

Serum markers, morphological index, RMI, and ROMA in preoperative diagnosis of ovarian cancer

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Abstract

Background/Aim: Ovarian cancer is the second most common gynecologic malignancy worldwide and is the deadliest among gynecological cancers. It is important that this cancer, which is usually diagnosed in advanced stages, is referred to a gynecologist oncologist without delay. An ideal screening method does not yet exist. Although CA 125 is still the most used tumor marker, it cannot detect early-stage ovarian cancer. Also, CA 125 is not specific for ovarian malignancy. Therefore, new serum markers, such as HE4, and more complex algorithms, like ROMA and RMI, have emerged. Here we evaluate the preoperative potential of patients with adnexal mass to have a malignant or benign mass with morphological index, CA 125, HE4, RMI, and ROMA tests.

Methods: This study is a prospective cohort study. A power analysis was done before starting the study. The sample size was at least 80 when the Type I error was set at 0.05, and the confidence interval was 95%. We included into the study 84 patients admitted to our clinic because of pelvic mass and underwent operation between March 2016 and October 2018. To homogenize the benign and malignant groups, 42 patients were collected from each group. CA 125 and HE4 levels of the samples were studied by the electrochemiluminescence method. ROMA and RMI values were calculated, and the data were entered into SPSS. Data were analyzed using SPSS 22.0 statistical package program.

Results: Each of the CA 125 ($P = 0.002$), HE4 ($P < 0.001$), morphological index ($P < 0.001$), ROMA ($P < 0.001$), and RMI ($P < 0.001$) tests has been successful in differentiating malignant masses from benign masses. In the malignant-benign differentiation of adnexal masses preoperatively, CA 125 was the test with the lowest sensitivity, and RMI had the highest sensitivity. However, in the ROC analysis, the morphological index has a higher area under the curve.

Conclusion: Although CA 125 is still the most frequently used marker in the preoperative evaluation of adnexal masses, it has low specificity and sensitivity, especially in premenopausal patients. The use of new tumor markers (e.g., HE4) and other algorithms (e.g., ROMA and RMI) is supported by our findings and the literature. However, here we show that an expert ultrasonographic evaluation with morphological index alone could be effective.

Keywords: Ovarian cancer, Pelvic mass, RMI, ROMA, CA 125, HE4, Morphological index

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Ethics Committee Approval

This study was approved by the Malatya Clinical Research Ethics Committee, 22.03.2017 and 2017/35.

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

This study has been supported by BAP Committee of the İnönü University Scientific Research Projects (2018/869).

Published

2022 April 12

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Published by JOSAM

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Introduction

Ovarian cancer is gynecological cancer with a high mortality rate and is usually diagnosed in an advanced stage. Besides, about 239,000 new cases are reported annually; it is estimated that one out of every 75 women will have ovarian cancer in their lifetime. One out of every 100 women diagnosed with ovarian cancer, which is ranked seventh among female cancers, will lose their life due to this disease and/or its complications [1]. Since cytoreductive surgery constitutes the most important component in treating epithelial ovarian cancer, true diagnosis of the patients in the preoperative period is very important.

Today, multiple methods, such as pelvic examination, imaging methods, and biochemical markers in serum, are used to diagnose ovarian cancer. Neither ultrasound, which gives information about the structure and size of the mass, nor serum markers (such as CA 125, HE 4), are insufficient for malignant-benign differentiation [2]. For this reason, combined tests came into use, in which clinical data are evaluated [such as the risk of malignancy index (RMI) and Risk of Ovarian Malignancy Algorithm (ROMA), and CA 125, HE 4, and the ultrasonographic features of mass] [3].

In addition, the morphological index, in which the ultrasonographic findings of the mass are evaluated (volume and structure properties of the mass), is used in the preoperative evaluation of the adnexal masses [4].

In this study, we discuss the effects of serum CA 125, HE 4, RMI, ROMA, and Morphological Index on the preoperative malignancy prediction of the patients who were diagnosed with adnexal mass and whose pathology results were finalized after surgery.

