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Original Research Article

Role of risk of malignancy index for evaluation and preoperative detection of pelvic malignancies compared with pathological diagnosis

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ABSTRACT

Background: Risk of malignancy index (RMI) is widely employed in the developed world in predicting malignant pelvic masses. The present study designed to confirm the effectiveness of the RMI to identify cases with high potential of ovarian malignancy, among patients with an adnexal mass.
Methods: This was a cross-sectional study was conducted over a period of two years in a government run tertiary healthcare centre of Srinagar, Kashmir, Jammu and Kashmir, India. Study included 72 patients who underwent surgery due to adnexal mass and were evaluated for ovarian malignancy by comparing RMI with histopathological diagnosis. Data collected included demographic characteristics, ultrasound findings, menopausal status, CA125 levels, and histopathological diagnosis. For each patient, RMI was calculated as per the standard formula.
Results: Analysis revealed ultrasound score had the highest sensitivity of 72.7%, while an RMI score ≥250 had the highest specificity of 88.5%. The latter also had the highest positive predictive value of 50%, while negative predictive value was highest for an ultrasound score of 3 (94%). The cut off points based on ROC analysis demonstrates significant predictive ability for ovarian cancer for both RMI and CA125 with AUC to the tune of 82.9% and 80.1% respectively.
Conclusions: RMI is a simple score system which can be applied directly into clinical practice and might be of value in pre-operative assessment, and hence selecting patients who need surgical team including gynecologic oncologists.

Keywords: Adnexal mass, CA-125, Risk of malignancy index, Sensitivity, Specificity

INTRODUCTION

Ovarian masses are a frequent cause of gynaecological consults; and ovarian cancer causes 4% of all female genital tract cancers in industrialised countries.[1] They are often detected during imaging studies or exploratory surgery for evaluation of abdominal or pelvic pain syndromes. Ovarian cancer prognosis remains poor with overall 5-year survival about 44%, according to SEER data.[2] Preoperative evaluation for benign and malignant ovarian tumours remains the cornerstone of management. Early referral to a gynaeco-oncologist can facilitate accurate staging of the disease and optimal cytoreductive treatment, enhancing patient survival.[3,4] Histopathology remains the gold standard for this cancer, and a definitive biomarker has not been yet identified. The level of CA 125 is elevated in less than half of epithelial ovarian cancers, and it is a non-specific marker of other benign

pathologies also. Risk of malignancy index (RMI), which considers the serum CA125 level, menopausal status, and ultrasonographic findings in predicting management of pelvic masses, is widely employed in the developed world.[5] It was further extended initially to RMI 1, and RMI 2 in 1996, and later on to RMI 3 1999.[6] It is a simple method that can be applied safely into clinical practice rather than high priced or complex methods such as MRI or CT. The present study was designed to confirm the effectiveness of the RMI to identify cases with high potential of ovarian malignancy, among patients with adnexal mass in a tertiary care hospital in India.

METHODS

A cross-sectional study was conducted in the department of obstetrics and gynecology associated with Government Medical College Srinagar, Kashmir which caters to the gynecological and obstetric needs of majority of the population. The data was collected over a period of two years and included 72 patients who underwent surgery because of an adnexal mass. Approval for the study protocol was obtained from the institutional ethical board and written informed consent of all patients were obtained.

A full history was obtained and a general and gynecological examination was performed. Patients then underwent a transabdominal (3.5 MHz transducer) or transvaginal ultrasound (7.5 MHz transducer) and/or Color Doppler. Adnexal masses were evaluated for sonographic morphological criteria which included bilaterality, solid areas, multilocularity, ascites and metastatic evidence. One point was given for each multilocularity, presence of solid areas, presence of ascites, bilaterality or presence of intra-abdominal metastasis. A total of 2 or more points gives U=3, zero or one point gives U=1. The numerical value of CA-125 was entered directly into the formula.

Patients with amenorrhoea for more than a year, had hysterectomy, and age more than 50 years were labelled as menopausal score 3. Others were labelled as menopausal score 1. Risk malignancy index which is a composite index was calculated for each patient using the standard formula which incorporates CA-125, USG score and menopausal score.[5] Histopathological diagnosis which is regarded as a gold standard for evaluation of results was done as per WHO classification.[7] The specimens were sent to the department of pathology for histopathological analysis and the results were correlated with RMI. Subjects with functional cysts <5 cms, and signs of advanced disease like hepatic, extensive peritoneal or lung metastasis were excluded. To assess the accuracy of RMI and CA-125 value estimates, receiver operating characteristic (ROC) curve was drawn using non parametric method in SPSS software. The optimal cut-off value was determined by giving equal weightage to specificity and sensitivity using Youden J statistic.

