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ORIGINAL ARTICLE

Comparing the Diagnostic Value of the Risk of Ovarian Malignancy Algorithm (ROMA) and Risk of Malignancy Index (RMI) in Women with an Adnexal Mass

Zahra Honarvar[1] · Mahdokht Monshi[2] · Fatemeh Karami Robati[3]

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Abstract

Purpose Ovarian cancer is the fifth leading cause of cancer death among women worldwide. This study aimed to compare the diagnostic value of the risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) in women with an adnexal mass.

Methods This cross-sectional study investigated 245 patients with adnexal mass in Afzalipour Hospital, Kerman, Iran, from 2016 to 2017. Before surgery, 10 cc of blood was taken from each patient. Tumor markers were measured using luminescence immunochemistry with HE4 and CA-125 kits. After surgery, tissue samples were sent to a medical diagnostic laboratory. World Health Organization criteria were applied for pathological classification. Based on CA-125 and HE4 levels and ultrasound findings and menopausal status of patients, ROMA and RMI were used to calculate the malignancy probability in each patient.

Results The average age of cases was 40.88 ± 14 years. Most tumors were benign (45%). The rate of mass metastasis was 2%. The mean levels of HE4 and CA-125 were 117.52 ± 161.49 and 160.945 ± 302.49, respectively. ROMA was more sensitive than RMI for diagnosis of malignancies, borderline and endometriosis. ROMA was of higher sensitivity and specificity for diagnosis of ovarian cancer in postmenopausal patients. Both ROMA and RMI were of higher sensitivity, specificity, positive and negative predictive values for diagnosis of malignancies.

Conclusion ROMA is more sensitive than RMI for the diagnosis of ovarian cancer. Accordingly, it can be applied as an appropriate method for diagnosing ovarian cancer as well as for treatment decisions in gynecological surgery wards.

Keywords Risk of ovarian malignancy algorithm (ROMA) · Risk of malignancy index (RMI) · Women · Ovarian neoplasms

Introduction

Ovarian cancer does not occur often; nevertheless, it is the fifth cancer mortality factor among women worldwide. According to the data gathered from 2013 to 2015, it is expected that approximately 1.3% of women suffer from ovarian cancer in their life [1]. Ovarian cancer is regarded as a type of malignant tumor, which appears in ovaries, afflicts more than 20,000 new cases, and causes about 140,000 annual deaths in women around the world [2].

Usually the early symptoms of ovarian cancer are not obvious. Therefore, it is hard to diagnose this disease in its early stages [1]. In fact, on the one hand, only 25% of ovarian masses are diagnosed in the early stages [3]; on the other hand, the mass metastasis is common in this disease,

✉ Zahra Honarvar
z.honarvar@kmu.ac.ir

Mahdokht Monshi
mahdokhymonshi@yahoo.com

Fatemeh Karami Robati
f.karami@kmu.ac.ir

[1] Department of Obstetrics and Gynecology, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

[2] Kerman University of Medical Sciences, Kerman, Iran

[3] Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

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so that more than 60% of the cases are diagnosed after the cancer starts to metastasize. Accordingly, ovarian cancer is diagnosed in most suffering patients in its advanced stages, which leads to incredibly high of mortality rates [4]. The estimation of 5-year continuation of ovarian cancer after it is diagnosed in the ovary is 92%, which reduces to 29% in case the disease is diagnosed in its last stages [5]. The strategy for the management of this disease is, therefore, to distinguish the biomarkers that are able to diagnose the ovarian cancer in its early stages with high sensitivity and specificity [1].

To distinguish between benign and malignant ovarian mass, a wide range of markers for vascular, morphological, and biochemical masses, as well as scoring systems, are used. The cancer antigen 125 (CA-125), which is also known as MUC16 or Mucin 16, usually increased in the blood of the patients suffering from certain types of cancer. That feature makes it appropriate as a biomarker for diagnosis of such diseases. CA-125 is highly used in diagnosing ovarian cancer, too [6]. However, using CA-125 as a biomarker for diagnosing ovarian cancer is still under question, because of its low sensitivity and specificity and high false negative or positive [7]. HE4 is regarded as an appropriate biomarker for diagnosing ovarian cancer, too; but increased HE4 levels are not seen in all types of ovarian cancer [8]. RMI and ROMA are also common methods for ovarian cancer diagnosis.

RMI is usually used for diagnosis in women with high risk of ovarian cancer. RMI is calculated by using CA-125 serum, ultrasound assessment, and menopausal status. ROMA is based on CA-125 serum level, HE-4 serum level, and menopausal status; it distinguishes between ovarian cancers and benign ovarian masses. The advantage of ROMA over RMI is that it includes HE-4 serum, which is of better specifications than CA-125 serum, and it does not include imaging. ROMA can be used even in low-income centers for women's triage, because it is a simple scoring only based on biomarkers and menopausal status. ROMA results are objective and renewable; they include no mental differentiation, unlike RMI [9].

