Estrogen receptor and programmed death ligand-1 expression in type 1

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Estrogen receptor and programmed death ligand-1 expression in type 1 endometrial cancer and its associated clinicopathological characteristics

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ABSTRACT

Background: This study aimed to determine the association of estrogen receptor (ER) and programmed death ligand-1 (PD-L1) expression with the clinicopathological characteristics of type 1 endometrial cancer.
Materials and methods: A total of 85 patients with type 1 endometrial cancer who underwent surgery at the Dr. Soetomo Hospital, Surabaya, Indonesia were retrospectively studied. Data about the age, menopausal status, body mass index, disease stage, cell differentiation, angiolymphatic invasion, myometrial invasion, and adjuvant therapy of the patients were collected from medical records. Immunohistochemistry with ER and PD-L1 antibodies was performed on all samples. The association between ER and PD-L1 expression and clinicopathological characteristics was statistically analyzed.
Results: The positivity rates of ER and PD-L1 in type 1 endometrial cancer were 68.2 % and 78.5 %, respectively. ER positivity was significantly correlated with body mass index (BMI) ≥25, premenopausal status, early stage of disease, <1/2 myometrial invasion, negative nodal metastasis, and lack of adjuvant therapy. It was also associated with age <55 years, low-grade cells, and angiolymphatic invasion, but the correlation was not significant. Meanwhile, PD-L1 positivity was significantly correlated with BMI <25, menopausal status, advanced stage of disease, high-grade cells, angiolymphatic invasion, and adjuvant therapy. It was also associated with age ≥55 years and nodal metastasis, but the correlation was not significant.
Conclusion: ER and PDL-1 positivity is associated with the clinicopathological characteristics of type 1 endometrial cancer.

1. Introduction

Endometrial cancer (EC) is the third leading cause of cancer-related deaths among women in Indonesia [1]. The incidence and death rates of this disease are predicted to increase by 20.3 % and 17.4 %, respectively, by 2025 [2]. The high percentage of cancer-related deaths indicates that research related to cancer therapy is still developing. The therapeutic paradigm has shifted with the advancement of research about EC and precision therapy. The National Comprehensive Cancer Network (NCCN) has recommended the use of immunotherapeutic agents, such as PD-1 inhibitors, for cancer therapy. However, PD-1 efficacy can be influenced by the expression of its ligands, such as PD-L1. The association of PD-L1 and estrogen receptor (ER) expression with EC is interesting and important for research.

ER, a member of the nuclear receptor superfamily, has two subtypes: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). When estrogen binds to the binding domain, the ER ligand is activated, translocates to the nucleus, acts on the estrogen response element located in the upstream promoter of the target gene, and activates the transcription of the target gene. ERα and ERβ differ in expression and function during the progression of gynecologic cancer, such as EC [3]. For instance, ERα mediates estrogen-induced mitogenic signaling in

Abbreviations: EC, endometrial cancer; BMI, body mass index; ER, estrogen receptor; LVSI, lymphovascular space invasion; OS, overall survival; PD-L1, programmed death ligand-1; NCCN, National Comprehensive Cancer Network.

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cancer, whereas ERβ inhibits the proliferative effects of estrogen on cancer cells and reduces the phosphorylation of AKT and Cyclin D1 proteins, thereby inhibiting the cancer cell cycle and promoting apoptosis.

The endometrial tissue is sensitive to steroid hormones. Through its receptors, estrogen supports the development and growth of EC. Endometrioid-type EC is characterized by changes in the expression of various ER subtypes. Type 1 EC without ER expression is associated with aggressive tumors and a poor survival rate [4].

PD-L1 on the surface of tumor cells interacts with its receptors on T cells, triggering T cell dysfunction in tumor tissues and inhibiting T cell-induced antitumor immunity. 17b-estradiol (E2) increases PD-L1 expression in a dose-dependent manner [5]. Bioinformatics and cell line studies in cancer showed that PD-L1 expression is lower in ERα--positive breast cancer than in ERα-negative breast cancer [6,7].

Next-generation sequencing revealed that treatment with E2 affects PD-L1 expression in MCF-7 cells, indicating that estrogen regulates PD-L1 at the transcriptional level [8,9]. The checkpoint immunity of EC to PD-L1 and PD-1 is a concern. The positivity rates of PD-1 and PD-L1 in primary tumors are 59 % and 63 %, respectively [10].

