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Value of Forkhead Box A1 (FOX A1) Immunohistochemical Expression in Epithelial Ovarian Carcinoma

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ABSTRACT

Background: Ovarian cancer is with the greatest fatality rate in the gynecological malignancy, with about two-thirds of patients receiving an advanced diagnosis because of late presentation. Additionally, 90% of patients experience recurrence and eventually develop chemo resistance. Finding new prognostic indicators and treatment targets tailored to that cancer is therefore highly desirable. It was discovered that FOX A1 plays a part in the growth and development of numerous tumours, including gliomas, breast, stomach, lung, and esophageal cancers, although its function in ovarian cancer has not been fully characterised. **Aim:** To assess the value of FOX A1 immunohistochemical expression in epithelial ovarian cancer and its relationship with clinicopathologic features.

Materials and methods: This is a retrospective cohort study that was carried out in the Pathology department, Faculty of Medicine, Zagazig University, in the period from November 2021 – to November 2022. All cases of epithelial ovarian cancer of different; grades, stages and histopathological subtypes with complete clinical data were included in the study. Specimens of paraffin blocks were obtained by total abdominal hysterectomy with bilateral salpingoophorectomy (TAH+BSO) with omentectomy and lymph node dissection. They were examined by two independent pathologist for evaluation grade and stage. FOX A1 immunohistochemical staining was done for all specimens.

Results: There was a statistically significant association between FOX A1 expression and patients' age, menopause, patients with bilateral lesions, ruptured capsule, positive peritoneal cytology, lymph node metastasis**,** omental deposits pathological grade and FIGO stage.- **Conclusion:** FOX A1 expression was related to poor prognostic predictors in EOC.

Keywords: FOX A1, Immunohistochemical, Epithelial Ovarian Carcinoma.

INTRODUCTION

Ovarian cancer is one of the most common gynecological cancers. After cervical and uterine carcinoma, it comes in third place [(1)]**,** 1,2% of all cancers in the world [(2)]**.** Ovarian cancer accounts for 21% of malignant genital system tumors and 2.7% of all female cancers in Egypt[(3)]**.** The majority of ovarian tumors (approximately 90%) are epithelial ovarian cancers (EOCs) [(4)]**.** Serous ovarian carcinoma, which comprises high-grade serous carcinoma (HGSC) (70%) and low-grade serous carcinoma (LGSC) (5%), mucinous ovarian cancer, endometrioid ovarian carcinoma, clear cell carcinoma, Brenner tumors, and other carcinomas are the categories into which EOCs fall [(5)]**.** The majority of people who are affected by EOC are asymptomatic or have nonspecific symptoms, and silent metastatic spread occurs in 60% of cases before diagnosis. EOC has a dismal prognosis and a deadly outcome [(6)]**.** Less than 29% of patients with advanced EOC survive five years [(7)]**.** There is a need to identify innovative prognostic markers to assess prognosis and enhance outcome due to the high rate of chemotherapy resistance, the prevalence of EOC, and the dearth of adequate screening tests [(1)].

Hepatocyte nuclear factor 3 α(/HNF3α), also known as forkhead box A1, is a gene that is encoded by FOX on human chromosome 14q21.1 [(8)]**.** The transcription factor FOX A1, which is widely expressed and involved in the expression of multiple crucial genes during the development of various types of human tissue for the growth of various tissues, including the liver, lungs, midbrain, and mammary glands. It can promote transcription by chromatin to allow for the binding of additional transcriptional factors and interacting with DNA through its forkhead binding domain [(9)]**,** it takes part in a variety of human disorders and may contribute to the development and spread of a number of tumors, including those that cause prostate, glioma, breast, stomach, lung, ovarian, and esophageal cancers [(10)]**.**

Poor prognosis in hepatocellular carcinoma and the development of metastatic prostatic cancer are linked to high levels of FOX A1 expression [(11)], and in cervical carcinoma is linked to treatment resistance [(12)]**.**

MATERIAL AND METHODS

A retrospective cohort study was conducted in the faculty of medicine's pathology department at Zagazig University, in the period from November 2021 – to November 2022 after taking an approval (ZU-IRP#9758) by the local ethics committee Institutional review board (IRB), faculty of medicine, Zagazig University.

The present study includes formalin, paraffin embedded tissue blocks from 46 cases of EOC including: 32 cases of serous ovarian carcinoma, 12 cases of mucinous ovarian carcinoma and 2 cases of endometroid ovarian carcinoma. They were gathered from the pathology department's archive at faculty of medicine,

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Zagazig University. Total abdominal hysterectomy with bilateral salpingoophorectomy (TAH+BSO) with omentectomy and lymph node dissection was used to obtain specimens for these paraffin blocks.

