RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-34
Cyprus J Med Sci 2023;8(4):276-286

New Lymph Node Parameters and a Comparison with the American Joint Committee on Cancer N-Stages in Breast Cancer

Nuket Özkavruk Eliyatkın[1], İnci Başkır[2], Akif İşlek[3], Baha Zengel[4]

[1]Department of Pathology, İzmir Katip Çelebi University Faculty of Medicine, İzmir, Türkiye
[2]Clinic of Obstetrics and Gynecology, Ankara City Hospital, Ankara, Türkiye
[3]Clinic of Otorhinolaryngology, Acıbadem Eskişehir Hospital, Eskişehir, Türkiye
[4]Department of Surgery, İzmir Ekonomi University Faculty of Medicine, İzmir, Türkiye

Abstract

BACKGROUND/AIMS: The N-stage of TNM systems considers only the number of metastatic lymph nodes (NMLN) in breast cancer (BC). However, new lymph node parameters refer to the number of harvested lymph nodes (NHLN) and negative lymph nodes (NNLN), which have had an increasing significance in the current literature. This study aimed to compare NHLN, NNLN, lymph node ratio (LNR), modified lymph node ratio (mLNR), and log odds of positive lymph nodes (LODDS) against the standard American Joint Committee on Cancer (AJCC) N-stage for the prognosis of BC patients.

MATERIALS AND METHODS: This study was designed retrospectively. The socio-demographic data, clinical features, histopathological factors, treatment modalities, receptor status of BC, and lymph node related parameters (AJCC N, LNR, mLNR, LODDS) were identified. Then, lymph node related parameters were compared for cancer-related mortality (CRM), cancer recurrence, disease-free survival (DFS), and overall survival (OS).

RESULTS: Eight hundred seven women who underwent surgery for BC were included in this study according to its eligibility criteria. The mean follow-up period was 113.34±74.85 (range: 6-378) months. The NHLN was 21.24±9.22, the NMLN was 4.85±7.38, the NNLN was 16.39±9.48, the LNR was 0.23±0.29, the mLNR was 5.38±7.38 and the LODDS was -0.74±0.80 on average. During the follow-up period, 42 (5.2%) patients had local recurrence, 188 (23.3%) had distant metastases, and 252 (31.2%) patients died due to BC. NMLN, LNR, mLNR, and LODDS were found to be significantly higher, and NNLN was significantly lower in those patients with cancer recurrence and CRM ($p<0.001$). AJCC N-stages, and also LNR, mLNR, and LODDS groups according to the calculated cut-off values, were significant for DFS and OS according to survival analysis. In Cox regression analysis, only LODDS was a significant independent risk factor for OS [$p=0.014$, heart rate (HR)=3.78, 95% confidence interval (CI) for HR: 1.30-10.94)].

CONCLUSION: The results indicated that LODDS was more successful compared to other lymph node staging systems, especially for OS. However, randomized prospective controlled studies with larger samples and homogeneous study groups are needed to create standard classification systems as alternatives to AJCC N.

Keywords: Modified lymph node ratio, breast cancer, log odds of positive lymph nodes, lymph node ratio, lymph node staging

To cite this article: Özkavruk Eliyatkın N, Başkır İ, İşlek A, Zengel B. New Lymph Node Parameters and a Comparison with the AJCC N-Stages in Breast Cancer. Cyprus J Med Sci 2023;8(4):276-286

ORCID IDs of the authors: N.Ö.E. 0000-0002-7784-5699; İ.B. 0000-0002-1020-5988; A.İ. 0000-0001-7058-3457; B.Z. 0000-0002-1812-6846.

Address for Correspondence: Nuket Özkavruk Eliyatkın
E-mail: nuket.ozkavruk.eliyatkin@ikcu.edu.tr
ORCID ID: orcid.org/0000-0002-7784-5699

Received: 06.04.2023
Accepted: 11.04.2023

INTRODUCTION

Breast cancer (BC) is the second most common malignancy after lung cancer worldwide. Moreover, BC is the most common cause of death due to cancer in women in a certain age group (40-49 years old), so this feature makes BC highly significant among other malignancies. Since most women with BC are non-metastatic at their time of diagnosis, very promising results have been reported with multidisciplinary management.[1] The management of BC depends on many different factors. The age, pathological stage of the BC, the biological characteristics of the BC [such as hormone receptor status, human epidermal growth factor receptor-2 (HER-2) status], and lymphatic or vascular invasion are just some prior determinants for treatment strategy. Axillary lymph node involvement and the number of metastatic lymph nodes (NMLN) were assumed to be the most important prognostic factors in the decision of adjuvant radiotherapy.[2] Under current clinical guidelines, pathological examination of at least 10 harvested lymph nodes with level 1-2 axillary dissection is accepted for the correct staging of the axillary lymph node stage.[3] However, axillary dissection cannot be surgically performed with the same intensity in every patient due to reasons such as the experience of the surgeon or the pathologist, the patient's age, the patient's anatomical structure, and/or concomitant diseases. The count of metastatic lymph nodes in the axillary dissection material is divided into three groups according to the N-stage of the American Joint Committee on Cancer (AJCC) 8th edition staging system. Under this classification, the total count of the harvested lymph nodes or the number of negative lymph nodes (NNLN) is not taken into account. As patients are classified by the number of "positive lymph nodes only", a heterogeneous group is actually formed. Thus, axillary lymph node staging with the current N classification may change, result in inadequate treatment, and/or may be insufficient in predicting the prognosis.[4] Therefore, it may be appropriate to consider not only the number of positive lymph nodes, but also the total number of lymph nodes and the number of NNLN in order to determine a more reliable prognosis for BC patients. There are new studies showing that the total lymph node count is a better prognostic parameter than the metastatic lymph node count.[5-7] Also, it has been supported by various studies that the pN classification, which evaluates the ratio lymph node ratio (LNR) of the NMLN to the number of harvested lymph nodes (NHLN), is more successful in determining the prognosis of BC.[4,5,8,9] However, as a limitation of LNR, the prognostic power of this value decreases in those patients with LNR values of "0 or 1".[10,11] Therefore, the "modified lymph node ratio (mLNR)" was calculated by modifying the LNR classification (by adding 0.5 to both the numerator and the denominator) thus eliminating the possibility of a mLNR value of 0.[11]

Another more complicated lymph node classification is the "log odds of positive lymph nodes (LODDS)", calculated as the logarithm of the odds ratio (OR) between positive and NNLN. There are studies in the literature reporting that LNR, mLNR, and LODDS for BC patients have better prognostic value than the pN classification made with only the number of lymph nodes with metastasis.[10-13] There have been different studies investigating the importance of one or more of the NHLN, the number of NNLN, LNR, mLNR and LODDS values in the prognosis of BC. However, the existing literature did not include studies with all these values as covariates in determining the prognosis of operated BC in a large series including different molecular subtypes, and long-term follow-up in our country. Therefore, this study aimed to compare NHLN, NNLN, LNR, mLNR, and LODDS against the standard AJCC N stage for the prognosis of BC patients.

