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Clinicopathological Features, Prognostic Impact and Treatment Outcome of EDIL3 and SOX4 Expressions in Endometrial Adenocarcinoma

Hanaa A. Atwa*♦, PhD candidate, Amira Elwan, MD, Nehal S. Abouhashem*, PhD**

**Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt*
***Department of Clinical Oncology, Faculty of Medicine, Zagazig University, Zagazig, Egypt*

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Abstract

Background: Endometrial cancer (EC) is a common gynecological cancer ranks as fifth cancer worldwide and the tenth common cancer in Egypt. Termed DEL-1 (EGF like repeats and discoid domains 3), is an embryonic endothelial cell protein. EDIL3 was associated with regulation of angiogenesis. SOX (sex-determining region Y-related high-mobility-group box transcription factor). SOX4 expression was altered in many human cancers. This research aimed to study the expression of EDIL3, SOX4 in EC in atrial to explore their relationship with clinicopathological parameters prognostic and treatment outcome.

Method: This retrospective study included 50 paraffin blocks of cases of endometrial adenocarcinoma (endometroid type) with different grades which were selected from the archives of the Pathology Department, Zagazig University, Egypt during a period from January 2015 to last of December 2019. The expression of EDIL3, SOX4 was evaluated using immunohistochemistry.

Results: 56% of the studied patients were >45 years old. 54% had well-differentiated adenocarcinoma, and 56% absent lymph node metastasis. EDIL3 and SOX4 expression is found in 70% and 84% of the studied patients. A statistically significant relation was detected between EDIL 3 and tumor grade, stage, lympho-vascular invasion (LVI), and lymph node metastasis (*P* value was 0.001, <0.001, 0.002, and 0.005, respectively). SOX4 was significantly correlated with tumor grade, stage, lymph node metastasis, and LVI (*P* value was 0.039, 0.002, 0.006, and 0.015, respectively).

Conclusion: expressions are associated with advanced clinicopathological parameters, unfavorable prognosis, and poor treatment response.

Keywords: Endometrial neoplasms, Novel markers, Immunohistochemistry, Prognosis

♦Corresponding Author:
Hanaa A. Atwa, PhD candidate
Department of Pathology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Tel: +201111811360
Email: hanaaatwa@yahoo.com

Introduction

Endometrial adenocarcinoma is a common gynecological cancer, ranks as fifth cancer worldwide and the tenth common cancer in Egypt.[1] There are two types of endometrial

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cancer (EC): type I and type II. Type I are estrogen-associated, low-grade (G1 and G2), usually diagnosed early which have good prognosis. Type II are hormone-independent, not associated with estrogen, high-grade (G3) with poor prognosis.[2]

Termed DEL-1 (EGF like repeats and discoid domains 3), is an embryonic endothelial cell protein and composed of three epidermal growth factor (EGF) domains and two discoid I-Like repeats. EDIL3 was associated with regulation of angiogenesis and cell adhesion. It is expressed in many tumor types.[3,4]

EDIL3 participates in endocytosis and programmed cell death.[5,6] It also plays an important role in the alteration of immunocytes' adhesion through interactions with leukocyte-specific integrins.[7]

There are 20 members in the SOX (sex-determining region Y-related high-mobility group box transcription factor) gene family.[8] SOX4; a member of the SOX gene family (group C); a crucial regulator of embryonic thymocyte, cardiac, and nervous system development and osteoblastic lineage differentiation.[9]

SOX4 expression was altered in multiple cancers like breast, hepatocellular carcinoma, and prostate cancer.[10] SOX4 was a regulator of epithelial-mesenchymal transition (EMT) acting by regulating the expression of Ezh2 which is an epigenetic modifier in breast cancer; therefore, SOX4 might be a marker for tumor progression.[11]

To date, the primary treatment for EC is surgery followed by adjuvant radiation therapy and chemotherapy.[12] However, these therapies have not effectively reduced the risk of EC mortality. The recurrence rates of EC are 60%-80%, that usually occur two to three years after surgery.[13]

Treatment modality was associated with decreased risk of relapse or death by 36%. Cancer-specific survival was significantly different and favored using the adjuvant chemotherapy in addition to radiotherapy.[14]

This study aimed to study the expression of EDIL3, SOX4 in EC in a trial to explore their relationship with clinicopathological parameters, the prognosis of patients, and treatment outcomes using immunohistochemistry.

