Gynecology; *and Gynecological Oncology*

Risk of Malignancy Index Has a Poor Sensitivity in Detecting Borderline Epithelial Tumors and Non-Epithelial Ovarian Tumors

Yasin DURMUS[1], Mehmet Mutlu MEYDANLI[2]

Ankara, Turkey

ABSTRACT

OBJECTIVES: To evaluate diagnostic accuracy of "Risk Of Malignancy İndex-1" (RMI-1) for postmenopausal adnexal masses.

STUDY DESIGN: Fifty postmenopausal women who had undergone surgery because of adnexal masses were included in this prospective study. RMI-1 scores were calculated through the formula: [RMI= Ultrasound Scorex Menopause Score x Serum Ca-125 Level] and noted preoperatively by the same sonographer for each case. "Final histopathological diagnosis" was accepted as gold standard for benign-malignant categorical distribution. Borderline tumors were categorized in malignant tumor group.

RESULTS: According to final histopathological results; 20 of the 50 patients had malignant adnexal masses. Twelve of them had invasive epithelial tumors. The remaining 8 patients had borderline epithelial tumors or non-epithelial ovarian cancers. When the RMI score ≥200 was accepted as a positive test result compatible with the literature; we calculated the sensitivity: 75%, specificity: 93%, positive predictive value: 88%, negative predictive value: 85% predicting malignant adnexal masses. All of the 12 patients with invasive epithelial tumors had RMI-1 scores higher than 200. Nevertheless, only 3 of the 8 patients with borderline epithelial tumors or non-epithelial ovarian cancers had RMI-1 scores higher than 200. We have found out that invasive epithelial tumors had higher USG Scores, Ca-125 Levels and RMI Scores when compared to borderline epithelial tumors and non-epithelial ovarian cancers and the difference was statistically significant.

CONCLUSIONS: RMI-1 is a valuable and applicable method in the initial evaluation of postmenopausal patients with adnexal masses. İt has a high diagnostic performance in detecting invasive epithelial ovarian cancers, but it has a poor sensitivity in detecting borderline ovarian tumors and non-epithelial ovarian cancers.

Keywords: Epithelial, Cancer, Ovarian, Non-epithelial, Risk of malignancy index

Gynecol Obstet Reprod Med 2019;25(2):101-106

[1] *Department of Gynecologic Oncology Etlik Zubeyde Hanim Women's Health Training and Research Hospital Faculty of Medicine University of Health Sciences, Ankara, Turkey*

[2] *Department of Gynecologic Oncology Zekai Tahir Burak Women's Health Training and Research Hospital Faculty of Medicine University of Health Sciences, Ankara, Turkey*

Address of Correspondence: *Yasin Durmus*
Department of Gynecologic Oncology, Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences, Etlik, Ankara, Turkey
dr_yasindurmus@hotmail.com

Submitted for Publication: *25.09.2018*
Accepted for Publication: *11.12.2018*

ORCID IDs of the authors:
Y.D.: 0000-0002-5404-0118, MM.M.: 0000-0001-6763-9720

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2018.847

How to cite this article: *Durmus Y. and Meydanli MM. Risk of Malignancy Index Has a Poor Sensitivity in Detecting Borderline Epithelial Tumors and Non-Epithelial Ovarian Tumors. Gynecol Obstet Reprod Med 2019;25 (2):101-106*

Introduction

Adnexal masses are common among women, and it is estimated that around 10% of women undergo surgical removal of such masses at some point during their life (1). The main challenge is to identify patients with malignant adnexal masses preoperatively. Prediction of malignancy is limited because of the lack of definitive noninvasive diagnostic tests. Sonography and serum tumor markers are almost standard methods for preoperative evaluation of adnexal masses but more sensitive and well-identified diagnostic tests discriminating benign-malignant adnexal masses preoperatively would help the optimization of ovarian cancer treatment. Early identification of ovarian cancer and referral to a gyneco-oncologist can facilitate accurate staging of the disease and optimal cytoreductive treatment, enhancing patient survival (2,3).