Considering that various parameters are used in diagnosing ovarian cancer, the performance comparison of such parameters would be helpful. Accordingly, this study investigated the diagnostic value of ROMA and RMI in women with adnexal mass who referred to Afzalipour Hospital in Kerman, Iran, for surgery.

Methods

Study Design and Sample Collection

This descriptive cross-sectional study investigated 245 patients with adnexal mass who were candidates for surgery in Afzalipour Hospital, Kerman, Iran, from 2016 to 2017. According to Ref. No. 3 (the 75% sensitivity of ROMA to pathology, 10% prevalence, and $d\text{^}2 = 0.05$, and on the basis of the following formula, the sample volume was taken as 150 persons, which was increased to 245 to give better results.

$$n = \frac{z_{\frac{\alpha}{2}}^2 \mathrm{se}(1-\mathrm{se})}{d^2.p}$$

After the ethical code was received from Kerman Medical Science University (Code: IR.KMU.AH.REC.1396.1553), informed consent was taken from all patients and demographic data questionnaire, including age, body mass index (BMI), reproductive history, period forms, family cancer history, prevention method, and menopause age, was filled. Then other information such as the patient's last ultrasonic report, and the amount of CA-125 were registered by the investigator.

Before surgery, 10 cc of blood was taken from each patient, which turned into coagulum after 10 min, and then, its serum was separated in centrifuge in 30 min, and the serum and plasma were kept in − 80 c for later analysis. Afterwards, the samples were sent to Besat Medical Clinic laboratory in order for determining the markers' tumor level, which was measured by method of Immune Chemiluminescence using HE4 and CA-125 kits manufactured by COBAS Co., Germany. Immune Chemiluminescence is immune diagnostic method in which antibody is used as an identifier factor.

After the surgery, the tissue sample was sent to Medical Laboratory of Afzalipour Hospital for pathological examination. An appropriate size of tissue cut was taken for that purpose, which was then put in 10% formaldehyde. Then, 99% alcohol was used for dehydrating. After this step was completed, it was made lucid with xylenol and fixed in paraffin. The cutting was colored for the final report by microtome, and the samples were assessed by a pathologist. World Health Organization criterion was used in order for pathological classification.

According to histopathological findings, the patients were divided into benign, malignant, and borderline groups. Based on the levels of CA-125 and HE4 as well as ultrasonic findings and the patients' menopause status, the possibility of a malignant mass was calculated for each patient with two methods of RMI and ROMA.

Calculation of RMI and ROMA

RMI included CA-125 serum (CA-125), menopause status (M), and evaluation of ultrasound (U), which was calculated according to the following formula:

RMI = U × M × CA-125.

Ultrasonic criteria (U): Multilocular cyst = 1, Solid areas = 1, Bilateral lesions = 1, Ascites = 1, Intraabdominal metastases = 1.

Score 0–1: U = 1.

Score 2–5: U = 3.

Menopause status (M): Premenopausal = 1, Postmenopausal = 3.

The real value of CA-125 (U/ML) was used.

ROMA was calculated by using the results of CA-125 and HE4 according to the manufacturer's advices (Abbott ARCHITECT ci8200; Abbott Laboratories, Illinois, US). In addition, according to the suggestion by Moore et al., predictive index (PI) was separately used for the premenopausal and postmenopausal patients on the basis of Eqs. 1 and 2 [10]:

PI for premenopausal women: PI = − 12 + 2.38*Ln (HE4) + 0.0626*Ln (CA-125).

PI for postmenopausal women: PI = − 8.09 + 1.04* Ln (HE4) + 0.732*Ln (CA-125).

Then ROMA score was obtained using the following formula:

ROMA (%) = e^PI / (1 + e^PI) × 100%

A score above 200 was regarded as high risk of malignancy.

A comparative study was done for investigating CA-125, HE4, RMI, and ROMA factors as well as credibility indexes such as sensitivity, specificity, positive predictive value, and negative predictive value. The curve of receiver operating characteristic (ROC) was calculated. The significance level was regarded to be $p < 0.05$. Data analysis was done using SPSS software version 24.

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Results

This cross-sectional study was done on 245 patients who had been candidates for surgery at Afzalipour Hospital. They had an average age of 40.88 ± 14 (13–75 years old). The average mass size was 10.47 ± 4.47 cm (3–30 cm). Most masses were benign (45%) and followed by malignant (28%), endometriosis (19%), and borderline (8%), respectively. The rate of mass metastasis was 2%. The average level of HE4 and CA-125 in the patients was 117.52 ± 161.49 (3–1234) and 160.945 ± 302.49 (4–2456), respectively.

