Clinical Research

Estrogen receptor expression in type 1 endometrial cancer and its association with lymphovascular space invasion

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ABSTRACT

BACKGROUND Endometrial cancer (EC) ranks sixth in female genital malignancy and originates in the endometrial lining. Estrogen receptor (ER) expression is important in EC prognosis and recurrence, influenced by the presence of lymphovascular space invasion (LVSI). This study aimed to determine the association between ER expression and LVSI in type 1 EC.

METHODS A retrospective analysis was conducted on 135 patients with type 1 EC who underwent surgery at the Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between January 2012 and December 2022. Immunohistochemistry (IHC) with ER antibodies was performed on all samples in April 2023. ER expression was evaluated using the Allred scoring system, and its association between ER expression (percentage and intensity stain) and LSVI was statistically analyzed.

RESULTS Of 135 samples, 44 (32.6%) were LVSI-positive. No significant association was found between IHC percentage stain and LVSI ($p = 0.994$). However, a significant association was found between IHC stain intensity and LVSI-positive in patients with type 1 EC ($p = 0.022$). ER intensity score 2 had a higher LVSI risk compared to score 1 and score 3 (from 51%, 26%, and 26%, respectively).

CONCLUSIONS ER expression is associated with LVSI of type 1 EC. While IHC stain percentage showed no correlation with LVSI, stain intensity was significantly linked to LVSI-positive in patients with type 1 EC. Regular assessment of ER expression can provide significant prognostic information, support hormonal therapy, and identifying clinical characteristics of tumors.

KEYWORDS endometrial cancer, estrogen receptor, lymphovascular invasion

Endometrial cancer (EC) is the sixth most common female genital malignancy worldwide and the third leading cause of cancer-related deaths in Indonesia.[1] EC is divided into estrogen-dependent (type 1) and estrogen-independent (type 2) types, with type 1 being the most prevalent. Estrogen receptor (ER) expression is strongly associated with estrogen exposure, stable mutational profiles, and common mutations, including the phosphatase and tensin homolog, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, and Kirsten rat sarcoma viral oncogene homolog, which influence estrogen-related intracellular signals transduction.[2] Moreover, ER-positive tumors have a better prognosis than ER-negative tumors do and play a key role in the response to hormonal and immunotherapy.[3]

EC has a recurrence rate of 15–20% within 36 months of the initial therapy. Given this high rate,

identifying risk factors is crucial, including advanced age, parity, histopathological grade, myometrial invasion of more than half the thickness of the myometrium, and lymphovascular space invasion (LVSI).[4] LVSI is histopathologically defined as the presence of tumor cells in the lymph vessels or small vessels around the tumor. A previous study reported LVSI reaches 35% of the patients with EC.[5] Notably, LVSI is associated with lower overall survival, higher recurrence risk, lymph node metastasis, and distant metastases, contributing to a poorer prognosis in EC, according to The International Federation of Obstetrics and Gynecology I–III.[6]

Immunohistochemistry (IHC) is a crucial surgical pathology technique that enables a precise diagnosis and offers effective treatment. Specifically, IHC staining is the most suitable modality for measuring ER expression[7] as it provides valuable prognostic information and aids in the strategic management of patients with EC. IHC results indicated the staining intensity, percentage of stained cells, and overall staining presence or absence. Previous studies have usually determined the association between ER expression and the LVSI of type 1 EC using the Allred scoring method, which combines cell staining intensity and percentage.[8] This study aimed to analyze the associations among ER percentage, ER intensity, and LVSI risk.

METHODS

This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital (No. KET-747/UN2.F1/ETIK/PPM.00.02/2022). This study was conducted at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. A total population sampling method was used. The study included 135 patients diagnosed with type 1 EC who underwent surgery at Cipto Mangunkusumo Hospital between January 2012 and December 2022; 24 participants were excluded because paraffin blocks lacked representative tumors for assessment, medical records were incomplete, or patients had type 2 EC. The selected participants were confirmed to have type 1 EC and LVSI based on histopathological reports by anatomical pathologists at Cipto Mangunkusumo Hospital.

Experiment protocol

This cross-sectional study included 135 participants who met the inclusion criteria: 44 with LVSI and 91 without LVSI. The IHC procedure used ER monoclonal antibodies (CRM301A; Biocare Medical, USA) diluted at 1:200. In this study, the positive controls for ER were normal endometrial glands and stroma, which exhibited nuclear ER expression.

