Review Article

A Survey on the Role of Cancer Antigen 125 (CA125), Human Epididymis Protein 4 (HE4), Risk of Ovarian Malignancy Algorithm (ROMA), and Risk of Malignancy Index (RMI) in Pelvic Mass

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Abstract

Context: Pelvic masses are a prevalent cause for referral to gynecologic oncology departments to evaluate the possibility of benign or malignant conditions. Pelvic mass often was found in pelvic examinations among females with ovarian. Tumor markers are advantageous biomarker in tumor diagnosis.

Evidence Acquisition: We performed a computerized search in Medline/PubMed databases and Google Scholar with key words: "Cancer antigen 125 (CA125), Human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), Risk of malignancy index (RMI), and Pelvic mass".

Results: The usage of tumor marker CA125 alone is associated with serious limitations like low sensitivity for early or stage I disease and lack of specificity especially in pre-menopausal women. Serum HE4 is a good biomarker for discriminating ovarian cancer from benign pelvic disease, but could be affected by several factors including pregnancy, age, and smoking. ROMA has a high sensitivity, specificity, and negative predictive value to predict the presence of ovarian cancer in women with a pelvic mass. RMI could differentiate between benign and malignant pelvic masses, but RMI expression was higher in women with 55 years or more.

Conclusions: According to the results of this study, combination of these biomarkers or at least 2 or 3 biomarkers are suggested for early stage diagnosis of pelvic mass with high sensitivity and specificity.

Keywords: Pelvic Mass, HE4, RMI, ROMA, CA125

1. Context

A pelvic mass is an enlargement or swelling in the pelvic region (1-5). The most common type of pelvic masses is ovarian masses which included cysts and tumors (1). Pelvic masses are a prevalent cause of referral to gynecologic oncology (2) departments to evaluate the possibility of benign or malignant conditions (3). Pelvic mass often was found in pelvic examinations among females with ovarian cancer. Annually, more than 200 000 women were admitted (4) by pelvic mass or ovarian cancer in United State (5). Ovarian cancer is a disease with 20% to 30% survival rate because of lack of trustful screening tools and non-specific early symptoms (6), so that more than 70% of patients are detected in progressive stage of ovarian cancer (7, 8). Therefore, early stage diagnosis is important, which needs a high sensitivity and specificity (6). Mass size, mobility, consistency, shape, possible internal aqueous component, and associated pain are beneficial characteristic to diagnose of mass nature (1). Moreover, tumor markers are advantageous instrument in tumor diagnosis (9). This paper evaluated biomarkers, including cancer antigen 125 (CA125), human epididymis protein 4 (HE4), risk of ovarian malignancy algorithm (ROMA), and risk of malignancy index (RMI) in pelvic mass.

2. Evidence Acquisition

In order to collect data about the role of CA125, HE4, ROMA and RMI in management of pelvic mass, we performed a computerized search in Medline/PubMed

databases and Google Scholar with key words CA125, HE4, ROMA, RMI, and pelvic mass.

2.1. CA125

Cancer antigen 125 (CA125) is a glycoprotein ([10], [11]). It was identified by the OC125 monoclonal antibody ([10]). Studies following molecular cloning reported that CA125 has many features of mucin. Therefore, due to these features, CA125 was considered a mucin and determined MUC16 ([12]). CA125 assay is interesting because it is largely noninvasive, relatively cheap, and widely available ([10]). CA125 is created by ovarian cancer cells or normal cells from coelomic epithelium ([13], [14]). The serum tumor marker CA125 is used for predicting pelvic mass, but the usage of CA125 alone is associated with serious limitations. First; low sensitivity for stage I disease, Second; its lack of specificity particularly in pre-menopausal women with pelvic mass ([10]). This causes that CA125 had a low positive predictive value to detect ovarian cancer ([10]). Moreover, most clinicians apply composition of biomarker to distinguish pelvic mass type due to confined specificity and sensitivity ([6]). Moreover, CA125 in combination of CA724, CA211, CA199, and CA153 can screen ovarian neoplasm of patients ([6]). Another study reported that the addition of CA72-4 to Ca125, ultra sound, and pelvic investigation leads to the discrimination of malignant and benign pelvic mass ([9]).

