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RESEARCH ARTICLE

Usefulness of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as a predictor of disease-free survival in breast cancer: A cross-sectional study [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: The relationship between neutrophil-lymphocyte ratio (NLR) with outcome is a complex issue. A high NLR reflects systemic inflammation. This study aimed to estimate the relationship between NLR, and platelet-lymphocyte ratio (PLR) in disease-free survival (DFS).

Methods: This was a cross-sectional study in which we reviewed the patient files of 102 patients with breast cancer treated at the Babylon Oncology Center from January 2009 to September 2014, who had follow-up for at least 36 months. The following data were collected from patient files: age, diagnosis date, date of recurrence and/or metastasis, follow-up, histological tumor type, tumor size, node metastasis stage, histological differentiation degree, estrogen and/or progesterone receptor expression, HER2 neu status, and metastasis site.

Results: The mean age of patients was 50.4 ± 11.7 years and lowest period of follow up was 40 months. Longest DFS was 62 months, with 5 years DFS in 52.5% of patients. Stage N0 was associated with a significantly higher DFS compared to stage N1. Isolated local recurrence was seen in 15% of patients and combined local recurrences with distant metastasis was observed 37%. NLR had the highest discrimination ability to predict recurrence and distant metastasis.

Conclusion: An increase in NLR was associated with poor DFS, and it can therefore be a predictive and prognostic factor. NLR's established prediction model warrants further investigation.

Keywords

Disease Free Survival, Neutrophil-lymphocyte ratio, Platelet lymphocyte ratio, Breast cancer

Open Peer Review

Approval Status

	1	2
version 1
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1. Shelly Kaushik , University of California San Francisco, San Francisco, USA		
Dhruv Thakar , University of California San Francisco, San Francisco, USA		
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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Worldwide, breast cancer is the most diagnosed cancer type among women¹. Animal models suggest “immune-editing” in which activation of immune mechanisms control the tumor, but over time lead to the selection of tumor cells that escape the immune pressure and grow progressively². Most tumor antigens identify as non-mutated self-antigens. Tumors are heterogeneous, and the antigens on cells of one tumor are variable, even within the same patient, so the down-regulation of major histocompatibility complex molecules and other components of the antigen-presentation process can occur¹. Tumors also do not express the ligands recognized by innate immune cells that microbes express or the co-stimulatory ligands necessary to stimulate adaptive T cells². The expression of Fas ligand by some tumor cells help to maintain a state of immune privilege that induce apoptosis. Tumor cells lead to the release of many cytokines and soluble factors, such as prostaglandin E2, that are not conducive to antitumor immunity. Cancer-associated factors have been shown to inhibit the production and stimulatory capacity of tumor cells³. T-helper cell responses skewed toward a Th2 phenotype, lead to inhibition of the Th1 response and cellular immunity that mediates tumor rejection⁴.

The evidence of the relationship between inflammation and cancers prognosis has increased in past years, especially gastrointestinal tumors and non-small-cell lung cancers, and even breast cancers. The systemic inflammatory responses may mimic biochemical or hematological markers, such as raised C-reactive protein and the elevation of white blood cells, neutrophils, and platelets. Elevation of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in breast cancer patients is not well studied in Iraq. This relationship is a complex and multifactorial process that is still poorly understood, but a high NLR may reflect systemic inflammation in enhancing angiogenesis, tumor growth and development of metastasis. Therefore, this study aimed to estimate the relationship between NLR, PLR and disease-free survival (DFS) in breast cancer patients in Iraq.

Methods

Study design and setting

This is a cross-sectional retrospective study. Breast cancer patients who were treated at Babylon Oncology Center, Baghdad, Iraq from January 2009 to September 2014 were included in this study. The data was collected between May 2017 and April 2018.

Participants

Inclusion criteria: Tumor stage up to stage IIA (T1-T2, N0/ T1, N1); follow-up for at least 36 months; availability of pretreatment complete blood count (CBC) with differential count.

