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Original Article

Low serum T3 levels are associated with false-positive results when using the risk of ovarian malignancy algorithm (ROMA) in women with benign ovarian disease

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ABSTRACT

Objective: We investigated factors that could cause false-positive results when using the risk of ovarian malignancy algorithm (ROMA) for assessing ovarian cancer risk.
Materials and methods: ROMA scores were calculated from patients followed surgery to remove a pelvic mass. We compared a false-positive group with a true-negative group of ROMA scores.
Results: We analyzed 324 patients using medical records. There were 22 with an epithelial ovarian cancer (EOC), 15 with a borderline ovarian tumor, and 287 with benign disease. Twenty-nine (10.1%) of the patients with benign disease showed high-risk ROMA score (false positive) and 13/37 (35%) patients with EOC, or borderline ovarian tumor showed low ROMA scores (false negatives). The median serum triiodothyronine (T3) level of the false-positive ROMA group in patients with benign disease was lower than in the true-negative ROMA group ($p < 0.001$) and the estimated glomerular filtration rate (eGFR) was also lower ($p = 0.001$) in the false-positive ROMA group. Median serum T3 levels in the true-positive ROMA group among patients with EOC, or borderline ovarian tumor were lower than in the false-negative ROMA group ($p = 0.043$).
Conclusion: Median serum T3 level and eGFR in the false-positive ROMA group in patients with benign ovarian disease were lower than in the true-negative group.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer and the seventh most commonly diagnosed cancer among women in the world. The main reason for the high death rate is the late presentation in most cases [1]. CA125 and the risk of ovarian malignancy algorithm (ROMA) have been utilized to help predict ovarian cancer in patients with a pelvic mass. However, there is no approved strategy for early diagnosis of EOC [2]. The CA125 level has low sensitivity and specificity. Many women with benign gynecologic diseases, such as endometriosis and adenomyosis, will have an elevated serum CA125 level [3,4].

The ROMA was developed for assessing the risk of ovarian cancer among women with a pelvic mass. The ROMA score is calculated based on serum human epididymis protein 4 (HE4) and CA125 concentrations and is then compared with cutoff values suggesting a high risk of ovarian cancer. ROMA can be used by primary physicians or gynecologists who are not oncology specialists to decide whether to refer a patient to an appropriate center for surgery [5–7]. The reported sensitivity and specificity of ROMA are variable. In several prospective, multicenter, double-blinded clinical trials, the sensitivity of ROMA for detecting EOC and a borderline ovarian tumor was approximately 88% and its specificity was 75%. However, a false-positive ROMA result in which the risk of malignancy was falsely reported to be elevated in patients with benign conditions was 25% [6,8]. Patients with false-positive ROMA results usually undergo additional studies and even unnecessary surgery. Until a high ROMA level is proven to be a false-positive result, patients can also suffer from anxiety and depression.

In addition to ovarian carcinoma, HE4 levels can be elevated in patients with benign diseases in the kidney, lung, liver, and heart [9–13]. HE4 gene expression level is also high in the normal human trachea, salivary gland, lung, prostate, pituitary gland, thyroid, and

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kidney [14,15]. Disease in organs with high HE4 gene expression might elevate HE4 levels and lead to false-positive ROMA scores. Here, we evaluated how the functions of the thyroid, liver, and kidney might affect ROMA scores and aimed to determine factors that might cause false-positive ROMA scores. Studying for factors that cause false-positive ROMA results will be helpful in the interpretation and clinical application of ROMA scores for patients with a pelvic mass.

Materials and methods

This study was conducted at the Catholic University of South Korea, Bucheon St. Mary's Hospital between January 2016 and March 2018. Potentially eligible patients included women aged >18 years for whom gynecologists had requested ROMA tests to evaluate a pelvic mass and in women following surgery. ROMA scores were calculated from measurements of HE4 and CA125 in blood specimens from 364 patients following surgery for a pelvic mass. A total of 40 patients were excluded. Thirty-nine patients did not have an ovarian lesion at surgery and one patient had a metastatic ovarian lesion from recurrent cervical cancer. We analyzed the remaining 324 patients using their medical records. This study was approved by the Institutional Review Board of the Catholic Medical Center at the Catholic University of Korea (HC18RES10082).

