

# Cervical invasion and lymphovascular space invasion as the most associated risk factors for lymph node metastases in endometrial cancer

Devita Kurniawati<sup>1</sup>, Brahmana Askandar Tjokoprawiro<sup>1\*</sup>, Primandono Perbowo<sup>1</sup>

## ABSTRACT

**Background:** Endometrial cancer is the second most common type of gynecologic malignancy. Studies on factors of lymphatic metastases are few. This study aimed to determine the clinical and pathological characteristics that can predict lymph node metastases.

**Purpose:** To determine the correlation of clinicopathological characteristics with LNM (Lymph Node Metastases) in Endometrial Cancer (EC).

**Methods:** This study used observational analysis and a cross-sectional methodology to examine medical records of endometrial cancer patients who underwent lymphadenectomy sampling surgery in 2018-2020. The risk factors are determined using multivariate analysis.

**Results:** The stage IB and IIIC1 patients accounted for the most (17.27%) of the 63 research participants. Only one patient (1.1%) is in stage IIIB. The rests are stage IA and IIIA, each including eight patients (8.13%), and stage II, which has twelve people (12.19%). There were 17 patients with endometrial cancer who had lymph node metastases (27%). The incidence of LNM is 23.2% in endometrioid types, while the incidence of metastases is 57.1% in non-endometrioid kinds. The incidence of LNM in EC was not linked with the patient's age ( $p=0.628$ ), BMI ( $p=0.190$ ), parity ( $p=0.194$ ), or menopausal status ( $p=0.970$ ). The study found no correlation between LNM and histological kinds ( $p=0.078$ ), histopathological degrees ( $p=0.514$ ), or myometrium invasion ( $p=0.134$ ) in EC. The risk factors most linked with LNM in EC are LVSI (+) (OR = 0.10; IK 95% 0.19–0.56;  $p = 0.009$ ) and cervical invasion (OR = 0.07; IK95 percent 0.008–0.64;  $p = 0.019$ ) according to the results of multivariate analysis.

**Conclusion:** Cervical invasion and LVSI (+) are the risk factors most associated with the incidence of LNM.

**Keywords:** Clinicopathological characteristics, Endometrial cancer, Lymph node metastases, Risk factors.

**Cite This Article:** Kurniawati, D., Tjokoprawiro, B.A., Perbowo, P. 2022. Cervical invasion and lymphovascular space invasion as the most associated risk factors for lymph node metastases in endometrial cancer. *Bali Medical Journal* 11(2): 797-802. DOI: 10.15562/bmj.v11i2.3645

<sup>1</sup>Departement Obstetrics & Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia;

\*Corresponding author:

Brahmana Askandar Tjokoprawiro;  
Departement Obstetrics & Gynecology,  
Faculty of Medicine, Universitas  
Airlangga, Dr. Soetomo General Hospital,  
Surabaya, Indonesia;  
[brahmanaaskandar@fk.unair.ac.id](mailto:brahmanaaskandar@fk.unair.ac.id)

Received: 2022-06-11

Accepted: 2022-07-31

Published: 2022-08-12

## INTRODUCTION

By 2021, the American Cancer Society estimates that 66,570 cases of uterine cancer will be diagnosed for the first time and that there will be an estimated 12,940 deaths from uterine cancer, which includes endometrial cancer and uterine sarcoma.<sup>1</sup> In developing countries, endometrial cancer is the second most common type of gynecologic malignancy after cervical cancer, with an incidence of 5.9 per 100,000 gynecologic cancers and a mortality rate of 1.7 per 100,000. From 2011 to 2015, 879 cases of endometrial cancer in Indonesia.<sup>2</sup>