Materials and methods

Patient group

In our study, 84 patients who were admitted to our clinic between March 2016 and October 2018 were not pregnant, without any known cancer disease, liver or kidney failure and operated for pelvic mass were included. The study was prospectively defined and conducted in a single center. Our study has been approved by the ethics committee of Inonu University Faculty of Medicine. Consent was obtained from the patients who were planned for operation. This research was supported by the Scientific Research Projects department, with the 2018/869 project number.

Data collection

Detailed anamnesis was obtained from patients; age, menopausal status, parity, family history, and history of known disease were examined and recorded. A single clinician took patients to a transvaginal ultrasonography examination using an IC5-9-D 7 MHz transducer of the Voluson E6 (GE Healthcare, Milwaukee, WI, USA) ultrasound device. In the ultrasonography, wall structure, septa thickness, presence of solid area, whether being bilateral, the presence of intraabdominal metastasis, and acid of the mass were evaluated. Blood (10 ml) was collected from the patients in routine biochemistry tubes on the morning of the operation. These blood samples were centrifuged at 3500 rpm, and the separated serum was transferred into microcentrifuge tubes. Samples were stored at -80°C until analysis. On the analysis day,

samples were thawed at room temperature and transferred to conical bottom polypropylene tubes and vortexed for homogenization. The prepared samples were analyzed using the electrochemiluminescence method with CA 125 and HE4 kits in Roche brand (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim) e601 model device.

Evaluation of the data

In the ultrasonography examination, the characteristics of the masses were evaluated according to the scoring system developed by Depriest et al. [5], and morphological indices were calculated. By force of this scoring system, the volume, width, length, and height of the mass were calculated by multiplying with the coefficient of 0.523. The volumes under 10 cm³ have received 0, 1, 2, 3, or 4 points (10–50 cm³, 1 point; 50–200 cm³, 2 points; 200–500 cm³, 3 points; > 500 cm³, 4 points). In addition, if the wall was thinner than 3 mm and flat, the score was 0; if it was thicker than 3 mm and flat, the score was 1 point; if it had a papillary projection smaller than 3 mm, the score was 2 points; if it has a papillary projection bigger than 3 mm, the score was 3 points; and if the solid areas were dominant, the score was 4 points. The masses without septa received 0 points; septa thinner than 3 mm received 1 point; septa between 3 mm and 10 mm received 2 points; 10 mm and more solid masses received 3 points; and totally solid masses received 4 points. According to this scoring system, the masses were evaluated with a score between 0 and 12 in total.

The percentages of ROMA were calculated by formulating the CA 125 and HE4 levels and the menopausal status of the patient. Women older than 50 years of age and who had a hysterectomy were accepted in the postmenopausal period. CA 125 and HE4 values were measured with IU/ml units [6].

For premenopausal women;

Predictive Index (PI) = $-12.0 + 2.38 \times \text{LN} [\text{HE4}] + 0.0626 \times \text{LN} [\text{CA 125}]$

For postmenopausal women;

Predictive Index (PI) = $-8.09 + 1.04 \times \text{LN} [\text{HE4}] + 0.732 \times \text{LN} [\text{CA 125}]$

The percentage of ROMA = $\text{calculated as } \exp(\text{PI}) / [1 + \exp(\text{PI})] \times 100$.

The RMI score was calculated by multiplying the patient's ultrasonography score with the menopausal condition and CA 125 value. Ultrasonography scores ranged from 0 to 3. Multiloculated cysts, solid areas, metastases, and presence of acid and bilateral lesions were each calculated as 1 point, and the value was presented as 0 if none of these were present, as 1 if one of these were present, and as 3 if two or more were present in the formula. If the patient is in the premenopausal period, the M score is evaluated as 1, and in the postmenopausal period, the M score is evaluated as 3. The CA 125 value was measured as IU/ml and placed in the formula [6].