PD-L1 positivity is associated with lympho-vascular space invasion (LVSI), histological type, myometrial invasion, and a good prognosis in EC survivors treated with immunotherapy [11,12]. A research in Egypt showed that the correlation of PD-L1 positivity with tumor and immune cells is stronger in older than in younger patients. Tumor and immune cells with PD-L1 expression are generally positive for LVSI, whereas those without PD-L1 expression are generally negative for LVSI [13]. High PD-L1 expression is a potential invasive mechanism against immune responses. PD-L1 increases the regulation of PD-1-positive tumor cells and is correlated with high tumor stages [14]. PD-L1 expression is also associated with LVSI, histology, myometrial invasion, and advanced stages [13].

Advanced gynecologic cancers have historically lacked effective treatment options. Immune checkpoint inhibitors (ICIs) have been approved by the US Food and Drug Administration for the treatment of cervical cancer and EC, offering durable responses for some patients [15]. The NCCN has recommended immunotherapeutic agents, such as PD-1 inhibitors (pembrolizumab), for the treatment of advanced EC with the microsatellite instability-high (MSI-H) or mismatch repair-deficient (MMRd) phenotype. MSI-H molecular subclasses are characterized by high numbers of CD3+/CD8+ tumor-infiltrating lymphocytes and an overexpression of PD-1 and PD-L1. Specifically, MSI-H/MMRd cancers are characterized by extremely high numbers of somatic mutations and have a relationship with MMR status and PD-1/PD-L1 expression in EC. EC cases with the MMRd phenotype have a higher cytotoxic T cell (CD8+) infiltration and PD-1/PD-L1 expression than those without this phenotype. The high immunogenicity of these tumors explains the strong rationale behind the use of immunotherapy in these subgroups of cancers [16].

In recent years, the MMRd phenotype has emerged as a predictive biomarker for immunotherapy, and ICIs such as pembrolizumab and dostarlimab have shown clinically meaningful activity as a monotherapy in patients with MMRd EC [17]. Moreover, ICIs and tyrosine kinase inhibitors have been extensively assessed, including tumors selected for DNA MMRd/MSI and PD-L1 expression status. Pembrolizumab plus lenvatinib is indicated for patients with unselected pretreated metastatic EC, whereas pembrolizumab monotherapy is a preferred option for patients with MMRd/MSI-H tumors [18].

2. Materials and methods

In this retrospective cross-sectional study, data about the age, menopausal status, body mass index (BMI), disease stage, cell differentiation, angiolymphatic invasion, myometrial invasion, and adjuvant therapy of patients with type 1 EC at Dr. Soetomo Hospital in Surabaya, Indonesia were obtained from medical records and histopathological results. Paraffin blocks from the Anatomical Pathology Laboratory of Dr. Soetomo Hospital containing a representative tumor mass collected from January 2018 to December 2022 were used to obtain ER and PD-L1 immunohistochemical data. PD-L1 expression was examined through immunohistochemical staining of endometrial tissue paraffin blocks using PD-L1 antibody from GenomeMe clone IHC411. ER expression was examined through immunohistochemical staining of endometrial tissue paraffin blocks using Biocare Medical ER. The tissues were examined using the LSAB II method and fixed using 10 % neutral buffered formalin (Fig. 2).

The association of ER and PD-L1 expression with the clinicopathological characteristics of patients with type 1 EC was analyzed using Fisher's exact, with $p < 0.05$ considered to indicate statistical significance (Fig. 3). This study was approved by the Research Ethics Committee of Dr. Soetomo Hospital Surabaya, Indonesia.

3. Results

A schematic of the patient selection is displayed in Fig. 1. A total of 105 patients with type 1 EC who underwent surgery in 2018–2022 were considered in this study. Among these patients, 20 were excluded because their paraffin blocks did not have a representative tumor to be assessed ($n = 12$) or their medical records were incomplete ($n = 8$). Thus, 85 eligible samples were included in this study (Fig. 1).

