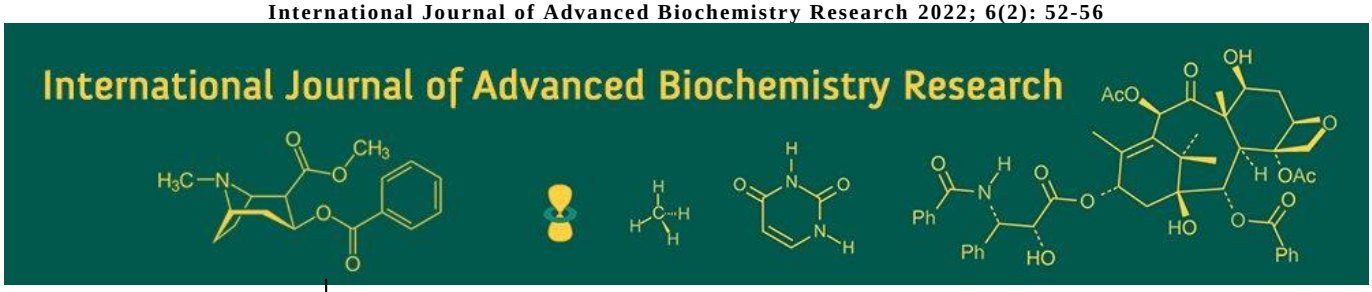

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Prognostic and diagnostic role of HE4 as a biomarker in ovarian cancer & comparison with CA125 in ovarian cancer patients with their menopausal status

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Abstract
Aim: to evaluate a new tumour marker HE4, in comparison with CA 125 and the Risk of Ovarian cancer in pre and postmenopausal women with ovarian cancer.
Method: The ovarian cancer female patients were recruited from OPD/IPD of Surgery and Oncology department of SMS Hospital, and evaluated serum human epididymis protein (HE4) and CA125 Patients were divided into two group's premenopausal and postmenopausal women with ovarian cancer.
Results: Serum HE4 and CA125 level significantly high in postmenopausal women as compared to premenopausal women of ovarian cancer. The result was significantly high. (p<0.001). AUC for CA125 was 0.680 (95% CI 0.587-0.773) and for HE4 was 0.893(0.95% CI0.840-0.946) (p=0.001) for distinguishing between ovarian cancer cases and control healthy subjects. HE4 showed positive correlation with CA125 (r=0.388, p=0.000). HE4 were significantly higher than CA125 in sensitivity and specificity (91% vs.82.3% and 94% vs 83%, respectively). Also the positive predictive values (PPV) and negative predictive values (NPV) for HE4 were significantly higher than CA125 (92.1% vs 79.1% and 91.7% vs 85.2%, respectively).
Conclusion: Serum HE4 level can predict ovarian cancer in postmenopausal women. Risk of ovarian cancer is increased with increase in HE4 level in postmenopausal women. HE4 level have more sensitivity and specificity compared with CA125 in diagnosing ovarian cancer.

Keywords: Human epididymis protein 4, ovarian cancer, positive predictive value and negative predictive value, postmenopausal women

Introduction
Ovarian cancer is the fifth most common cause of cancer death in women. Despite advances in treatment, there has been little change in the mortality rate of ovarian cancer. A diagnostic approach based on the use of CA 125 in association with ultrasonography has been suggested for the early diagnosis of ovarian cancer [1-4]. However, this approach has several drawbacks including low sensitivity and specificity; however, the use of CA125 is compromised by its low specificity, particularly in premenopausal women. HE4, also known as whey acidic four disulphide core 2 protein (WFDC2) is a novel ovarian cancer biomarker, which was initially identified in the epithelium of the epididymis and originally predicted to be a proteinase inhibitor involved in sperm maturation. It belongs to a family of WFDC proteins [5-7], It is over expressed in ovarian cancer and has demonstrated higher specificity compared with serum CA 125 in detecting ovarian cancer [8-11]. The HE4 protein, frequently over expressed in ovarian cancers, especially in serous and endometrioid histology [12-14]. HE4 was more specific than CA 125 in benign and malignant conditions. HE4 serum levels may be abnormal mainly in patients with renal failure or effusions and in patients with lung carcinomas. Studies suggest that HE4 has a more sensitivity to CA125, and increased specificity in patients with ovarian malignancies a [15]. Likewise, different studies propose the use of a Risk of Ovarian Malignancy Algorithm (ROMA) to improve the sensitivity and specificity of the combined use of both tumour markers in patients with abdominal masses [16- 18].

