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Impact Of Neutrophil to Lymphocyte Ratio On The Outcome Of Women With Metastatic Breast Cancer

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Abstract

Introduction: Breast cancer is one of the most common cancers in women throughout the world. The neutrophil/lymphocyte ratio (NLR) is a simple and cost-effective inflammatory indicator that is linked to cancer patient prognosis and treatment response. Our aim was to evaluate the prognostic impact of NLR on the outcome of women with metastatic breast cancer. **Material and methods:** This study is a retrospective analysis of data obtained from sixty female patients diagnosed with metastatic breast cancer (MBC)and treated in Medical Oncology Department, Zagazig University from January 2015 to December 2017. A number of data were retrieved anonymously from a patient's medical record and then transcribed into an Excel spreadsheet. Personal information, medical history, pathological data concerning the extent of metastasis, tumor estrogen/progesterone receptor (ER/PR), HER2 status, and Ki67 evaluation and follow-up data after adjuvant therapy ended. The NLR was calculated using receiver operating curve (ROC) analysis. **Results:** The overall survival (OS) and progression free survival(PFS) were calculated by the Kaplan-Meier method and Survival curves were found a negative significant difference between NLR level with cutoff (>1.9) and OS of patients(p=<0.001),so a high NLR was associated with short OS. Univariate analysis of all clinco-pathological parameters showed an association of menopausal state (p=0.015) and family history (p=0.047) with OS of the studied patients. On the other side ,there were no statistically significant differences between NLR and PFS with p-value (0.987). **Conclusion:** NLR are significantly associated with OS in patients with MBC.

Keywords: Breast, Cancer, Metastatic, Neutrophil, Lymphocyte, Ratio.

Introduction:

Breast cancer is one of the most common cancers in women throughout the world. Breast cancer is the second leading cause of cancer-related death among women., and prevention is still a struggle across the world. Due to early identification and prevention, breast cancer patients in many industrialized countries have a 5-year relative survival rate of more than 80%. As a result, substantial progress has been made in both breast cancer understanding and the development of preventative strategies [1].

Metastatic breast cancer (MBC) is responsible for the majority of breast cancer-related deaths. However, some people with MBC who get multimodal treatment have a complete clinical response and survive for a long time [2].

Inflammation linked to cancer plays a significant role in the origin and progression of cancer, and it may also influence treatment outcomes. The systemic inflammatory response has been discovered to be an independent prognostic predictor in cancer patients.[3]. The neutrophil/lymphocyte ratio

(NLR) is a simple and low-cost inflammatory indicator that is linked to patient prognosis and treatment response. Neutrophils secreting substances that promote tumor proliferation, invasion, and distant metastasis. On the other hand, lymphocytes play a part in the antitumor immune response by inducing apoptosis and reducing tumor development,. As a result, they are essential for immunity [4].
Aim and objectives: To evaluate the prognostic impact of neutrophil/lymphocyte ratio on the outcome of women with metastatic breast cancer (MBC).

Subjects and methods:
Technical design: After approval by the research ethical committee of Faculty of Medicine, Zagazig University (Institutional Research Board "IRB"). The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans ,which assessed the sample size, procedures and scientific background .This study retrospectively analyzed sixty female patients diagnosed with metastatic breast cancer either de novo or post early presentation treatment, who were treated according to their primary physican plan with hormonal therapy, chemotherapy and or targeted therapy in medical oncology department at Zagazig University from January 2015 to December 2017. Female patients with metastatic breast cancer who are ≥18 years and have complete data are included. Male breast cancer patients, patients with inadequate data, and patients with malignancies other than breast cancer were excluded from the research.
Methods: A number of data were retrieved anonymously from a patient's medical record and then transcribed into an Excel spreadsheet. Personal information, medical history, surveillance/follow-up data after adjuvant therapy ended, and pathological data concerning the extent of metastasis, tumor estrogen/progesterone receptor (ER/PR), HER2 status, and Ki67 evaluation were among the variables. The NLR was calculated as(absolute neutrophilic count/ absolute lymphocytic count) which were documented at time of metastasis before starting any treatment by applying receiver operating curve (ROC) analysis. The relationship between the neutrophil/lymphocyte ratio (NLR) and clinicopathological data from metastatic breast cancer patients ,in addition to the relationship between the neutrophil/lymphocyte ratio (NLR) and progression free survival (PFS) (the time between the start of treatment and the onset of disease progression) and overall survival (OS) (the time from diagnosis to death or the last follow-up visit) in metastatic breast cancer were analyzed.

