EJMI

DOI: 10.14744/ejmi.2021.21203
EJMI 2021;5(2):225–231

Research Article

Could Systemic Inflammation-Based Prognostic Scores Predict the Clinical Outcome in Patients with Breast Cancer Treated with Everolimus Plus Exemestane?

Emir Celik,[1] Nilay Sengul Samanci,[1] Mehmet Karadag,[2] Nebi Serkan Demirci,[1] Fuat Hulusi Demirelli[1]

[1]Department of Medical Oncology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey
[2]Department of Biostatistics, Hatay Mustafa Kemal University Faculty of Medicine, Hatay, Turkey

Abstract

Objectives: No study to clarify which inflammation score could best reflect survival in a cohort of metastatic breast cancer (mBC) patients who received everolimus plus exemestane.

Methods: The impact of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and prognostic nutritional index (PNI) on PFS and OS was evaluated.

Results: A total of 80 mBC patients were included. Median PFS was 8.9 months and median overall survival (OS) was 31.8 months. We found that there was no significant difference between NLR, PLR, SII, and PNI groups for median PFS and OS.

Conclusion: Inflammation-based prognostic scores were not correlated with prognosis in patients with mBC who had been treated with everolimus plus exemestane.

Keywords: Breast cancer, biomarkers, everolimus, systemic inflammation-based prognostic scores

Cite This Article: *Celik E, Sengul Samanci N, Karadag M, Demirci NS, Demirelli FH. Could Systemic Inflammation-Based Prognostic Scores Predict the Clinical Outcome in Patients with Breast Cancer Treated with Everolimus Plus Exemestane? EJMI 2021;5(2):225–231.*

Breast cancer was the second most common cancer overall worldwide and the most common cancer in women in 2012.[1] The American Cancer Society reported that in the United States in 2019, a new breast cancer was diagnosed with an estimated 268.600 American women and 41.760 patients died due to breast cancer.[2] About 75% of breast cancers are classified as hormone receptor-positive (expressing the estrogen receptor and/or the progesterone receptor) and HER2-negative.[3] Estrogen receptor targeted treatments are an important part of metastatic breast cancer (mBC) treatment, but eventually, the endocrine treatment resistance improves.[4] The BOLERO-2 randomized controlled trial, which conducted with the patients resistant to non-steroidal aromatase inhibitor treatment, revealed that combining endocrine therapy with the mammalian target of rapamycin (mTOR) inhibitor everolimus prolongs progression-free survival (PFS) in postmenopausal patients with hormone receptor-positive, HER2-negative mBC comparison to endocrine therapy alone.[5]

Address for correspondence: Emir Celik, MD. Department of Medical Oncology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey
Phone: +90 212 414 30 00 **E-mail:** emircelikk@gmail.com

Submitted Date: September 19, 2020 **Accepted Date:** February 04, 2021 **Available Online Date:** May 25, 2021

Systemic inflammation is now known to play an important role in the development, progression, and metastasis of tumours.[6] In recent years, the prognostic significance of a variety of systemic inflammation-based prognostic scores such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and prognostic nutritional index (PNI) has been investigated in various cancers such as malignant melanoma,[7] operable ampullary carcinoma,[8] prostate cancer[9] and renal cell carcinoma.[10] However, there has been no study to clarify which inflammation-based prognostic score could best reflect survival in a cohort of mBC patients who received everolimus plus exemestane. Therefore, we aimed to assess the prognostic and predictive significance of pre-treatment inflammation-based prognostic scores in our mBC patients treated with everolimus plus exemestane.

Methods

Study Participants and Data Collection

We retrospectively evaluated 80 postmenopausal patients whose data were fully accessible with mBC treated with everolimus plus exemestane between January 2013 and May 2020 in our university hospital. Both everolimus and exemestane were administered orally, the starting dose was 10 mg/day and 25 mg/day, respectively. Patients with no available pre-treatment data on NLR, PLR, SII, PNI, and those with infection or underlying comorbidities such as chronic inflammatory diseases, chronic lymphocytic leukemia, recent treatment with steroids, granulocyte colony-stimulating factor or cytokines were excluded from this analysis.

