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Research Article

Neutrophil / Lymphocyte Ratio (NLR) – Trombocyte / Lymphocyte Ratio (TLR): A Predictor of Axillary Lymph Node Metastasis in Breast Cancer Patients?

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Abstract

Background: This study evaluated the relationship between preoperative neutrophil / lymphocyte ratio - platelet / lymphocyte ratio, clinicopathological, radiological factors, and axillary lymph node metastasis in stage I-III breast cancer to determine if axillary surgery can be safely omitted in selected patients.

Methods: The study included 158 Stage I-III breast cancer patients operated on at Baskent University Zubeyde Hanim Research Center between 2011 and 2018. The incidence of axillary lymph node metastasis was correlated with clinical, radiological, pathological, and laboratory (neutrophil count to lymphocyte count, platelet count to lymphocyte count) findings by univariate and multivariate analyses. Sensitivity and specificity calculations, positive predictive value, negative predictive value, positive and negative Likelihood Ratio (accuracy ratio), and exact accuracy were calculated for neutrophil/lymphocyte ratio cut-off values of 3.5 and 1.

Results: Neutrophil and platelet values were significantly higher in patients with lymph node metastasis. Neutrophil / lymphocyte ratio - platelet / lymphocyte ratio values were higher in patients with axillary lymph node metastasis, but this was not statistically significant. Axillary lymph node metastasis was not associated with age, lymphocyte, monocyte count, estrogen receptor, progesterone receptor, or c-erb B2 status. The incidence of axillary lymph node metastasis was statistically significantly higher in the presence of lymphovascular invasion. Sensitivity, specificity, positive predictive value, and negative predictive value were 93.85%, 16.67%, 44.9%, and 78.9% respectively for axillary lymph node metastasis while the neutrophil / lymphocyte ratio was ≥ 3.5. Specificity, sensitivity, positive predictive value, and negative predictive value were 97.78%, 9.23%, 75.0%, and 59.9% respectively for axillary lymph node metastasis while the neutrophil / lymphocyte ratio < 1.

Conclusions: For axillary lymph node metastasis, neutrophil, platelet counts, lymphovascular invasion status, radiological and pathological mass size, and presence of radiological axillary lymphadenopathy are the statistically significant independent variables. They provide information that can help surgeons decide on the treatment of breast cancer patients with certain neutrophil / lymphocyte ratio values (neutrophil / lymphocyte ratio < 1 and neutrophil / lymphocyte ratio ≥ 3.5).

Keywords: Neutrophil / Lymphocyte Ratio; Trombocyte / Lymphocyte Ratio; Lymph Node Metastasis; Breast Cancer

Introduction

Sentinel lymph node biopsy is the standard application for assessing axillary disease in breast cancer patients. The Z0011 study by the American College of Surgeons Oncology Group (ACOSOG) emphasizes that axillary dissection (AD) is not required in selected patients with positive sentinel lymph nodes (SLN) [1]. It is known that axillary lymph node status is an important prognostic indicator in patients with invasive breast cancer [2,3]. Sentinel lymph node biopsy (SLNB) has been reported to cause fewer complications than axillary lymph node dissection (ALND), although extensive studies have shown wound infection, seroma, hematoma, paresthesia, and allergic reactions to isosulfan blue dye [4,5].

As components of the systemic inflammatory response, lymphocytes, neutrophils, and platelets are increasingly accepted as playing an important role in carcinogenesis and tumor progression [6]. Neutrophil / lymphocyte ratio (NLR), trombocyte / lymphocyte ratio (TLR) and Glasgow Prognostic Score are prognostic markers in cancer [7]. High NLR (> 3.3) is associated with larger tumors and later stages [8]. Similarly, high TLR has been reported to adversely affect survival in gastrointestinal cancers [9]. NLR and TLR reflect systemic inflammation and have independent prognostic value for various cancer patients [6,10]. However, the role of these biomarkers in breast cancer prognosis is less well known.

Researchers have questioned whether NLR and TLR help to predict the axillary situation. This study therefore evaluated the relationships between preoperative NLR, TLR, clinicopathological factors, and axillary lymph node metastasis in stage I-III breast cancer.