All cases of epithelial ovarian cancer of different; grades, stages and histopathological subtypes with complete clinical data were included in the study. Non epithelial ovarian malignancies, cases with insufficient tissue for staining, cases with incomplete clinical data and cases with history of chemotherapy or radiotherapy were excluded.

Clinical data as age, tumor size, surgical stage, presence of ascites, positive lymph nodes metastasis, uni/bilaterality and gross features were obtained retrospectively from the patients' files.

Histopathological evaluation:

Paraffin blocks of all cases were sectioned at 4 microns thickness and stained by hematoxyline and eosin to confirm diagnosis and assess tumor grading based on the World Health Organization (WHO) criteria [(13)]. Tumor staging was done according to International Federation of Gynecology and Obstetrics (FIGO) staging system that correlates with the widely used TNM classification system [(14)]. Histological sub-type was done according to The World Health Organization (WHO) classification (2020) of EOC [(12)].

Immunohistochemichal staining:

Primary antibodies were used in the streptavidin-biotin immunoperoxidase system for the immunohistochemical responses. The characters of commercial primary antibody for FOX A1: rabbit polyclonal antibody (IGg), (cat no: A15278, ABclonal Company, USA) , starting dilution 1:50, dilution range (1:50-1:200). Positive control: colon tissue , negative control were made using the same method but without the 1ry antibody.

Interpretation of FOX A1immuostaining:

The nuclei of tumor cells that were stained brownish were regarded as positive. The degree of positive expressiveness was rated as follows: Negative =0, 1-50%=1, 51-74%=2, and more than 75% =3. The staining intensity was evaluated as follows: weak =1, intermediate=2, and strong =3. The two grades were multiplied to obtain a final score :0 = -,1-2 = +,3-4 =++, 6-9 =+++ [(15)]. For statistical considerate a final score (0 and +) was considered as a low expression and final score (++ , +++) as high expression [(16)].

Ethics approval: The protocol for this study was approved by both the Institutional Review Board [IRB] and the local ethics committee at Zagazig University's Faculty of Medicine. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to process the data, SPSS version 25 was used for data checking, entering, and analysis. **Chi- square test (X^2)** was used to find the association between row and column variables. **Fischer exact test** is used instead of the chi-square test if one cell less than 5. *P* value of < 0.05 indicates significant results.

RESULTS

Table (1): Clinico-pathological data of the studied group:

Variables	***The studied group No= 46 (%)***
Age *(years)*	*Mean ± SD* *48.6± 15.5* *Median* *46* *(Range)* (28-75)
Menopause	
Premenopause	25 (54.3%)
Menopause	21 (45.7%)
Parity	
Nulliparous	18 (39.1%)
Parous	28 (60.9%)
Lateriaty	
Unilateral	23 (50.0%)
Bilateral	23 (50.0%)
Capsule rupture	
No	27 (58.7%)
Yes	19 (41.3%)
Peritoneal cytology	
No	25 (54.3%)
Yes	21 (45.7%)
Lymph node metastasis	
No	31 (67.4%)
Yes	15 (32.6%)
Omental deposits	
Negative	31 (67.4%)
Positive	15 (32.6%)
Histological type	
Serous	32 (69.6%)
Mucinous	12 (26.1%)
Endometroid	2 (4.35%)
Pathological grade	
Low	23 (50.0%)
High	23 (50.0%)
FIGO stage	
Stage I	19 (41.3%)
Stage II	11 (23.9%)
Stage III	14 (30.4%)
Stage IV	2 (4.3%)
FOX A1	
Low	18 (39.1%)
High	28(60.9%)

The mean average age of the studied group was (48.6± 15.5) ranging from (28 to 75) years, (54.3%) were menopause and (60.9%) were parous. Regarding tumor characteristics, half of the studied group (50.0%) had a unilateral lesion and (50.0%) had bilateral lesions, less than half of the studied group (41.3%) had a ruptured capsule, (45.7%) had positive peritoneal cytology, (32.6%) lymph node metastasis ,(32.6%) had omental deposits. Regarding histological types of Serous tumors were the commonest histological type followed by mucinous then endometroid (69.6%> 26.1%> 4.35%). Regarding FIGO staging, stage I was the commonest followed by stage III then Stage II and lastly stage IV (41.3% > 30.4%>23.9% >4.3%). Half of the studied group (50.0%) had a low-grade tumor and half of them (50.0%) had high-grade tumors and more than half of them (60.9%) had a high FOX A1 expression among the studied group (Table 1).