Clinical, demographic, and histopathological data such as Eastern Cooperative Oncology Group performance status (ECOG PS), gender, age, metastatic sites, body mass index (BMI), treatments received, number of lines of therapy, outcomes of everolimus plus exemestane treatment including best overall tumor response, PFS, and OS were obtained from the patient archive files. After the treatment of everolimus plus exemestane started, the time until tumor progression has been defined as the PFS. OS was defined as the time from the everolimus plus exemestane to the date of death from any cause. The response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Absolute neutrophil count, absolute lymphocyte count, hemoglobin (g/dl), platelet count, LDH (IU/L), albumin (g/dl), and C-reactive protein (CRP, mg/L) were recorded prior to (1–7 days) initiating Everolimus plus exemestane treatment. The scores of NLR, PLR, SII, and PNI were calculated according to the following formulas:

a) NLR: Absolute neutrophil count/Absolute lymphocyte count

b) PLR: Platelet count/Absolute lymphocyte count

c) SII: Platelet count × Absolute neutrophil count/Absolute lymphocyte count

d) PNI: 10×albumin (g/dl)+0.005×Absolute lymphocyte count

We constructed the receiver operated characteristics (ROC) curves to determine the cut-off values for NLR, PLR, SII, and PNI. However, no statistically significant cut-off values were found. Therefore, cut-off values determined for NLR, PLR, SII, and PNI with previous studies were used.[9,11] Data collection and analysis of all subjects was approved by the ethics committee of the study site.

Primary Objective and Statistical Analysis

The primary objective of this study was to evaluate the ability of inflammation-based prognostic scores (NLR, PLR, SII, and PNI) to predict the PFS and OS in patients with mBC treated with everolimus plus exemestane. OS and PFS was estimated using the Kaplan–Meier method and difference in survival was calculated using the log-rank test. Cox proportional hazard analysis was used to estimate the level of significance and the relative risks with 95% confidence interval (CI). Categorical variables were presented as percentages. Continuous variables were expressed as mean±standard deviation (median and interquartile range). PFS and OS were presented as median value with two-sided 95% confidence interval (CI). P-value of <0.05 was considered statistically significant. The clinical data was analyzed using IBM SPSS version 23.0.

Results

Patient, Disease and Treatment Characteristics

Between January 2013 and May 2020, 80 female patients treated with everolimus plus exemestane combination with HER2-negative and hormone receptor-positive mBC were included in the study. Baseline characteristics are shown in Table 1. The mean age was 58±12.1 and all of the patients were postmenopausal. ECOG PS was ≤1 in 93.7% of patients. None of the patients had cranial metastasis. 66.3% of the patients were not metastatic at the time of first diagnosis and 47.5% of the patients had a history of neoadjuvant or adjuvant chemotherapy. The rates of visceral metastasis and bone metastases were 40% and 78.8%, respectively. Everolimus treatment line was ≤3rd in 66.3% of patients.

Patients were divided into NLR ≥3 (high), PLR ≥210 (high), SII ≥535 (high) and PNI <45 (low) groups according to their inflammation-based prognostic score levels. Table 1 shows

Table 1. Baseline clinic and demographic characteristics of 80 patients with metastatic breast cancer