To reduce the diagnostic dilemma between benign and malignant ovarian masses, a formula-based scoring system known as risk of malignancy index (RMI) was introduced by Jacobs et al. (4) in 1990, which was termed as RMI-1. It is a product of ultrasound findings (U), the menopausal status (M),

and serum CA-125 levels (RMI=UxMxCA-125). It was shown that RMI-1 was a better predictor of ovarian cancer than Ca-125 or ultrasound scoring alone (4). The original RMI (RMI-1) has been modified in 1996 by Tingulstadet al. (5) known as RMI-2 and has been remodified by Tingulstad et al. (6) again in 1999 known as RMI-3. Finally, in 2009, Yamamoto et al. proposed RMI-4 by including an additional ultrasound parameter in the RMI-1 formula (7).

Transvaginal ultrasonography is the standard initial approach to assess adnexal masses and allows a rapid evaluation. However "the subjective assessment by an expert sonographer" (also called "pattern recognition") is shown superior to other methods for the triage of adnexal masses before surgery, an expert sonographer is not always available for most of the gynecology clinics (8-11). So, many scoring systems have been developed in order to interpret of ultrasonography more objective and feasible by any ultrasonography performer with varying levels of training and experience. Among these scoring systems, the risk of Malignancy Index-1 (RMI-1) is the most commonly used in clinical practice as it is recommended by many international guidelines (12,13).

In this prospective study, the predictive efficiency of RMI-1 was assessed among 50 postmenopausal women with adnexal masses who underwent surgery and the results were checked against current literature data.

Material and Method

Fifty postmenopausal women with adnexal masses who applied to Adnan Menderes University Hospital Obstetrics & Gynecology Clinic between 24.06.2011-31.12.2011 were included to our study. All patients provided an informed consent regarding research use of their medical information at admission. This study was approved by the Local Ethics Committee (23/6/2011 #6). In all steps of the study, the authors followed the rules of Helsinki Declaration. Post-menopause was defined as ≥1-year amenorrhea story. Patients with adnexal masses who had a previous hysterectomy operation story were also included if she was ≥50 years old. RMI scores were calculated and noted preoperatively by the same sonographer (Y.D) for each case.

Serum Ca-125 levels were evaluated by Cabos E 601 Analyzer System-Electro Chemical Luminisans technique with Elecsys 341 kits. Medison Sonoace x 8 3.75 Mhz convex abdominal and 5 Mhz vaginal probes were used for ultrasound scan. RMI-1 was calculated through the formula: [RMI= Ultrasound Score x Menopause Score x Serum Ca-125 Level] as suggested by Jacobs et al. (4). All the patients included to the study were post-menopausal, so all menopause scores were scored as "3" points. The ultrasound scoring system which Jacobs et al. suggested was used for calculating the ultrasound score. Patients were scanned for multilocularity, existence of solid areas, existence of metastasis, existence of ascites and bilaterality during ultrasound examination. Ultrasound score was calculated as "0" for patients who had none of the criteria above, as "1" for patients who had 1 criterion, and as "3" for patients who had 2 or more criteria at the ultrasound scan.

Forty-seven specimens were sent to intraoperative pathology consultation for frozen section diagnosis after removal of the adnexal mass. "Final histopathological diagnosis" was accepted as the gold standard for benign-malignant categorical distribution. Borderline tumors were categorized in malignant tumor group.

All the data analyses were performed with SPSS Statistics 20 (IBM Corp, Los Angeles, California, USA). Data were presented as mean±standard deviation. Kolmogorov-Smirnov Test was done for qualifying the normality of the data. When there was a homogeneous distribution the t-test was used for independent groups and if not the Mann-Whitney U-Test was used to determine the statistical significance of differences. Diagnostic performance of different parameters in case of predicting malignity was evaluated by using the receiver-operating characteristics (ROC) and the most favorable threshold values were calculated. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for meaningful cut-off values. A p-value <0.05 was considered statistically significant.

