International Journal of Current Research and Review
DOI: 10.7324/IJCRR.2018.10806

Research Article

IJCRR
Section: Healthcare Sci. Journal
Impact Factor 4.016
ICV: 71.54

Predictive Importance of Platelet to Lymphocyte Ratio and Neutrophil to Lymphocyte Ratio for Pathologic Complete Response in Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

Caglayan Geredeli[1], Serdar Arici[2]

[1,2]Okmeydani Training and Research Hospital, Medical Oncology Clinic, Istanbul, Turkey.

ABSTRACT

Background: The peripheral blood platelet–lymphocyte ratio (PLR) and neutrophil- lymphocyte ratio (NLR) has been proposed as an indicator for evaluating systemic inflammatory responses in cancer patients.

Materials and Method: PLR and NLR was evaluated retrospectively in 167 breast cancer patients treated with the NACT and subsequent curative surgery.

Results: A total of 167 patients were analyzed.The median age of patients was 50 (min 22 – max 84). 113 patients (67,6%) were stage II and 54 (32,4%) were stage III. Patients with pathologically complete response (pCR) according to Miller-Payne grading system, constituted 55 (32.9%) of all patients 76.3% of patients with pCR had stage IIdisease and of 23.7% had stage III disease. Complete pathologic response rate was statistically significant higher in stage II group than stage III group (p=0.001). In subgroup analysis, pCR rates were 44.2%, 26.9%, 29.7% and 17.6% in HER 2 positive, Luminal B, triple negative and Luminal A groups, respectivly. No statistically significant relationship was found between peripheral blood NLR, PLR before neoadjuvant therapy and pCR in all groups (p = 0.244). However, there was a significant difference between peripheral blood PLR before neoadjuvant therapy in Stage II patients and pCR (p = 0.002)

Conclusion: In peripheral blood NLR and PLR was not effective predictive marker for pCR in patients who will receive NACT for stageII and stage III breast cancer but in peripheral blood low PLR was an effective predictive marker for pCR in patients who will receive NACT for stage III breast cancer.

Key Words: Platelet to Lymphocyte Ratio, Neutrophil to Lymphocyte Ratio, Pathologic Complete Response, Locally Advanced Breast Cancer, Neoadjuvant Chemotherapy

INTRODUCTION

Globally, breast cancer is the most frequently diagnosed malignancy, It is also the leading cause of cancer death in women worldwide (1).

Most patients with non-metastatic breast cancer should receive neoadjuvant chemotherapy therapy (NACT). The goal of treatment is to induce a tumor response before surgery and enable breast conservation. In a meta-analysis, by Mieog JS et al. demonstrated outcomes of NACT; compared with adjuvant chemotherapy reduced risk of radical mastectomy, increased risk of locoregional recurrence and equivalent overall survival and disease free survival (DFS) (2). Mostly anthracycline based regimens used in neoadjuvant setting but non-anthracycline based regimens may be used. All of patients treated with NACT should undergo surgery.

Corresponding Author:
Caglayan Geredeli, Department of Medical Oncology, Okmeydani Training and Research Hospital Sisli, Istanbul, Turkey.
Mobile: +90 532 7495542; Email: caglayange@hotmail.com

ISSN: 2231-2196 (Print) **ISSN:** 0975-5241 (Online)
Received: 19.03.2018 **Revised:** 01.04.2018 **Accepted:** 12.04.2018

Pathologic complete response (pCR) is associated with improvement in DFS (3, 4). Miller-Payne histopatologic scoring system is used to asses the pathologic response by comparing cancer cellularity in core biopsy (before treatment) with the resected tumor (after treatment). pCR shows reduction in tumor cellularity higher than 90% and no residual invasive cancer (5).

Inflammation and cancer are closely related to each other. As a parameter that can reflect inflammation and host immune reaction, elevated blood neutrophil to lymphocyte ratio (NLR) has been reported to be correlated with poor prognosis in a variety of cancers,one of them breast cancer (6-10). Some studies reported controversial results (11, 12).

Recently, platelet-to-lymphocyte ratio (PLR) has become an attractive, convenient, and cost-effective blood-derived prognostic marker as well as an inflammation-related and immune-related prognostic score to evaluate the prognosis of several solid tumors likely NLR. Association between PLR and colorectal, gastric and lung cancer is evaluated in some trials and reported PLR was a predictive marker for poor prognosis (13-17). However, breast cancer and PLR association is controversial.

