**Research Article**

# The Risk of Ovarian Malignancy Algorithm (ROMA) as a Predictor of Ovarian Tumor Malignancy

## *Risk of Ovarian Malignancy Algorithm (ROMA) sebagai Prediktor Keganasan Ovarium*

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## Abstract

**Objective**: To assess the diagnostic value of Risk of Ovarian Malignancy Algorithm (ROMA) in predicting ovarian malignancy.

**Methods**: Diagnostic test was performed at dr. Mohammad Hoesin Hospital Palembang during June 2016 to November 2016. Data were analized with SPSS version 21.0 and Med-calc statistic.

**Results**: A total of 57 subjects were recruited in this study. Subjects were divided into two groups: the premenopausal and postmenopausal group. Analysis with ROC curve was performed, the ROMA optimal cut-off of ROMA was 23.7% and 48.15% in the premenopausal and the post-menopausal group, respectively. With the optimal cut-off, the sensitivity was 79.41% and specivicity was 75%, positive predictive value wa 73.07% and negative predictive value 83.77% with accuracy 76.92% in diagnosing ovarian malignancy. Compared to RMI-3, the sensitivity was 65.5% and specivicity was 85.7% with accuracy 75.44%.

**Conclusion**: ROMA is not a reliable diagnostic tools of ovarian malignancy.

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**Keywords**: CA125, HE4, ovarian cancer, risk of ovarian malignancy-algorithm/ROMA, risk of ovarian malignancy index/RMI

## *Abstrak*

***Tujuan**: Menilai nilai diagnostik Risk of Ovarian Malignancy Algorithm (ROMA) dalam memprediksi keganasan ovarium.*

***Metode**: Penelitian uji diagnostik dilakukan di RSUP dr. Mohammad Hoesin Palembang selama periode Juni 2016 - November 2016, sebanyak 61 wanita dengan tumor ovarium dimasukkan sebagai subjek penelitian, 4 pasien dieksklusi karena perbedaan diagnosis saat intraoperatif. Data kemudian dianalisis dengan menggunakan software SPSS versi 21.0 dan Med-calc statistic.*

***Hasil**: Dari 57 pasien yang memenuhi kriteria inklusi dan eksklusi. Pasien dibagi menjadi dua kelompok yaitu kelompok premenopause dan menopause. Dilakukan analisis dengan kurva ROC didapatkan cut-off optimal ROMA pada penelitian ini yaitu 23,7% untuk kelompok premenopause dan 48,15% untuk kelompok menopause. Dilakukan uji diagnostik, didapatkan sensitivitas 79,41% dan spesifisitas 75%, nilai duga positif adalah 73,07% dan nilai duga negatif 83,77% dengan nilai akurasi 76,92% dalam mendiagnosa keganasan ovarium. Dibandingkan dengan RMI-3, didapatkan nilai sensitivitas 65,5% dan spesifisitas 85,7% dengan nilai akurasi 75,44%.*

***Kesimpulan**: Pemeriksaan ROMA bukan merupakan uji diagnostik keganasan ovarium yang akurat.*

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***Kata kunci**: CA-125, HE-4, kanker ovarium, risk of ovarian malignancy algorithm, risk of ovarian malignancy index*

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## INTRODUCTION

Ovarian cancer is the sixth most common malignancy in women after uterine cervical, breast, colorectal, skin, and lymphoma cancer. Up to 70% of ovarian cancer is diagnosed at advanced stage that have spread into upper abdominal cavity (stage III) or wider (stage IV) with 5 years survival rate at 15-20%, whereas survival rate at stage I and stage II are predicted at lower rate of 90% and 70%.[1,2]

Patients are mostly diagnosed at more advanced stage as early diagnostic tool is still not available. One of the mostly used tumor markers is cancer antigen (CA) 125. To date, CA 125 is the best tumor marker available in diagnosing and monitoring ovarian cancer patients. However, CA 125 increases only in 80% of patients in late stages and 50% of patients in early stages. About 20% of patients of early stages ovarian cancer have normal CA 125 values.[2]

Several biomarkers have been tested lately as alternatives or additional markers to differentiate benign from malignant tumor. Human Epididymis4 (HE4) is a promising biomarker to be used. HE4, a glycoprotein, is over expressed in ovarian cancer particularly.[3]

Moore et al. designed Risk of Ovarian Malignancy Algorithm (ROMA), using blood test algorithm, as a simpler biomarker compared to RMI (risk malignancy index) that requires ultrasonography. They reported significant increase in sensitivity and specificity when HE4 and CA125 are used in combination. In a further study comparing ROMA and RMI, Moore et al. reported higher sensitivity and specificity in ROMA.[4,5]

Karlsen et al. reported a high sensitivity (94.8%) and specificity (75%) results of ROMA in diagnosing ovarian cancer.[6] Molina et al. also reported a better sensitivity (90.1%) and specificity (87.1%) results of ROMA compare to CA125, but it is might further improved if it is used with normal HE4 and abnormal CA125.[7]

