ORIGINAL RESEARCH

Comparison of Four Risk of Malignancy Indices in Preoperative Evaluation of Patients with Adnexal Masses

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Abstract

Background: The purpose of the study was to evaluate the efficacy of the risk of malignancy index (RMI) in differentiating benign from malignant adnexal lesions. This study also aims to find out the most appropriate index to diagnose the malignancy of the adnexal mass by comparison of four RMIs.

Materials and methods: Cross-sectional observational study of 75 women of all ages attending a gynecology outpatient clinic and admitted for exploratory surgery for a pelvic mass in a tertiary care hospital in central India during 2018–2020 has been carried out. Study parameters included the menopausal status, ultrasound features and sensitivity, specificity and positive predictive value of serum CA125 and RMI 1, RMI 2, RMI 3, and RMI 4 were calculated to determine whether the pelvic mass was benign or malignant.

Results: All four indices (RMI 1, RMI 2, RMI 3, and RMI 4) were significantly correlated with histopathological findings with a p-value < 0.001. On comparison, no statistically significant difference was observed among the four RMIs to differentiate malignant from benign ovarian masses ($p > 0.05$).

Conclusion: We concluded that the RMI is a simple, noninvasive, easily accessible and applicable, affordable, and inexpensive scoring system for assessing the adnexal masses. The four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) can precisely distinguish the benign from malignant pelvic masses.

Keywords: Adnexal mass, CA 125, Risk of malignancy indices.

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Introduction

Adnexa refers to appendages, which include the ovaries, fallopian tubes, and other pelvic organs. "An adnexal lesion is the part of an ovary or an adnexal mass which is defined as inconsistent with the normal physiologic function, based on ultrasound imaging evaluation" according to the International Ovarian Tumor Analysis (IOTA) definition.[1] These can be of malignant or benign nature with varying degree of severity.

Adnexal masses are commonly seen among both premenopausal and postmenopausal women.[2] In premenopausal women, the most common causes of adnexal masses are ectopic pregnancy, ovarian cysts, tumors, polycystic ovaries and abscesses. Malignant adnexal masses are usually seen among postmenopausal women, though the majority of these women have benign pathologies.[3,4] Thus in menopause, common causes include fibroids and malignant tumors. The decision to undergo surgical intervention depends upon the clinical profile of the patient and associated risk of malignancy of the lesion.

In gynecologic practice, adnexal masses are among the most prevalent pathological conditions observed. The right course of treatment for adnexal masses depends upon correct diagnosis. The benefits of precise and correct diagnosis include the timely referral of women with high risk for malignancy to a gynecologic oncologist for accurate surgical staging and/or necessary surgical management and avoiding of unnecessary surgery in benign adnexal pathologies.[5]

In most cases, these cysts are asymptomatic and may be diagnosed incidentally during an ultrasound in early pregnancy or in patients with abdominal distension due to increasing size. Pain could be sudden onset or chronic, is an indicator of rupture, bleeding, venous stasis, or torsion.[6]

Prevalence of malignant adnexal/pelvic tumor, one of the most common problems in women, is 24% in premenopausal group which becomes 64% in postmenopausal women. Malignant adnexal masses require surgical management. Preoperative diagnosis of malignancy which is essential for an optimal surgical plan, is not always possible. Combining different testing modalities resulted into risk of malignancy index (RMI), a diagnostic model that combines the demographic, ultrasonography, and biochemical data. RMI is a score calculated as the product of ultrasound score (U), menopausal score (M), and serum level of CA 125. RMI = U × M × CA 125.[7–10]

The RMI is an easy scoring system that combines various clinical parameters. It has been developed to improve the efficacy

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of ovarian mass diagnosis. This helps in referring relevant patients to oncology centers.

In peripheral healthcare centers, RMIs can be directly used without any expensive or complicated methods (CT, MRI, and PET scan). The purpose of this study was to determine and compare the ability of four risks of malignancy indices to differentiate benign from malignant pelvic lesions.

Materials and Methods

Study design: Cross-sectional observational study

Study area: Gynecology OPD at tertiary care hospital

Study duration: 20 months (2018–2020)

Sample size: 75

Study subjects: All cases between 18–75 years coming to tertiary care hospital in a single working unit as observed from data from the last few years.