	n (%)		n (%)
Age, (Mean±SD)	58±12.1	Neoadjuvant or adjuvant chemotherapy	38 (47.5)
ECOG PS			
0-1	75 (93.7)	Treatment of metastatic disease	
2	5 (6.3)	Chemotherapy	68 (85)
Smoking		Tamoxifen	15 (18.8)
Yes	17 (21.3)	Fulvestrant	20 (25)
No	63 (78.8)		
Body mass index		Anemia (hgb <11 g/dl)	
≥30 kg/m^2	26 (32.5)	Yes	16 (20)
<30 kg/m^2	54 (67.5)	No	64 (80)
De novo metastatic disease		Lactate Dehydrogenase (LDH)	
Yes	27 (33.8)	High (>250 IU/L)	30 (37.5)
No	53 (66.3)	Normal	50 (62.5)
Visceral metastasis		C-reactive protein (CRP)	
Yes	32 (40)	High (>5 mg/L)	38 (47.5)
No	48 (60)	Normal	42 (52.5)
Bone metastasis		Neutrophil to lymphocyte ratio	
Yes	63 (78.8)	≥3	29 (36.3)
No	17 (21.3)	<3	51 (63.7)
Treatment line of everolimus		Platelets to lymphocyte ratio	
≤3rd	53 (66.3)	≥210	21 (26.3)
>3rd	27 (33.8)	<210	59 (73.8)
Best response		Sysemic immune-inflammation index	
CR	1 (1.2)	≥535	45 (56.3)
PR	23 (28.8)	<535	35 (43.8)
SD	33 (41.2)	Prognostic nutritional index	
PD	23 (28.8)	≥45	68 (85)
		<45	12 (18)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

the patient distributions in each group. The proportion of patients with LDH and CRP above normal limits was 37.5% and 47.5%, respectively.

Response Rate and Survival

Median PFS of 80 patients was 8.9 months (95% CI 7.48 10.32) and median OS was 31.80 months (95% CI 25.02 38.58). Figure 1 shows the median PFS of the high vs. low groups for NLR, PLR, SII, and PNI with p values and as a result, no significant PFS difference was detected between the groups. When the best overall response was examined under everolimus plus exemestane treatment, the complete response (CR) rate was 1.2%, the partial response (PR) rate was 28.8%, the stable disease (SD) rate was 41.2% and the progressive disease (PD) rate was 28.8%.

When the high vs. low groups for NLR, PLR, SII, and PNI were examined, there were no significant differences in terms of median OS. Median OS for the groups were 31.47 months (95% CI 9.96-52.97) in high NLR, 32.07 months (95% CI 23.83 40.31) (p=0.599) in low NLR, 32.23 months (95% CI 27.66 36.80) in high PLR, 29.30 months (95% CI 23.27 35.33) (p=0.695) in low PLR, 31.47 months (95% CI 21.78 41.15) in high SII, 32.06 months (95% CI 8.17 55.97) (p=0.341) in low SII and 31.80 months (95% CI 9.60 54.00) in low PNI, and 32.23 months (95% CI 14.48 49.98) in high PNI (p=0.107).

The potential predictors as seen in Table 2 were assessed using a Cox proportional hazard model. The univariate analysis showed that both PFS and OS were longer in patients with ECOG PS≤1 and CR+PR with everolimus best overall response. In addition, according to the univariate analysis results, OS was shorter in patients with denovo metastatic disease and CRP high, while OS was longer in patients with a history of neoadjuvant/adjuvant chemotherapy. According to the multivariate analysis results (Table 3), only best overall response (HR 0.24 95% CI 0.11 0.49, p=0.001) for PFS; in addition, best overall response (HR 0.28 95% CI 0.10 0.74,

Table 2. Univariate cox regression analysis for progression-free survival and overall survival