RMI is one of the most frequent used methods in identifying malignancy and considered as a simple method which uses menopause status, ultrasound and CA125 level. Jacobs et al. obtained sensitivity of 85.4% and specificity of 96.9% using cut-off 200. However, Andriata et al. obtained a different results in using the same RMI method: sensitivity of 8.4% and specificity of 76.9%.[8]

Anton et al. from Brazil did the same comparison of ROMA and RMI and no significant difference was found between diagnostic values of ROMA and RMI.[9] Normal value of biomarkers such as CA125 and HE4 varies in different population. Pauler et al. reported a difference in normal value of CA125 in Caucasian and Asian. Several studies have been done to find normal values of these markers in different populations. This difference in normal values could alter the outcome of ROMA. Therefore, Karen et al. proposed different cut-off values for different population to accommodate this variation of normal values in different population.[10] This study is aimed to assess the diagnostic value of ROMA in predicting ovarian malignancy.

## METHODS

Diagnostic tests and cross sectional design were used on 61 women with ovarian cancer and were planned for operative procedure. This research was conducted at Obstetrics and Gynecologic Department of Dr. Mohammad Hoesin Palembang Hospital from June 2016 to November 2016.

Inclusion criteria were women diagnosed with ovarian cancer who are being planned to undergo surgical procedures. The diagnosis of ovarian cancer was based on anamnesis, physical examination, and ultrasonography. Exclusion criteria were women diagnosed with non-gynecologic malignancies, pregnancy, kidney failure or intra-operative mass of non-ovarian origin.

Gestational age, parity, education level, occupation, smoking, contraception, physical examination, ultrasonography, post-operative CA125 and HE4 of the subjects were recorded. CA125 and HE4 tests were carried out by using architect reagent and histopathology results were masked. ROMA score was calculated by software downloaded from http://romatools.he4test.com/.

Data were analyzed with SPSS 21.0. The cut-off point value of ROMA was determined by Receiving Operating Characteristic (ROC) curve. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio were calculated by med-calc statistic.

## RESULTS

Demographic and the tumor characteristics of the subjects are presented in Table 1. Mean age of samples was 40.51 years old with majority of the patients were from pre-menopause group (56.1%) and higher tendency found in multipara (43.9%).

**Table 1.** Demographic and Tumor Characteristics of the Subjects

| Characteristic | Frequency | |
|---|---|---|
| | N | % |
| Age, mean±SD | 40.51±16.32 (6-64) | |
| Pre-menopause | 32 | 56.1 |
| Menopause | 25 | 43.9 |
| Parity | | |
| Not Married | 11 | 19.3 |
| Primipara | 21 | 36.8 |
| Multipara | 25 | 43.9 |
| Pathology | | |
| Malignant | 24 | 42.2 |
| Borderline | 5 | 8.7 |
| Benign | 28 | 49 |

| | | |
|---|---|---|
| Type | | |
| Epithelial | 45 | 78.9 |
| Non-Epithelial | 12 | 21.1 |
| Total | 57 | 100 |

In this study, alternative cut-off point of ROMA was determined by using ROC curve. Patients were divided into two groups, consisting of the pre-menopausal and post-menopausal group. For the post-menopausal the group, the optimal cut-off point of ROMA was obtained at 58.15% with sensitivity of 47.15%, specificity of 71.4%, positive predictive value of 86.6% and negative predictive value of 50% as shown in Figure 1 below.

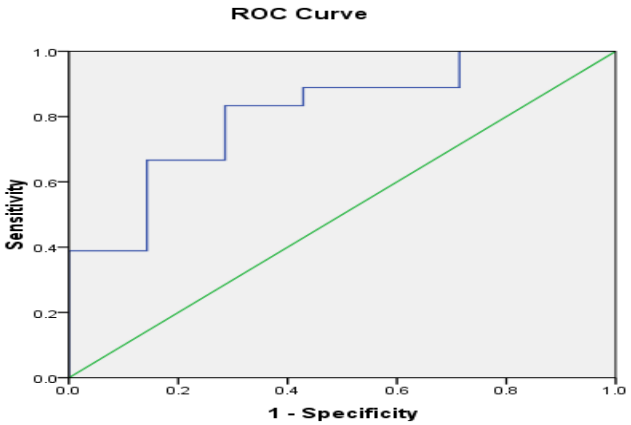


**Figure 1.** ROC curve of ROMA of the post-menopausal group

In the pre-menopausal group, the optimal cut-off point of ROMA was obtained at 23.7% with sensitivity of 72.72% and specificity of 76.19%, positive predictive value of 61.54% and negative predictive value of 84.21% (Figure 2).