MATERIALS AND METHODS

Design

The study was designed retrospectively. Our study population consisted of patients treated and followed up for breast carcinoma between the years of 1989-2021 in University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital. Permission was obtained from the necessary places for data sharing.

Eligibility Criteria

Patients with bilateral BC, male BC cases, those who received neoadjuvant therapy, those cases without follow-up, or those with missing data were excluded. During the examination of the records, 1,873 patients were investigated. The final number of patients according to the eligibility criteria was determined to be 807 patients. All patients, in the final analysis, underwent breast-conserving surgery or mastectomy with axillary dissection. After surgery, all patients were administered adjuvant chemotherapy and/or radiotherapy and/or endocrine therapy according to NCCN guidelines.

Outcome Parameters

The patient's demographics, clinical and pathological factors, and treatment modalities (types of surgery, adjuvant therapy, or hormone therapy) were identified. The tumor characteristics including the histologic type of tumor (invasive ductal carcinoma, invasive lobular carcinoma, mixed carcinoma, and special types), the histologic grade, the tumor size, the histologic features, and the presence of lymphovascular (LVI) were determined. Estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, or unknown), and HER-2 status (positive, negative, or unknown) were determined. Finally, tumor molecular subtypes were classified as luminal A (ER-positive and/or PR positive/HER-2 negative), luminal B (ER-positive and/or PR positive/HER-2 positive), HER-2 overexpressing (ER-negative/PR negative/HER-2 positive) or triple negative (ER-negative/PR negative/HER-2 negative). The pT stages and pN stages were determined according to the TNM classification of the relevant diagnostic pathology report of the AJCC 8th edition. The NHLN and the number of NNLN were also recorded in detail. The LNR was defined as the ratio of NMLN to NHLN. mLDR was calculated with the formula [LD (+) + 0.5]/[LDT + 0.5]. LODDS was determined by taking the logarithm of the ratio as follows: Log [LD (+) + 0.5]/[LD (-) + 0.5]. Optimal cut-off points were analyzed for all these pN staging parameters, and their sensitivity and specificity were determined. Cancer-related mortalities (CRM) and cancer recurrences during follow-up were determined. Lymph node parameters were compared for disease-free survival (DFS) and overall survival (OS).

Statistical Analysis

Statistical analysis was performed by the SPSS 22.0 program (IBM Corp., Armonk, NY, USA). Nominal variables were compared with the chi-squared test. Scale variables were tested for normality distribution by the Kolmogorov-Smirnov test. Scale variables between two groups were compared using the t-test or the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was used to determine the significant cut-off value for mLNR. Kaplan-Meier survival analysis with log-rank comparisons was performed in groups consisting of lymph node-related parameters. Also, significant variables for recurrence and cancer-related deaths according to univariate analysis underwent a Cox regression model for DFS and OS.

RESULTS

Eight hundred seven women who underwent surgery for BC were included in this study according to the eligibility criteria. Their mean age was 53.98±13.14 (range: 23-99) years. While the most common BC histological type was invasive carcinoma-NOS (n=554, 69.2%), according to the molecular classification, the patients were mainly in the Luminal A group (n=338, 54.3%). The mean follow-up period was 113.34±74.85 (range: 6-378) months. The histopathological findings of the tumors are given in Table 1. The NHLN was 21.24±9.22, the NMLN was 4.85±7.38, the NNLN was 16.39±9.48, the LNR was 0.23±0.29, the mLNR was 5.38±7.38 and the LODDS was -0.74±0.80 on average (Table 2).

During the follow-up period, 42 (5.2%) patients experienced local recurrence and 188 (23.3%) had distant metastases, resulting in 252 (31.2%) deaths due to BC. The one-year overall survival (OS) rate was 0.984, the 3-year rate was 0.926, the 5-year rate was 0.849, and the 10-year rate was 0.708 for all patients. The one-year DFS rate was 0.981, the 3-year rate was 0.911, the 5-year rate was 0.842, and the 10-year rate was 0.741 for all patients. While the NHLNs in patients with CRM and cancer recurrence were similar, conversely, in those patients who did not develop recurrence and survived, NMLN, LNR, mLNR, and LODDS were found to be significantly lower compared to those with cancer recurrence or CRM (Table 3). In contrast to this, the number of NNLN was found to be significantly lower in those patients with cancer recurrence and CRM ($p<0.001$). The rate of cancer recurrence and CRM were significantly higher in those patients with mLNR >2.52 [Table 1, OR: 2.55, 95% confidence interval (CI) for OR: 1.84-3.55 and OR: 2.12, 95% CI for OR: 1.55-2.91]. Conversely, cancer recurrence (NNLN >13.0) and CRM (NNLN >15.5) were significantly lower in those patients with NNLN 14 and above (Table 1, OR: 2.40, 95% CI for OR: 1.74-3.32 and OR: 1.81, 95% CI for OR: 1.33-2.48). According to Cox regression analysis, increased NNLN was significantly related to a lower risk of cancer recurrence in non-metastatic patients (TNM N0) ($p<0.001$, HR: 15.87, 95% CI: 3.78-66.67). Also, in N0 patients, increased NNLN was significantly related to a lower risk of CRM ($p<0.017$, HR: 3.58, 95% CI: 1.26-10.21). However, in N0 patients, no significant cut-off value was found for cancer recurrence and CRM in the ROC analysis of the NNLN (log-rank: 0.963 and 0.609).

Mastectomy ($p<0.001$), positive HER-2 (0.028), LVI invasion ($p<0.001$), advanced T-stage ($p<0.001$), advanced N-stage ($p<0.001$), LNR >0.140 ($p<0.001$), mLNR >2.52 ($p<0.001$) and LODDS >-0.728 ($p<0.001$) were significantly related with cancer recurrence. Also, mastectomy ($p<0.001$), positive PR (0.032), LVI invasion (0.048), advanced T-stage ($p<0.001$), advanced N-stage ($p<0.001$), LNR >0.117 ($p<0.001$), mLNR >2.52 ($p<0.001$) and LODDS >-0.805 ($p<0.001$) were significantly related with CRM (Table 4).

