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Research Article

Sex-determining region y (SRY)-Box2 (SOX2) & L1-cell adhesion molecule (L1CAM) expressions in endometrioid carcinoma of the uterus; An Immunohistochemical Study

Abstract

Background: activation of cancer stem cells and disturbances in cell adhesion pathways are recently incriminated in endometrioid carcinoma progression, invasion and metastases which consequently leads to dismal patients outcome. Sex-determining region y (SRY)-Box2 (SOX2) is a member of SOX family and it has many roles in malignant stem cells control. L1-cell adhesion molecule (L1CAM) is a membrane glycoprotein which is a member of immunoglobulin family.

The aim of the work: is to evaluate prognostic, clinical and pathological values of Sox2& L1CAM expression in tissues of endometrioid carcinoma of the uterus.

Patients and methods: Sox2& L1CAM tissue protein expression was assessed by immunohistochemistry in sections from sixty paraffin blocks which are retrieved from 60 patients with endometrioid carcinoma of the uterus then correlations between their levels of expression, clinical, pathological data, progression and recurrence of the tumor and patients outcome were analyzed..

Results: SOX-2 expression in endometrioid carcinoma was associated with old age of the patient ($p=0.003$), larger tumor size($p=0.004$), higher grade, advanced stage, presence of L.N and distant metastases ($p<0.001$), presence of myometrial invasion, cervical stromal invasion ($p=0.006$), lymphovascular ($p=0.02$) & parametrial ($p=0.007$), serosal ($p=0.03$), and adnexal invasions ($p=0.008$), shorter 5-year overall survival rate ($p=0.003$), and shorter 5-year disease free survival rate ($p=0.005$).

L1CAM expression in endometrioid carcinoma was associated with larger tumor size ($p=0.017$), higher grade ($p=0.043$), advanced stage($p=0.031$), presence of L.N ($p=0.033$), and distant metastases($p=0.049$), presence of myometrial invasion ($p=0.027$), cervical stromal invasion ($p=0.026$), lymphovascular ($p=0.02$) & parametrial ($p=0.012$), serosal ($p=0.042$), and adnexal invasions ($p=0.034$), shorter 5-year overall survival rate ($p=0.002$), and shorter 5-year disease free survival rate ($p=0.006$). We found a positive relationship between SOX-2 and L1CAM (r (Correlation Coefficient) = $+0.735$ ($P<0.001$)).

Conclusion: Sox-2& L1CAM expression correlates with poor clinicopathological parameters of endometrioid carcinoma

Introduction

Malignant epithelial tumor which originated from the endometrium is named as endometrial carcinoma (EC) and it forms about 20–30% of cancer of the female gynecological malignancies. Due to high incidence of hypertension, obesity, diabetes and increased life span; EC incidence and fatality has been markedly increased [1]. Moreover, endometrial carcinoma is still ranking the commonest gynecologic malignancy

in developed countries and the second commonest in the developing countries, while, cancer cervix is still the first [2]. The majority of endometrial carcinomas are classified as type I endometrioid endometrial carcinoma and type II non-endometrioid endometrial carcinoma [3]. Endometrioid carcinoma is the commonest subtype of endometrial carcinoma [4]. Recently the role of stem cells, especially cancer stem cells has gained attention to be responsible for progression, invasion and spread of several malignancies [5,6]. Genetic

mutations which could derive cancer occurrence happen over years, and only cancer stem cells which were found to have long life span is incriminated to accumulate the genetic mutations that are sufficient to initiate cancer and leads to malignant progression. So, cancer stem cells are responsible for invasion, carcinogenesis and spread of cancer cells in different organs [5]. Data about role of cancer stem cells in malignant progression have directed researchers to detect novel targeted therapies against these cells, which lead to improvement therapeutic response and patients' outcome, there are so many biomarkers that are responsible for identification of cancer stem cells, studying and targeted them is the recent hope for improving cancer management [7]. Sex-determining-region-y (SRY)-Box2 (SOX-2) is a member of SOX family of transcription factors which plays an essential role in controlling cancer stem cell properties [8,9]. The disturbances in adhesion of malignant epithelial cells are responsible for invasion and spread of those cells so studying the detailed role of adhesion molecules in cancer helps to detect its pathogenesis and detection of new therapeutic targets that decreased invasion and metastases. L1-cell adhesion molecule (L1CAM) is considered a membrane glycoprotein which is an immunoglobulin superfamily member and it is involved in neurogenesis processes [10]. In addition, to its physiological role it plays an essential role in progression of many tumors [11].

