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**Research Article**

# THE USE OF RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA) AS A PREDICTOR OF EPITHELIAL OVARIAN CANCER IN WOMEN WITH ADNEXAL MASS.

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**ABSTRACT:** Ovarian cancer is the most common gynecological cancer associated with increased mortality due to delay in diagnosis. Most of the ovarian cancers are diagnosed at advanced stages and are associated with poorer prognosis and a lower survival rate. Early diagnosis is an important factor in improving the survival rate. **Objectives:** 1. To evaluate the usefulness of the ROMA algorithm (which uses serum levels of CA125 and HE4.) 2. To compare the performance of CA125 serum HE4 and ROMA algorithm using specificity and sensitivity concerning the prediction of malignancy. **Method:** Patients >35years of age, both premenopausal and postmenopausal, with adnexal mass were included in the study. Informed consent was obtained, and patients were subjected to detailed history taking and general, systemic and gynecological examination. The serum samples of the selected patients were collected preoperatively and serum concentrations of CA125 and HE4 were measured. The risk of malignancy was predicted as low risk or high-risk using ROMA. After the patients underwent surgery, the histopathology report was noted. All predicted values were compared with the final pathologic diagnosis. **Results:** Sixty patients were included in the study, out of which 36 were benign, 6 were borderline and 18 were malignant. Out of the 18 malignant cases, 16 were Epithelial ovarian cancers. Among the postmenopausal group, the sensitivity of serum CA125, serum HE4, and ROMA for differentiating benign masses from malignant epithelial ovarian cancer were 63.60%, 90.90%, and 90.90% respectively. In the premenopausal group, the sensitivity of serum CA125, serum HE4, and ROMA were 100% for all but specificity was 41.2%, 70.60%, and 64.70% respectively.
**Conclusion:** ROMA can be the best tool for predicting ovarian cancers in adnexal masses. HE4 as an individual marker can be used in differentiating benign ovarian masses from malignant masses especially in premenopausal women.
**Keywords:** Ovarian cancer; ROMA; CA125; HE4; Tumor markers.

**INTRODUCTION:** Ovarian cancer (OC) is the fifth most common cause of cancer death in women worldwide[1]. This cancer affects mainly women in the postmenopausal state with a peak between 55 and 65 years [2]. In India, the incidence of ovarian cancer is 5.4 to 8.0 per 100000 population in different parts of the country.[3] Because mortality is closely related to disease stage, the 5-year survival is higher than 70% in stage I or II but decreases to 40 and 20% in stage III or IV, respectively.[4] An early differential diagnosis and a timely surgical and/or chemotherapeutic treatment are very important[5]. A great majority of ovarian cancer patients come with the presentation of an adnexal
mass. Because of nonspecific clinical symptoms and lack of reliable screening, it is difficult to differentiate patients with ovarian cancer from patients with benign adnexal masses. Because of that, it is very important to find an efficient, reliable, and cost-effective way to detect patients with adnexal mass, who are likely to have ovarian cancer. Serum cancer antigen CA125 is the most widely accepted tumor marker to discriminate ovarian cancer from benign neoplasms in patients with a pelvic mass,

although it also elevates in some benign conditions such as pelvic inflammatory disease (PID) and ovarian endometriosis, which greatly decreases its specificity.

Moreover, the CA125 assay does not have enough sensitivity to identify early-stage ovarian cancer. Only approximately 50% of the early-stage ovarian cancer is associated with elevated CA125.[6] Human epididymal secretory protein E4 (HE4) is a newly identified serological tumor marker for the diagnosis of ovarian cancer. There have been pilot studies indicating that HE4 has increased sensitivity to discriminate ovarian cancer from benign ovarian neoplasms compared with CA125, especially in stage I disease.[7,8] Apart from its use as a single marker, serum HE4 has been evaluated in combination with CA125 in an algorithm in which also the menopausal status information is needed: this algorithm called ROMA (Risk of Ovarian Malignancy Algorithm) has been proposed by Moore. The ROMA algorithm was presented by Moore et al. in 2009.[9] A study published by Moore et al. resulted in a 95% specificity for HE4+CA125 and a sensitivity of 76.4%.[7]

This study aims to evaluate the clinical performance of ROMA and serum CA125 and serum HE4 individually in the triage of patients with an adnexal mass undergoing surgery, to discriminate benign from malignant disease.

