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The Relationship between Preoperative Serum Levels of HE4 and Epithelial Ovarian Cancer

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Cancer,
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A B S T R A C T

Ovarian cancer is the most common malignancy in the world and the fifth leading cause of death from cancer among women. HE-4 or (Human Epididymis protein 4) is a new marker introduced for diagnosis and follow-up of ovarian cancer. The aim of this study is to examine the association between preoperative serum levels of the marker of HE4 and epithelial ovarian cancer based on FIGO system to evaluate this marker in predicting the ovarian cancer stage. This analytical retrospective study is conducted on 62 patients with ovarian masses hospitalized in Ahwaz Imam Khomeini Hospital for surgery. The records of the patients who had been hospitalized within the years of 2011-2013 was analyzed and the HE4 serum level was measured by ELISA method and also the information in the patient records were recorded in demographic questionnaires. The data were analyzed with SPSS software version 18. In this study 62 patients with ovarian masses were studied among whom 26 cases (41.9%) were postmenopausal. Statistical test results showed that the HE-4 levels in postmenopausal women had no significant difference with other patients ($P > 0.05$), but the mean HE-4 level in different stages showed that by increasing the stage the HE-4 level is increased significantly ($P = 0.007$). This increase was also applied in patients' grade and HE-4 was significantly higher in severe cases the ($P = 0.003$). Also HE-4 level was significantly higher in malignant patients than the benign patients ($P = 0.001$). Based on the results obtained in this study it can be concluded that HE4 is a good diagnostic marker for differentiating benign and malignant ovarian tumors and more importantly in malignant patients its level is increased as the grade and stage of the disease increase and thus it is recommended to apply it in patients with a diagnosis of ovarian tumors.

Introduction

Today cancer is a widespread public health problem that affects different tissues (Firoozabadi *et al.*, 2015; Rahmani *et al.*, 2016; Mohammad *et al.*, 2015). Ovarian cancer is the most common malignancy in the world and the fifth leading cause of death caused by cancer among women. In Iran ovarian cancer is the eighth most common cancer in women and its five-year survival rate has been reported as 6% (Arab *et al.*, 2010). Ovarian cancer has multiple histopathologic types. In a study in Iran the prevalence of these forms is reported as 81.6% epithelial, 12.2% germ cell and 5.1% granulosa cell. The average age of ovarian cancer in Iran is lower than the Western countries and a high percentage of patients are diagnosed at the advanced stages (Khodabakhshi *et al.*, 2007). Ovarian cancer mortality rate is around 75% but its diagnosis in early stages of the disease reduces the mortality rate to about 10%. Strategies to diagnose the disease in early stages require tests with high sensitivity and specificity over 75% and 99.6% so that the positive predictive value is reduced to a minimum level of 10%. The early stages of ovarian cancer has ambiguous are non-specific symptoms; therefore most patients refer at the advanced stages of the disease and thus several tumor markers are introduced for screening and diagnosis of cancer particularly ovarian cancer (Ilana, 2008).

HE-4 or (Human Epididymis protein 4) is a new marker introduced for diagnosis and follow-up of ovarian cancer (Moore *et al.*, 2008). This marker is discovered by comparing RNA sequences expressions in normal and malignant ovarian epithelial cells. Studies have demonstrated that the concurrent use of CA125 and HE4 markers had the sensitivity equivalent to 76.46% and specificity equivalent to 100% to diagnose and investigate recurrent ovarian cancer.

Among the few studies in this area, in one study the high levels of HE-4 have been associated with the advanced stages of tumor and serous ovarian cancer (Paek *et al.*, 2011). Moreover the use of this marker is developing for staging and invading the endometrial cancer myometrium (Moore *et al.*, 2011). The importance of staging ovarian cancer is more specific than any other cancers because the microscopic metastases are serious problems in the preoperative treatment. Unfortunately, in Iran and many other countries, staging is not fully exercised due to technical issues and therefore the lack of proper staging leads to inappropriate treatment of many patients. The study on the tumor markers in addition to the early diagnosis, follow up after diagnosis and treatment could predict the tumor stage based on serum levels is increasing (Arab *et al.*, 2010). In line with this objective, in this study the association between preoperative serum levels of the marker of HE4 and epithelial ovarian cancer based on FIGO system to evaluate this marker in predicting the ovarian cancer stage is studied to evaluate this marker in predicting the ovarian cancer stage and help the early diagnosis of the disease in early stages and treat the patient more effectively.