Patients and Methods

This is a retrospective study included 50 paraffin blocks of cases of endometrial adenocarcinoma (endometroid type) with different grades which were selected from the archives of Pathology Department Zagazig University, Egypt during a period from January 2015 to last of

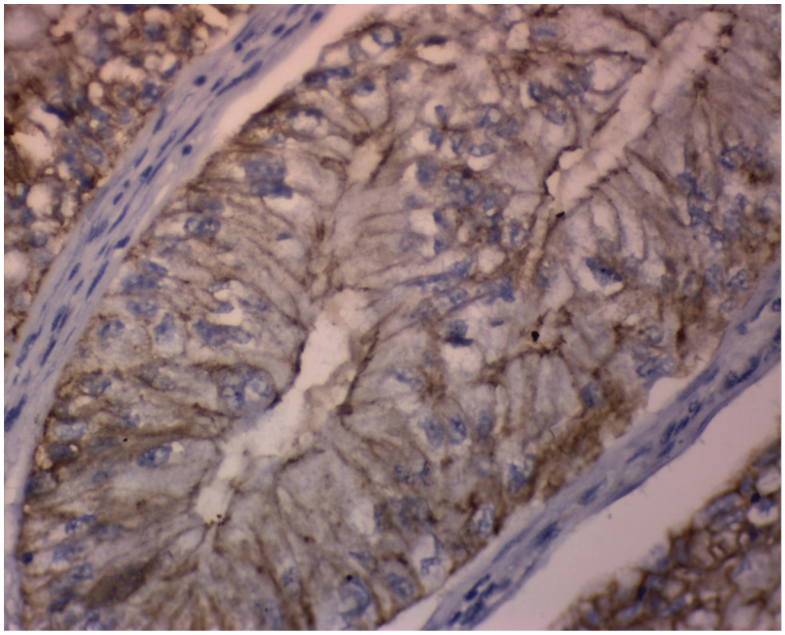

Figure 1. This figure shows a case of well-differentiated endometroid endometrial adenocarcinoma showing the low EDIL3 membranous expression (Immunohistochemistry; IHC ×400).

December 2019. Written concents were taken from all patients and the study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by ethical research committee of Faculty of Medicine, Zagazig University, the IRB code is 9049.

All patients were conducted to Clinical Oncology Department, Zagazig University Hospitals where they underwent regular visits and follow-up by clinical examination and radiological evaluation such as vaginal US, pelvic CT, MRI, etc. The patients underwent a biopsy ± hysteroscopy. Total abdominal hysterectomy, bilateral salpingo-oophrectomy + lymph node assessment were done. The patients stage 1 without risk features underwent observation, the patients were proposed their treatment protocols either, post- operative radiotherapy ± chemotherapy, chemo ± radiation, and palliative chemotherapy or aromatase inhibitor, and palliative irradiation. Carboplatin and paclitaxel used as chemotherapeutic agents.

Immunohistochemical staining

Polyclonal rabbit antibody NBp2-16146, dilution 1/100, Abcam against EDIL3 antibody, and mouse monoclonal antibody Ab243739, dilution 1/100, Abcam anti SOX4 antibody were utilized in the streptavidine-biotin method. Sections from paraffin blocks were treated with an antigen retrieval solution (pH 6.0) before being incubated with EDIL3 and SOX4 monoclonal antibodies. Antibody binding was identified using Dako's Envision kit, which included DAB as a chromogen and hematoxylin as a counterstain.