Results

Fifty postmenopausal patients were included in the study. All the patients underwent different types of surgery ranging from cystectomy to wide cytoreductive surgery. Forty-seven patients' specimens were sent to intraoperative pathology consultation for intraoperative frozen section (IFS) analysis. Intraoperative pathology consultation reported the frozen section results as benign, borderline or malignant. Forty-six of the 47 specimens' intraoperative frozen section results were compatible with final histopathology results. One mucinous cystadenoma was misdiagnosed and was reported as a borderline mucinous tumor in IFS analysis. The accuracy rate of frozen section evaluation was 97.9% in our study. According to final histopathological results; 30 (60%) patients had benign masses, 2 (4%) had borderline masses and 18 (36%) had malignant masses. The mean age of the patients with benign adnexal masses was 60.2 (range 42-77). The mean age of the patients with malignant adnexal masses was 58.1 (range 46-77). There was no statistically significant difference between the two groups (p >0.05).

The most frequent histopathological type among benign adnexal masses was "Simple Ovarian Cyst" (n=8, 27%). The most frequent histopathological type among malignant adnexal masses was "Serous Adenocarcinoma" (n=9, 45%). Other histopathological types with benign-malign adnexal masses were summarized in table I.

Table I: *Clinicopathological characteristics of the study group*

Total Study Group (n:50)						*p* value
Patients with benign adnexal masses (n=30 60%)			Patients with malignant adnexal masses (n=20 40%)			
Mean age=60.2			Mean age=58.1			*p* >0.05 Independent samples *t*-test
Final histopathological result	n	%	Final histopathological result	n	%	
Simple ovarian cyst	8	27	Serous adenocarcinoma	9	45	
Serous cystadenoma	5	17	Borderline serous tumor	2	10	
Matur cystic teratoma	4	13	Clear cell carcinoma	2	10	
Tubal-paratubal cyst	2	7	Malign epithelial tumor			
Endometrioma	2	7	Not otherwise classified	1	5	
Mucinous cystadenoma	2	7	Granulosa-cell tumor	3	15	
Leimyoma	2	7	Immature teratoma	1	5	
Serous cystadenofibroma	1	3	Small-cell neuroendocrine			
Fibroadenoma	1	3	Carcinoma	1	5	
Fibroma	1	3	Carcinoid tumor	1	5	
Tubaovarian abscess	1	3				
Epidermoid cyst	1	3				
Median Ca-125 Level (±SD)= 9.96 (6.66-20.17)			Median Ca-125 Level (±SD)=50.15 (26.25-303.3)			*p* <0.001 Mann Whitney u-test
Median RMI-1 Score (±SD)=33 (22.5-69.6)			Median RMI-1 Score (±SD)=451.4 (191.32072.1)			*p* <0.001 Mann whitney u-test

n: Number, SD: Standard deviation, RMI: Risk of malignancy index, Ca-125: Cancer antigen-125

Median Ca-125 level in the benign group was 9.96 (6.66-20.17). Median Ca-125 level in the malignant group was 50.15 (26.25-303.3). There was a statistically significant difference between the two groups (p <0,001). Median RMI score in benign group was 33(22.5-69.6) and median RMI score in malignant group was 451.4(191.3-2072.1). There was statistically significant difference between the two groups (p<0,001) (Table I).

When Ca-125 level ≥50 U/mL was accepted as a positive test result compatible with the literature; we calculated the sensitivity: 50%, specificity: 90%, positive predictive value: 77 %, negative predictive value: 73% for serum Ca-125 test discriminating benign and malignant post-menopausal adnexal masses. When the Ultrasound Score=3 was accepted as a positive test result; we calculated the sensitivity: 80%, specificity: 83%, positive predictive value: 76%, negative predictive value: 86% for ultrasound scoring. When the RMI score ≥200 was accepted as a positive test result compatible with the literature; we calculated the sensitivity: 75%, specificity: 93%, positive predictive value: 88%, negative predictive value: 85% for RMI scoring for predicting malignant adnexal masses (Table II).

According to the ROC analysis, the most favorable threshold score for RMI was calculated as 131.4. When we applied the threshold score as 131.4; the sensitivity was 80%, specificity was 90%, positive predictive value was 84%, negative predictive value was 87% (Figure 1).