**OBJECTIVES:**

1. To evaluate the usefulness of the ROMA algorithm (which uses serum levels of CA125 and HE4.)
2. To compare the performance of CA125, HE4 and ROMA algorithm using specificity and sensitivity concerning the prediction of malignancy.

**METHODLOGY:**

**Source of data**: A validation study was conducted in Department of Obstetrics and Gynecology and Department of Surgical Oncology, at Father Muller Medical College, Mangalore, India. All women who presented with ovarian/ adnexal mass or masses/ cyst or cysts, from November 2017 to June 2019 who were scheduled to undergo surgery were enrolled in the study.

**Inclusion criteria:**

- Premenopausal women aged > 35years
- Postmenopausal women

**Exclusion criteria:**

- Women on concomitant chemotherapies for ovarian malignancy
- Women diagnosed with ovarian carcinoma
- Women who have undergone B/L salpingo-oophorectomy
- Women who are not consenting for the study

The women included in the study based on the inclusion and exclusion criteria were asked to give their consent for the test to be done for this study. The serum samples of the selected patients were collected preoperatively and serum concentrations of CA125 and HE4 were measured. The risk of malignancy was predicted as low risk or high-risk using ROMA. After the patient underwent surgery,

all surgically obtained tissue samples were examined by the pathologist. All predicted values were compared with the final pathologic diagnosis. The cut off values for serum CA125 and serum HE4 are shown in table 1.

**Table 1. SERUM CA125 AND HE4 ASSAYS:**

| **Tumor marker** | **Cut off values** |
|---|---|
| **CA125** | **35 (U/mL)** |
| **HE4**<br><br>**Premenopausal**<br><br>**Postmenopausal** | <br><br>**<70 (pmol/L)**<br>**<140 (pmol/L)** |

**ROMA ALGORITHM**

ROMA algorithm to classify patients as being at low or at high risk for malignant EOC was calculated using the following equations, where PI is the predictive index:

Premenopausal: PI = −12.0 + 2.38 × LN(HE4) + 0.0626 × LN(CA125) Postmenopausal: PI = −8.09 +

1.04 × LN(HE4) + 0.732 × LN(CA125)

Predicted Probability (ROMA %) = exp (PI)/[1 + exp (PI)] ×100

LN is Natural Logarithm with a value of 2.71 (not log10.)