The aim of the work; is to evaluate prognostic, clinical and pathological values of Sox2& L1CAM expression in tissues of endometrioid carcinoma of the uterus.

Patients and Methods

We have performed the current study on a cohort of sixty patients of endometrioid carcinoma that were surgically managed in Gynecology and Obstetrics Department Faculty of Medicine Zagazig University and the specimen sent to Pathology Department Faculty of Medicine Zagazig University where we have prepared 60 paraffin block of endometrioid carcinoma in the period from May 2013 to May 2018. All data were collected from patients file and completed by examinations of all slides. To stage and grade all cases we have used international-federation of gynecology and obstetrics' (FIGO) staging system [12]. We have evaluated SOX-2 and L1CAM expressions using immunohistochemistry in sections prepared from all the 60 paraffin blocks correlate their expression with clinic-pathological parameters and follow-up data. We have followed up patients for 5 years, follow up and survival data were collected from Oncology Departments, Faculty of medicine, Zagazig University. Follow up dead line was May 2018. Adjuvant radio-therapy with or without platinum-based chemotherapy was given according to surgical staging.

Immunohistochemical staining

We used Streptavidine-biotin technique for immunohistochemical staining [13]. Sections were incubated overnight with primary anti-mouse monoclonal antibodies; anti-SOX2 antibody (ab171380) & Anti-L1CAM antibody [2C2] (ab24345) (abcam, UK). We used section from human lung squamous carcinoma tissue and nervous system tissue as an external positive control for SOX-2& L1CAM respectively.

Evaluation of immunohistochemical expression of SOX-2& L1CAM:

Nuclear expression was considered positive for SOX-2, while cytoplasmic and membranous expression was considered positive for L1CAM.

To score all the slides adequately and to reach a suitable final stain score we have combined scores of intensity and extent of the stain by multiplying both of them after examination of most fields of the tumor cells. The intensity was scored as followed (0, negative stain expression; 1, weak stain expression; 2, moderate stain expression and 3, strong stain expression and the extent was scored as followed (0 if stain expression in less than 1% of cancer cells; 1 if stain expression in 1-10% of tumor cells; 2 if stain expression in 10-25% of tumor cells; 3 if stain expression in 25-50% of tumor cells and 4 if stain expression in > 50% of tumor cells. Final immunoreactivity scores which resulted from multiplication of both intensity of stain and extent of stain scores ranged from 0-12, we have considered the value of 4 as a cutoff value above which is high expression and below which is low expression for adequate statistical analysis [14,15].

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version. Data were tested for normal distribution using the Shapiro Walk test.

Chi square and Fisher exact tests have been used to calculate differences among qualitative variables. P-value \leq 0.05 indicates significant, $p < 0.001$ indicates highly significant difference.

Spearman's Rho Rank correlation test was used for correlating variables.

Survival analysis: Kaplan & Meier method has been used to estimate overall and disease free survival rates. Overall survival (OS) rate: was calculated as the time between the date of cancer diagnosis to death and last seen alive date.

Results

Patient clinical and pathological results

Clinical and pathological features of the included sixty patients with endometrioid carcinoma are detailed in table 1.

Immunohistochemical results

SOX-2 expression and association with clinical, pathological and follow-up findings tables 2,3, Figures 1,3,4

SOX-2 was overexpressed in 29 out of 60 (58%) cases of endometrioid carcinoma and it was associated with old age of the patient ($p=0.003$), larger tumor size($p=0.004$), higher grade, advanced stage, presence of L.N and distant metastases ($p<0.001$), presence of myometrium invasion, cervical stromal invasion ($p=0.006$), lymphovascular ($p=0.02$)& parametrial ($p=0.007$), serosa ($p=0.03$), adnexal invasions ($p=0.008$),

shorter 5-year overall survival rate ($p=0.003$), and shorter 5-year disease free survival rate ($p=0.005$).