Table (2): Relation between FOX A1 expression and patients' age, menopause, parity, laterality, capsule rupture, peritoneal cytology

Variables	***Low FOX A1 No= 18 (%)***	***High FOX A1 No=28 (%)***	**Test**	**P-value^**
Age				
≤46 years (no=23)	13 (56.5%)	10 (43.5%)	5.8	**0.01***
>46 years(no=23)	5 (21.7%)	18 (78.3%)		
Menopause				
Premenopause (no=25)	14 (56.0%)	11 (44.0%)		
Menopause (no=21)	4 (19.0%)	17 (81.0%)	6.5	**0.01***
Parity				
Nulliparous (no=18)	6 (33.3%)	12 (66.7%)	0.4	0.5
Parous(no=28)	12(42.9%)	16 (57.1%)		
Lateriaty				
Unilateral(no=23)	15 (65.2%)	8 (34.8%)	F	**<0.001****
Bilateral(no=23)	3 (13.0%)	20 (87.0%)		
Capsule rupture				
No(no=27)	18 (66.7%)	9 (33.3%)	F	**<0.001****
Yes(no=19)	0 (0.0%)	19 (100%)		
Peritoneal cytology				
-ve (no=25)	18 (72.0%)	7 (28.0%)	F	**<0.001****
+ve (no=21)	0 (0.0%)	21 (100%)		
Lymph node metastasis				
No (no=31)	18 (58.1%)	13 (41.9%)	**<0.001****	
yes (no=15)	0 (0.0%)	15 (100.0%)		
Omental deposits				
Negative (no=31)	18 (58.1%)	13 (41.9%)	**<0.001****	
Positive (no=15)	0 (0.0%)	15 (100.0%)		
Histological type				
Serous(no=32)	13 (40.6%)	19 (59.4%)	0.3	0.8
Mucinous(no=12)	4 (33.3%)	8 (66.7%)		
Endometroid(no=2)	1 (50.0%)	1 (50.0%)		
Pathological grade				
Low(no=23)	18 (78.3%)	5 (21.7%)	F	**<0.001****
High(no=23)	0 (0.0%)	23 (100.0%)		
FIGO stage				
Stage I (no=19)	12 (63.2%)	7 (36.8%)		
Stage II (no=11)	6 (54.5%)0	5 (45.5%)	**15.9**	**<0.001****
Stage III (no=14)	0 (0.0%)	14 (100.0%)		
Stage IV (no=2)	0 (0.0%)	2 (100.0%)		

A statistically significant relationship existed between FOX A1 expression and patients' age, menopause, patients with bilateral lesions. EOC with ruptured capsule showed high FOXA1 tissue expression with high statistical significance($p<0.001$). This table shows that there was a statistically significant high FOX A1 expression among the patients with positive peritoneal cytology. There was a statistically significant connection between lymph node and FOX A1 expression metastasis as all patients (100.0%) with positive omental deposits had high FOX A1.

There was a statistically There was a statistically significant connection between lymph node and FOX A1 expression deposits as all patients (100.0%) with positive omental deposits had high FOX A1. The relationship between FOX A1 expression and pathogenic grade was significantly significant (P 0.001). FOX A1 expression and FIGO stage were statistically significantly correlated (P 0.001). There is no statistically significant correlation between parity and FOX A1 expression (0.5). In the group under study, there was no statistically significant correlation between FOX A1 expression and histological type (P = 0.8) (Table 2).