The IHC staining results were evaluated under a light microscope by two anatomical pathologists (NCS and TH) and by researchers in April 2023. ER expression was assessed semi-quantitatively using the Allred scoring system, which measures ER intensity using color.[9,10] The percentage score for ER-positive cells is classified as follows: 0 (no cells ER + ve), 1 (≤1% ER + ve), 2 (1–10% ER + ve), 3 (11–33% ER + ve), 4 (34–66% ER + ve), 5 (67–100% ER + ve). The intensity was categorized as 0 (negative), 1 (weak), 2 (intermediate), or 3 (strong).

Allred method

The intensity of staining was crucial for calculating the Allred score. Higher color intensity yields a higher Allred score, as it represents greater numerical values (0, 1, 2, or 3) that contribute to a more significant total score. Analyzing the intensity and percentage of ER expression separately in EC provides a more comprehensive assessment. While intensity reflects the strength of receptor expression, the percentage indicates the proportion of cells exhibiting ER expression.

Statistical analysis

The association between ER expression and LVSI in patients with type 1 EC was analyzed using the chi-square test, with statistical significance set at $p<0.05$. Statistical analyses were performed using SPSS software version 20.0 (IBM Corp., USA). Nonparametric methods, including the chi-square and Kolmogorov–Smirnov tests, were used to evaluate the associations between variables. $p<0.05$ indicated significant results.

RESULTS

A schematic representation of the patient selection process is shown in Figure 1. This study included 159 EC patients who underwent surgery between 2012 and 2022. Of these, 19 were excluded because of nonrepresentative tumor samples in their

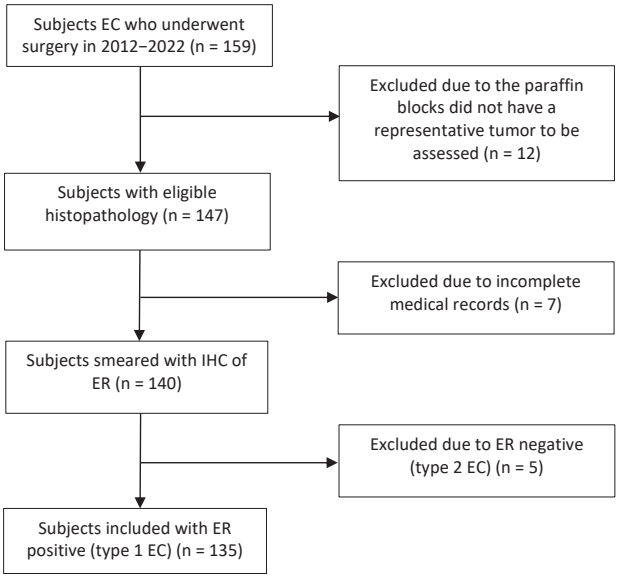

Figure 1. Flowchart of subject selection. EC=endometrial cancer; ER=estrogen receptor; IHC=immunohistochemistry

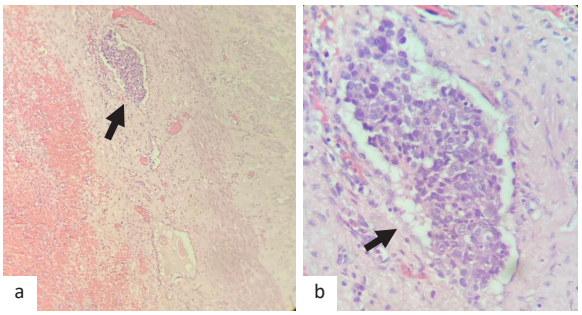

Figure 2. H&E stained section from an endometriosis endometrial tumor. (a) Magnification 10×; (b) magnification 40×. LVSI can be observed by the presence of cohesive tumor cells within a space surrounded by endothelial cells (arrows). H&E=hematoxylin and eosin; LVSI=lymphovascular space invasion

paraffin blocks (n = 12) or incomplete medical records (n = 7). IHC staining was performed to detect ER (n = 140), and five samples were identified as ER-negative (type 2 EC). Therefore, 135 eligible patients with type 1 EC were included in this study.

