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The use of CA125, human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), risk of malignancy index (RMI) and subjective assessment (SA) in preoperative diagnosing of ovarian tumors

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ABSTRACT

Objectives: To compare utility of carcinoma antigen 125 (CA125), human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), risk of malignancy index (RMI) and subjective assessment (SA) in preoperative diagnosis of ovarian tumors.

Material and methods: Research was conducted among 456 patients qualified for surgery due to ovarian tumor. Preoperatively, CA125 and HE4 serum levels were estimated, and transvaginal ultrasound was performed. ROMA and RMI values and SA qualifications were obtained. Results were compared with pathomorphological findings.

Results: Receiver operating characteristic (ROC)-area under curve (AUC) values for CA125, HE4, ROMA, RMI and SA in preoperative diagnosis of malignant lesions were 0.819, 0.909, 0.911, 0.895 and 0.895, respectively.

Combinations of biochemical and sonographic methods increased sensitivity in diagnosis of ovarian tumors. Combinations utilizing serum HE4 concentrations were most useful.

Conclusions: CA125, HE4, ROMA, RMI and SA proved to be useful in preoperative diagnosis of ovarian tumors. HE4 and ROMA occurred to be the most useful.

Ultrasonographic methods are considerably useful in diagnosis of ovarian tumors. RMI and SA present similar overall diagnostic value.

Keywords: serum tumor markers; preoperative assessment of adnexal mass; ovarian cancer; endometriosis

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INTRODUCTION

Approximately 20% of women suffer from ovarian cyst or tumor at least once in their lifetime [1]. Most of these lesions are benign allowing women to avoid surgery or be operated by general gynecologists. Nevertheless, small portion of ovarian masses are malignant [2]. Ovarian cancer patients benefit significantly when being treated by gynecologic oncologists compared to general gynecologists or surgeons [3]. Therefore, it is essential to select patients with suspected ovarian mass and refer them to multidisciplinary centers where they can be managed by gynecologic oncologists.

The first ovarian cancer biomarker with a reasonable place in clinical practice was carcinoma antigen 125 (CA125). Although it is commonly used to assess patients with adnexal masses, its sensitivity and specificity are unsatisfactory [4, 5]. Many algorithms, which utilized both CA125 serum levels and ultrasonographic features of tumors, were designed to improve preoperative differentiation of ovarian cancer from benign lesions. Among them risk of malignancy index (RMI) occurred to be most effective and is often applied in daily clinical practice [6].

A lot of research was conducted to discover novel biomarkers for ovarian cancer [1, 7–9]. Milestone effort was made

by Moore et al. who proved human epididymis protein 4 (HE4) to be useful and implemented it into daily practice [1, 5]. Moreover, they elaborated risk of ovarian malignancy algorithm (ROMA), utilizing serum levels of both CA125 and HE4, which occurred to be more effective than RMI in preoperative detection of ovarian cancer [10–13]. Although many studies confirmed preliminary results of ROMA, some authors questioned its utility in ovarian cancer diagnosis [14, 15].

Some authors show superiority of sonographic methods for diagnosis of ovarian tumors over ROMA [15]. Among them, subjective assessment, which is ultrasound evaluation based on sonographer's knowledge and experience without using mathematical formulas and indices, is considered most effective [15, 16]. According to Van Gorp et al. [15] RMI is more useful in diagnosis of ovarian tumors than ROMA. Moreover, subjective assessment is more effective than these indices.

Objectives

To compare the utility of CA125, HE4, ROMA, RMI and subjective assessment (SA) in preoperative diagnosis of ovarian tumors.

MATERIAL AND METHODS

Our research was conducted from 2011 to 2016 in the Department of Operative Gynecology and Gynecologic Oncology of Polish Mother's Memorial Hospital — Research Institute in Lodz, Poland. A total of 456 women (225 pre- and 231 postmenopausal), qualified for surgery due to pelvic mass, took part in the study. Preoperatively their blood samples were taken, and transvaginal ultrasound scans were performed. Serum concentrations of HE4 and CA125 were evaluated by means of Roche Elecsys HE4 and elecsys CA125 II diagnostics sets. Carcinoma antigen 125 cut-off value was 35 U/mL. Cut-off values for HE4 are presented in Table 1. ROMA and RMI values were calculated, according to formulas elaborated by Moore et al. and Jacobs et al., respectively [6, 10]. Cut-off values for ROMA were 11.4% in pre- and 29.9% in postmenopausal women, and for RMI — 200.