Materials and Methods

After obtaining permission from Ethics Committee of the University, this analytical – retrospective study was conducted on 62 patients with ovarian masses hospitalized in Ahwaz Imam Khomeini Hospital for surgery. The records of the patients who had been hospitalized within the years of 2011-2013 were analyzed and the HE4 serum level was measured by ELISA method and also the information in the patient records were recorded in demographic questionnaire. The cut-off levels of He4 was considered as 70 Pmol/Lit. Moreover the kit He 4 EIA of Can Ag USA company was

used. After collecting the required data using SPSS version 18 software the collected data was analyzed and for the qualitative variables the frequency and frequency percentage and for quantitative variables the mean and standard deviations were calculated. In order to evaluate hypotheses the independent t-test and ANOVA were used and the level of significance for the interpretation of the results was considered as 0.05.

Results and Discussion

In this study, 62 patients with ovarian tumors were studied among whom 26 cases (41.9%) were postmenopausal. Pathologically 24.2% had serous cyst adenoma, 17.7% had mucinous cyst adenoma, 3.2% had adeno-fibroma cysts, 27.4% had serous carcinoma, 24.2% had mucinous carcinoma and 3.2% had endometrioid (Figure 1). Analyzing the patients' stage showed that 11.8% were in the first stage, 38.2% were in the second

stage, 41.7% were in the third stage and 2.9% were in the fourth stage (Figure 2). 20.6% were in mild grade, 29.4% were in moderate grade and 50% were in severe grade (Figure 3).

In case of the type of tumor in 28 cases (45.2%) the tumors were benign and in 34 cases (54.8) the tumors were malignant. In case of HE-4 level it was observed that the patients' average HE-4 was 276.1 ± 316.1 and 50% of patients had HE-4 above 169. Statistical test results showed that the HE-4 levels in postmenopausal women had no significant difference with other patients ($P > 0.05$), but the mean HE-4 level in different stages showed that by increasing the stage the HE-4 level is increased significantly ($P = 0.007$). This increase was also applied in patients' grade and HE-4 was significantly higher in severe cases the ($P = 0.003$). Also HE-4 level was significantly higher in malignant patients than the benign patients ($P = 0.001$) (Table 1).

Table.1 Association between HE4 and Variables

Variable	Sub-Variable	HE4 level		P-Value
		Mean	SD	
Type	Benign	144/92	60/93	0/001
	Malignant	384/04	393/71	
Menopause	Yes	379/82	421/87	>0/05
	No	207/61	188/37	
Stage	I	106/75	12/84	0/007
	II	187/8	81/49	
	III	581/56	472/78	
	IV	884	0	
Grade	Mild (1)	122/57	58/92	0/001
	Moderate (2)	201/04	77/53	
	Severe (3)	384/04	393/71	

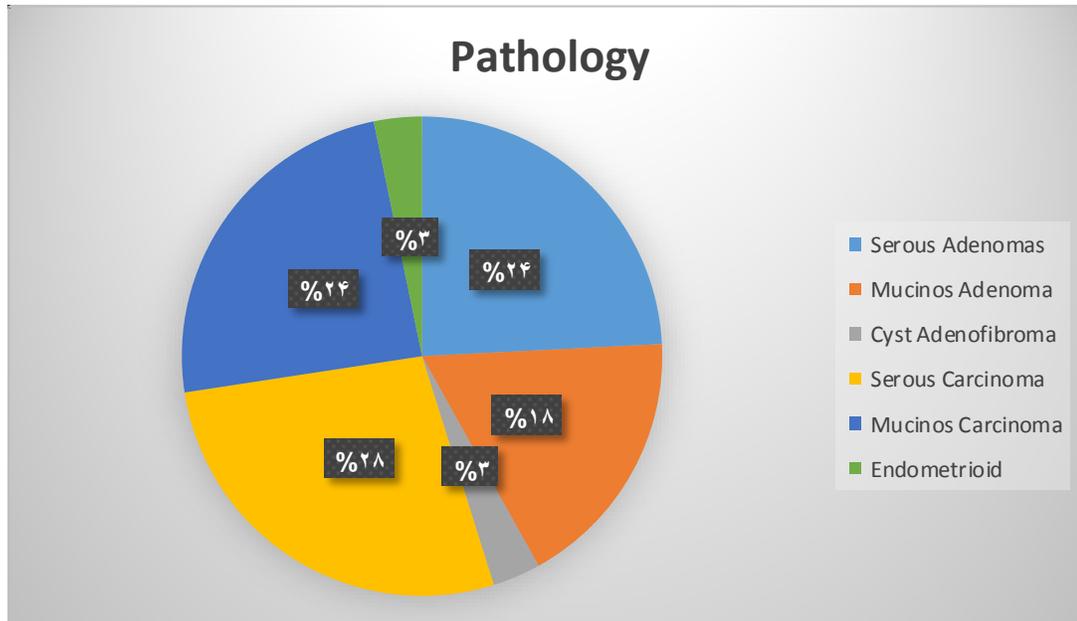


Figure.1 Frequency distribution of the pathology in patients (%)