Table 1. Baseline characteristics of the studied patients

	N=50	%
Age		
≤ 45 year	22	44
>45 year	28	56
Grading		
I	27	54
II	13	26
III	10	20
FIGO Staging		
I	11	22
II	17	34
III	6	12
IV	16	32
Lymph node metastasis		
Negative	28	56
Positive	22	44
LVI		
No	30	60
Yes	20	40
Estrogen intake*		
No	15	30
Yes	35	70
EDIL3		
Negative	15	30
Positive	35	70
SOX4		
Negative	8	16
Positive	42	84
Death		
No	21	42
Yes	29	58
Relapse		
No	26	62
Yes	8	38

(*Estrogen intake e. g contraceptive pills, hormone replacement therapy and Tamoxifen intake); LVI: lympho-vascular invasion, FIGO: The International Federation of Gynecology and Obstetrics

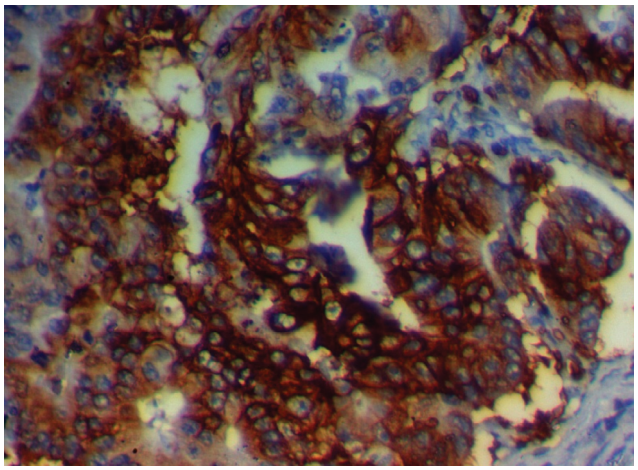

Figure 2. This figure represents a case of moderately-differentiated endometroid endometrial adenocarcinoma showing the EDIL3 high expression (Immunohistochemistry; IHC ×400).

Evaluation of EDIL3 immunostaining

Regarding EDIL3 expression, it was categorized as follows: 0 for negative staining; low for positive expression with 1:10% stained cells; and high expression for more than 10% positive cells.[15]

SOX4 evaluation, the staining intensity was scored 0 for negative expression, 1 for mild, 2 for moderate, and 3 for strong expression. The percentage of positive cells was scored as follows: 0 to 5 %, 0 point; 6 % to 25 %, 1 point; 26 % to 50 %, 2 points; 51 % to 75%, 3 points; and> 75%, 4 points. The overall score was the sum of

Table 2. Relation between, EDIL3, SOX4and both baseline characteristics and the outcome of the studied patients

Parameters	Total N=50	EDIL3 Negative N=35(%)	EDIL3 Positive N=15(%)	*P*	SOX4 Negative N=8 (%)	SOX4 Positive N=42 (%)	*P*
Age							
≤ 45 year	22	3 (13.6)	19 (86.4)	0.025*‡	2 (9.1)	20 (90.9)	0.439‡
>45 year	28	12 (42.9)	16 (57.1)		6 (21.4)	22 (78.6)	
Grading							
I	27	26 (96.3)	1 (3.7)	0.001¥*	7 (28.6)	20 (71.4)	0.039¥*
II	13	9 (69.2)	4 (30.8)		1 (7.7)	12 (92.3)	
III	10	0 (0)	10 (100)		0 (0)	10 (100)	
FIGO Staging							
I	11	8 (72.7)	3 (27.3)	<0.001¥*	5 (45.5)	6 (54.5)	0.002¥*
II	17	5 (29.4)	12 (70.4)		3 (17.6)	14 (82.4)	
III	6	2 (33.3)	4 (66.7)		0 (0)	6 (100)	
IV	16	0 (0)	16 (100)		0 (0)	16 (100)	
LVI							
No	30	26 (86.7)	4 (13.3)	0.002‡*	8 (26.7)	22 (73.3)	0.015‡*
Yes	20	9 (45)	11 (55)		0 (0)	20 (100)	
Lymph node metastasis							
Negative	28	13 (46.4)	15 (53.6)	0.005‡*	8 (28.6)	20 (71.4)	0.006‡*
Positive	22	2 (9.1)	20 (90.9)		0 (0)	22 (100)	
Relapse (n=34)							
No	26	14 (53.8)	12 (46.2)	0.053‡	7 (26.9)	19 (73.1)	0.644‡
Yes	8	1 (12.5)	7 (87.5)		1 (12.5)	7 (87.5)	
Response							
CR	4	3 (75)	1 (25)	0.021*∞	3 (75)	1 (25)	<0.001*∞
PR	7	5 (71.4)	2 (28.6)		5 (71.4)	2 (28.6)	
PD	5	1 (20)	5 (80)		0 (0)	5 (100)	
SD	6	1 (16.7)	5 (83.3)		0 (0)	6 (100)	
Death							
No	29	11 (37.9)	18 (62.1)	0.150‡	5 (17.2)	24 (82.8)	>0.999‡
Yes	21	4 (19.0)	17 (81.0)		3 (14.3)	18 (85.7)	