The clinicopathologic characteristics of the included patients are shown in Table 1. A total of 85 patients were eligible, of whom 41 (48.2 %) were aged <55 years and 44 (51.8 %) were aged >55 years. In terms of BMI, the patients were grouped as follows: underweight ($n = 6$, 7.1 %), normal ($n = 36$, 42.4 %), overweight ($n = 14$, 16.5 %), obesity class I ($n = 23$, 27.1 %), and obesity class II ($n = 6$, 7.1 %). In terms of menopausal status, they were classified as follows: premenopausal ($n = 39$, 45.9 %) and menopausal ($n = 46$, 54.1 %). In terms of disease stage, they were grouped as follows: early ($n = 45$, 52.9 %) and advanced ($n = 40$, 47.1 %). In terms of cell differentiation, they were classified as follows: low grade ($n = 54$, 63.5 %) and high grade ($n = 31$, 36.5 %). In terms of nodal metastasis, they were grouped into those without nodal metastasis ($n = 76$, 89.4 %) and those with nodal mestastasis ($n = 9$, 10.6 %). With regard LVSI, the patients were divided into those without LVSI ($n = 59$, 69.4 %) and those with LVSI ($n = 26$, 30.6 %). In terms of myometrial invasion, the patients were classified into those with < ½ myometrial invasion ($n = 22$, 25.9 %) and those with ≥½ myometrial invasion ($n = 63$, 74.1 %). In terms of adjuvant therapy, the patients either did not receive ($n = 19$, 22.4 %) or received ($n = 66$, 77.6 %) adjuvant therapy. (Table 1)

Association of ER and PD-L1 expression with the clinicopathological characteristics of type 1 EC

The ER expression in type 1 EC was higher in the patients aged <55 years than in those aged ≥55 years, but the difference was not statistically significant ($p = 0.050$). By contrast, the PD-L1 expression was higher in the patients aged ≥55 years than in those aged <55 years, but the difference was not statistically significant ($p = 0.067$; Table 2).

The ER positivity rates in the patients with BMI overweight, obesity class I, and obesity class II were 78.6 %, 95.7 %, and 100 %, respectively ($p = 0.0001$). By contrast, the PD-L1 positivity rates in the patients with BMI underweight and normal weight were 100 % and 97.2 %, respectively ($p = 0.0001$). The ER expression was higher in the premenopausal than in the menopausal patients with type 1 EC ($p = 0.034$), whereas the PD-L1 expression was significantly higher in the menopausal than in the premenopausal patients ($p = 0.042$; Table 2).

Based on disease stage, the ER expression was significantly higher in the early-stage group than in the advanced-stage group ($p = 0.0001$), whereas the PD-L1 expression was significantly higher in the advanced-stage than in the early-stage group ($p = 0.0001$). Based on myometrial invasion, the ER expression was significantly more prominent in the patients with <1/2 myometrial invasion than in those with ≥1/2 myometrial invasion ($p = 0.028$). Meanwhile, the PD-L1 expression was

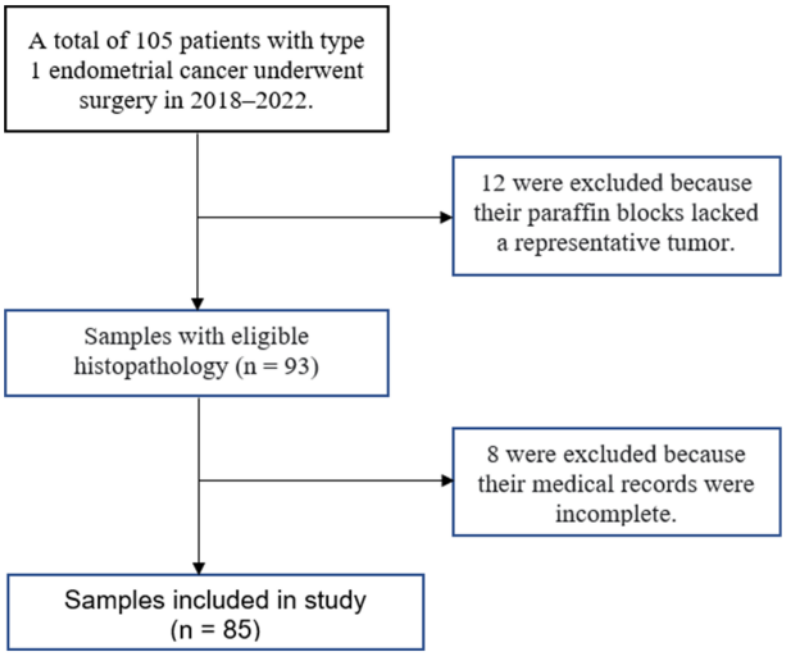

Fig. 1. Flowchart of sample selection.