Statistical Analysis:
A receiver operating characteristic (ROC) curve was constructed to permit selection of the cut-off point of AGR for survival outcome (dead/alive) of MBC patients. Data were tested for normal distribution using the Shapiro-Walk test. Categorical covariates were compared using the Chi-square test or Fisher's exact test. Mann-Whitney U Test was used to calculate difference between quantitative variables in more than two groups with Dunn's Post hoc test for multiple comparisons. Spearman's correlation test was used for correlating non-parametric variables. The OS and PFS were calculated by the Kaplan-Meier method and Survival curves were compared using the log-rank test. All tests were two-sided and a p value ≤0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS 24 Inc. Chicago, IL, USA).

Results:
Table (1) shows the baseline patient characteristics. The median age of our patients with MBC was 52.5 years (range 23-70 years). There were (13.3%) of patients with +ve family history. Most of

patients (75%) were invasive ductal carcinoma(IDC) and (61.7%) of them were postmenopausal. The majority of patients (48.3%) had histological grade II tumors. In 25 patients of the studied group Ki-67 were high (41.66%). Eighteen of patients were HER2neu status positive (30%). Hormonal status among them showed that ER positive patients were (66.7%). Regarding to progesterone receptor (PR) status, (55%)were positive. Half of patients were luminal A (50%), while luminal B represents(31.67%)while, triple negative (6.67%) and HER-2 enriched (11.67%) of them. The site of metastasis is multiple rather than single (65%). The median value of absolute neutrophilic count was (5.6)and the median value of absolute lymphocytic count was(2). The median value of NLR was (1.95). **Table (2);** According to the therapy before diagnosis of metastatic breast cancer , we found that 40 patients(66.6%) were on hormonal therapy and 18 patients(30%)were on targeted therapy,41 of them (68.3%) treated with chemotherapy, while 17 patients(28.3%) were newly diagnosed. **Table (3)** clears the receiver operating characteristic curve (ROC) and area under the curve (AUC) for NLR at diagnosis for survival analysis. NLR with cutoff >1.9 had an AUC of 0.899 (95% CI,0.794 - 0.962) with a sensitivity of 76.92% (95% CI,60.7 - 88.9%) and a specificity of 100% (95% CI,83.9 - 100.0%) to predicted survival outcome. **Table (4)** reveals the baseline patient characteristics based on the NLR Level. The sixty adult patients with metastatic breast cancer were classified according their initial NLR into 2 groups low, and high: including 30 (50%), and 30 (50%) patients. **Table (5)** analyzed the survival outcomes based on the NLR level. A correlation between the NLR at diagnosis and other parameters was demonstrated in **Table (6)** as age and surface area of the body. No statistically significant correlations were found between them. The 5-year OS rate in relation to NLR and the 5-year PFS rate in relation to NLR were demonstrated in **Table (7)** and **Table (8)** respectively. We found a high significant difference between NLR level high/low with cutoff (>1.9) and overall survival of patients, p=<0.001. Number of deaths with high NLR was 30 (100%) but number of deaths with low NLR was 9 (30%) so a high NLR was associated with short OS. **Table (9)** shows a univariate and multivariate Cox regression analyses for overall survival. Cox regression was performed to ascertain the effects of age, menopausal state, surface area, family history, histopathology, grading, hormonal state(ER, PR, HER2neu, KI67), molecular type, number of metastases, progression free survival and NLR on the likelihood that participants have survived (OS). Univariate analysis of all parameters showed an association of menopausal state (p=0.015) and family history (p=0.047) with OS. Multivariate analysis that included all the parameters which were significant in univariate analysis (≤0.05) revealed that only NLR was independently associated with OS (HR; 3.6 [1.3-10.1], P <0.014). High NLR is a prognostic factor of short OS and doesn't depend on other parameters.