Patients and Methods

The study recruited 158 Stage I-III breast cancer patients operated on at Baskent University Zubeyde Hanim Research Center between 2011 and 2018. Sentinel lymph node biopsy and axillary lymph node clearance in the presence of sentinel lymph node metastasis was performed on all the patients. Their medical records were examined and their medical history, age, radiological and pathological results, and laboratory data were collected. Patients who had received chemotherapy or received immunosuppressive drugs, such as glucocorticoids, cyclosporine, tacrolimus, or interferon, were excluded.

The pathological data were analyzed and size of tumor, histological grade, axillary lymph node status, hormone receptor status, Cerb B2 status, presence of lymphovascular invasion (LVI) and perineural invasion (PNI), radiological results, and laboratory data were evaluated.

Estrogen receptor (ER) and progesterone receptor (PR) status were studied immunohistochemically (IHC). Venous blood samples were taken just before surgery. The ratio of neutrophil and trombocyte count to lymphocyte count, and NLR cut-off values were calculated for both 3.5 and 1.

Statistical analysis

Data were analyzed using SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Mean ± standard deviation, percentage and frequency values of the variables were used. Variables were evaluated after checking for normality and homogeneity of variances (Shapiro Wilk and Levene Test). The analysis showed that the prerequisites for independent 2-group t test (Student's t test) where not met, so Mann Whitney-U test was used to compare the two groups. Categorical data were analyzed by Fisher's Exact Test and Chi-Square Test. In cases where the expected frequencies are less than 20%, the Monte Carlo Simulation Method was used to analyze these frequencies, ROC for distinguishing + from – lymph node metastases, and to assess cut-off point. Sensitivity and specificity calculations, positive predictive value, negative predictive value, positive and negative Likelihood Ratio (accuracy ratio), and exact accuracy were calculated. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ were accepted.

Results

The mean age of our patients was 59.41 ± 14.34. Only 1 was male. 32% had stage I, 50.9% stage II, and 16.9% stage III disease. 62.7% had invasive ductal carcinoma, 8.7% invasive lobular carcinoma, and 28.6% other types of carcinoma. 2.2% patients had histological grade 1, 59.3% histological grade 2, and 38.5% histological grade 3. Lymphovascular invasion was detected in 31.6% patients and perineural invasion in 19.1%. 32.9% patients were C-erb B2 negative, 22.1% patients were 1 +, 15.7% patients 2 +, and 29.3% patients 3 +. In the physical examination, only 29.5% patients had palpable axillary lymph nodes while 23% patients had suspected axillary lymph nodes radiologically.

38% patients underwent modified radical mastectomy, 36.7% patients had breast-conserving surgery + sentinel lymph node biopsy, 20.3% patients had breast-conserving surgery + axillary dissection, and 5.1% patients had simple mastectomy + sentinel lymph node biopsy. There were 65 (41.9%) patients with lymph node metastases (Table 1).

		n	%
GENDER	Men	1	0.6
	Women	157	99.4
Breast Examination (Palpable Breast Mass)	-	22	15.2
	+	123	84.8
Axillary Examination	-	103	70.5
	+	43	29.5
AXILLARY USG	-	104	77.0
	+	31	23.0
BIRADS Breast Imaging-Reporting and Data System	Birads3	2	1.5
	Birads4	14	10.3
	Birads4a	2	1.5
	Birads4b	3	2.2
	Birads4c	31	22.8
	Birads5	84	61.8
Histology	IDC	94	62.7
	ILC	13	8.7
	INVASIVE CANCER	33	22.0
	MUSINOUS	3	2.0
	MEDULLARY	1	0.7
	PAPILLARY	3	2.0
	POORLY DIFFERENTIATED	1	0.7
Grade	Grade1	3	2.2
	Grade2	80	59.3
	Grade3	52	38.5
LVI	+	78	68.4
	-	36	31.6
PNI	-	76	80.9
	+	18	19.1
C Erb-B2	0	46	32.9
	1	31	22.1
	2	22	15.7
	3	41	29.3
Stage	1	49	32.0
	2a	53	34.6
	2b	25	16.3
	3a	12	7.8
	3b	2	1.3
	3c	12	7.8
Operation	MRM	60	38.0
	BCS+SLB	58	36.7
	BCS+AD	32	20.3
	SM+SLB	8	5.1
Lymph Node Metastasis	-	90	58.1
	+	65	41.9

Table 1: Patient characteristics, clinical, radiological, and pathological findings.