According to ROC analysis, LNR, mLNR, and LODDS were found to be significant variables for both cancer recurrence and CRM, but the sensitivity and specificity for the calculated cut-off values were low (Table 5, Figure 1, 2). According to Kaplan-Meier survival analysis, both DFS and OS differed significantly in LNR groups determined according to the cut-off value and four LNRs ($p<0.001$, Figure 3-6). Also, the LODDS and mLNR groups determined according to the cut-off value were significant for DFS and OS according to survival analysis ($p<0.001$, Figure 7-10). Similarly, AJCC N staging was found to be significant for DFS and OS according to the survey analysis (Figure 11, 12). According to Cox regression analysis, among the lymph node parameters, only LODDS were found to be significant independent risk factors for OS [$p=0.014$, HR: 3.78, 95% CI for HR: 1.30-10.94, (Table 6)].

Table 1. An overall summary of findings

		n	%
Side	Right	406	50%
	Left	401	50%
Surgery	Mastectomy	664	82%
	Breast conserving surgery	143	18%
Histological type	Invasive ductal carcinoma	554	69%
	Invasive lobular carcinoma	66	8%
	Mixed carcinoma	72	9%
	Special types	109	14%
Grade	Grade 1	27	5%
	Grade 2	333	61%
	Grade 3	189	34%
Nuclear grade	Grade 1	14	4%
	Grade 2	207	66%
	Grade 3	91	29%
Lymphovascular Invasion	Negative	280	59%
	Positive	197	41%
Perinodal involvement	Negative	197	51%
	Positive	190	49%
ER	Negative	289	38%
	Positive	470	62%
PR	Negative	291	39%
	Positive	462	61%
HER-2	Negative	448	73%
	Positive	164	27%
Ki67	Negative	188	30%
	Positive	430	70%
Molecular classification	Luminal A	338	54%
	Luminal B	118	19%
	Triple negative	115	18%
	HER-2-positive	52	8%
T-stage	T1	204	25%
	T2	469	58%
	T3	85	11%
	T4A	6	1%
	T4B	29	4%
	T4C	1	0%
	T4D	3	0%
N-stage	N0	237	29%
	Isolated tumor cell	2	0%
	Micro-metastasis	4	0%
	N1	258	32%
	N2	174	22%
	N3	132	16%
M-stage	None	787	98%
	Distant metastasis	20	2%

Table 1. Continued

		n	%
TNM-stage	1A	83	10%
	1B	3	0%
	2A	194	24%
	2B	181	22%
	3A	174	22%
	3B	20	2%
	3C	122	15%
	4	22	3%
Local recurrence	None	765	95%
	Yes	42	5%
Survival	Survived	454	56%
	Died	252	31%
	Missed	101	13%
LNR groups (literature)	LNR=0	237	29%
	0< LNR ≤0.2	290	36%
	0.2< LNR ≤0.65	173	21%
	LNR >0.65	107	13%
LODDS groups (literature)	LODDS ≤-1.5	169	21%
	-1.5< LODDS ≤-1.0	176	22%
	-1.0< LODDS ≤-0.5	198	25%
	-0.5< LODDS ≤0	106	13%
	LODDS >0	158	20%
mLNR risk groups recurrence/ survival	mLNR ≤2.52	415	51%
	mLNR >2.52	392	48.%
NHLN risk groups recurrence/ survival	NHLN ≤19.50	389	48%
	NHLN >19.50	418	52%
NMLN risk groups for recurrence/ survival	NMLN ≤2.50 (low risk)	448	56%
	NMLN >2.50 (high risk)	359	44%
NNLN risk groups for recurrence	NNLN ≤13.00 (low risk)	320	40%
	NNLN >13.00 (high risk)	487	60%
NNLN risk groups for survival	NNLN ≤15.50 (low risk)	387	48%
	NNLN >15.50 (high risk)	420	52%
LNR risk groups for recurrence	LNR ≤0.140 (low risk)	456	57%
	LNR >0.140 (high risk)	351	43%
LNR risk groups for survival	LNR ≤0.117 (low risk)	425	53%
	LNR >0.117 (high risk)	382	47%
LODDS risk groups for recurrence	LODDS ≤-0.728 (low risk)	456	57%
	LODDS >-0.728 (high risk)	351	43%
LODDS risk groups for survival	LODDS ≤-0.805 (low risk)	419	52%
	LODDS >-0.805 (high risk)	388	48%

Distribution of patients in risk groups according to calculated cut-off values of lymph node parameters is also given. NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor-2.

Table 2. The mean, standard deviation, minimum and maximum values of the dissected lymph node parameters

	m	SD	Minimum	Maximum
NHLN	21,242	9,221	1,000	71,000
NMLN	4,850	7,381	0.001	53,000
NNLN	16,392	9.486	0.001	70,000
LNR	0.229	0.285	0.001	1,000
mLNR	5,380	7.378	0.509	53,509
LODDS	-0.739	0.796	-2.061	1,949

NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, m: Mean, SD: Standard deviation.

DISCUSSION

The AJCC pN staging classification is based only on the absolute number of positive lymph nodes. This classification does not take into account the density of axillary lymph node dissection in surgical dissection, and it is instead dependent on the number of lymph nodes detected in the postoperative axillary dissection material. This is particularly relevant when the number of lymph nodes detected in axillary dissection is very low and thus not able to be accurately evaluated pathologically. However, the lower limit of the number of lymph nodes to be evaluated in axillary lymph node dissection materials is not clearly defined. As a guideline, it is recommended to assess at least 10 dissected lymph nodes for pN staging.[14] A mathematical model of axillary lymph node involvement was tested in a large series of 1,446 patients with invasive BC, and it was shown that pN staging can be achieved with 90% accuracy by evaluating at least 10 lymph nodes which have been dissected.[15] The mean NHLN found in our study was much higher than the number suggested by the literature. NHLN was not a significant factor for cancer recurrence, CRM, DFS, or OS in this study, but as the number of NNLNs increased, recurrence and CRM decreased, and DFS and OS increased. NHLN was more than double the number recommended in the literature, which is sufficient for NMLN and NNLN-dependent staging. For this reason, a classification which includes or combines NMLN and NNLN variables may provide more information.