EC and IHC

LVSI refers to embolic tumor invasion into the lymphatic space, blood vessels, or both in the peritumoral area. Histopathologically, tumor cell embolisms were observed within the endothelial-lined spaces (Figure 2). Representative samples of different ER expression patterns are shown in Figure 3. Examples of other patterns include the intensity score for IHC expression in EC.

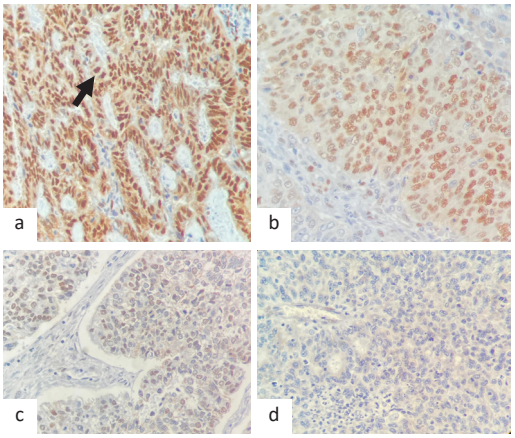

Figure 3. IHC stain intensity score, expression of ER in the cell nucleus EC (brown color) (400× magnification). (a) score 3 – strong expression of ER on the cell nucleus (arrow); (b) score 2 – intermediate expression of ER on the cell nucleus; (c) score 1 – weak expression of ER on the cell nucleus; (d) score 0 – negative expression of ER on the cell nucleus. EC=endometrial cancer; ER=estrogen receptor; IHC=immunohistochemistry

Determinant factors with LVSI in type 1 EC

LVSI was identified in patients with myometrial invasion exceeding 50%. Statistical analysis revealed a significant association between myometrial invasion and LVSI detection ($p = 0.023$). The association between these determinants and LVSI can be seen in Table 1.

A significant association was observed between IHC staining intensity and LVSI positivity in patients with type 1 EC ($p = 0.022$). The risk of LVSI is minimal at low and high intensities; however, the risk increases significantly at moderate intensity. The association between ER and LVSI expression can be seen in Table 2.

Association of ER component with LVSI in type 1 EC

Because myometrial invasion was significantly associated with LVSI, further analysis was performed to stratify myometrial invasion and determine the relationship between IHC and LVSI staining intensities.

Table 3 shows the relationship of IHC staining intensity and LVSI with myometrial invasion, being higher than 50% ($p = 0.011$).

DISCUSSION

This study found no significant association between histopathological grade and LSVI in patients with type 1 EC. Histopathologists assessed the degree of cancer cell differentiation. Conversely, LVSI is more closely related to the ability of the tumor to spread to the

Table 1. Association of determinant factors with LVSI in type 1 EC

Determinant factor	LVSI		*p**
	Positive, n (%)	Negative, n (%)	
Grade			0.698
High	15 (35)	28 (65)	
Low	29 (32)	63 (68)	
Myometrial invasion			**0.023**
≥50%	34 (40)	52 (60)	
<50%	10 (20)	39 (80)	

EC=endometrial cancer; LVSI=lymphovascular space invasion
*Chi-square test

Table 2. Association of ER component with LVSI in type 1 EC

ER component	LVSI		*p*
	Positive, n (%)	Negative, n (%)	
Percentage			0.994*
Score 2	1 (25)	3 (75)	
Score 3	14 (40)	21 (60)	
Score 4	26 (32)	55 (68)	
Score 5	3 (20)	12 (80)	
Intensity			**0.022**†
Score 1 (weak)	8 (26)	23 (74)	
Score 2 (moderate)	18 (51)	17 (49)	
Score 3 (strong)	18 (26)	51 (74)	

EC=endometrial cancer; ER=estrogen receptor; LVSI=lymphovascular space invasion
*Kolmogorov–Smirnov test; †chi-square test

Table 3. Association of IHC stain intensity with LVSI adjusted by level of myometrium invasion

IHC stain intensity	LVSI		*p**
	Positive, n (%)	Negative, n (%)	
Myometrium invasion <50%			
Intensity			0.179
Score 1 (weak)	2 (50)	2 (50)	
Score 2 (moderate)	5 (100)	0 (0)	
Score 3 (strong)	32 (80)	8 (20)	
Myometrium invasion ≥50%			
Intensity			**0.011**
Score 1 (weak)	21 (78)	6 (22)	
Score 2 (moderate)	12 (40)	18 (60)	
Score 3 (strong)	19 (66)	10 (34)	

IHC=immunohistochemistry; LVSI=lymphovascular space invasion
*Chi-square test

blood vessels or lymph. Although the histopathological grade provides information about the aggressiveness of cancer, it does not always correlate with the LVSI that occurs in EC. In a study by Siegenthaler et al[11] involving 40 patients with EC polymerase epsilon mutations, LVSI was not associated with tumor size (p = 0.28), high-grade histology (p = 0.06), or lymph node involvement (p = 0.66).

