



UTILITY OF NEUTROPHIL LYMPHOCYTE RATIO (NLR) AND PLATELET LYMPHOCYTE RATIO (PLR) IN PATIENTS WITH BENIGN BREAST DISEASE AND CARCINOMA BREAST.

Pathology

Hemani Yadav	Department of Pathology, JIPMER, Pondicherry, India.
Jinkala Sree Rekha	Department of Pathology, JIPMER, Pondicherry, India.
Smita Kayal	Department of Medical Oncology, JIPMER, Pondicherry, India.
Prem Ramasubramani*	Department of Preventive and Social medicine, JIPMER, Pondicherry, India. *Corresponding Author

ABSTRACT

Background: Inflammation has an important role to play in tumor progression and dissemination. Neutrophil lymphocyte ratio (NLR) and Platelet Lymphocyte Ratio (PLR) can reflect this inflammatory state and predict the tumor behavior. We studied utility of NLR and PLR in differentiating between a. Benign breast disease and Carcinoma breast b. Non-metastatic and metastatic breast carcinoma. **Methods:** Retrospective analysis of clinic-pathological data of patients with benign breast disease and Carcinoma breast in a tertiary care centre in South India for a period of six months was done. Independent T test was used to find out, if NLR and PLR can differentiate between a. Benign breast diseases and Carcinoma Breast b. Carcinoma breast with and without metastasis and c. Carcinoma breast with local and distant metastasis. Receiver operative characteristic curve (ROC) was used to find the cut-off NLR and PLR between the groups as mentioned above. **Results:** Forty four cases of benign breast disease and 84 carcinoma breast cases were retrospectively analyzed. PLR was able to differentiate between benign breast disease and carcinoma breast with cut-off of 93.5 with 71% sensitivity. The optimal cut-off for NLR and PLR to differentiate local and distant metastasis was 1.9 and PLR 105.9 respectively. **Conclusion:** PLR was able to differentiate between benign and malignant breast diseases. NLR showed increasing trend and significant difference in non-metastatic, local & distant metastasis cases of carcinoma breast.

KEYWORDS

Benign breast disease, Carcinoma breast, NLR, PLR

INTRODUCTION:

Cellular-mediated inflammatory response is increasingly being recognized as having an important role in tumorigenesis and carcinogenesis.^[1] The peripheral Neutrophil Lymphocyte ratio (NLR) and Platelet Lymphocyte ratio (PLR) are thought to be proxies of the on-going inflammatory process in the tumour microenvironment. NLR and PLR reflect the delicate balance between inflammatory response (represented by neutrophils and platelets) and anti-tumor immune response (represented by lymphocytes).^[2] The NLR and PLR have been studied in various solid malignancies to predict the outcome of the disease. In this context, imbalances in the ratio of the peripheral neutrophils/platelets to lymphocytes may provide an insight into underlying tumour progression and prognosis in individuals with breast cancer. We aimed to study the difference in the NLR and PLR between Benign breast disease and Carcinoma breast.

METHODOLOGY:

This is a retrospective analysis of clinicopathological data of patients diagnosed with benign breast disease and Carcinoma breast at our Institute over a period of six months. The clinicopathological data and hemogram details were obtained from histopathology requisition form, clinical case files and Hospital Information system (HIS). Patients with Acute inflammatory/infectious disorders, Haematological disorders, Autoimmune disorders and Chronic disorders where NLR and PLR can be affected are excluded from the study. For NLR and PLR calculation, hemogram report at the time of initial evaluation/pre-treatment was taken into consideration in all the cases. Statistical analysis was done by SPSS Software V20. Independent T test was used to find out the if NLR and PLR can differentiate between

- benign breast diseases and carcinoma breast
- metastatic and non-metastatic carcinoma breast and
- carcinoma breast with local (regional lymph node) vs distant metastasis.

Receiver operative characteristic curve (ROC) was used to find out cut-off NLR and PLR to differentiate between the above conditions

RESULTS:

During this period, we have diagnosed 44 cases of benign breast diseases which included 38 cases of fibroadenoma, two cases of fibrocystic breast disease and four cases of benign phyllodes tumor. There were 84 newly diagnosed cases of carcinoma breast, of which two cases were bilateral. In carcinoma breast cases, 23 did not show metastasis, 40 showed regional lymph node metastasis and 21 showed distant metastasis.

a. Benign breast vs Carcinoma Breast:

The mean NLR in benign breast diseases was 2.23 ± 0.9 and carcinoma breast was 2.09 ± 0.85 with a p value of 0.33 (not significant). The mean PLR in benign breast diseases was 91.97 ± 32.7 and carcinoma breast was 122.66 ± 54.6 with a p value of 0.04 (table 1). The cut-off of PLR for differentiating between benign breast disease and carcinoma breast is 93.27 with a sensitivity of 71.4% and specificity of 61.4% (figure 1a).

b. Carcinoma breast with and without metastasis:

The mean NLR in carcinoma breast cases without metastasis was 1.78 ± 0.44 and with metastasis was 2.20 ± 0.94 with a p value of 0.004. The cut-off of NLR for differentiating between carcinoma breast without and with metastasis 1.72 with a sensitivity of 63.9% and specificity of 52.2% (figure 1b). The mean PLR in carcinoma breast cases without metastasis was 124.84 ± 46.79 and with metastasis was 121.84 ± 57.61 with a p value of 0.57 (Table 1).

c. Carcinoma breast with local vs distant metastasis:

The mean NLR in carcinoma breast cases with local metastasis was 2.03 ± 0.99 and with distant metastasis was 2.54 ± 0.73 with a p value of 0.008. The cut-off of NLR for differentiating between carcinoma breast with local versus distant metastasis is 1.98 with a sensitivity of 81% and specificity of 67.5%.

The mean PLR in carcinoma breast cases with local metastasis was 116.87 ± 63.0 and with distant metastasis was 131.31 ± 45.40 with a p value of 0.003. The cut-off of PLR for differentiating between carcinoma breast cases with local metastasis and carcinoma breast with distant metastasis is 87.23 with a sensitivity of 90.5% and specificity of 30.2% (Table 1).

DISCUSSION:

In the last decade, the markers of systemic inflammatory response including neutrophil, platelet and lymphocyte have been investigated in various types of malignant tumors.^[3] Evidence suggests that neutrophils and platelets are associated with pro-tumour activities in vivo such as enhanced angiogenesis, which contribute to tumour cell proliferation and promote metastatic potential of the tumour cells.^[4] Lymphocytes, on the other hand, have an important role in cancer immune surveillance. An increased concentration of intratumoral CD8 cytotoxic lymphocytes in breast cancer has been strongly associated with decreased recurrence, better response to chemotherapy and higher survival outcomes.^[5] Absolute neutrophil, platelet, lymphocyte counts are affected by a number of physiological and pathological factors. NLR and PLR are more stable hence superior to absolute cell counts.

NLR and PLR are readily available markers of systemic inflammation which can help understanding the systemic inflammatory response. Both the increased neutrophil and platelet, and conversely, decreased lymphocyte can be associated with poor prognosis.

Eroglu et al in their study found a statistically significant difference in the NLR value in patients with carcinoma breast and benign breast diseases.^[6] However, they did not find difference in the PLR values in these two groups. Contrary to that, in our study, we found statistically significant difference in the PLR in carcinoma breast and benign breast diseases. In our study, we noticed an increasing trend of NLR in patients with carcinoma breast, in terms of no metastasis, local metastasis and distant metastasis.

There was significant difference in NLR between patients without metastasis and with metastasis and cut-off of 1.72 is used to differentiate them. The NLR and PLR are also significantly more in patients with distant metastasis compared to those with local metastasis. However, the sensitivity and specificity of the observed cut-offs are relatively low in our study and has to be validated in larger independent cohort.

There are various studies done in the past to establish an association between elevated NLR, PLR and clinicopathological factors and survival in breast carcinoma.^[7,8] These studies in general suggest that higher NLR and PLR are associated with poor clinical outcome in breast cancer patients but the association of NLR and PLR with various clinicopathological factors is not well understood and show conflicting results.

The predictive ability of NLR and PLR was shown to vary across the breast cancer subtypes and according to nature of treatment received.^[9,10] However, in our short report we have not analyzed association between NLR, PLR and clinicopathological factors or survival.

There are few problems encountered in conducting these studies on NLR and PLR. As the values of neutrophils, lymphocytes and platelets show some geographical variations, first population-based reference ranges for NLR and PLR should be obtained. And, it is better to prospectively collect data for analysis of NLR and PLR at different time points to study the association of these indices with clinicopathological factors, treatment response and survival.

Limitations for our study are small sample size, and consequently low sensitivity and specificity of the observed cut off. And also, absence of data and analysis on other baseline clinical and pathological factors and survival outcomes. Larger prospective studies are needed to find out the association of these indices in Indian patients with breast carcinoma and possibly with measurement of these ratios at different time points for better understanding of the role of these inflammatory markers during the disease course.