Subjective assessment of pelvic tumors was performed by experienced sonographer. He qualified adnexal masses as benign or malignant and defined his level of certainty in making decision. As a result, six values of subjective assessment were given (1 — benign, 2 — probably benign, 3 — indecisive — rather benign, 4 — indecisive — rather malignant, 5 — probably malignant, 6 — malignant). Values 1–3 qualified lesion as benign and values 4–6 — as malignant.

After surgery, pathomorphological examination of specimens was performed. According to its results, patients were divided into groups of malignant and benign lesions.

Table 1. Cut-off values for serum human epididymis protein 4 (HE4)

Age [years]	Cut-off value
< 40	< 60.5 pM
40–49	< 76.5 pM
50–59	< 74.3 pM
60–69	< 82.9 pM
> 70	< 104 pM

pM — unit of polar concentration (pmol/L)
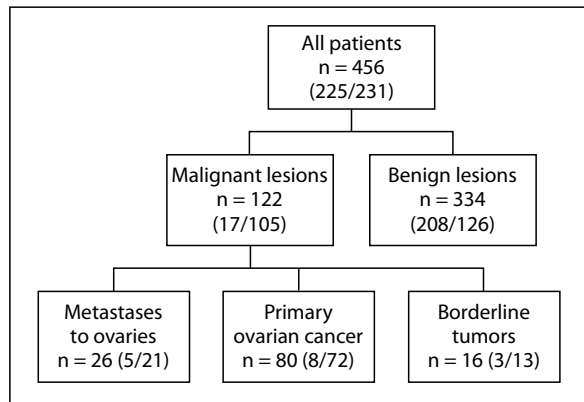
Figure 1. Pathomorphological findings in the study group; N — number of patients; in brackets — number of patients before and after menopause

Malignant tumors were further subdivided into primary ovarian cancer, borderline ovarian tumors and metastases to ovaries. Distribution of pathomorphological diagnoses is presented in Figure 1. Among patients with primary ovarian cancer, 9 (11.3%) of them have been graded as G1, 31 (38.8%) — G2 and 40 (50%) — G3. As far as staging of ovarian cancer is concerned, 13 (16.3%) patients were qualified to FIGO stage I, 9 (11.3%) — to stage II, 53 (66.3%) — stage III and 5 (6.3%) — stage IV. Among metastases to ovaries, they originated from endometrial cancer in 10 patients, uterine sarcoma — 1 patient, gastrointestinal malignancies — 8 patients and breast cancer — 7 patients.

Statistical analyses

Medians and interquartile ranges (IQR) were calculated for CA125 and HE4 levels as well as for ROMA and RMI values. To compare distribution of values between groups of patients Kruskal-Wallis test was used. For each analyzed diagnostic method receiver operating characteristic (ROC) curve was constructed and area under curve (AUC) was calculated. sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were also calculated for each method evaluated in the study.

Table 2. Median and interquartile range (IQR) values of carcinoma antigen 125 (CA125) in patients with specific pathomorphological diagnoses [U/mL]

Pathomorphological diagnosis	All patients		Premenopausal		Postmenopausal	
	Median	IQR	Median	IQR	Median	IQR
Malignant lesions	248	646.2	313.3	866.1	227.2	636.1
Primary ovarian cancer	411.6	1011.3	346.2	998.9	421.9	943.9
Serous type	431.7	1212.9	515	995.1	431.7	1233.3
Borderline ovarian tumors	29.1	52.6	280	918.7	28.6	26.1
Metastases to ovaries	62.9	380.3	562.2	438.5	53.3	85.6
Benign lesions	22.9	27.4	24.7	36.5	16.3	19.5
Endometriosis	50.9	56.9	53.9	59.9	36.5	32.6
Teratomas	18.9	14.4	18.9	12.3	23.6	14.8
Serous	16.4	14.2	20.5	21.5	14.5	10.5
Mucinous	15.7	11.8	19.2	8.8	13.4	10.5
Fibromas	24.7	24.1	23.4	2.6	27.7	95.0
Inflammatory lesions	28.2	34.5	22.9	72.0	30.3	4.8
Uterine myomas	23.1	12.0	23.1	7.1	56.9	43.7

Table 3. Median and interquartile range (IQR) values of human epididymis protein 4 (HE4) in patients with specific pathomorphological diagnoses [pM]