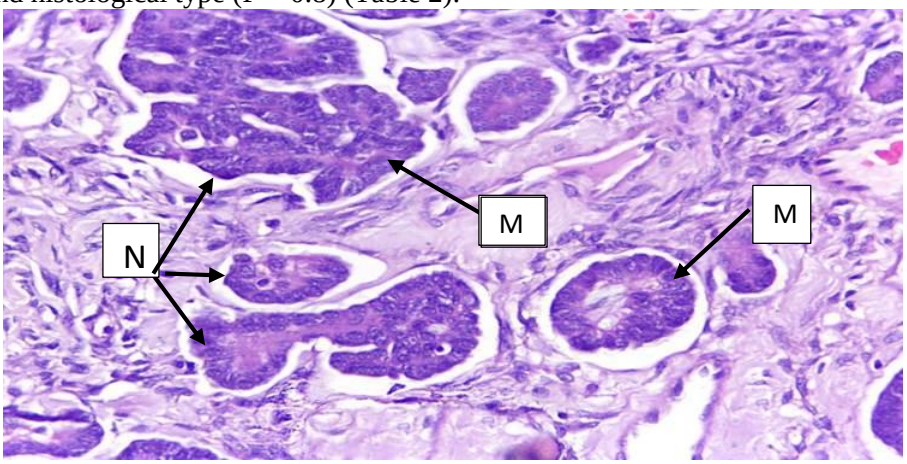

Figure (1): Photomicrograph of a section of Low-grade serous carcinoma showing irregular shaped infiltrative nests (N) liningby malignant epithelial with moderate cytological atypia with low mitotic activity(M). (H&E, X: 400)

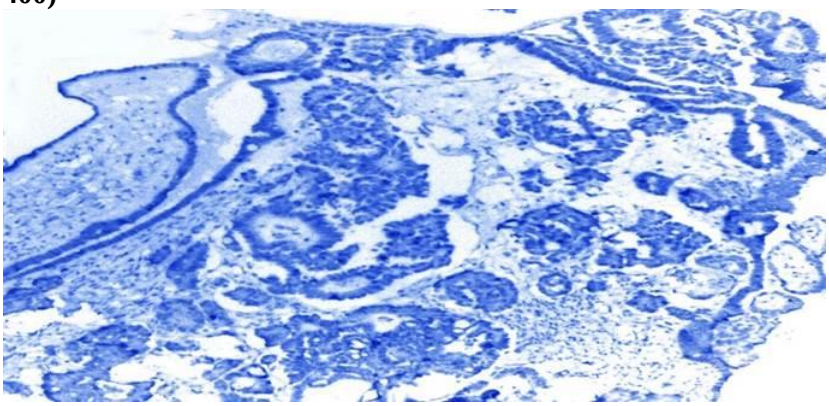

Figure (2): Photomicrograph of a section of serous carcinoma showing negative FOX A1 nuclear immunostaining. (IHC, X: 100)

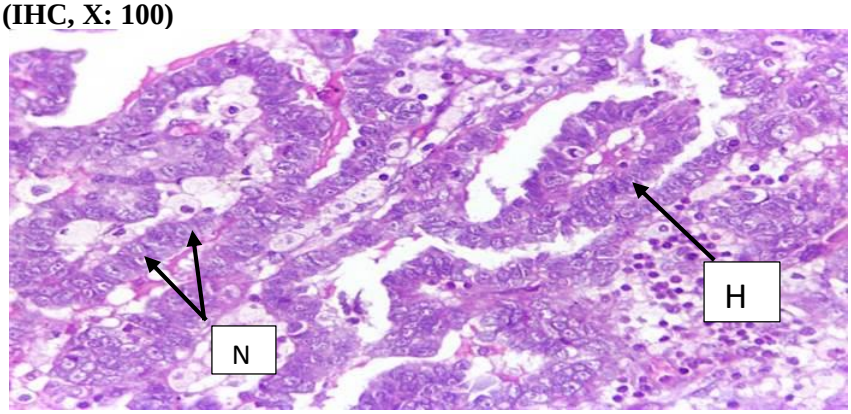

Figure (3): Photomicrograph of a section of High-grade serous carcinoma showing nuclear atypia(N), hyperchromatic and mitotic activity(H). (H&E, X: 400)

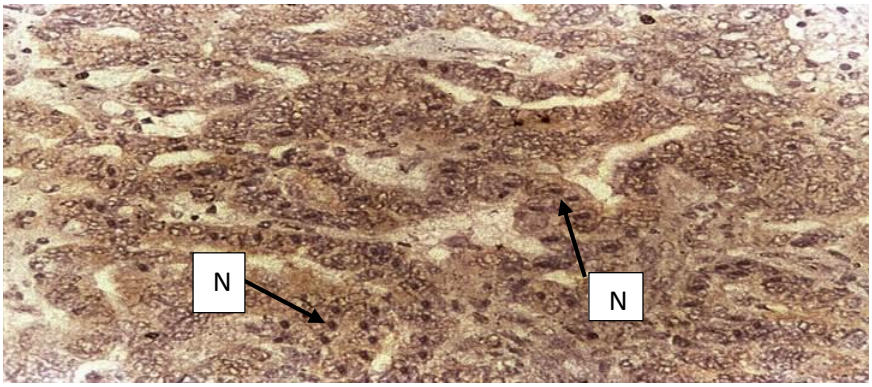

Figure (4): Photomicrograph of a section of High grade serous carcinoma with strong nuclear(N) expression of FOX A1. (Immunohistochemical stain, X :400).