In this study, we aimed to determine predictive impact of PLR and NLR by comparing with pCR, in patients treated by NACT.

MATERIAL AND METHODS

This study was planned as a retrospective single center study. Medical informations were obtained from the archive files of patients who were treated anthracyclin and taksan-based neoadjuvant chemotherapy between 2010-2017 years, for breast cancer in the medical oncology clinic of Istanbul Okmeydan education and research hospital. Patients without pathology report and laboratory test results were excluded. Disease staging was performed according to TNM 7. The age, menopausal status, pathologic results such as tumor size, histological type, lymph node status, grade, hormonal status, human epidermal growth factor receptor 2 (HER2) receptor status and laboratory data were obtained from the archive files of patients. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were calculated from complete blood count obtained before first chemotherapy. The histological response for breast and axilla was assesedaccording to Miller-Payne grading system (MPG) .

STATISTICAL METHODS

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics was given as number and percentage for categorical variables, average, standard deviation, minimum, maximum for numeric variables. Two independent group comparisons of the numerical variable were performed with the Mann Whitney U test when normal distribution condition was not achieved. Comparisons of categorical variables ratios in groups were made with Chi Square Analysis. Monte Carlo simulation was applied when conditions were not met. Statistical significance level of alpha was accepted as $p < 0,05$

RESULTS

For this study, 183 patients files who received NACT between 2010 and 2017 years, were scanned. Pathologic responses of 167 patients were reached from archive files. The median age of patients was 50 (min 22 – max 84). 113 (67,6%) patients were stage II and of 54 (32,4%) were stage III. The median age of patients with stage II disease was 49.6 (min 24 – max 84) and of patients with stage III disease was 52.6 (min 27 – max 77). Average tumor diameters were 25 mm, 22 mm and 31 mm for general, stage II group and stage III group, respectively. There was statistically significant difference of tumor size between stage II and III groups (p=0.018). While, 48.8% of patients were post-menoupausal, 51.2 % of were pre-menoupausal (Table 1).

61 patients (36.5%) were HER 2 positive, 22.1% of were triple negative, 31.1% of luminal B and 10% of luminal A. Histologically, 160 of patients had invasive ductal carcinoma (Table 1).

Patients with pathologically complete response (pCR) according to Miller-Payne grading system, constituted 55 (32.9%) of all patients (Table 1). 76.3% of patients with pCR had stage II disease and of 23.7% had stage II disease. Complete pathologic response rate was statistically significant higher in stage II group than stage III group (p=0.001). In subgroup analysis, pCR rates were 44.2%, 26.9%, 29.7% and 17.6% in HER 2 positive, Luminal B, triple negative and Luminal A groups, respectivly (Table 2).

When pCR patients and non-pCR patients were evaluated in terms of NLR and PLR, There were not statistically significant differences between the two groups in NLR (2.46) in Stage II patients with PCR and NLR (2.94) in stage II patients without pCR ($p = 0.244$) (Table 3). There were statistically significant differences between the two groups in PLR (144) in Stage II patients with PCR and PLR (169) in stage II patients without pCR ($p = 0.002$) (Table 3).

There were not statistically significant differences between the two groups in NLR (2.51) in Stage III patients with PCR and NLR (2.69) in stage III patients without pCR ($p = 0.595$) (Table 3). There were not statistically significant differences between the two groups in PLR (148) in Stage III patients with PCR and PLR (139) in stage III patients without pCR ($p = 0.384$) (Table 3).

In subgroup analysis ,there were not statistically significant differences between the NLR and pCR, PLR and pCR in the HER2 positive group, the triple negative group and in the luminal B group (Table 3).

DISCUSSION

This was a retrospective analysis to determine the predictive effect of NLR and PLR in patients with breast cancer treated by NACT.

In the present study, patients with pathologically complete response (pCR) according to Miller-Payne grading system, constituted 55 (32.9%) of all patients (table 1) and pCR rates were 44.2%, 26.9%, 29.7% and 17.6% in HER 2 positive, Luminal B, triple negative and Luminal A groups, respectively. Liedtke C et al reported that pathological response of 1118 women with breast cancer who received NACT. Overall, 163 patients (15%) experienced pCR compared with 945 patients (85%) with residual disease. In multivariate analysis, increased pCR rates were observed for patients with triple negative breast cancer (TNBC) compared with non-TNBC (3). von Minckwitz G et al described pCR as a predictive marker for DFS in patients who treated with NACT (4).