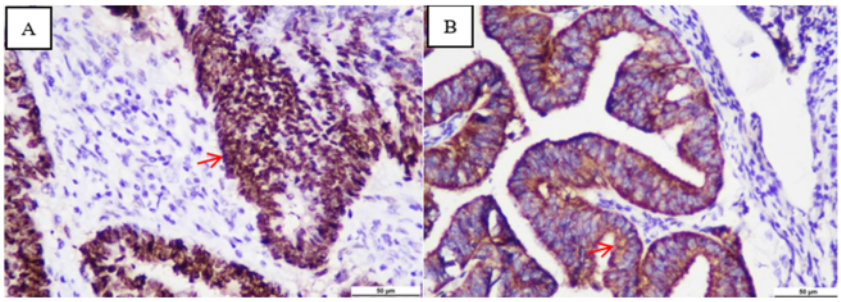

Fig. 2. Expression of ER in the cell nucleus (A). Expression of PD-L1 in the cell membrane (B) (magnification: 400×, scale bar: 50 mm).

significantly more prominent in the patients with ≥1/2 myometrial invasion than in those with <1/2 myometrial invasion. Based on the nodal metastatic group, the ER expression was higher in the non-nodal metastatic group than in the nodal metastatic group ($p = 0.0001$), whereas the PD-L1 expression was higher in the nodal metastatic group than in the non-nodal metastatic group, but the difference was not statistically significant ($p = 0.104$; Table 2).

The ER expression was higher in the patients with low-grade type 1 EC than in those with high-grade type 1 EC, but the difference was not statistically significant ($p = 0.201$). By contrast, the PD-L1 expression was significantly higher in the patients with high-grade type 1 EC than in those with low-grade type 1 EC ($p = 0.042$). Based on the LVSI group, the ER expression was higher in the group without LVSI than that with LVSI, but the difference was not statistically significant ($p = 0.129$), whereas the PD-L1 expression was higher in the group with LVSI than in that without LVSI ($p = 0.001$; Table 2).

The ER expression was significantly higher in the patients who did not receive or require adjuvant therapy than in those who received adjuvant therapy ($p = 0.019$), whereas the PD-L1 expression was significantly higher in the patients who received adjuvant therapy than in those who did not receive or require adjuvant therapy ($p = 0.0001$; Table 2).

4. Discussion

In the present study, the ER positivity rate in the patients with type 1 EC was 68.2 %, which is close to that (59.8 %) obtained by Wang et al. [19] in patients with EC in China. Meanwhile, the PD-L1 positivity rate in the patients with type 1 EC in the present study was 78.8 %, which is in accordance with that (70.15 %) obtained by Zhang et al. [20] in EC and that (63 %) obtained by Engerud et al. (2020) in primary tumors [10]. Gene expression analysis has shown that PD-L1 expression is upregulated in PD-1-positive tumor cells [21]. By contrast, Pasanen et al. [22] conducted a study in Finland and reported a PD-L1 positivity of only 8.58 %. This difference is likely due to the racial differences of the patients. However, whether a relationship exists between PD-L1 expression and race requires further research.