Based on its nature and characteristics,

endometrial cancer is grouped into type 1 endometrial cancer and type 2 endometrial cancer. Type 1 endometrial cancer is the most common type of endometrial cancer (~70–80%), consisting of endometrioid, low grade, diploid, and moderately differentiated or well-differentiated hormone receptors (hormone-receptor-positive), and is more common in obese women. Patients with type 1 endometrial cancer tend to have tumors localized to the uterus and have a relatively better prognosis. Risk factors for type 1 endometrial cancer include obesity, anovulation, nulliparity, diabetes mellitus (DM), neoplasms that produce estrogen, and exposure to exogenous

estrogens. In contrast, type 2 endometrial cancer is more common in non-obese women, non-endometrioid histological type, high-grade, aneuploid, poorly differentiated, lacks hormone receptors (hormone-receptor negative), and tends to have a high risk of metastases and poor prognosis. Type 2 endometrial cancer is not affected by estrogen exposure and is characterized by a more aggressive clinical course.<sup>3,4</sup>

Most endometrial cancer cases tend to occur in postmenopausal patients; about 10% of endometrial cancer cases occur in pre-menopausal and reproductive age patients.<sup>5</sup> The incidence of endometrial cancer in pre-menopausal women tends

to increase over time, where the incidence of endometrial cancer in women aged <40 years is 2–14% and in women aged <50 years is 5–30%. The prognosis for endometrial cancer in pre-menopausal women with early-stage endometrial cancer is relatively good, with a five-year survival rate >90%. Women of reproductive/pre-menopausal age with endometrial cancer are also more likely to be diagnosed at an earlier stage than postmenopausal women and have better overall survival rates.<sup>6,7</sup>

Lymphatic metastases are a strong prognostic factor for determining mortality in patients with endometrial cancer. Some consensus has suggested doing lymphadenectomy as a series of endometrial cancer therapy. One of the complications of lymphadenectomy that is often found in the long term is lymphedema, where the incidence will continue to increase with age. Specific predictor factors are needed to determine the tendency of lymphatic metastases in endometrial cancer, so lymphadenectomy can be performed with a clearer target and does not become a universal therapy in all patients with endometrial cancer. Several predictor factors that previous studies have studied include tumor histology, tumor grade, DNA ploidy, and myometrial invasion.<sup>8</sup>

Several studies studying the predictor factors for lymphatic metastases in endometrial cancer cases still have few conclusive results, especially for predicting lymphatic metastases in endometrial cancer based on tumor characteristics. A few studies still evaluate the factors that predict lymphatic metastases in cases of endometrial cancer in Indonesia or Dr. Soetomo Teaching Hospital Surabaya. This study aimed to determine the clinical and pathological characteristics that can predict lymph node metastases in endometrial cancer.

## MATERIALS AND METHODS

This study was conducted using observational analysis and has a cross-sectional design on medical records of endometrial cancer patients surgically performed with lymphadenectomy sampling in 2018 - 2020. We included

parameters like age, BMI, parity, menopausal status, myometrial invasion; histopathological type; histopathology degree; LVSI; cervical invasion, and lymph node metastases. From the data obtained, the analysis is done using SPSS. Bivariate and multivariate analyzes were performed to compare the variables of tumor characteristics between the two groups. The chi-square test was used to assess the relationship between the dependent and independent variables if they were eligible; if they were not, Fisher's exact test was utilized. The logistic regression was applied to offer a multivariate analysis of all variables. Patients with a history of cancer other than endometrial cancer, those who had surgery at Dr. Soetomo Teaching Facility Surabaya or an outside hospital without KGB sampling, and those with inadequate or missing medical information were all removed. The ethical committees of the Faculty of Medicine at Universitas Airlangga-Dr. Soetomo Teaching Hospital (Surabaya, Indonesia) approved the study protocol.

