의학석사 학위 논문

수술 후 영상적 종양 아형에 따른 양성 및 조기 악성 난소 종양의 감별 도구로서 **ROMA** 검사와 **CA 125**의 비교

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이 논문을 의학석사 학위 논문으로 제출함

2019년 8월

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ABSTRACT

Comparison of ROMA (risk of ovarian malignancy algorithm) and cancer antigen 125 to discriminate between benign ovarian tumor and early-stage ovarian cancer according to imaging tumor subtypes

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Objective: To compare the accuracy of the ROMA (risk of ovarian malignancy algorithm) and cancer antigen (CA) 125 as tools to discriminate between benign ovarian tumor and early-stage ovarian cancer according to tumor subtypes diagnosed by imaging and postoperative histopathologic findings.

Materials and Methods: A total of 1207 patients were identified who underwent ROMA test due to suspicion of early-stage ovarian cancer and underwent surgery at Asan Medical Center from September 2014 to March 2018. A total of 981 patients who met inclusion criteria were included in the retrospective analysis.

Results: Among 981 study patients, 816 had benign tumors and 165 had malignant tumors, including borderline tumors. Among patients diagnosed with ovarian cancer or borderline tumor, 47.3% was judged as high risk by the ROMA test, and 58.2% showed CA125 over 35 U/ml. Specificity and accuracy of ROMA were higher than those of CA125 in premenopausal women. However, the superiority of the ROMA test in discrimination of malignant ovarian tumors compared to CA125 was observed only in patients with endometriotic type (Net reclassification index 0.379). The comparative advantages were not seen in the other tumor subtypes.

Conclusion: In the endometriotic type of ovarian tumor, the superiority of the ROMA test compared to CA125 was confirmed for triage of ovarian tumor. However, sensitivity and specificity were similar as a discriminating tool in other tumor types.

Key words: idiagnostic techniques; ovarian cancer; CA125 antigen; biomarkers

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INTRODUCTION

Ovarian cancer is the leading cause of death in gynecologic malignancies, and approximately 70% of patients are diagnosed at an advanced stage.[1)] Therefore, it is very important to distinguish benign ovarian masses from early-stage malignant ovarian tumors to decide whether to operate, the method of operation, and to prevent cancer progression.

The cancer antigen 125 (MUC16 protein, CA125) is currently used as a conventional marker for epithelial ovarian cancer (EOC). However, the serum CA125 level frequently increases, and false positive results may be seen with certain benign uterine tumors and medical conditions such as leiomyomas, adenomyosis, infection, liver cirrhosis, pregnancy, pelvic endometriosis, etc..[2-3)] Serum CA125 level is often in the normal range in early-stage invasive ovarian cancer.[4)] Therefore, CA125 is not recommended for discrimination of ovarian tumors due to low specificity. Recently, human epididymis protein 4 (HE4) that is involved in neoplastic processes of EOC has been used to overcome these limitations in discrimination of ovarian tumors.[5-6)] HE4 increases in some ovarian cancers and has the advantage of not being affected by the physiologic condition (like occurs with CA125).[7-8)] Serum HE4 level is not affected by the menstrual cycle, hormonal treatment, and endometriosis, but the level may increase with age and smoking.[9-10)] Therefore, the “risk of ovarian malignancy algorithm (ROMA)” test was developed using CA125, HE4, and menopausal status. The algorithm test is now widely used to discriminate benign and early-stage malignant ovarian tumors.[11-12)]

Previous studies on the efficacy of the ROMA test have had inconsistent results due to the different distribution of tumor subtypes in the patient population in each study. Expression of HE4 in tumors depends on histologic subtype. Drapkin et al. demonstrated that 100% of endometrioid and 93% of serous EOCs expressed HE4, but only 50% of clear cell carcinomas and none of mucinous tumors were HE4 positive.[13)] Nevertheless, none of the previous studies have evaluated the efficacy of the ROMA test by tumor subtype, and most previous studies have only focused on

the fact that ROMA is more useful in differentiating endometriosis compared to CA125.[14-15] In addition, these studies have included several hydrosalpinx, paratubal cysts, inclusion cysts, and advanced ovarian cancer that could be distinguished from each other by ultrasonography, as well as functional cysts that spontaneously disappeared in analysis follow-up period.

Therefore, we investigated the efficacy of the ROMA test compare with CA125 as a tool for discriminating between benign and early-stage ovarian cancer according to imaging tumor subtypes associated with postoperative histopathologic findings.

MATERIALS AND METHODS

Patients

After obtaining approval from the institutional review board at the Asan Medical Center (IRB No.2019-0616), we retrospectively reviewed the medical records of patients who underwent ROMA test due to suspicion of early-stage ovarian cancer and underwent surgery at Asan Medical Center from September 2014 to March 2018. Clinicopathologic data were collected, including age, menopause status, pre-operation results of CA125 and ROMA test, results of imaging test (tumor size and volume, histologic subtype), and International Federation of Gynecology and Obstetrics (FIGO) stage in malignant cases.