Inclusion criteria: (1) Patients willing to participate in the study. (2) All patients with adnexal/ovarian masses of significant size diagnosed clinically and by imaging modalities in adolescent, reproductive and peri/postmenopausal age groups posted for laparoscopy/laparotomy. (3) Patients with final histopathological diagnosis of the tumor mass.

Exclusion criteria: (1) Ovarian masses of small size with clear cysts in reproductive age group on conservative treatment. (2) Women with adnexal masses not fit for and/or not willing for surgical management. (3) Non-gynecological origin of adnexal masses (4) Patient previously diagnosed with malignant ovarian cancer by cytology or histopathological examination. (5) Incomplete medical records and non-compliant patients. (6) Patient undergoing second look laparotomy following previous treatment for malignant ovarian tumor. (7) Not willing to participate.

Data collection: This is a cross-sectional observational study included a total of 75 women of all age groups at the tertiary care hospital in a single working unit from 2018 to 2020. Their consent was taken to become part of the study. Details were collected using a standardized questionnaire including demography, family history of adnexal/ovarian mass or other malignancy, including breast, colon, and obstetric history of the patients. Their menstrual history was adequately studied noting age of menarche, menstrual regularity, and age of menopause wherever applicable. Women who had hysterectomy or her amenorrhea lasting for >1 year or age >50 years were considered as postmenopausal. All other women participating in the study were considered premenopausal. A detailed history of the presenting complaints was recorded. USG abdomen and pelvis was noted for all patients including the nature, location and characteristics of adnexal masses, such as bilaterality, multi-locular cyst, the presence of solid component, metastasis, and ascites. In some patients, pelvic MRI was also performed to obtain a detailed assessment of the adnexal mass depending upon the case profile. Tumor marker CA125 was tested for all patients. RMI imaging score was assigned to each patient using the appropriate formulae. Details of the surgical procedure done for each patient were recorded. Histopathological reports were noted for detailed and exact diagnosis of the adnexal masses of all patients.

The use of the four methods are as follows:[11]

- RMI 1 (Jacobs et al.) = U × M × CA-125, where a total ultrasound score of 0 made U = 0, a score of 1 made U = 1, and a score of >2 made U = 3; premenopausal status made M = 1 and postmenopausal M = 3. The serum level of CA125 was applied directly to the calculation.[7]
- RMI 2 (Tingulstad et al.) = U × M × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥2 made U = 4; premenopausal status made M = 1 and postmenopausal M = 4. The serum level of CA-125 was applied directly to the calculation.[8]
- RMI 3 (Tingulstad et al.) = U × M × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥2 made U = 3; premenopausal status made M = 1 and postmenopausal M = 3. The serum level of CA-125 was applied directly to the calculation.[9]
- RMI 4 (Yamamoto et al.) = U × M × S (size in centimeters) × CA-125, where a total ultrasound score of 0 or 1 made U = 1, and a score of ≥2 made U = 4. Premenopausal status made M = 1 and postmenopausal status made M = 4. A tumor size (single greatest diameter) of <7 cm made S = 1, and ≥7 cm made S = 2. The serum level of CA-125 was applied directly to the calculation.[10]

Results

The result of histological examination of these surgical specimens of 75 patients revealed that 63 cases presented with benign masses and 12 were with malignant masses, most common benign mass according to histopathological diagnosis was serous cystadenoma 15 (23.80%) followed by Simple cyst with necrotic contents 12 (19.04%), similarly in malignant masses most common was Serous cystadenocarcinoma 7 (58.33%) (Table 1).

All benign and malignant cases were distributed and studied based on age, menopausal status, family history of malignancy, tumor size and serum CA-125. The risk of malignancy increases with age and has been found to be even greater in postmenopausal women (58.33%) (Table 2).

Correlation of diagnosis of the tumor by CA125 marker and histopathology, among patients with a benign tumor revealed that 36 (57.14%) patients had CA 125 35 U/mL while among the patients with malignant tumor, 3 (25%) had CA 125 35 U/mL. Thus, a statistically significant correlation was found between CA 125 marker and histopathology findings with p-value < 0.05 (Table 3).

During the study of the correlation of four indices and histopathological diagnosis of tumor, we found that all four risk of malignancy indices (RMI-1, RMI-2, RMI-3, and RMI-4) in preoperative evaluation of patients with adnexal masses shows significant correlation with histopathological diagnosis of the tumor with p-value < 0.001 (Table 4).