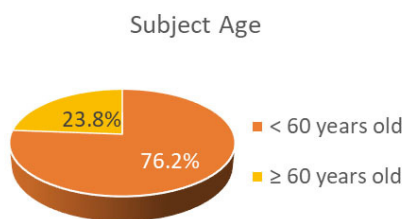
## RESULTS

### Profile of Study Subject

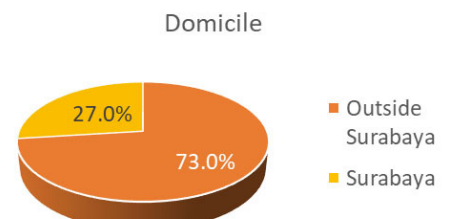
This study consisted of 63 subjects with endometrial cancer diagnosed from 2018 to 2020 at Dr. Soetomo Teaching Hospital

Surabaya. Most of the subjects, 46 of 63 subjects (73.0%), were domiciled outside Surabaya (Figure 2). A total of 48 of the 63 subjects (76.2%) were less than 60 years old when diagnosed with endometrial cancer, while 15 subjects (23.8%) were ≥60 years old (Figure 1). A total of 36 of the 63 subjects (57.1%) had a body mass index (BMI) < 30 kg/m<sup>2</sup>, while the remaining 27 subjects (42.9%) had a BMI ≥ 30 kg/m<sup>2</sup>, which was classified as obesity grade II (Figure 3). Of the subjects, 49 of 63 subjects (77.8%) were multiparous subjects, while 14 (22.2%) were nulliparous (Figure 4). A total of 41 subjects (65.1%) were found to have experienced menopause, while only 22 subjects (34.9%) had not experienced menopause (Figure 5).

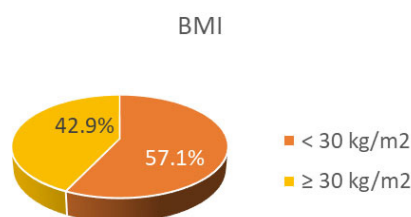
This study's histopathological grades of endometrial cancer were dominated by grades G1 and G3, each with 22 subjects (34.9%), followed by grade G2 in 19 subjects (30.2%). Myometrial invasion of ≥50% (deep myometrial invasion) was found in 52 subjects (82.5%), while the remaining 11 subjects (17.5%) had <50% myometrial invasion. Endometrial cancer also invaded the cervix in 35 of 63 subjects (55.6%). LVSI was found in 30 of 63 subjects (47.6%), and lymph node metastases were found in 17 of 63 subjects (27.0%) (Figures 6, 7, 8, and 9).



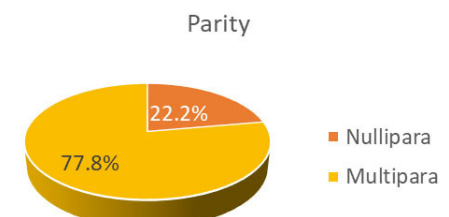
**Figure 1.** Proportion of subjects by age group.



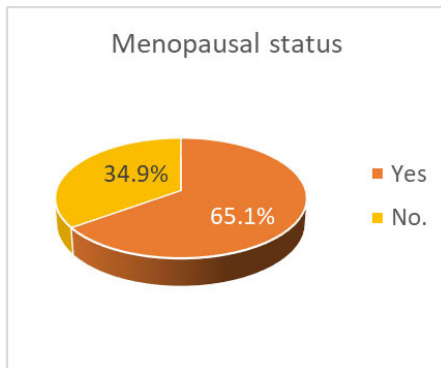
**Figure 2.** Proportion of subjects by domicile



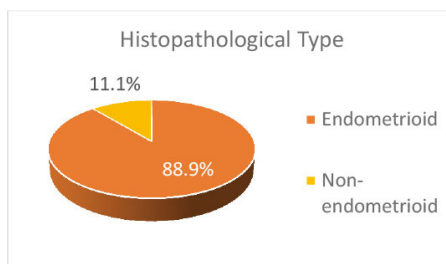
**Figure 3.** Proportion of subjects by BMI group.