L1CAM expression and association with clinical, pathological and follow-up findings tables 2,4, Figures 2-4

L1CAM was overexpressed in 32 out of 60 (68%) cases of endometrioid carcinoma and it was associated with larger tumor size ($p=0.017$), higher grade ($p=0.043$), advanced stage ($p=0.031$), presence of L.N ($p=0.033$), and distant metastases ($p=0.049$), presence of myometrium invasion ($p=0.027$), cervical stromal invasion ($p=0.026$), lymphovascular ($p=0.02$) & parametrial ($p=0.012$), serosa ($p=0.042$), adnexal invasions ($p=0.034$), shorter 5-year overall survival rate ($p=0.002$), and shorter 5-year disease free survival rate ($p=0.006$). There are no significant relations between L1CAM expression and age of the patient.

Table 1: The clinicopathological features of patients with endometrioid carcinoma

Clinicopathological feature	No. (%)
Age group	<55y 39 (65.0%)
	>55y 21 (35.0%)
Grade	1 19 (31.7%)
	2 24 (40.0%)
	3 17 (28.3%)
Size	<4cm 19 (31.7%)
	>4cm 41 (68.3%)
Extent of myometrial invasion	<50% 19 (31.7%)
	>50% 41 (68.3%)
LVSI	Absent 35 (58.3%)
	Present 25 (41.7%)
Cervical stromal invasion	Absent 27 (45.0%)
	Present 33 (55.0%)
Parametrial extension	Absent 36 (60.0%)
	Present 24 (40.0%)
Serosal invasion	Absent 38 (63.3%)
	Present 22 (36.7%)
Adnexal invasion	Absent 40 (66.7%)
	Present 20 (33.3%)
Lymph node	Negative 35 (58.3%)
	Positive 25 (41.7%)
Distant metastasis	Negative 44 (73.3%)
	Positive 16 (26.7%)
FIGO stage	IA 15 (25.0%)
	IB 6 (10.0%)
	IC 3 (5.0%)
	IIA 7 (11.7%)
	IIB 5 (8.3%)
	IIIA 2 (3.3%)
	IIIB 2 (3.3%)
	IIIC 4 (6.7%)
	IV 16 (26.7%)
Stage	Stage I 24 (40.0%)
	Stage II 12 (20.0%)
	Stage III 8 (13.3%)
	Stage IV 16 (26.7%)

Table 2: SOX-2 & L1CAM expressions in patients with endometrioid carcinoma.

Markers	No. (%)
SOX-2	Low 31 (53.3%)
	High 29 (46.7%)
L1CAM	Low 28 (48.0%)
	High 32 (52.0%)

Table 3: Association of clinicopathological features and SOX-2 expression in patients with endometrioid carcinoma.