Additionally, there are also studies investigating the predictive values of the NNLN number in the survival of BC. The predictive value of the intact lymph node count in BC patients remains uncertain.[16,17] In our study, 239 patients did not have lymph node metastases. A significant cut-off value for NNLN could not be determined in these patients, but it was shown that both DFS and OS increased significantly with increasing NNLN. Among all patients, an NNLN of 13 or more for cancer recurrence and 15.5 or more for CRM was determined as a good prognostic factor. Similarly, Kuru[18] indicated that an NNLN number over 15 was significantly associated with a better prognosis. In another study, NNLN was found to affect survival in BC with 4 or more metastatic lymph nodes.[19] In another case series of 455 cases in which the NNLN cut-off value was determined as 5, it was shown that DFS and OS were better in those with NNLN numbers of 5 and above. However, when multivariate analysis was performed in that same study, no difference was found in DFS and OS.[20] In our study, only the LODDS variable for OS was found to be significant among the lymph node parameters in multivariate analysis. However, the ACOSOG Z0011 randomized trial demonstrated that the extension of axillary lymph node dissection did

Table 3. Distribution of lymph node parameters according to recurrence and mortality groups with t-test statistics

	Recurrence					Survival				
	None		Recurrence		p	Survive		Ex		p
	m	SD	m	SD		m	SD	m	SD	
NHLN	21,122	8,865	21,584	10,186	0.819	21,051	8,605	22,147	10,603	0.495
NMLN	3,629	5,699	8,344	10,067	<0.001	3,456	5,199	7,214	9,776	<0.001
NNLN	17,493	9,288	13,239	9,361	<0.001	17,595	9,194	14,933	10,107	<0.001
LNR	0.179	0.246	0.373	0.337	<0.001	0.176	0.246	0.315	0.324	<0.001
mLNR	4,158	5,696	8,875	10,060	<0.001	3,985	5,196	7,743	9,770	<0.001
LODDS	-0.873	0.717	-0.355	0.881	<0.001	-0.884	0.707	-0.498	0.884	<0.001

NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes, m: Mean, SD: Standard deviation.

Table 4. Distribution of nominal variables according to recurrence and mortality groups with chi-square statistics

		Recurrence					Survival				
		None		Recurrence		p	Ex		Survive		p
		n	%	n	%		n	%	n	%	
Surgery	Mastectomy	470	79%	194	93%	**<0.001**	238	94%	331	73%	**<0.001**
	Breast conserving surgery	128	21%	15	7%		14	6%	123	27%	
ER status	Negative	203	36%	86	44%	0.061	99	42%	146	34%	**0.038**
	Positive	359	64%	111	56%		139	58%	289	66%	
PR	Negative	211	38%	80	41%	0.428	99	42%	143	33%	**0.032**
	Positive	347	62%	115	59%		139	58%	287	67%	
HER-2	Negative	340	76%	108	67%	**0.028**	131	70%	270	76%	0.121
	Positive	110	24%	54	33%		57	30%	86	24%	
Lymphovascular Invasion	Negative	228	64%	52	42%	**<0.001**	76	52%	182	62%	**0.048**
	Positive	126	36%	71	58%		70	48%	112	38%	
Molecular classification	Luminal A	263	57%	75	46%	<0.075	94	49%	216	60%	0.084
	Luminal B	82	18%	36	22%		41	21%	65	18%	
	Triple negative	80	17%	35	21%		40	21%	56	16%	
	HER-2 overexpressed	34	7%	18	11%		18	9%	24	7%	
T-stage	T1	178	30%	26	13%	**<0.001**	47	19%	142	32%	**<0.001**
	T2	352	60%	117	57%		143	58%	255	57%	
	T3	46	8%	39	19%		33	13%	41	9%	
	T4	15	3%	24	12%		24	10%	11	2%	
N-stage	N0	200	33%	39	19%	**<0.001**	56	22%	153	34%	**<0.001**
	N1	216	36%	46	22%		68	27%	164	36%	
	N2	117	20%	57	27%		61	24%	90	20%	
	N3	65	11%	67	32%		67	27%	47	10%	
M-stage	None	598	100%	189	90%	**<0.001**	242	96%	444	98%	0.176
	Distant metastasis	0	0%	20	10%		10	4%	10	2%	
LNR groups (literature)	LNR=0	199	25%	38	5%	**<0.001**	55	7%	152	19%	**<0.001**
	0< LNR ≤0.2	232	29%	58	7%		77	10%	183	23%	
	0.2< LNR ≤0.65	116	14%	57	7%		67	8%	81	10%	
	LNR >0.65	51	6%	56	7%		53	7%	38	5%	
LODDS groups (literature)	LODDS ≤-1.5	144	24%	25	12%	**<0.001**	40	16%	110	24%	**<0.001**
	-1.5< LODDS ≤-1.0	148	25%	28	13%		38	15%	117	26%	
	-1.0< LODDS ≤-0.5	150	25%	48	23%		62	25%	114	25%	
	-0.5< LODDS ≤0	78	13%	28	13%		37	15%	52	11%	
	LODDS >0	78	13%	80	38%		75	30%	61	13%	

Table 4. Continued

		Recurrence					Survival				
		None		Recurrence		p	Ex		Survive		p
		n	%	n	%		n	%	n	%	
mLNR cut-off groups	mLNR ≤2.5257	343	57%	72	34%	**<0.001**	99	39%	263	58%	**<0.001**
	mLNR >2.5257	255	43%	137	66%		153	61%	191	42%	
NHLN risk groups recurrence/ survival	NHLN ≤19.50	291	36%	98	12%	0.659	119	15%	218	27%	0.839
	NHLN >19.50	307	38%	111	14%		133	16%	236	29%	
NMLN risk groups for recurrence/ survival	NMLN ≤2.5	371	46%	77	10%	**<0.001**	109	14%	283	35%	**<0.001**
	NMLN >2.5	227	28%	132	16%		143	18%	171	21%	
NNLN risk groups for recurrence	NNLN ≤13.0	204	25%	116	14%	**<0.001**	117	14%	152	19%	
	NNLN >13.0	394	49%	93	12%		135	17%	302	37%	
NNLN risk groups for survival	NNLN ≤15.5	254	31%	133	16%		140	17%	185	23%	**<0.001**
	NNLN >15.5	344	43%	76	9%		112	14%	269	33%	
LNR risk groups for recurrence	LNR ≤0.140	379	47%	77	10%	**<0.001**	111	14%	290	36%	
	LNR >0.140	219	27%	132	16%		141	17%	164	20%	
LNR risk groups for survival	LNR ≤0.117	353	44%	72	9%		104	13%	269	33%	**<0.001**
	LNR >0.117	245	30%	137	17%		148	18%	185	23%	
LODDS risk groups for recurrence	LODDS ≤-0.728	377	47%	79	10%	**<0.001**	114	14%	289	36%	
	LODDS >-0.728	221	27%	130	16%		138	17%	165	20%	
LODDS risk groups for survival	LODDS ≤-0.805	348	43%	71	9%		100	12%	268	33%	
	LODDS >-0.805	250	31%	138	17%		152	19%	186	23%	**<0.001**

ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor-2, LNR: Lymph node ratio, LODDS: Log odds of positive lymph nodes, mLNR: Modified lymph node ratio, NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes.