**Figure 4.** Proportion of subjects by parity status.



**Figure 5.** The proportion of menopausal status in the samples.



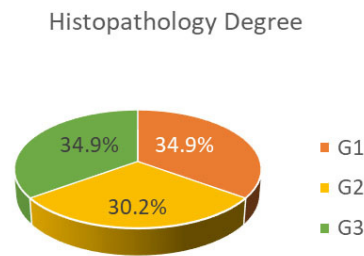
**Figure 6.** Proportion of subjects by type of endometrial cancer.

**The Relationship between Demographic and Clinical Characteristics with Lymph Node Metastases in Endometrial Cancer**

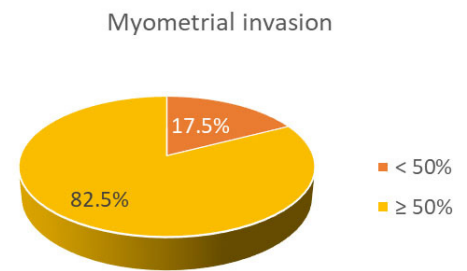
Demographic characteristics in this study include age and body mass index, while clinical characteristics include parity and menopausal status. In the age analysis, the subjects were grouped into the age group <60 years and the age group ≥60 years, while in the body mass index (BMI) analysis, the subjects were grouped into the BMI <30 kg/m<sup>2</sup> group and the BMI group ≥30 kg/m<sup>2</sup>. Based on the results of the analysis using the Chi-square test and Fisher's exact test, there was no statistically significant relationship between demographic and clinical characteristics with the incidence of lymph node metastases in endometrial cancer (p>0.05) (Table 1).

**The Relationship between Tumor Characteristics and Lymph Node Metastases in Endometrial Cancer**

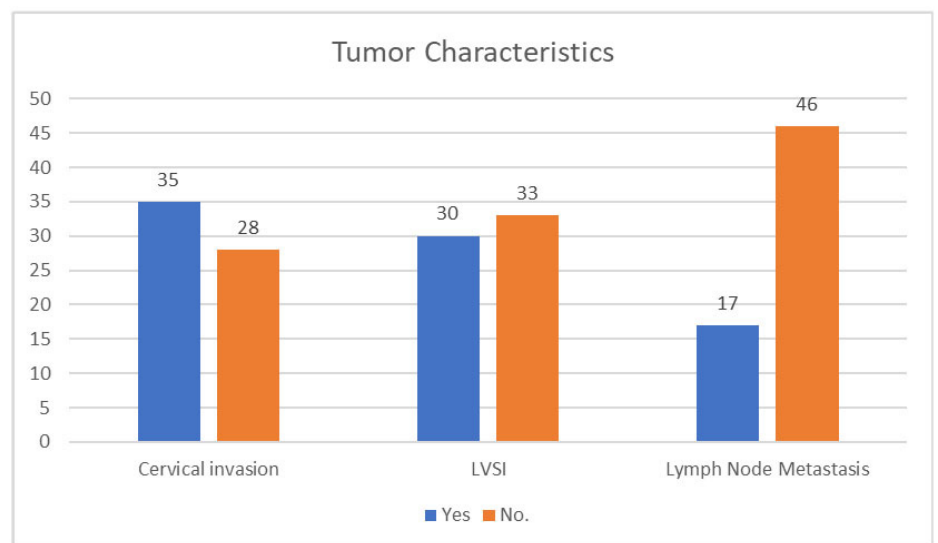
Based on the results of the analysis using Fisher's exact test, there was no significant relationship between tumor type and lymph node metastases in endometrial cancer (Figure 10). Based on the results of the analysis using the Chi-square test,