		SOX-2		p
		Low	High	
		N=31	N=29	
Age group	<55y	26 (86.7%)	13 (43.3%)	0.003
	>55y	4 (13.3%)	17 (56.7%)	
Grade	Grade 1	15 (50.0%)	4 (13.3%)	<0.001
	Grade 2	13 (43.3%)	11 (36.7%)	
	Grade 3	2 (6.7%)	15 (50.0%)	
Size	<4cm	15 (50.0%)	4 (13.3%)	0.004
	>4cm	15 (50.0%)	26 (86.7%)	
Extent of myometrial invasion	<50%	15 (50.0%)	4 (13.3%)	0.006
	>50%	15 (50.0%)	26 (86.7%)	
LVSI	Absent	26 (86.7%)	9 (30.0%)	0.02
	Present	4 (13.3%)	21 (70.0%)	
Cervical stromal invasion	Absent	20 (66.7%)	7 (23.3%)	0.006
	Present	10 (33.3%)	23 (76.7%)	
Parametrial extension	Absent	27 (90.0%)	9 (30.0%)	0.007
	Present	3 (10.0%)	21 (70.0%)	
Serosal invasion	Absent	26 (86.7%)	12 (40.0%)	0.03
	Present	4 (13.3%)	18 (60.0%)	
Adnexal invasion	Absent	27 (90.0%)	13 (43.3%)	0.008
	Present	3 (10.0%)	17 (56.7%)	
Lymph node	Negative	26 (86.7%)	9 (30.0%)	0.009
	Positive	4 (13.3%)	21 (70.0%)	
Distant metastasis	Negative	28 (93.3%)	16 (53.3%)	0.01
	Positive	2 (6.7%)	14 (46.7%)	
FIGO stage	IA	12 (40.0%)	3 (10.0%)	0.002
	IB	4 (13.3%)	2 (6.7%)	
	IC	3 (10.0%)	0 (0.0%)	
	IIA	5 (16.7%)	2 (6.7%)	
	IIB	3 (10.0%)	2 (6.7%)	
	IIIA	1 (3.3%)	1 (3.3%)	
	IIIB	0 (0.0%)	2 (6.7%)	
	IIIC	0 (0.0%)	4 (13.3%)	
	IV	2 (6.7%)	14 (46.7%)	
Stage	Stage I	19 (63.3%)	5 (16.7%)	<0.001
	Stage II	8 (26.7%)	4 (13.3%)	
	Stage III	1 (3.3%)	7 (23.3%)	
	Stage IV	2 (6.7%)	14 (46.7%)	
	CTh	1 (3.3%)	12 (40.0%)	
L1CAM	Low	27 (90.0%)	5 (16.7%)	<0.001
	High	3 (10.0%)	25 (83.3%)	

We found a direct relationship between SOX-2 and L1CAM expression in endometrioid carcinoma tissues; r (Correlation Coefficient) = +0.735 ($P<0.001$).

Discussion

The novel roles of SOX-2 as a transcription factor and stem cell marker are previously described to have many roles in cancer progression and metastasis in cancers of many organs [17]. More over increased SOX-2 expression is related to unfavorable clinco-pathological criteria and poorer outcomes of cancer patients [16-19]. There are still conflicting results regarding its role in progression and stem cells activation in endometrioid carcinoma of the uterus.

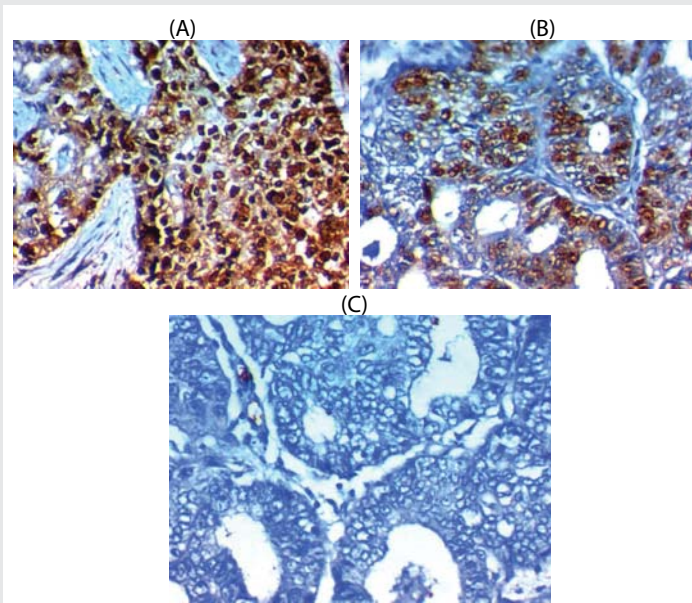


Figure 1: SOX-2 expression in endometrioid carcinoma of the uterus: (A) High expression in the nucleus of endometrioid carcinoma grade III and Stage IV x 400; (B) High expression in the nucleus of endometrioid carcinoma grade II Stage IV x 400 (C) Low expression in the nucleus of endometrioid carcinoma grade I and stage Ix400.