Statistical analysis

Data are given by mean (standard deviation) and number (percentage). The normality of the data distribution was tested using the Shapiro-Wilk test. In statistical analysis, Mann-Whitney U test, Yate's corrected chi-square test, Pearson correlation coefficient and diagnostic tests (e.g., Roc analysis, sensitivity, and specificity) were used where applicable. IBM SPSS Statistics 22.0

program was used in the analysis. P-values < 0.05 was considered statistically significant.

Results

A total of 84 patients diagnosed with adnexal mass were included in our study. The pathology results of 42 patients were evaluated as benign, and the remaining 42 were evaluated as malignant. The average age of the patients who had benign pathology was 47.8 (15.08) years, and the average age of the patients who had malignant pathology was 51.3 (16.2). The first serum test applied to patients who have adnexal masses was CA 125, a glycoprotein. While 21.4% (n = 9) of the patients with benign pathology had a bilateral mass, 35.7% (n = 15) of the patients with malignant pathology had a bilateral mass. The final pathology results of the patients were compared with acid, which is a finding suggestive of malignant disease. While acid was present in 19% (n = 8) of patients reported as benign due to pathology, it was present in 40.5% (n = 17) of the patients reported as malignant as a result of pathology. When the pathology results of the patients were examined, in the benign patient group, 20 patients (47.6%) were diagnosed with serous cystadenoma, and 12 patients were diagnosed with mucinous cystadenoma (28.5%), and 10 patients (23.8%) were diagnosed with mature cystic teratoma. In the malignant patient group, 28 patients were diagnosed with serous carcinoma (66.6%), and 14 patients were diagnosed with mucinous carcinoma (33.3%). When the performed surgeries were examined, only cystectomy was performed in 3 patients (8%), unilateral salpingo-oophorectomy (USO) in 27 patients (64%), and total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) in 12 patients (28%). Only the USO procedure was performed in the malignant patient group in four patients (9%). Seventeen patients underwent TAH + BSO + omentectomy and pelvic paraaortic lymphadenectomy (PPLND) (41%), and 21 patients (50%) underwent cytoreductive surgery. The pathology result of all patients who underwent USO in the malignant patient group was serous carcinoma, and severe intraabdominal tumor involvement was determined. However, neoadjuvant chemotherapy was considered appropriate after surgery because they could not tolerate cytoreductive surgery due to their advanced age and current comorbidities. In patients diagnosed with serous or mucinous carcinoma, TAH + BSO + PPLND + omentectomy was performed if distant organ (such as liver, abdominopelvic peritoneum, spleen) metastasis was not detected. In patients with distant organ metastases, lymphadenectomy was performed after cytoreductive surgery (Table 1).

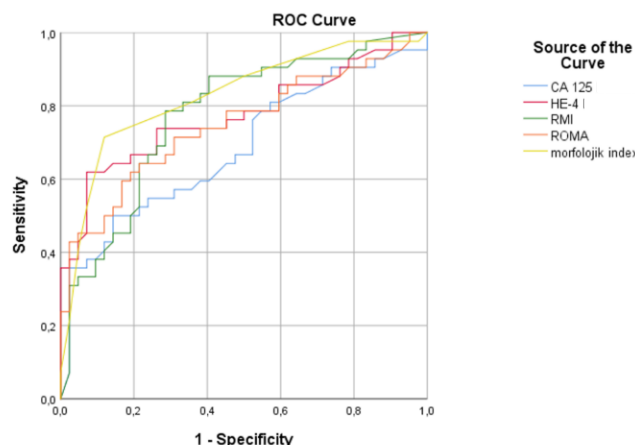
Table 1: Characteristics of patients included in the study

