RESEARCH ARTICLE

Comparison of Two Ovarian Malignancy Prediction Models Based on Age Sonographic Findings and Serum Ca125 Measurement

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Abstract

Objective: The aim of our study is to compare an ovarian malignancy prediction model based on age and four sonographic findings (OMPS1) with a new model called OMPS2 which differs just by adding serum CA125 measurement to (OMPS1). Methods: In a cross sectional comparative study OMPS1 was validated in 830 operated ovarian masses within a 3 years period (2006-2009). Logistic regression analysis was used to construct OMPS2 based on OMPS1 adding serum CA125 findings. The area under the curve for two models was compared in 411 patients. Results: OMPS2 was calculated as follows: OMPS1 + 1.444 (if serum CA125= 36-200) or 3.842 (if serum CA125 is more than 200). AUC of OMPS2 was increased to 84.3% (CI 95% 78.1- 89.8) in comparison to OMPS1 with AUC of 78.1% (CI 95% 71.8-84.5). Conclusion: Our second model is more accurate in prediction of ovarian malignancy, compared with our first model.

Keywords: Logistic model - ovarian mass - ultrasound - serum CA125 - ovarian cancer

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Introduction

Ovarian cancer is in the top list of mortality due to cancer in Europe and the United States (Baker, 1994; Boente, 1999; Oriel, 1999; Holschneider, 2000; Benjapibal, 2007). Tumors of the ovary generally present as adnexal masses (Campos et al., 2002). Proper management of an adnexal mass depends greatly on predicting the chance of malignancy to decide correctly by whom and where the patient should be operated on (Marjunath, 2001; Mederiros, 2005). In the case of malignancy the best prognosis is achieved if the patient is referred to tertiary care hospitals and primary operations done by expert surgeons in Gyneco – oncology field (Benedet, 2000; Soegaard, 2003; Valentin, 2004; Vernooij, 2007).

There are many different parameters and models to predict the risk of malignancy in ovarian masses. Sonographic features and serum CA125 are two main predictors which are widely studied regarding their Sensitivity and specificity as ovarian malignancy predictors (Depriest, 1999; Kinkel, 2000; BenJopibal, 2003; Szpurek, 2005; Javitt, 2007).

In a previous study sonography by an expert was superior to CA125 for the prediction of malignancy and there was no improvement by adding CA125 to sonographic findings in prediction of malignancy (Valentin, 1999).

We have previously constructed an Ovarian Malignancy Prediction Scoring model (OMPS) based on age and 4 sonographic findings including size , solid area , ascitis and bilateralism to predict malignancy and presented it as a simple and accurate clinical tool for ovarian malignancy prediction (Arab, 2010). The OMPS model was constructed based on 3303 adnexal mass surgeries in tehran, 2000-2006. With the score number of 3.65 as cutoff value of malignancy prediction by OMPS1, the sensitivity of 77.9% and specificity of 72.9% was achieved with ROC curve AUC of 83%95%CI: 79-87%.Model construction was based on 80% of total 3303 patients and validation was done by the 20% of randomly separated cases, who has not been included in the model construction (Arab, 2010).

Other models have been constructed by other researchers with different predicting accuracy namely Risk of Malignancy Index (RMI) number 1-5 based on sonographic findings, menopausal status and CA125 level (Soegaard, 2003; Obeidat, 2004; Leelahakorn, 2005; Ulusoy, 2007; Moolthiya, 2009).

In the present study, our previous Ovarian Malignancy Prediction Scoring model (OMPS1) based on age and four sonographic findings was validated and compared with a new constructed method of prediction called OMPS2, which differs just in having the serum CA125 value as an additional parameter.

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Materials and Methods

In a cross sectional analytical study, pathologic reports of operated adnexal masses in 8 secondary and tertiary care hospitals in Tehran (7 centers) and Hamadan (one Center) were reviewed from 2006-2009. Cases operated on due to other indications such as bleeding, fibroma or other causes were excluded and the ovarian masses, with size of less than 3 centimeters before surgery, were excluded as well. Finally 830 operated adnexal masses were included in our study. In every case Ovarian Malignancy Probability Score (OMPS1) was calculated based on age and sonographic findings using the following formula:

Age X0.062+tumor size (cm) X0.012+1.172 (if the tumor is solid)+1.289 (if ascites is present)+0.758 (if the tumor is bilateral)

Age and sonographic features were recorded based on existing patients' files.

In this step the sensitivity, specificity, the likelihood ratio the ROC curve and AUC were calculated to validate OMPS1 in this population in comparison to sensitivity and AUC of ROC curve reported in the primary study.