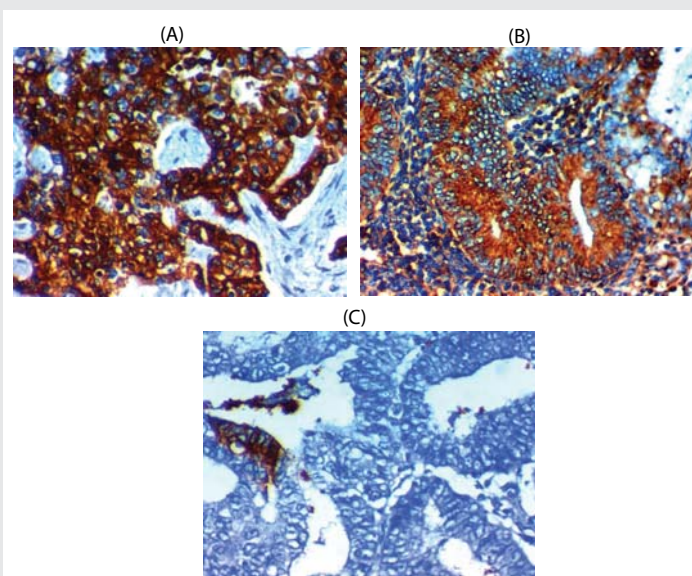


Figure 2: Immunohistochemical staining of L1CAM in endometrioid carcinoma : (A) High expression in the cytoplasm of endometrioid carcinoma grade III and Stage IV x 400 (B) High expression in the cytoplasm of endometrioid carcinoma grade II and Stage IV x 400 (C) Low expression in the cytoplasm of endometrioid carcinoma grade and stage Ix400.

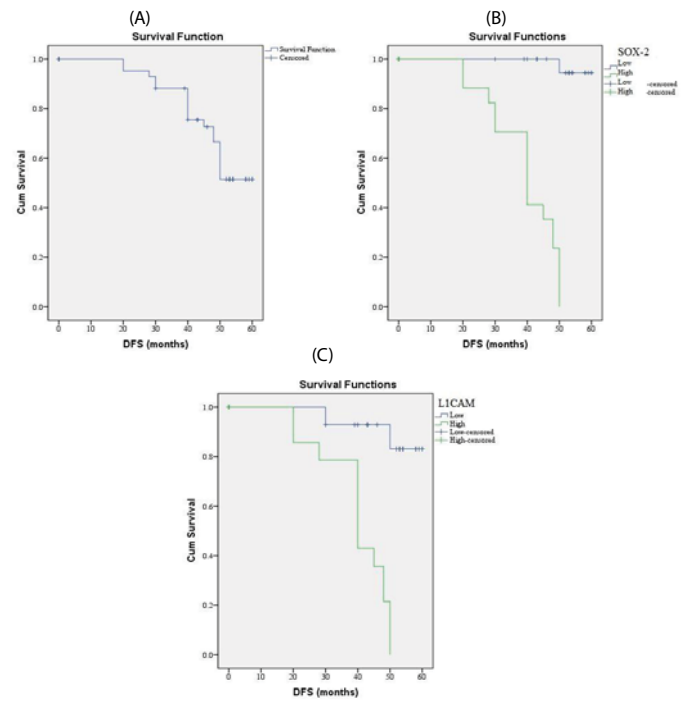


Figure 3: 5-year Disease-Free survival (DFS) Rate. A, DFS rate of all cases, B, DFS rate stratified according to SOX-2 expression in the studied cases C; DFS rate stratified according to L1CAM expression in the studied cases.