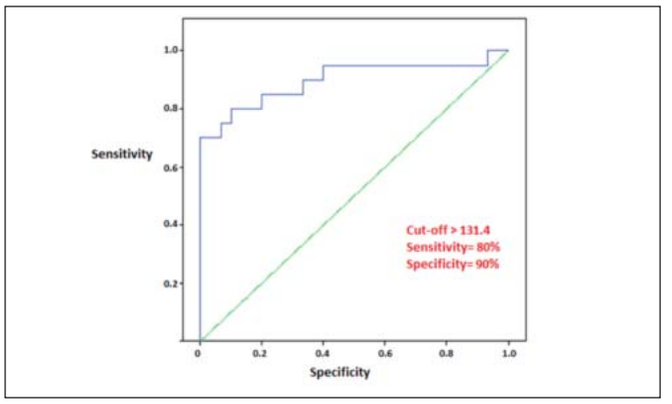
Twenty of the 50 patients had malignant adnexal masses in our study. Twelve of them had invasive epithelial tumors. The remaining 8 patients had borderline epithelial tumors or non-epithelial ovarian tumors. All of the 12 patients with invasive epithelial tumors had RMI-1 scores higher than 200. Nevertheless, only 3 of the 8 patients with borderline epithelial tumors or non-epithelial ovarian tumors had RMI-1 scores

Table II: *Diagnostic accuracy of ultrasonography score, cancer antigen-125 level and risk of malignancy index*

		Histopathological subgroup		Total (n)	Sensivity (%)	Specifity (%)	PPV (%)	NPV (%)
		Benign group (n)	Malign group (n)					
USG score	U=0 or U=1	25	4	29	80	83	76	86
	U=3	5	16	21				
Ca-125 level	<50 IU/mL	27	10	37	50	90	77	73
	≥50 IU/mL	3	10	13				
RMI score	<200	28	5	33	75	93	88	95
	≥200	2	15	17				

n: Number, PPV: Positive predictive value, NPV: Negative predictive value, USG: Ultrasonography, U: Ultrasonography score, IU: International unit, ml: Mililiter

Figure 1: *The calculated optimal Cut-Off value for risk of malignancy index-1 in the current study*



* *Receiver-operating characteristics analyse was used.*

higher than 200. We have found out that invasive epithelial tumors had higher USG Scores, Ca-125 Levels and RMI Scores when compared to borderline epithelial tumors and non-epithelial ovarian tumors and the difference was statistically significant (Table III).

Discussion

Ovarian cancer is the fifth most common cause of cancer-related death among women in Europe (14). It was shown that there was a 6-9 months median survival benefit for patients operated by gynecologic oncologists rather than general gynecologists and/or general surgeons so it was recommended that initial surgical management for epithelial ovarian cancer should be performed by a gynecologic oncologist (15). In this

Table III: *List of patients with malignant tumors and diagnostic deficiency of risk of malignancy index-1 for borderline epithelial tumors and non-epithelial ovarian tumors*

İnvasive Epithelial Ovarian Tumors						Borderline ovarian tumors and Non-epithelial ovarian tumors						*p* value
P	Age	USG Score	Ca-125 (IU/ML)	RMI	Final Histopathology	P	Age	USG Score	Ca-125 (IU/ML)	RMI	Final Histopathology	
1	55	3	352	3168	Serous Adenoca.	1	58	1	16.8	50.4	Borderline Serous T.	
2.	55	3	55.2	496.8	Serous Adenoca.	2	77	3	24.4	219.6	Granulosa-Cell T.	
3.	60	3	48.2	433.8	Serous Adenoca.	3.	71	3	79.1	711.9	İmmature Teratoma	
4.	62	3	261	2349	Clear Cell Ca.	4.	52	1	4.9	14.7	Granulosa-Cell T.	
5.	68	3	52.1	468.9	Serous Adenoca.	5.	51	3	20.2	181.8	Carcinoid T.	
6.	48	3	45.1	405.9	Serous Adenoca.	6.	60	1	31.8	95.4	Borderline Serous T.	
7.	59	3	45.7	411.3	Malign Epithelial T.	7.	46	1	13.5	40.5	Granulosa-Cell T.	
8.	56	3	44.8	403.2	Serous Adenoca.	8.	55	3	104.9	944.1	Small-Cell Carcinoma	
9.	66	3	317.4	2856.6	Serous Adenoca.							
10.	66	3	413.8	1241.4	Serous Adenoca.							
11.	48	3	535.4	4816.6	Serous Adenoca.							
12.	49	3	1853	16677	Clear Cell Ca.							
Mean Age= 57.7						Mean Age=58.7						*p*> 0.05 Independent Samples T-Test
Mean USG Score=3 Median USG Score= 3 SD=0						Mean USG Score=2 Median USG Score=2 SD: 1.1						*p*=0.008 Mann Whitney U-Test
Median Ca-125 Level=158.1 Mean Ca-125 Level=335.3 SD=508.9						Median Ca-125 Level=22.3 Mean Ca-125 Level=36.9 SD=35.5						*p*=0.005 Mann Whitney U-Test
Median RMI-1 Score=869.1 Mean RMI-1 Score=2810.7 SD= 4601.6						Median RMI-1 Score=138.6 Mean RMI-1 Score=282.3 SD=349.5						*p*=0.005 Mann Whitney U-Test