At the next step in 411 out of the total 830 patients, a single CA125 measurement of this population was added to logistic regression model resulting in OMPS2. In this 411 patients OMPS1 and OMPS2 was calculated and its accuracy in prediction of malignancy was compared.

All Statistical analysis was performed using SPSS version 18. For describing data we utilized mean, standard deviation, median, 95% CI, frequency and percentage.

In order to find the best cutoff value, we utilized some criteria such as sensitivity, specificity, likelihood ratio and Youden index.

Results

Malignant pathologic results were found in 68 (8.2%) out of 830 total patients based on pathology findings.

Comparison of age, tumor size, solid pattern, ascitis and bilaterality in benign and malignant pathologic reports are presented in Table1.

Based on OMPS1, in 830 patients showed a sensitivity of 68.5% and specificity of 75.6% in predicting the malignancy.

AUC of ROC curve in validation of OMPS1 in the new population of 830 patients was 77.2% 95% CI:70.9-83.5% compared to 83% 95% CI :79-87% in basic study of OMPS1 model construction. This difference was not significant (P=0.167)

Malignant pathologic results were found in 54 (13%) out of 411 patients with available single serum CA125 results.

Table 1. Comparison of Age and Sonographic Findings of Malignant and Benign Tumors in 830 Patients

Parameter	Malignant N=68	Benign N=762	Difference	CI 95%	P-Value
Age	43.8±16†	35±13†	8.4	4.5 -12.3	<0.001
Size (cm)	11.3±6.7†	7.5±3.5†	3.8	2.1 -5.4	<0.001
Solid pattern	45(66.2)‡	154(20.2)‡	46	34 -57	<0.001
Ascitis	14(20.6)‡	101(13.3)‡	7	2 -17	0.009
Bilateral	17 (25)‡	81(10.6)‡	14	3 -25	<0.001

†Mean±SD, ‡Number (Percentage)

Table 2. Comparison of Age, Sonograhic Findings and Serum CA125 of Malignant and Benign Tumors in 411 Patients

Parameter	Malignant N= 54	Benign N=357	Difference	CI 95%	P-value
Age	46.1±15†	37.8±14.1†	8.4	4.3-12.3	<0.001
Size (cm)	12±6.7†	8.2±3.9†	3.8	1.9-5.7	<0.001
Solid pattern	36(66.7)‡	91(25.5)‡	41.2	27.8-54.5	<0.001
Ascitis	13(24.1)‡	32 (9)‡	15.1	3.3-26.7	0.001
Bilateral	16(29.6)‡	52(14.6)‡	15.1	2.3-27.8	0.005
<35 CA125	14(25.9)‡	267(74.8)‡	-46.9	(-61.4-36.3)	<0.001
CA125:36-200	18(33.3)‡	81(22.7)‡	10.6	2.6-18.6	0.044
>200 CA125	22(40.7)‡	9 (2.5)‡	38.5	25.0-51.4	<0.001
Serum CA125 Value					
	295±404†	33±49†	262	151-372	<0.001

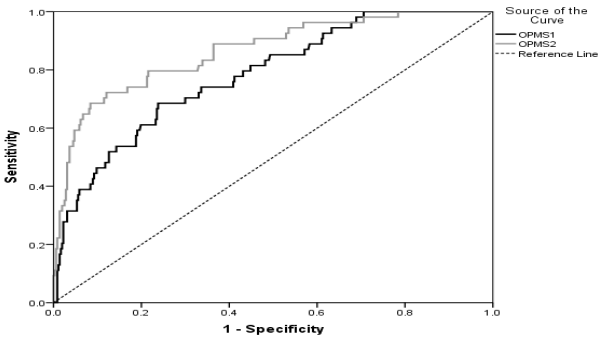

Figure 1. Comparison of AUC of ROC Curves of OMPS1 and OMPS2 in Malignancy Prediction of Adnexal Masses.

Comparison of age, tumor size, solid pattern, ascitis, bilaterality and serum CA125 value in benign and malignant pathologic reports of this group are presented in Table 2.

Calculation of OMPS1 in group of 411 patients revealed ROC curve AUC of 78.1% (CI 95% 71.8-84.5).

A single serum CA125 value was relevant to malignancy pathologic report in our study and the cut off value of 200 was significant. In logistic regression analysis of serum CA125 values in the range of 36-200 and more than 200, the extracted multiplier resulted in formulation of OMPS2 as follows:

OMPS2= OMPS1+1.444 (if serum CA125 is between 36 and 200) or 3.842(if serum CA125 is more than 200). We found a ROC curve AUC of 84.3% for OMPS2 (CI 95 78.1-89.8).