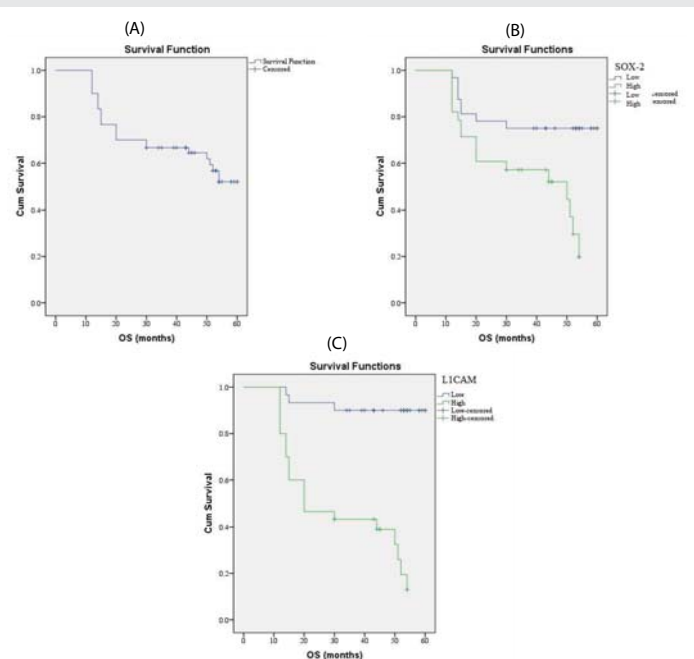


Figure 4: 5-year Overall survival (OS) Rate. A, OS rate of all cases, B, OS rate stratified according to SOX-2 expression in the studied cases C; OS rate stratified according to L1CAM expression in the studied cases.

In this study, we found that high expression of SOX2 was positively correlated with unfavorable clinco-pathological criteria and poorer outcomes of cancer patients e.g. older age of the patient, higher grade, increased size, advanced stage of the tumor, presence of lymphatic and blood metastases, myometrial, lymphovascular, serosal, cervical and adnexal invasions. These results are similar to results of Pityński et al., who found a similar association between increased Sox-2 expression higher

grade of endometrial carcinoma but they found no association between such expression and stage or presence of metastases as they performed their research on early stage endometrial carcinoma only [14], so a point of strength in our study is that we included all stages of endometrial carcinoma to detect association between its expression and stage of the tumor in our study, similarly, Yang et al., demonstrated that SOX-2 overexpression is related to higher grade, advanced stage and presence of lymph node metastases in patients with small cell lung cancer [20]. More over Neumann et al., proved that SOX2 expression was positively associated with higher incidence of nodal and distant metastasis in right-sided colon cancer [21].

Table 4: Association of clinicopathological feature and L1CAM expression in patients with endometrioid carcinoma.

		L1CAM		p
		Low	High	
		N=28	N=32	
Age group	<55y	23 (71.9%)	16 (57.1%)	0.233
	>55y	9 (28.1%)	12 (42.9%)	
Grade	Grade 1	13 (40.6%)	6 (21.4%)	0.043
	Grade 2	14 (43.8%)	10 (35.7%)	
	Grade 3	5 (15.6%)	12 (42.9%)	
Size	<4cm	13 (40.6%)	6 (21.4%)	0.017
	>4cm	19 (59.4%)	22 (78.6%)	
Extent of myometrial invasion	<50%	13 (40.6%)	6 (21.4%)	0.027
	>50%	19 (59.4%)	22 (78.6%)	
LVSI	Absent	23 (71.9%)	12 (42.9%)	0.012
	Present	9 (28.1%)	16 (57.1%)	
Cervical stromal invasion	Absent	19 (59.4%)	8 (28.6%)	0.026
	Present	13 (40.6%)	20 (71.4%)	
Parametrial extension	Absent	24 (75.0%)	12 (42.9%)	0.031
	Present	8 (25.0%)	16 (57.1%)	
Serosal invasion	Absent	24 (75.0%)	14 (50.0%)	0.042
	Present	8 (25.0%)	14 (50.0%)	
Adnexal invasion	Absent	25 (78.1%)	15 (53.6%)	0.034
	Present	7 (21.9%)	13 (46.4%)	
Lymph node	Negative	23 (71.9%)	12 (42.9%)	0.033
	Positive	9 (28.1%)	16 (57.1%)	
Distant metastasis	Negative	27 (84.4%)	17 (60.7%)	0.049
	Positive	5 (15.6%)	11 (39.3%)	
FIGO stage	IA	11 (34.4%)	4 (14.3%)	0.03
	IB	3 (9.4%)	3 (10.7%)	
	IC	3 (9.4%)	0 (0.0%)	
	IIA	4 (12.5%)	3 (10.7%)	
	IIB	3 (9.4%)	2 (7.1%)	
	IIIA	1 (3.1%)	1 (3.6%)	
	IIIB	0 (0.0%)	2 (7.1%)	
	IIIC	2 (6.3%)	2 (7.1%)	
Stage	Stage I	17 (53.1%)	7 (25.0%)	0.031
	Stage II	7 (21.9%)	5 (17.9%)	
	Stage III	3 (9.4%)	5 (17.9%)	
	Stage IV	5 (15.6%)	11 (39.3%)	
SOX-2	Low	27 (90.0%)	5 (16.7%)	<0.001
	High	3 (10.0%)	25 (83.3%)	