Table (1): Baseline patient characteristics [median (range) or n (%)]:

Variable	***Total N=60***	
	N	%

Age, years		52.5 (23-70)	
Surface area of the body		1.7 (1.5-2)	
Menopausal state	PRE	23	38.33%
	POST	37	61.67%
Family history	yes	8	13.33%
	No	52	86.67%
Histopathology	IDC	45	75.00%
	ILC	15	25.00%
Grade	G1	6	10.00%
	G2	29	48.33%
	G3	25	41.66%
Estrogen Receptor	Positive	40	66.67%
	Negative	20	33.33%
Progesteron Receptor	Positive	33	55.00%
	Negative	27	45.00%
HER2neu	Positive	18	30.00%
	Negative	42	70.00%
KI67	High	25	41.66%
	Low	35	58.44 %
Molecular type	Luminal A	30	50.00%
	Luminal B	19	31.67%
	Her_2 Enriched	7	11.67%
	Triple -Ve	4	6.67%
Number of metastasis	Single	21	35.00%
	Multiple	39	65.00%
Median Follow-up period, years		3 (1-5)	
Absolute Neutrophilic count		5.6 (2.1-7.4)	
Absolute lymphocytic count		2 (1.1-4.5)	
Neutrophil/lymphocytic Ratio		1.95 (0.9-6.6)	

Continuous data are presented as median (range) or n (%).

Table (2):Type of therapy before diagnosis of metastatic breast cancer:

	Total number : 60	
Type of therapy	**Number**	**%**

Chemotherapy	**41**	**68.3%**
Targeted therapy	**18**	**30%**
Hormonal therapy	**40**	**66.6%**
No therapy(de novo cases)	**17**	**28.3%**

Denovo cases; primary diagnosed with metastatic breast cancer.

Table (3): Receiver operating characteristic curve (ROC) and area under the curve (AUC) for Neutrophil/lymphocytic Ratio (NLR)at diagnosis for survival analysis:

Cut-off	*Sensitivity % 95% CI*	*Specificity % 95% CI*	*PPV % 95% CI*	*NPV % 95% CI*	*AUC 95% CI*	*P*
Neutrophil/lymphocytic Ratio>1.9	76.92 60.7 - 88.9	100 83.9 - 100.0	100	70 56.8 - 80.5	0.899 0.794 - 0.962	<0.001

A receiver operating characteristic (ROC) curve. P= <0.001.

Table (4): Sixty adult patients with MBC, were classified according their initial Neutrophil/lymphocytic Ratio (NLR) into 2 groups low, and high; including; 30 (50%), and 30 (50%) patients, respectively:

		NLR Level				***P***
		Low N=30		High N=30		
		N	%	N	%	
Age, years*		49 (25-70)		54 (23-70)		0.784
Surface area of the body*		1.7 (1.5-2)		1.7 (1.5-2)		0.283
Menopausal state	Pre	15	50.00%	8	26.67%	0.063
	Post	15	50.00%	22	73.33%	
Family history	yes	5	16.67%	3	10.00%	0.347
	No	25	83.33%	27	90.00%	
Histopathology	IDC	22	73.33%	23	76.67%	0.766
	ILC	8	26.67%	7	23.33%	
Grade	G1	2	6.67%	4	13.33%	0.673
	G2	11	37.93%	18	62.06%	
	G3	10	40.00%	15	60.00%	
Estrogen Receptor	Positive	18	60.00%	22	.33%	0.273
	Negative	12	40.00%	738	26.67%	
Progesteron Receptor	Positive	16	53.33%	17	56.67%	0.795
	Negative	14	46.67%	13	43.33%	
HER2neu	Positive	8	26.67%	10	33.33%	0.286
	Negative	22	73.33%	20	66.67%	
KI67	High	11	44.00%	14	56.00%	0.039
	Low	19	54.28%	16	45.71%	
Molecular type	Luminal A	15	50.00%	15	50.00%	0.736
	Luminal B	9	30.00%	10	33.33%	
	Her2	4	13.33%	3	10.00%	

	Triple -Ve	2	6.67%	2	6.67%	
N.of mets	Single	13	43.33%	8	26.67%	0.176
	Multiple	17	56.67%	22	73.33%	
Progression	Yes	13	43.33%	13	43.33%	1
	No	17	56.67%	17	56.67%	
Death	Yes	9	30.00%	30	100.00%	<0.001
	No	21	70.00%	0	0.00%	
Absolute neutrophilic count*		5.35 (2.1-7.2)		6 (3.2-7.4)		0.052
Absolute lymphocytic count*		3.5 (1.2-4.5)		1.6 (1.1-2.4)		<0.001
Neutrophil/lymphocytic Ratio*		1.55 (0.9-1.9)		3.25 (2-6.6)		<0.001

All variables were compared using Chi-square X^2 test except (*) Mann Whitney test.