Only patients with histologically-confirmed diagnosis after surgery were included in the analysis. Patients with advanced ovarian cancer with ascites and peritoneal carcinomatosis that were sufficiently predictable by sonography or abdominopelvic computed tomography (APCT) before surgery were excluded. Patients with only hydrosalpinx or paratubal cyst, inclusion cysts by pelvic adhesion, and inflammatory lesions including tubo-ovarian abscess were excluded from the analysis, because these cases should have been excluded from suspicion of ovarian cancer by preoperative evaluation with imaging test or inflammatory test. When ovarian masses were bilateral, they were included in the analysis if they were of the same subtype and excluded if they were of the different subtypes. The presences of two or more tumor subtypes in one ovary were excluded from the analysis, because it was not known which tumor subtype affected the blood test. Patients were excluded if there was more than three months between the operation and the blood test. Patients diagnosed with ovarian masses during pregnancy were excluded due to changes in the CA125 level following the gestation period. Patients with end-stage renal disease, diabetic nephropathy, nephrotic syndrome, renal cancer, or urosepsis were excluded because HE4 could be abnormally high due to decreased elimination or increased production from the damaged renal tubules.[16] Patients diagnosed with metastatic ovarian cancer, including Krukenburg's tumor, were excluded, as the degree of effect from primary

site carcinoma could not be estimated. Patients who were diagnosed with other malignancy within five years were excluded. Patients with transient cell carcinoma, undifferentiated carcinoma, squamous cell carcinoma, and mixed Müllerian malignant tumor were excluded from the analysis due to rarity of cases.

Methods

This study used the ARCHITECT CA125 II assay (Reagent Kit No. 2P45) and ARCHITECT HE4 assay (Reagent Kit No. 2P54) (Abbott Diagnostics, IL, USA) for the quantitative determination of CA125 and HE4.[17] These were two-step immunoassays using chemiluminescent microparticle immunoassay (CMIA) technology. The cut-off value was 35.0 U/ml for CA125 and 70 pmol/ml for HE4. Patients were stratified into low or high-risk groups based on laboratory methods to calculate ROMA score and menopausal status. Predictive index (PI) and predicted probability were calculated using the following algorithms proposed by Moore et al.[11]:

Pre-menopausal PI = −12.0 + 2.38 x LN (HE4) + 0.0626 x LN (CA125)

Post-menopausal PI = −8.09 + 1.04 x LN (HE4) + 0.7320 x LN (CA125)

Predicted probability (ROMA, %) = exp (PI) / [1 + exp (PI)] x 100

The cut-off value for ROMA was 7.4 for premenopausal women and 25.3 for postmenopausal women. For menopausal status, postmenopausal was defined as one year or more after menstrual bleeding cessation. For patients who underwent hysterectomy before menopause, age of 50 or older was defined as postmenopausal.

For the imaging study, sonography or APCT was used. There were no definite criteria for the size or number of leiomyomas affecting the CA125 level. Therefore, one or more leiomyoma larger than 3 cm was considered positive for the presence of leiomyoma. All images were interpreted by experts in radiology, and total ovarian tumor volume was calculated.

Imaging subtypes of tumors were classified for analysis as associated with postoperative histologic findings as follows: serous cystadenoma, corpus luteal cyst, simple cyst, serous borderline tumor, and serous adenocarcinoma were classified as “serous type”; mucinous cystadenoma, mucinous borderline tumor, and mucinous

adenocarcinoma were classified as “mucinous type”; endometriotic cyst, seromucinous borderline tumor, endometrioid adenocarcinoma, and clear cell carcinoma were classified as “endometriotic type”; and mature cystic teratoma, fibroma, Brenner tumor, germ cell tumor, and sex-cord stromal cell tumor were classified as “solid type”.

Statistical analysis

Relationships between variable characteristics and ovarian tumors were assessed by Welch’s test and Kruskal-Wallis test. We assessed the correlation between CA125, ROMA test, and menopausal status, leiomyomas, and adenomyosis in differentiating patients with suspected ovarian cancer. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CA125 and ROMA test were identified by imaging tumor subtype. For the analysis of discrepancies in the two prediction methods, McNemar's test was used to assess how the two measurements differed without considering the outcome data. Net reclassification index (NRI) showed how much ROMA test improved prediction compared to CA125 using outcome data. Because ROMA test had different scales for premenopause and postmenopause, receiver operator characteristics (ROC) analysis was also separately obtained. The p-values comparing the two ROC curves were calculated as Delong's test for two correlated ROC curves. All statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL).