Pathomorphological diagnosis	All patients		Premenopausal		Postmenopausal	
	Median	IQR	Median	IQR	Median	IQR
Malignant lesions	279.7	809	151.2	378.1	315.6	817.3
Primary ovarian cancer	527.9	1090.1	164.7	332.5	784.2	1236.3
Serous type	736.5	1130.3	183.9	393.7	789.5	1278.5
Borderline ovarian tumors	74.9	30.1	94.4	72.9	73.3	18.7
Metastases to ovaries	136.7	372.9	244.4	425.6	136.7	194.2
Benign lesions	51.7	22.2	48.3	13.4	65.1	36.4
Endometriosis	50.1	14.4	49.8	13.4	56.5	15.3
Teratomas	48.1	14.2	46.7	12.2	74.8	42.5
Serous	53	23.1	46.1	15	63.2	30.2
Mucinous	55.6	31.5	43	9.2	69.1	49.7
Fibromas	68.1	32.5	47.5	21.9	70.4	32.5
Inflammatory lesions	95.6	112.3	100.5	59.7	90.6	130.2
Uterine myomas	52.2	11.9	52.2	4.9	55.0	10.1

IQR — interquartile range

RESULTS

Median and interquartile range (IQR) values of CA125 and HE4 in the groups of patients are presented in Table 2 and Table 3.

Sensitivity, specificity, positive and negative predictive values and ROC-AUC values of CA125, HE4, RMI, ROMA and subjective assessment in diagnosis of malignant tumors of the ovaries are presented in Table 4. In diagnosis of all malignant tumors CA125 achieved significantly lower ROC--AUC than HE4 (0.819 vs 0.909, p = 0.0001), ROMA (0.819 vs 0.911, p < 0.0001), RMI (0.819 vs 0.895, p = 0.0114) and subjective assessment (0.819 vs 0.895, p = 0.0454). ROC-AUC for HE4 was significantly higher than for RMI (0.909 vs 0.895, p = 0.0391). Receiver operating characteristic-area under curve for HE4 occurred to be higher than for subjective assessment but the difference was below statistical significance (0.909 vs 0.895, p = 0.0504). ROC-AUC for HE4 and ROMA did not differ significantly (0.909 vs 0.911, p = 0.7316). Risk of ovarian malignancy algorithm achieved significantly higher ROC-AUC compared to RMI

Table 4. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and area under curve-area under curve (ROC-AUC) values of carcinoma antigen 125 (CA125), human epididymis protein 4 (HE4), risk of malignancy index (RMI), risk of ovarian malignancy algorithm (ROMA) and subjective assessment in diagnosis of malignant ovarian tumors

	CA125	HE4	ROMA	RMI	Subjective assessment
All patients					
Sensitivity	79.51%	78.69%	78.69%	72.16%	76.29%
Specificity	68.86%	86.83%	81.74%	91.21%	89.01%
PPV	48.23%	68.57%	61.15%	74.47%	71.15%
NPV	90.20%	91.77%	91.30%	90.22%	91.35%
ROC-AUC	0.819	0.909	0.911	0.895	0.895
Premenopausal					
Sensitivity	88.24%	70.59%	76.47%	66.67%	92.31%
Specificity	62.98%	94.71%	84.13%	95.32%	89.47%
PPV	16.30%	52.17%	28.26%	55.56%	40%
NPV	98.5%	97.52%	97.77%	97.02%	99.35%
ROC-AUC	0.879	0.854	0.863	0.89	0.965
Postmenopausal					
Sensitivity	78.10%	80.0%	79.05%	84.51%	75.61%
Specificity	78.57%	73.81%	77.78%	85.29%	76.47%
PPV	75.23%`	71.79%	74.77%	80.0%	72.09%
NPV	81.15%	81.58%	81.67%	88.78%	79.59%
ROC-AUC	0.841	0.873	0.869	0.87	0.813

Table 5. Comparison of area under curve-area under curve (ROC-AUC) between carcinoma antigen 125 (CA125), human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), risk of malignancy index (RMI) and subjective assessment in diagnosis of malignant tumors of ovaries (p values)

	CA-125	RMI	ROMA	HE4	SA
CA-125	–				
RMI	0.0114	–			
ROMA	<0.0001	0.0075	–		
HE4	0.0001	0.0391	0.7316	–	
SA	0.0454	0.9962	0.0249	0.0504	–

(0.911 vs 0.895, p = 0.0075) and subjective assessment (0.911 vs 0.895, p = 0.0249). Both RMI and subjective assessment achieved equal ROC-AUC values (0.895, p = 0.9962). Comparisons of ROC-AUC between analyzed diagnostic methods are presented in Table 5.