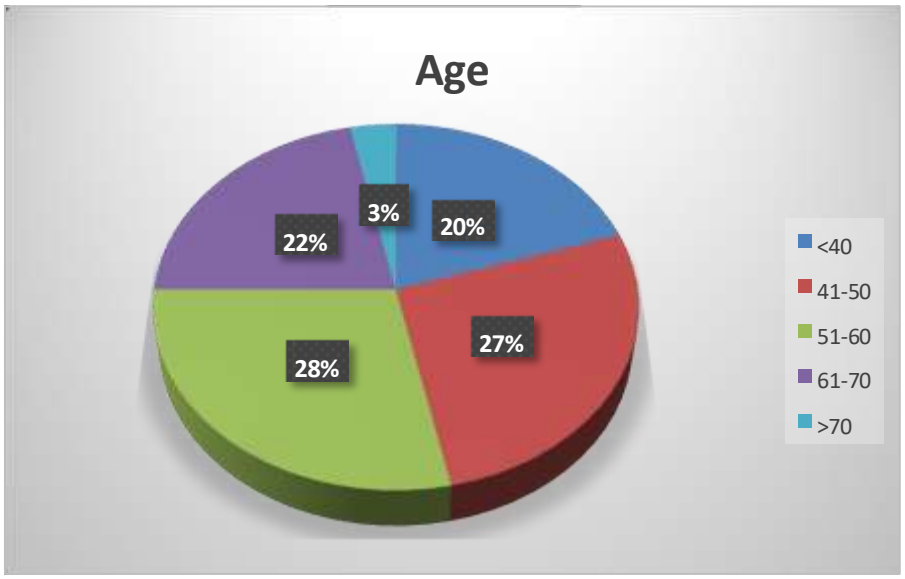
**TABLE 2. Cut off values for ROMA**

| CUT OFF VALUE | PRE-MENOPAUSAL | POST MENOPAUSAL |
|---|---|---|
| ROMA % | ≥13.1% | ≥27.7% |

**RESULTS:**

**Age distribution**

**Figure 1. Age distribution**




Twenty-eight percent of the patients belonged to the 51-60 years age group. The mean age in our study was found to be 51.8years.

**TABLE 3. MENOPAUSAL STATUS**

| **Menopausal status** | | **Valid Percent** |
|---|---|---|
| **Postmenopausal** | 35 | 58.3 |
| **Premenopausal** | 25 | 41.7 |
| **Total** | 60 | 100 |

Thirty-five patients belonged to the postmenopausal group and the rest 25 belonged to the premenopausal group.

**Histopathology:**

TABLE 4. HISTOPATHOLOGY

| | HPE | Valid Percent |
|---|---|---|
| **Benign** | 36 | 60 |
| **Borderline** | 6 | 10 |
| **Malignant EOC** | 16 | 26.7 |
| **Malignant Non EOC** | 2 | 3.3 |
| **Total** | 60 | 100 |

As shown in Table 4, out of 60 patients 55% were reported to have benign ovarian masses. 10% were reported as borderline ovarian tumors. 30% (n=18) patients were found to have malignant ovarian mass i.e. 26.7% (n=16) were malignant epithelial ovarian tumors and 3.3% (n=2) were non-epithelial ovarian tumors.

**TABLE 5. CLINICOPATHOLOGIC CHARACTERISTICS OF THE PATIENTS**

| PATHOLOGY | PREMENOPAUSAL | POSTMENOPAUSAL | ΠIENTS NO. (%) |
|---|---|---|---|
| BENIGN | | | |
| 1. Serous cystadenoma | 4 | 7 | 11 (18.3%) |
| 2. Mucinous cystadenoma | 2 | 3 | 5 (8.3%) |
| 3. Mixed tumors | 1 | 2 | 3 (5%) |
| 4. Endometriosis | 6 | 1 | 7 (11.6%) |
| 5. Others | 5 | 5 | 10 (16.6%) |
| BORDERLINE | | | |
| 1. Serous cystadenoma | 0 | 0 | 0 |
| 2. Mucinous cystadenoma | 3 | 3 | 6 (10%) |
| MALIGNANT | | | |

| | | | |
|---|---|---|---|
| I.EPITHELIAL OVARIAN CANCER | | | |
| 1. Serous | 2 | 6 | 8 (13.3%) |
| 2. Mucinous | 0 | 1 | 1 (1.6%) |
| 3. Endometrioid | 3 | 2 | 5 (8.3%) |
| 4. Clear cell | 0 | 2 | 2 (3.3%) |
| II.NON EOC | | | |
| 1. Germ cell tumor | 0 | 1 | 1 (1.6%) |
| 2. Adult granulosa cell tumor | 0 | 1 | 1 (1.6%) |