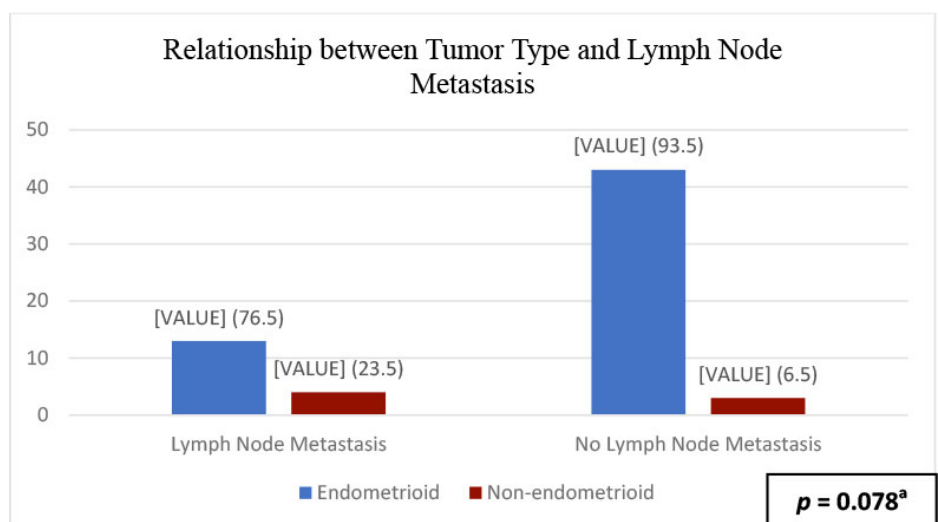
**Figure 7.** Proportion of subjects based on the degree of tumor histopathology.



**Figure 8.** Proportion of subjects by degree of myometrial invasion.



**Figure 9.** Proportion of subjects based on tumor characteristics.



<sup>a</sup>: Fisher's exact test

**Figure 10.** The Relationship between Tumor Type and Lymph Node Metastases.

there was no significant relationship between tumor grade and lymph node metastases in endometrial cancer (Figure 11).

Based on the results of the analysis using the Chi-square test, the proportion of subjects with positive LVSI status was found to be significantly higher in the group of subjects with lymph node metastases (88.2% vs. 32.6%;  $p < 0.001$ ) (Figure 12). Based on the results of the analysis using Fisher's exact test, there was no significant relationship between myometrial invasion and lymph node metastases in endometrial cancer (Figure 13). Based on the results of the analysis using the Chi-square test, there was a significant relationship between cervical invasion status and lymph node metastases in endometrial cancer, where the proportion of subjects with cervix endometrial cancer invasion was found to be higher in the group with lymph node metastases (94.1% vs. 41,3%;  $p < 0.001$ ) (Figure 14).

**Factors that Predict the Incidence of Lymph Node Metastases in Endometrial Cancer**

In this study, multivariate analysis using logistic regression was performed to determine the demographic, clinical, and tumor characteristics that can predict the incidence of lymph node metastases in endometrial cancer. The variables included in the multivariate analysis were variables with a p-value  $< 0.25$  based on bivariate analysis: BMI, parity, cancer type, LVSI, myometrial invasion, and cervical invasion. Based on multivariate analysis, the factor that proved to be an independent predictor of lymph node metastases in endometrial cancer was LVSI (+) (OR = 0.10; 95% CI 0.19–0.56;  $p = 0.009$ ) and followed by cervical invasion (OR = 0.07; 95% CI 0.008–0.64;  $p = 0.019$ ) (Table 2 & 3).

**DISCUSSION**

Endometrial cancer can occur both during reproductive age and after menopause. One study showed that the median age of endometrial adenocarcinoma was 61 years; Most of the patients were in the age range of 50 to 59 years. About 5% of endometrial cancer cases occur before age 40, and 20% to 25% of cases are diagnosed before menopause. Postmenopausal bleeding and pre-menopausal bleeding disorders are the main symptoms of endometrial cancer.

