$/l	250 (157–435)
Lymphocytes median, 95% CI $\times 10^9$/l	1.80 (1.00–2.90)
NLR	
Median, 95% CI	2.21 (1.14–12.14)
• < 3	100 (70)
• ≥ 3	43 (30)
PLR	
Median, 95% CI	253 (157–456)
• < 185	30 (21)
• ≥ 185	113 (79)
SII	
Median, 95% CI	537 (223–3342)
• < 600	79 (55)
• ≥ 600	64 (45)
GFR CG median, range (ml/min/1.73 m^2)	101.12 (47.94–213.16)
GFR CG	
• < 60 (ml/min/1.73 m^2)	12 (8)
• ≥ 60 (ml/min/1.73 m^2)	131 (92)
BMI median, range (kg/m^2)	26.99 (15.23–43.91)
BMI (kg/m^2)	
• < 25	52 (36)
• ≥ 25	91 (64)
BMI (kg/m^2)	
• < 30	96 (67)
• ≥ 30	47 (33)

AC – adjuvant chemotherapy; AJCC – American Joint Committee on Cancer; BMI – body mass index; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; GFR CG – glomerular filtration rate based on Cockcroft-Gault formula; M – metastases; N – lymph nodes; NAC – neoadjuvant chemotherapy; NLR – neutrophil to lymphocyte ratio; PC – palliative chemotherapy; PLR – platelet to lymphocyte ratio; PS – performance status; SII – systemic immune-inflammation index; T – tumour.

Assessment of systemic markers of inflammation and immunity

All patients with TNBC were divided according to the cut-off points described in the study methodology into either low- or high-NLR groups. Similarly, the patients also dissolved into the low-PLR and the high-PLR groups and into the low-SII and the high-SII groups (tab. 2).

We found a relationship between high NLR, PLR, and SII groups and more advanced local advancement features, i.e. T3/ T4, and positive regional lymph nodes. Additionally, we observed a relationship between high NLR and SII groups and the occurrence of distant metastases and a worse performance status than ECOG 0. As demonstrated in table 2, significant difference was observed in clinicopathologic characteristics between patients with TNBC with low and high PLR/NLR and SII as BMI, age, glomerular filtration rate (GFR CG).

Prognostic factors for OS

The clinical parameters that correlated with OS identified in the univariate analysis are presented in table 3. Statistical significance was found for the following factors: NLR (fig. 1A), SII (fig. 1B), overweight, performance status, metastatic disease. Age, PLR, obese and glomerular filtration rate (GFR CG) were not correlated with OS.

In the multivariate analysis, metastatic disease, worse performance status than ECOG 0 and high NLR (HR: 4.48 [2.05–9.80], P = 0.0002; 2.23 [1.24–4.03], P = 0.0010; and 2.23 [1.24–4.03], P = 0.0075, respectively) were independent adverse prognostic factors (tab. 4).

DISCUSSION

In recent years, the role of inflammatory factors in the development and progression of cancer has been recognized, mainly due to the potential influence of the tumor microenvironment in inducing a systemic pro-inflammatory response. In several types of cancer, inflammatory biomarkers have been accepted as recognized in the prognostic score, such as the International Metastatic RCC Database Consortium (IMDC) score in advanced renal cell carcinoma [19, 20].

Recently, an increased neutrophil to peripheral lymphocyte (NLR) ratio has been considered as a poor prognostic indicator in breast cancer [17, 21]. The statistical significance of SII and NLR impact on OS may seem to be dependent on each other, being probably mostly dictated by the method of calculating those indexes based on neutrophile blood serum levels. Our study has shown that with high level of NLR 3-year overall survival was worse compared to low level NLR in TNBC patients. High level of SII was also an indicator for poorer prognosis compared to

Table 2. Association between NLR, PLR and SII and clinicopathological parameters in patients with TNBC (n = 143).