IDC; invasive ductal carcinoma. ILC; invasive lobular carcinoma.

Table (5): Survival outcomes based on the Neutrophil/lymphocytic Ratio (NLR) level:

Outcome		***Total N=60***		***Neutrophil/lymphocytic Ratio (NLR)Level***				***P***
				Low N=30		High N=30		
		N	%	N	%	N	%	
Progression	Yes	26	43.3%	13	43.3%	13	43.3%	1.0
	No	34	56.7%	17	56.7%	17	56.7%	
Death	Yes	39	65.0%	9	30.0%	30	100.0%	**<0.001**
	No	21	35.0%	21	70.0%	0	0.0%	

All variables were compared using Chi-square X^2 test except (*) Mann Whitney test.

Table (6): correlation between the Neutrophil/lymphocytic Ratio (NLR)at diagnosis and other studied parameters:

Parameters	***NLR***	
	r	P
Age, years	-0.03	0.82
surface area of the body.	+0.171	0.192

r = Correlation Coefficient, $P \leq 0.05$= significant

Table (7): The 5-year OS rate in relation to Neutrophil/lymphocytic Ratio (NLR):

Overall Survival	***Total N***		***N of Events***	***Censored***		***Overall Survival Rate%***	***p***	***Survival Time (Years)***			
				N	Percent			Mean ±SE	95% CI	Median ±SE	95% CI
NLR level	High	30	30	0	0.00%	0.00%	**<0.001**	2.83 ±0.17	2.51-3.16	2 ±0.17	2.68-3.31
	Low	30	9	21	70.00%	70.00%		4.23 ±0.22	3.79-4.67	NR	
Overall	60		39	21	35.00%	35.00%		3.53 ±0.17	3.21-3.86	3 ±0.3	2.42-3.58

SE:std. error, 95% Confidence Interval.

Table (8): The 5-year PFS rate in relation to Neutrophil/lymphocytic Ratio (NLR):

Progression free survival		***Total N***	***N of Events***	***Censored***		***Survival Rate%***	***p***	***Survival Time (Years)***			
				N	%			Mean ±SE	95% CI	Median ±SE	95% CI
NLR Level	Low	30	13	17	56.7%	56.7%	0.987	3.08 ±0.4	2.29-3.87	NR	
	High	30	13	17	56.7%	56.7%		2.5 ±0.31	1.89-3.12	NR	
Overall		60	26	34	56.7%	56.7%		3.07 ±0.28	2.51-3.63	NR	

SE:std. error, 95% Confidence Interval, NR: not reached

Table (9): Univariate and multivariate Cox regression analyses for overall survival:

Variable	***Univariate***				***Multivariate***			
	Sig.	**HR**	**95.0% CI for HR**		**Sig.**	**HR**	**95.0% CI for HR**	
			Lower	**Upper**			**Lower**	**Upper**
Age, years	0.094	1.02	1.00	1.05	0.525	0.98	0.93	1.04
Menopausal state	0.015	2.44	1.19	5.04	0.312	2.22	0.47	10.47
Surface area of the body	0.175	2.99	0.61	14.61				
Family history	0.047	2.59	1.01	6.65	0.085	3.54	0.84	14.93
Histopathology	0.463	1.32	0.63	2.78				
Grade 1	0.067	2.14	0.85	5.76	0.54	0.63	0.19	1.57
Grade 2	0.079	2.31	0.91	5.88	0.195	0.49	0.17	1.44
Grade 3	0.857	1.07	0.53	2.13	0.55	0.74	0.27	2.00
ER	0.352	1.36	0.71	2.59				
PR	0.206	1.50	0.80	2.82				
HER2neu	0.645	1.17	0.60	2.28				
KI67	0.122	0.60	0.32	1.14				
Molecular type Luminal A	0.653	1.32	0.32	4.76	0.732	0.74	0.13	3.18
Molecular type Luminal B	0.658	1.26	0.46	3.43	0.82	1.16	0.32	4.16
Molecular type Triple -Ve	0.688	1.31	0.35	4.88	0.722	0.76	0.17	3.48
Molecular type Her2 Enriched	0.071	2.57	0.92	7.16	0.066	3.43	0.92	12.74
Number of mets	0.238	1.23	0.87	1.75				
Progression	0.256	1.21	0.87	1.67				
NLR. Low vs high	**<0.001**	0.21	0.10	0.45	**0.014**	3.61	1.29	10.08

HR: hazard ratio.