CONCLUSION:

In our study we conclude that PLR was able to differentiate between benign and malignant breast diseases. NLR showed increasing trend and significant difference in non- metastatic, local & distant metastasis cases of carcinoma breast.

Acknowledgements:

We would like to acknowledge the Department of Medical oncology for providing access to the case files of patients

Funding:

This project was done under the GJ- Straus Projects for encouraging undergraduate students for doing research projects in JIPMER, Pondicherry

Competing interests: The authors declare no competing interests

Table 1: NLR and PLR in Benign breast disease and Carcinoma Breast (with and without metastasis)

a. Benign Breast disease Versus Carcinoma breast						
Mean ± SD	Benign cases n=44	C a r c i n o m a Breast n=84	P value*	Cut- off	Sn	Sp
NLR	2.23 ± 0.9	2.09 ± 0.85	0.33	-	-	-
PLR	91.97 ± 32.7	122.66 ± 54.6	0.04	93.27	71.4	61.4
b. Carcinoma breast without Versus with Metastasis						
76	International Journal of Scientific Research					

Mean ± SD n=84	Ca. Breast without metastasis	Ca. Breast with metastasis	P value*	Cut- off	Sn	Sp
NLR	1.78 ± 0.44	2.20 ± 0.94	0.004	1.72	63.9	52.2
PLR	124.84 ± 46.79	121.84 ± 57.61	0.57	-	-	-

c. Carcinoma Breast with local Versus distant metastasis						
Mean ± SD n=84	Ca. Breast with local metastasis	Ca. Breast with distant metastasis	Pvalue*	Cut- off	Sn	Sp
NLR	2.03 ± 0.99	2.54 ± 0.73	0.008	1.98	81	67.5
PLR	116 ± 63.0	131.31 ± 45.40	0.003	87.23	90.5	30.2

*- Independent T test; Sn – Sensitivity; Sp- specificity

*- Independent T test; Sn – Sensitivity; Sp- specificity

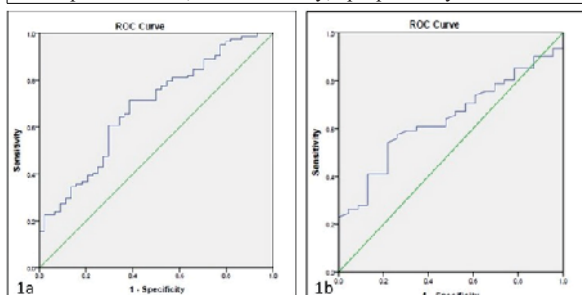


Figure 1a: ROC curve for PLR in benign breast disease versus carcinoma breast with Area under curve (AUC) of 68.3% & Sn of 71.4%

1b: ROC curve for NLR for Non-metastatic versus metastatic breast carcinoma with AUC of 68.3% & Sn of 63.9%

REFERENCES:

- Faria SS, Fernandes PC, Silva MJB, Lima VC, Fontes W, Freitas-Junior R, et al. The neutrophil-to-lymphocyte ratio: a narrative review. [Internet] ecanermedicalscience; 2016[cited 2019 Oct 17]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5221645/>
- World Health Organization. Breast cancer [Internet]. WHO. [cited 2019 Oct 17]. Available from: <http://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en>
- Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149-163.
- De Larco JE, Wuertz BRK, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res. 2004; 10(15): 4895-900.
- De Larco JE, Wuertz BRK, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res. 2004; 10(15): 4895-900.
- Eroglu A, Akbulut S. The Role of Pretreatment Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in the Diagnosis of Breast Cancer: Predicting Lymph Node Metastasis. World J Oncol. 2013; 4: 262-3
- Koh C-H, Bhoo-Pathy N, Ng K-L, Jabir RS, Tan G-H, See M-H, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer. 2015; 113(1):150-8.
- Krenn-Pilko S, Langsenlehner U, Stojakovic T, Pichler M, Gerger A, Kapp KS, et al. The elevated preoperative derived neutrophil-to-lymphocyte ratio predicts poor clinical outcome in breast cancer patients. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2016;37(1):361-8.
- Ulas A, Avci N, Kos T, Cubukcu E, Olmez OF, Bulut N, et al. Are neutrophil/lymphocyte ratio and platelet/lymphocyte ratio associated with prognosis in patients with HER2-positive early breast cancer receiving adjuvant trastuzumab? J BUON. 2015; 20(3): 714-22.
- Pistelli M, De Lisa M, Ballatore Z, Caramanti M, Pagliacci A, Battelli N, et al. Pre-treatment neutrophil to lymphocyte ratio may be a useful tool in predicting survival in early triple negative breast cancer patients. BMC Cancer. 2015;15:195.