A Study to Evaluate Risk of Ovarian Malignancy Algorithm (ROMA) in Patients with Ovarian Masses

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Abstract

Objective The aim of this study was to evaluate risk of ovarian malignancy algorithm (ROMA) in premenopausal patients with ovarian masses.

Materials and Methods A mixed observational study was conducted in the Department of Obstetrics and Gynecology at Lilavati Hospital and Research Centre, Mumbai, from the month of June 2017 to March 2018. In this study, premenopausal females with ovarian masses, satisfying the inclusion criteria, were evaluated for the purpose of preoperative analysis.

Results In premenopausal females, ROMA less than 11.4% is normal and more than or equal to 1.4% is increased. Considering histopathology reports as the gold standard, significant association was present between ROMA score and premenopausal status.

Conclusion ROMA includes two recognized markers that are being used in the current scenario for the purpose of preoperative risk assessment of ovarian cancer, cancer antigen 125 (CA125), and human epididymis protein 4 (HE4). CA125 has been shown to be elevated in most ovarian cancer cells but has a low specificity for ovarian malignancies. HE4 is a recently developed biomarker that is elevated in ovarian cancers, as well as few other cancers, and has been shown to have higher specificity than CA125. Combining CA125 and HE4 provides a relatively more accurate prediction of malignancy than either test alone. ROMA culminates the benefits of the combined CA125 and HE4 biomarkers along with menopausal status to help assign a numeric risk stratification of malignancy in cases of ovarian tumors.

Keywords► risk of ovarian malignancy algorithm (ROMA)► ovarian masses► premenopausal

Introduction

Ovarian cancer is one of the commonest malignancies of the female genital tract and it kills more women every year than cancers of all other genital sites. Unlike carcinoma of cervix or endometrium, ovarian cancer does not have preclinical stage where screening is possible. Majority of women with ovarian cancer are asymptomatic till the late stage or report vague, nonspecific abdominal complaints. In such a scenario, there is a genuine need of reliable diagnostic technique for...
early detection of the ovarian masses. Regarding the nature of tumor whether benign or malignant, it is equally important for the management and counseling of patients. The traditional strategy for establishing the final diagnosis in ovarian mass has been to perform an exploratory laparotomy.

Ovarian mass is a multifaceted entity and hence evaluation of ovarian mass is based upon clinical presentation, pelvic examination, radiological investigations like trans-abdominal or transvaginal ultrasound and tumor markers studies, especially when malignancy is suspected.

Patients with an ovarian mass may present with varying symptoms—A woman presenting with abdominal or pelvic pain, bleeding per vaginum, and positive pregnancy test may test positive for an ectopic pregnancy. A female who complains of sudden onset of severe and pain localized to one side, along with vomiting with nausea, may raise suspicion of an underlying ovarian torsion. These symptoms warrant a surgical or medical emergency as they can have catastrophic consequences. Pelvic pain with a more gradual onset associated with fever, nausea, or discharge per vaginum may be indicative of pelvic inflammatory disease or a tubo-ovarian abscess. Patients with exacerbation of pain during menstruation may have an endometrioma. Dysmenorrhea and menorrhagia may lean toward a diagnosis of leiomyoma rather than an ovarian mass. Patients presenting with amenorrhea, menorrhagia or oligomenorrhea, accompanied with obesity and hirsutism may have polycystic ovary syndrome. Post-menopausal or premenarchal bleeding maybe suggestive of a granulosa cell tumor. A corpus luteal cyst or ruptured follicular cyst may present with pain after intercourse.

Risk of ovarian malignancy algorithm (ROMA) is a test that combines human epididymis protein 4 (HE4), cancer antigen 125 (CA125), and menopausal status and a numerical score is calculated to assess whether a woman who presents with ovarian mass is at high or low likelihood of finding malignancy on surgery. ROMA score has been studied in detail and it was found that it was possible to differentiate between benign and malignant ovarian masses in both pre- and postmenopausal groups, suggesting that this quick approach could provide a strong basis for clinical diagnosis and treatment.\(^1,2\)

ROMA is an U.S. Food and Drug Administration-approved risk stratification tool that incorporates CA125, HE4, and menopausal status and calculates a numerical score that indicates the risk of malignancy for pelvic masses.\(^3\) ROMA is indicated as an aid in assessing likelihood of malignancy in women along with clinical evaluation who present with an ovarian mass.\(^3\)

In recent years, the use of novel biomarkers such as HE4 has been studied to improve the sensitivity and specificity of the diagnosis of ovarian malignancy. HE4 is primarily expressed in the reproductive and respiratory tracts and is overexpressed in epithelial ovarian cancer. The HE4 gene product is an N-glycosylated protein that is secreted into the extracellular environment and can be detected in the bloodstream of patients with ovarian cancer. HE4 was found to be elevated in more than half of ovarian tumors that do not express CA125. This finding prompted the development of a dual marker algorithm that combined HE4 and CA125 with the pre- and postmenopausal statuses of the patient, known as ROMA.