2.2. HE4

Human epididymis protein 4 or HE4 as an acidic protein was detected by Kirchhoff et al. in 1991 ([15]). It was the first biomarker after CA125 approved by FDA for ovarian cancer ([16]). HE4 was discovered as a result of the WFDC2 gene transcript ([17]). HE4 as an 11-kDa protein ([18]) pertains to family of four-disulfide core protein ([15]) and acts as proteinase inhibitors (reducing the serine proteases activity) ([19]), which degrades collagen ([14]). HE4 was expressed in many normal and malignant tissues ([14]). It was also overexpressed in epithelial ovarian cancer ([6]), particularly serous (93%) and endometrioid tumors (100%) ([15]). Therefore, the highest level of HE4 was observed in ovarian cancer for women and moderate level of HE4 was seen in lung adenocarcinoma ([15]) Moreover, the lowest level of HE4 was found in breast, transitional cell, gastric, and pancreatic carcinomas ([15], [20-22]). But, in no mucinous tumors, HE4 was seen ([15]). Therefore, HE4 as a new marker in the assessment of ovarian cancer ([6]) can be considered as one of the most hopeful biomarkers in gynecology oncology ([17]). Moreover, several factors other than malignancy may affect the level of serum HE4. HE4 level is influenced by pregnancy, so that pregnant women have lower level of HE4 in

comparison to non-pregnant women ([15]). Moreover, older women, smokers, and women with later menarche had significantly higher level of HE4 in comparison to control group ([15]). Furthermore, factors like menstrual cycle, endometriosis, and estrogen and progestin contraceptive usage did not change HE4 serum ([15]).

2.3. Risk of Ovarian Malignancy Algorithm (ROMA)

ROMA was applied for differentiating malignant from pelvic tumor ([15]). As a logistic regression algorithm, it uses HE4 and CA125 biomarker along menopause to evaluate benign or malignant ovarian mass ([5]). It is detected that ROMA has sensitivity 100%, specificity 47.7%, and negative predictive value 100% to predict ovarian cancer ([5]). Several studies have reported that ROMA has a pleasant efficacy to distinguish benign and malignant pelvic mass. But, another study reported that ROMA algorithm is better than in pre-menopausal women in comparison to post-menopausal population ([23]).

2.4. Risk of Malignancy Index (RMI)

Risk of malignancy index (RMI) was created in 1995 by Jacobas ultrasound findings $\times$ serum CA125 level $\times$ menstrual situation ([1]). RMI is an easy, simple, and convenient method to evaluate pelvic mass before surgery and affirms prior studies indicated RMI recovers differentiation between non-malignant and malignant pelvic masses. Extended index was reported as RMI1 and RMI2 in 1996 ([1]). Moreover, further extended indices including RM1, RM2 and RM3 were considered in 1999 ([1]). Yamamoto et al. reported a new index as RMI4 in 2009, which augments tumor size. The difference between these indices is due to U and M score allocation. For RMI1, if abnormal something is not observed in the ultrasonographic report, U is considered zero (U = 0); if abnormal something is observed, it will be U = 1; and if two or more abnormal findings was observed, it will be U = 2. Menopausal situation (M) is either post-menopausal (more than 1 year since the last menstruation or age > 50 if hysterectomy for any reason) (M = 3) or pre-menopausal (M = 1) ([1]). CA125 concentration is also considered in the formula. For RMI1, a cut-off value of 200 was considered as the best discrimination point with high sensitivity and specificity levels for benign and malignant pelvic masses diagnosis ([1]). For RMI 2, if there is 0 - 1 abnormal findings, U will be 1 and if 2 or more abnormal findings are existed, U will be 4. Moreover, M will be 1 and 4 for pre-menopausal and post-menopausal women, respectively. The serum concentration of CA125 is directly entered in the formula again ([1]). For RMI3, U = 1 in the presence of 0 - 1 abnormal findings and U = 1 in the presence of two or more abnormal findings. M is 1 and 3 for

pre-menopausal and post-menopausal, respectively. The serum level of CA125 is directly considered in the formula again. For RMI4, the formula is considered as U × CA125 × M × S. When 0 - 1 and 2 or more abnormal findings is existed, U will be 1 and 4, respectively. In pre-menopausal and post-menopausal women, M will be 1 and 4, respectively. The serum level of CA125 is directly entered in the formula. S shows the largest diameter of the mass, which is 1 if < 7 cm, and 2 if ≥ 7 cm (24). Any of 4 malignancy risk indices (RMI1, RMI2, RMI3, and RMI4) can be used for election of cases for optimal therapy (25). Akturk et al. reported that no significant difference was seen in the efficiency of these 4 different malignancy risk indices (RMI1, RMI2, RMI3, and RMI4) in discriminating malignancy (25). Manjunath et al. in 2001 compared RMI1, RMI2, and RMI3 with each other. They reported that for benign malignancy discrimination, there is no difference between these indices (26). Another study reported that RMI2 was more trustful for discriminating benign and malignant disease. Morgante et al. also obtained similar result and reported that RMI2 performance was better than RMI1 (27). Moreover, RMI was significantly higher in women aged 55 or above comparing to younger women (2).