We evaluated functions of the thyroid, liver, kidney, lung, and heart that might affect ROMA scores. In preoperative evaluation of patients, there were no pleural effusion seen in chest X-rays and other abnormal findings related to chronic heart failure in EKGs and chest X-rays. Blood specimens for the ROMA score, triiodothyronine (T3), free thyroxine (T4), thyroid-stimulating hormone (TSH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and estimated glomerular filtration rate (eGFR) were drawn prior to the pelvic mass surgery. HE4 and CA125 concentrations were measured on the day of blood collection using the ARCHITECT HE4 assay (Product Number B2K540) and the CA125 II assay (Product Number B2K450; Abbott Diagnostics, Abbott Park, Lake Bluff, IL, USA). The ROMA score was calculated using the following equations, according to the manufacturer's instructions:

Premenopausal prediction

$$index = -12.0 + 2.38 \times \ln(HE4) + 0.0626 \times \ln(CA125)$$

Postmenopausal prediction

$$index = -8.09 + 1.04 \times \ln(HE4) + 0.732 \times \ln(CA125)$$

ROMA score (predictive probability) = exp(prediction index) / (1 + exp(prediction index)) × 100

ROMA scores >7.4% in premenopausal and >25.3% in postmenopausal women were considered high-risk, according to the manufacturer's instructions. Menopause was defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea [16]. Artificial menopause was also defined as hysterectomy with bilateral oophorectomy, bilateral oophorectomy alone, ovarian failure secondary to radiation and ovarian failure secondary to chemicals/medication. We compared the false-positive ROMA group as being patients with a benign disease with high-risk ROMA score and a true-negative ROMA group as being patients with a benign disease with a low-risk ROMA score. We also evaluated differences between the false-negative ROMA group who had a low-risk ROMA score among those with EOC or borderline ovarian tumor and a true-positive ROMA group with a high-risk ROMA score among those with EOC or borderline ovarian tumor.

Statistical analysis

The Mann-Whitney-Wilcoxon nonparametric and $\chi 2$ test were used for comparisons of continuous and categorical variables between patients with EOC or borderline ovarian tumor and those with benign disease. Patients were grouped into four, true negative, false positive, false negative, and true positive, based on comparison of ROMA against the biopsy-confirmed target condition status. Data for age, eGFR, T3, free T4, TSH, AST, and ALT were summarized as median and IQR. They were compared among the four groups with Kruskal–Wallis rank sum test. For multiple comparisons, post-hoc Dunn's test with Bonferroni adjustment were used. Analyses were performed using R3.4.3 (www.r-project.org/).

Results

The pathology diagnosis of the study patients are shown in Table 1. High-grade serous carcinoma was the most common type in patients with EOC and endometrial cysts were the most common in those with a benign disease. The clinical and laboratory test results of the patients are shown in Table 2. The mean ages in the EOC and borderline ovarian tumor groups were higher than in the benign disease group. The median T3 level was lower in the EOC and borderline ovarian tumor groups ($p = 0.020$) and thyroid function showed a tendency to decrease in these groups. However, the eGFR was not significantly different between these two groups. ROMA scores are compared with the pathology diagnosis in Table 3. Thirteen of 37 (35%) patients with EOC or borderline ovarian tumor showed a low-risk ROMA score and 29 of 287 (10.1%) patients with

Table 1
Pathologic diagnoses of study patients (N = 324).

	Pathologic diagnosis	N
Epithelial ovarian cancer (n = 22)	High-grade serous carcinoma	13
	Tubal intraepithelial carcinoma	3
	Clear cell carcinoma	2
	Seromucinous carcinoma	2
	Endometrioid cystadenocarcinoma	1
	Mucinous carcinoma	1
Borderline ovarian tumor (n = 15)	Mucinous borderline tumor	5
	Seromucinous borderline tumor	5
	Serous borderline tumor	5
Benign disease (n = 287)	Endometrial cyst	84
	Dermoid cyst	58
	Mucinous cystadenoma	47
	Serous cystadenoma	14
	Corpus luteal cyst	12
	Fibroma	11
	Tubo-ovarian abscess	9
	Seromucinous cystadenoma	8
	Paratubal cyst	6
	Benign struma ovarii	4
	Hemorrhagic cyst	4
	Hydrosalpinx	4
	Pseudocyst	4
	Parovarian cyst	3
	Benign Brenner tumor	2
	Endometrial cyst + fibroma	2
	Follicular cyst	2
	Serous cystadenofibroma	2
	Serous cystadenoma torsion	2
	Dermoid cyst with small carcinoid	1
	Endometrial cyst + Tubo-ovarian abscess	1
	Mucinous cystadenofibroma	1
	Paramesonephric (Müllerian) cyst	1
	Parovarian cyst torsion	1
	Peritoneal tuberculosis	1
	Seromucinous cystadenofibroma	1
	Serous cystedenofibroma	1
	Tubal pregnancy	1

Table 2
Distribution of clinical characteristics of study patients (median ± IQR).