		Progression-free survival		Overall survival	
Variable	**n**	**Hazard ratio (95% CI)**	**p**	**Hazard ratio (95% CI)**	**p**
Age	80	0.99 (0.97 1.02)	0.820	1.01 (0.98 1.03)	0.950
ECOG PS >1	5	4.03 (1.57 10.39)	0,004	4.83 (1.86 12.53)	0.001
Smoking	17	1.08 (0.57 2.05)	0.081	1.18 (0.54 2.58)	0.647
De novo metastatic disease (1)	27	1.60 (0.90 2.84)	0.101	2.59 (1.35 4.96)	0.004
Neoadjuvant or adjuvant chemotherapy (1)	38	0.64 (0.39 1.06)	0.084	0.48 (0.26 0.89)	0.021
Chemotherapy for metastatic disease (1)	68	1.22 (0.63 2.36)	0.557	2.30 (0.92 5.71)	0.073
Everolimus line: ≤3rd	53	1.25 (0.70 2,21)	0.450	1.08 (0.50 2.33)	0.839
Tamoxifen for metastatic disease	15	0.80 (0.39 1.64)	0.545	1.69 (0.77 3.73)	0.192
Fulvestrant for metastatic disease	20	0.65 (0.35 1.23)	0.186	0.54 (0.21 1.40)	0.205
Bone metastasis (1)	17	1.36 (0.73 2.53)	0.331	1.30 (0.62 2.75)	0.491
Visceral metastasis (1)	32	1.57 (0.95 2.58)	0.076	1.34 (0.72 2.47)	0.357
BMI ≥30 kg/m^2	26	0.69 (0.40 1.18)	0.174	0.87 (0.44 1.76)	0.705
Anemia (1)	16	1.06 (0.58 1.94)	0.846	0.99 (0.48 2.09)	0.994
NLR ≥3	29	1.06 (0.64 1.76)	0.811	1.18 (0.63 2.20)	0.599
PLR ≥210	21	1.41 (0.81 2.45)	0.226	0.867 (0.42 1.77)	0.695
SII ≥535	45	1.36 (0.82 2.26)	0.240	1.36 (0.72 2.55)	0.343
PNI ≥45	68	0.96 (0.47 1.95)	0.908	0.52 (0.22 1.17)	0.114
High LDH	30	1.37 (0.83 2.28)	0.220	1.18 (0.63 2.18)	0.619
High CRP	38	1.12 (0.68 1.83)	0.663	2.05 (1.09 3.85)	0.026
Best response (CR+PR vs. SD)	24	0.26 (0.13 0.53)	0.001	0.39 (0.17 0.89)	0.025

(1) Means it exist.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CR: Complete response; PR: Partial response; SD: Stable disease; BMI: Body mass index; CI: Confidence interval.

Table 3. Multivariate analysis for progression-free survival and overall survival

	Progression-free survival		Overall survival	
Variable	**Hazard ratio (95% CI)**	**p**	**Hazard ratio (95% CI)**	**p**
Best response (CR+PR vs. SD)	0.24 (0.11 0.49)	0.001	0.28 (0.10 0.74)	0.010
ECOG PS >1	4.81 (0.60 38.77)	0.141	8.34 (0.86 80.56)	0.067
High CRP	-		3.34 (1.39 8.02)	0.007
De novo metastatic disease	-		0.71 (0.22 2.29)	0.565
Neoadjuvant or adjuvant chemotherapy	-		0.50 (0.19 1.32)	0.163

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CR: Complete response; PR: Partial response; SD: Stable disease; CI: Confidence interval.

p=0.01) and high CRP (HR 3.34 95% CI 1.39 8.02, p=0.007) for OS were still identified as independent prognostic factors. In patients responding to everolimus plus exemestane treatment, CR+PR patients are expected to have longer PFS and OS than SD patients. Cox regression analysis results also confirmed that high NLR, PLR and SII and low PNI were not independent prognostic factors for both PFS and OS.

Discussion

To our knowledge, this is the first study in the literature to assess the prognostic role of inflammation-based prognostic scores (NLR, PLR, SII, and PNI) in mBC cohort receiving everolimus plus exemestane therapy. Our study results showed that pre-treatment inflammation-based prognostic scores were not independent prognostic factors for PFS or OS when evaluated in combination with other clinicopathological features. Univariate and multivariate analyses revealed that all factors except the best response were ineffective on PFS. As a result, the biomarkers predicting how much benefit the patient will receive from treatment before starting everolimus plus exemestane treatment in mBC remain obscure and NLR, PLR, SII, PNI are not reliable.

