

Original article

## Axillary lymph node ratio is an independent prognostic factor in Thai breast cancer patients

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### ABSTRACT

**Background:** The number of metastatic lymph nodes to the total number of dissected axillary lymph nodes (lymph node ratio: LNR) is described as an independent prognostic factor in breast cancer patients, beside the traditional account of the number of axillary lymph node metastasis (pN stage). We investigated the correlation between LNR and prognosis among Thai patients with invasive breast cancer.

**Materials and methods:** We retrospectively analyzed the prognostic value of LNR from the survival outcomes in patients with non-metastatic breast cancer from the medical records of 122 female Thai patients who underwent modified radical mastectomy, from 2009 to 2011. The median length of follow-up was 44 months. Based on the LNR, the patients were divided into low (LNR 0.01-0.20), intermediate (LNR 0.21-0.65) and high (LNR 0.66-1) risk groups. Survival outcomes were estimated by the Kaplan-Meier method while the log rank test was used to assess the significance of groups compared in survival. Exploring potential variables for their independent prognostic effects were determined by Cox proportional-hazards regression model.

**Results:** Univariate analysis indicated that high LNR, as well as the presence of lymphovascular space invasion and local recurrent tumor were correlated with poor overall survival. In contrast, tumor expression of the estrogen receptor and patients receiving anti-hormonal therapy were associated with better survival outcomes (p-values <0.05). Multivariate analysis found anti-hormonal and LNR were independent predictors of overall survival (p-values <0.017).

**Conclusion:** Our findings support LNR as an independent predictor of survival in node positive breast cancer.

**Keywords:** breast cancer, lymph node ratio, prognostic factor, modified mastectomy, Thailand

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## INTRODUCTION

Metastasis status of axillary lymph node determined by pathologic examination is one of the most important prognostic factors in breast cancer<sup>1,2</sup>. American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system (2002), classified lymph node burden (pN staging) based on the number of positive axillary lymph nodes into three groups: pN1, 1-3 metastatic lymph node(s); pN2, 4-9 metastatic lymph nodes; and pN3, 10 or more metastatic lymph nodes<sup>2,3</sup>. Higher nodal disease is associated with poor overall survival and increased risk for locoregional recurrence<sup>4</sup>. In the past decade, several studies that included positive lymph nodes and total dissected lymph nodes reported that the LNR or percentage of involved nodes (LNR x 100) had improved the prognostic indicator of axillary node burden<sup>5,6,7,8</sup>. Vinh-Hung *et al.* identified the cutoff points of LNR in breast cancer and categorized them as low (LNR 0.01 - 0.20), intermediate (LNR 0.21 - 0.65) and high risk groups (LNR 0.66 - 1.00)<sup>7,8</sup>. He showed that LNR predicts survival in breast cancer more accurately than the pN staging<sup>7,8</sup>. However, there were inconsistent findings of the prognostic value of LNR on Asian breast cancer patients<sup>9,10</sup>. To the best of our knowledge, this is first study to evaluate the prognostic value of LNR in Thai breast cancer patients.

## MATERIALS AND METHODS

We retrospectively analyzed the medical records of 122 women who were diagnosed with invasive ductal carcinoma, NOS. All of them underwent modified radical mastectomy between January 2009 and December 2011. The patients with evidence of metastasis at the time of diagnosis were not included. The study (MSKH58/007) was approved by the Human Investigation Committee,

Maha Sarakham Hospital. Clinicopathological data included: age, tumor size, tumor grade, T stages, N stages, M stages, pTNM stages, presence of lymphovascular space invasion (LVSI), local recurrent, number of total axillary nodes examined, number of metastatic lymph nodes, estrogen receptor (ER) status, progesterone receptor (PgR) status, Her-2 status, chemotherapy, radiotherapy and anti-hormonal drug. Follow up for each patient was calculated from the date of operation to the date of death or date of last follow-up (Sep, 15 2014) (Table 1). The endpoint was overall survival (OS) defined as the time from any cause of death. They were obtained from the hospital records and by linkage with provincial department of dead registry.

In terms of LNR, it was subcategorized into three groups; low (LNR 0.01 - 0.20); intermediate (LNR 0.21 - 0.65) and high risk group (LNR 0.66 - 1.00). The LNR cutoff ratios were based on previously published analyses<sup>8,7</sup>.