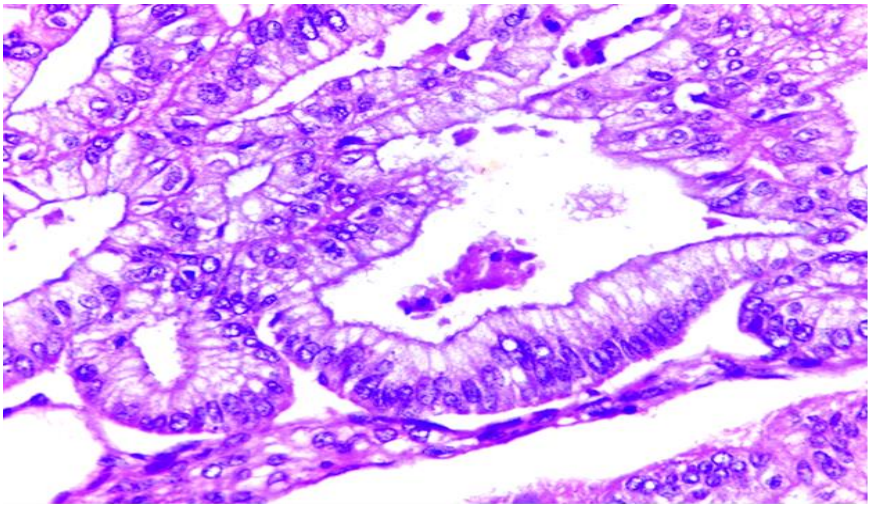

Figure (5): Photomicrograph of a section of Mucinous adenocarcinoma with pleomorphic hyperchromatic malignant mucinous epithelial cells.(H&E, X: 400).

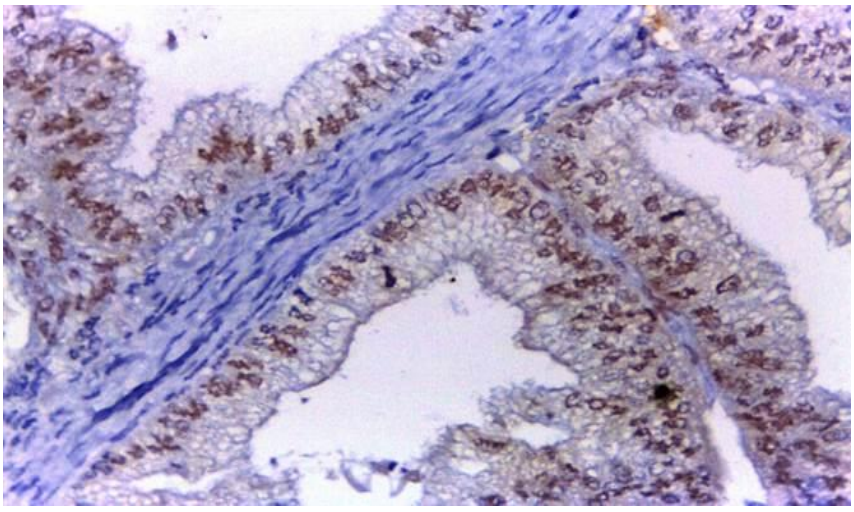

Figure (6): Photomicrograph of a section of Mucinous cystadenocarcinoma showing high nuclear staining for FOXA1 (Immunohistochemical stain, X:400)