Figure 1 compares AUC of OMPS1 and OMPS2 showing more accuracy for OMPS2.

Discussion

In a meta- analysis including 5159 cases in 46 studies, ROC curve of combined methods was more accurate in comparison to a single method such as sonography or serum CA125 alone (Kurjak, 1992; Caruso, 1996; Rufford, 2003). Sonography alone is highly sensitive in detection of ovarian mass malignancy, but its specificity is relatively low (Valentin, 2001; Diamandis, 2003; Valentin, 2004; Szpurek, 2005; Enakpene, 2009). In the other hand,

serum CA125 measurement is a specific test in prediction of ovarian malignancy (Edgell, 2010).

The present study revealed that OMPS1 model is valid in our 830 patients group with sensitivity of 68.5% and specificity of 75.6% in prediction of ovarian malignancy.

We found that in the cutoff point of 2.3 or above, our OMPS1 model of prediction has a sensitivity of 100% (Arab, 2010) so it has good value as a first screening protocol.

In 411 patients group the accuracy of malignancy prediction by OMPS2 increased from 78.1%95% CI :71.8-84.5% for OMPS1 to 84.3% 95% CI :78.1-89.9% for OMPS2.Considering the results of multiple logistic regression analysis (Table 2),adding CA125 to OMPS1 (sonographic findings) significantly increases the accuracy of malignancy prediction (P<0.001).

These findings of our study might confirm the role of sonography as a sensitive and serum CA125 measurement as a specific test. OMPS1 is mostly based on sonography and OMPS2 just add serum CA125 measurement to OMPS1.SO, OMPS1 could be regarded a sensitive and OMPS2 a specific model.

If we are in a position to choose between a secondary or tertiary care hospitals to refer the patient a prediction model with high sensitivity is needed. So, a very low score of OMPS1 (below 2.3) might rule out malignancy as a sensitive tool, while numbers above this for OMPS2 can guide to more specifically determined probability of malignancy.

In malignant cases, optimal surgical debulking and appropriate staging are the key points of improving survival (Trim, 2003; Winter, 2007). These optimal results are achieved mostly in tertiary care hospitals (Mederiros, 2005). OMPS1 might be used in the first step of triage and with very low scores (below 2.3) , malignancy is ruled out with 100% sensitivity and there is no need to pay attention to CA125 results or requesting this test and If OMPS1 is more than 2.3, patient can be reevaluated using OMPS2 at second step.

Another reason to propose this two step approach is the high levels of CA125 in some benign ovarian masses such as endometrioma and tuberculosis, which might mislead the practitioner to malignancy if CA125 is used in the first step (Campos et al., 2002; Moolthiya, 2009).

In conclusion OMPS2 in comparison to OMPS1 was more accurate and specific in prediction of malignancy especially in high score OMPS1 patients.

References

Arab M, Yaseri M, Farzaneh M, et al (2010). The construction and validation of a new ovarian malignancy probability score (OMPS) for prediction of ovarian malignancy. *Iran J Cancer Prev*, **3**, 132-8.

Baker TR, Piver MS (1994). Etiology, biology , and epidemiology of Ovarian Cancer. *Semin Surg Oncol*, **10**, 242-8.

Benedet JL, Bender H, Jones lll (2000). Ngan hys, pecorelli s. figo staging classifications and clinical practice guidelines in the management of gynecologic cancers. *Int J Gynecol Oobstet*, **70**, 409-62.

Benjapibal M, Neungton C (2007). Pre-operative prediction of serum CA125 level in women with Ovarian masses. *J Med Assoc Thai*, **90**, 1986-91.

BenJopibal M, Sunsancvitayakul P, Phatihattakorn C, Suphanit I, lamurairat W (2003). Sonographic morphological pattern in the pre-operative prediction of ovarian masses. *J Med Assoc Thai*, **86**, 332-7.

Boente MP, Schilder R, Ozols RF (1999). Gynecological Cancers. *Cancer Chemother Biol Response Modif*, **18**, 418-34.

Campos Torres JC, Mauricette Derchain SF, Faundes A, et al (2002). Risk of malignancy index in preoperative evaluation of clinically restricted ovarian cancer. *Sao Paulo Med j*, **120**, 72-6.

Caruso A, Caforio L, Testa Ac, et al (1996). Transvaginal color doppler ultrasonography in the presurgical characterization of adnexal masses. *Gynecol Oncol*, **63**, 184-91.

Depriest PD, Vartner E, Powell J (1999). The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi – institution of investigation. *Gynecol Oncol*, **55**, 174-8.