Table 5. Cut-off values of lymph node parameters calculated by ROC analysis for cancer recurrence and cancer-related mortality with their sensitivity and specificity

Variable(s)	Area	p	Cut-off value	Sensitivity	Specificity		
			Lower	Upper			
Recurrence							
NHLN	0.505	0.819	0.458	0.552	**19,500**	**0.531**	**0.487**
NMLN	0.666	0	0.621	0.710	**2,500**	**0.632**	**0.620**
NNLN	0.362	0	0.317	0.407	**13**	**0.445**	**0.341**
LNR	0.673	0	0.629	0.717	0.140	0.632	0.634
mLNR	0.670	0	0.625	0.714	2,524	0.675	0.676
LODDS	0.674	0	0.630	0.718	-0.728	0.622	0.630
Survival							
NHLN	0.521	0.340	0.477	0.565	**19,500**	**0.528**	**0.586**
NMLN	0.617	0	0.574	0.660	**2,500**	**0.567**	**0.506**
NNLN	0.426	0.001	0.382	0.470	**15,500**	**0.444**	**0.445**
LNR	0.388	0	0.348	0.427	0.117	0.407	0.442
mLNR	0.391	0	0.352	0.431	2,526	0.421	0.431
LODDS	0.448	0.448	0.448	0.448	0.448	0.448	0.448

ROC: Receiver operating characteristic, NHLN: Number of harvested lymph nodes, NMLN: Number of metastatic lymph nodes, NNLN: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio, LODDS: Log odds of positive lymph nodes.

not improve the survival of BC patients compared to negative or less than three positive sentinel lymph nodes after surgery. Also, expanded axillary lymph node dissection was recommended to be avoided. They showed that radical axillary lymph node dissection followed by axillary radiotherapy was associated with higher morbidity.[21]

LNR staging is recommended as another lymph node staging in BC patients. There are different reasons for this. Firstly, LNR has been shown to be more advantageous over pN stage, especially in those patients with low NHLN counts.[5] Another factor is that LNR makes the staging system more comparable between different oncological managements.[22]

Finally, it partially prevents pN deviations.[23,24] The importance of LNR in BC is increasing currently, but the cut-off values recommended for LNR varies widely in the literature.[25,26] Although LNR is generally divided into groups according to different threshold values in studies, there is no general agreement. The most accepted classification was proposed by Vinh-Hung et al.[12] This recommended classification was based on 1,829 patient results. In that study, LNR rates were divided into three risk groups (low, ≤0.20; intermediate, 0.21-0.65; and high, >0.65). There have been studies using this classification[27]. In our study, we tested this classification and analyzed a cut-off value in our own population. Both the classification reported in the literature and the dual classification according to the cut-off values determined in this study were significant for DFS and OS. However, the cut-off values in this study were in the low-risk group according to the classification in the literature and were partially compatible (0.140 for recurrence and 0.117 for CRM). A sufficient number of original studies and meta-analysis studies are needed for a universally used LNR classification.

In order to increase the prognostic power of the LNR value over time, especially for those patients with LNRs of "0 or 1", mLNR has been suggested and it is thought to be more powerful. However, there are limited studies in the literature on this subject. Wen et al.[11] recommended groupings as 0.5 and below vs. above 0.5 for the mLNR ratio in a large series (n=3,339). In their study, it was shown

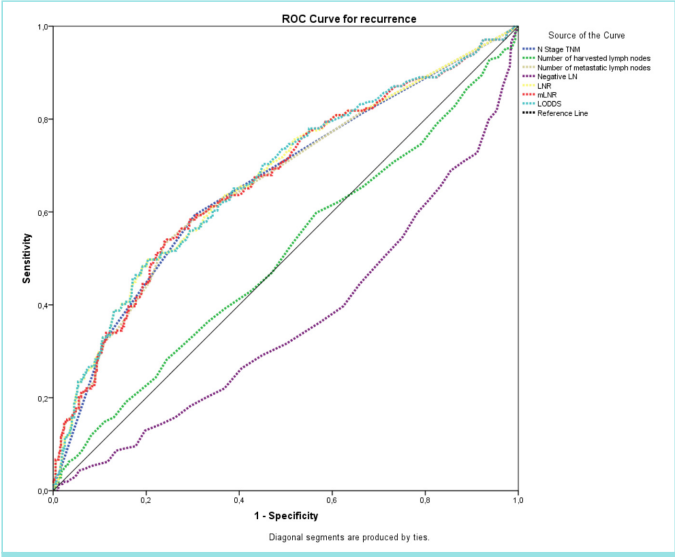

Figure 1. ROC curves of lymph node parameters for cancer recurrence.

ROC: Receiver operating characteristic.

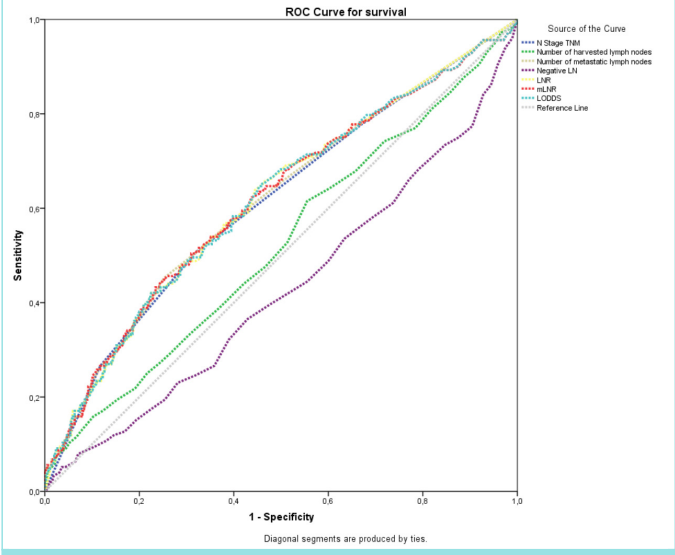

Figure 2. ROC curves of lymph node parameters for cancer related mortality.