Association of ER and PD-L1 expression with the clinicopathological of type 1 EC

In the present study, the ER expression in type 1 EC was higher in the

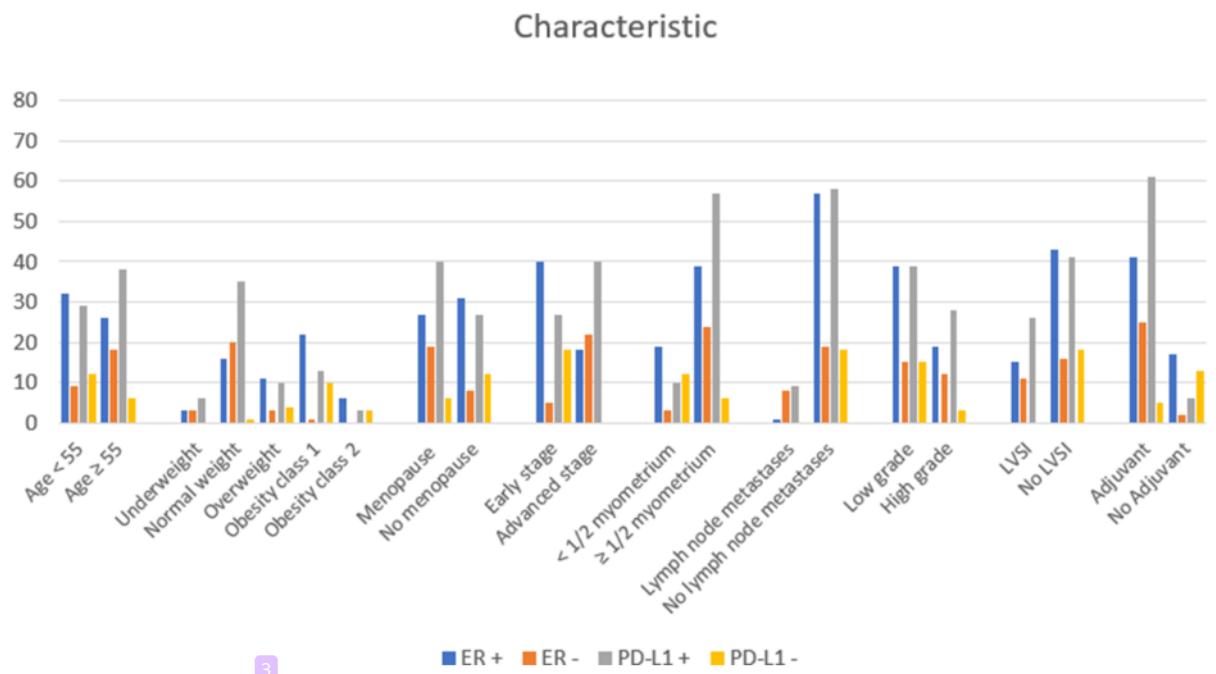

Fig. 3. Diagrams of association between ER and PD-L1 expression with clinicopathological characteristics of type 1 endometrial cancer.

patients aged <55 years than in those aged ≥55 years, but the difference was not statistically significant. Research by Shah et al. [23] in Pakistan suggested a significant relationship between age and ER expression. By contrast, other studies on the effect of young age on hormone receptors reported no significant association between age and ER or PR expression status. These differences may be due to the smaller sample sizes, racial variations, and different age groups in these studies [23].

In the present study, the PD-L1 expression was higher in the ≥55-year-old patient group than in the <55-year-old patient group with type 1 EC, but the difference was not significant. This result is in accordance with the findings of Zhang et al. [20] that PD-L1 expression is higher in women >60 years old than in those <60 years old. A study in Egypt found that patients positive for PD-L1 expression in tumor and immune cells are significantly older than those negative for PD-L1 expression [13].

The results of the present study showed that the ER expression was higher in the patients with a high BMI. This result is in accordance with the report of Chauhan et al. [24] that ER expression is higher in patients with BMI > 25. By contrast, PD-L1 expression was significantly higher in the patients with a normal or low BMI. Similarly, the study by Moreira et al. [25] in Brazil suggested that PD-L1 expression is higher in non-obese women than in obese women, but the difference is not significant.

In the present study, the patients in the premenopausal and non-menopausal groups significantly differed in ER expression. This result agrees with the findings of Milkov et al. [26] that menopause reduces ER expression because of low estrogen levels. Low estrogen levels in menopausal women decrease ER expression to capture estrogen. In the present study, PD-L1 expression was significantly higher in the menopausal group than in the premenopausal group. This result agrees with the report by Kim et al. [27].

In the present study, the ER expression was higher in the early-stage group than in the advanced-stage group. This result agrees with the findings of Wang et al. [19] in Shaanxi, China that ER expression is associated with low-disease-stage (stage I) EC. Meanwhile, the PD-L1 expression was higher in the advanced-stage group than in the early-stage group in the present study. This result agrees with the research findings of Kim et al. [27].

With regard myometrial invasion, the ER expression was higher in the group with <1/2 myometrial invasion than in that with ≥1/2 myometrial invasion. Wang et al. [19] found no significant difference between ER expression and myometrial invasion in patients with EC but reported ER negativity in patients with deep myometrial invasion and cervical invasion. Moreover, the present study showed that the relationship between PD-L1 expression and ≥1/2 myometrial invasion was significant, which is in accordance with the results of Kim et al. [27] that PD-L1 expression in EC is significantly associated with deep myometrial invasion.