Materials and Methods
The present comparative study was conducted in the Department of Biochemistry, in association with the Department of Surgery and Oncology SMS Medical College and

Attached group of Hospitals, Jaipur. Further ovarian cancer subjects were also divided on the basis of menopausal status. Total 131 subjects included in this study and divided into two groups as follows: Group 1 included 61 premenopausal and Group 2 included 70 postmenopausal women with ovarian cancer. Out of 131 patients with ovarian cancer 30 were stage I, 30 were stage II, 40 were stage III and 31 were stage IV Female patients (age >23 years) diagnosed with ovarian cancer were included in this study. Exclusion Criteria was taken to rule out other diseases which can alter the result of the study like patients having other cancer, previously diagnosed case of cancer who is taking chemotherapy or radiotherapy, History of OCP & Pregnancy, Patients with benign ovarian diseases. Venous blood sample was withdrawn for investigations taking all aseptic precautions. Serum was separated and investigated for HE4 by ELISA, and CA125 by Chemiluminescence method [22].

Ethical approval and Informed consent The Protocol was approved by institutional Ethics committee. Informed written consent was obtained from all study subjects.

Statistical Analysis The data was analyzed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations were calculated. The statistical tests applied for the analysis were one-way ANOVA. The confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

Results

Table 1: Demonstrates serum HE4 and CA125 mean value in pre and postmenopausal female with ovarian cancer groups. Mean serum HE4, CA125 level were 196.50±100.78 & 140.31±204.23 in premenopausal women and 416.07±158.66 & 283.40±328.37 in postmenopausal women respectively. The mean value of HE4 and CA125 was higher in postmenopausal ovarian cancer women as compare with premenopausal ovarian cancer women. (Figure 1) The result was significantly high. (p<0.001), (p-0.004)

Table 2 shows AUC for HE4 and CA125 in ovarian cancer patients regarding healthy control with 95% Cl. AUC for CA125 was 0.680 (95% CI 0.587-0.773) and for HE4 was 0.893 (0.95% CI 0.840-0.946) (p=0.001) for distinguishing between ovarian cancer cases and control healthy subjects.

Table 3 shows the Pearson correlation of serum HE4 with serum CA125 in ovarian cancer subjects. HE4 showed positive correlation with CA125 (r=0.388, p= 0.000).

Table 4 shows that HE4 were significantly higher than CA125 in sensitivity and specificity (91% vs. 82.3% and 94%vs 83%, respectively). Also the positive predictive values (PPV) and negative predictive values (NPV) for HE4 were significantly higher than CA125 (92.1%vs 79.1% and 91.7%vs 85.2%, respectively).

Table 1: Serum HE4 (Pmol/l) and CA125 (U/ml) level in premenopausal and postmenopausal women with ovarian cancer.

Markers	Menses	
	Pre (N=61)	Post (N=70)
	Mean ±SD	Mean ±SD
HE-4	196.5082 ±100.78056	416.0714 ±158.66246
t-value	-9.295	
p-value	0.001 (Sig.)	
CA-125	140.3115 ±204.23528	283.4000 ± 328.37427
t-value	-2.943	
p-value	0.04 (Sig.)	

Test applied: Independent sample t-test

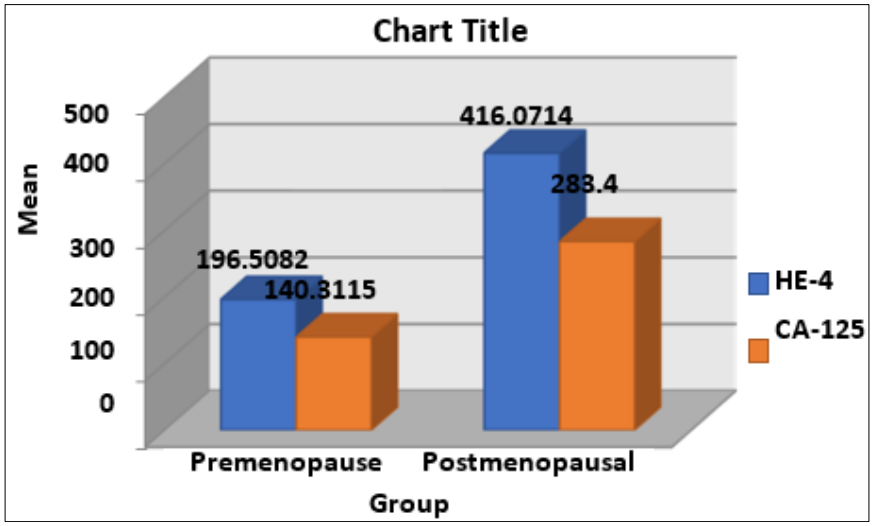

Fig 1: Serum HE4 (Pmol/l) and CA125 (U/ml) level in premenopausal and postmenopausal women with ovarian cancer