The patients' mean neutrophil, lymphocyte, and platelet counts were 4549.13 ± 1991.2, 2484.66 ± 1105.47, and 276575.95 ± 68361.1 respectively. The mean tumor radiological size was 19.44 ± 11.34mm, mean number of lymph node metastases 2.19 ± 5.6, mean tumor size 20.3 ± 14.8 mm and mean number of resected lymph nodes 11.73 ± 8.9. The mean TLR was 123.81 ± 54.29 while the mean NLR was 1.98 ± 0.83 (Table 2).

	Min	Max	± Std. Deviation
Age	27	92	59.41 ± 14.349
Neutrophil /µl	1470	21002	4549.13 ± 1991.242
Lymphocyte / µl	741	12785	2484.66 ± 1105.47
Platelet / µl	30000	470000	276575.95 ± 68361.096
Radiological Tumor Size mm	0	60.0	19.439 ± 11.3431
Tumor Size mm	4	150.0	20.297 ± 14.8128
Lymph Node Resected	1	40	11.73 ± 8.863
Metastatic Lymph Node Count	0	34	2.19 ± 5.609
ER	0	100	65.32 ± 37.588
PR	0	100	47.58 ± 38.878
TLR	8.02	551.96	123.81 ± 54.29
NLR	0.72	5.16	1.98 ± 0.83

Table 2: Patient characteristics, clinical, radiological, pathological, and and laboratory findings.

We found statistically significant differences between patients with and without lymph node metastasis in neutrophil, platelet count, and (radiological and pathological) tumor size. Neutrophil and trombocyte values were significantly higher in patients with lymph node metastasis. NLR and TLR values were higher in patients with axillary lymph node metastasis, although this was not statistically significant. Axillary lymph node metastasis was not associated with age, lymphocyte, monocyte, ER, or PR. As expected, tumor size was statistically significantly lower in patients without lymph node metastases (Table 3).

There were statistically significant relationships between axillary lymph node metastasis and palpability of breast mass and the axillary lymph node, lymphovascular invasion, and radiological BIRADS score of the mass. However, there were no statistically significant relationships between tumor histology, grade, presence of perineural invasion, C erb B2 status, and lymph node metastasis. Axillary lymph node metastasis was statistically significantly more frequent in the presence of LVI. As expected, axillary lymph node metastasis was statistically significantly more frequent in the presence of palpable mass and palpable axillary lymph nodes in the physical examination, with lymphadenopathy detected by the radiological examination, and with high BIRADS scores (Table 4).

	Axillary lymph node metastasis -	Axillary lymph node metastasis +	p
	n=90	n=65	
Age	59.04 ± 14.33	60.12 ± 14.63	0.650
NEUTROPHIL / µl	4328 ± 1622.77	4882.8 ± 2406.99	0.040*
LYMPHOCYTE / µl	2448.77 ± 781.18	2501.17 ± 1490.63	0.780
PLATELET / µl	271277.78 ± 70241.16	280430.77 ± 63076.83	0.040*
MONOSIT / µl	460.53 ± 169.43	1194.82 ± 5342.55	0.270
Radiological tumor size (mm)	18.04 ± 10.88	22.14 ± 11.81	0.040*
ER	65.62 ± 36.72	64.92 ± 39.01	0.910
PR	48.38 ± 39.12	46.54 ± 38.86	0.780
Pathological tumor size (mm)	16.82 ± 9.5	25.01 ± 18.96	0.001*
TLR	126.4 ± 95.82	132.31 ± 70.17	0.674
NLR	2.02 ± 1.8	2.18 ± 0.94	0.530

Table 3: Association between axillary lymph node metastasis and clinicopathological factors.

*p<0.05, **p<0.01.