In a trial of Noh et al, were detected and showed poorer disease-specific survival patients with elevated pretreatment NLR than patients without elevated NLR (18). Eryılmaz MK et al study showed no relationship between the pCR and pretreatment NLR values (19). However in Cihan YB et al study, there was no effect of NLR on prognosis in patients with breast cancer who underwent surgery and received adjuvant systemic therapy and radiotherapy (11) In our study, there was not statistically significant correlation between pretreatement NLR value and pCR.

In a meta-analysis included 24 studies with a total of 13719 patients with colorectal cancer, were reported that increased PLR predicated a worse OS and DFS in patients who underwent surgery, and this prognostic role also shown both in metastatic and nonmetastatic patients (13). In another meta-analysis involving a total of 13 trials, was showed a high PLR significantly predicted poor OS in Caucasian populations, patients with gastric cancer receiving chemotherapy and patients at advanced stage (15). Similarly, in another meta-analysis involving patients with lung cancer, the data showed that elevated PLR predicted poor OS and poor DFS /PFS (17). Yuka Asano et al showed that for patients with breast cancer treated with NACT, a low PLR indicated high chemotherapy sensitivity, suggesting that PLR could serve as a predictive marker of the therapeutic effect of NACT. (20) In our study, there was statistically significant correlation between low PLR and pCR in patients with stage 2 disease breast cancer treated with NACT.

There were limitations in our study. First, we could not offer DFS in our study because of the inability to reach median time. But there is proven correlation between DFS and pCR for this reason we presented correlation between pCR and NLR and PLR. Second limitation of our study was low number of patients in groups for subgroup analysis. Therefore additional large trials are needed to correct subgroup analysis.

CONCLUSION

In conclusion peripheral blood NLR and PLR was not effective predictive marker for pCR in patients who will receive NACT for stage II and stage III breast cancer but in peripheral blood low PLR was an effective predictive marker for pCR in patients who will receive NACT for stage 2 breast cancer. The predictive utility of PLR might help to selection of patients for using NACT

ACKNOWLEDGEMENTS

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

REFERENCES

1. Cancer statistics, 2018. Siegel RL, Miller KD, Jemal A. CA Cancer J Clin. 2018 Jan;68(1):7-30. doi: 10.3322/caac.21442. Epub 2018 Jan 4.
2. Mieog JS, van der hage ja, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005002
3. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer.J Clin Oncol. 2008 Mar 10;26(8):1275-81. doi: 10.1200/JCO.2007.14.4147. Epub 2008 Feb 4
4. Von Minckwitz G, Untch M, Blohmer JU , Costa SD, Eidtmann H, Fasching PA et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012 May;30(15):1796-804. Epub 2012 Apr 16.
5. Ogston KN, Miller ID, Payne S, Hutcheon AW, Sarkar TK, Smith I et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: Prognostic significance and survival. Breast. 2003 Oct;12(5):320-7.
6. Jiang Y, Xu H, Jiang H, Ding S, Zheng T et al. Pretreatment neutrophil-lymphocyte count ratio may associate with gastric cancer presence. Cancer Biomark 2016;16:523–8.
7. Minardi D, Scartozzi M, Montesi L, Santoni M, Burattini L, Bianconi M et al. Neutrophil-to-lymphocyte ratio may be associated with the outcome in patients with prostate cancer. SpringerPlus 2015;4:255.

8. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015;113:150–8.
9. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q et al. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J Exp Med 2015;236:297–304.
10. Chen J, Hong D, Zhai Y,Shen P. Meta-analysis of associations between neutrophil-to-lymphocyte ratio and prognosis of gastric cancer. World J Surg Oncol 2015;13:122.
11. Cihan YB, Arslan A, Cetindag MF, Mutlu H. Lack of prognostic value of blood parameters in patients receiving adjuvant radiotherapy for breast cancer. Asian Pac J Cancer Prev 2014;15:4225–31.
12. 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;20:714–22.
13. Chen N., Li W., Huang K., Yang W, Huang L, Cong T et al. Increased platelet-lymphocyte ratio closely relates to inferior clinical features and worse long-term survival in both resected and metastatic colorectal cancer: an updated systematic review and meta-analysis of 24 studies. Oncotarget. 2017;8(19):32356–32369. doi: 10.18632/oncotarget.16020.
14. You J., Zhu G.-Q., Xie L, Liu WY, Shi L, Wang OC et al. Preoperative platelet to lymphocyte ratio is a valuable prognostic biomarker in patients with colorectal cancer. Oncotarget. 2016;7(18):25516–25527. doi: 10.18632/oncotarget.8334.
15. Gu X, Gao X.-S, Cui M, Xie M, Peng C, Bai Y et al. Clinicopathological and prognostic significance of platelet to lymphocyte ratio in patients with gastric cancer. Oncotarget. 2016;7(31):49878–49887. doi: 10.18632/oncotarget.10490.
16. Lian L., Xia Y.-Y., Zhou C., Shen XM, Li XL, Han SG et al. Application of platelet/lymphocyte and neutrophil/lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. Cancer Biomarkers. 2015;15(6):899–907. doi: 10.3233/CBM-150534.
17. Gu X., Sun S., Gao X.-S., Xiong W, Qin S, Qi X et al. Prognostic value of platelet to lymphocyte ratio in non-small cell lung cancer: Evidence from 3,430 patients. Scientific Reports. 2016;6 doi: 10.1038/srep23893.23893
18. Noh H, Eomm M, Han A.J. Breast Cancer. 2013 Mar;16(1):55-9. doi: 10.4048/jbc.2013.16.1.55. Epub 2013 Mar 31
19. Melek Karakurt Eryilmaz, Hasan Mutlu, Derya Kivrak Salim, Fatma Yalcin Musri, Deniz Tural, Hasan Senol Coskun. The Neutrophil to Lymphocyte Ratio has a High Negative Predictive Value for Pathologic Complete Response in Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy. doi: http://dx.doi.org/10.7314/APJCP.2014.15.18.7737
20. Yuka Asano, Shinichiro Kashiwagi, Naoyoshi Onoda, Satoru Noda, Hidemi Kawajiri, Tsutomu Takashima, Masahiko Ohsawa, Seiichi Kitagawa, and Kosei Hirakawa Platelet–Lymphocyte Ratio as a Useful Predictor of the Therapeutic Effect of Neoadjuvant Chemotherapy in Breast Cancer PLoS One. 2016; 11(7): e0153459. Published online 2016 Jul 29. doi: 10.1371/journal.pone.0153459.

Table 1: Patients characteristics

	n	%
Total number of patients	183	
Patients with pathology result	167	
Histological type		
Invasive ductal carcinoma	160	95.8%
Other histology	7	4.2%
Age	50.48	Range 22-84
Age (Stage II)	49.6	Range 24-84
Age (Stage III)	52.6	Range 22-77
Stage II	113	67.6%
Stage III	54	32.4%
Tumor diameter (All patients)	25 mm	Range 10-85
Tumor diameter (Stage II)	22 mm	Range10-77
Tumor diameter (Stage III)	31 mm	Range 10-85
Premenapousal	81	48.5%
Postmenapousal	86	51.5%
Biological subgroup		
HER2 positive	61	36.5%
Triple negative	37	22.1%
Luminal B	52	31.1%
Luminal A	17	10.1%

Table 2: Pathological complete response rates

	Number of Patients	Patological complete response	%
All Patients	167	55	32.9
HER2 positive	61	27	44.2
Triple negative	37	11	29.7
Luminal B	52	14	26.9
Luminal A	17	3	17.6
Stage II	113	42	37.1
Stage III	54	13	24.0

Table 3: NLR and PLR ratios of those with pathological complete response and those without

		Patological Complete Response				
		% 100		<% 100		
		Mean±SD	Median	Mean±SD	Median	p
Stage II		n=42		n=71		
	NLR	2,46±2,27	1,95	2,94±3,22	2,07	0,244
	PLR	144,0±61,1	136	169,8±91,0	137,0	0,002
Stage III		n=13		n=41		
	NLR	2,51±1,22	2,58	2,69±2,31	2,03	0,595
	PLR	148,4±62,7	139,7	139,9±80,1	120,2	0,384
HER2 Poz		N=27		N=34		
	NLR	2,75±2,75	1,95	3,28±4,25	2,15	0,959
	PLR	147,7±62,1	131,7	160,9±97,1	124,9	0,908
Triple negative		N=11		N=26		
	NLR	2,03±0,83	1,87	3,09±2,36	2,32	0,143
	PLR	144,8±78,7	102,1	176,0±89,9	146,8	0,192
Luminal B		N=14		N=38		
	NLR	2,27±1,10	2,16	2,49±2,21	1,95	0,757
	PLR	140,7±48,2	147,2	156,0±89,9	135,2	0,984