Exclusion criteria: Locally advanced and metastatic breast cancer (T3-T4, N1-N3, M1); neoadjuvant treated patients; patients with data lacking for follow-up and pretreatment CBC with differential count; known causes of neutrophilia (those who already have this disease such as infections, inflammation, burns, heart attack, and drugs, e.g. steroids).

Data sources

The following data were collected from patient files: age, diagnosis date, date of recurrence and/or metastasis, follow-up, histological tumor type, tumor size, node metastasis stage, histological differentiation degree, estrogen and/or progesterone receptor expression, HER2 neu status, and metastasis site.

Statistical methods

The statistical analysis used the following tests: Anderson darling test, a statistical test of whether a given sample of data is drawn from a given probability distribution; Kaplan–Meier analysis, a non-parametric statistic used to estimate the survival function from lifetime data, which was used to assess DFS; hazard ratio (HR), the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable; ROC curve, a performance measurement for classification of problems at various thresholds settings; sensitivity analysis for test quality; and specificity analysis for test extension. SPSS 20.0 software package was used for statistical analysis. P-value of <0.05 was considered significant. Patients who had missing data for variables were excluded from the analysis.

Ethical considerations

The Medical Ethical Committee of The Iraqi Board for Medical Specializations approved this study [CODE: 2015; date, 24-09-2013]. Participant consent was waived by the committee, since only patient files were reviewed.

Results

Out of a total of 1167 case files only 102 patients fit the eligibility criteria and completed the study, with a mean age of 50.4 ± 11.7 years (range, 23–75 years, the rest of the disease characteristic illustrated in (Table 1). Local recurrence had the lowest rate, while combined local and distant recurrence had the highest rate (Table 1). The median DFS was 62 months with 5 years DFS in 52.5% patients, patients with stage N0 had a significantly higher DFS compared to stage N1, and those patients with a positive hormonal status have a significantly better DFS compared to those with a negative hormonal status (Table 2; Figures 1A–D). NLR had the highest discrimination ability to predict recurrence (since AUC between 0.7 – 0.79), while the rest of the variables show poor discrimination ability, as illustrated in Table 3 and Table 4 and Figures 1E and F. NLR fair specificity (76.9%) with lower sensitivity (62.2%), with optimal cut point of >2.194 to predict all recurrence. NLR also showed similar predictability for distant metastasis, while for local recurrence NLR had poor ability to predict local recurrence (Table 5 and Table 6; Figure 1G and Figure 2). Table 7 shows uni- and multivariate analysis of predictors of DFS with a significant *p*-value (*p*=0.007) for NLR, which means that it is an independent risk factor (Figure 3).

Discussion

This is the first study to show an association between high NLR and poor prognosis in Iraqi breast cancer patients. A higher NLR independently reflected a higher risk of local recurrence

Table 1. Demographic and disease characteristics of all patients (n=102).

Variables	Value
Age (years), mean $\pm$ SD (range)	50.4 $\pm$ 11.7 (23-75)
<i>T staging, n (%)</i>	
1	40 (39.2)
2	62 (60.8)
<i>N staging, n (%)</i>	
0	50 (49.0)
1	52 (51.0)
Positive hormonal status, n (%)	77 (75.5)
Positive Her-2 status, n (%)	32 (31.4)
Duration of follow-up (months), mean (range)	46.0 (40.0-57.25)
Neutrophils (* 10 ³ cells/ μ L), mean $\pm$ SD (range)	5.487 $\pm$ 2.410 (2.4-14.0)
Lymphocytes (* 10 ³ cells/ μ L), mean $\pm$ SD (range)	2.764 $\pm$ 0.934 (1.1-6.0)
Neutrophil-lymphocyte ratio (* 10 ³ cells/ μ L), mean $\pm$ SD (range)	2.111 $\pm$ 0.980 (0.76-6.33)
Platelets (* 10 ³ cells/ μ L), mean $\pm$ SD (range)	334.78 $\pm$ 110.07 (142.0-726.0)
Platelet-lymphocyte ratio (* 10 ³ cells/ μ L), mean $\pm$ SD (range)	133.85 $\pm$ 65.44 (0.40-433.64)
Isolated local recurrence, n (%)	15 (14.7)
Isolated distant metastasis, n (%)	32 (31.4)
Combined local and distant recurrence, n (%)	37 (36.3)

Table 2. Median disease-free survival (DFS), n=102.