Age	
Benign patient group	47.8 (15.08)
Malignant patient group	51.3 (16.2)
Bilaterality	
Benign patient group	21.4%, n = 9
Malignant patient group	35.7%, n = 15
The presence of ascites	
Benign patient group	19%, n = 8
Malignant patient group	40.5%, n = 17
Pathology	
Benign patient group	
Serous cystadenoma	47.5%, n = 20
Mucinous cystadenoma	28.5%, n = 12
Mature cystic teratoma	23.8%, n = 10
Malignant patient group	
Serous cystadenocarcinoma	66.6%, n = 28
Mucinous cystadenocarcinoma	33.3%, n = 14
Surgical procedure	
Benign patient group	
Cystectomy	8%, n = 3
USO	64%, n = 27
TAH+BSO	28%, n = 12
Malignant patient group	
TAH+BSO+PPLND+Omentectomy	41%, n = 17
Cytoreductive surgery	50%, n = 21
USO	9%, n = 4

n: number of patients, USO: unilateral salpingo-oophorectomy, TAH + BSO: total abdominal hysterectomy + bilateral salpingo-oophorectomy, PPLND: pelvic and para-aortic lymphadenectomy

Each of the CA 125, HE4, morphological index, ROMA, and RMI tests were evaluated preoperatively. For CA 125, the sensitivity was 50% (95% CI: 34.1–65.8), the specificity was 85.7% (95% CI: 71.4–94.5), the positive predictive value was 77% (95% CI: 61.1–88.6), and the negative predictive value was 63.1% (95% CI: 55.2–70.3). For HE4, the sensitivity was 61.9% (95% CI: 45.6–76.4), the specificity was 92.86% (95% CI: 80.5–98.5), the positive predictive value was 89.66% (95% CI: 73.9–96.3), and the negative predictive value was 70.9% (95% CI: 62.1–78.3). For the morphological index, the sensitivity was 71.4% (95% CI: 55.4–84.2), the specificity was 88.1% (95% CI: 74.3–96.03), the positive predictive value was 85.71% (95% CI: 72–93.3), and the negative predictive value was 75.5% (95% CI: 65.3–83.4). For RMI, the sensitivity was 78.5% (95% CI: 63.1–89.7), the specificity was 71.4% (95% CI: 55.4–84.2), the positive predictive value was 73.3% (95% CI: 62.4–81.9), and the negative predictive value was 76.9% (95% CI: 64.4–85.9). For ROMA, the sensitivity was 64.2% (95% CI: 48–78), the specificity was 78.5% (95% CI: 63.1–89.7), the positive predictive value was 75% (95% CI: 61.7–84.8), the negative predictive value was 68.7% (95% CI: 58.7–77.2) (Table 2, Figure 1).

Figure 1: ROC curves of the tests used in the malignant-benign differentiation of adnexal masses in the preoperative period



CA 125: Cancer antigen 125, HE4: Human epididymis protein 4, RMI: Risk of malignancy index, ROMA: Risk of ovarian malignancy algorithm.

Table 2: Sensitivity, specificity, PPV, NPV percentages, area under the ROC curve and *P*-values of CA 125, HE 4, ROMA, RMI tests and morphological index used in preoperative evaluation of adnexal masses. Optimal cut-off values were determined with ROC curves.

	Optimal cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	<i>P</i> -values
CA-125	52.4	50	85.7	77	63.1%	0.685	0.002
HE 4	83.4	61.9	92.86	89.6	70.9	0.775	< 0.001
ROMA	16.1	64.2	78.5	75	68.7	0.749	< 0.001
RMI	53.7	78.5	71.4	73.3	76.9	0.775	< 0.001
Morphological Index	7	71.4	88.1	85.7	75.5	0.828	< 0.001

CA 125: Cancer antigen 125, HE 4: Human epididymis protein 4, ROMA: Risk of ovarian malignancy algorithm, RMI: Risk of malignancy index, PPV: Positive predictive value, NPV: Negative predictive value

Discussion

Although early diagnosis is possible in some tissue and organ cancers, given today's technological potential, especially in epithelial ovarian cancers, there is no possibility of early diagnosis. Since most patients are asymptomatic or have unclear complaints in the early stage, the patients are typically referred to the physician in advanced stages, and the disease appears to have intrapelvic and/or intraabdominal widespread metastases at the time of diagnosis. This has led modern to the use and development of tests that provide early diagnosis [1].