Statistical analysis: Survival outcomes were estimated by the Kaplan-Meier method while the log rank test was used to assess the significance of groups compared in survival. Stepwise Cox proportional-hazards regression model was used to determine potential variables for their independent prognostic effect. Statistical analyses were performed with SPSS 17.0 (KKU license). All statistical assessment values of  $p < 0.05$  were considered significant.

## RESULTS

### Patients and clinicopathological data

Patients and clinicopathological data were summarized in Table 1. The median age at diagnosis was 50 years (range 31-86 years). Of 122 cases of invasive breast carcinoma, NOS, 76 cases (62.6%) had axillary lymph node metastasis. The median number of total lymph node removed and examined in each patient was 12 (range: 1-39).

4.09% of patients (5/122) had less than 6 nodes removed. 58.2% of patients (71/122) had more than 10 nodes removed. The mean of metastatic axillary lymph nodes was 3.2 (range: 1-30). According to AJCC/UICC staging system, the numbers of patients classified into pN0 were 46 patients (37.7%); pN1, 47 patients (38.5%); pN2, 20 patients (16.4%); and pN3, 9 patients (7.4%). The mean LNR calculated was 0.22 (range: 0.01-1.00). The low-risk LNR group had 26 patients (21.3%); the intermediate-risk group had 40 patients (32.8%); and the high-risk group had 10 patients (8.2%). The node negative group (LNR 0) included 46 patients (37.7%).

#### Analysis of predictive factors for survival outcome

Median length of follow-up was 44 months (range: 4.4-68.8 months).

Cumulative survival of patients classified by axillary lymph node status was significant (p-value < 0.045) (Figure 1A).

The overall 1 - 3 - 5 year-survival of pN

stages were: pN0 (93.2 - 92.3 - 70.0%); pN1 (83.0 - 80.5 - 52.9%); pN2 (75.0 - 70.6 - 44.4%) and pN3 (66.7 - 62.5 - 25.5%) (Figure 1B).

The overall 1 - 3 - 5 year-survival of LNRs were: node negative group (93.2 - 92.3 - 70.0%), low risk group (88.5 - 87.0 - 66.7%), intermediate risk group (80.0 - 77.1 - 50.0%), and high risk group (50.0 - 37.5 - 0%) (Figure 1C).

We conducted univariate analysis and adverse prognostic factors included: ER negative (p-value = 0.024); the presence of LVSI (p-value = 0.007); and recurrent cancer (p-value < 0.0001). The favored prognostic factors were LNR and receiving anti hormonal therapy (p-value < 0.0001).

The N stage was close to predicting survival outcome (p-value = 0.056), (Table 1, Figure 1B). However, LNR had a stronger predictive value (p-value < 0.0001) (Table 1, Figure 1C).

For multivariate analysis, we used the Cox proportional-hazards regression model to show the independent prognostic effect of LNR on patient survival (p-value < 0.0017) (Table 2).

**Table 1** Univariate analysis of survival of clinicopathological data.

Variable		N	Percent	Mean survival in days (95%CI)	p-value
Age at the time of operation	< 50 years	58	48.3%	1894.43 (1775.25-2013.61)	0.254
	≥ 50 years	64	51.7%	1723.90 (1577.96-1869.84)	
Tumor grade	Grade 1	5	4.1 %	NA	0.501
	Grade 2	39	32.0%	1644.14 (1491.15-1797.12)	
	Grade 3	37	30.3%	1896.19 (1757.80-2034.57)	
	Unknown	41	33.6%		
Number of total axillary nodes	Range 1 to 39 nodes (mean 13.13)				0.172
	≥ 10 nodes	71	58.2 %	1897.22 (1764.11-2030.34)	
	< 10 nodes	51	41.8 %	1784.05 (1650.94-1917.17)	
	< 6	5	4.09 %	1373.40 (802.84-1943.95)	