Parameter	NLR		*P*-value	PLR		*P*-value	SII		*P*-value
Age (years)	low	high		low	high		low	high	
< 70	83	40	0.1862	24	99	0.2871	68	55	0.9811
≥ 70	17	3		6	14		11	9	
Metastases									
M0	96	35	**0,0105***	28	103	0.9897	77	54	0.0123*
M1	4	8		2	10		2	10	
BMI (kg/m^2)									
< 25	35	17	0.6052	7	45	0.0963	28	24	0.7993
≥ 25	65	26		23	68		51	40	
BMI (kg/m^2)									
< 30	66	30	0.6601	18	78	0.3495	56	40	0.2884
≥ 30	34	13		12	35		23	24	
GFR CG (ml/min/1.73 m^2)									
≥ 60	91	40	0.9432	27	104	0.9897	73	58	0.7036
< 60	9	3		3	9		6	6	
ECOG PS									
0	82	26	**0.0060**	25	83	0.2648	66	42	0.0132*
≥ 1	18	17		5	30		13	22	
T									
1–2	79	17	**0.0001***	24	64	**0.0198***	60	28	0.0001*
3–4	29	26		6	49		19	36	
N									
negative	57	12	**0.0014***	21	48	**0.0075***	45	24	0.0206*
positive	43	31		9	65		34	40	

BMI – body mass index; ECOG PS – The Eastern Cooperative Oncology Group scale of performance status; GFR CG – glomerular filtration rate based on Cockcroft- Gault formula; M – metastases; N – lymph nodes; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index; T – tumour. * The value of the probability of a statistically significant (P < 0.05).

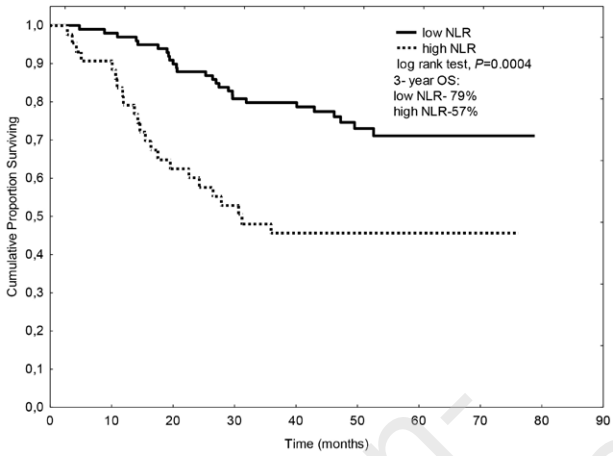
Table 3. Impact of clinicopathological parameters on overall survival in patients with TNBC (univariate analysis; N = 143).

Parameter	Patients		3-year OS (%)	*P*-value
	N	%		
Age (years)				
< 70	123	86	70	0.1714
≥ 70	20	14	68	
GFR CG (ml/min/1.73 m^2)				
≥ 60	131	92	70	0.5467
< 60	12	8	67	
BMI (kg/m^2)				
< 25	52	36	77	**0.0301***
≥ 25	91	64	65	
BMI (kg/m^2)				
< 30	96	67	69	0.9376
≥ 30	47	33	69	
ECOG PS				
0	108	76	79	**< 0.0001***
≥ 1	35	24	39	
AJCC stage				
I–III	131	92	74	**< 0.0001***
IV	12	8	17	
NLR				
low	100	70	80	**0.0004***
high	43	30	46	
PLR				
low	30	21	65	0.72486
high	113	79	71	
SII				
low	79	55	79	**0.0045***
high	64	45	57	

AJCC – American Joint Committee on Cancer; BMI – body mass index; ECOG – The Eastern Cooperative Oncology Group scale of performance status; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index. * The value of the probability of a statistically significant (P < 0.05).