**Table 1. Relationship between Demographic and Clinical Characteristics with Lymph Node Metastases in Endometrial Cancer.**

Risk Factor	Lymph Node Metastases		p
	Yes n (%)	No n (%)	
<b>Age at diagnosis</b>			
< 60 years old	13 (76.5)	35 (76.1)	0.628 <sup>a</sup>
≥ 60 years old	4 (23.5)	11 (23.9)	
<b>Body mass index</b>			
< 30 kg/m <sup>2</sup>	12 (70.6)	24 (52.2)	0.190 <sup>b</sup>
≥ 30 kg/m <sup>2</sup>	5 (29.4)	22 (47.8)	
<b>Parity</b>			
Nullipara	2 (11.8)	12 (26.1)	0.194 <sup>a</sup>
Multipara	15 (88.2)	34 (73.9)	
<b>Menopausal status</b>			
Yes	11 (64.7)	30 (65.2)	0.970 <sup>b</sup>
No	6 (35.3)	16 (34.8)	
<b>Total</b>	<b>17 (100)</b>	<b>46 (100)</b>	

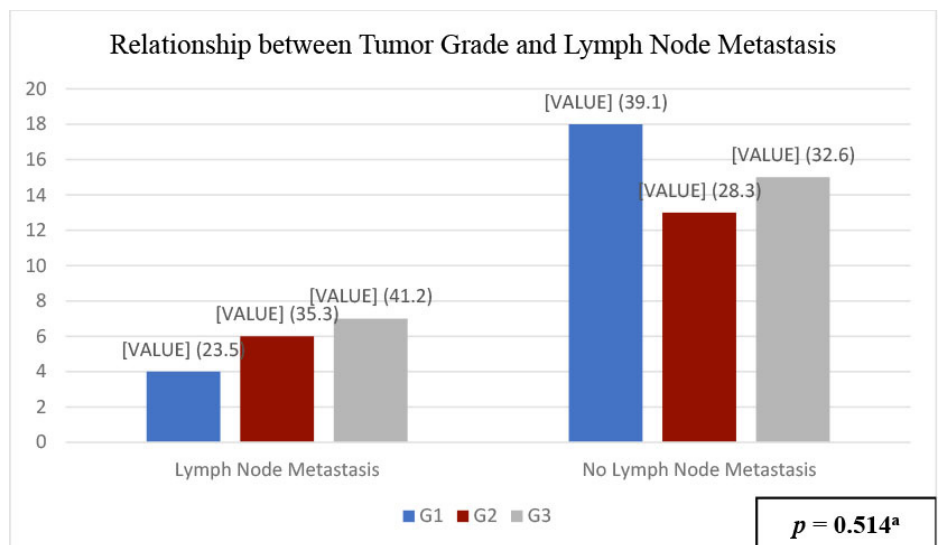
Note: <sup>a</sup> = Fisher's exact test, <sup>b</sup> = Chi-square test

**Table 2. Results of multivariate logistic regression analysis.**

	Coefficient	P-value	OR	95% CI	
				Min	Max
LVSI (+)	-2.26	0.009	0.10	0.19	0.56
Cervical Invasion	-2.62	0.019	0.07	0.008	0.64
Constant	4.392	0.001	80.774		

**Table 3. Probability Analysis Results.**

	LVSI (+)	Cervical Invasion	y	p
1	1	1	9.27	99.99
2	0	0	6.65	99.99
3	1	0	7.01	99.92
4	0	1	4.39	99.99