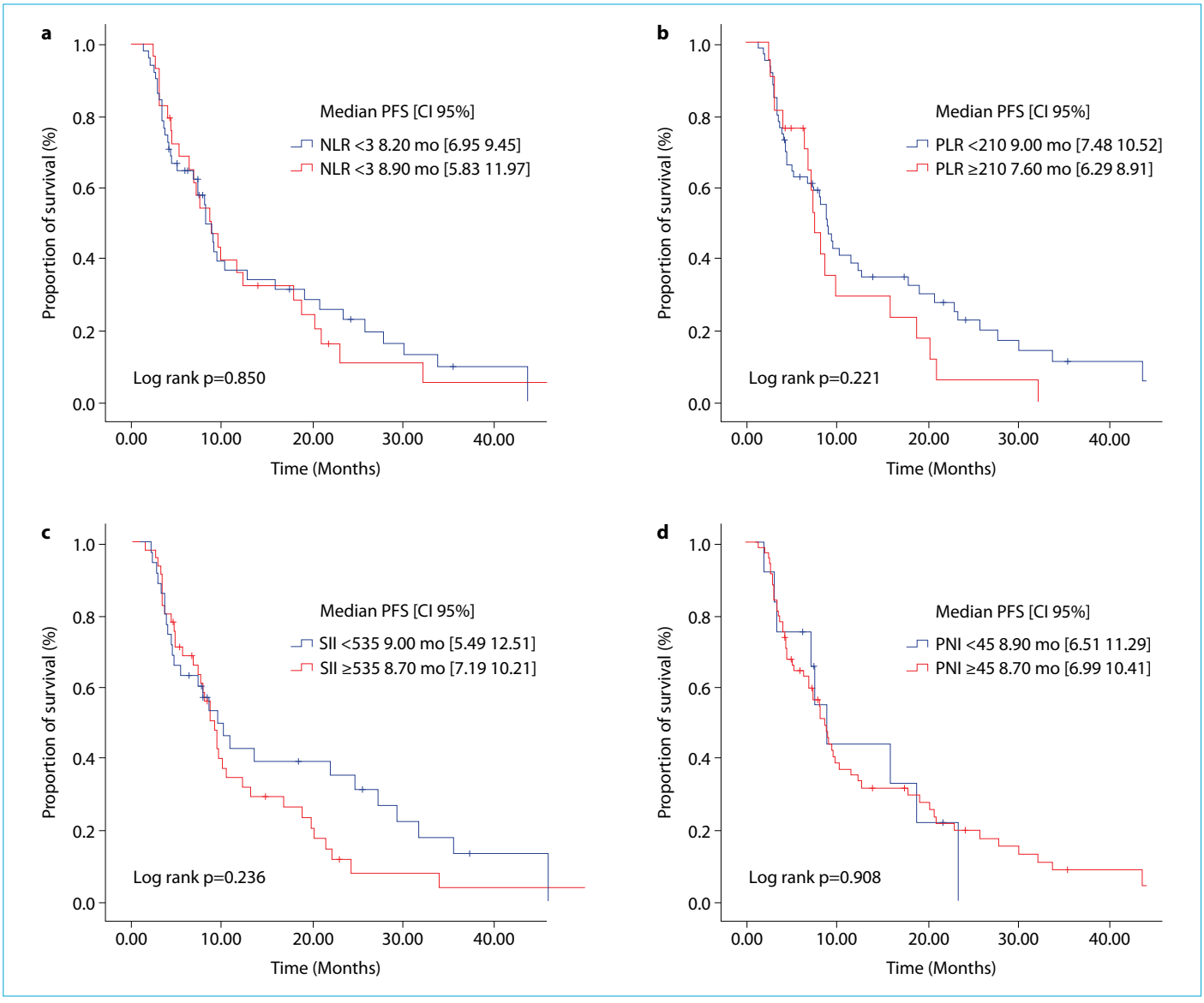

Figure 1. Kaplan–Meier curves of progression-free survival (PFS) for **(a)** neutrophil/lymphocyte ratio (NLR), **(b)** platelet/lymphocyte ratio (PLR), **(c)** systemic immune-inflammation index (SII), and **(d)** prognostic nutritional index (PNI).