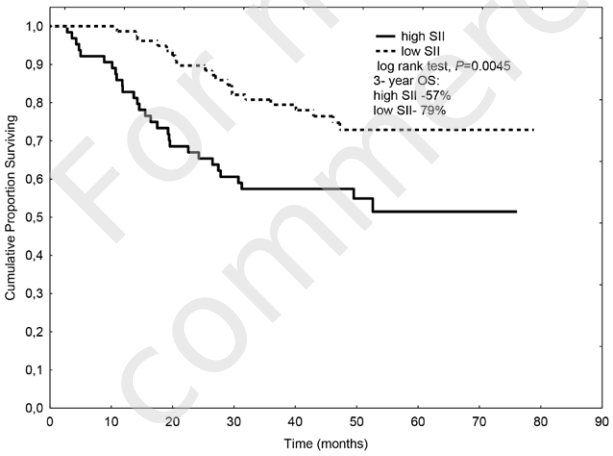
Figure 1. A. Overall survival by neutrophil to lymphocyte ratio. B. Overall survival by systemic immune-inflammation index. \s P – the value of the probability of a statistically significant; OS – overall survival; NLR – neutrophil to lymphocyte ratio

A



P – the value of the probability of a statistically significant; OS – overall survival; SII – systemic immune-inflammation index.

B



low level. No statistically significant correlation has been found to PLR as biomarker of inflammatory status. Several studies have investigated correlation between SII, NLR and PLR and prognosis in cancer patients. In a published recently article by Liu et al. [22] the significance of prognostic value of SII has been described. In this study clinical information from a group of 160 patients was collected and analysed. The authors found increased SII correlated with poor OS in univariate and multivariate analysis models. The disease-free survival (DFS) and distant metastases-free survival (DMFS) of patients with high SII were 18.8 and 23.8 months, respectively, while those of patients with low SII were 29 and 45.2 months, respectively ($p < 0.001$). Further more univariate analyses showed a significant correlation between SII and DFS and DMFS, while results from multivariate analyses suggested that SII was an independent prognostic factor for DFS, but not for DMFS.

Table 4. Multivariate analysis for overall survival in patients with TNBC (N = 143).

Parameter	Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value
ECOG PS • 0 • ≥ 1	2.86 (1.53–5.37)	0.0010*
AJCC stage • I–III • IV	4.48 (2.05–9.80)	0.0002*
NLR • low • high	2.23(1.24–4.03)	0.0075*
PLR • low • high	-	NS
SII • low • high	-	NS
BMI (kg/m^2) • < 25 • ≥ 25	-	NS

AJCC – American Joint Committee on Cancer; BMI – body mass index; CI – confidence interval; ECOG PS – The Eastern Cooperative Oncology Group scale of performance status; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index. * The value of the probability of a statistically significant ($P < 0.05$).

The area under the receiver operating characteristics curves for SII to differentiate between long and short OS, DFS, and DMFS were 0.69, 0.60, and 0.64, respectively. As seen a similar outcome concerning OS has been achieved in this study.

Huszno et al. [9] published a paper on the topic of the prognostic value of PLR and NLR ratio in breast cancer patients. In retrospective observation in 436 patients with different types of breast cancer was found trend of shorter 5-year OS in the high NLR group compared with the low NLR group in the entire study population, but it was significantly shorter in the subgroup of TNBC patients. The 5-year OS was shorter in patients with high PLR compared with that in the low PLR group. A poor OS rate associated with an elevated PLR was also observed in the subgroups with TNBC. Multivariate analysis revealed that the NLR and PLR were non-significant prognostic factors, except for the subgroup of patients with ER(–) tumors, where an elevated NLR and a higher PLR were independent prognostic factors for poor OS together with lymph node metastasis. These results revealed that an elevated NLR and PLR were associated with poor OS in BC patients. In the ER(–) subgroup of patients, an elevated NLR and PLR were significant independent prognostic factors. In comparison to our study, where NLR showed some statistical significance

with no significance coming from PLR, this study showed the impact of both of those factors as independent in poor OS prognosis in TNBC patients. Our results are inconsistent with the results of the metanalysis by Guo et al. [17], although we adopted the same cut-off point for PRL – 185 after them. Based on a total of 12 studies with 6930 patients explored the prognostic role of PRL in predicting OS of patients with breast cancer authors suggested that patients with higher PRL had a significantly poor prognosis. We did not observe this effect in our study. The intercession for such an occurrence is unknown to us, but it may be caused by belonging to Caucasian race. The race affects the distribution of adipose tissue, influencing inflammatory process and immune system [23, 24]. There is possibility of BMI having a connection with different data derived from complete blood count.

