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## Clinical Research

# Association between axillary lymph node involvement and clinicopathological features of breast cancer among Indonesian women

Dody Novrial,<sup>1</sup> Gita Nawangtantrini,<sup>1</sup> Hidayat Sulisty,<sup>1</sup> Henida Dwi Sari,<sup>2</sup> Wahyu Djatmiko<sup>3</sup>



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## Authors' affiliations:

<sup>1</sup>Department of Anatomical Pathology, Faculty of Medicine, Universitas Jenderal Soedirman, Margono Soekarjo Hospital, Purwokerto, Indonesia, <sup>2</sup>Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Indonesia, <sup>3</sup>Department of Internal Medicine, Faculty of Medicine, Universitas Jenderal Soedirman, Margono Soekarjo Hospital, Purwokerto, Indonesia

## Corresponding author:

Dody Novrial  
 Department of Anatomical Pathology, Faculty of Medicine, Universitas Jenderal Soedirman, Margono Soekarjo Hospital, Jalan Dr. Gumbreg No. 1, East Purwokerto, Banyumas, Central Java 53112, Indonesia  
 Tel/Fax: +62-81-622022/+62-81-624990  
 E-mail: [dodynovrial@unsoed.ac.id](mailto:dodynovrial@unsoed.ac.id)

## ABSTRACT

**BACKGROUND** Some clinicopathological features play roles in the spread of breast cancer to axillary lymph node (ALN). However, their roles as predictive factors are not well-established. This study was conducted to determine the correlation between the clinicopathological features of breast cancer and the risk of ALN involvement in Indonesian women.

**METHODS** This cross-sectional study was conducted in Margono Soekarjo Hospital using archival data from January 2017 to June 2018. All subjects with breast cancer who had undergone modified radical mastectomies without any evidence of distant metastasis were included. Chi-square and Fisher's exact tests were performed to assess the relationship between ALN involvement and age, menopausal status, laterality, tumor size, tumor stage, histological type, tumor grade, lymphovascular space invasion (LVSI), skin or nipple infiltration, perineural invasion, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status. The odds ratio of each variable was evaluated using ordinal regression analysis.

**RESULTS** Stage 3 breast cancer had the worst status of ALN involvement compared with stage 1 (OR = 3.49; 95% CI = 1.51–8.08) and stage 2 (OR = 3.04; 95% CI = 1.32–6.98). Likewise, positive LVSI also had the worst status of ALN involvement compared with negative LVSI (OR = 8.68; 95% CI = 4.23–17.81).

**CONCLUSIONS** Tumor stage and LVSI could be considered as independent predictive factors of ALN involvement in patients with breast cancer, especially among Indonesian women.

**KEYWORDS** breast cancer, lymph node metastases, lymphovascular space invasion, tumor stage

Breast cancer is the most common malignancy and the leading cause of cancer deaths among female.<sup>1</sup> There were 2.1 million new cases of female breast cancers in 2018 worldwide, accounting for almost 1 in 4 cancer cases among women.<sup>2</sup> In Indonesia, the incidence of breast cancer was approximately 40 per 1,000 with high mortality rate.<sup>3,4</sup> Hence, it is important to understand the clinical and pathological features that influence the prognostic factors of breast cancer.

The development of metastases is the most important poor prognostic outcome in all cancers. In breast cancer, axillary lymph node (ALN) involvement becomes a crucial step before metastases.<sup>5</sup> It is used for predicting the prognosis of breast cancer in the absence of distant metastases. Breast cancer patient with ALN involvement have a poorer prognosis.<sup>6</sup> However, up to 30% of patients with ALN-negative breast cancer have a low disease-free survival in 5 and 10

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years after their initial diagnosis.<sup>6</sup> This study was aimed to investigate breast cancer with ALN involvement among Indonesian women, and its correlation with several clinicopathological features. There might be considerable variation in its presentation according to the region.

## METHODS

This study was conducted at Margono Soekarjo Hospital Purwokerto and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Jenderal Soedirman (No: 2978/UN23.07.5.1/PN.1/2018). We reviewed the details of pathologically diagnosed patients with breast cancer recorded from January 2017 to June 2018. A total of 107 from 177 patients with breast cancer were included consecutively in this cross-sectional study. Only patients with invasive breast cancer who underwent modified mastectomies, followed by ALN resection (level I, II, or III), with no evidence of distant metastases were included in this study. Patients who had received radiation to the affected side of breast or the axilla or had undergone neoadjuvant chemotherapy were excluded. Clinicopathological profiles of patients with breast cancer, including age, menopausal status, laterality, tumor size, tumor stage, histological type, tumor grade, lymphovascular space invasion (LVSI), skin or nipple infiltration, perineural invasion, hormonal status, and human epidermal growth factor receptor 2 (HER2) expression were analyzed.