**ROC CURVE ANALYSIS**

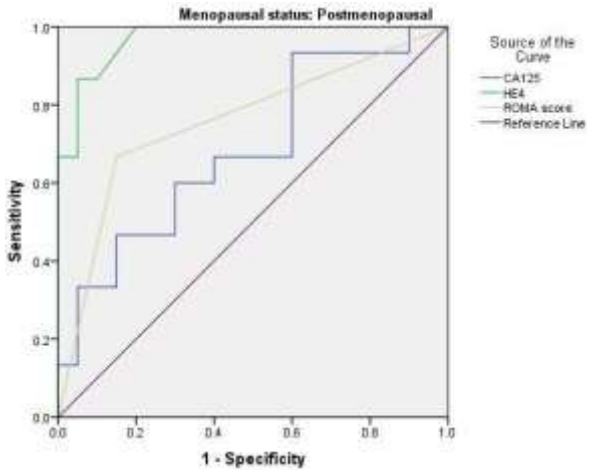



**FIGURE 2.1** ROC Curve in Postmenopausal group in Benign vs Malignant + Borderline ovarian tumors

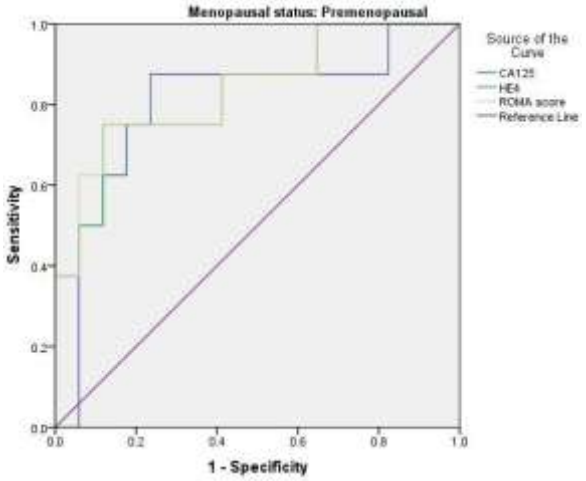
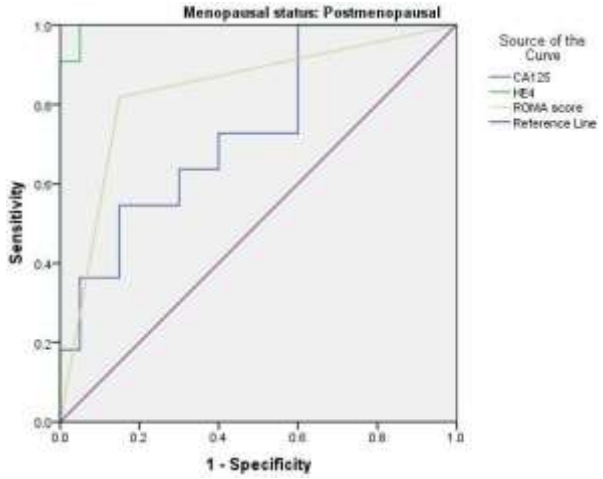



**FIGURE 2.2** ROC Curve in Premenopausal group in Benign vs Malignant + Borderline ovarian tumors

TABLE 6.1 AUC- ROC for Serum CA125, Serum HE4, AND ROMA for Benign Vs Borderline + Malignant Masses

| Menopausal status | Test Result Variable(s) | Area | Std. Error | c 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Postmenopausal | CA125 | .683 | .092 | .503 | .864 |
| | HE4 | .970 | .024 | .924 | 1.000 |
| | ROMA score | .758 | .087 | .588 | .929 |
| Premenopausal | CA125 | .801 | .105 | .596 | 1.000 |
| | HE4 | .831 | .092 | .651 | 1.000 |
| | ROMA score | .838 | .091 | .660 | 1.000 |

As shown in figure 2.1, in the premenopausal group, the AUC for all three tests was comparable, but HE4 and ROMA had better value indicating better performance.
Comparing the ROC-AUC in figure 2.2, in postmenopausal women, HE4 had the highest AUC of 0.970, compared to ROMA, with AUC of 0.758, which in turn was better than CA125 (AUC of 0.683).
ROC CURVE ANALYSIS



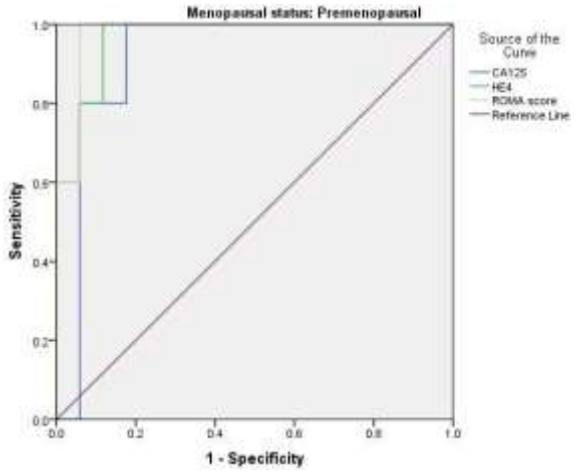




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**FIGURE 2.3** ROC Curve in Postmenopausal group in Benign vs Malignant Epithelial ovarian tumors