	EOC or Borderline ovarian tumor (n = 37)	Benign disease (n = 287)	p[a]
Menopausal state (%)	57% (21/37)	24.0% (69/287)	<0.001
Age (y)	50.0 ± 12.0	39.0 ± 21.5	<0.001
ROMA (%)	24.3 ± 55.9	3.7 ± 4.2	<0.001
CA125 (kU/L)	96.8 ± 306.8	22.6 ± 37.7	<0.001
HE4 (pmol/L)	70.7 ± 71.3	33.5 ± 13.1	<0.001
eGFR (mL/min/1.73 m^2)	98.0 ± 34.0	100.0 ± 25.0	0.132
T3 (ng/dL)	108.2 ± 41.8	122.5 ± 30.6	0.020
FreeT4 (pg/mL)	12.2 ± 1.9	12.8 ± 2.1	0.054
TSH (mIU/L)	2.7 ± 1.7	2.0 ± 1.7	0.054
AST (IU/L)	17.0 ± 7.0	17.0 ± 7.0	0.121
ALT (IU/L)	14.0 ± 10.0	13.0 ± 9.0	0.625

EOC, epithelial ovarian cancer; IQR, interquartile range.
[a] p values were estimated by $\chi 2$ test for menopausal status and the Mann–Whitney–Wilcoxon test for other variables.

Table 3
Classification from ROMA compared with pathology diagnosis.

		EOC or Borderline ovarian tumor (n = 37)	Benign disease (n = 287)
ROMA	High	24 (64.9%)	29 (10.1%)
	Low	13 (35.1%)	258 (89.9%)

EOC, epithelial ovarian cancer.

benign diseases showed a high-risk ROMA score. That is, a false-positive rate of 10.1% was observed in those with a benign ovarian disease and a false-negative rate of 35.1% in those with EOC or borderline ovarian tumor. The sensitivity of the ROMA score for detecting EOC and borderline ovarian tumor was 65% (24/37) and the specificity was 89.9% (258/287). The median T3 level in the false-positive ROMA score group in those with a benign disease was significantly lower than in the true-negative ROMA group ($p < 0.001$) and eGFR was also lower ($p = 0.001$; Table 4; Fig. 1). The median T3 level among those with a true-positive ROMA score in patients with EOC or borderline ovarian tumor was lower than in those with a false-negative ROMA score ($p = 0.043$; Table 5). Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio for positive results (LRP), and likelihood ratio for negative results (LRN) of ROMA in decreased T3 levels (<80 ng/dL) and unaltered T3 (≥80 ng/dL) groups are shown in Table 6. The lower limit of the reference range for T3 in our hospital is 80 ng/dL. In the group with decreased T3 levels, the specificity (95% CI) of ROMA was 0.250 (0.055–0.572), which was significantly lower than in the unaltered T3 group [0.927 (0.889–0.956)]. Likewise, the LRP of ROMA in the decreased T3 group was significantly lower than in the unaltered T3 group [1.111 (0.684–1.804) vs 8.242 (4.889–13.896)]. The 95% CIs of sensitivity, PPV, NPV, and LRN of the two groups overlapped, meaning that the observed difference between them were not significant.

Table 4
Comparison of variables between false-positive and true-negative ROMA groups.

ROMA	False-positive group (n = 29)	True-negative group (n = 258)	p[a]
	Median ± IQR	Median ± IQR	
Age (y)	46.0 ± 23.0	39.0 ± 21.8	0.087
eGFR (mL/min/1.73 m^2)	83.0 ± 38.0	101.0 ± 23.0	0.001
T3 (ng/dL)	100.5 ± 47.8	123.7 ± 29.1	<0.001
FreeT4 (pg/mL)	12.5 ± 2.4	12.8 ± 2.1	0.268
TSH (mIU/L)	2.0 ± 2.3	2.1 ± 1.7	0.757
AST (IU/L)	16.0 ± 7.0	17.0 ± 7.0	0.263
ALT (IU/L)	11.0 ± 8.0	14.0 ± 9.0	0.076

IQR, interquartile range.
[a] Mann–Whitney–Wilcoxon test.