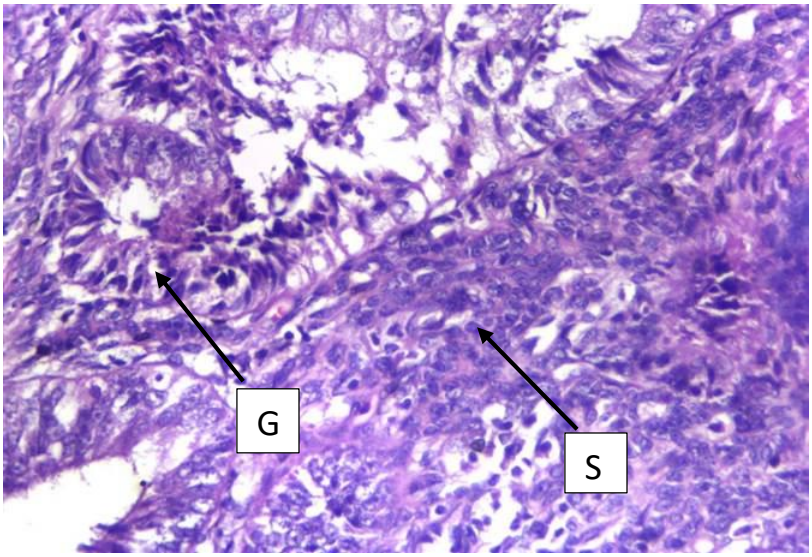

Figure (7): Photomicrograph of a section of High grade Endometroid ovarian carcinoma showing solid area(S) and few glands(G), the malignant epithelial cells show moderate to severe atypia . (H&E, X :400)

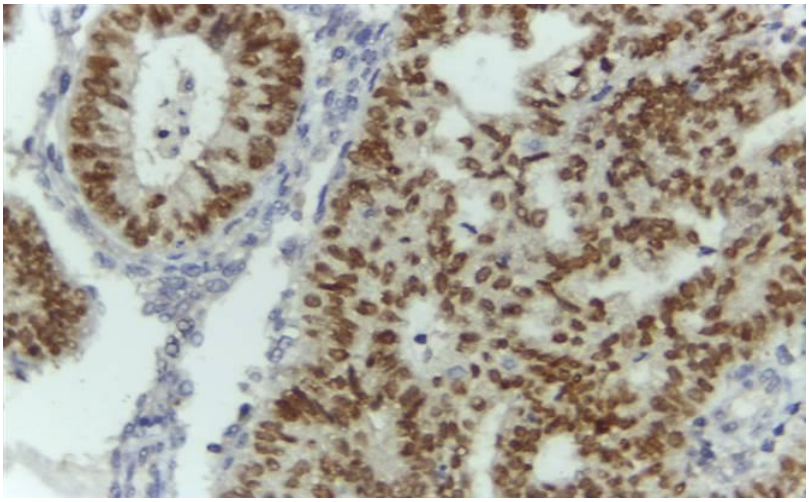

Fig (8) Immunohistochemical staining of endometroid adenocarcinoma showing High staining for FOXA1. (Immunohistochemical stain, X :400).

DISCUSSION

Gynecological tumors are a significant issue for Egyptian women. In Egypt, ovarian cancer is the fourth most prevalent type of cancer [(16)].

Ovarian cancer has an average lifetime risk of 1.3%, which is equal to 1 in 78 women [(2)]. Incidence and mortality rates for gynecological cancers are third highest globally are linked to epithelial ovarian cancer (EOC) [(1)].

There is an urgent need to find novel biomarkers that may be utilized to enhance patient care because there are few effective therapeutic choices and a high rate of chemotherapy resistance in high-grade EOC [(17)].

When it comes to the onset and development of breast cancer, FOX A1 interacts with both the estrogen and androgen receptors [(18)]. Since EOC is a condition that is also influenced by hormones, FOXA1 affects EOC [(19)].

To our knowledge, not many prior research have looked at FOXA1 expression in EOC [(13, 15, 20)], without being clear whether FOXA1 expression will improve or worsen a patient's prognosis or chance of survival.

In an attempt to fill this gap, this study concerned with evaluating immune-hitochemical expression of FOX A1 in EOC with different subtypes to clarify it's prognostic value in epithelial ovarian carcinoma.

Age and race/ethnicity affect epithelial ovarian cancer incidence differently. When compared to other epithelial subtypes, serous carcinoma has an older age distribution, peaking in the seventh rather than the fifth decade of life [(21)].

In our work the mean age of studied group was (48.6± 15.5) ranging from 28 to 75 years , and (60.9%) were parous.

This finding was nearer to that found by **Elnashar *et al.*** [(22)] who reported that the mean age of the cases was 52.27 years and to that reported by **Wang *et al.*** [(13)] found that the patient's mean age was 54.5 years .Additionally,

Sheta *et al.* [8] reported that the mean age of the patients was 57.1. **Abouhashem *et al.*** [16] found that the mean age of patients was 58.7 ±6.2 years.

We discovered a strong correlation between FOX A1 expression and advanced patients' age (P=0.01). This came in agreement with **Elnashar *et al.*** [22]. However, it disagreed by **Abouhashem *et al.*** [16] who revealed that there was no association between patient age and FOXA1 expression. This could be explained by different sample size.