In terms of nodal metastasis, the ER expression was higher in the group without nodal metastasis than in that with nodal metastasis. This result agrees with the report of Manan et al. [28] that loss of ER expression is significantly associated with lymph node metastasis in African and American women. Loss of ER independently predicts lymph node metastasis in women with EC. In the present study, PD-L1 expression was higher in the group with nodal metastasis than in that without nodal metastasis, but the difference was not significant. This result can be ascribed to the unbalanced distribution of samples. The results are in accordance with the findings of Li et al. [29] that PD-L1 levels are significantly higher in lymph node tumor cells. PD-L1 expression is also higher in tumor-positive lymph nodes than in tumor-negative lymph nodes. Disease-free survival and overall survival (OS) are worse in patients with lymph node metastasis.

In the present study, the ER expression was higher in the group with low-grade EC than in that with high-grade EC. Similarly, Jeffery et al. [30] conducted a study in Utah, USA and found that ER expression is associated with low cell differentiation. Moreover, the higher PD-L1 expression in the group with high-grade EC than in that with low-grade EC in the present study is consistent with the result of Kim et al. [27] that PD-L1 expression is associated with high cell differentiation.

In terms of LVSI, the ER expression was higher in the group without LVSI, but the difference was not significant, whereas the PD-L1

Table 1
Clinicopathological characteristics and ER and PD-L1 expression of patients with type 1 endometrial cancer.

Characteristics	Frequency	Percentage
Age	Mean: 53.42	
<55 years	41	48.2 %
≥55 years	44	51.8 %
BMI		
Underweight	6	7.1 %
Normal weight	36	42.4 %
Overweight	14	16.5 %
Obesity class 1	23	27.1 %
Obesity class 2	6	7.1 %
Obesity class 3	0	0 %
Menopausal status		
Yes	46	54.1 %
No	39	45.9 %
Cancer stage		
Early stage (I, II)	45	52.9 %
Advanced stage (III, IV)	40	47.1 %
Myometrial invasion:		
<1/2 myometrium	22	25.9 %
≥1/2 myometrium	63	74.1 %
Nodal metastasis:		
Yes	9	10.6 %
No	76	89.4 %
Cell differentiation (tumor grade):		
Low grades (I and II)	54	63.5 %
High grades (III and IV)	31	36.5 %
LVSI:		
Yes	26	30.6 %
No	59	69.4 %
Adjuvant therapy:		
Yes	66	77.6 %
No	19	22.4 %
Expression of ER:		
Positive	58	68.2 %
Negative	27	31.8 %
Expression of PD-L1:		
Positive	67	78.8 %
Negative	18	21.2 %

expression was higher in the group with LVSI than in that without LVSI. These results are in accordance with those of several studies, such as those conducted by Zhang et al. [20] in Tsukuba, which stated that PD-L1 is associated with LVSI positivity in EC and poor OS. Other studies have suggested that PD-L1 positivity is associated with LVSI, histological type, and myometrial invasion and is an effective immunotherapy [11, 12]. A research in Egypt demonstrated that tumor and immune cells expressing PD-L1 are mostly positive for LVSI, whereas those not expressing PD-L1 are mostly negative for LVSI [13].

In the present study, the ER expression was significantly higher in the patients who did not require adjuvant therapy than in those who did. This result can be ascribed to the association of ER expression with low risk factors for EC, such as age <55 years, early stage, low-grade cell, endometrioid cell, absence of lymph node involvement, and absence of LVSI. Meanwhile, the PD-L1 expression was significantly higher in the patients who required adjuvant therapy than in those who did not. This result is in accordance with the findings of Kim et al. [27] that PD-L1 expression is significantly related to the need for adjuvant therapy in EC.

The present study is the first to examine the correlation of ER and PD-L1 expression with the clinicopathological characteristics of type 1 EC. With the rapid development of EC therapy, anti-PD-1 immunotherapy has been introduced, and ligand expression (PD-L1) in immune and tumor cells has been proven to increase the effectiveness of this therapeutic strategy. The results of the present study can be used as a basis for further research on the roles of ER and PD-L1 in the prognosis and immunotherapy of EC. Considering that the future of cancer treatment is expected to rely on the combination of therapeutic strategies, several ongoing studies are evaluating the efficacy of ICIs used in combination with other immunotherapeutic agents, hormonal therapy, chemotherapy, radiotherapy, and targeted therapies.

Clinical evidence has suggested a strong correlation between ER and PD-L1 regulation in different types of cancer. Therefore, the combined use of ER inhibitors and anti-PD-L1 agents could exert synergistic effects. Further research is warranted to find novel combination therapy strategies and specific biomarkers for accurate immunotherapy response prediction. Hormonal and immune checkpoints have high potential as novel biomarkers or therapeutic agents in EC.