Discussion

We aimed to determine which factors could cause high ROMA scores among patients without EOC or borderline ovarian tumor. Elevation of CA125 or HE4 levels can lead to high-risk ROMA scores. In our study, 18 of 29 (62%) patients with a false-positive ROMA score without EOC or borderline ovarian tumor showed elevated serum CA125 levels, but 80 of 258 (31.0%) patients with a true-negative ROMA score only had elevated serum CA125 levels. We also found that 7/29 (24%) of patients with a false-positive ROMA score showed elevated serum HE4 levels, but no patient with a true-negative ROMA score had increased serum HE4 levels. CA125 is a widely used marker for ovarian epithelial cancer. However, its lack of specificity is a problem as multiple benign diseases—both gynecological and nongynecological—can lead to elevated serum levels. HE4 has been proposed as a tumor marker for ovarian cancer, but levels can also be elevated in patients with benign diseases, such as renal failure, effusion, liver disease, lung disease, and chronic heart failure [9–13]. HE4 can be expressed in the distal convoluted tubules of the kidney and renal cellular injury or renal fibrosis can cause elevated levels [15]. Additionally, renal dysfunction can decrease HE4 clearance and elevate HE4 levels. Yuan et al. reported that serum HE4 levels were significantly higher in patients with chronic kidney disease compared with healthy control individuals [10]. Naqy et al. showed significantly increased HE4 concentrations in individuals with decreased eGFR compared with clinical controls [11]. Piek et al. also reported that a low eGFR level was associated with high HE4 levels [12]. In our study, the median eGFR in the false-positive group who had high-risk ROMA scores without EOC or borderline ovarian tumor was also lower than in the true-negative group. However, levels of the liver enzymes AST and ALT were not different between the false-positive and true-negative ROMA groups in patients with benign ovarian disease.

In addition to ovarian carcinoma, HE4 gene expression was high in normal human trachea, salivary gland, lung, prostate, pituitary gland, thyroid, and kidney [14,15]. Therefore we checked thyroid function, liver enzyme, and eGFR in this study. We found that patients with a false-positive ROMA score had significantly lower median serum T3 levels than among those with a true-negative ROMA score in those with benign ovarian disease, and a true-positive ROMA group in patients with EOC or borderline ovarian tumor also showed significantly lower serum T3 levels than in the false-negative ROMA group. As far as we know, no study has analyzed the relationship between ROMA scores and serum T3 levels. However, a relationship between CA125 level and thyroid function was reported by Hashimoto et al. who showed that the mean serum CA125 concentration in hypothyroid patients was higher than in normal and hyperthyroid patients, and also reported there was a significant inverse correlation between CA125 with T3 level [17]. Levels of thyroid hormones change during illness. There is an initial fall in circulating T3, a reciprocal increase in reverse T3 (rT3), and finally a decline in T4. Despite the lower circulating levels of T3 and T4, thyrotropin levels usually remain within the normal range. This pattern has been well characterized during calorie restriction, after surgery, and in patients with a variety of acute and chronic medical illnesses [13]. Critical illness, sepsis, cardiac surgery, and major trauma or burns are also typical condition in which circulating levels of T3 are decreased. Low T3 syndrome is a situation in which a low serum T3 level is the most common thyroid hormone disturbance during illness. In our study, 14 of 287 patients with benign ovarian disease had tuboovarian abscesses, cyst torsion, or peritoneal tuberculosis, which were related to pelvic