The epithelial ovarian cancer is considered mainly a postmenopausal disease, it is difficult to diagnose EOC early: older patients have significantly worse survival rates [23]**.** In this study, 45,7% of cases was postmenopausal. FOX A1 expression and statistically significant relationship and menopausal state (p=0.01)

In our study, half of the studied group (50.0%) had a unilateral lesion and (50.0%) had bilateral lesions. This finding was similar to that of **Wang *et al.*** [13] who noted that 46.4% of tumors were bilateral. However other studies found that bilaterality of tumors were predominant[22]**,** while **Sheta *et al.*** [8] found that unilateral was the predominant .

FOX A1 expression was significantly correlated with tumor), bilaterality (P < 0.001), in this work .This results agreed with **Elnashar *et al.*** [22]**, Wang *et al.*** [13]**,** and disagreed with **Sheta *et al.*** [8] they reported that although there was a propensity for unilateral tumors to express more FOXA1 than bilateral ones, this difference did not achieve statistical significance.

Powerful prognostic indicators that are frequently utilized to establish the tumor stage include the condition of the capsule and the occurrence of ascites [24]**.** Regarding tumor characteristics among the studied group, less than half of the studied group (41.3%) had a ruptured capsules and (45.7%) had positive peritoneal cytology. we found that all cases with ruptured capsule and positive peritoneal cytology had a high FOX A1 expression among the studied group (p<0.001).

These results were close to **Yousef *et al.*** [25] who noted that 55.8% of cases and 57.7% of cases, respectively, involved capsule rupture had positive peritoneal cytology and demonstrated high expression of FOX A1 in these cases of EOC. Also, **Elnashar *et al.*** [22] found that FOXA1 expression was highly significantly associated with tumors that had ruptured capsules and ascites.

This can be explained by the fact that ascites is present at diagnosis in almost all instances of ovarian cancer and in more than one-third of cases of relapse. Osteoprotegerin, a pro-tumorigenic protein, is one of the soluble factors secreted by mesothelial and endothelial cells originating from ascites and factors which promote tumor cell growth and invasion [26]**.**

Regarding tumor metastasis we found lymph node metastasis in (32.6%) of cases , and omental deposits in (32.6%)of cases, this was nearer to that found by **Sheta *et al.*** [8]. regarding lymph node metastasis (24.5%) , while omental deposits was higher (63.3%) . In our study there was a statistically significant association between FOX A1 expression and lymph node metastasis (**<0.001**)., and omental deposits (**<0.001**).

These result agreed with that of **Sheta *et al.*** [8] who reported that independent predictors of high FOXA1 expression were lymph node metastasis and omental deposits.

Iwagoi *et al.* [27] found that the omentum is one of the most popular locations for metastasis during ovarian cancer metastatic spread and frequently develops a huge mass known as a "omental cake" omental deposits. These results showed that omental metastasis is associated with higher chemoresistance in stage III-IV ovarian carcinoma and represents a clinical indicator for poor survival outcomes in individuals with advanced ovarian cancer.

In ovarian cancer, FOXA1 facilitates cyclic adenosine monophosphate response element-binding protein-mediated transcription of YAP-associated protein. High YAP activation results in increased cellular migration, proliferation, and resistance to chemotherapy [28]**.** This can explain the significant statistical association between high FOX A1expression and tumor metastasis.

According to histological subtype, our cases showed that serous tumors were the commonest histological type followed by mucinous then endometroid (69.6%, 26.1%, 4.35% respectively). Similarity, **Elnashar *et al.*** [22] showed that serous carcinoma was present in more than (70%) of the cases that were investigated. **Leong *et al.*** [29] More than 70% of the cases studied had serous carcinoma. Also, **Sheta *et al.*** [8] reported that 55.1% of tumors were high-grade serous carcinoma (HGSC). Additionally, **Wang *et al.*** [13] reported that 40% of tumors were HGSC. Furthermore, **Amanullah *et al.*** [30] 48.3% of tumors were classified as severe.

There was no statistically significant relationship in the current investigation of FOX A1 expression and histological subtypes. In agreement with our study, **Wang *et al.*** [15] FOXA1 expression and histopathological subtype were found to be unrelated. Also, **Wang *et al.***[13] about 55% of serous carcinomas tested positive for FOXA1, with no significant correlation.