**FIGURE 2.4** ROC Curve in Premenopausal group in Benign vs Malignant Epithelial ovarian tumors

TABLE 6.2 AUC- ROC for Serum CA125, Serum HE4, AND ROMA for Benign Vs Malignant EOC

| Menopausal status | Test Result Variable(s) | Area | Std. Error | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Postmenopausal | CA125 | .736 | .093 | .555 | .918 |
| | HE4 | .995 | .008 | .981 | 1.000 |
| | ROMA score | .834 | .083 | .672 | .996 |
| Premenopausal | CA125 | .918 | .063 | .794 | 1.000 |
| | HE4 | .965 | .036 | .894 | 1.000 |
| | ROMA score | .976 | .029 | .920 | 1.000 |

As shown in figure 2.3, in the premenopausal group, the AUC for all the three tests were comparable, but HE4 (0.965) and ROMA (0.976) had better value compared to CA125. Comparing the ROC-AUC in figure 2.4, in postmenopausal women, HE4 had the highest AUC of 0.995, compared to ROMA, with AUC of 0.834, which in turn was better than CA125 (AUC of 0.736) indicating the superior performance of HE4 and ROMA over CA125 in the study.

TABLE 7.1 COMPARISON OF PERFORMANCE OF SERUM CA125, SERUM HE4 AND ROMA IN PREMENOPAUSAL GROUP

| PATHOLOGY | PARAMETER | SN | SP | PPV | NPV | DIAGNOSTIC ACCURACY | P VALUE |
|---|---|---|---|---|---|---|---|
| Benign Vs Malignant +B0rderline | CA125 | 87.50% | 41.20% | 41.20% | 87.50% | 56.00% | 0.2050 |
| Benign Vs Malignant +B0rderline | HE4 | 75.00% | 70.60% | 54.50% | 85.70% | 72.00% | 0.0810 |
| Benign Vs Malignant +B0rderline | ROMA | 75.00% | 64.70% | 50.00% | 84.60% | 68.00% | 0.0970 |
| Benign Vs Eoc | CA125 | 100.00% | 41.20% | 33.30% | 100.00% | 54.55% | 0.1350 |
| Benign Vs Eoc | HE4 | 100.00% | 70.60% | 50.00% | 100.00% | 77.27% | 0.0100 |
| Benign Vs Eoc | ROMA | 100.00% | 64.70% | 45.50% | 100.00% | 72.73% | 0.0350 |

Regarding table 7.1, the overall comparison of the performance of serum CA-125, serum HE4 and ROMA was made in the premenopausal group. In differentiating benign from malignant tumors (malignant + borderline), serum HE4 and ROMA had a sensitivity of 75%, but serum CA125 had a better sensitivity of 87.50%. The diagnostic accuracy of HE4 was 72% and ROMA was 68%, which was better than serum CA125 (56%). None had a significant p-value.

In differentiating benign from malignant EOC, all three had sensitivity and negative predictive value of 100%, but only serum HE4 and serum ROMA had p-values 0.0100 and 0.0350 respectively, which were statistically significant. And serum HE4 had a better specificity of 70.6% compared to ROMA (64.70%) and CA125 (41.20%). The diagnostic accuracy of HE4 (77,27%) and ROMA (72.73%) were better compared to CA125 (54.55%).