In their study Jiang et al. [25] made a comparison between NLR and SII making an assumption, that SII has a better prognostic utility of OS in patients with breast cancer treated with NAC. The cut-off values for patient grouping were SII 547($\times 10^9$/l), NLR 2.13 ($\times 10^9$/l), and PLR 88.23 ($\times 10^9$/l). The comparison of area under the curve (AUC) between the SII and NLR showed superiority of SII. In comparison, in our study NLR was proven to have a bigger impact on 3-year OS, but this study covered patients diagnosed with all kinds of breast cancer, not just TNBC.

Our study has shown statistical importance but meagre effect on OS for patients with BMI same or higher than 25 kg/m^2 (defined as overweight) compared with patients with BMI lower than 25 kg/m^2. With BMI ≥ 30.0 kg/m^2 as cut-out point there seems to be no difference in OS but no statistical importance has been found. Such an outcome may be caused by small number of eligible patients, leaving a possibility a different result for bigger group.

An explanation can be found in a paper on the topic regarding obesity and its protumor changes in the body. Wang et al. [26] presented new approaches to addressing the question of the influence of body weight and oncogenesis. They shown that elevated macrophage activity, as seen in obese patients, may be linked to PD-L1 expression in TNBC. Through several tests (such as western blot, RNA interference, ELISA, qRT-PCR, immunohistochemistry etc.) conducted on tumor samples from chosen TNBC patients they have made a comparison between expression of PD-L1 mRNA and DNA in tumor and healthy breast tissue. Released from macrophages Il-6 and other cytokines promotes further microenvironmental changes leading to higher PD-L1 expression.

Jarroudi et. al [27] have concluded that BMI may be used as OS prognostic factor for postmenopausal patients being much more helpful than while being used for premenopausal patients. The observed group consisted of 115 women with 82 of them identified as overweight, with BMI ≥ 25 kg/m^2. Also, this group of patients had bigger tumors (> 3 cm in diameter). The overweight patient group had significantly higher rates of overall mortality and disease progression.

Mowad et al. [28] based on observation of 183 patients described a higher T stage, and higher tumor grade in overweight patients (BMI > 25 kg/m^2). The authors not found impact of overweight on decreased overall survival or DFS in patients with TNBC. In our study patients with feature T3 or T4 in TNM staging have shown correlation with increased NRL, PLR and SII values but no statistical significance has been shown between elevated levels of NLR, PLR, SII and overweight.

Furuncuoglu et al. [24] found a positive linear correlation between high BMI and WBC, neutrophil count, leukocyte count, platelet count and SII. Increased levels of those parameters have been observed in patients with BMI above 25 kg/m^2 (cut-out point for overweight). It is possible that the increase in both neutrophil and leukocyte count and SII as peripheral indicators of systemic inflammation may be due to a disorders in the course of overweight.

The body mass index may seem like great instrument for patients' body assessment, but it does not include body composition, thus the amount of adipose tissue may not be properly assessed. There is a possibility for patients with e.g. sarcopenia, to have BMI within normal range on account of having smaller share in percentage of body composition of muscle tissue with bigger percentage of adipose tissue. BMI level does not seem to be a sufficient determinant for poorer OS and DFS in TNBC [29]. Our study suggests no correlation between obesity and inflammation indicators due to no statistical significance in our study. In spite of all, more research should be conducted regarding this topic, best by eliminating negative aspects of our study (bigger number of patients, prospectiveness instead of retrospectiveness). Even though with increased body weight there are some physiological changes associated with higher inflammation level leading theoretically to higher WBC count in complete blood count. This may lead to a conclusion that increased weight, NLR, PLR and SII status may not be a single determinant leading to poorer OS and DFS, but other physiological changes coming with overweight [30].