Moore et al proposed the ROMA algorithm as a useful tool for triaging women with a pelvic mass into high or low risk groups for ovarian cancers.\(^4\) ROMA is a quantitative test that combines HE4, CA 125, and menopausal status into a numerical score to assess whether a woman who presents with ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery.\(^5\)

### Materials and Methods

**Study area**: Department of Obstetrics and Gynecology, Lilavati hospital and Research Centre, Mumbai.

**Study population**: All premenopausal patients admitted to Lilavati Hospital with ovarian masses and planned for surgical intervention, satisfying the inclusion criteria and willing to be a part of the study, were asked to participate in the study.

**Study design**: Mixed (Retrospective and Prospective) Observational Study conducted in department of Obstetrics and Gynecology at Lilavati Hospital and Research Centre.

**Study duration**: June 2017 to March 2019 (Institutional Ethics Committee and Research Advisory Committee Approval taken)

- **Retrospective data**: June 2017 to February 2018
- **Prospective data**: March 2018 to March 2019

**Inclusion Criteria**

- All patients presenting to the hospital with ovarian masses more than 18 years and who have not attained menopause.
- Women with pelvic masses of ovarian origin as diagnosed by ultrasonography, computed tomography, or magnetic resonance imaging.
- Admitted electively or in emergency for ovarian pathologies and planned for the surgery.

**Exclusion Criteria**

- Pregnant females
- Postmenopausal females with ovarian masses
- Women with known relapse of a previous cancer
- Women with co-existence of cancer in other sites, previously diagnosed disease commonly associated with an increase in CA125 (such as mesothelioma), and nonovarian tumors, like uterine fibroids.

**Study approval**: The study is approved by the Research Advisory Committee and Institutional Ethics Committee of the Hospital. Approval letters of committees were obtained.

**Ethical consideration**: The study did not include any experimentation; only the clinical data of patients was used for study purpose. The patient was informed in detail about the study and a written consent obtained. No one received any benefits for personal or professional use from this study, directly or indirectly.
**Method of measurement of outcome of interest:** ROMA, CA 125, histopathology report (HPE) of postoperative specimen sent for analysis;

**Data collection methods:** Clearance from the Research Advisory Committee and Institutional Ethics Committee were taken for the study.

**Retrospective data:** After obtaining the Institutional Ethics Committee approval, the data was collected from the medical records department. The consent for retrospective data was waived by the committee.

**Prospective data:** Data collection via the data collection form was initiated after obtaining clearance from Institutional Ethics Committee. Data was collected from the respondents by direct interview after getting written informed consents from them.

**Statistical analysis:** Data was analyzed using SPSS V15.0 (Statistical Package for Social Sciences, Version 15.0). Data was given as mean ± standard deviation (n) for continuous data and number (percentage) for categorical data. Comparison of means was performed by Student’s unpaired t-test for numerical data. Fisher’s exact probability test or chi-squared tests were applied to compare percentages for categorical data. Student’s paired t-test was applied to compare paired data at pre and postmenopausal status. If the data are non-normal, corresponding nonparametric tests such as Mann–Whitney U test to be applied to non-normal data. Histopathological diagnosis is considered as gold standard for defining outcome and its classification as benign or malignant. If malignancy is present, type of malignancy is specified; ROMA index will be evaluated for sensitivity and specificity with reference to the actual presence of a malignant or benign ovarian mass. The area under curve of receiver operating characteristics was calculated for comparison of all three methods. All statistical tests were two tailed. Alpha (α) level of significance was taken as p less than 0.05.

**Results**

Out of 49 cases of premenopausal cases, 42.85% had serum CA 125 values more than 35 IU/mL (**Table 1**)

Out of 16 premenopausal females with ROMA score more than or equal to 11.4%—high risk, 10 (58.8%) were malignant, and 6 (18.8%) were benign (**Table 2**). Out of 33 premenopausal females with ROMA score less than 11.4% were of low risk, 7 (41.2%) were malignant, and 26 (81.2%) were benign (**Table 2**). The statistical analysis was done using Fisher’s exact probability test.