Adenoca: Adenocarcinoma, T: Tumor, Ca: Carcinoma, USG: Ultrasonography, SD: Standard deviation, RMI: Risk of malignancy index, Ca-125: Cancer antigen-125

background, better prediction of ovarian malignancy and referral to a specialist cancer center may help improving ovarian cancer survival rates. However, many diagnostic models have been developed to assist clinicians to triage patients to appropriate treatment pathways; none of them has gained universal acceptance in routine daily practice. Biomarkers like Ca-125, HE-4 (Human Epididymis Protein 4); combined multimarker decision algorithms such as the Risk of Ovarian Malignancy Algorithm (ROMA) and OVA-1; other diagnostic models based on clinical information and ultrasound features like International Ovarian Tumour Analysis (IOTA) models and rules (LR2 and Simple Rules) are other prediction models developed in order to perform an optimal triage (16).

Previous studies demonstrated that RMI is a better predictor of ovarian cancer than Ca-125 or ultrasound scoring alone and suggested the threshold value 200 (4,17,18).Our study aimed to test the diagnostic performance of RMI-1 in postmenopausal patients and calculated 75% sensitivity, 93% specificity, 88% positive predictive value and 85% negative predictive value when the cut-off score was ≥200. A recent meta-analysis assessing 23 previous studies calculated RMI-1 sensitivity and specificity as %72 and %92 respectively with the threshold score ≥200. Sensitivity and specificity rates for RMI-2 were %75 and %87, for RMI-3 were %70 and %91, for RMI-4 were %68 and %94 respectively (16). Our study showed similar diagnostic accuracy rates with previous studies.

When we assessed the diagnostic performance of RMI-1 and the low sensitivity ratio, we revealed that all of the malignant cases omitted by RMI-1 scoring system were either borderline epithelial tumors or non-epithelial ovarian cancers. RMI-1 scoring system was able to predict 12 of 12 invasive epithelial tumors as malignant tumors. By contrast, only 3 of 8 patients with non-epithelial ovarian cancer or borderline epithelial ovarian tumor had a RMI score higher than 200. We revealed that patients with non-epithelial ovarian cancer or borderline epithelial ovarian tumor tended to have lower Ca-125 levels, lower USG Scores and lower RMI scores compared to patients with invasive epithelial cancers (Table III). Several studies confirmed that RMI had a poor sensitivity in detecting borderline ovarian tumors and non-epithelial ovarian cancers (19-21).

Our study group contained 2 patients with false-positive RMI-1 scoring (Table IV). Serum Ca-125 can show a false-positive increase in numerous benign tumors or conditions that irritate the pelvic peritoneum (e.g. endometriosis, fibroids, pregnancy, infection and surgery) (22). So, false positive Ca-125 elevations may cause false positive RMI scoring and decrease the diagnostic accuracy of the RMI.

In conclusion, the present study has demonstrated the RMI-1 to be a valuable and applicable method in the initial evaluation of postmenopausal patients with adnexal masses. It is an objective method for selecting high-risk patients and referring them to appropriate gynecological oncology centers. RMI-1 has a high diagnostic performance in detecting invasive epithelial ovarian cancers, but it has a poor sensitivity in detecting borderline ovarian tumors and non-epithelial ovarian tumors. Other models of preoperative diagnosis should be developed and used in order to improve the detection rate of non-epithelial ovarian cancers and borderline ovarian tumors.