	Median DFS (months)	95%CI of median	P value (Log rank)
Overall	62.0	55.31 – 68.69	-
<i>T staging</i>			
1 (n=40)	60.0	55.50 – 64.50	0.668
2 (n=62)	65.0	54.42 – 75.58	
<i>N staging</i>			
0 (n=50)	78.0	62.51 – 93.48	0.004
1 (n=52)	57.0	50.36 – 63.64	
<i>Hormonal status</i>			
Negative n=(25)	60.0	45.48 – 74.53	0.029
Positive (n=77)	67.0	52.46 – 81.54	
<i>Her2 status</i>			
Negative (n=70)	63.0	54.67 – 71.33	0.235
Positive (n=32)	60.0	46.05 – 73.95	
<i>Histopathology</i>			
Ductal	63.0	55.67 – 70.33	0.524
Lobular	50.0	-	
Other	56.0	-

Figure 1. Kaplan Meier curves for disease free survival (DFS). **A:** DFS for all patients, **B:** median DFS (MDFS) by T staging, **C:** MDFS by N staging, **D:** MDFS by hormonal status, **E:** NLR MDFS by months, **F:** PLR MDFS by months, **G:** Kaplan-Meier estimator of DFS using NLR cut point (2.194).

Table 3. ROC analysis to predict recurrence.

	Area under the curve	P value (Z-score)
Lymphocytes	0.594	0.117
Neutrophils	0.626	0.026
Platelets	0.543	0.467
Neutrophil-lymphocyte ratio	0.713	<0.001
Platelet-lymphocyte ratio	0.546	0.455

Table 4. Median disease-free survival (DFS) according to the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), n=102.

	Median DFS (months)	95%CI of median	P value
Overall	62.0	55.31 – 68.69	-
NLR			
<1.3915	-	-	0.006
1.3915 – <2.0	67.0	50.01 – 83.99	
2.0 - <2.5208	58.0	25.65 – 90.35	
≥2.5208	56.0	50.74 – 61.26	
PLR			
<94.19	67.0	47.38 – 86.62	0.215
94.19 – 119.22	78.0	58.74 – 97.26	
119.23 – 159.38	60.0	49.74 – 70.26	
≥159.39	57.0	49.85 – 64.15	

The linear trend for each level of NLR and PLR was used (-3, -1, +1, +3)

Table 5. Neutrophil-lymphocyte ratio validity as a predictor for recurrence.

	AUC	Cut off point	Sensitivity	Specificity	PPV	NPV
All recurrence	0.713	>2.194	62.2%	76.9%	60.5%	78.1%
Local recurrence	0.644	>1.556	93.3%	36.8%	20.3%	97.0%
Distant metastasis	0.715	>2.194	62.5%	74.3%	52.6%	81.2%

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

Table 6. Disease-free survival according to neutrophil-lymphocyte ratio (NLR; 2.194 cut off point).

NLR	Median	95%CI of median	P value
≤2.194	72.0	59.47 – 84.53	0.004
>2.194	56.0	49.89 – 62.11

Figure 2. ROC curve of neutrophil-lymphocyte ratio (NLR) to predict recurrence.

Table 7. Univariate and multivariate analysis of predictor of disease-free survival.