5. Conclusion

ER expression was significantly associated with BMI ≥ 25, premenopausal status, early-stage disease, <1/2 myometrial invasion, no nodal metastasis, and lack of adjuvant therapy. It was also associated with age <55 years, low-grade cells, and angiolymphatic invasion, but the relationship was not statistically significant. PD-L1 expression was significantly associated with BMI < 25, menopausal status, advanced disease stage, high-grade cell, angiolymphatic invasion, and adjuvant therapy. It was also associated with age ≥ 55 years and lymph node metastasis, but the relationship was not statistically significant.

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Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish the case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions.

Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

This was a retrospective study that used medical record for the data

Table 2
Association of ER and PD-L1 expression with clinicopathological characteristics of type 1 endometrial cancer.

Characteristic	Expression ER		p-value	Expression PD-L1		p-value
	ER negative	ER positive		PD-L1 negative	PD-L1 positive	
Age			0.050			0.067
<55 years	9 (22.0 %)	32 (78.0 %)		12 (29.3 %)	29 (70.7 %)	
≥55 years	18 (40.9 %)	26 (59.1 %)		6 (13.6 %)	38 (86.4 %)	
BMI	3 (50.0 %)	3 (50.0 %)	0.0001			0.0001
Underweight	20 (55.6 %)	16 (44.4 %)		0 (0.0 %)	6 (100 %)	
Normal weight	3 (21.4 %)	11 (78.6 %)		1 (2.8 %)	35 (97.2 %)	
Overweight	1 (4.3 %)	22 (95.7 %)		4 (28.6 %)	10 (71.4 %)	
Obesity class 1	0 (0 %)	6 (100 %)		10 (43.5 %)	13 (56.5 %)	
Obesity class 2				3 (50.0 %)	3 (50.0 %)	
Status menopause			0.034			0.042
Yes	19 (41.3 %)	27 (58.7 %)		6 (13.0 %)	40 (87.0 %)	
No	8 (20.5 %)	31 (79.5 %)		12 (30.8 %)	27 (69.2 %)	
Cancer stage			0.0001			0.0001
Early stage (I and II)	5 (11.1 %)	40 (88.9 %)		18 (40.0 %)	27 (60.0 %)	
Advanced stage (III and IV)	22 (55.0 %)	18 (45 %)		0 (0.0 %)	40 (100 %)	
Myometrial invasion:			0.028			0.0001
<1/2	3 (13.6 %)	19 (86.4 %)		12 (54.5 %)	10 (45.5 %)	
≥1/2	24 (38.1 %)	39 (61.9 %)		6 (9.5 %)	57 (90.5 %)	
Lymph node metastases:			0.0001			0.104
Yes	8 (88.9 %)	1 (11.1 %)		0(0.0 %)	9 (100 %)	
No	19 (25.0 %)	57 (75.0 %)		18 (23.7 %)	58 (76.3 %)	
Cell differentiation (tumor grade):			0.211			0.042
Low grades (I and II)	15 (27.8 %)	39 (72.2 %)		15 (27.8 %)	39 (72.2 %)	
High grades (III and IV)	12 (38.7 %)	19 (61.3 %)		3 (9.7 %)	28 (90.3 %)	
LVSI:			0.129			0.001
Yes	11 (42.3 %)	15 (57.7 %)		0(0.0 %)	26 (100 %)	
No	16 (27.1 %)	43 (72.9 %)		18 (30.5 %)	41 (69.5 %)	
Adjuvant treatment:			0.019			0.0001
Yes	25 (37.9 %)	41 (62.1 %)		5 (7.6 %)	61 (92.4 %)	
No	2 (10.5 %)	17 (89.5 %)		13 (68.4 %)	6 (31.6 %)	

Description: Statistical analysis with Fisher's exact test, with $p < 0.05$ indicating significance.

source.

The ethic of this study approved by the Research Ethics Committee of Dr.Soetomo General Academic Hospital Suabaya, Indonesia.

CRediT authorship contribution statement

Setyo Teguh Waluyo: Conceptualization, Methodology, Writing – original draft. **Brahmana Askandar Tjokroprawiro:** Conceptualization, Writing – review & editing. **Anny Setijo Rahaju:** Methodology, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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