<sup>a</sup>: Chi-square test

**Figure 11.** The Relationship between Tumor Grade and Lymph Node Metastases.

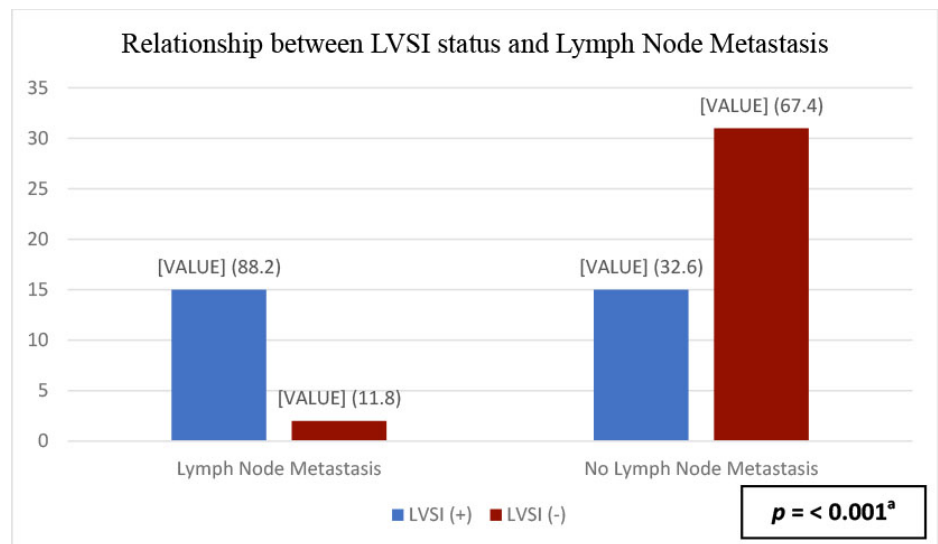
Thus, the possibility of endometrial cancer with complaints of postmenopausal bleeding needs to be considered in every woman. According to one study, the



probability of malignancy is up to 50% in women > 70 years who experience vaginal bleeding.<sup>9</sup> Based on a meta-analysis study by Jenabi et al. (2015), the relative risk (RR) and odds ratio (OR) of endometrial cancer increase with increasing BMI. Elevated levels of free estrogen and imbalance between estrogen and progesterone levels are some risk factors for endometrial cancer. Multiparous women have a 20% to 40% lower risk of developing endometrial cancer than nulliparous women. Various hypotheses have been proposed to explain this. Increased progesterone levels during pregnancy can inhibit the proliferation of endometrial cells mediated by estrogen and support the differentiation and apoptosis of endometrial cells. A vaginal delivery or postpartum uterine involution also facilitates the shedding of precancerous and cancerous cells from the endometrial lining. Older menopausal women tend to have higher hormone levels and longer exposure to estrogen, so older menopausal age is associated with various gynecological malignancies, including breast cancer and endometrial cancer.<sup>10</sup>

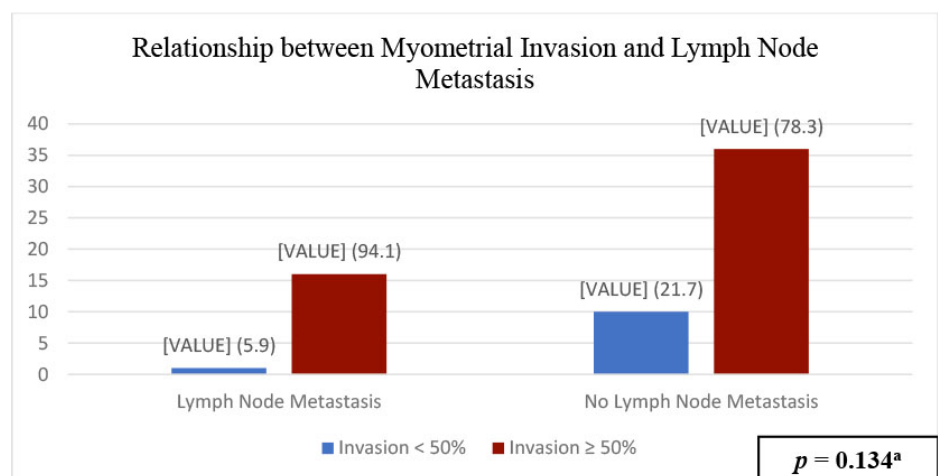
KGB metastases were found in 27% of the subjects in this study. This figure is relatively higher compared to several other studies. In the study by Ignat et al. in 206 adenocarcinoma patients who underwent pelvic and/or paraaortic lymphadenectomy, the lymph node metastases rate was 4.4%.<sup>5</sup> This study showed an association between LVSI status and lymph node metastases, where the proportion of subjects with LVSI (+) status was higher in the group with lymph node metastases. The results of this study are in agreement with Stalberg et al. (2019), who proved that the presence of LVSI was the strongest predictor of lymph node metastases (RR = 5.46; 95% CI 3.69–8.07;  $p < 0.001$ ) and a poor prognosis in patients with endometrioid endometrial cancer. The impact of LVSI on the prognosis of women with endometrial adenocarcinoma is not clearly understood, and the role of LVSI in clinical decision-making in endometrial cancer cases is still unclear. Regarding tumor progression and metastases, LVSI seems to be associated with the metastatic process so that it can be a marker of lymph node metastases.