By using ROMA index, the high and low malignancy risks were observed as 44.1 and 55.9 percent of the patients. Such amount in RMI showed high malignancy risk for 31% of the patients and low malignancy risk for 69% of the patients. In the premenopausal group, ROMA reported high malignancy risk for 67.2% of the patients and low malignancy risk for 32.8% of the patients. In the postmenopausal group, these amounts were 83.9% and 16.1%, respectively. Such difference between the two groups was significant ($p = 0.01$).

The sensitivity, specificity, and positive as well as negative predictive value of ROMA index were the following: for diagnosing malignancy cases were 92.8, 86.2, 59.2, and 68.6%, respectively; for diagnosing borderline cases were 75, 25, 13.8, and 3.6%, respectively; and for diagnosing endometriosis cases were 29.8, 70.2, 12.9, and 24%, respectively. The sensitivity, specificity, and positive as well as negative predictive value of RMI index were the following: for diagnosing malignancy cases were 85.5, 100, 77.6, and 64.5%, respectively; for diagnosing borderline cases were 35, 65, 9.2 and 7.6%, respectively; and for diagnosing endometriosis cases were 21.3, 78.7, 13.1, and 21.8%, respectively (Table 1).

Sensitivity, specificity, positive and negative predictive values of ROMA in premenopausal patients were 84, 86, 34.4 and 66.4%, respectively, and in postmenopausal patients were 97.7, 88.9, 91.4 and 88.8%, respectively. Sensitivity, specificity, positive and negative predictive values of RMI in premenopausal patients were 72, 100, 54.5 and 64.1%, respectively, and in postmenopausal patients were 93.2, 100, 95.3 and 62.9%, respectively (Table 2).

Figure 1 shows the ROC curve of ROMA and RMI in all patients (Fig. 1).

Discussion

One of the ongoing challenges for the physicians is ovarian cancer screening, a topic which is still under study both in national and in international levels. Although many of the criteria have been determined, the results are still controversial and require more studies. Due to the difficult access to the ovary tissue, histological screening of ovarian cancer is not possible. Therefore, serum examinations or biomarker platforms may be beneficial to help diagnose the cancer and cancer recurrence and also as tools for monitoring response to treatment [11].

In the present study, the average serum level of CA-125 and HE4 was 160.945 ± 302.49 and 117.52 ± 161.49, respectively. In Al-Ogaidi study, approximately 80–90

Table 1 Diagnostic value of ROMA and RMI in diagnosing malignant, borderline and endometriosis cases of ovarian cancer

Index		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ROMA	Malignancy	92.8	86.2	59.2	68.6
	Borderline	75	25	13.8	3.6
	Endometriosis	29.8	70.2	12.9	24
RMI	Malignancy	85.5	100	77.6	64.5
	Borderline	35	65	9.2	7.6
	Endometriosis	21.3	78.7	13.1	21.8

Table 2 Diagnostic value of ROMA and RMI in diagnosing premenopausal and postmenopausal ovarian cancer

Index	Group	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ROMA	Premenopausal	84	86	34.4	66.4
	Postmenopausal	97.7	88.9	91.4	88.8
RMI	Premenopausal	72	100	54.5	64.1
	Postmenopausal	93.2	100	95.3	62.9

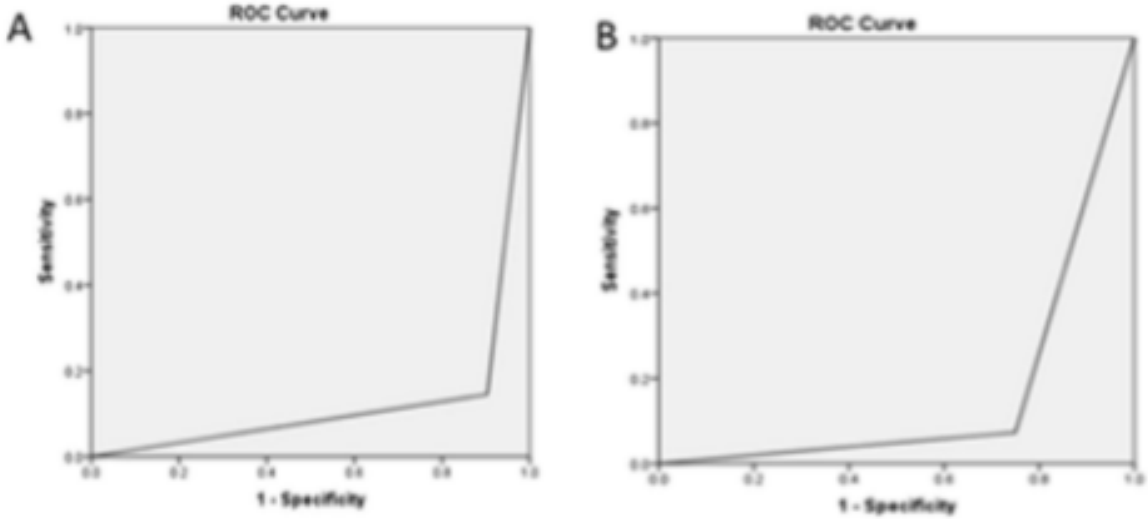

Fig. 1 Receiver operating characteristic (ROC) curve of **a** RMI and **b** ROMA for all patients