**Table 1** Univariate analysis of survival of clinicopathological data. (con.)

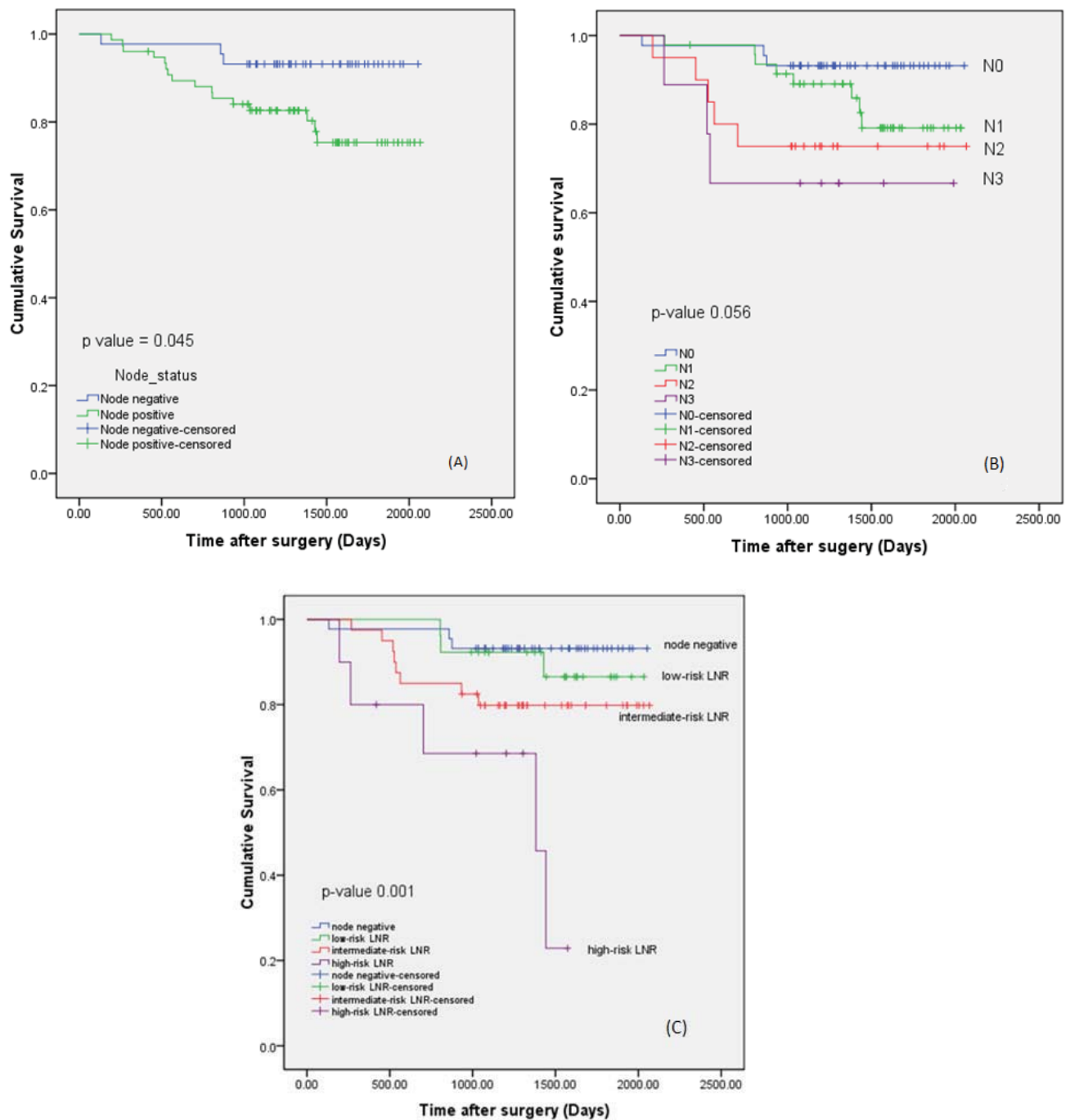
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	< 6	5	4.09 %	1373.40 (802.84-1943.95)	
Lymph node ratio (LNR)	Mean 0.221				0.001
	Node negative	46	37.7%	1956.31 (1846.32-2066.31)	
	Low (0.01-0.20)	26	21.3%	1904.59 (1765.81-2043.38)	
	Intermediate (0.21-0.65)	40	32.8%	1771.93 (1587.09-1956.77)	
	High (0.66-1.00)	10	8.2%	1131.05 (803.72-1458.39)	
pT stage					0.851
	T1	14	11.5%	1827.76 (1523.71-2131.82)	
	T2	68	55.7 %	1850.13 (1725.45-1974.82)	
	T3	37	30.3 %	1773.66 (1595.64-1951.69)	
	T4	3	2.5 %	NA	
pN stage					0.056
	N0	46	37.7 %	1956.31 (1846.32-2066.31)	
	N1	47	38.5 %	1835.11 (1706.94-1963.28)	
	N2	20	16.4 %	1671.40 (1369.62-1973.17)	
	N3	9	7.4 %	1473.22 (993.41-1953.02)	
pTNM stage					0.242
	1	9	7.4 %	1813.75 (1373.27-2254.22)	
	2	63	51.6 %	1918.20 (1832.48-2003.93)	
	3	50	41.0 %	1692.44 (1507.34-1877.54)	
Lymphovascular space invasion (LVSI)					0.007
	Presence of LVSI	47	38.5 %	1605.87 (1417.44-1794.29)	
	Absence of LVSI	75	61.5%	1937.08 (1844.93-2029.23)	
ER status					0.024
	Positive	65	53.3 %	1951.64 (1854.47-2048.81)	
	Negative	41	33.6%	1709.94 (1520.79-1899.09)	
	Unknown	16	13.1%		
PgR status					0.114
	Positive	55	45.1 %	1934.25 (1822.96-2045.54)	
	Negative	51	41.8%	1699.47 (1552.23-1846.70)	
	Unknown	16	13.1%		