In order to enhance the accuracy of investigated diagnostic tools we decided to evaluate the utility of combination of sonographic diagnostic methods (RMI, Subjective Assessment) with biochemical ones (CA125, HE4, ROMA). Sensitivity, specificity, positive and negative predictive values of such combinations in diagnosis of malignant tumors of ovaries are presented in Table 6. Combination of CA125 with subjective assessment achieved sensitivity and specificity at the level of 87.63% and 63.74%, respectively. Sensitiv-

ity and specificity of combination of HE4 with subjective assessment were 89.69% and 74.36%, respectively. Combination of HE4 and RMI reached sensitivity and specificity at the level of 87.63% and 75.82%. Combination of ROMA and RMI achieved sensitivity and specificity at the level of 79.38% and 76.19%. Combination of ROMA and subjective assessment reached sensitivity and specificity at the level of 87.63% and 73.63%.

DISCUSSION

As we previously stated, it is essential to differentiate patients with ovarian tumors suspected of malignancy from other pelvic masses. Although nowadays many methods are used to assess adnexal masses, none of them is undeniably

Table 6. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of combinations of analyzed methods in diagnosis of malignant tumors of ovaries

	CA125 + SA	HE4 + SA	HE4 + RMI	ROMA + RMI	ROMA + SA
All patients					
Sensitivity	87.63%	89.69%	87.63%	79.38%	87.63%
Specificity	63.74%	74.36%	75.82%	76.19%	73.63%
PPV	46.20%	55.41%	56.29%	54.23%	54.14%
NPV	93.55%	95.31%	94.52%	91.23%	94.37%
Premenopausal					
Sensitivity	100%	93.33%	86.67%	80.0%	93.33%
Specificity	62.57%	84.21%	83.04%	78.95%	80.12%
PPV	18.99%	34.15%	30.95%	25.0%	29.17%
NPV	100%	99.31%	98.61%	97.23%	99.28%
Postmenopausal					
Sensitivity	85.37%	89.02%	87.8%	79.27%	86.59%
Specificity	65.69%	57.84%	63.73%	71.57%	62.75%
PPV	66.67%	62.93%	66.06%	69.15%	65.14%
NPV	84.81%	86.76%	86.67%	81.11%	85.33%

CA125 — carcinoma antigen 125; HE4 — human epididymis protein 4; NPV — negative predictive value; PPV — positive predictive value; RMI — risk of malignancy index; ROMA — risk of ovarian malignancy algorithm; SA — subjective assessment

proven to be superior to others. This study was conducted to compare utility of biochemical (CA125, HE4, ROMA) and ultrasonographic methods (RMI, subjective assessment) in preoperative diagnosis of ovarian tumors.

Not surprisingly, low specificity of CA125 can be observed in our study. Many of its false positive results may be due to endometriosis but also other benign ovarian tumors and non-gynecological diseases. According to Bottoni et al. [4] levels of CA125 exceed cut-off values in patients suffering from hepatitis, hepatic cirrhosis, pelvic inflammatory disease, first trimester of pregnancy and 1–2% of healthy women.

Noteworthy but not surprising is the relatively high specificity of HE4 which has been also observed by other researchers [17]. Moore et al. [5] reported elevated levels of CA125 in 29% and HE4 levels in 7% of patients with benign ovarian tumors. In the study conducted by Zhang et al. [18] CA125 levels were falsely elevated in 29% and HE4 in only 1% of women with benign ovarian tumors. Interestingly, in our study high specificity of HE4 is restricted to premenopausal women. In postmenopausal patients' specificity of CA125 occurred to be slightly superior to HE4. Such observation has not been reported in any publication known to authors of current study. Low specificity of HE4 in this group of patients might result from imperfect cut-off values in elderly women, because HE4 levels are proven to be strictly correlated with the age of patients [19]. Moreover, such non-gynecological conditions as renal or heart failure, pulmonary or hepatic diseases can also cause false positive results of HE4 [19, 20].

In the literature, ROMA, with sensitivity higher than HE4 and specificity higher than CA125, is considered to present a more balanced diagnostic value than any of these markers alone [21]. In our study diagnostic performance of ROMA was well-balanced as well.