The first serum test applied to patients who have adnexal masses was CA 125, a glycoprotein. However, it has been reported that this serum antigen increases in many physiological and pathological scenarios, including gynecological and non-gynecological causes, making this test not useful for early diagnosis [7]. HE4 is an alternative serum marker used in recent years. HE4 seems a more advantageous serum antigen because it is secreted minimally in normal ovarian tissue and endometriosis but has an increased secretion in ovarian epithelial tumors [6]. In a study in which the CA 125 and HE4 tests were used to differentiate malignant and benign adnexal masses, the sensitivities in detecting malignancy were 83.3% and 90%, respectively [8]. In another extensive study, HE4 was a more sensitive test than CA 125 for detecting malignancy in the adnexal mass [9]. Here we report sensitivities for detecting preoperative malignancy of ovarian pathologies of 61.9% and 50% for HE4 and CA 125.

Although the superiority of the HE4 test over CA 125 in the early diagnosis of ovarian cancer has been presented in our study and similar studies in the literature, combined tests (such as ROMA and RMI) are widely used for this purpose, where the patient's age, ultrasonographic findings of the mass, and both tumor markers are considered. When the studies conducted in the literature about the use of combined tests are examined, it is observed that there are different results Jacobs et al. [10] reported the sensitivity of RMI as 85% and specificity as 97% in a study involving 101 benign and 42 malignant ovarian tumors. In another study conducted by Liest et al. [11], it was shown that ROMA and RMI tests did not have superiority over each other in the preoperative malignant-benign differentiation of the adnexal mass of 784 patients. While in another study conducted on 457 patients with an adnexal mass, the ROMA test was superior to RMI (sensitivity 89% vs. 80.7%) [12]. In another study conducted by Oranratanaphan et al. [13], the ROMA test did not show a significant superiority over the RMI test in the malignant-benign differentiation of the preoperative adnexal masses. In our study, the RMI test was sensitive according to the ROMA test (sensitivity 78.5% vs. 64.2%) in malignancy differentiation.

It is an unquestionable fact that the combined tests used in the preoperative evaluation of adnexal masses are more

advantageous than the serum markers used alone. In a study conducted by Karlsen et al. [14] on the comparison CA 125, HE4, ROMA, and RMI tests in preoperative malignancy analysis of adnexal masses in 1218 patients, ROMA and RMI tests had sensitivities close to each other, but the specificity of both tests was higher than that of CA 125 and HE4 tests alone. Similar results were obtained in another study conducted for this purpose; the sensitivity of ROMA and RMI tests was higher than those of CA 125 and HE4 tests [15]. Our study concluded that the sensitivity of the RMI and ROMA combined test was higher than tests relying on other serum markers.

Although various serum markers and advanced combined tests are used in the evaluation of adnexal masses, the morphological index based on totally non-invasive ultrasonographic findings [where tumor size, volume, and content of the mass (septa structure, papillary projection, heterogeneity) are evaluated] might be the best currently available diagnostic method. In the study conducted by Pavlik et al. [16], the sensitivity of ultrasonography in the detection of malignancy was 73.3%, and the sensitivity of detection of benign masses was 91.3%. In another study conducted on 216 patients diagnosed with ovarian cancer and 144 patients whose benign ovarian tumors were detected, it was concluded that neither the HE4 nor the ROMA test alone was superior to the morphological index (ultrasonography) in the preoperative evaluation of the masses [17]. In our study, the morphological index test, which is based on the ultrasonographic examination of the mass, has a sensitivity of 71.4%, which was close to that of the best performing method (the RMI test).

Limitations

The person's experience performing the ultrasound can be considered a limitation. However, in this study, ultrasound was performed by the most experienced available specialist.

Conclusion

In conclusion, the early diagnosis of ovarian epithelial tumors, which are rare but deadly, is important. Early diagnosis for this pathology, for which a screening program has not yet been developed for the healthy population, is an important goal. Although serum markers used alone have been used for this purpose, the results were disappointing, necessitating the development of combined tests. Indeed, the superiority of combined tests is supported in our study and the literature. However, besides these invasive and expensive tests, the malignant-benign differentiation of the masses can be performed successfully in the preoperative period by an ultrasound procedure when performed by an experienced physician.

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