Immunity and inflammation blood indicators, including NLR, PLR, and SII have been studied in many cancers including breast cancer.[7,9,10,12] Low ratio of these indexes shows a systemic background of decreased inflammation and immune system activation, which contributes to improved treatment response. Strong links between immunosuppression and chronic inflammation and malignancy development and progression of existing malignancy have been demonstrated in previous studies.[13] Low absolute lymphocyte counts have been described as being associated with a generalized immunosuppression state in several types of cancer, which appears to be associated with impaired survival in these patients.[14] NLR, PLR, SII, and PNI are also associated with immune function, in addition to its role as an inflammation marker. While neutrophils suppress lymphocyte functions with the cytokines they secreted, platelets also induce epithelial-mesenchymal transition in circulating tumour cells and promote their extravasation to metastatic sites.[15,16] Modulation of the inflammatory microenvironment of tumours can thus influence the progression of cancer.

mBC is not a high producer of neoantigens.[17] Consistent with such a role of the immune system, response rates to immune checkpoint inhibitor treatment in BC are lower than malignancies such as melanoma, metastatic renal cell carcinoma (mRCC) and lung cancer.[18] In the literature, it has been more clearly revealed that high NLR is associated with poor prognosis in early-stage BC, while there are contradictory results in mBC.[12,19-21] A recent study by Rubio et al. investigated the effect of pre-treatment NLR on PFS and

OS in 263 mBC patients and concluded that NLR is not an independent factor for PFS or OS in mBC when consideration is given to other factors, especially ECOG PS, sites of metastases and stage (early vs. advanced) at diagnosis.[20] Inclusion of all hormone receptor/HER2 positive and negative mBC patients in this study led to the formation of a heterogeneous patient population and this should be taken into account when interpreting the results. In addition, as clearly emphasized in this study, univariate and multivariate analysis should be performed by including other possible variables while evaluating the effect of inflammatory-based prognostic scores on prognosis in any tumor type.

To investigate the prognostic and predictive significance of inflammation-based prognostic scores in combination with other clinical variables in a homogeneous population, we analyzed patients diagnosed with HER2-negative, hormone receptor-positive mBC and in whom everolimus plus exemestane treatment was to be initiated. We found that there was no significant effect of any variable, including inflammatory-based prognostic scores, CRP, LDH, anemia, and sites of metastases for PFS, except best overall response (Fig. 1, Table 3).

Although univariate analysis results showed that ECOG, stage at diagnosis, neoadjuvant/adjuvant chemotherapy history, high CRP, best overall response were significant variables for OS; multivariate analysis results confirmed that only high CRP and best overall responses were significant variables. According to the results, pre-treatment inflammation-based prognostic scores may not be a reliable biomarker for mBC treated with everolimus plus exemestane. A previous study conducted with 97 metastatic RCC patients treated with everolimus showed that pre-treatment NLR is an independent prognostic factor.[10] According to the results of this study, both PFS and OS were statistically significantly shorter in NLR high patients. As a result, the effects of inflammation-based prognostic scores on survival in tumors with significant inflammation such as RCC have been better understood, while the effect on clinical outcome in mBC patients has not yet been fully elucidated.

This study presents important limiting points. The first is the study's retrospective nature that restricts patient interaction with healthy control group. The second limitation is the comparatively limited number of patients. The third is the possible effects of previous chemotherapy treatments on bone marrow function. Prospective cohort studies are needed to validate the data outlined in the study.

Conclusion

In conclusion, we found that pre-treatment inflammation-based prognostic scores, including NLR, PLR, SII, and PNI were not correlated with prognosis in patients with mBC who had been treated with everolimus plus exemestane. To confirm these findings, larger prospective studies are required in the future.