Multivariate analysis in this study



<sup>a</sup>: Chi-square test

**Figure 12.** The Relationship between LVSI status and Lymph Node Metastases



<sup>a</sup>: Fisher's exact test

**Figure 13.** The Relationship between Myometrial Invasion and Lymph Node Metastases.

showed that cervical invasion and positive LVSI status were independent predictors of lymph node metastases in endometrial cancer. This study showed that endometrial cancer patients with cervical involvement were 14 times more likely to have lymph node metastases than those without cervical involvement. Cancer patients with positive LVSI status had a ten times higher probability of developing lymph node metastases than endometrial cancer patients with LVSI status.

## CONCLUSION

There was a significant relationship in 2 of 5 pathological characteristics with

lymph node metastases in endometrial cancer, with a significant relationship between LVSI and lymph node metastases in endometrial cancer patients. Cervical invasion and LVSI are the risk factors most related to lymph node metastases in endometrial cancer patients.

## DISCLOSURE

The author reports no conflicts of interest in this work.

## AUTHOR CONTRIBUTION

DK as the first author and researcher; BA as a researcher; PP as a researcher.

## ETHICAL CONSIDERATION

The Dr. Soetomo Ethic Health Research Committee has approved this study with a letter-number: 0889/104/4/VIII/2021.

## SOURCE OF FUNDINGS

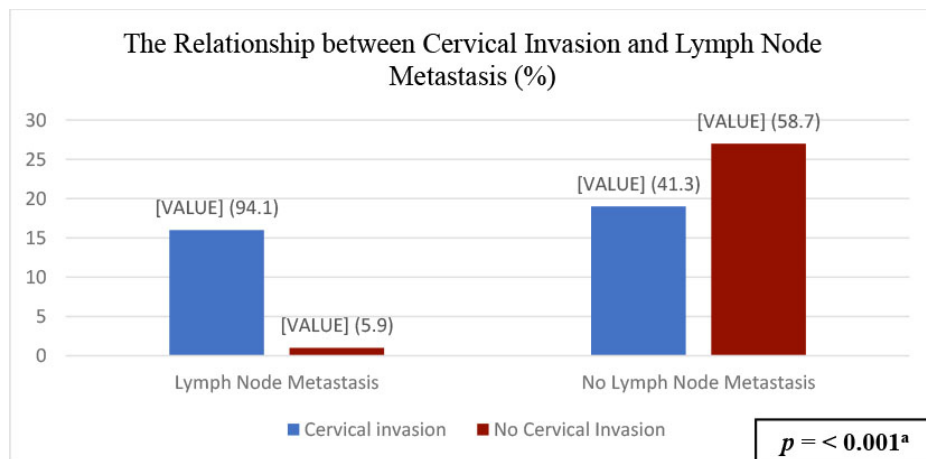
None of the funding.

## CONFLICT OF INTEREST

The authors stated that there is no conflict of interest.

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<sup>a</sup>: Chi-square test

**Figure 14.** The Relationship between Cervical Invasion and Lymph Node Metastases.

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