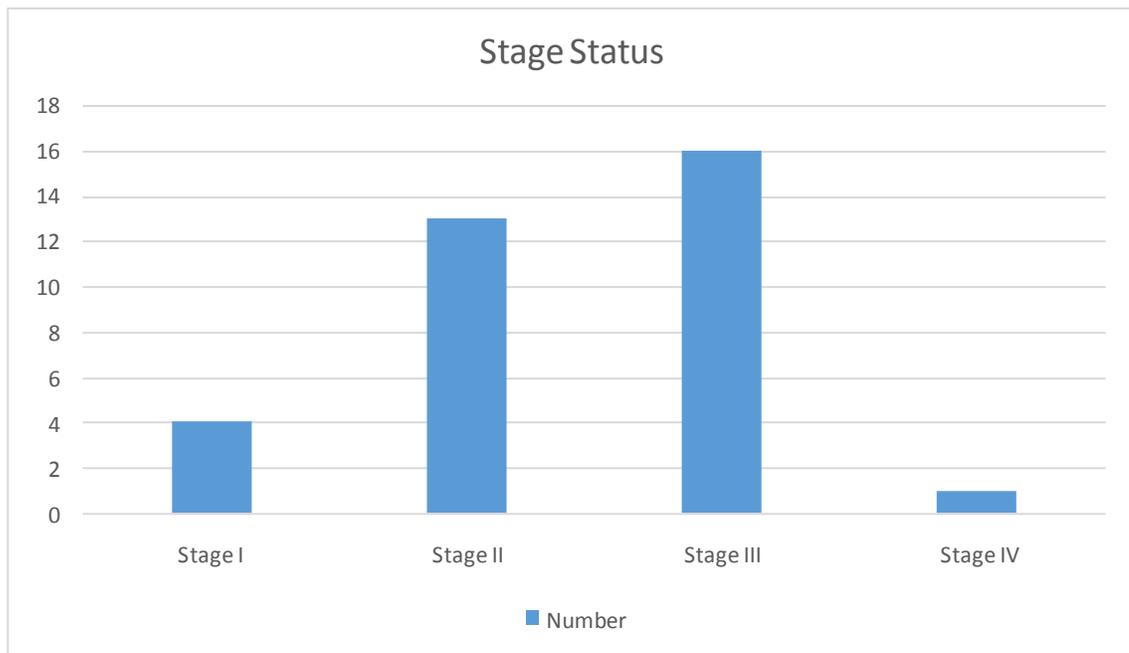


Figure.2 Frequency distribution of stage in patients with epithelial ovarian cancer (n)