In disagreement with our results, **Yousef *et al.*** [25] FOX A1 expression and histology serous type were found to have a statistically significant relationship. In another study by **Karpathiou *et al.*** [20]**,** 19% of EOC strongly and diffusely expressed FOXA1 and 75% of these EOC were of the mucinous followed by serous histology, but endometrioid and CCCs were completely negative. In **Elnashar *et al.*** [22] **study** , FOXA1 expression was

discovered to have a strong relationship with tumor histologic subtype. The disparity in sample size and the sensitivity of the approach may be to blame for this discrepancy between the results.

In our study, half of the studied group (50.0%) were high -grade tumors and the remaining were low -grade tumors.

Elnashar *et al.* [22] reported that the majority of cases (73.0%) were confirmed to have high-grade tumors. **Ndukwe *et al.*** [31] who stated that 34% of cases had low-grade neoplasms and 66% of tumors were high-grade neoplasms.

In the present study, There was a strong association between FOX A1 expression and pathological high grade as all pathological high grade had high FOX A1 expression.

In agreement with our study, **Abouhashem *et al.*** [16] and **Yousef *et al.*** [25] reported that the largest percentage of FOX A1 expression was discovered to be present in high grade malignancies. According to these results, FOX A1 expression was linked to a poor prognosis.

Because of how FOXA1 affects cyclin-dependent kinase 1, phosphatidylinositol-3 kinase, E2F transcription factor 1, B-cell lymphoma 2, and vascular endothelial growth factor, it has been suggested that FOXA1 may have an oncogenic role in the development and progression of EOC. EOC cells may proliferate, migrate, develop independently, and withstand apoptosis and chemotherapeutic treatments thanks to a protein pathway [13].

As regard EOC grading, **Wang *et al.*** [15]**,** shown that regardless of age, histological type, tumor size, or location, greater FOXA1 expression is linked to an increased EOC tumor grade and poorer differentiation. High FOX A1 expression and tumor grade were shown to be statistically significantly correlated in this study ($p = 0.01$). This was also concomitant with the study of **Wang *et al.*** [13] who noted that substantial FOXA1 expression of tumor cells was seen in 41/62 cases of moderately differentiated and poorly differentiated EOC, which was statistically significant. These results imply that poor prognostic indicators in EOC were related to FOX A1 expression.

Considering FIGO staging, stage I was the commonest followed by stage III then Stage II and lastly stage IV (41.3%, 30.4%, 23.9%, 4.3% respectively) in our study. We found a statistically significant association between FOX A1 expression and FIGO stage III and IV as all patients in stage III and IV had high FOX A1 expression ($p<0.001$). This was close to **Yousef *et al.*** [25] **and Sheta *et al.*** [8] who found the same results. In addition, **Elnashar *et al.*** [22] reported that FOXA1 was positive in 90.48% of cases at stages III and IV.

Wang *et al.* [15] found that FOXA1 regulates the expression of several proteins, acting as an oncogene in the pathogenesis and growth of ovarian cancer. Their findings showed that cellular proliferation, migration, and invasion in FOXA1-silenced ovarian cancer cell lines were decreased; apoptotic activity was up-regulated with induction of S-phase arrest. The expression of numerous factors, including the YAP, CDK1, CCND1, PI3K, E2F1, Bcl-2, and VEGFA proteins, was decreased when the FOXA1 protein was silenced.

High FOXA1 expression affected the prognosis of EOC patients and can indicate worse clinical outcomes in ovarian cancer patients, such as inadequate differentiation and shortened overall survival time [32].

The result of the present study showed a statistically significant link between high FOX A1 expression and poor prognostic predictors in EOC as high grade of differentiation ,omental deposits lymph node metastasis as well as high FIGO stage. So, FOX A1 may play a significant role in EOC, and it may also be a promising therapeutic target and prognostic indicator.

Our study's limitations include:

1) A small number of patients.
2) The study was single center study so we cannot do generalization to the data.
3) Other histological types not found.
4) We used only immunohistochemical evaluation of the marker.

CONCLUSION

IHC expression of FOX A1 in EOC was significant association with high advanced stage so it may play a role in tumor carcinogenesis. FOX A1 expression was related to poor prognostic predictors in EOC. FOX A1 expression is significantly corelated with FIGO stage, and pathological grade as all patients with FIGO stage III , IV and high pathological grade, patients with bilateral tumors had high FOX A1. Additionally high FOX A1 expression among patients with ruptured capsules, peritoneal cytology and lymph node metastasis. According to the current study's findings, FOXA1 may be a key player in EOC and a prospective therapeutic target as well as a prognostic factor.

Conflicts of interest: None.
Financial disclosures: None.

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