RESULTS

Among 1207 patients identified by initial search, 981 patients who met inclusion criteria and exclusion criteria were included in the retrospective analysis. Of these patients, 816 (83.2%) were diagnosed with benign disease, 75 (7.6%) with borderline, and 90 (9.2%) with cancer. Characteristics of the patients are summarized in Table 1. Patients who were diagnosed with ovarian cancer were older and more likely to be menopausal. Of patients diagnosed with ovarian cancer, 63.3% were judged as high risk by the ROMA test, and 71.7% showed a CA125 over 35 U/ml. This sensitivity was further reduced by including patients with borderline tumors: 47.3% were judged as high risk by the ROMA test, and 58.2% showed a CA125 over 35 U/ml. In the same patient group, a total 65.5% were judged as high risk by the ROMA test and/or showed a CA125 over 35 U/ml. Tumor volume was the largest in borderline tumors. One or more leiomyomas over 3 cm were found in 119 patients (12.1%). Adenomyosis was suspected by imaging in 118 patients (12.0%).

Table 2 summarizes correlation between CA125, ROMA, and menopausal status, leiomyomas, and adenomyosis in differentiating patients with suspected ovarian cancer. Sensitivity of CA125 compared to ROMA was higher in premenopausal women but not in postmenopausal women. Alternatively, specificity, PPV, and accuracy of ROMA were higher than those of CA125 in premenopausal women but not in postmenopausal women. Specificity and accuracy of ROMA in all patients were higher than those of CA125, regardless of leiomyomas or adenomyosis. However, this difference was not observed in postmenopausal women. All these differences probably occurred because most endometriotic types were included in premenopausal women.

Table 3 shows the efficacy of CA125 and ROMA according to tumor subtype. The subtypes of tumors were classified based on postoperative histologic findings. As a result, 189 cases (19.3 %) were serous type, 196 cases (20.0%) were mucinous type, 346 cases (35.3%) were endometriotic type, and 250 cases (25.5%) were solid type. In analysis by tumor subtype, ROMA test showed much better efficacy in specificity,

PPV, NPV, and accuracy than CA125 in endometriotic type and somewhat superior results in specificity and accuracy in solid type. In serous type and mucinous type, the efficacy of ROMA test was not significantly different from that of CA125. Rather, the sensitivity of CA125 in serous type was higher.

Table 4 shows the analysis of discrepancies for the two prediction methods. A total of 276 patients (28.1%) had discrepancies between results of the two predictive methods. A total of 151 patients, more than one-half of these patients, were endometriotic type who showed CA125 higher than normal level but were judged to be low risk in the ROMA test (McNemar's test p value < 0.001). These results demonstrated that ROMA test improved prediction in the endometriotic type compared to CA125 (NRI 0.379). However, there was no significant difference between the results of the two predictive methods in the mucinous and solid type. In the serous type, the use of the ROMA could inhibit the prediction. However, the NRI values compared with CA125 showed that ROMA did not improve the prediction in the mucinous type and solid type and could worsen the prediction in the serous type (NRI -0.153).

Figure 1 shows the ROC curve for each tumor type in premenopausal and postmenopausal women. The ROMA test showed better prediction accuracy compared with CA125 in the overall ROC curve based on the analysis of premenopausal patients. However, as a result of tumor subtype analysis, these comparative advantages were only seen in premenopausal women with endometriotic type. The comparative advantages were not seen in the other tumor subtypes and postmenopausal women.

Table 1. Characteristics of study participants

Parameter	Benign disease (n = 816)	Borderline disease (n = 75)	Ovarian cancer (n = 90)	*p* value
Age, years				
Median [IQR]	41.00 [31.00, 49.00]	41.00 [30.50, 54.00]	49.50 [42.00, 55.00]	< 0.001
Menopause				
Pre-	628 (77.0%)	51 (68.0%)	50 (55.6%)	< 0.001
Post-	188 (23.0%)	24 (32.0%)	40 (44.4%)	< 0.001
CA125 (median [IQR], U/mL)	24.00 [14.00, 57.10]	33.50 [18.50, 62.20]	61.50 [25.60, 238.82]	< 0.001
HE4 level (median [IQR], pmol/L)	39.80 [33.50, 48.60]	45.00 [35.15, 52.90]	64.45 [43.58, 93.78]	< 0.001
ROMA, High risk, n (%)	135 (16.5)	21 (28.0)	57 (63.3)	< 0.001
Tumor volume (median [IQR], cm^3)	153.50 [60.00, 371.25]	1300.00 [227.50, 3154.50]	548.00 [214.75, 1554.00]	< 0.001
Pathologic findings, n (%)				
Serous cystadenoma	67 (8.2)	0 (0.0)	0 (0.0)	
Mucinous cystadenoma	128 (15.7)	0 (0.0)	0 (0.0)	
Endometriotic cyst	304 (37.3)	0 (0.0)	0 (0.0)	
Mature cystic teratoma	177 (21.7)	0 (0.0)	0 (0.0)	
Corpus luteal cyst	37 (4.5)	0 (0.0)	0 (0.0)	
Fibroma	54 (6.6)	0 (0.0)	0 (0.0)	