Disclosures

Acknowledgement: We thank all breast cancer patients and their families for making this research possible.

Ethics Committee Approval: Cerrahpasa Medical Faculty Ethics Committee, Date: 05.06.2020, No: 68541.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – E.C., N.S.S.; N.S.D.; F.H.D.; Design – E.C., N.S.S.; M.K.; N.S.D., F.H.D.; Supervision – E.C., F.H.D.; Materials – E.C., N.S.S.; Data collection &/or processing – E.C., N.S.S.; Analysis and/or interpretation – E.C., N.S.S., M.K., N.S.D., F.H.D.; Literature search – E.C., N.S.S., N.S.D., F.H.D.; Writing – E.C., N.S.S., M.K., N.S.D., F.H.D.; Critical review – E.C., F.H.D.

References

1. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012; 2012. Available at: http://globocan.iarc.fr/Default.aspx. Accessed Dec 1, 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
3. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LAG, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106:dju055.
4. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011;62:233–47.
5. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. N Engl J Med 2012;366:520–9.
6. Liu J, Lin PC, Zhou BP. Inflammation fuels tumor progress and metastasis. Curr Pharm Des 2015;21:3032–40.
7. Mirili C, Yılmaz A, Demirkan S, Bilici M, Basol Tekin S. Clinical significance of prognostic nutritional index (PNI) in malignant melanoma. Int J Clin Oncol 2019;24:1301–10.
8. Demirci NS, Erdem GU. Prognostic role of neutrophil-to-lymphocyte ratio (NLR) in patients with operable ampullary carcinoma. Bosn J Basic Med Sci 2018;18:268–74.
9. Lolli C, Caffo O, Scarpi E, Aieta M, Conteduca V, Maines F, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with mCRPC treated with abiraterone.

Front Pharmacol 2016;7:376.
10. Santoni M, De Giorgi U, Iacovelli R, Conti A, Burattini L, Rossi L, et al. Pre-treatment neutrophil-to-lymphocyte ratio may be associated with the outcome in patients treated with everolimus for metastatic renal cell carcinoma. Br J Cancer 2013;109:1755–9.
11. Wang J, Yu B, Ye Y, Shen J, Ding N, Tang H, et al. Predictive value of nutritional risk screening 2002 and prognostic nutritional index for esophageal cancer patients undergoing definitive radiochemotherapy. Nutr Cancer 2018;70:879–85.
12. Duan J, Pan L, Yang M. Preoperative elevated neutrophil-to-lymphocyte ratio (NLR) and derived NLR are associated with poor prognosis in patients with breast cancer: A meta-analysis. Medicine 2018;97:e13340.
13. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. Nat Rev Clin Oncol 2015;12:584–96.
14. Rashid F, Waraich N, Bhatti I, Saha S, Khan RN, Ahmed J, et al. A pre-operative elevated neutrophil: lymphocyte ratio does not predict survival from oesophageal cancer resection. World J Surg Onc 2010;8:1.
15. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013;13:350.
16. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011;20:576–90.
17. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science 2015;348:69–74.
18. Wein L, Luen SJ, Savas P, Salgado R, Loi S. Checkpoint blockade in the treatment of breast cancer: current status and future directions. Br J Cancer 2018;119:4–11.
19. Graziano V, Grassadonia A, Iezzi L, Vici P, Pizzuti L, Barba M, et al. Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. Breast 2019;44:33–8.
20. Ivars Rubio A, Yufera JC, de la Morena P, Fernández Sánchez A, Navarro Manzano E, García Garre E, et al. Neutrophil-lymphocyte ratio in metastatic breast cancer is not an independent predictor of survival, but depends on other variables. Sci Rep 2019;9:16979.
21. Vernieri C, Mennitto A, Prisciandaro M, Huber V, Milano M, Rinaldi L, et al. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict efficacy of platinum-based chemotherapy in patients with metastatic triple negative breast cancer. Sci Rep 2018;8:8703.