The 8<sup>th</sup> edition of the breast cancer staging system from the American Joint Committee on Cancer was used to assess the tumor.<sup>7</sup> Breast cancer cases were classified based on tumor size (T1: <2 cm, T2: 2–5 cm, T3: >5 cm, and T4: any size with evidence of chest wall or skin infiltration) and nodal status (No: negative ALN involvement, N1: 1–3 ALN involvement, N2: 4–9 ALN involvement, and N3: ≥10 ALN involvement). Staging was classified according to the TNM staging system<sup>7</sup> and histological grading of the tumor was based on the modified Scarff-Bloom-Richardson.<sup>8</sup> Histological data included LVSI, perineural invasion, and skin or nipple infiltration. Immunohistochemical analyses were conducted to determine the estrogen receptor (ER), progesterone receptor (PR), and HER2 status of breast cancer. The ER and PR were interpreted as positive when >1% of tumor cells demonstrated positive nuclear staining.<sup>9</sup> Score of 3+ (strong

complete membrane staining in >10% of tumor cells) was considered as HER2 positive.<sup>10</sup>

Bivariate analysis was performed using chi-square or Fisher's exact probability test to determine the associations between variables. The complementary log-log link function was used in the multivariate ordinal regression analysis with ALN involvement as an outcome variable, and the significant clinicopathological presentations in bivariate analysis as independent variables. Odds ratios (ORs) were calculated to assess the relative risk of having ALN involvement, and the nature of palindromic invariance was used to facilitate interpretation.<sup>11</sup> A *p*-value <0.05 was considered significant.

## RESULTS

Table 1 shows the clinicopathological features of patients with breast cancer. The mean (standard deviation) age of the patients was 52.7 (10.12) years, and most of them were >40 year-old age. More than half of the patients were postmenopausal women. Right-sided breast cancers were diagnosed in most of the patients. Majority of breast cancer patients had a grade tumor size of T2, and most of them were in stage I with grade 2 invasive ductal type carcinoma. Hormonal status and HER2 expression were positive in more than half of the patients.

In the bivariate analysis, premenopausal women, left-sided breast cancer, larger tumor size, advanced tumor stage, and positive LVSI were significant risks for ALN involvement. Table 2 shows the results of the multivariate analysis with ALN involvement as dependent variable. We found that tumor stage and LVSI had a significant influence on ALN involvement. Using palindromic invariance properties, we discovered that patients with stage 3 breast cancer tended to have the worst status of ALN involvement compared with stage 1 (OR = 3.49; 95% CI = 1.51–8.08) and stage 2 (OR = 3.04; 95% CI = 1.32–6.98). Meanwhile, breast cancer patients with positive LVSI also tended to have ALN involvement compared with negative LVSI (OR=8.68; 95% CI = 4.23–17.81).

## DISCUSSION

ALN status is an important predictor for breast cancer prognosis. Several previous institutional studies have demonstrated the role of positive ALN