In recent years, many publications have shown that renal failure often occurs in patients with solid tumors [31, 32]. In our study, renal failure measured with eGFR < 60 ml/min/1.73 m^2 according to the

C-G formula occurred in 8% of patients. A similar result of the frequency of renal failure was observed in the study by Launay-Vacher et al. [33], where eGFR below 60 ml/min/1.73 m^2 measured with the same formula, in the group of 1321 patients with breast cancer without bone metastases was approximately 11%. Another element analyzed in the population of cancer patients was the assessment of the impact of renal failure on overall survival. Many studies confirmed correlation between the incidence of renal failure and increased mortality in cancer patients [34]. In our study, we did not show a significant relationship between eGFR according to the C-G formula and inflammatory biomarkers as NRL, PLR and SII and impact on prognosis. The lack of relationship between the assessed glomerular filtration rate and increased mortality may result from smaller size of our group compared to other studies. In the literature, no studies were available on the relationship between the inflammatory biomarkers analyzed in our study: NRL, PLR, SII and eGFR in patients with breast cancer.

Also, comparing our study with studies about the utility of tumor-infiltrating lymphocytes (TILs) may be important [35]. It has been observed that higher levels of lymphocyte infiltration is associated with effective antitumor response [36]. Phase III of ECOG 2197 and 1199 randomized trials resulted in confirmation of the importance of TILs in TNBC [37]. The results stated for every 10% increase of TILs comes reduction of recurrence or death (by 14%, $p = 0.02$). Tumor-infiltrating lymphocytes (TILs) may be associated with host cell-mediated immunity, which may be reflected in part by the count of peripheral blood cells [38]. Lymphocyte-predominant breast cancer (LPBC, defined as tumors with high TIL ≥ 50%) showed a favorable prognosis for TNBC. Yoon et al. [39] assessed whether the number of peripheral blood cells is related to LPBC. In the group of 810 patients, the LPBC subtype was found in 16%. When assessing the 3 biomarkers of peripheral blood counts: absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and neutrophil to lymphocyte ratio (NLR), LPBC had significantly lower mean ANC than non-LPBC. Significant inverse correlations between continuous AND and TIL were observed in the ER-negative and high Ki67 subgroups. The authors concluded that low peripheral ANC may be associated with LPBC, supporting the hypothesis that systemic immune cell counts may be related to the tumor immune microenvironment [39].

The main limitation of our study was its retrospective nature. It was a single center study with a representative group of 143 patients eligible for analysis, but still too small to draw an unambiguous conclusion. There is a possibility that with a greater number of participants the outcomes could slightly differ. Also, as we have collected the retrospective data from prior made tests, in a prospective study we could have include more detailed laboratory examinations assessing the inflammation markers in patients and from more patients. Time of observation after collecting data may also have an importance for this study. With longer observation more patients could possibly be included in this study, but at the same time the lethality of TNBC calculated from derived data could increase. There is a possibility, that with longer observation time, the impact of BMI, SII and NLR on OS could slightly differ.

CONCLUSIONS

Before chemotherapy, immune status biomarkers such as NLR and SII turned out to be important prognostic factors for OS in patients with TNBC. High NLR turned out to be particularly significant in combination with other parameters like with a worse performance status according to ECOG and the presence of distant metastases as an adverse independent prognostic factor. Based on these results, we suggest that NLR be included in the routine evaluation of TNBC breast cancer patients prior to enrolment in chemotherapy. Identifying high-risk TNBC patients can allow for early interventions and improved cancer outcomes. Further studies should be conducted for better understanding of this topic.

Availability of data and materials:
The datasets supporting the conclusions of this article are included within the article and its additional files.

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