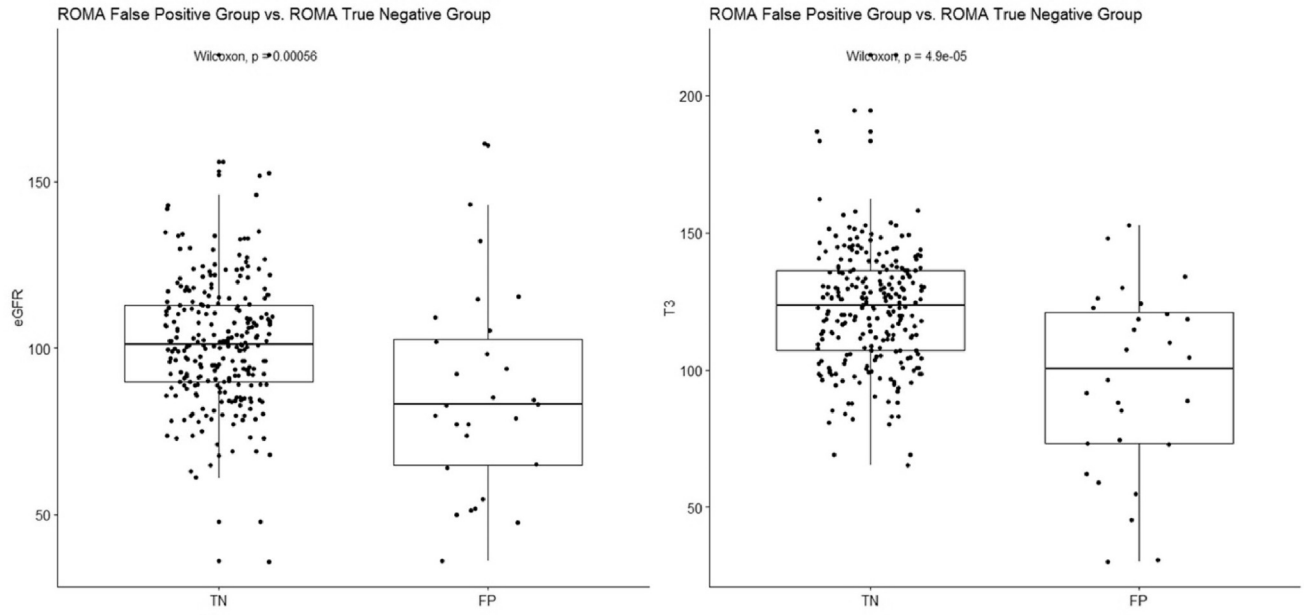

Fig. 1. Distribution of eGFR and T3 levels between the false-positive and true-negative ROMA groups. Footnote: eGFR, estimated glomerular filtration rate; T3, triiodothyronine; TN, true negative; FP, false positive.

Table 5
Comparison of variables between false-negative and true-positive ROMA groups.

ROMA	False-negative group (n = 13)	True-positive group (n = 24)	p[a]
	Median ± IQR	Median ± IQR	
Age (y)	50.0 ± 20.0	49.5 ± 9.5	1.000
eGFR (mL/min/1.73 m^2)	83.0 ± 29.0	98.0 ± 39.0	0.258
T3 (ng/dL)	132.8 ± 42.3	104.1 ± 33.7	0.043
FreeT4 (pg/mL)	11.8 ± 1.3	12.4 ± 2.3	0.459
TSH (mIU/L)	2.7 ± 3.0	2.7 ± 1.3	0.937
AST (IU/L)	20.0 ± 4.0	17.0 ± 7.5	0.354
ALT (IU/L)	14.0 ± 5.0	14.5 ± 11.0	0.750

IQR, interquartile range.
[a] p values by Mann–Whitney–Wilcoxon test.

Table 6
Diagnostic accuracy (95% CI) of ROMA in subgroups according to the lower limit of reference range for T3 (80 ng/dL) (n = 309; target condition: EOC + BOT [n = 36] vs Benign disease [n = 273]).

	T3 < 80 ng/dL (n = 18)	T3 ≥ 80 ng/dL (n = 291)	Total (n = 309)
Sensitivity	0.833 (0.359, 0.996)	0.600 (0.406, 0.773)	0.639 (0.462, 0.792)
Specificity	0.250 (0.055, 0.572)	0.927 (0.889, 0.956)	0.897 (0.855, 0.931)
PPV	0.357 (0.088, 0.963)	0.486 (0.372, 0.683)	0.451 (0.357, 0.638)
NPV	0.750 (0.251, 0.923)	0.953 (0.902, 0.971)	0.950 (0.902, 0.967)
LRP	1.111 (0.684, 1.804)	8.242 (4.889, 13.896)	6.229 (4.059, 9.560)
LRN	0.667 (0.087, 5.127)	0.431 (0.278, 0.670)	0.402 (0.260, 0.623)

EOC, epithelial ovarian cancer; BOT, borderline ovarian tumor; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LRP, likelihood ratio for positive results; LRN, likelihood ratio for negative results.

inflammation. Six of 14 patients (43%) who had pelvic inflammation showed a false-positive ROMA score and all of those patients showed serum T3 levels below the normal range. The other eight patients who had pelvic inflammation showed a true-negative ROMA score and six of them had normal range serum T3 levels. Low serum T3 levels induced by pelvic inflammation seems to be one cause of false-positive ROMA scores in patient with benign ovarian disease. However, additional studies are needed to explain why the serum T3 level is lower in false-positive ROMA group more detail. For correct interpretation of ROMA scores, it is important to check diseases or situations which affect CA125 and HE4 levels. Additionally—if possible—clinicians should check their patients' serum T3 levels.