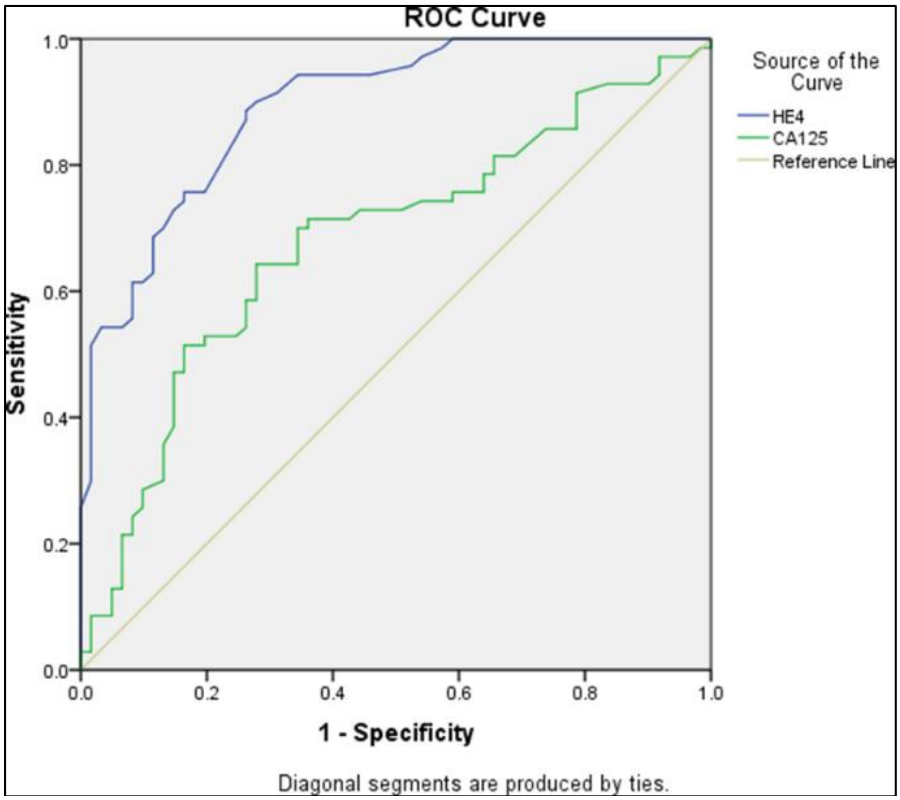

Fig 2: The receiver operating characteristic analysis (ROC) plot all women with ovarian cancer ROC curve between CA125 and HE4

Table 2: Area under the curve

	Area Under the Curve	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
HE4	0.893	0.840	0.946
CA125	0.680	0.587	0.773
P-VALUE	0.001		

Table 3: Pearson correlation of serum HE4 with serum CA125 in ovarian cancer subjects

		CA125
HE4	Pearson Correlation	0.388**
	P value	0.000

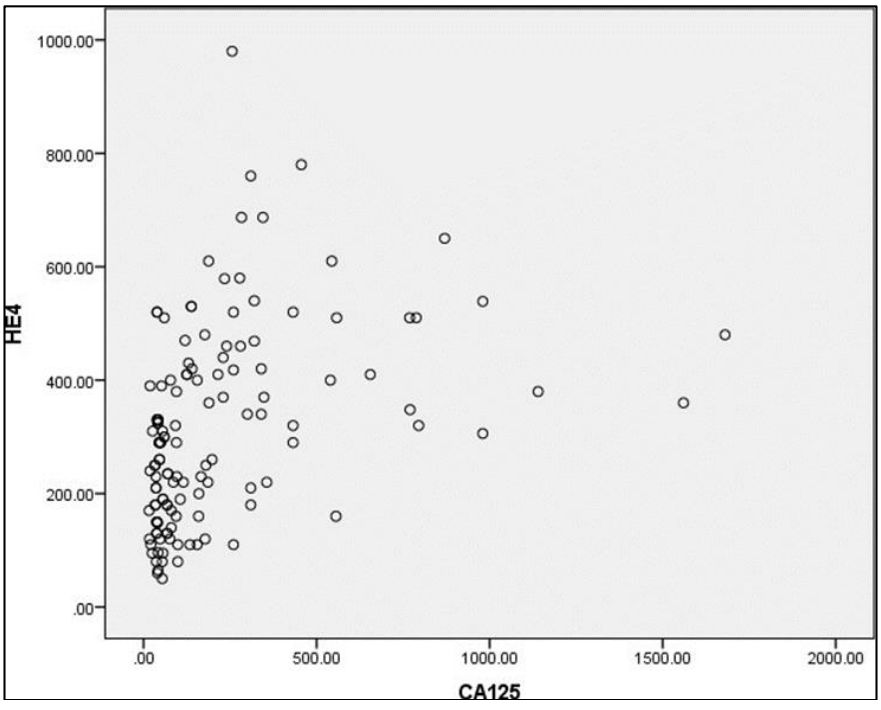

Fig 3: correlation between HE4 & CA125

Table 4: comparison of the diagnostic accuracy

	Sensitivity	Specificity	PPV	NPV
HE4	91%	94%	92.1%	91.7%
CA125	82.3%	83%	79.7%	85.2%