A comparison of the effectiveness of four indices (RMI-1, RMI-2, RMI-3, and RMI-4) with different cut-off values was done. For RMI-1, the cut-off value was set at 200 which yielded 70.01% sensitivity, 91.42% specificity, 74.20% positive predictive value and 88.16% negative predictive value. For RMI-2, the cut-off value was set at 200 which yielded 71.24% sensitivity, 90.23% specificity, 70.31% PPV, and 89.83% negative predictive value. For RMI-3, the cut-off value of 200 yielded 69.89% sensitivity, 91.34% specificity, 74.01% PPV, and 88.16% NPV. For RMI-4, the cut-off value was set at 450

Table 1: Distribution of study subjects according to histopathological diagnosis of benign and malignant masses

Types of masses	*Histopathological diagnosis*	*Number*	*Percentage*
Benign masses ($n = 63$)	Simple ovarian cyst	5	7.93
	Simple cyst with necrotic contents within	12	19.04
	Benign serous para ovarian cyst	2	3.17
	Endometrioma	7	11.11
	Dermoid cyst	7	11.11
	Corpus luteal cyst	5	7.93
	Hemorrhagic corpus luteal cyst	1	1.58
	Serous cystadenoma	15	23.80
	Bilateral serous cystadenoma	2	3.17
	Mucinous cystadenoma	7	11.11
Malignant masses ($n = 12$)	Dysgerminoma	3	25
	Granulosa cell tumor	1	8.33
	Mucinous cystadenocarcinoma	1	8.33
	Serous cystadenocarcinoma	7	58.33

Table 2: Distribution of benign and malignant cases by age, menopausal status, family history of malignancy, tumor size, and serum CA-125

Variables	*Benign (n = 63); n (%)*	*Malignant (n = 12); n (%)*
Age		
≤30	29 (36.50%)	2 (16.66%)
31–40	7 (11.11%)	1 (8.33%)
41–50	17 (26.98%)	2 (16.66%)
≥50	10 (15.87%)	7 (58.33%)
Menopausal status		
Premenopausal	46 (73.01%)	5 (41.66%)
Postmenopausal	17 (26.98%)	7 (58.33%)
Family history of malignancy		
No	63 (100%)	09 (75%)
Yes	00 (0.0%)	03 (25%)
Tumor size		
<7	6 (9.52%)	1 (8.33%)
≥8	59 (93.65%)	11 (91.66%)
CA-125 (IU/mL)		
<35 IU/mL	36 (92.30%)	03 (7.69%)
>35 IU/mL	27 (75%)	09 (25%)

Table 3: Correlation of diagnosis of the tumor by CA 125 marker and histopathology

	CA 125 (IU/mL)		
Histopathology	*<35 IU/mL*	*>35 IU/mL*	*Total*
Benign	36 (57.14%)	27 (42.85%)	63 (100%)
Malignant	03 (25%)	09 (75%)	12 (100%)
CA 125			
p-value		0.02	
Sensitivity		75%	
Specificity		55.38%	
Positive predictive value		25%	
Negative predictive value		92.30%	

Table 4: Correlation of RMI-1, RMI-2, RMI-3, and RMI-4 and histopathological diagnosis of tumor

RMI 1–4	*Benign*	*Malignant*	*p-value*
RMI 1 (cutoff 200)			
<200	62 (95.38%)	03 (4.61%)	<0.001
>200	01 (10%)	09 (90%)	
RMI 2 (cutoff 200)			
<200	59 (95.16%)	03 (4.83%)	<0.001
>200	4 (30.76%)	09 (69.23%)	
RMI 3 (cutoff 200)			
<200	62 (95.38%)	03 (4.61%)	<0.001
>200	01 (10%)	09 (90%)	
RMI 4 (cutoff 450)			
<450	61 (95.31%)	03 (4.68%)	<0.001
>450	02 (18.18%)	09 (81.81%)	

Table 5: Comparison of the efficiencies of RMI 1–4 with different cut-off values

RMI 1–4	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
RMI 1 (cutoff 200)	70.01%	91.42%	74.20%	88.16%
RMI 2 (cutoff 200)	71.24%	90.23%	70.31%	89.83%
RMI 3 (cutoff 200)	69.89%	91.34%	74.01%	88.16%
RMI 4 (cutoff 450)	76.12%	92.6%	73.83%	90.12%
p-value	0.084	0.067	0.176	0.093

which yielded 76.12% sensitivity, 92.6% specificity, 73.83% PPV, and 90.12% NPV. There was no significant difference observed in sensitivity, specificity, PPV, and NPV with a *p*-value of >0.05 with defined cut-off values (Table 5).