Simple cyst	45 (5.5)	0 (0.0)	0 (0.0)
Brenner tumor	4 (0.5)	0 (0.0)	0 (0.0)
Serous borderline tumor	0 (0.0)	17 (22.7)	0 (0.0)
Mucinous borderline tumor	0 (0.0)	48 (64.0)	0 (0.0)
Seromucinous borderline tumor	0 (0.0)	10 (13.3)	0 (0.0)
Serous adenocarcinoma	0 (0.0)	0 (0.0)	23 (25.6)
Mucinous adenocarcinoma	0 (0.0)	0 (0.0)	20 (22.2)
Endometrioid adenocarcinoma	0 (0.0)	0 (0.0)	18 (20.0)
Clear cell carcinoma	0 (0.0)	0 (0.0)	14 (15.6)
Germ cell tumor	0 (0.0)	0 (0.0)	6 (6.7)
Sex-cord stromal cell tumor	0 (0.0)	0 (0.0)	9 (10.0)
FIGO stage, n (%)			
I	0 (0.0)	74 (98.7%)	67 (74.4%)
II, III	0 (0.0)	1 (1.3%)	23 (25.6%)
Grade			
Well differentiated	0 (0.0)	0 (0.0)	26 (28.9%)
Moderate differentiated	0 (0.0)	0 (0.0)	11 (12.2%)
Poorly differentiated	0 (0.0)	0 (0.0)	44 (48.9%)
Unknown	0 (0.0)	0 (0.0)	9 (10.0%)

IQR = interquartile range; CA125 = cancer antigen 125; HE4 = human epididymis protein 4; ROMA = risk of ovarian malignancy algorithm; FIGO = International Federation of Gynecology and Obstetrics

Table 2. Correlation between CA125, ROMA, and menopausal status, leiomyoma, and adenomyosis in differentiating patients with ovarian tumors

		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Pre-menopause	CA125	0.584 (0.482–0.681)	0.556 (0.516–0.595)	0.175 (0.136–0.219)	0.893 (0.858–0.921)	0.56 (0.523–0.596)
	ROMA	0.455 (0.356–0.558)	0.818 (0.786–0.848)	0.288 (0.219–0.364)	0.903 (0.876–0.926)	0.768 (0.736–0.798)
Post-menopause	CA125	0.578 (0.448–0.701)	0.883 (0.828–0.925)	0.627 (0.491–0.75)	0.86 (0.803–0.906)	0.806 (0.751–0.853)
	ROMA	0.5 (0.372–0.628)	0.888 (0.834–0.93)	0.604 (0.46–0.735)	0.839 (0.781–0.887)	0.79 (0.734–0.838)
Leiomyoma (-)	CA125	0.573 (0.49–0.654)	0.659 (0.623–0.694)	0.261 (0.215–0.312)	0.88 (0.849–0.906)	0.644 (0.611–0.676)
	ROMA	0.447 (0.366–0.53)	0.857 (0.829–0.882)	0.396 (0.322–0.474)	0.88 (0.854–0.903)	0.785 (0.756–0.812)
Leiomyoma (+)	CA125	0.667 (0.384–0.882)	0.442 (0.345–0.543)	0.147 (0.073–0.254)	0.902 (0.786–0.967)	0.471 (0.378–0.564)
	ROMA	0.733 (0.449–0.922)	0.683 (0.584–0.771)	0.25 (0.132–0.403)	0.947 (0.869–0.985)	0.689 (0.598–0.771)
Adenomyosis (-)	CA125	0.565 (0.483–0.645)	0.688 (0.653–0.722)	0.282 (0.233–0.336)	0.879 (0.849–0.905)	0.666 (0.634–0.698)
	ROMA	0.461 (0.381–0.543)	0.87 (0.843–0.894)	0.436 (0.358–0.515)	0.881 (0.855–0.904)	0.797 (0.769–0.824)
Adenomyosis (+)	CA125	0.818 (0.482–0.977)	0.252 (0.173–0.346)	0.101 (0.047–0.183)	0.931 (0.772–0.992)	0.305 (0.224–0.397)
	ROMA	0.636 (0.308–0.891)	0.598 (0.499–0.692)	0.14 (0.058–0.267)	0.941 (0.856–0.984)	0.602 (0.507–0.691)

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; CA125 = cancer antigen 125; ROMA = risk of ovarian malignancy algorithm