Discussion:

The interaction of cancer cells with the immune system of the host is gaining attention. Breast cancer has a unique and complex microenvironment that is rich in growth factors, proteinases, and inflammatory cytokines that aid in the proliferation, invasion, and dissemination of breast cancer cells [5]. Both systemic and local inflammatory responses rely heavily on neutrophils. Lymphocyte numbers can suggest endogenous immune system cancer resistance. Tumor-infiltrating lymphocytes, on the other hand, are critical participants in the immune surveillance of tumors. In breast cancer, its invasion has been shown to have a predictive and prognostic influence [6]. High NLR levels have been proven to be a potential indication of poor prognosis for patients with gastrointestinal tract malignancies, hepatocellular carcinoma, pancreatic cancer, non-small cell lung cancer, and cervical cancer [7].

The current study is a retrospective study evaluating the prognostic impact of neutrophil/lymphocyte ratio (NLR) on the outcome of 60 metastatic breast cancer women with recorded data in Medical Oncology Department, Zagazig University Hospitals which collected from January 2015 to December 2017.

The sixty adult patients with MBC were classified according their initial NLR into 2 groups low, and high; NLR with cutoff >1.9 determined by used receiver operating characteristic (ROC) curve analysis had an AUC of 0.899 (95% CI,0.794 - 0.962) with a sensitivity of 76.92% (95% CI, 60.7 - 88.9%) and a specificity of 100% (95%CI, 83.9 - 100.0%), respectively

The median value of NLR among studied patients was 1.9 (range, 0.9-6.6) in contrast to Xuan Q, et al. who found that median value of NLR was 2.32 (range1.70–3.50) among large studied group includes 286 patients with triple negative breast cancer. [8].

The median age of our patients with MBC was 52.5 years (range 23-70 years) and it is similar to Liu et al, whose reported a median age of 51 (range 22–75) years of their studied groups with different breast cancer stages(I–IV) and stage IV represented(37.9%) of their patients.[9], while Rubio et al, reported the median age of their patients (59Y) which may be explained by large number of patients with different demographic features included [10].

We found that there were (13.3%) of patients with positive family history . Murat et al, show near result with (11.4%) positive family history of 63 patients with single bone metastasis .[11]

In comparison with Adamowicz K, et al, 53 patients (15%) of 351 patients with metastatic breast cancer showed positive family history .[12]

Most of patients had invasive-ductal carcinoma(IDC) (75%) , Zewenghiel et al, results is similar with (76%) of their patients(IDC) [13], and near to Petekkaya et al, whose results showed that (71.6%) of 81 total patients included in their study . [14]

This study is agree with Simon, J et al. results according to postmenopausal status was ,(61.7% - 59%) of patients respectively ,[15] while Petekkaya et al, .represented only (2.5%) of postmenopausal patients as the median age of them at diagnosis was 47 years (rang 26-83).[14]

The majority of patients (48.3%) had histological grade II tumors. This result is near to Petekkaya et al, with grade II represented(52.6%)of their patients.[14]. We noticed that in 25 patients (41.66%) ; Ki-67 were high with cut off value is (>20%). while high levels were seen in majority of cases (82.2%) in Shao, Y et al, their cut off value of Ki-67(>14%)considered high.[16]

According to HER2-neu status 18 patients were positive (30%), while Hormonal status among studied groups showed estrogen receptor(ER) positive patients were(66.7%) and progesterone receptor (PR) positive were(55%) this is comparable to Matikas et al. whose results revealed