	Hazard Ratio (HR)	95% CI of HR	P value
NLR	2.543	1.296 – 4.990	0.007
Age	0.996	0.967 – 1.025	0.678
<i>Histopathology</i>			
Ductal	0.859	0.115 – 6.391	0.882
Lobular	2.007	0.181 – 22.221	0.570
Other	1.0	-	-
T staging	0.856	0.416 – 1.762	0.673
N staging	2.806	1.341 – 5.873	0.006
Hormonal status	0.466	0.228 – 0.952	0.036
Her2 status	1.486	0.762 – 2.899	0.245
NLR	2.474	1.225 – 4.996	0.012
N staging	1.923	0.851 – 4.344	0.116
Hormonal status	0.534	0.242 – 1.180	0.121

NLR, neutrophil-lymphocyte ratio

Figure 3. Disease-free survival according to neutrophil-lymphocyte ratio (NLR; cut off value: 2.194) after performing multivariate analysis.

and distant metastasis in women with early breast cancer with a cutoff point of 2.194.

We found significant differences in DFS (16 months) according to our NLR cut off point with significant p -value ($p=0.004$). The role of lymphocytes in cancer is exemplified by the strong association between high densities of tumor-infiltrating lymphocytes and better responses to both cytotoxic treatments and outcome in patients^{5,6}. Two meta-analysis studies have confirmed the association between elevated NLR and poor prognosis for breast cancer^{7,8}; however, studies about these values are rare and not done in Iraq. In this study, we validated the usefulness of high NLR in early stage breast cancer up to stage IIA and to estimate DFS for at least 36 months follow-up.

In our univariate and multivariate analysis, we found hazard ratio (HR) for NLR 2.5 with significant p -value ($p=0.007$), while in the univariate analysis the nodal status and hormonal status were significant as dependent prognostic factors. Comparing our result with Ethier *et al.*, a meta-analysis which comprised patients with reported HRs for DFS, and included only non-metastatic cases⁹, our result has the same significance with good sample size and follow-up period; however, we couldn't calculate overall

survival (OS). Although another study shown that PLR was not related with DFS or OS in women⁹, in our study PLR was neither sensitive nor specific with non-significant p -value, so it will not considered as a prognostic index.

Conclusion

The role of NLR is a prognostic marker and elevated NLR is correlated with poor DFS in early breast cancer patients.

Data availability

Underlying data

Zenodo: Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in early stage breast cancer as predictor of disease-free survival. <https://doi.org/10.5281/zenodo.2531124>¹⁰.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Current Peer Review Status:

Version 1

Reviewer Report 29 June 2020

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Hutcha Sriplung

Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

The title, objective, and abstract don't say that the analysis is limited to stage I up to IIA diseases. If you find the NLR and PLR are not homogeneous to stage III of the disease, it is better to stratify analysis and clearly show the difference in survival according to the stage, or clearly state why you chose stages I - IIA in your study.

In the first paragraph of the result, is the proportion of exclusion from the analysis too big? Please give the reasons why you excluded them. I think you walked through steps of case selection, and many cases probably were not in your inclusion criteria, but you counted in 1167 files.

Am I right that you recruited the cohort and measured all the predictors in the past? And then you followed them up for 36 months and saw the results at the end of the follow up when the event occurred or at the end of the follow-up time.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.**Reviewer Expertise:** Cancer epidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 10 May 2019

<https://doi.org/10.5256/f1000research.19786.r48267>

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Dhruv Thakar

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In this study, Al-Bairmany *et al* attempt to explore the effect of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) on Disease Free Survival (DFS) in patients with breast cancer. In this retrospective study, the authors find that high NLR correlates with poor DFS, suggesting its use as a prognostic marker in breast cancer. While the study attempts to address an important question, that of a clinically unmet challenge of finding robust biomarkers that can predict/prognosticate breast cancer survival, the manuscript is poorly written and referenced, the results are inadequately presented with not enough information in either the methods, figure legends or the plots to derive and interpret the information and results. While the authors claim that the prognostic role of NLR is controversial, they do not discuss the controversy adequately either in the introduction or discussion. For specific comments, please refer to the point-by-point review below.

Many Grammatical errors, choice of words and awkward sentence structure make it very difficult to read through and review and manuscript, starting from the abstract. We advise the authors to kindly revise the manuscript thoroughly and correct the language such that the reviewers can focus on critiquing the data rather than the linguistic shortcomings of the manuscript. Additionally, several references are missing (as highlighted in the comments below) making it difficult to get a solid understanding of the background through cross-referencing. Also, a lot of these references are outdated and the field has progressed profoundly in the last few years. The authors need to thoroughly review recent literature.