**Table 1.** Associations between clinicopathological features and ALN involvement

Features	ALN involvement, n (%)				p*
	N0	N1	N2	N3	
Age (years)					0.294 <sup>†</sup>
≤40	3 (5.2)	2 (6.3)	3 (18.8)	1 (100.0)	
>40	55 (94.8)	30 (93.7)	13 (81.2)	0 (0.0)	
Menopausal status					<b>0.005</b>
Premenopause	15 (25.9)	16 (50.0)	8 (50.0)	1 (100.0)	
Postmenopause	43 (74.1)	16 (50.0)	8 (50.0)	0 (0.0)	
Laterality					<b>0.007</b>
Right breast	39 (67.2)	14 (43.7)	7 (43.8)	0 (0.0)	
Left breast	19 (32.8)	18 (56.3)	9 (56.2)	1 (100.0)	
Tumor size					<b>0.040</b>
T1	9 (15.5)	5 (15.6)	0 (0.0)	0 (0.0)	
T2	34 (58.6)	17 (53.1)	5 (31.3)	0 (0.0)	
T3	10 (17.2)	7 (21.9)	10 (62.5)	0 (0.0)	
T4	5 (8.7)	3 (9.4)	1 (6.2)	1 (100.0)	
Tumor stage					<b>&lt;0.001</b>
I	32 (55.2)	13 (40.6)	2 (12.5)	0 (0.0)	
II	19 (32.8)	11 (34.4)	1 (6.3)	0 (0.0)	
III	7 (12.0)	8 (25.0)	13 (81.2)	1 (100.0)	
Histological type					1.000 <sup>†</sup>
Invasive ductal	53 (91.4)	32 (100.0)	12 (75.0)	1 (100.0)	
Invasive lobular	5 (8.6)	0 (0.0)	4 (25.0)	0 (0.0)	
Tumor grade					0.546
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade 2	37 (63.8)	21 (65.6)	11 (68.8)	1 (100.0)	
Grade 3	21 (36.2)	11 (34.4)	5 (31.2)	0 (0.0)	
LVSI					<b>&lt;0.001</b>
Negative	51 (87.9)	5 (15.6)	0 (0.0)	0 (0.0)	
Positive	7 (12.1)	27 (84.4)	16 (100.0)	1 (100.0)	
Skin or nipple infiltration					0.367
Negative	53 (91.4)	27 (84.4)	15 (93.8)	0 (0.0)	
Positive	5 (8.6)	5 (15.6)	1 (6.2)	1 (100.0)	
Perineural invasion					0.128
Negative	39 (67.2)	27 (84.4)	12 (75.0)	1 (100.0)	
Positive	19 (32.8)	5 (15.6)	4 (25.0)	0 (0.0)	
Estrogen receptor					1.000
Negative	24 (41.4)	11 (34.4)	9 (56.3)	1 (100.0)	
Positive	34 (58.6)	21 (65.6)	7 (43.7)	0 (0.0)	
Progesterone receptor					0.700
Negative	27 (46.6)	14 (43.8)	9 (56.3)	1 (100.0)	
Positive	31 (53.4)	18 (56.2)	7 (43.7)	0 (0.0)	
HER2 receptor					0.844
Negative	22 (37.9)	15 (46.9)	6 (37.5)	0 (0.0)	
Positive	36 (62.1)	17 (53.1)	10 (62.5)	1 (100.0)	

ALN=axillary lymph node; LVSI=lymphovascular space invasion; HER2=human epidermal growth factor receptor 2

\*p-value was analyzed using chi-square by combining N1-N3 as positive ALN involvement and N0 as negative ALN involvement; <sup>†</sup>Fisher's exact test

involvement in developing distant metastases and breast cancer recurrences.<sup>12–14</sup> However, there were differences in these study results, which might be due to differences in demographics and research methods. In this study, ALN involvement among Indonesian breast cancer patients and its correlation with several clinicopathological variables were evaluated.

Our results revealed the relationship between ALN involvement and several clinicopathological features of breast cancer patients such as menopausal status, laterality, tumor size, tumor stage, and LVSI. These findings were consistent with a similar study in Pakistan, except for laterality.<sup>14</sup> Another study in Brazil also reported a relationship between tumor size, LVSI, and ALN involvement.<sup>15</sup> Meanwhile, a study in China demonstrated that tumor size was one of three independent predictive factors of sentinel lymph node metastases in early breast cancer, other than age and tumor grade.<sup>16</sup> In contrast, other studies in the USA<sup>17</sup> and Sudan<sup>18</sup> reported that tumor size was not related to ALN involvement as well as tumor grade, age, ER, PR, and HER2 status. It is likely due to the small sample of their studies as much as 64 and 81 samples, respectively.

Studies have described menopausal status as one of predictive factors of ALN involvement.<sup>14,19</sup> This

study reported ALN involvement in premenopausal patients with breast cancer was higher than in postmenopausal patients. There was a similar study showed premenopausal patients in breast cancer were more likely to have an advanced stage of tumor, higher histological grade, larger tumor size, and ALN involvement.<sup>20</sup>

Several studies have consistently documented that unilateral breast cancer in women is more frequent in the left breast than in the right breast. A large cohort study conducted in the UK reported an incidence ratio (left to right) of 1.07 for breast cancer.<sup>21</sup> Amer reported that breast cancer was detected predominantly on the left side with a left to right ratio of 1.1 in all age groups, except for patients aged 50–59, <30, and >90 years.<sup>22</sup> Interestingly, we found a higher incidence of right-sided breast cancer (56.1%) than left-sided breast cancer in this study. This difference might be due to the most of our subjects (62.6%) were older women (aged >50 years), and 43.9% of them were aged 50–59 years. The heterogeneous nature of breast cancer might also play a role in this result as reported by Melnik et al<sup>23</sup> that patients born in the Middle East or Asian countries had a predominance of right-sided tumors, whereas those born elsewhere had a left-sided predominance.