Table 5: Univariate analysis of overall and Disease-Free Survival in relation to SOX-2 & L1CAM expression in patients with endometrioid carcinoma.

Variables		5-year overall survival Rate (%)	p-value	5-year Disease Free survival Rate (%)	p-value
SOX-2	Low	90%	0.003	83.1%	0.005
	High	13%		0.0%	
L1CAM	Low	75%	0.002	94.4%	0.006
	High	19.8%		0.0%	

P value< 0.05 is significant.

Ruan et al., have proved results that are similar to ours that increased SOX-2 expression in bladder cancer was positively correlated with increased cancer size and grade [17]. Regarding the association of SOX-2 expression and higher grade of endometrioid carcinoma there are many previous studies which have proved the same association in cancer cervix, breast, colon and lung and these studied explained their results by association of SOX-2 with cancer stem cells in many cancers [14,17].

All these results in addition to ours, clarified the essential role of SOX-2 in the carcinogenesis process which controls cancer cell proliferation potential.

We have proved that increased Sox 2 expression in endometrial carcinoma was related to older age of the patient which was slightly different from results of Wilbertz T et al. that showed increased SOX2 expression is associated with younger patient age in squamous cell lung cancer [22]. Yang et al., have proved that that increased Sox2 expression is a predictive biomarker in gastric cancer with earlier stage (Stages I & II), but they have not find that similar association with advanced stages (Stages III & IV) [23], but in the current study we have its prognostic roles in advanced and early stages of EMC. There are many explanations for the prognostic and predictive role of Sox-2 expression; SOX-2 is considered a transcription factor which has many roles in oncogenesis and cancer biology [24,25]. Due to different results regarding the prognostic roles of SOX-2, it was proved that it may have oncogenic or onco-suppressor roles according to type of cancer, Otsubo et al., explained the tumor suppressor role of SOX-2 by that it could inhibit of cell growth by inhibition of cyclin D1 and regulation of phosphorylated Rb [26]. SOX-2 might also activate PTEN directly [27]. Additionally, Sox2 could inhibit spread of cancer cells by increasing the expression of p21 [28].

The tumor initiating and oncogenic role of Sox2 was found in gastric cancer cells and blocking such role reduced invasion and metastases of gastric cancer cell [29], such oncogenic role is explained by that the aberrant expression of stem cell transcription factor; SOX-2 could impair the malignant stem cell like phenotype [30]. The cancer stem cells (CSCs) hypothesis affects the cancer management as so many novel targeted therapies depend on identification of CSCs specific bio-markers and that targeting these markers may be used as novel therapies in addition to the currently used therapies, to strengthen our findings we have assessed another adhesion biomarker which is L1CAM in endometrial carcinoma tissues and correlate it with the CSC marker SOX-2 to detect the