Abstract:

1. Please amend sentence to: "the relationship between neutrophil-lymphocyte ration (NLR) and outcome is controversial". Also, do the authors mean Survival outcome? If yes, please clarify.
2. Please amend to: "this study aims to explore the relationship between NLR...". Also, the authors mention PLR in the same sentence. However, unlike NLR, they do not clarify why the relationship between PLR and "outcome" (DFS?) is important. They need to introduce PLR alongside NLR.
3. What does "lowest period of follow-up" mean? 40 months was the shortest time between diagnosis and follow-up?

Introduction:

1. "Animal models suggest "immune-editing" in which activation of immune mechanisms control the tumor, but over time lead to the selection of tumor cells that escape the immune pressure and grow progressively." I am not sure if the authors here are trying to define immune-editing, suggesting that immune-editing has been shown in animal models or implicating immune-editing as a therapeutic option for when tumor cells evade the immune system?
2. "Tumors are heterogeneous, and the antigens on cells of one tumor are variable, even within the same patient, so the down-regulation of major histocompatibility complex molecules and other components of the antigen-presentation process can occur." I am not sure how tumor heterogeneity in terms of antigen variability can contribute to down-regulation of the major histocompatibility complex? Are the authors trying to say that cells can express variable antigens even within the same tumor and that some of these antigens can be immune-suppressive through their down-regulation of the MHC?
3. How can the expression of Fas ligand by tumor cells, while maintaining immune privilege, also induce apoptosis? Are the authors suggesting that the apoptosis is induced in the surveilling immune cells? Also, the authors need to provide a reference for this claim.
4. The authors need to provide reference for "Tumor cells lead to the release of many cytokines...antitumor immunity"
5. The authors cite Rayman *et al* to talk about tumor cells skewing the immune response to Th2 phenotype. This is a 2004 paper and the field has since shifted to suggest that the contribution of these phenotypes to cancer is fluid and controversial. We urge the authors to review the most recent literature on the subject and state the facts with the most recent/accurate references.
6. Please provide reference for "the evidence of the relationship between inflammation and cancer prognosis....even breast cancers".
7. The authors need to include more information on other studies that have done the NLR and PLR analysis in breast or other cancers and what these results are.

Results:

1. "Local recurrence had the lowest rate"? Are the authors talking about rate of incidence? The term "Lowest rate" is vague.
2. All panels of Figure 1 need p-values. How do we know if the survival is significant between different groups if the appropriate statistical analysis has not been depicted in the figures or at least mentioned in the legends?
3. Figure 1B: Is this correct that patients with stage T1 tumors with less aggressive tumors have worse prognosis than stage 2, which is more aggressive? Please explain this outcome.
4. Figures 1E-F: What are Q1-Q4? Please make this clear in the figure and the legend. Without knowing what these are how can we interpret the robustness of the data or appreciate the differences in survival?
5. Figure 1G: Why is the red curve cut short? One would expect a tail with patients that have an NLR of greater than 2.194?
6. Also, how was the cutoff value of 2.194 determined? This information is missing from Methods.
7. Neutrophil-lymphocyte ratio or NLR: were these derived from blood samples or biopsies? As demonstrated in other cancers such as brain tumors, the presence of neutrophils in the blood versus in the tumor can predict response to treatment. The authors need to mention in their methods where the neutrophils, lymphocytes and platelets are derived from (blood, biopsy etc) and explain how they were quantified.
8. Also, the patients who were included in the study, are they treated in any way i.e. surgery, radiation and chemotherapy? The therapeutic strategy also affects DFS and as such should be explicitly stated by the authors.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer Biology, treatment resistance, tumor recurrence, cell biology, molecular biology, biochemistry, breast cancer, brain cancer, mechanobiology, tissue tension

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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