Table 3. Efficacy of CA125 and ROMA according to imaging tumor subtype

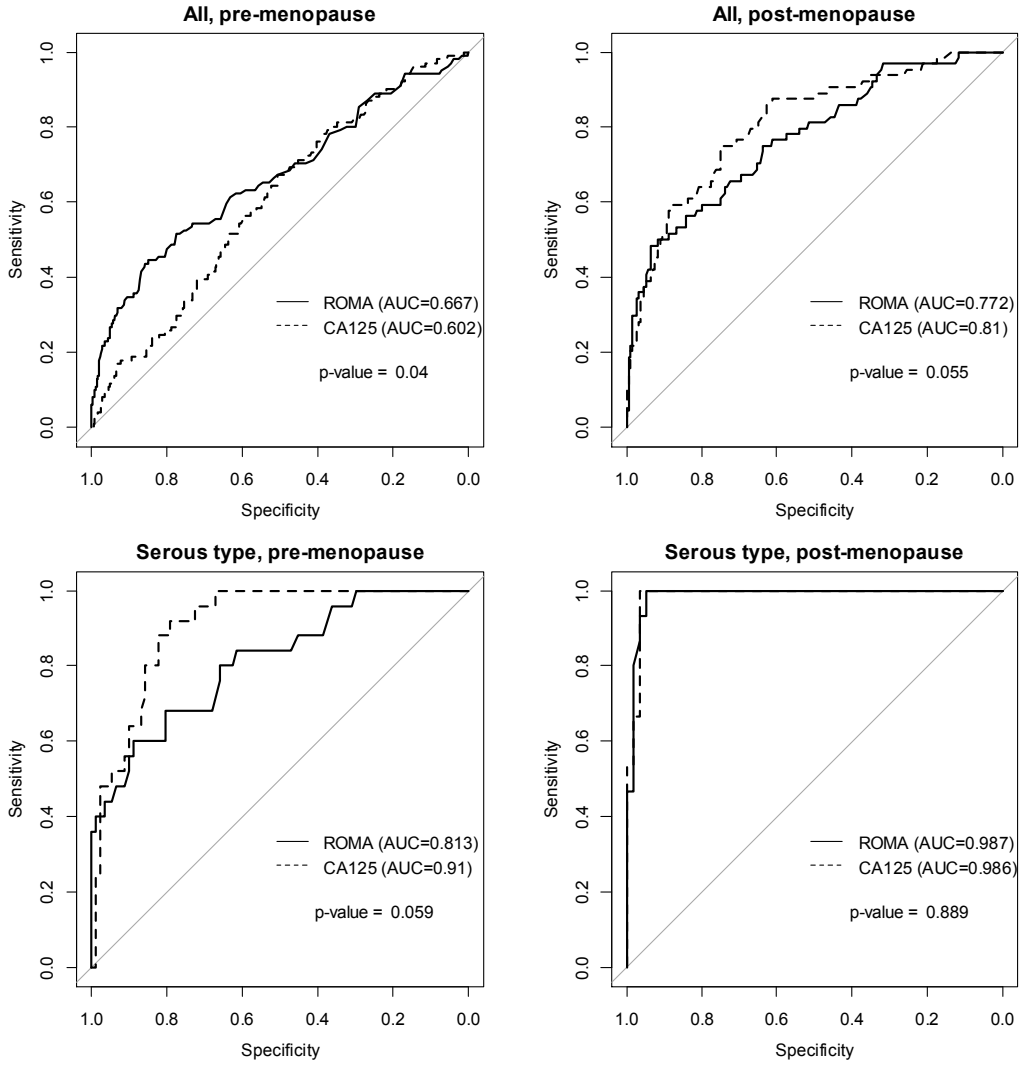
		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Serous type (n = 189)	CA125	0.95 (0.831–0.994)	0.846 (0.777–0.9)	0.623 (0.49–0.744)	0.984 (0.945–0.998)	0.868 (0.811–0.913)
	ROMA	0.75 (0.588–0.873)	0.893 (0.831–0.937)	0.652 (0.498–0.786)	0.93 (0.875–0.966)	0.862 (0.805–0.908)
Mucinous type (n = 196)	CA125	0.338 (0.228–0.463)	0.867 (0.796–0.921)	0.575 (0.409–0.73)	0.712 (0.634–0.781)	0.684 (0.614–0.748)
	ROMA	0.235 (0.141–0.354)	0.875 (0.805–0.927)	0.5 (0.319–0.681)	0.683 (0.606–0.753)	0.653 (0.582–0.719)
Endometriotic type (n = 346)	CA125	0.69 (0.529–0.824)	0.303 (0.251–0.358)	0.12 (0.082–0.168)	0.876 (0.798–0.932)	0.35 (0.299–0.403)
	ROMA	0.619 (0.456–0.764)	0.753 (0.701–0.801)	0.257 (0.176–0.354)	0.935 (0.896–0.962)	0.737 (0.687–0.783)
Solid type (n = 250)	CA125	0.4 (0.163–0.677)	0.791 (0.734–0.842)	0.109 (0.041–0.222)	0.954 (0.914–0.979)	0.768 (0.711–0.819)
	ROMA	0.4 (0.163–0.677)	0.881 (0.832–0.919)	0.176 (0.068–0.345)	0.958 (0.922–0.981)	0.852 (0.802–0.894)