‡Chi square test *$P < 0.05$ is statistically significant ¥Chi square for trend test; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; LVI: lympho-vascular invasion; FIGO: The International Federation of Gynecology and Obstetrics

the staining intensity and the percentage of positive cells: 0, negative; 2 to 3, weakly positive; 4 to 5, moderate; and 6 to 7, strongly positive.[16]

Statistical analysis

The statistical package for the social sciences (SPSS) version 20 was used to analyze the data. The means and standard deviations of quantitative variables were used to characterize them. The absolute frequencies of categorical variables were used to characterize them, and the chi-square test for trend test were used to compare them. For comparing survival curves in two or more groups, the Kaplan Meier plot and the Mantel Cox test were utilized. The time it took to get to the incident of interest, or the time it took to follow up, was referred to as survival time. If P <0.05, the statistical significance threshold was specified.

Results

Clinicopathological results

56% of the studied patients were >45 years old. 54% had tumor grade I and 56% of patients did not have lymph node metastasis. Regarding staging, 22%, 34%, 12% and 32% of studied cases had stage I, II, III and IV, respectively. EDIL3 and SOX4 expression was found in 70% and 84% of the studied patients (Table1).

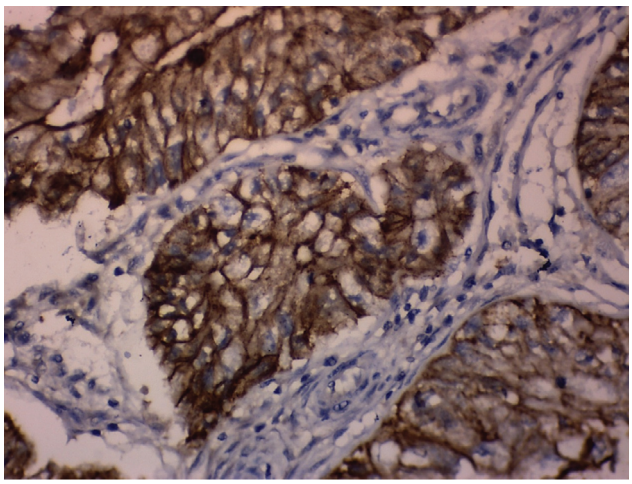

Figure 3. This figure shows a case of poorly-differentiated endometroid endometrial adenocarcinoma showing the EDIL3 high expression (Immunohistochemistry; IHC ×400).

Table 3. Survival time outcome as regarding markers expressions of the studied patients

	Total N	N of Events	Censored		Survival time, Months				*P*
			N	%	Mean		Median		
					Estimate ± SD	95% CI	Estimate ±SD	95% CI	
EDIL3									
Positive	35	17	18	73.3%	42.5 ± 1.68	39.2-45.8	45.0 ± 3.53	38.1-51.9	0.066
Negative	15	4	11	51.4%	47.26 ± 2.4	42.6-522.0			
SOX4									
Positive	42	18	24	57.1%	42.9 ± 1.6	39.9-46.0	49.0		0.294
Negative	8	3	5	62.5%	49.1 ± 1.0	47.2-51.1	50.0 ± 3.62	42.9-57.1	
Overall	50	21	29	58%	44.0 ± 1.4	41.3-46.7	50.0		

P for log rank test; SD: Standard deviation; CI: Confidence interval

Immunohistochemical results (Table2)

There is statistically significant relation between EDIL 3 and all of patient age, tumor grade, stage, lymphovascular invasion (LVI) and lymph node metastasis *P*-value was 0.025, 0.001, <0.001, 0.002, and 0.005, respectively) (Figures 1-3).