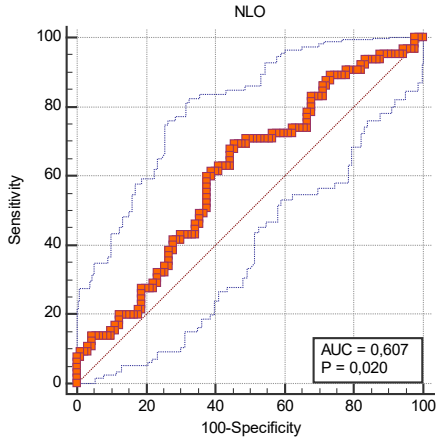
			Ln Met		Total	p
			-	+		
Breast examination	-	n (%)	19 (90,5)	2 (9,5)	21 (100)	0.002**
	+	n (%)	67 (54.9)	55 (45.1)	122 (100)	
Axillary examination	-	n (%)	71 (70.3)	30 (29.7)	101 (100)	0.001**
	+	n (%)	15 (34.9)	28 (65.1)	43 (100)	
Radiological examination of axilla	-	n (%)	72 (71.3)	29 (28.7)	101 (100)	0.001**
	+	n (%)	9 (29.0)	22 (71.0)	31 (100)	
Histology	Invasive ductal Cancer (IDC)	n (%)	55 (58.5)	39 (41.5)	94 (100)	0.479
	Invasive Lobuler Cancer (ILC)	n (%)	5 (38.5)	8 (61.5)	13 (100)	
	Invasive Cancer (IC)	n (%)	21 (63.6)	12 (36.4)	33 (100)	
	Musinous Cancer	n (%)	2 (66.7)	1 (33.3)	3 (100)	
	Medullary Cancer	n (%)	0 (0.0)	1 (100.0)	1 (100)	
	Papillary Cancer	n (%)	2 (66.7)	1 (33.3)	3 (100)	
	Nondiferantiated	n (%)	0 (0.0)	1 (100.0)	1 (100)	
	IDC,Musinous	n (%)	2 (100.0)	0 (0.0)	2 (100)	
GRADE	GRADE1	n (%)	3 (100.0)	0 (0.0)	3 (100.0)	0.271
	GRADE 2	n (%)	47 (58.8)	33 (41.3)	80 (100)	
	GRADE 3	n (%)	28 (53.8)	24 (46.2)	52 (100)	
LVI	-	n (%)	58 (74.4)	20 (25.6)	78 (100)	0.001**
	+	n (%)	9 (25.0)	27 (75.0)	36 (100)	

PNI	-	n (%)	48 (63.2)	28 (36.8)	76 (100)	0.146
	+	n (%)	8 (44.4)	10 (55.6)	18 (100)	
CERB2	0	n (%)	29 (63.0)	17 (37.0)	46 (100)	0.729
	1	n (%)	17 (54.8)	14 (45.2)	31 (100)	
	2	n (%)	12 (54.5)	10 (45.5)	22 (100)	
	3	n (%)	21 (51.2)	20 (48.8)	41 (100)	
BIRADS Breast Imaging-Reporting and Data System	BIRADS3	n (%)	2 (100.0)	0 (0.0)	2 (100)	0.002**
	BIRADS4	n (%)	12 (85.7)	2 (14.3)	14 (100)	
	BIRADS4A	n (%)	2 (100.0)	0 (0.0)	2 (100)	
	BIRADS4B	n (%)	3 (100.0)	0 (0.0)	3 (100)	
	BIRADS4C	n (%)	22 (71.0)	9 (29.0)	31 (100)	
	BIRADS5	n (%)	39 (47.0)	44 (53.0)	83 (100)	
GENDER	Men	n (%)	1 (100.0)	0 (0.0)	1 (100.0)	0.394
	Women	n (%)	89 (57.8)	65 (42.2)	154 (100)	

Table 4: Association between axillary lymph node metastasis and clinicopathological factors.

*p<0.05, **p<0.01,

Sensitivity, specificity, PPV, and NPV were 93.85%, 16.67%, 44.9%, and 78.9% respectively for axillary lymph node metastasis while NLO ≥ 3.54. This indicates that for values of NLR equal or above 3.5, test sensitivity is high. This demonstrates the ability of the test to correctly identify those with axillary lymph node metastasis (Table 5).



Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
>3,5462	93,85	85,0 - 98,3	16,67	9,6 - 26,0	1,13	1,0 - 1,3	0,37	0,1 - 1,1	44,9	42,1 - 47,6	78,9	56,6 - 91,5
1,0905	9,23	3,5 - 19,0	97,78	92,2 - 99,7	4,15	0,9 - 19,9	0,93	0,9 - 1,0	75,0	38,5 - 93,5	59,9	57,8 - 61,9

Table 5: ROC Curve.

Specificity, sensitivity, PPV, and NPV were 97.78%, 9.23%, 75.0%, and 59.9% respectively for axillary lymph node metastasis while NLR < 1. This indicates that for NLR values below 1, the specificity of the test is high to reliably identify patients without axillary lymph node metastasis (true negative rate) (Table 5). Sensitivity and specificity are prevalence-independent test characteristics, as their values are intrinsic to the test and do not depend on disease prevalence in the population of interest.