TABLE 7.2 COMPARISON OF PERFORMANCE OF SERUM CA125, SERUM HE4 AND ROMA IN POSTMENOPAUSAL GROUP

| PATHOLOGY | PARAMETER | **SN** | **SP** | **PPV** | **NPV** | DIAGNOSTIC ACCURACY | P VAL |
|---|---|---|---|---|---|---|---|
| BENIGN VS MALIGNANT +B0RDERLINE | CA125 | 60.00% | 60.00% | 52.90% | 66.70% | 60.00% | 0.3150 |
| BENIGN VS MALIGNANT +B0RDERLINE | HE4 | 66.70% | 95.00% | 90.90% | 79.20% | 82.86% | <0.001 |
| BENIGN VS MALIGNANT +B0RDERLINE | ROMA | 80.00% | 70.00% | 66.70% | 82.40% | 74.29% | 0.0060 |
| BENIGN VS EOC | CA125 | 63.60% | 60.00% | 46.70% | 75.00% | 61.29% | 0.2730 |
| BENIGN VS EOC | HE4 | 90.90% | 95.00% | 90.90% | 95.00% | 93.55% | <0.001 |
| BENIGN VS EOC | ROMA | 90.90% | 70.00% | 62.50% | 93.30% | 77.42% | 0.0020 |

Regarding table 7.2, the overall comparison of the performance of serum CA-125, serum HE4 and ROMA was made in the postmenopausal group. In differentiating benign from malignant tumors (malignant + borderline), serum HE4 had better specificity of 95% compared to ROMA (70%) and serum CA-125 (60%). Whereas, ROMA had a better sensitivity of 80.90% compared to serum HE4 (66.70%) and serum CA125 (60%). Diagnostic accuracy of serum HE4 and ROMA were 82.86% and 74.29% respectively, with *p*-values of <0.001 and 0.0060 respectively, which were significant compared to serum CA125 (60%, *p*-value of 0.3150).

In differentiating benign from malignant EOC, both ROMA and serum HE4 had a sensitivity of 90.90%, but serum HE4 had a better specificity of 95%. The diagnostic accuracy of serum HE4 i.e. 93.55% was highest, compared to ROMA (77.42%) and serum CA125 (61.29%). The p-values of HE4 and ROMA being <0.001 and 0.0020 were significant.

## DISCUSSION

The study was conducted to validate the use of serum CA-125, serum HE4, and ROMA in discriminating benign from malignant ovarian masses. The recommended cut off

value was taken as 35U/ml for CA125. For serum HE4, the cut off was 70pmol/L in premenopausal women and 140pmol/L in postmenopausal women. The recommended cut off value for ROMA was taken as 13.1% in premenopausal women and 27.7% in postmenopausal women.

In our study, out of 60 patients, 28% (n=17) belonged to the age group of 51 -60 years, similar to the observation in studies conducted by Huy et al[10] and Lycke et al.[11]

In the study conducted by Romagnolo et al[12] with 387 subjects, 61.7% were premenopausal and 38.2% were postmenopausal. Khadija et al[13] in their study with 108 subjects, reported that 63.8% of cases belonged to the premenopausal group and

37.9% belonged to the postmenopausal group. In contrast, our study had 58.3% (n=35) postmenopausal women and 41.7% (n=25) premenopausal women.

**SERUM CA-125:** In the study by Karlsen et al[14], the AUC for serum CA125 was 0.925 in premenopausal group and 0.921 postmenopausal group. Khadija et al[13] reported the AUC as 0.804 in the premenopausal group and 0.934 in the postmenopausal group. In our study, we achieved the AUC of 0.918 in premenopausal, which was comparable to Karlsen et al[14], but for the postmenopausal group, we achieved a lower AUC of 0.736.

**SERUM HE4:** In discriminating benign from malignant EOC cases, Zheng et al[15] achieved an AUC of 0.962 in the premenopausal group and 0.904 in the postmenopausal group. In our study, the AUC for the premenopausal group was 0.965 and we observed a superior AUC for the postmenopausal group i.e. 0.995. Yanaranop et al[16] reported a lower AUC i.e. 0.844 in the premenopausal group and 0.771 in the postmenopausal group. Serum HE4 individually has performed better.