Moreover, in our study ROMA and HE4 achieved similar ROC-AUC values, higher than CA125 and sonographic methods — RMI and subjective assessment. Many researchers reported high utility of HE4 but also suggested that its combination with CA125 (ROMA) improves preoperative diagnosis of ovarian tumors [22]. On the other hand, some authors did not reveal any significant advantage of ROMA over determination of HE4 levels alone [23]. Moore et al. [13] and other researchers reported higher diagnostic value of ROMA than RMI in diagnosis of ovarian cancer [24]. Karlsen et al. [25] and Richards et al. [26] found performance of ROMA comparable to RMI, demonstrating the utility of ROMA in the preoperative management of ovarian masses.

In our research, sonographic methods (RMI and subjective assessment) proved to be very useful in preoperative diagnosis of ovarian tumors. Interestingly, they were severely more specific than CA125, HE4 and ROMA. Such observations confirm the conclusions of other researchers [6, 15]. However, Van Gorp et al. [15] reported higher specificity for Subjective Assessment than RMI. In the presented study, ROC-AUC for both sonographic diagnostic methods occured to depend on menopausal status of patients. Subjective Assessment achieved higher AUC value

in premenopausal women and RMI — in patients after menopause, which is similar to findings described by Moszynski et al [27].

Dependence of sonographic diagnostic methods on sonographer's experience has been proven [28]. Subjective assessment is ultrasound evaluation of adnexal mass based strictly on knowledge and experience of sonographer. It seems that determination of RMI value is less dependent on experience of person performing ultrasound examination because calculation of this index requires assessment of specific features of tumor. Despite differences in diagnostic performance of RMI and Subjective Assessment in pre- and postmenopausal women, performance of both indices among all patients was similar. Therefore, RMI might be a considerable alternative for Subjective Assessment for sonographers who are less experienced in gynecologic oncology.

Reasonable performance of sonographic methods prompted us to combine them with biochemical methods. In the presented study, almost all combinations resulted in increased sensitivity in preoperative diagnosis of malignant ovarian tumors. Interestingly, although most combinations achieved similar specificity, combination of CA125 with subjective assessment occurred to be visibly less specific than other combinations. Most importantly, this is the only combination that does not include determination of HE4 levels. Therefore, it seems that combinations utilizing serum levels of HE4 are especially valuable. Kaijser et al. [29] and Moszynski et al. [30] reported that HE4 and ROMA do not improve preoperative diagnosis of adnexal masses after subjective assessment by an experienced sonographer. Except these publications, the authors of current study did not come across research evaluating combination of subjective assessment or RMI with HE4 or ROMA. Therefore, it seems worth considering elaborating algorithm combining sonographic assessment with HE4 determinations, which perhaps could further improve preoperative diagnosis of ovarian tumors.

Current study presents evaluation of utility of the most recognized methods in preoperative diagnosis of ovarian tumors. It was carried out on a reasonable number of 456 patients who underwent surgery due to ovarian lesions. Therefore, it can be important contribution to broad worldwide discussion on strategy of management of adnexal tumors, considering both biochemical and sonographic diagnostic methods.

The main limitation of this study is that it does not consider the assessment of utility of the IOTA ADNEX model, which recently entered clinical practice. When IOTA ADNEX was developed, current study was already very advanced, so it was impossible to include this algorithm in the panel of assessed diagnostic methods.

CONCLUSIONS

CA125, HE4, ROMA, RMI and subjective assessment proved to be useful in pre-operative diagnosis of ovarian tumors. Among evaluated methods, the assessment of serum HE4 concentrations and calculation of ROMA occurred to be the most useful.

Assessment of serum HE4 concentrations is the most specific among all biochemical methods (CA125, HE4, ROMA) in pre-operative diagnosing of ovarian tumors.

Ultrasonographic methods (RMI, subjective assessment) are characterized by considerable utility in diagnosis of ovarian tumors. subjective assessment is highly useful, especially among premenopausal women, and RMI — among postmenopausal women.

Risk of malignancy index and subjective assessment present similar overall diagnostic values. Therefore, RMI may be an alternative to subjective assessment for less experienced sonographers.

Combination of biochemical and ultrasonographic methods allows to increase the sensitivity of preoperative diagnosis of malignant ovarian lesions. Combinations incorporating serum HE4 concentrations are particularly useful.

Article information and declarations

Conflict of interest

All authors declare no conflicts of interests.

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