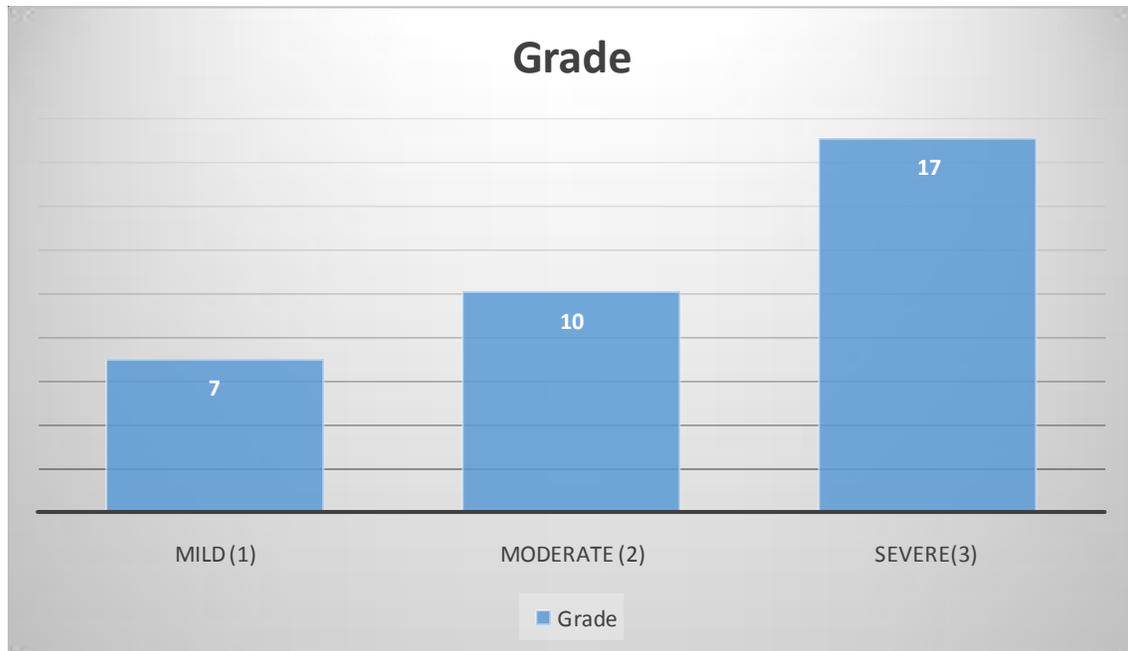


Figure.3 Frequency distribution of drade in patients with epithelial ovarian cancer

The study on the tumor markers in addition to the early diagnosis, follow up after diagnosis and treatment could predict the tumor stage based on serum levels is increasing. In line with this objective, in this study the association between preoperative serum levels of the marker of HE4 and epithelial ovarian cancer based on FIGO system to evaluate this marker in predicting the ovarian cancer stage is studied to evaluate this marker in predicting the ovarian cancer stage and help the early diagnosis of the disease in early stages and treat the patient more effectively.

In this study the patients' average HE-4 was 276.1 ± 316.1 . HE-4 frequency was significantly different based on benign or malignant patients ($P < 0.05$) and was higher in malignant cases. Moreover HE-4 was higher in patients with greater stage and grade. Obviously to achieve an effective result of the existing data it is necessary to compare the results with the results of other similar articles. For example Throdel *et al.*,

in Canada studied the possibility of prediction of death and prognosis in patients with ovarian cancer and it was found that HE4 was an effective marker to predict mortality (Trudel *et al.*, 2012) Of course the present study was cross-sectional and patients' mortality and factors affecting were not analyzed. Zhijun Yang *et al.*, (2000-2013) in China performed a study to evaluate the diagnostic value of HE4 serum level in ovarian cancer and concluded that HE4 has higher sensitivity (79%) and specificity (89%) than CA125 and therefore this study indicates that HE4 can be considered as a marker to diagnose ovarian cancer that the diagnosis between benign and malignant tumors is investigated in the present study.

Also Shin Hye Chung (2005-2010) conducted a case-control study to compare serum levels of HE4 and CA125 in ovarian cancer in Korea. Accordingly the HE4 serum levels of 32 female patients diagnosed with ovarian cancer and 34 healthy subjects

were measured and it was concluded that the serum level of this marker was higher than the benign tumors which is consistent with the results of the present study. Also Richard *et al.*, (2007) conducted a prospective study to use a new cancer marker in the diagnosis of ovarian cancer in 2059 patients with aviary ovarian mass and concluded that HE4 alone has the highest sensitivity in the diagnosis of ovarian cancer which is in line with the results of the present study.

In Hala Abdel-Azeez *et al.*, (2010) for the early diagnosis of ovarian cancer in 65 patients with pelvic mass it was concluded that HE4 has the highest sensitivity in ovarian tumor diagnosis especially in the early stages of the disease (Hala *et al.*, 2010) which confirms the results of the present study. Peek *et al.*, (2011) conducted a cohort study to determine the HE4 serum level in patients with epithelial ovarian cancer and HE4 serum level was measured before the operation and it was finally concluded that high preoperative HE4 serum levels was associated with tumor stage and serous ovarian type of tumor. However, in the present study there was no correlation with the pathological type but there was a significant correlation with advanced stages. Hamed *et al.*, (2011-2012) showed that HE4 serum concentration was significantly higher in malignant than the benign ovarian tumors, which is similar to the results of the present study. It is indicated in Lenhard *et al.*, in Germany that HE4 can be used as auxiliary method in patients with ovarian cancer (Lenhard *et al.*, 2011), which is in line with the results of the present study. Molina *et al* (2011) in Spain concluded that HE4 has a significant area under the curve in diagnosing the benign and malignant ovarian and uterine tumors that is consistent with the results of the present study.

In general based on the results of this study it can be concluded that HE4 is a good

marker with higher efficiency to differentiate the benign and malignant ovarian tumors and more importantly in malignant patients its level is increased as the grade and stage of the disease increase and thus it is recommended to apply it in patients with a diagnosis of ovarian tumors. In the end it is proposed to conduct the future multi-center studies with higher sample volume and to confirm these results.

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