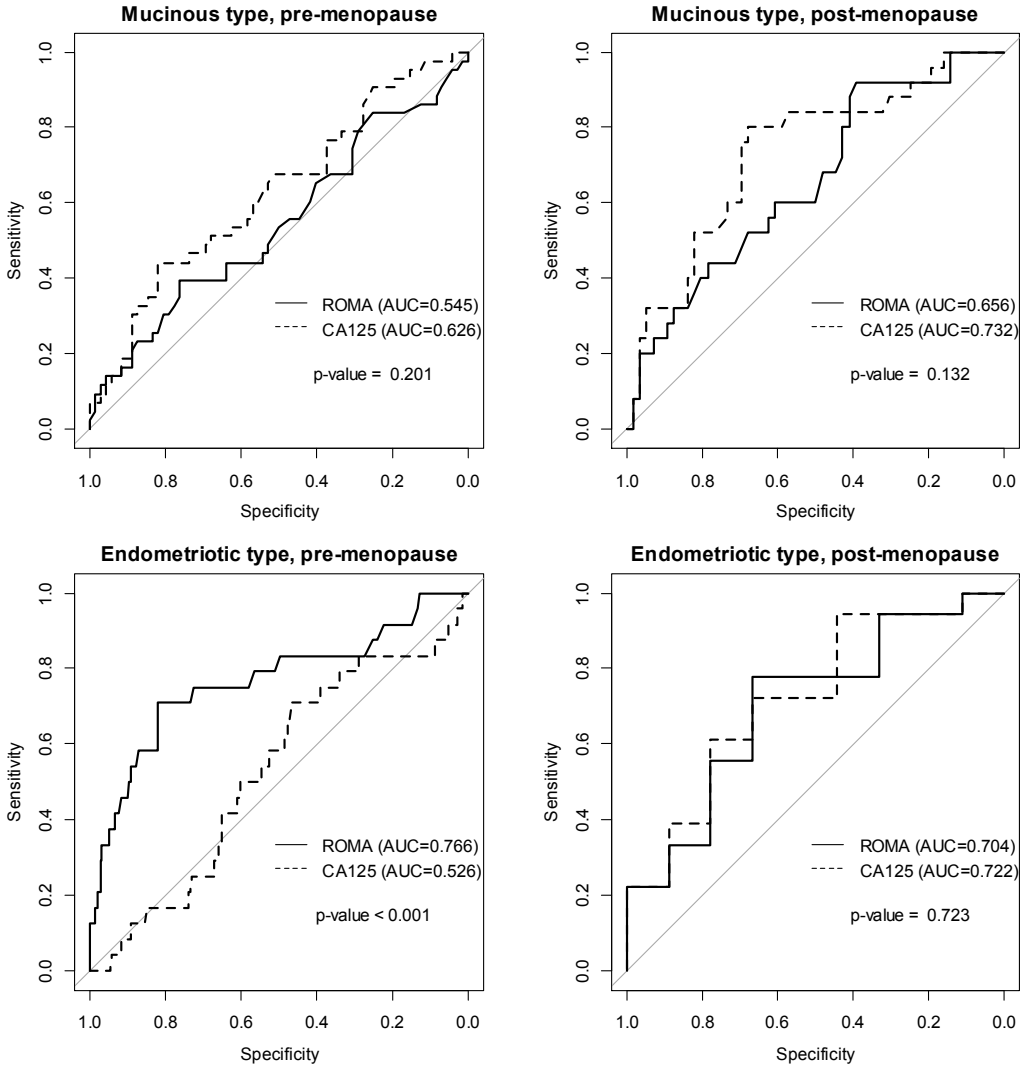
CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; CA125 = cancer antigen 125; ROMA = risk of ovarian malignancy algorithm

Table 4. Analysis of discrepancies in two prediction methods

	Both Low	CA125 High ROMA Low	CA125 Low ROMA High	Both High	McNemar's test *p* value	NRI
Serous type (n = 189)	116 (61.4%)	27 (14.3%)	12 (6.3%)	34 (18%)	0.025	-0.153
Mucinous type (n = 196)	143 (73%)	21 (10.7%)	13 (6.6%)	19 (9.7%)	0.23	-0.095
Endometriotic type (n = 346)	94 (27.2%)	151 (43.6%)	11 (3.2%)	90 (26%)	<0.001	0.379
Solid type (n = 250)	185 (74%)	31 (12.4%)	10 (4%)	24 (9.6%)	0.002	0.089
All (n = 981)	538 (54.8%)	230 (23.4%)	46 (4.7%)	167 (17%)	< 0.001	0.094