Diamandis EP, Scorilas A, Fracchioli S (2003). Human kallikrein 6(HK6): a new potential serum biomarker for diagnosing and prognosis of ovarian carcinoma. *J clin oncol*, **21**, 1035-43.

Edgell T, Roussety GM, Barker G, et al (2010). Phase II biomarker Trial of a multimarker diagnostic for Ovarian Cancer, **136**, 1079-88.

Enakpene CA, Omigbodun AO, Geocke TW, Odukogbe AT, Beckmann MW (2009). Preoperative evaluation and triage of women with Suspicious adnexal masses using risk of malignancy index. *J Obstet Gynecol*, **35**, 131-8.

Holschneider CH, Berek JS (2000). Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol*, **19**, 3-10.

Javitt MC (2007). ACR appropriateness criteria on staging and follow up of ovarian cancer. *J AM Coll Radiol*, **4**, 586-9.

Kinkel K, Hricak H, IU Y, Tsuda K, Filly RA (2000). Us characterization of ovarian masses: a meta-analysis. *Radiology*, **217**, 803-11.

Kurjak A, Predanic M (1992). New scoring system for prediction of ovarian malignancy based on transvaginal color dopplor sonography. *J Ultrasound Med*, **11**, 631-8.

Leelahakorn S, TangjiTamol S, Manusirivithaya (2005). Comparison of ultrasound Score, CA125, Menopausal Status , and risk of malignancy index in differentiating between benign and borderline or malignant Ovarian tumors. *J Med Assoc Thai*, **88**, 22-30.

Marjunath AP, Pratapkumar, Sujatha K, Vani R (2001). Comparison of three risk of malignancy indices in evaluation of pelvic masses. *Gynecol Oncol*, **81**, 225-9.

Mederiros LR, Fachel JM, Garry K, Stein AT, Furness S (2005). Laparascopy versus laparatomy for benign ovarian tumors. *Cochrane Database of Systematic Reviews*, **3**, 1002-10.

Moolthiya W, Yuenyao P (2009). The risk of malignancy index (rmi) in diagnisis of ovarian malignancy. *Asian Pac J Cancer Prev*, **10**, 865-68.

Obeidat BR, Amarin ZO, Latimer JA (2004). Risk of malignancy index in the preoperative evaluation of pelvic masses. *Int J Gynaecol Obstet*, **85**, 255-8.

Oriel KA, Hartenbach EM, Remington PL (1999). Trends in United States Ovarian Cancer mortality, 1979-1995. *Obstet Gynecol*, **93**, 30-3.

Rufford BD, Jacobs J (2003). Ovarian cysts in postmen opausal women. *RCOG Guided*, **34**, 1-8.

Soegaard R, Knudsen A, Rix P (2003). Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. *Gynecol oncol*, **90**, 109-12.

Szpurek D, Moszynski R, Smolen A, Sajdak S (2005). Artificial

neural network computer prediction of ovarian malignancy in women with adnexal masses. *Int J Gynecol Obstet*, **89**, 108-13.

Szpurek O, Moszynski P, zietkowiak W, Spaczynski M, Sajdak S (2005).An ultrasonographic morphological index for prediction of ovarian tumor malignancy. *Eur J Gynecol Oncol*, **26**, 51-4.

Trim Bus JB,Vergote I, Bolis G, et al (2003). Impact of adjuvant chemotherapy and Surgical Staging in early – stage ovarian carcinoma: european organization for research and treatment of cancer – adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst*, **95**, 113-25.

Ulusoy S, Akbayir O, Numanoglu C (2007). The risk of malignancy index in discrimination of adnexal masses. *Int J Gynecol Obstet*, **96**, 186-91.

Valentin L (1999). Prospective cross-validation of Doppler ultrasound examination and gray – scale ultrasound imaging for discrimination of benign and malignant pelvic masses. *Ultrasound Obstet Gynecol*, **14**, 273-83.

Valentin L, Hagen B, Tingulstad S, Eik-Nes S (2001). Comparison of pattern recognition and logistic regression models for discrimination between benign and malignant pelvic masses: a prospective cross validation. *Ultrasound Obstet Gynecol*, **18**, 357-65.

Valentin L (2004). Use of morphology to characterize and manage common adnexal masses. *Best Pract Res Clin Obstet Gynaecol*, **18**, 71-89.

Vernooij F, Heintz P, Witteveen E, Vendergraf Y (2007). The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecl Oncol*, **105**, 801-12.

Winter WE, Maxwel GL, Tian C, et al (2007). Prognostic factors for stage iii epithelial ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*, **23**, 3621-7.