Figures 1 and 2 show the NLR and TLR ratios for patients with or without axillary lymph node metastases. Although NLR and TLR values were higher in patients with axillary lymph node metastasis, this was not statistically significant.

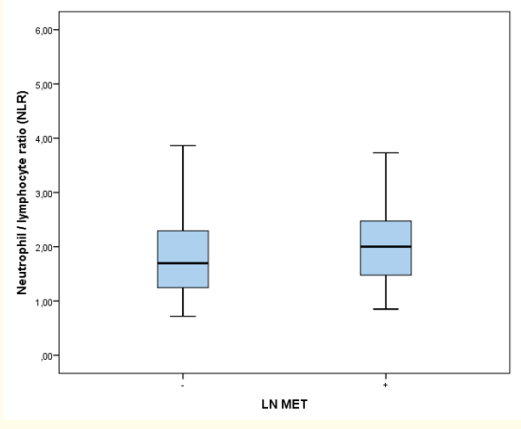


Figure 1: Neutrophil / lymphocyte ratio (NLR) and axillary lymph node status for 158 patients with breast cancer.

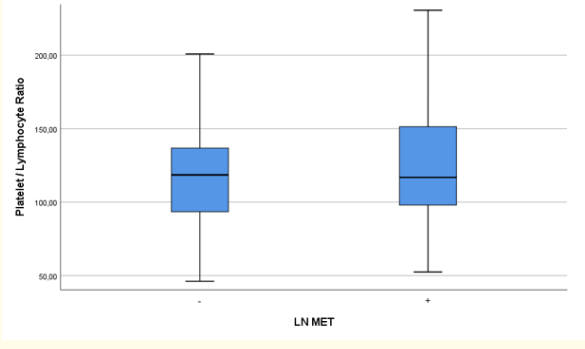


Figure 2: Trombocyte / lymphocyte ratio (TLR) and axillary lymph node status for 158 patients with breast cancer.

Discussion and conclusion

As components of systemic inflammatory response, lymphocytes, neutrophils, and platelets are increasingly accepted as playing an important role in carcinogenesis and tumor progression [5]. NLR and TLR reflect systemic inflammation and have independent prognostic value for various cancer patients [6,10]. However, the role of these biomarkers in breast cancer prognosis is less well known. Some studies have shown that high NLR is associated with malignant tumor prognosis, including breast cancer [11]. However, other studies do not support this result [12-13]. We found that neutrophil and platelet values were statistically significantly higher in patients with lymph node metastasis. We also found that NLR and TLO values were higher in patients with axillary lymph node metastasis, but this was not statistically significant. In addition, axillary lymph node metastasis was not associated with lymphocyte and monocyte values.

In this study axillary lymph node metastasis was statistically significantly more frequent in the presence of LVI. Similarly, Chua., *et al*. reported that palpable primary tumor, palpable axillary lymph node, larger pathological and radiological tumor size, and LVI presence are independent predictors for axillary lymph node metastasis [14]. We have previously reported that for early stage breast cancer patients the sensitivity and specificity of axillary ultrasound for detecting ALN disease was 69.2% and 98%, respectively, with an NPV of 86.4% and PPVof 94.7% [15]. The present study also showed a statistical significant correlation between axillary metastasis and axillary ultrasound results.

Sensitivity, specificity, PPV, and NPV were 93.85%, 16.67%, 44.9%, and 78.9% respectively for axillary lymph node metastasis while NLR ≥ 3.5. Sensitivity (also called the true positive rate, or probability of detection) measures the correctly identified proportion of actual positives. Specificity, sensitivity, PPV, NPV were 97.78%, 9.23%, 75.0%, and 59.9% respectively for axillary lymph node metastasis and NLR< 1. Specificity (also called the true negative rate) measures the proportion of correctly identified actual negatives. A sensitivity of 93.85% in patients with an NLR of 3.5 and above and a specificity of 97.78% in patients with an NLR of less than 1 may indicate the condition of the axillary lymph node, but NLR values in between are insufficient to comment on the axilla.

This was a retrospective study, so prospective studies with more patients would be useful. In conclusion, for axillary lymph node

metastasis, neutrophil, platelet counts, LVI status, radiological and pathological mass size, and presence of radiological axillary lymphadenopathy are statistically significant independent variables. They can therefore provide information to help surgeons decide on the treatment of breast cancer patients with certain NLR values (NLR < 1 and NLR ≥ 3.5).

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