ROC: Receiver operating characteristic.

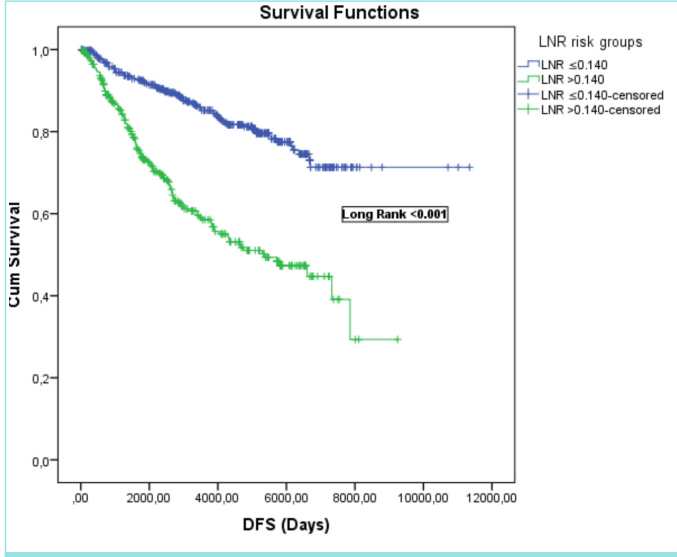

Figure 3. Kaplan-Meier DFS graph of LNR groups by cut-off values.

DFS: Disease-free survival, LNR: Lymph node ratio.

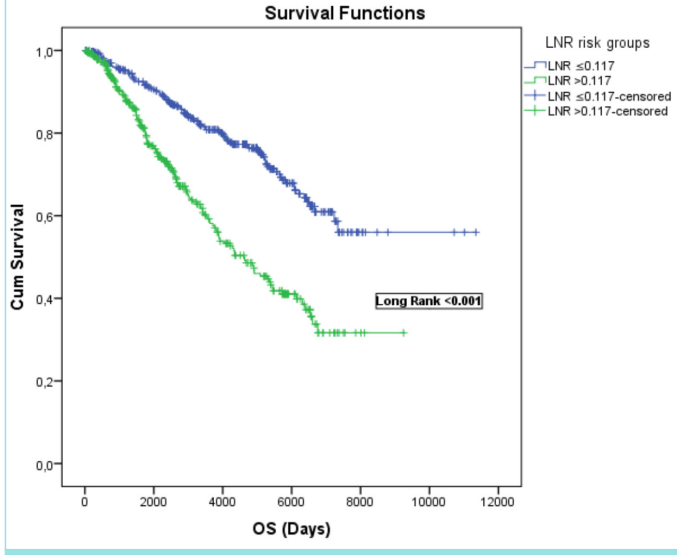

Figure 4. Kaplan-Meier OS graph of LNR groups by cut-off values.

OS: Overall survival, LNR: Lymph node ratio.

that mLNR is an independent parameter in cancer-specific survival and is a much stronger prognostic factor than classical pN staging, especially in those patients with limited lymph node counts. Similarly, the importance of mLNR was supported by a much larger number of BC patients (n=264,096) and two cut-off values for mLNR were recommended in that study; 0.20 and 0.50 were suggested.[10] In the present study, the cut-off value of mLNR was found to be 2.52, with this value being higher than the previously recommended values. Despite the high number of NHLNs in our study, this finding may be due to large number of axillary dissections or heterogeneity in the patient groups.

The LODDS is a similar parameter derived from NMLN and NNLN and it is discussed in the literature with different cut-off values. In the literature, the LODDS classification has been shown to be a convenient prognostic factor in determining survival in different cancers.[28,29] It was also an independent prognostic factor in BC and it was superior to pN staging.[12] In some studies, similar LODDS classifications were used, but their effects on survival were found to be different. This may be due to the small number of BC cases in these studies.[30] The cut-off values of LODDS for cancer recurrence (-0.728) and CRM (-0.805) in our study provided a useful distinction for DFS and OS. Also, according to multivariate analysis, LODDS was reported to be an independent risk factor for OS among all lymph node staging systems.

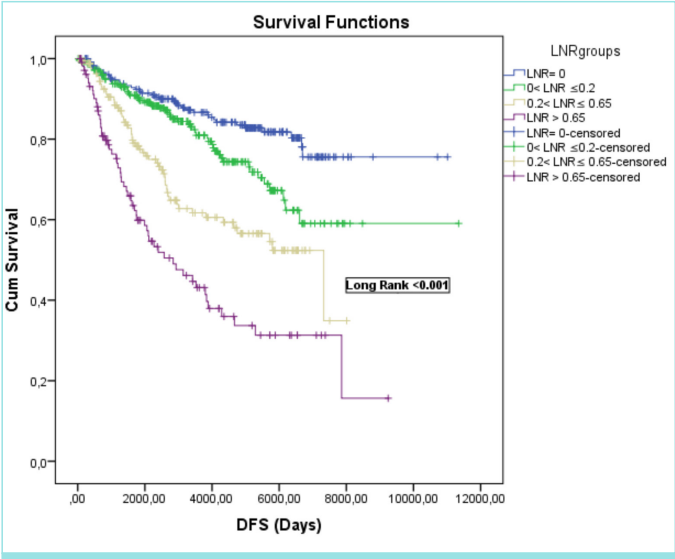

Figure 5. Kaplan-Meier DFS graph of LNR groups cited in the literature.

DFS: Disease-free survival, LNR: Lymph node ratio.