SOX4 was significantly correlated with tumor grade, stage, lymph node metastasis and LVI (*P*-value was 0.039, 0.002, 0.006, and 0.015) (Figures 4 and 5).

Treatment outcome and survival analysis

Regarding treatment outcome, studied patients had shown statistically significant relation between EDIL3, SOX4 expressions, and treatment response with $P = 0.021$ and ≤ 0.001, respectively. Considering disease-free survival (DFS), EDIL3 (Mean 5year DFS in EDIL3 negative expression was 47.2 ± 2.7 months versus 37.7 ± 3.9 months in those with EDIL3 positive, $P = 0.048$) with a significant difference. Non-significant relation was observed between DFS and SOX4 (Mean 5-year DFS in SOX4 negative was 47.6 ± 1.3 months versus 40 ± 3.3 months in those with SOX4 positive, $P = 0.359$), data not tabulated.

We reported non-significant relation between overall survival (OS) and SOX4 (Mean 5-year OS in SOX4 negative was 49.1 ± 1 months versus 42.9 ± 1.6 months in those with SOX4 positive, $P = 0.290$) and EDIL3 (Mean 5-year OS in EDIL3 negative was 47.26 ± 2.4 months versus 42.5 ± 1.6 months in those with EDIL3 positive, $P = 0.066$ (Table 3, Figures 6 and 7).

Discussion

We found that 56% of the studied patients were >45 years old. 54% had tumor grade I and 56% of the patients did not have lymph node metastasis. Regarding staging, 22%, 34%, 12%, and 32% of studied cases had stage I, II, III, and IV, respectively. EDIL3 and SOX4 expression was found in 70% and 84% of the studied patients.

EDIL3 expression was found in 70% of our cases. High EDIL3 expression was observed to be associated with higher tumor grade, stage, LVI, and lymph node metastasis (*P* values <0.001, 0.002, and 0.005, respectively). The findings were comparable to those of Lopes-Bastos.[17] EDIL3 is described as an extracellular matrix protein, interacts and adjust the tumor microenvironment via the management of angiogenic pathways.[18]

Xia et al.[19] reported that EDIL3 activates TGF-β and ERK pathways via the effect of EDIL3 on the TGF-β signaling pathway and EMT. Reduced expression of EDIL3 was associated with decreased α-actin, vimentin level, SMAD2 and SMAD3 phosphorylation and enhancement of

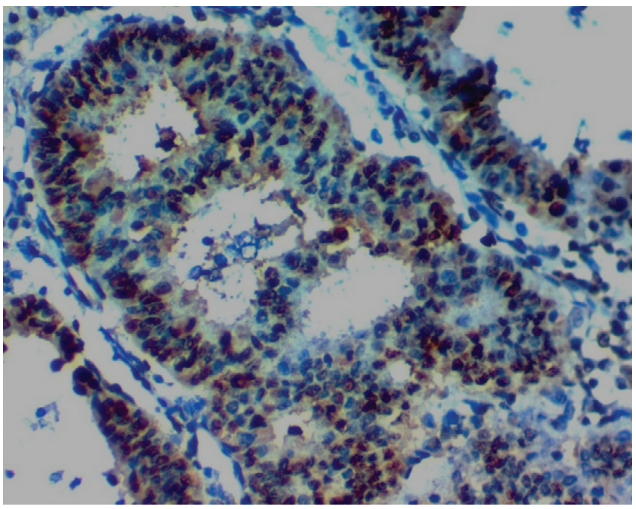

Figure 4. This figure shows a case of well-differentiated endometroid endometrial adenocarcinoma showing the moderate SOX4 nuclear expression (Immunohistochemistry; IHC ×400).

extracellular signal-regulated kinase (ERK).