**ROMA:** Khadija et al[13] reported a good AUC for ROMA in the EOC group with a value of 0.957 in premenopausal women and 0.944 in postmenopausal women. Similar to this study, results were reported by Sandri et al[17] with AUC of 0.910 in premenopausal women and 0.930 in postmenopausal women. Our study achieved a superior AUC of 0.965 in the premenopausal group and 0.995 in the postmenopausal group compared to other studies mentioned in table number. The number of subjects in our study was 60, compared to 260, 108, 349, 277 and 1218 in Yanaranop et al[16], Khadija et al[13], Sandri et al[17], Huy et al[10] and Karlsen et al[14] respectively.

In our study, when we compared the sensitivity and specificity of serum CA-125, serum HE4, and ROMA, in discriminating benign from malignant EOC, we observed that in premenopausal group, all three had a sensitivity of 100%, but HE4 had a better specificity of 70% than ROMA (64.70%) and serum CA-125 which had the lowest specificity of 41.20%. we achieved a statistically significant *p*-value for serum HE4 and ROMA i.e. 0.001 and 0.035 respectively. In the postmenopausal group, serum HE4 and ROMA had similar performance with a sensitivity of 90.9%, but HE4 had a superior specificity of 95% than ROMA (75%). The *p*-value was statistically significant for serum HE4 and ROMA i.e. <0.001 and 0.0020, respectively.

Serum HE4 as an individual marker performed better compared to serum CA-125 and ROMA.

Zheng et al[15], in their study, reported sensitivity of 50% and the specificity of 98.38% for serum HE4 and concluded that serum HE4 testing is a more accurate and powerful tool than serum CA-125 assay in discriminating EOC from benign conditions like endometriosis and PID.

Musalhi et al[18] in their study summarized that HE4 and ROMA had a very high specificity (93%) than serum CA-125 but were less sensitive than serum CA-125 in the premenopausal group. Serum HE4 and ROMA had a comparable sensitivity in the postmenopausal group in their study.

In our study among the premenopausal group, in discriminating benign from malignant and borderline masses, serum CA-125 had a superior sensitivity of 87.5% compared to serum HE4 and ROMA with a sensitivity of 75% each, but HE4 had the highest specificity of 70.60% among all three tests. The p-values of all the tests were not statistically significant in this group for premenopausal women.

In the postmenopausal group we observed a superior performance by ROMA with sensitivity 80% and also serum HE4 performed better with specificity 95% compared to serum CA125 (sensitivity and specificity of 60%). Serum HE4 and ROMA had statistically significant p-values i.e. <0.001 and 0.006 respectively. Serum CA-125 had a sensitivity and specificity of 60%, with a p-value of 0.3150 which was not statistically significant. As an individual marker, serum HE4 had the highest diagnostic accuracy of 72% compared to ROMA (68%) and serum CA125 which had the lowest diagnostic accuracy of 55% in this group.

Our study results have been consistent with the superior performance of serum HE4 and ROMA in the prediction of ovarian cancer, similar to the observations being reported by the studies conducted to validate these markers.

## LIMITATIONS

- As our cut off for age was taken as low as 35years, this included relatively younger women where benign disease is much commoner.
- We have included the minimum number of subjects needed for the study.
- The ROMA includes testing of serum levels of both CA215 and HE4. The HE4 testing is expensive currently and the diagnostic laboratories conducting this test are limited in number and location.
- The performance of individual markers in predicting malignant disease, concerning the clinical stage of the disease is not included.

## CONCLUSION

- Serum HE4 as an individual marker can be a useful diagnostic test to differentiate benign from ovarian cancers, especially in premenopausal women.
- To conclude ROMA could be a diagnostic tool in predicting the risk of malignancy in ovarian masses in both premenopausal and postmenopausal women, as it uses both CA125 and HE4 values.
- ROMA could potentially be a better algorithm used to shorten the time between diagnosis and primary treatment, and importantly triage the cases for involvement of the gynecologic oncologist/ oncosurgeon. `

## PROVISION FOR FUTURE RESEARCH

- Studies with larger cohorts could be conducted for evaluating the usefulness of these markers in diagnosing ovarian cancer.
- Studies to evaluate the effect of demographic and lifestyle factors on serum HE4.
- To evaluate the validity of the three markers concerning different clinical stages of malignant disease.

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