There was statistically no difference in serum T3 level between false-positive ROMA group and true-positive ROMA group (data not shown). It seems impossible to distinguish between two groups with only lower serum T3 level without imaging study. However the difference in average value of ROMA score between false-positive ROMA group and true-positive ROMA group was almost double in both of premenopausal and postmenopausal patients. Average value of ROMA score in false-positive vs. true-positive group was 20.6% vs. 41.0% in premenopausal patients ($p = 0.046$) and 35.4% vs. 68.9% in postmenopausal patients ($p < 0.001$). In patients with normal or benign ovarian feature in imaging study and high risk ROMA score, low serum T3 level may be one reason for false-positive ROMA score, when value of ROMA score is especially relatively low. However, because patients with ovarian cancer may also have low serum T3 level and high risk ROMA score, we should be careful for interpretation and use imaging study together.

Moore et al. validated ROMA scoring for the prediction of ovarian cancer in 531 patients with a pelvic mass [6]. That study was a prospective, multicenter, blinded clinical trial. They reported that 89/352 (25.3%) patients with benign ovarian disease showed a high-risk ROMA score and 17/151 (11.3%) patients with EOC or borderline ovarian tumor had low-risk ROMA scores. In that study the sensitivity of the ROMA score was 88.7% and its specificity was 74.7%. Another study by Moore et al. analyzed 472 patients with an adnexal mass and reported similar results [8]. They found a 25.1% false-positive rate, a 11.9% false-negative rate, 88.1% sensitivity, and 74.9% specificity. Karlsen et al. reported a sensitivity of 93.9%/97.5% (pre/postmenopausal women) and a specificity of 52.6%/57.0% (pre/postmenopausal women) when identifying EOC [18]. In our study, the false-positive rate for ROMA scores was 10.1% and this was low compared with the studies by Moore et al. However, the false-negative rate was high at 35.1%. The specificity rate of 89.9% was higher than those reported by Moore et al. and Karlsen et al. but the

sensitivity (64.9%) was lower. There are several possible reasons for the difference among studies in false-positive and false-negative rates, sensitivity, and specificity. First, the method of measuring ROMA scores differed between studies. We used the ARCHITECT HE4 assay and the CA125II assay while Moore's group used the HE4 EIA assay (Fujirebio Diagnostics Inc., Malvern, PA, USA) and the ARCHITECT CA125II assay (Abbott Diagnostics). Second was the difference in populations studied. Third was differences in the prevalence of EOC and borderline ovarian tumor, which was 32.0% in the study by Moore et al. and the EOC prevalence was 21.0% in the study by Karlsen et al. [5,18]. However, the EOC and borderline ovarian tumor prevalence was relatively low at 11.4% in our study.

The relatively high false-negative rates and low sensitivity rate in our study might have increased the risk of missing the occurrences of EOC and borderline ovarian tumor. To improve the diagnostic accuracy of the ROMA score, we analyzed its diagnostic accuracy among 443 patients who visited our hospital with a pelvic mass [19]. The sensitivity and specificity rates at the 7.4%/25.3% (premenopausal/postmenopausal women) suggested cutoff value were 63.6% and 90.7%, respectively. Sensitivity was 81.8% at the 4.65%/13.71% adjusted cutoff set to a specificity of 75.0%. In other words, when the cutoff value was modified to set the specificity to 75.0%, the sensitivity increased to a level above the acceptable minimum.

Our study had several weak points. We studied these cases retrospectively from medical records in a single hospital and the study size was small. However, we expect that the results from this study might be helpful for minimizing the misreading of ROMA scores in patients with an ovarian mass.

In conclusion, median serum T3 level and eGFR levels in the false-positive ROMA group in patients with benign ovarian disease were lower than in the true-negative ROMA group. For correct interpretation of ROMA scores, it is important to check diseases or situations which might affect CA125 and HE4 levels; moreover, measurement of serum T3 levels will also be helpful. In patients with normal or benign ovarian feature in imaging study and high risk ROMA score, low serum T3 level may be one reason for false-positive ROMA score, when value of ROMA score is especially relatively low. This finding will help to reduce misreading for ROMA score and also prevent unnecessary studies and surgery.

Conclusion

Median serum T3 level and eGFR in the false-positive ROMA group in patients with benign ovarian disease were lower than in the true-negative group.

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Conflict of interest

The authors have no conflicts of interest relevant to this article.

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