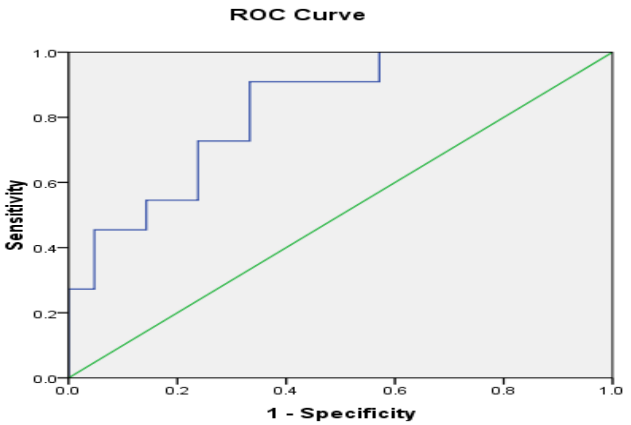


**Figure 2.** ROC curve of ROMA of the pre-menopausal group

Diagnostic test was done with alternative cut-off with borderline histopathology was included as malignant group. Results obtained were then compared to those of standard cut-off. As RMI-3 is frequently used to predict malignant to benign ovarian tumor, we also compared ROMA to RMI-3 with standard cut-off > 200 for prediction of malignancy (Table 2).

**Table 2.** Diagnostic Value of RMI-3 vs ROMA Alternative vs ROMA Standard with Borderline Included

| Benign vs Malignant + Borderline | ROMA alternative | ROMA standard | RMI-3 |
|---|---|---|---|
| Sensitivity, % | 65.5 | 82.7 | 65.5 |
| Specificity, % | 85.7 | 64.2 | 85.7 |
| PPV, % | 82.6 | 70.5 | 82.6 |
| NPV, % | 70.5 | 78.2 | 70.5 |
| Accuracy, % | 75.44 | 73.68 | 75.44 |

If samples with borderline histopathology were not included as malignant group, better diagnostic results were obtained. RMI-3 have better sensitivity and specificity compared to ROMA results without borderline histopathology included as shown in Table 3.

**Table 3.** Diagnostic Value of RMI-3 vs ROMA Alternative vs ROMA Standard with Borderline Excluded

| Benign vs Malignant | ROMA alternative | ROMA standard | RMI-3 |
|---|---|---|---|
| Sensitivity, % | 79.41 | 91.67 | 70.83 |
| Specificity, % | 75 | 64.2 | 85.7 |
| PPV, % | 73.07 | 68.75 | 90.47 |
| NPV, % | 83.77 | 90.00 | 77.41 |
| Accuracy, % | 76.92 | 76.92 | 78.84 |

## DISCUSSION

Almost 70% of ovarian cancer were diagnosed at later stage with 5-year survival rate at about 15-20%, whereas survival rate at stage I and stage II were predicted at 90% and 70%.

ROMA, a test using combination of CA125, HE4, and menopause status, is an effective diagnostic tool to diagnose ovarian cancer. The effectiveness of ROMA as pre-operative diagnosis tool in patients with pelvic mass have been proven by several

studies though there are still doubts of its superiority due to variations in cut-off values to diagnose malignancy.

Gorp et al. and Anton et al. have shown different cut-off values for different populations resulting in different diagnostic values. Hence, this study is aimed to find an alternative cut-off value to be compared with standard cut-off value and RMI which often used as a diagnostic tool.[7,8,11,12]

In this research, by using ROC analysis, alternative cut-off values were obtained at 23.7% for pre-menopause and 48.15% for menopause (72.41% sensitivity, 75% specificity, 73.68% accuracy) when patients with borderline histopathology were included as malignant group. Better results were obtained (79.41% sensitivity, 75% specificity, 76.68% accuracy) when patients with borderline histopathology were not included in malignant group. Using standard cut-off, ROMA has better sensitivity (82.7% including borderline; 91.67% if borderline was excluded).

RMI-3 diagnostic value was also improved when borderline histopathology was not included in the malignant group: 70.83% for sensitivity; 85.7% for specificity; and 78.84% for accuracy.

In this study, the median age was 40.51 years old which is close to Winarto's median age of 41 years old, and the proportion of the post-menopausal women was 37.8%. There were also differences in the dominant type of tumor. Mucinous type of ovarian carcinoma was more dominant (41%) in this research compared to Moore's, Molina's and Karlsen's in which serous type of ovarian cancer was more dominant (>75%).[4,5,9,10]

Sensitivity and specificity of ROMA in this study are lower compared to Moore's, Van Gorp's and Chudezka's. These differences may be attributed to different demographic data in which past menopausal patients were more dominant in Moore's (53.3%), Van Gorp's (53.2%) and Chudezka (61.9%) while in this study pre-menopausal group was dominant (56.1%).[4,11,12] In this study, when diagnostic test was done for post-menopausal group, ROMA with standard cut-off gives better sensitivity and accuracy (88.9% and 80%). This result showed that ROMA probably gave a better performance when used in the menopausal group.

RMI method was first designed by Jacobs et al. by using ultrasonography combined with CA125 value. In this study, no difference was found between RMI and ROMA. However, the accuracy of RMI3 was the highest, which is amounted to 78.85% in subjects with borderline histopathology not included as malignancy.

The limitations of this study were smaller samples compared to previous studies and no FSH measurement done to differentiate post-menopausal and pre-menopausal subjects.

## CONCLUSION

ROMA is not a reliable diagnostic tool. Compared to RMI3, ROMA has lower sensitivity. Overall, RMI3 has a better diagnostic value compare to ROMA.

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