3. Results

3.1. CA125 and HE4

Studies about the role of CA125 in pelvic mass were shown in Table 1.

Studies about HE4 in pelvic mass were shown in Table 2.

3.1.1. Comparison Between HE4 with CA125 in Patients with Pelvic Mass

• HE4 is a strong instrument in comparison to CA125 to diagnosis of epithelial ovarian cancer (31).

• HE4 is better than CA125 in terms of specificity in the identification of malignant pelvic mass (6).

• HE4 has higher sensitivity than CA125 (90% vs. 83.3%), higher specificity compared to CA125 (95% vs. 85%), higher positive and negative predictive value (93.1% vs. 80.7%), and (92.7% vs. 87.2%) than CA125 (34).

• HE4 has better performance than CA125 with respect to specificity (P = 0.022) for diagnosis of ovarian cancer, especially in pre-menopausal women in Australian population (17).

• Mean value of CA125 and HE4 was more in patients with EOC compared to benign tumors (P < 0.0001) (35).

Opinion about the combination of CA125 and HE4 in patients with pelvic mass is shown in Table 3.

3.2. ROMA

Studies about the role of ROMA in pelvic mass were shown in Table 4.

3.2.1. Comparison of ROMA with CA125 and HE4

• Accuracy value of CA125 (pre-menopausal status) and ROMA (post-menopausal patients) was 89.8% and 93.3%, respectively. Area under the curve (AUC) for ROMA in post-menopausal patients was higher than CA125 (P = 0.001) (39).

• The sensitivity and specificity of ROMA was detected 0.873, 0.855, sensitivity and specificity of CA125 was 0.796, 0.825 and sensitivity and specificity of HE4 was 0.817, 0.851 in patients with ovarian cancer (40).

• HE4 and ROMA have better performance considering specificity and worse efficacy in terms of sensitivity compared to CA125 and RMI in pre-menopausal women (41).

• Higher sensitivity of ROMA was observed than RMI to distinguish benign status from epithelial ovarian cancer (42).

• HE4 or ROMA can help differentiating ovarian cancer from other pelvic masses even in early stage of cancer (19).

• Sensitivity of ROMA was 94.3% and RMI 84.6% at a set specificity of 75% for the prediction of epithelial ovarian cancer in patients with a pelvic mass (34).

3.3. RMI

Studies about the role of RMI in pelvic mass were shown in Table 5.

3.3.1. Comparison Between RMI with CA125, HE4, and ROMA

• Both CA125 and RMI can be applied in ovarian cancer diagnosis. Sensitivity of CA 125 is higher, but specificity of RMI is higher than CA125 (41).

• RMI has lower sensitivity than ROMA (94%) at specificity of 75% (4).

• RMI and ROMA acted equally to differentiate benign pelvic masses and ovarian cancer (45).

• Sensitivity of ROMA was reported 94.3% in comparison with sensitivity of RMI 84.6 % for distinguishing of benign mass from epithelial ovarian cancer in patients with a pelvic mass (5).

• Sensitivity and specificity of CA125 was 92.3% and 59.4%, HE4 84.6% and 94.2%, and ROMA 84.6% and 81.2% for epithelial ovarian cancer in pre-menopausal women (46).

• Sensitivity and specificity of CA125 was 94.3% and 82.3%, HE4 78.2% and 99.0% and ROMA 93.1% and 84.4% in epithelial ovarian cancer in post-menopausal women (46).

• Specificity of CA125 was 62.2, HE4 63.2, ROMA 76.5 and RMI (81.5) to different ovarian cancer from benign disease at a set sensitivity of 94.4 (45).

Table 1. Studies About the Role of CA125 in Pelvic Mass

Study	Result	Country	Number
Moore et al., 2008 (28)	Serum tumor marker CA125 with prediction of malignancy has low sensitivity and specificity in both pre- and post-menopausal women.	USA	259
Park et al., 2012 (8)	Results of this study demonstrated 4 RMIs and serum CA125 can correctly identify benign and malignant pelvic masses.	Korea	547
Cho et al., 2014 (29)	Serum CA125 is frequently increased in benign situation like pelvic inflammatory disease and in malignant disorders.	Korea	27
Karimi-Zarchi et al., 2014 (30)	CA125 is a prognostic and diagnostic biomarker in patients with newly-discovered pelvic mass, however, it cannot predict complication of malignant pelvic mass after surgery.	Iran	203
Lokich et al., 2015 (5)	Serum level of CA125 is elevated in multiple benign gynecologic tumors.	USA	498
Chen et al., 2015 (6)	Marker CA125 can be used for predicting pelvic masses.	China	232
Zhang et al., 2015 (31)	Serum cancer antigen (CA125) discriminate neoplasm tumors from benign tumors.	China	2481

Abbreviation: CA125, cancer antigen 125.