**Table 2.** Odds ratio for clinicopathological predictors of ALN involvement

Features	Coeff	OR	95% CI	p*
Menopausal status				0.170
Premenopause	-0.361	0.69	0.416–1.166	
Postmenopause		1.00		
Laterality				0.332
Right breast	-0.247	0.78	0.474–1.287	
Left breast		1.00		
Tumor size				
T1	0.797	2.21	0.647–7.606	0.205
T2	0.151	1.16	0.410–3.300	0.776
T3	0.513	1.67	0.634–4.393	0.299
T4		1.00		
Tumor stage				
I	-1.252	0.28	0.124–0.661	<b>0.003</b>
II	-1.112	0.32	0.143–0.756	<b>0.009</b>
III		1.00		
LVSI				<b>&lt;0.001</b>
Negative	-2.162	0.11	0.056–0.236	
Positive		1.00		

ALN=axillary lymph node; OR=odds ratio; CI=confidence interval; LVSI=lymphovascular space invasion  
\*p-value was analyzed using multivariate ordinal regression analysis



The possible explanation for our finding is the breastfeeding pattern. Most of the population is right-handed, and most of the nursing mothers would use their left arm to hold the baby while feeding, and therefore the left breast is more often used for lactation than the right one. This finding is similar to that of a previous study in the Chinese Tanka population. In that study, the women had a tradition of wearing clothes with the opening part on the right side, and hence, they feed their baby only with the right breast. It was observed that among Tanka's postmenopausal women who had breastfed unilaterally, the risk of developing breast cancer was significantly higher in the contra lateral (unsucked) breast.<sup>24</sup> Furthermore, it has been consistently documented that lactation is a protective factor for breast cancer.<sup>25</sup> The protection offered by breastfeeding could persist in postmenopausal women even after age 50 year since the first lactation.<sup>26</sup> However, we did not collect data about the patient's history of breastfeeding in this study, and therefore further research is necessary to confirm this hypothesis.

In this study, patients with left-sided breast cancer had a higher rate of ALN involvement than those with right-sided breast cancer. Excess of being left-sided over right sided breast cancer remains a controversy. In an investigational study about the effect of cancer laterality in five major paired organs, the authors stated that there was no significant difference in breast cancer.<sup>14</sup> On the other hand, a study on 4,215 patients with breast cancer demonstrated that left laterality is an independent prognostic factor of metastases in patients with breast cancer in N3 stage. It was associated with a shorter time to first metastases, an increase in the risk for distant metastases, and axial bone involvement.<sup>5</sup>

Most of studies on breast cancer have reported larger tumor size as a risk factor for ALN involvement. Patients with breast cancer with tumor size >2 cm are associated with advanced stage, higher risk for nodal metastases, and poor prognosis.<sup>14,27,28</sup> Although there was a relationship between menopausal status, laterality, and tumor size with ALN involvement of patients with breast cancer in this study, however, they could not be used as predictive factors based on the multivariate analysis.

In this study, tumor stage and LVSI were found to be the two clinicopathological variables that showed significant results in both bivariate and multivariate analyses. A higher stage of tumor tends to have

a worse ALN status. This finding agrees with the literature, suggesting that more advanced staging has a worse prognosis for breast cancer.<sup>29,30</sup> A similar result from a study in Pakistan also supported our finding. The researchers reported that the highest risk of nodal metastases was seen in stage IV patients with breast cancer.<sup>14</sup>

LVSI is determined based on the presence of tumor emboli within definite endothelial-lined space that could be observed in histological breast cancer slides. Two studies conducted in South Korea reported the relationship between LVSI and poor prognosis of both operable invasive breast cancer and breast cancer treated with neoadjuvant chemotherapy.<sup>31,32</sup> LVSI as a predictor of node metastases<sup>27</sup> and prognostic factor of breast cancer<sup>31,32</sup> also has been reported. Their results were similar with our study that showed 47.7% of patients with breast cancer had positive LVSI, and 86.3% of them had ALN involvement. In conclusion, tumor stage and LVSI could be considered as two independent predictive factors of ALN involvement in patients with breast cancer, especially among Indonesian women. However, we acknowledge, as a limitation of this study, that the effect of clinical and pathological variables of breast cancer on ALN involvement needs to be explored in a larger population.

#### Conflict of interest

The authors affirm no conflict of interest in this study.

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