Deep myometrial invasion (>50%) correlates with LVSI positivity, lymph node metastasis positivity, and EC recurrence, making it a valuable evaluation criterion associated with clinical outcomes and prognosis of EC. This study found a significant relationship between LVSI and myometrial invasion exceeding 50% of myometrial thickness. Similarly, Tortorella et al[12] reported that diffuse LVSI correlated significantly with histopathological grade, deeper myometrial infiltration, and larger tumor size. Additionally, many studies claim that LVSI is a significant prognostic factor often associated with deep myometrial invasion, with LVSI-positive tumors being strongly associated with deep myometrial invasion beyond 50% (p<0.001).[13] Our findings align with these studies, as LVSI was present in the endometrioid type with extensive myometrial invasion in the outer half, demonstrating a significant association.

There was no association between IHC staining percentage and LVSI detection. Several factors influenced this lack of association. ER is primarily associated with early-stage tumors and benign diseases, whereas LVSI is associated with high-risk tumors and aggressive diseases. The quantitative assessment of ER examined here included the percentage of tumor cell nuclei that stained positive for ER, unlike ER intensity, which reflects increased binding to ER antigens and can be considered a surrogate measure of concentration or density.[14]

Various studies have investigated the association between LVSI and ER status, with findings suggesting that LVSI is not significantly associated with ER status due to the independent nature of LVSI, ER, and recurrence-free survival in various cancers, including high-grade serous ovarian cancer. However, no significant correlation was observed between LVSI status and ER positivity, suggesting that tumors with high ER expression do not necessarily have an

increased likelihood of developing LVSI.[15] While LVSI is often considered a marker for aggressive disease and poor prognosis, its independence from ER status indicates that other factors play a more critical role in tumor behavior and patient outcomes. This emphasizes the complexity of cancer biology, in which multiple pathways drive tumor progression independently of specific markers.[16]

Understanding that the LVSI is not correlated with ER status can aid in treatment decisions. Patients with ER-positive tumors may still exhibit LVSI without affecting the hormone receptor status, which is crucial for determining endocrine therapy eligibility.[8] Additionally, one study reported a negative correlation between ER expression and programmed death-ligand 1 (PD-L1) expression in EC type 1, suggesting that high ER expression may be linked to decreased PD-L1 expression, potentially influencing the immune response and lowering the risk of LVSI.[17]

This study demonstrates an association between IHC staining intensity and LVSI positivity in patients with type 1 EC. Higher IHC ER staining intensity may indicate stronger ER activity in cancer cells, potentially enhancing their invasive abilities.[18] Estrogen and ER play essential roles in developing endometrioid EC, as prolonged endometrial exposure can lead to endometrial hyperplasia and subsequent EC development. Increased ER intensity suggests greater ER antigen binding, reflecting higher ER concentration or density, unlike ER percentage staining, which only shows the proportion of stained cells.[14] ER contributes to endometrial malignant transformation through three main mechanisms[2]: 1) upstream regulators of estrogen receptor alpha (ERα) regulate the transcriptional activity of ER, influencing EC development, especially cell proliferation; 2) interaction with co-regulators to promote EC occurrence; and 3) mediation of EC proliferation, metastasis, and apoptosis via downstream proteins or target genes. While previous studies contradict the results of this study due to its limitation to type 1 EC only, our data suggest that an increase in ER staining intensity was associated with LVSI occurrence.