EMT is a process wherein differentiated epithelial cells acquire a mesenchymal phenotype characterized by the loss of cell-cell connections and cellular polarity. The mesenchymal phenotype is involved in metastasis, increased resistance to apoptosis and increase production of extracellular matrix components.[20] EDIL3 overexpression lead to tumorigenesis by decreasing apoptosis in cancer cells and enhancing cancer vascularization.[4]

It was reported that knockdown of EDIL3 by shRNA-containing plasmids promotes anoikis; specific form of apoptosis; inhibits tumor growth in a pancreatic ductal adenocarcinoma cell line.[3]

Jiang et al.[21] found that EDIL3 expression is associated with hepatocellular carcinoma invasion, and they indicated that this is due to tumor angiogenesis and EMT, as well as interactions between cancer cells and endothelial cells.[22] Their finding was explained by Lee et al.[23] who reported that ERK signaling pathway can reduce EDIL3-mediated angiogenesis and invasion in a hepatocellular carcinoma mouse model via the activation of TGF-β by interacting with αvβ3 integrin.

Regarding the DFS in the present study, EDIL3 was associated with poor prognosis with 5-year DFS in EDIL3 negative was 47.2 ± 2.7 months versus 37.7 ± 3.9 months in those with EDIL3 positive, (P = 0.048) with significant difference; similar results were reported by Lee et al.[24] who found EDIL3 expression is associated with poor prognosis in breast cancer, they explained these results by the effect of EDIL3 on the balance between pro- and anti-apoptotic proteins.

The relationship between OS and EDIL3 was found to be non-significant. In lung cancer; however, Jeong et al.[25] found that EDIL3 is an independent predictor of OS. By examining EMT markers (E-cadherin, -catenin, vimentin, and CD31), they discovered a link between EDIL3 and the mesenchymal phenotype of tumor cells. SOX4 in 84% of EC tissues was significantly higher in tumor cells, these results are consistent Liao and Lin[26] who found SOX4 expression in 76.5% of their studied cases. The present study showed that high SOX4 expression is correlated with tumor differentiation, advanced FIGO stage and lymph node metastasis. Our results were close to those reported by previous studies.[9, 26, 27, 28] Previous studies reported that SOX4 can act as an oncogene and is involved in tumor invasion, metastasis and recurrence. Andersen et al.[29] reported that SOX4 associated with higher recurrence rate in colorectal cancer patients.

The overexpression of SOX4 acts on transforming growth factor-beta (TGF-β)-induced EMT and enhancer of zeste homolog 2 (EzH2)-mediated H3K27me3, so can modulate EMT in breast and esophageal cancers.[30]

The current study showed non-significant relation between both DFS, OS, and SOX4 expression.

Positive SOX4, EDIL 3 expression was related with poor treatment response to chemotherapy and radiation with significant differences. In a comparison of patients with positive expressions of SOX4, EDIL 3 to negative expressions of SOX4, EDIL 3, we found high mortality, higher recurrence rates, and poor 5-year DFS and OS in patients with positive expressions of SOX4, EDIL 3 without significance except for DFS of EDIL 3. This was due to the small sample size. We agreed with Vervoort et al.[31] who reported that SOX4 expression increases with the advancement of clinical stage and associated with poor

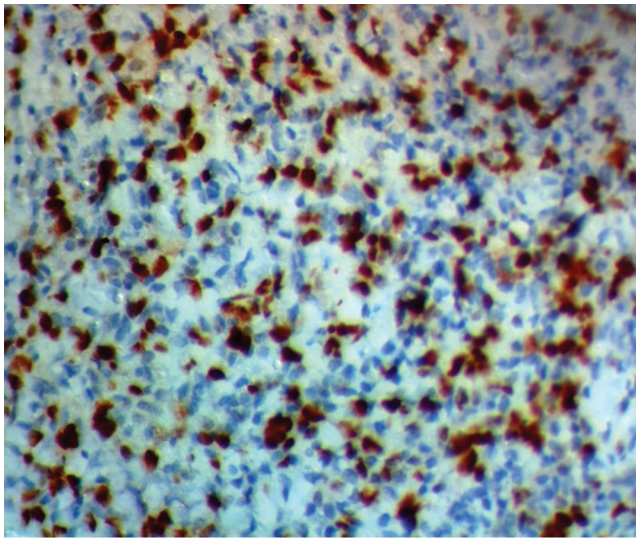

Figure 5. This figure shows a case of poorly-differentiated endometroid endometrial adenocarcinoma showing the strong SOX4 nuclear expression (Immunohistochemistry; IHC ×100).