**Table 1** Univariate analysis of survival of clinicopathological data. (con.)

Variable		N	Percent	Mean survival in days (95%CI)	p-value
HER2 status	Negative	60	49.2 %	1869.80 (1741.50-1998.10)	0.740
	Equivocal	11	9.0 %	NA	
	Positive	34	27.9 %	1620.58 (1447.88-1793.27)	
	Unknown	17	13.9 %		
Local recurrence	Presence	24	19.7 %	1428.00 (1206.63-1649.38)	<0.0001
	Absence	98	80.3%	1914.42 (1819.13-2009.72)	
Treatment	Chemotherapy	116	95.1 %	1826.48 (1726.54-1926.43)	0.351
	Radiotherapy	23	18.9 %	1699.79 (1480.59-1918.99)	0.372
	Anti-hormonal therapy	100	82.0 %	1928.61 (1739.97-1932.52)	<0.0001

**Table 2** Multivariate analysis for survival probabilities and hazard ratios for all cause mortality.

	Hazard ratio	95% CI		p-value
		Lower	Upper	
Age (<50 years)				
≥ 50 years	2.368	0.532	10.551	0.258
pT stage (T1)				
T2	5.078	0.000	9.358	0.954
T3	1.509	0.000	2.720	0.948
T4	1.598	0.000	2.862	0.948
pN stage (N0)				
N1	2.494	0.096	64.748	0.582
N2	2.287	0.263	19.900	0.454
N3	1.134	0.176	7.289	0.895
pTNM Stage (Stage1)				
pTNM Stage2	0.000	0.000	8.451	0.978
pTNM Stage3	0.002	0.000	1.954	0.969
LVI (Absence)				
Presence)	0.299	0.063	1.428	0.130
ER status (negative)				
positive	0.167	0.002	11.809	0.410
PgR status (negative)				
positive	6.436	0.085	488.354	0.399
HER2 status (negative)				
positive	1.620	0.418	6.282	0.485
Local recurrence (NO)				
Yes	0.440	0.118	1.643	0.222
Anti hormonal therapy (No)				
Yes	.051	0.010	0.268	<0.0001
LNR (node negative)				
Low-risk (0-0.20)	7.04	1.70	32.0	<0.0001
Intermediate-risk (0.21-0.65)	11.1	2.60	47.7	0.03
High-risk (0.66-1.00)	25.3	8.10	78.4	0.017



**Figure 1** (A) Cumulative survival of patients classified by axillary lymph node status.  
 (B) Cumulative survival of patients classified by pN stages: pN0, pN1, pN2 and pN3.  
 (C) Cumulative survival of patients classified by LNR: node negative, low-risk (LNR 0 - 0.20), intermediate-risk (LNR 0.21 - 0.65) and high-risk (LNR 0.66 - 1) groups.