percent of the women suffering from advanced ovarian cancer showed CA-125 level increase in their blood. The higher level of CA-125 usually indicates therapeutic results; it is a weak prognosis of the disease [12]. Due to the function of CA-125 in protecting female genital epithelium against negative effects of infectious agents and external particles, CA-125 and HE4 levels usually increase in the serum of the patients suffering from various types of ovarian cancer [13, 14]. In Zhang et al.'s study, CA-125 and HE4 levels had increased with ovarian cancer progression, so that their amounts in malignant as well as borderline groups were significantly higher than those in benign group [6]. Different types of pathology influence the function of biomarkers significantly. Accordingly, it is important to choose appropriate biomarkers for accurate diagnosis of various types of ovarian cancer.

One of the main problems regarding preoperative assessment of pelvic masses is the recognition of unlikely malignant tumors or borderline and endometriosis tumors. Endometriosis cyst does not always guarantee surgery, and its treatment method is quite different than that of ovarian malignancy. Ovarian borderline tumors are an independent subgroup of tumors, which may be difficult to diagnose in serology. In the present study, overall prevalence of ovarian borderline tumors was 8%, whereas in similar studies, it was reported to be 14% [9, 15]. Our study showed the

sensitivity of ROMA and RMI in diagnosing borderline cases to be 75% and 35%, respectively, whereas similar studies showed them to be 40% [9, 15–18]. According to the results of our study, the sensitivity, specificity, positive and negative predictive values of ROMA and RMI were higher in diagnosing malignant cases. In Priyanka et al.'s study, too, the diagnostic accuracy of all parameters including ROMA and RMI was better in diagnosing malignant lesions than borderline tumors [9].

In the present research, the sensitivity of ROMA in malignant, borderline and endometriosis cases was more than those of RMI, but its specificity was less than that of RMI. Consistent with these results, in the study done by Priyanka et al., the sensitivity of ROMA was more than that of RMI. ROMA index functioned better than RMI in distinguishing pelvic masses in premenopausal and postmenopausal women [9]. That is while in Al Musalhi et al.'s study, ROMA had a very high specificity in diagnosing ovarian cancer, but it had less sensitivity than RMI in premenopausal women. ROMA showed no significant difference between ovary benign and endometriosis lesions, whereas RMI results showed significantly higher levels in endometriosis. When CA-125 level has a false increase particularly in endometriosis cases, ROMA can be a useful marker. According to Al Musalhi et al., RMI is comparable with ROMA; however, an essential investigation in that field may be required, because in their study, RMI score was calculated by external ultrasonic examination, a process that simply depends on the gynecologist's experiment. In case ultrasonic examination is done by untrained staff such as primary care physicians, it may affect RMI value [19].

In our study, the sensitivity and specificity of ROMA were more in diagnosing postmenopausal ovarian cancer than in premenopausal ovarian cancer. In Zhang et al.'s study, too, the sensitivity and specificity of ROMA were significantly higher in diagnosing postmenopausal ovarian cancer [6]. In a recent meta-analysis that was done to compare the accuracy of CA125, HE4 and ROMA in diagnosing ovarian cancer, HE4 functioned significantly better than CA125 or ROMA. The specificity of HE4 in diagnosing ovarian cancer in all patients, whether premenopausal or postmenopausal, was 100%, which was much more than that of CA125 or ROMA. That shows that using HE4 can increase accurate diagnosis of this disease. In their study consistent with our study, ROMA functioned better in menopause subgroup than in premenopausal groups [20].

In the present study, the sensitivity of ROMA was more than that of RMI in diagnosing ovarian cancer. Also, the sensitivity and specificity of ROMA were more in diagnosing postmenopausal ovarian cancer than in premenopausal. Since the early diagnosis and treatment of ovarian cancer are crucial for the treatment of this disease, it is suggested that more similar studies be done to investigate various diagnostic methods, and ROMA method and other similar methods be used for treatment decision-makings in gynecological surgery units.

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Declarations

Conflict of interests The authors declare that they have no conflict of interests.

Consent to participate Informed consent was taken from all patients.

Ethics approval This study was approved by the Ethics Committee of Kerman University of Medical Sciences in Iran (Ethical Code: IR.KMU. AH.REC.1396.1553).

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