(22.5%- 52%-42.6%) respectively[17],and it is similar to Mills, J et al. whose results revealed HER2-neu positive(27%), ER positive (64%) and PR positive (52%) of their patients.[18]
. Regarding to molecular subtypes ,half of patients were luminal A (50%), while luminal B represents (31.67%)of patients, triple negative was (6.67%) and HER2-new enriched was (11.67%).This results were near to Lohmann et al. whose found that hormone receptor–positive patients collectively were (87.5%), while HER2–enriched (15.6%), and triple-negative (10.4%) [19] . In this study, the site of metastasis is multiple rather than single (65%) this is near to Bahgat, T et al, whose reported (60%) of their patients with multiple visceral metastasis.[20]
On the other hand, De Giorgi et al, show that 211 patients (40.8%) of the studied groups with 3 or more metastatic sites, 113 (53.6%) mostely visceral metastasis(61.8%) had <5 circulating tumor cells(CTCs) and 98 (46.4%) patients had ⩾5 circulating tumor cells ($p = 0.005$). [21]
According to the type of therapy we found that,41 of the patients (68.3%) treated with chemotherapy, 18 patients(30%)were on targeted therapy while 40 patients(66.6%) were on hormonal therapy with median time of hormonal treatment was 8.9 months (range 3-30 months)and 17 patients(28.3%) were newly diagnosed ,in comparable with Lohmann et al, whose found that 53 (55.2%) of studied patients received chemotherapy,8(8.3%) with targeted therapy and 33(34.4%) with hormonal therapy.[19]

Most of our patients were IDC (75%) and is show no significant relation with NLR (p=0.766) comparable to Bahgat, T *et al.* with (p=0.099) [20]. The histological grade of our patients has no effect on NLR with p value=0.673. Hormonal and molecular status among our studied groups showed no effect on NLR with p=(0.736) unlike Bahget,T *et al.* with significant relation(P<0.001)between low NLR in triple negative breast cancer phenotype which represent only (10.4%) of our patients. [20].

After a median follow-up period of 3 years (range, 1-5years) and the median value of NLR was 1.95 (range, 0.9-6.6), PFS showed no significant difference with NLR P-value (0.98) and the study of Noh et al, PFS were similarly not affected by NLR of total 442 patients, 327 patients had NLR less than 2.5 as a cut off value, and 115 patients had NLR equal to or higher than 2.5 [22]. In addition, Rubio *et al.* with median NLR was 2.42 (range: 0.70–4.33) showed that NLR was not independent factor for PFS [10].Huszno et al. showed that NLR was identified as independent prognostic factor for DFS of metastatic renal cell carcinoma[23]. Ethier *et al.* concluded that NLR was a prognostic factor for overall survival [24]. There is a high significant negative correlation between NLR and OS in our study as p-value (<0.001) and number of deaths is 30 in high NLR group (100%) of patients in contrast to 9 (70%) dead ones in low NLR group not dependent on other clinical variables and this is similar to Guo *et al.* who evaluated the prognostic value of NLR on overall survival (OS) and disease-free survival (PFS) for BC patients. They suggested that elevated NLR was associated with poor OS as well as high risk of recurrence for BC patients [25]. On the other hand, Rubio *et al.* determined that NLR prognostic and predictive value in metastatic breast cancer was dependent on other clinical variables and found a significant association of higher values of NLR with worse performance status , visceral metastasis, visceral crisis, and CNS metastasis [10].

Chae S *et al*, also evaluated the prognostic value of the NLR in (OS) of patients with triple-negative breast cancer that was assessed by univariate and multivariate analysis. The 5-year OS was lower in the NLR >2.65 compared with that in the NLR≤2.65 group, They revealed that an elevated NLR is significantly associated with poor OS .[26].

There were a number of limitations in our study. Firstly, the cohort reported on was small. Secondly, since the study was retrospective, patient records were heavily relied upon.

Conclusion and recommendations:

Cox regression was performed to ascertain the effects of Age, Menopausal state, Surface area of the body, Family history, Histopathology, Grading, Hormonal state(ER, PR, HER2neu, KI67), Molecular subtypes, Number of metastasis and NLR in relation to Progression free survival(PFS),and overall survival(OS). Multivariate analysis that included only the parameters which were significant in univariate analysis ($p \leq 0.05$) revealed that high NLR is correlate with poor OS. Because of the wide heterogeneity of breast cancer, the particular NLR cut-off value was limited to patients with MBC. It is recommended to conduct further prospective prognostic studies on larger sample of MBC patients in multi-centers.

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