: Conflict of Interest: Authors declare that there is neither financial nor academic support of relationships that may pose potential conflict of interest.
Funding: None
Acknowledgement: None

References

1. Hilger WS, Magrina JF, Magtibay PM. Laparoscopic management of the adnexal mass. Clin Obstet Gynecol. 2006;49(3):535-48.
2. McGowan L. Patterns of care in carcinoma of the ovary. Cancer. 1993;71(2 Suppl):628-33.
3. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20(5):1248-59.
4. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97(10):922-9.
5. Tingulstad S, Hagen B, Skjeldestad FE, Onsrud M, Kiserud T, Halvorsen T, et al. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Br J Obstet Gynaecol. 1996;103(8):826-31.
6. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals.

Table IV: *Patients with false-positive risk of malignancy index-1 scoring*

Patient	Age	USG Score	Ca-125 (IU/ml)	RMI-1	Final Histopathology
1.	42	1	125	375	Fibroadenoma
2.	59	3	44	396	Tubaovarian Abscess

USG: Ultrasonography, IU: International unit, ml: Mililiter, RMI: Risk of malignancy index

Obstet Gynecol. 1999;93(3):448-52.

7. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J Obstet Gynecol Reprod Biol. 2009;144(2):163-7.
8. Van Gorp T, Veldman J, Van Calster B, Cadron I, Leunen K, Amant F, et al. Subjective assessment by ultrasound is superior to the risk of malignancy index (RMI) or the risk of ovarian malignancy algorithm (ROMA) in discriminating benign from malignant adnexal masses. Eur J Cancer. 2012;48(11):1649-56.
9. Valentin L, Jurkovic D, Van Calster B, Testa A, Van Holsbeke C, Bourne T, et al. Adding a single CA 125 measurement to ultrasound imaging performed by an experienced examiner does not improve preoperative discrimination between benign and malignant adnexal masses. Ultrasound Obstet Gynecol. 2009;34(3):345-54.
10. Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839.
11. Timmerman D. The use of mathematical models to evaluate pelvic masses; can they beat an expert operator? Best Pract Res Clin Obstet Gynaecol. 2004;18(1):91-104.
12. Ovarian cancer: recognition and initial management Clinical guideline [CG122] Published date: April 2011 https://www.nice.org.uk/guidance/cg122 (Accessed at 06.09.2018).
13. Ovarian Masses in Premenopausal Women, Management of Suspected (Green-top Guideline No. 62) Published: 02/12/2011https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg62/(Accessed at 06.09.2018).
14. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356-87.
15. Giede KC, Kieser K, Dodge J, Rosen B. Who should operate on patients with ovarian cancer? An evidence-based review. Gynecol Oncol. 2005;99(2):447-61.
16. Kaijser J, Sayasneh A, Van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, et al. Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis. Human Reprod Update. 2014;20(3):449-62.
17. Manjunath AP, Pratapkumar, Sujatha K, Vani R. Comparison of three risk of malignancy indices in evaluation of pelvic masses. Gynecol Oncol. 2001;81(2):225-9.
18. Ma S, Shen K, Lang J. A risk of malignancy index in preoperative diagnosis of ovarian cancer. Chinese Med J 2003;116(3):396-9.
19. Andersen ES, Knudsen A, Rix P, Johansen B. Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. Gynecol Oncol 2003;90(1):109-12.
20. Campos C, Sarian LO, Jales RM, Hartman C, Araújo KG, Pitta D, et al. Performance of the risk of malignancy index for discriminating malignant tumors in women with adnexal masses. J Ultrasound Medicine 2016;35(1):143-52.
21. Arun-Muthuvel V, Jaya V. Pre-operative evaluation of ovarian tumors by risk of malignancy index, CA125 and ultrasound. Asian Pac J Cancer Prev. 2014;15(6):2929-32.
22. Sevinc A, Adli M, Kalender ME, Camci C. Benign causes of increased serum CA-125 concentration. Lancet Oncol. 2007;8(12):1054-5.