**Statistical Analysis—**Fisher’s exact probability test. 

\[ p = 0.009; \text{DF} = 1. \]

**Conclusion**—Significant association was present between ROMA score and premenopausal status. Raised value of ROMA score with malignancy present was found in 10 out of 16 premenopausal females.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ROMA in diagnosing ovarian masses as benign or malignant in premenopausal females are 58.82, 81.25, 62.50, 78.79, and 73.47%, respectively (**Table 3**).

**Table 1** Distribution of serum CA125 in premenopausal cases

<table>
<thead>
<tr>
<th>CA125 (IU/mL)</th>
<th>Premenopausal age group (n = 49)</th>
<th>Percentage of premenopausal age group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>28</td>
<td>57.14</td>
</tr>
<tr>
<td>&gt;35</td>
<td>21</td>
<td>42.85</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Abbreviation: CA125, cancer antigen 125.

**Table 2** Evaluation of validity of ROMA with HPE in premenopausal female

<table>
<thead>
<tr>
<th>ROMA</th>
<th>HPE</th>
<th>Total (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥11.4%</td>
<td>Malignant</td>
<td>Benign</td>
</tr>
<tr>
<td></td>
<td>n1 = 17</td>
<td>n2 = 32</td>
</tr>
<tr>
<td>≥11.4%</td>
<td>10 (58.8%)</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>&lt;11.4%</td>
<td>7 (41.2%)</td>
<td>26 (81.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>32</td>
</tr>
</tbody>
</table>

Abbreviations: HPE, histopathology report; ROMA, risk of ovarian malignancy algorithm.

**Table 3** Evaluation of validity of ROMA score in premenopausal females

<table>
<thead>
<tr>
<th>Statistical parameter</th>
<th>Percentage (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>58.82</td>
<td>32.92–81.56</td>
</tr>
<tr>
<td>Specificity</td>
<td>81.25</td>
<td>63.56, 92.79</td>
</tr>
<tr>
<td>PPV</td>
<td>62.50</td>
<td>42.24, 79.16</td>
</tr>
<tr>
<td>NPV</td>
<td>78.79</td>
<td>67.26, 87.04</td>
</tr>
<tr>
<td>Accuracy</td>
<td>73.47</td>
<td>58.92, 85.05</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; ROMA, risk of ovarian malignancy algorithm.
Comparison of validity of ROMA score in premenopausal female is shown in Table 4: In this study, low sensitivity of 58.82% is seen, similar to the sensitivity in the studies done by Al Musalhi et al (52%) and Montagnana et al (53.3%). The specificity (81.25%) is similar to the specificity seen in the studies done by Montagnana et al (80.6%), Huy et al (82.9%), Wei et al (88.52%), and Oranratanaphan et al (88.52%). The NPV of this study is 73.47% similar to the NPV seen in the study of Al Musalhi et al (71%).

In this study, significant association is seen between ROMA score and HPE reports of the samples of premenopausal women. Raised value of ROMA score with malignancy present was found in 10 out of 16 premenopausal females.

### Discussion

According to Al Musalhi et al, HE4 demonstrated a high specificity of 90% in the whole population and in the premenopausal group it was 93%. CA125 has a sensitivity of 67% in the premenopausal females, a low value for any tumor marker. Both HE4 and ROMA score showed high specificity in the premenopausal age group, whereas risk malignancy index and CA125 had high sensitivity in this age group. The tumor maker HE4 did not have high sensitivity and specificity for diagnosing borderline ovarian markers.

According to Wei et al, HE4 was found to have high specificity and PPV in the diagnosis of premenopausal ovarian cancers.

According to Oranratanaphan et al, HE4 at a cutoff value of 70 pmol/L placed it at a sensitivity and specificity similar to that of ROMA, while significantly reducing the costs of ROMA scoring. ROMA had higher specificity (79.8%) and positive predictive value (50.5%) as compared with CA125. This study highlights the feasibility of HE4 alone instead of ROMA (HE4 + CA125) as markers for ovarian carcinoma, especially epithelial ovarian cancers.

### Conclusion

The diagnosis of ovarian cancers in premenopausal females with pelvic masses of ovarian origin has been a difficult entity to conquer considering the vague nature of presentation of the disease. It is of paramount importance that we devise a tumor marker or parameter with high specificity in diagnosing such malignancies. ROMA score offers tremendous potential and viability for future use as a tumor marker in premenopausal females.

ROMA score incorporates easily available parameters to give an estimate of the pathology that we as gynecologists are potentially dealing with. The important consideration here is to keep in mind the cost of such tests so as to not overburden the healthcare system.

Also, HE4 should be studied statistically as a marker for tumor recurrence in such patients treated for ovarian malignancies.

### Conflict of Interest

None declared.

### References