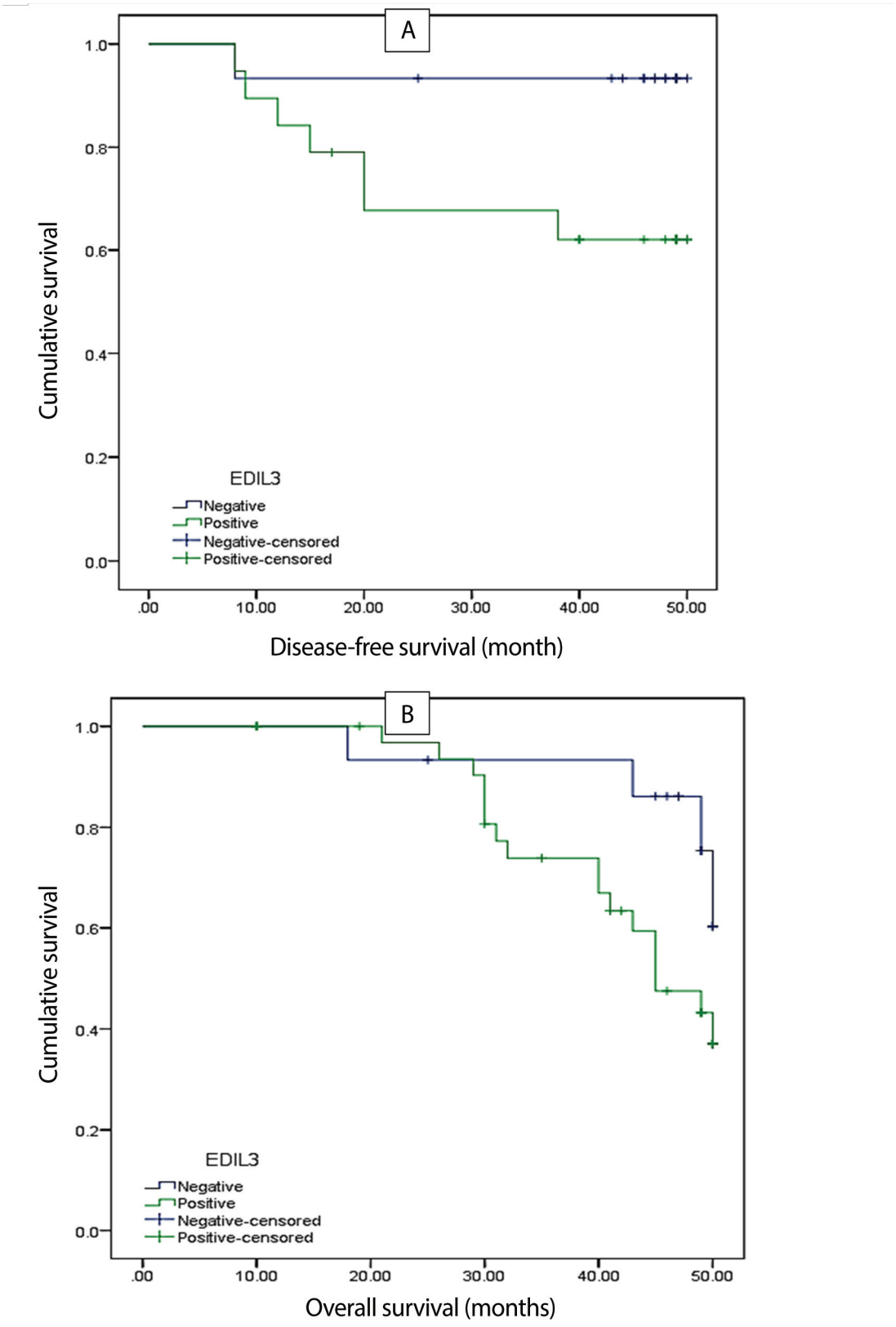

Figure 6. (A): Kaplan Meier plot showing the significant relation between EDIL3 expression and disease- free survival (Mean survival in EDIL3 negative expression was 47.2 ± 2.7 months versus 37.7 ± 3.9 months in those with EDIL3 positive). (B): Kaplan Meier plot showing significant relation between EDIL3 expression and overall survival (Mean overall survival in EDIL3 negative was 47.26 ± 2.4 months versus 42.5 ± 1.6 months in those with EDIL3 positive).