Table 2. Studies about HE4 in Pelvic Mass

Study	Result	Country	Number
Montagnana et al., 2009 (32)	HE4 might be a favorable and excellent biomarker for diagnosis of pelvic masses.	Italy	99
Abdel-Azeez et al., 2010 (33)	HE4 has the highest sensitivity to detect ovarian cancer in patients with pelvic masses particularly early stage disease.	Egypt	65
Richards et al., 2015 (17)	Human epididymis protein 4 (HE4) is a modern biomarker for epithelial ovarian cancer diagnosis.	Australia	50
Chen et al., 2015 (6)	HE4 was associated with growth and cancer cell adhesion.	China	232
Cho et al., 2014 (29)	HE4 is a good diagnostic marker for epithelial ovarian cancer in Korean women with pelvic mass.	Korea	27

Abbreviation: HE4, human epididymis protein 4.

Table 3. Opinion About Combination of CA125 and HE4 in Patients with Pelvic Mass

Study	Results	Country	Number
Chen et al., 2015 (6)	HE4 in combination with CA125 improves specificity for ovarian cancer.	China	100 malignant ,132 benign
Asher et al., 2010 (36)	Combination of HE4 and CA125 supply the highest discrimination between benign and malignant cancer.	UK	1 case
Zhang et al., 2015 (31)	Combination of HE4 with CA125 and ROMA can be effective for malignancy evaluation.	China	2481
Moore et al., 2008 (28)	A combination of CA125 and HE4 caused significant elevation in sensitivity and specificity.	USA	249

Abbreviations: CA125, cancer antigen 125; HE4, human epididymis protein 4.

Table 4. Studies About the Role of ROMA in Patients with Pelvic Masses

Study	Result	Country	Number
Moore et al., 2009 (35)	ROMA had 92.3% sensitivity in post-menopausal women and 76.5% in pre-menopausal women with pelvic mass.	USA	531
Sandri et al., 2013 (37)	ROMA index can help triage of pelvic mass in post-menopausal women.	Italy	349
Lokich et al., 2015 (5)	ROMA with clinical assessment can identify women with a pelvic mass.	USA	498
Zhang et al, 2015 (31)	ROMA can be used for discriminating benign pelvic mass (BPM) and epithelial ovarian cancer.	China	2481
Lokich et al., 2015 (5)	ROMA has a high sensitivity, specificity, and negative predictive value for predicting the presence of ovarian cancer in women with a pelvic mass.	USA	498
Romagno et al., 2016 (38)	ROMA algorithm shows the better diagnostic impression to differentiate epithelial ovarian cancer.	Italy	405
Yanaranop et al., 2017 (39)	ROMA can be used in women with pelvic masses to arrange risk groups for ovarian cancer.	Thailand	260

Abbreviation: ROMA, risk of ovarian malignancy algorithm.

Table 5. Studies About the Role of RMI in Pelvic Mass

Study	Result	Country	Number of Patients
Van den Akker et al., 2010 (43)	RMI improves differentiation between malignant and non-malignant pelvic masses.	Netherlands	548
Akturk et al., 2011 (25)	RMI can correctly differentiate benign from malignant pelvic masses.	Turkey	100
Bouzari et al., 2011 (3)	RMI is the best technique to differentiate benign and malignant pelvic masses.	Iran	182
Hakansson et al., 2012 (44)	RMI with sensitivity of 92% can distinguish benign pelvic masses and ovarian cancer.	Denmark	78 with pelvic mass and 251 with ovarian cancer
Park et al., 2012 (8)	Four RMIs as diagnostic criteria can discriminate benign and malignant pelvic masses.	Korea	547
Karimi-Zarchi et al., 2014 (30)	RMI2 had sensitivity (79.36%), specificity (78.95%), accuracy (78.93%) and negative predictive value (90.08%).	Iran	200

Abbreviation: RMI, risk of malignancy index.

• Sensitivity and specificity of CA125 was 91% and 24.6%; HE4 83.6% and 65%, RMI 80.6% and 65.6% and ROMA 91.0% and 42.6% (47).

• The sensitivity and specificity to discriminate ovarian cancer from benign tumor for HE4 was 86.2 %, 87.4, CA125 86.2 % and 78.9 and ROMA 93.1 % and 90.7% (48).

4. Conclusions

According to the results of this study, the combination of these biomarkers or at least 2 or 3 biomarkers are suggested for early stage diagnosis of pelvic mass with high sensitivity and specificity.

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Footnotes

Authors' Contribution: None declared.

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