CA125 = cancer antigen 125; ROMA = risk of ovarian malignancy algorithm; NRI = net reclassification index


All, pre-menopause
Sensitivity
Specificity
ROMA (AUC=0.667)
CA125 (AUC=0.602)
p-value = 0.04
All, post-menopause
Sensitivity
Specificity
ROMA (AUC=0.772)
CA125 (AUC=0.81)
p-value = 0.055
Serous type, pre-menopause
Sensitivity
Specificity
ROMA (AUC=0.813)
CA125 (AUC=0.91)
p-value = 0.059
Serous type, post-menopause
Sensitivity
Specificity
ROMA (AUC=0.987)
CA125 (AUC=0.986)
p-value = 0.889


Mucinous type, pre-menopause
Sensitivity
Specificity
ROMA (AUC=0.545)
CA125 (AUC=0.626)
p-value = 0.201
Mucinous type, post-menopause
Sensitivity
Specificity
ROMA (AUC=0.656)
CA125 (AUC=0.732)
p-value = 0.132
Endometriotic type, pre-menopause
Sensitivity
Specificity
ROMA (AUC=0.766)
CA125 (AUC=0.526)
p-value < 0.001
Endometriotic type, post-menopause
Sensitivity
Specificity
ROMA (AUC=0.704)
CA125 (AUC=0.722)
p-value = 0.723

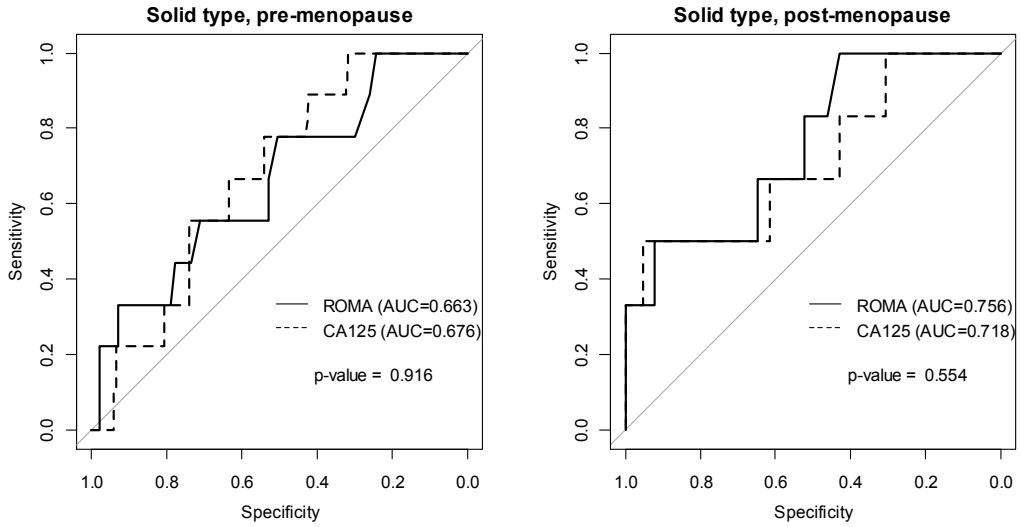


Fig 1. Receiver operating characteristics (ROC) curve for ROMA test and CA125 for each tumor type in premenopausal and postmenopausal women

DISCUSSION

All previous studies about the ROMA test showed and emphasized the superiority of specificity compared with the CA125 test. However, these studies did not separately analyze by histologic subtypes of ovarian tumors.[18-20] Although Kim et al. studied diagnostic performance of ROMA for ovarian cancer, two-thirds of the study patients did not have ovarian tumors but had adenomyosis, leiomyomas, endometrial pathology, or ovarian tumors without biopsy.[14] As previously mentioned, expression of HE4 in tumors is very different depending on histologic subtype. Therefore, it is necessary to analyze the expected degree of prediction accuracy of ROMA test compared with CA125 in discrimination of ovarian tumor in each tumor subtype. According to the results of the current study, the superiority of the ROMA test in the differentiation of malignant ovarian tumors compared to CA125 is observed only in premenopausal patients with endometriotic type. Comparative advantages are not seen in other tumor subtypes.