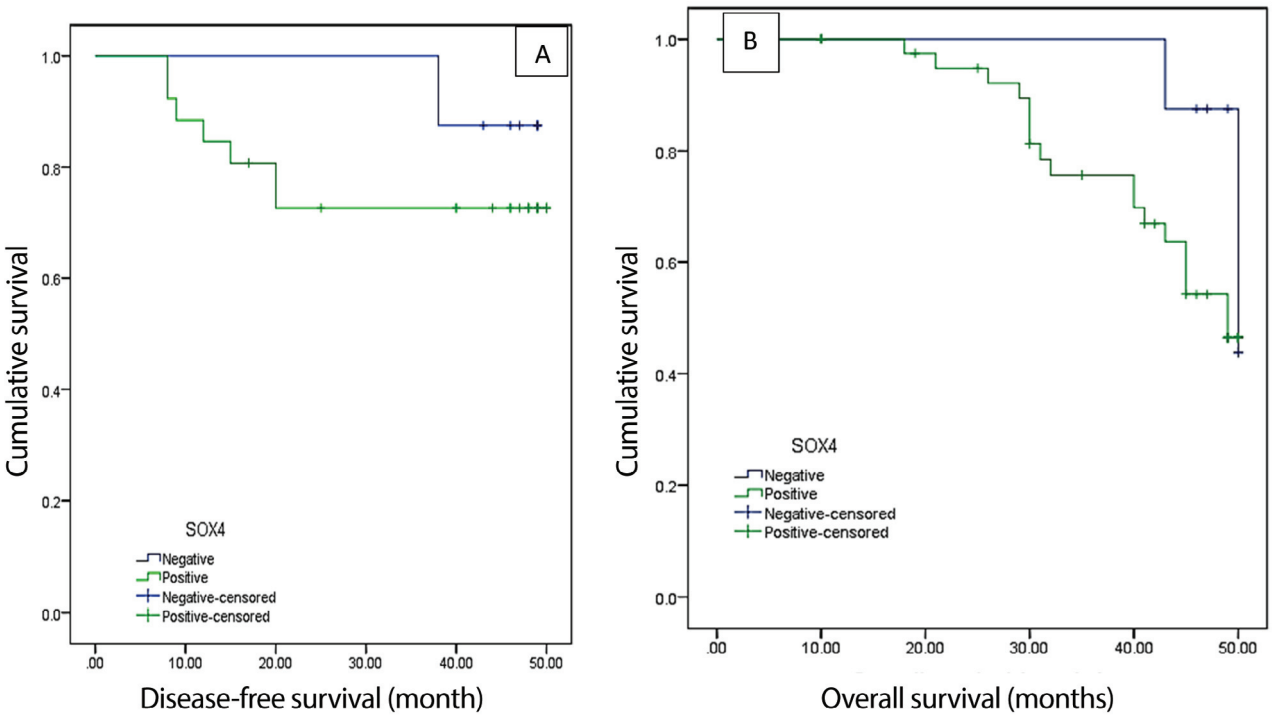

Figure 7. (A): Kaplan Meier plot showing the relation between SOX4 expression and disease- free survival (Mean disease-free survival) in SOX4 negative was 47.6 ± 1.3 months versus 40 ± 3.3 months in those with SOX4 positive). (B): Kaplan Meier plot showing relation between SOX4 expression and overall survival (Mean overall survival in SOX4 negative was 49.1 ± 1 months versus 42.9 ± 1.6 months in those with SOX4 positive).

prognosis of patients.

EC is common gynecological malignancy and its incidence is increasing last years in Egypt by increasing mortality rates. Up to our Knowledge, a statistical analysis involving the expression of EDIL3 and SOX4 in EC was not carried out in the literature. Few researches were done to evaluate their role affecting prognosis and outcome of endometrial cancer.

The study has some limitation due to small number of cases and has to be supported using gene study.

Conclusion

EDIL3 and SOX4 expressions are associated with advanced clinicopathological parameters, unfavorable prognosis, and poor treatment response in endometrial adenocarcinoma.

Conflict of Interest

None declared.

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