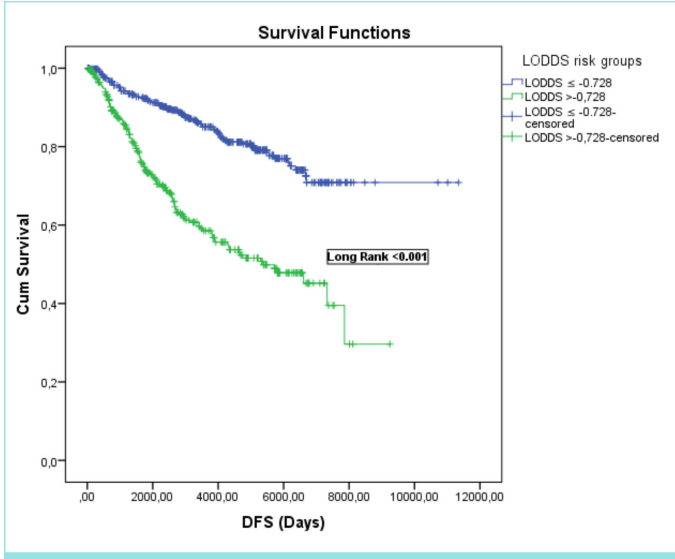

Figure 7. Kaplan-Meier DFS graph of LODDS groups by cut-off values.

DFS: Disease-free survival, LODDS: Log odds of positive lymph nodes.

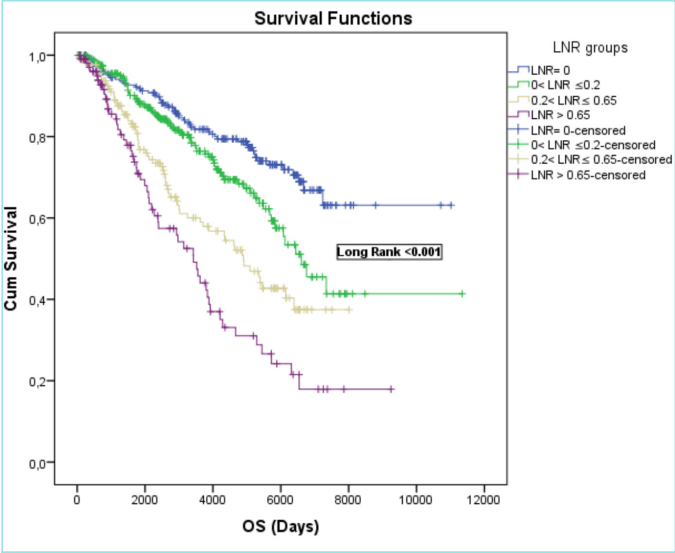

Figure 6. Kaplan-Meier OS graph of LNR groups cited in the literature.

OS: Overall survival, LNR: Lymph node ratio.

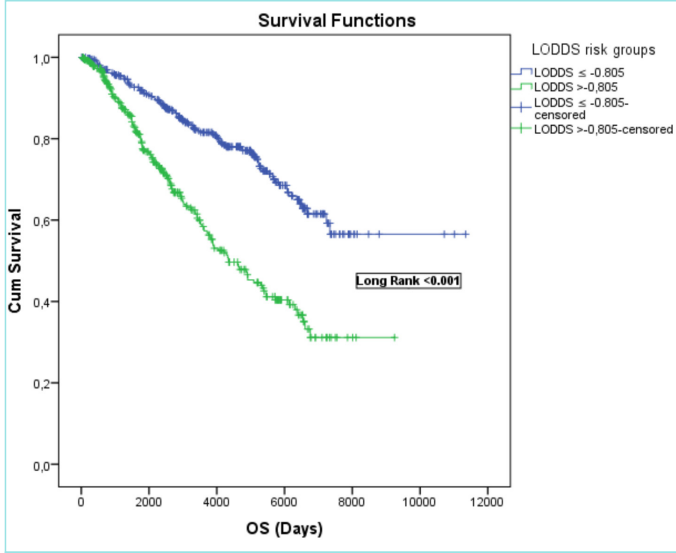

Figure 8. Kaplan-Meier OS graph of LODDS groups by cut-off values.

OS: Overall survival, LODDS: Log odds of positive lymph nodes.

Study Limitations

The present study has a list of limitations which should be considered. Firstly, the retrospective design of this study may have caused data to be lacking. Additionally, the sampling of this study was from a single center which may have caused selection bias despite the large sample size. Also, the time of initial diagnosis of some cases goes back to 1989, so HER-2 status could not be accurately identified in some patients. However, this situation was not an obstacle to our primary purpose in this study. Thirdly, the changes in treatment options over time may have affected outcomes. Therefore, we cannot apply detailed therapy categories to the prognostic models.

CONCLUSION

In the present study, we assessed the survival of BC patients in Türkiye in order to determine different parameters of lymph node status (NHLN, NNLN) and the prognostic value of some different lymph node staging methods (AJCC N-stage, LNR, mLNR, LODDS). Until now, there had been no study comparing the different parameters of lymph node status and the N-stage for predicting BC outcomes with surgery in the Turkish population. The results showed that LODDS seems to be a better option compared to pN classification for OS, which is consistent with previous studies. The present study demonstrated that LODDS has greater usefulness in determining BC patients with distant metastasis compared with the AJCC pN classification.

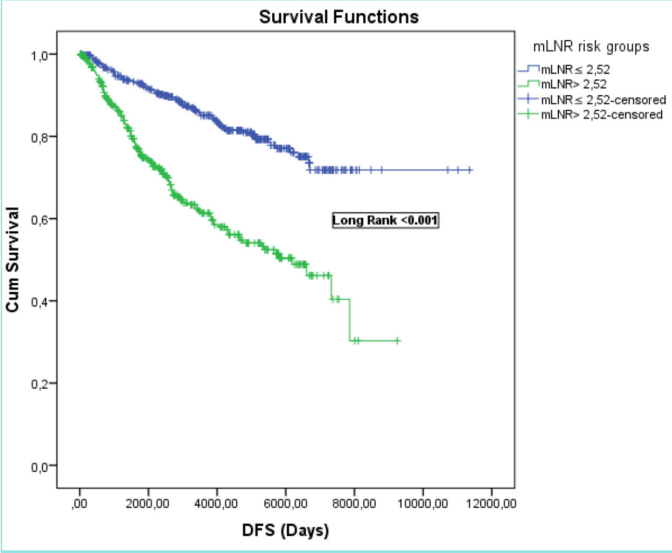

Figure 9. Kaplan-Meier DFS graph of mLNR groups by cut-off values.

DFS: Disease-free survival, mLNR: Modified lymph node ratio.