Specificity and accuracy of ROMA were higher than those of CA125 regardless of leiomyomas or adenomyosis in premenopausal women but not in postmenopausal women (Table 2). This difference may be because most endometriotic types are found in premenopausal women, and ROMA is far superior to CA125 in discrimination of endometriotic type ovarian tumor. Leiomyomas and adenomyosis decrease the specificity and accuracy of CA125 and ROMA. However, the specificity and accuracy of CA125 decreases more than ROMA test. This may be due to the inclusion of HE4, which is not affected by leiomyomas or adenomyosis.

According to a recent meta-analysis of the previous five studies, ROMA showed sensitivity of 0.873 (95% CI 0.752-0.940) and specificity of 0.855 (95% CI 0.719-0.932).[21] In this study, the sensitivity of ROMA (0.455 in premenopausal women, 0.5 in postmenopausal women) and CA125 (0.584 in premenopausal women, 0.578 in postmenopausal women) were lower than the previously reported results. This may be because the current study included only histologically-confirmed patients after surgery and excluded from the analysis advanced ovarian cancer or hydrosalpinx

that were sufficiently predictable by imaging. The inclusion of many patients with borderline tumors may also be the cause of these results.

In actual clinical practice, gynecologists establish the prediction marker after determining the approximate tumor subtype and degree of doubt about malignancy through imaging test. With determination of the approximate tumor subtype through sonography or APCT, knowing the accuracy of the prediction marker for each tumor subtype makes it possible to select the test according to the expectancy of each test. The current study compared and suggested the predictive values of CA125 and ROMA test for differentiating ovarian tumors according to tumor subtypes by imaging that were associated with postoperative histologic findings. We reaffirmed the imaging test that was performed in all patients to confirm the suspicion of leiomyomas or adenomyosis, to determine whether these factors affected the accuracy of the tests. Previous studies on ROMA have focused only on epithelial ovarian tumors and have not reported on malignant germ cell tumors or epithelial borderline tumors. The present study evaluated the utility of prediction markers in more diverse tumors, including 75 borderline tumors and 15 germ cell or sex-cord stromal cell tumors.

This study has some limitations. First, it has a retrospective design. Because of this, it is not possible to identify any physical condition that may affect CA125 or HE4, such as inflammation or smoking at the time of examination. Second, this study has a precondition that the type of ovarian tumor can be clearly distinguished through sonography or APCT. Most ovarian tumors can be distinguished as accurate tumor types by imaging test. However, some hemorrhagic corpus luteal cysts can be difficult to differentiate from endometriotic cysts. Third, adenomyosis in this study is a suspicious finding in the image, but it is not the result of histopathologic confirmation. However, if adenomyosis is severe enough to affect the CA125 level, it should be detected on ultrasound.

CONCLUSION

In the endometriotic type ovarian tumor, the superiority of the ROMA test compared to CA125 was confirmed in triage of ovarian tumor. However, these comparative advantages are not seen in the other tumor subtypes and postmenopausal women. Therefore, it seems to be beneficial to use the ROMA test rather than conventional CA125 as triage biomarker only in ovarian tumors considered as endometriotic type through imaging. This highlights the need to develop better tumor-specific biomarkers, such as circulating tumor DNA.

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국문 요약

목적: 수술 후 조직병리적 진단과 연관된 영상적 종양 아형에 따라 양성 난소 종양과 조기 난소암을 감별하는 도구로서 CA 125와 비교하여 ROMA (난소암 위험도 알고리즘)의 정확성을 조사하고자 한다.

대상 및 방법: 2014년 9월부터 2018년 3월까지 난소암 의심 소견으로 서울아산병원에 방문하여 ROMA 검사를 시행 후 수술을 받은 총 1207명 환자 중 연구 포함조건에 알맞은 981명의 임상 자료를 후향적으로 분석하였다.

결과: 연구 대상 환자 981 명 중 816 명이 양성 종양이었고 165 명은 경계성 종양을 포함한 악성 종양이었다. 난소암 또는 경계성 종양으로 진단된 환자 중 47.3 %는 ROMA 검사로 고위험군으로, 58.2 %는 35 U/ml 이상의 CA 125를 보였다. 폐경 전 여성에서 ROMA의 특이도와 정확도는 CA 125의 특이도와 정확도보다 높았다. 그러나 악성 난소 종양 감별에 있어서 CA 125와 비교한 ROMA 검사의 우월성은 자궁내막증 아형 환자에서만 관찰되었다 (순 재분류 지수 0.379). 이러한 비교 우위는 다른 종양 아형에서는 관찰되지 않았다.

결론: 자궁내막증 아형 난소 종양에서는 난소 종양의 선별에서 CA 125와 비교하여 ROMA 검사의 우월성이 확인되었으나 다른 종양 아형에서는 민감도와 특이성이 CA 125와 유사하였다. 따라서 향후 난소 종양 선별을 위한 더 나은 종양 특이적 생체표지자의 개발이 필요하다.

중심 단어: 진단 기술; 난소암; CA 125 항원; 생체표지자