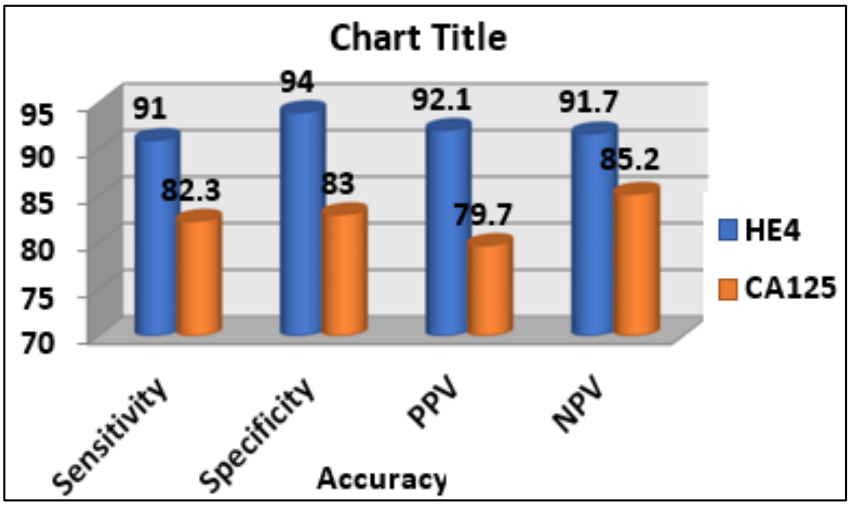

Fig 5: comparison of the diagnostic accuracy

Discussion

HE4 is a tumour marker with higher efficacy than CA 125. HE4 positive predictive value is 92.1% (high) compare to ca125 (79.7%) in our study in premenopausal and postmenopausal women with ovarian cancer [18]. HE4 showed a higher sensitivity than CA 125 in early stages and by contrast CA 125 was the most sensitive tumour marker in an advance stage. CA 125 can be used together with HE4 but the problem is the high proportion of false positive results (PPV+ 52.6%), mainly in premenopausal women. In our study we found that HE4 were significantly higher than CA125 in sensitivity and specificity (91%vs.82.3% and 94%vs 83%, respectively). Also the positive predictive values (PPV) and negative predictive values (NPV) for HE4 were significantly higher than CA125 (92.1%vs 79.1% and 91.7%vs 85.2%, respectively). HE4 showed positive corelation with CA125 (r=0.388, p= 0.000). These results are in concordance with the last publication of Montagnana *et al*. [19, 21] that reported that ROMA is mainly useful in postmenopausal women reported that HE4 is the most efficient tumour marker, with no clear advantages including CA 125, as we found in our study. More studies are necessary to clarify the addition of CA 125 and ROMA trying to increase sensitivity is not optimal in those patients with abnormal HE4 because the high specificity of HE4 already indicates a high risk for ovarian cancer. The PPV of HE4 is 96.7% and increases until 97.8% when ROMA is also abnormal. In summary, the use of ROMA algorithm in HE4 patients does not increase sensitivity but only increases the PPV by 3.2% (three patients). Our results are consistent with observation made by van Gorp *et al*. [20] A prospective study by Richards *et al* noted that HE4 had a better specificity than CA125 for the diagnosis of ovarian cancer in all women as well as in premenopausal women in addition to the higher ROC- AUC for HE4 compared to CA125 in all women. Moszynski *et al* studied the usefulness of HE4 as a second- line test in the assessment of women with suspicious ovarian tumors. They concluded that HE4 had a higher specificity, accuracy, and positive predictive value than CA125.

Conclusion

HE4 is the noval tumour marker in ovarian cancer, with a higher sensitivity in early stages, HE4 showed a higher sensitivity than CA 125 in early stages and by contrast CA 125 was the most sensitive tumour marker in an advance stage. HE4 can be used alone and together with CA125 as a prognostic and diagnostic marker for early detection of ovarian cancer in post and premenopausal women. The use of this combination allows increasing the tumour marker utility in the early diagnosis of ovarian cancer with a sensitivity of 91.0% and a specificity of 94%.

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