Discussion

In the present study, out of 75 patients, 63 (84%) were presented with benign adnexal lesions and 12 (16%) had malignant tumors. Yamamoto et al. observed that of 296 patients, 74 (25.0%) had

the malignant disease and 222 (75.0%) were benign. Aktürk et al. reported that out of 100 patients, 80 (80%) were benign and 20 (20%) were the malignant adnexal mass.

The mean age of our study population was 52 + 6.49 years. Yamamoto et al. in their study revealed that the overall mean age of the women was 52 ± 6.49 years with 56.3 ± 15.7 years seen in malignant disease and for those with benign mass, it was 43.6 ± 15.4 years.

In this study, 73.01% of the study population in the premenopausal age group had benign lesions at diagnosis as compared with 26.98% of postmenopausal women. Among women with malignancy, 58.33% of the population was in postmenopausal age group and 41.66% was premenopausal.

Yamamoto et al.,[10] in their study, had comparable observations as 74.8% of the premenopausal women had benign lesions, whereas out of total postmenopausal women, 63.5% had malignant lesions.

Most of the patients with a benign lesion (90.76%) had a >7 cm tumor size on USG and 91.66% of women with malignant lesions had a tumor size of >7 cm. Similar observations were seen in the study of Yamamoto et al.[10] where 51.8% of cases with benign tumors and 73% of the malignant cases had a tumor size of >7 cm.

In the present study, the mean serum CA 125 for malignant lesions was 145.91 IU/mL and the mean serum CA 125 for benign lesions was 40.41 IU/mL. This was comparable with the study by Zhang et al.[12] where the mean serum CA 125 levels for benign and malignant tumors were 34.77 ± 6.6 IU/mL and 192.15 ± 98.13 IU/mL, respectively.

In the present study sensitivity of RMIs 1, 2, 3, and 4 was 70.01, 71.24, 69.89, and 76.12%, respectively. The specificity of RMIs 1, 2, 3, and 4 was 91.42, 90.23, 91.34, and 92.6%, respectively. Yamamoto et al.,[10] in their study, reported that the sensitivity of RMIs 1, 2, 3, and 4 was 92.9, 97.6, 92.9, and 95.2%, respectively. The specificity of RMIs 1, 2, 3, and 4 was 88.6, 83.5, 88.6, and 86.6%, respectively.

Further studies reported that the sensitivity of RMIs 1, 2, 3, and 4 was 73.0, 81.1, 73.0, and 77.0%, respectively. The specificity of RMIs 1, 2, 3, and 4 was 93.7, 89.6, 93.7, and 92.3%, respectively.[13–15] This study showed no significant difference between all four RMIs 1, 2, 3, and 4. All four RMIs show a significant correlation with the tumor histopathological findings. Similarly, there was no statistical difference among these three indices in benign and malignancy differentiation in the study conducted by Manjunath et al.[16]

In contrast to our findings, the study by Yamamoto et al.[10] of four indices showed that RMI 2 was significantly superior in diagnosing malignancy than RMIs 1 and 3 ($p = 0.04$). No statistically significant difference was observed in the performance of RMIs 2 and 4.

Conclusion

From this study, it can be concluded that the four malignancy risk indices (RMI 1, RMI 2, RMI 3, and RMI 4) can precisely discriminate malignant and benign adnexal masses. The conclusion of this study is, when used with a defined cut-off value, no statistically significant difference was observed among the four RMIs in differentiating malignant from benign ovarian masses.

Clinical Significance

The RMI is a simple, noninvasive, easily accessible and applicable, favorable and affordable scoring system for adnexal masses. This study has concluded that the RMI is a useful tool for appropriate and prompt referral of patients to specialized centers for further surgical treatment of malignancy.

Ethical Approval

The study was approved by the ethics and research committee of the institution.

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