In this study, ER intensity was associated with an increased risk of LVSI at an intensity score of 2 compared with an intensity score of 1. However, at an intensity score of 3, the risk of LVSI decreased significantly; at high ER intensity (intensity score 3), the risk of LVSI was not substantial. Very high ER intensity is not always correlated with a higher incidence of LVSI in patients with EC. This can be explained by several factors, including the role of estrogen receptor beta (ERβ), which acts as a negative modulator of ERα. ERβ can inhibit ERα-induced cancer cell proliferation, potentially reducing LVSI risk by limiting tumor proliferation and cancer cell migration. Hypomethylation of the ERβ promoter gene can increase ERβ mRNA expression. Higher ERβ mRNA gene expression in endometriosis tissues can inhibit ERα mRNA, reducing the ERα/ERβ ratio. A lower ratio may reduce the potential for LVSI due to ERα mRNA deficiency linked to progesterone resistance and endometriosis tissue. Hypoxia factors also regulate ERβ expression, activating transcription pathways that help prevent LVSI. This suggests that the tumor microenvironment plays a key role in ER function during invasion.

This study found an association between IHC staining intensity and LVSI in cases of significant myometrial invasion exceeding 50%, highlighting that myometrial invasion is a critical factor in predicting LVSI. Although ER expression was high, LVSI was more affected by the invasion depth.[19] The results indicate a significant association between myometrial invasion, ER staining intensity, and LVSI risk. Deeper myometrial invasion increases the likelihood of cancer cells reaching the lymphatic system and blood vessels, thereby facilitating LVSI.[20] Increased estrogen levels promote matrix metalloproteinase (MMP) production, which drives myometrial invasion through extracellular matrix degradation, release of chemotactic signals, expression of proteins supporting invasion, interaction with tumor cell signaling pathways, and influence on the microenvironment. MMP2 facilitates tumor cell migration and myometrial invasion. In contrast, MMP can also reduce the incidence of LVSI in EC by regulating extracellular matrix degradation, interacting with inhibitors such as tissue inhibitors of metalloproteinases (TIMPs), influencing cancer cell proliferation, regulating growth factors, and affecting myometrial invasion. An imbalance between MMP and TIMP expression, along with other factors, is essential for determining the potential for LVSI in EC cells.[21,22] Additionally, claudin-4 is expressed in abnormal endometrial epithelial cells and promotes invasion into the myometrium. Therefore, clinical practice should not rely solely on ER intensity as an indicator of LVSI risk. A thorough evaluation of other factors, including

TIMP, MMP, and claudin-4 expression, as well as other clinicopathological characteristics, is essential to determine prognosis and appropriate therapeutic strategies.

This study aimed to analyze the risk of LVSI before surgery to assist in grading EC, emphasizing the need for careful histopathological analysis to determine whether myometrial invasion exceeds or is less than 50%. Pathologists should examine surgical samples, such as those from hysterectomy procedures. If curettage results confirm EC, further assessments such as hysteroscopy, magnetic resonance imaging, or hysterectomy may be necessary to accurately determine the depth of myometrial invasion. The routine assessment of ER intensity in EC has significant clinical implications for prognosis, hormonal therapy management, tumor characterization, and potential responses to immunotherapy. Regular evaluations can improve patient care and support clinical decision-making.

However, these results require further validation in future studies. Variations may be due to differences in sample size, primary antibodies, immunohistochemical assessment results, and the timing of endometrial tissue retrieval during surgery, as endometrial mucosa undergoes hormone-dependent changes and estrogen levels fluctuate throughout the menstrual cycle. ER is highly expressed in both glandular and stromal cells during the proliferative and early secretory phases. ER expression is much lower in both glandular and stromal cells during the late secretory phase.[23] Because IHC staining of the ER peaks in the proliferative phase and declines in the secretory phase, identifying the menstrual cycle phase at the time of surgery is important, whether it is the proliferative phase, initial secretory phase, late secretory phase, or menopause. Type 1 EC, the most common type, is often associated with excess estrogen and typically shows positive ER expression.[24]

This study was conducted exclusively on samples of type I EC; therefore, the findings cannot be directly generalized to other types of EC that possess distinct biological characteristics. Further research is warranted to address this limitation and to clarify the relationship between ER expression and lymphovascular invasion in other subtypes of EC. In conclusion, ER expression correlated with LVSI in type 1 EC. While no association was found between IHC staining percentage and LVSI, IHC staining intensity correlated with LVSI positivity in patients with type 1 EC. Regular ER expression assessments can provide significant prognostic information, support hormonal therapy management, and identify clinical characteristics of tumors.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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