## DISCUSSION

Although the axillary lymph nodes status is considered the most important prognostic factor in breast cancer patients<sup>1,2,4</sup>. The ideal means by which to classify lymph status remains controversial. The current AJCC staging system uses the increasing absolute number of positive nodes to classify patients (pN stage)<sup>2,3</sup>. Vinh-Hung and colleagues identified and verified classified cutoff values for LNR<sup>7,8</sup>. They concluded that these LNR cutoff points define breast cancer prognosis more adequately than the pN categories<sup>7,8</sup>. Several subsequent studies and a meta-analysis had confirmed the validity of risk categorization according to this hypothesis<sup>11,12,13</sup>. We tested the applicability of these cutoff points on our data. The presented data confirm node status as a strong independent factor in univariate and Cox regression multivariate analysis. We found that LNR could not only predict overall survival, but this variable had prognostic value independent of traditional clinicopathologic factors. Moreover, LNR was a stronger prognostic variable for overall survival than the currently used variable, pN staging. Univariate analysis showed that the pN stage was the favorable variable in predicting the overall survival of patients, however it was not statistically significant ( $p = 0.056$ ). Various factors might explain these findings: (1) the number of patients was too small to detect a small effect on survival; (2) a relatively short follow up time, and (3) the number of inadequate axillary node dissections causing the under staging of the pN stage. In the current staging system, the pN stage for predicting disease burden was confounded by the number of nodes removed<sup>14</sup>. The minimal number of nodes required to establish lymph node metastasis is unclear. The American Joint Committee on Cancer (AJCC) recommends that at least 6 axillary lymph nodes should be removed and examined<sup>2,15</sup>.

However, it is generally accepted that at least 10 nodes should be removed to accurately stage the axillary lymph nodes<sup>6,15,16</sup>. While only 5 out of 122 patients had less than 6 axillary lymph nodes, 51 out of 122 had less than 10 axillary lymph nodes. The latter group could cause under staging in the pN stage, because it is likely to find positive nodes in the axilla increasing with the number of nodes dissected and nodes examined. Additionally, the most obvious change of prognosis occurred between node negative to node positive status<sup>17</sup>. If all patients underwent the same extensive axillary dissection, the distinction between a number-based and a ratio-based staging would disappear<sup>18</sup>. A possible explanation for the better prognostic value of the node ratio might be that the node ratio can be interpreted as a more standardized form that reflects both the number of node positive and the number of nodes examined<sup>6,18</sup>. In other words, 2 positive nodes out of a total 6 nodes examined has a different implication than 2 positive node out of a total 10 nodes examined in LNR, however, the implication is the same in pN staging. At least 10 axillary lymph nodes are required in axillary dissection; however, in routine practice heterogeneity of lymph node retrieved is commonly utilized<sup>19</sup>. Our results support studies that considered LNR as a prognostic factor in cases with a limited number of lymph node dissections<sup>14,15,19</sup>.

Outside lymph node involvement other known factors are relevant to breast cancer prognosis, univariate analysis indicated that the expression status of the estrogen receptor, local recurrent and anti-hormonal therapy were associated with survival rate. Our study included breast cancer, NOS type patients, in whom the majority were luminal A and B type breast cancers. Patients with this type of breast cancer usually have good prognosis and are resistant to chemotherapy while exhibiting sensitivity to hormonal therapy<sup>2,17</sup>.

Our study clearly has a number of limitations. It is a retrospective study within a single institution, in which the small sample size did not represent the greater population. It may be biased in terms of patients and treatment selection. The advantages of this study include the time allowed for follow up; the uniform guidelines utilized in surgical intervention and uniform pathological examination. All the patients underwent modified radical mastectomy, making it possible to compare the patients in axillary node negative and node positive groups. Since the Thai population registry department does not register the cause of death, only all-cause mortality could be determined. Therefore we were only able to determine the role of LNR as a prognostic factor for overall survival and not for breast cancer-specific survival.

The patients in this study were treated in the pre-sentinel biopsy node era. However, a number of studies have demonstrated the value of evaluating the ratio of the number of positive sentinel lymph nodes to the total number of sentinel nodes removed to determine the probability of axillary node metastasis<sup>20</sup>. No further dissection is performed when the sentinel nodes show no tumor involvement. However, when a sentinel node is involved, a complete axillary dissection is recommended<sup>20,21</sup>. Our results support the use of LNR as a tool for more accurate prognostic assessment than using the pN stage. In addition to breast cancer, LNR has been widely demonstrated to be a useful alternative node classification to predict prognosis in many other cancers, including gastric cancer<sup>22</sup>, colon cancer<sup>23,24</sup> and pancreatic cancer<sup>26</sup>. The concept of this ratio suggests that cancer is a disease of progressively increasing severity<sup>21,26</sup>.

## CONCLUSION

This study confirmed that the percent of positive axillary lymph node metastasis could predict survival in patients with non-metastatic breast cancer. We further suggest that the LNR should be included in pathological reports of modified radical mastectomy specimens.

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