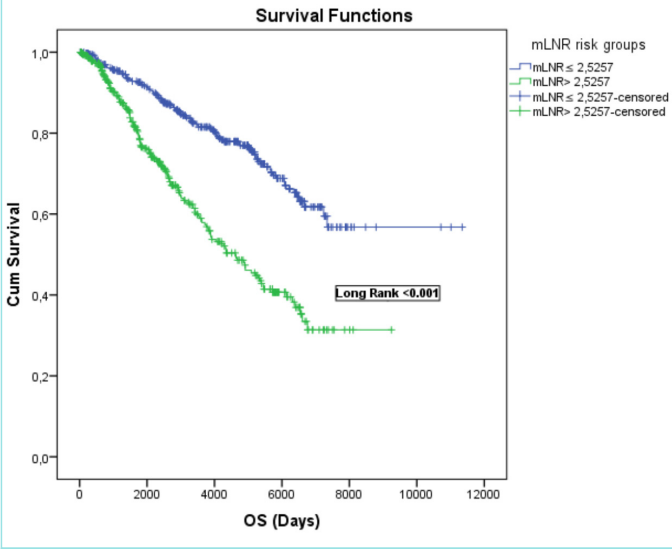

Figure 10. Kaplan-Meier OS graph of mLNR groups by cut-off values.

OS: Overall survival, mLNR: Modified lymph node ratio.

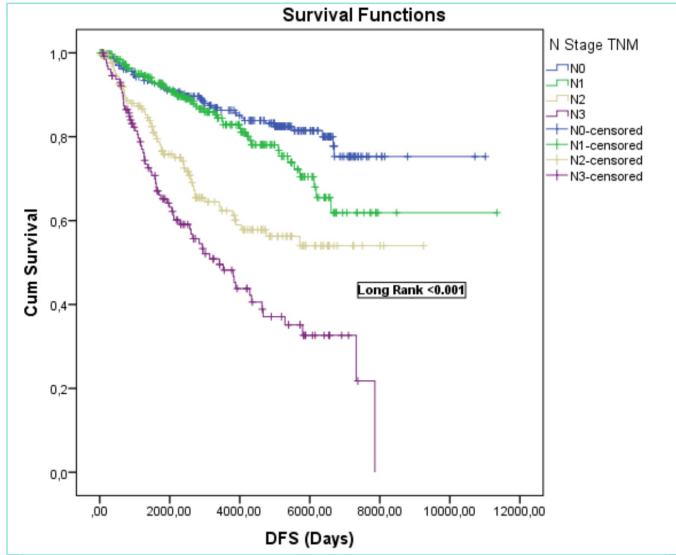

Figure 11. Kaplan-Meier DFS graph of AJCC N-stages.

DFS: Disease-free survival, AJCC: American Joint Committee on Cancer.

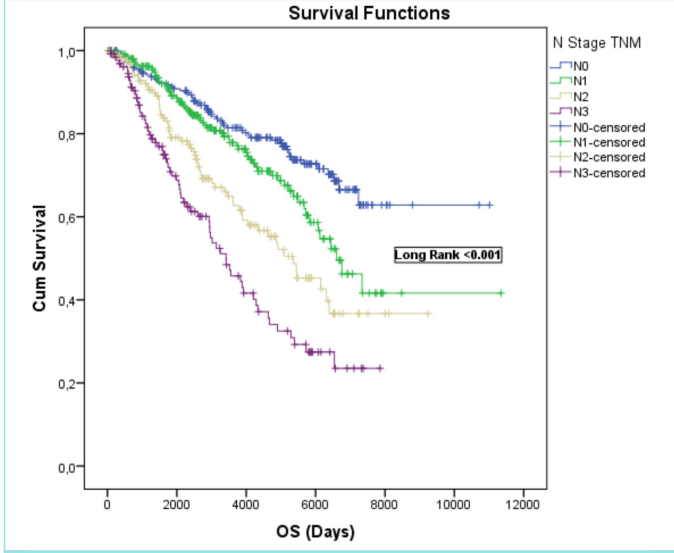

Figure 12. Kaplan-Meier OS graph of AJCC N-stages.

OS: Overall survival, AJCC: American Joint Committee on Cancer.

Table 6. Cox regression analysis of lymph node parameters for disease-free survival and overall survival

Disease-free survival					
	B	p	HR	95% CI for HR	
				Lower	Upper
N-stage (N0)	-	0.617	-	-	-
N-stage (N1)	0.016	0.962	1,016	0.521	1,981
N-stage (N2)	0.336	0.263	1,399	0.777	2,519
N-stage (N3)	0.155	0.627	1,167	0.626	2,175
LNR	-0.050	0.968	0.951	0.083	10,957
mLNR	0.027	0.084	1,027	0.996	1,058
LODDS	0.425	0.481	1,529	0.470	4,980
NNLN	-0.007	0.656	0.993	0.964	1,023
Overall survival					
	B	p	HR	95% CI for HR	
				Lower	Upper
N-stage (N0)	-	0.766	-	-	-
N-stage (N1)	-0.303	0.311	0.739	0.411	1,327
N-stage (N2)	-0.216	0.428	0.805	0.472	1,376
N-stage (N3)	-0.175	0.571	0.839	0.458	1,538
LNR	-1,534	0.174	0.216	0.024	1,970
mLNR	0.025	0.112	1,026	0.994	1,058
LODDS	1,331	0.014	3,784	1,308	10,947
NNLN	0.023	0.068	1,023	0.998	1,049

CI: Confidence interval, HR: Heart rate, LODDS: Log odds of positive lymph nodes, NHLN: Number of harvested lymph nodes, NNLH: Number of negative lymph nodes, LNR: Lymph node ratio, mLNR: Modified lymph node ratio.

MAIN POINTS

- In this article study, we assessed the survival of Turkish patients with breast cancer to determine different parameters of lymph node status (NHLN, NNLN) and the prognostic value of different lymph node staging methods (AJCC N-stage, LNR, mLNR, LODDS.
- Until now, no study comparing different parameters of lymph node status and the lymph node staging methods for predicting outcome in BC patients with mastectomy has been reported in Turkish population.
- The results indicated that LODDS is superior to pN classification for OS.
- We can say that the LODDS has obvious advantages in discriminating patients in non-distant metastatic BC compared with the AJCC pN classification.

ETHICS

Ethics Committee Approval: The study was designed retrospectively. Permission was obtained from the necessary places for data sharing.

Informed Consent: Informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ö.E., A.İ., B.Z., Concept: N.Ö.E., İ.B., B.Z., Design: N.Ö.E., A.İ., B.Z., Data Collection or Processing: N.Ö.E., A.İ., Analysis or Interpretation: N.Ö.E., İ.B., A.İ., Literature Search: N.Ö.E., İ.B., Writing: N.Ö.E., İ.B.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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