possibility of using them as recent therapies for such type of cancer. We have found that there is increased the expression of L1CAM in endometrial carcinoma tissues and its expression was associated with poor tumor differentiation, metastatic disease in addition to association with poor response to therapy and unfavorable survival rates which clarified the poor prognostic effect of such biomarker and our results were similar to those of Kommos et al., who have assessed the prognostic role of L1CAM expression in patients with endometroid carcinoma and find a similar association between L1CAM expression and poor prognostic parameters and higher risk group which proved that L1CAM allow better risk stratification of patients [31]. Results of the current study is similar to results of previous studies Smogeli et al. that have reported that increased L1CAM expression in endometrial carcinoma is related to unfavorable outcome [32]. and other poor prognostic parameters e.g. non-endometrioid histopathology, LVSI and high grade of the tumor and also our results are similar to results of many previous studies about the prognostic role of L1CAM expression in cancer [33–35], similarly Zeimet et al. proved that L1CAM is a marker of cancer prognosis and increased its expression has been associate with a poor outcome of patients with endometroid carcinoma [35]. Moreover, our results regarding the association of L1CAM expression and unfavorable prognosis in endometroid carcinoma was similar to results of previous studies [37,38]. Endometroid carcinoma is usually a diseases of favorable prognosis and previous studies found that the cause of poor prognosis of certain cases of endometroid carcinoma is the presence of non-endometroid foci in them Geels et al., which was in line with our results that we have found positive association between L1CAM expression and presence of non-endometroid foci in endometroid carcinoma [34]. In the current study we have proved that high L1CAM expression was associated with dismal 5-year survival rates and with recurrent tumor after successive therapy that was also similar to Geels et al. [34].

Similarly, Sagae et al., have detect the association of L1CAM expression and presence of non-endometrioid foci and it was increased in non-endometroid carcinoma serous subtype II carcinomas, and they have proved that L1CAM overexpression was associated with poor clinical, pathological criteria and patient outcome [39].

L1CAM has many actions that explained its association with aggressive behavior and more invasive pattern of malignancies that showed increased tissue protein expression of such marker through increasing malignant cell invasion and motility via activation of Wnt signaling pathway which could be able to stimulate the epithelial mesenchyme transition (EMT) process which is incriminated in cancer metastases [36], and that it could act as a pro-angiogenic factor which is responsible for neo-angiogenesis in cancer tissues that increased its invasion and metastases [40].

The role of L1CAM in neo-angiogenesis in cancer tissues and invasion of the blood vessels that explained its role as a poor prognostic marker could be explained by Kommos et al., Geels et al. 2016 and Putten et al. 2016 results who found

positive correlation between L1CAM and lymphovascular and stromal invasion (LVSI) [31,34,35].

These results clarified the values of adding LVSI in recent ESMO risk stratification guidelines, and highlight the need for evaluation of LVSI as an important parameter during histopathological evaluations of endometrial carcinoma. We have found that high L1CAM expression is associated with higher incidence of recurrence after successive therapy which was similar to results of Kommos et al., and Colombo et al. [31,41]. So, it will be beneficial to predict recurrence in endometrial carcinoma cases with increased L1CAM expression.

Additionally our data and results of previous studies regarding the association between increased L1CAM expression, poor clinicopathological features and dismal patients outcome, suggested that those patients may benefit from targeted therapies against mediated L1CAM [42].

Previous studies clarified L1CAM role in EMT by activation of beta-catenin/TCF pathway in plethora cancers of different organs [15,43,44]. Moreover, L1CAM has been linked to the cancer stem cell (CSC) theory and identified as CSC marker [45], Bao et al., explained that by expression of L1CAM in glioma cells with high CD133 expression that is a CSC marker [36].

To clarify its role as a CSC marker we correlate its expression with SOX-2 that is a stem cell biomarker in endometrial carcinoma tissue and we have find a significant positive association between both markers expression and that overexpression of both of them were associated with poor clinicopathological and prognostic findings which suggested that molecular targeted therapy against them could be used as novel therapies for endometrial carcinoma.

In summary, we have hypothesized that both Sox-2 and L1CAM expressions might be able to induce CSCs activation and stimulate EMT in endometroid carcinoma cells which facilitate, progression, invasion and metastases, so targeted therapies against them might be novel promising therapies which could improve patients prognosis in addition to the currently used therapies.

In conclusion, increased Sox-2 and L1CAM expression are markers of poor prognosis and dismal outcome of patients with endometrioid carcinoma of the uterus.

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