RESULTS

The age of the patients ranged from 18 to 63 years with a mean of 37.6±12.4 years Demographic and diagnostic characteristics of the patients are presented in Table 1 and Table 2.

Table 1: Distribution of cases in the study.

Histopathological diagnosis	Benign n (%)	Borderline n (%)	Malignant n (%)	Total n (%)
	57 (79.2)	4 (5.6)	11 (15.2)	72 (100)
Age (years)				
≤20	4 (5.5)	0 (0)	1 (1.4)	5 (6.9)
20-39	35 (48.6)	2 (2.7)	2 (2.7)	39 (54.2)
40-59	14 (19.4)	2 (2.7)	6 (8.3)	22 (30.6)
≥60	4 (5.5)	0 (0)	2 (2.7)	6 (8.3)
Menopausal status				
Premenopausal	46 (63.8)	3 (4.2)	5 (6.9)	54 (75)
Postmenopausal	11 (15.3)	1 (1.4)	6 (8.3)	18 (25)
USG score				
USG score 1	44 (61.1)	3 (4.2)	3 (4.2)	50 (69.4)
USG score 3	13 (8.05)	1 (1.38)	8 (11.1)	22 (30.6)
CA-125				
CA-125 ≥35	23 (31.9)	4 (5.6)	9 (12.5)	36 (50)
CA-125 <35	34 (47.2)	0 (0)	2 (2.7)	36 (50)
RMI groups				
≤50	31 (43.5)	0 (0)	1 (1.4)	32 (44.4)
50.1-249.9	22 (30.6)	1 (1.4)	3 (4.2)	26 (36.1)
≥250	4 (5.6)	3 (4.2)	7 (9.7)	14 (19.4)

Table 2: Summary of ultrasound findings in the study.

USG findings	Frequency (%)
Nature of cyst	
Unilocular	28 (38.9)
Multilocular	44 (61.1)
Bilateral cysts	6 (8.3)
Unilateral cyst	66 (91.7)
Presence of solid areas	22 (30.6)
Absence of solid areas	50 (69.4)
Evidence of metastasis	3 (4.2)
No evidence (absent)	69 (95.8)
Presence of ascites	5 (6.9)
Absence of ascites	67 (93.1)
USG score	
Score 1	50 (69.4)
Score 3	22 (30.6)

Table 3: Histopathological diagnosis of pelvic mass.

Pathological diagnosis	N (%)	Pathological diagnosis	N (%)
Non-malignant disease	57 (79.2)	Borderline/malignant disease	15 (20.8)
Endometrioma	11	Borderline ovarian tumours (mucinous/serous)	4
Ovarian cyst (simple/haemorrhagic)	7	Malignant disease	11
Tubo-ovarian abscess	5	Mucinous cystadenocarcinoma	2
Mature cystic teratoma	8	Serous cystadenocarcinoma	3
Mucinous cystadenoma	3	Endometrioid tumour	1
Serous cystadenoma	6	Dysgerminoma	1
Ovarian fibroma	1	Granulosa cell tumour	1
Adenofibroma	3	Metastatic ovarian cancer	2
Mucinous cyst adenofibroma	1	Uterine sarcoma	1
Thecoma	2		
Others*	10		

*others include genital tuberculosis, chronic ectopic, para ovarian cyst, leiomyoma.

Table 4: Diagnostic performance of the criteria evaluated.

Criteria evaluated	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	*+LR ratio (95% CI)	#-LR ratio (95% CI)
RMI ≥250	63.4% (35.4-84.8)	88.5% (78.1-94.3)	50% (26.8-73.2)	93.1% (83.6-97.3)	5.5% (3.6-8.6)	0.41% (0.7-31)
CA-125 ≥35	81.8% (52.3-94.9)	55.7% (43.3-67.5)	25% (13.8-41.1)	94.4% 81.9-98.4	1.8% (1.6-2.1)	0.3% (0.9-1.1)
USG score 3	72.7% (43.4-90.2)	77.1% (65.1-85.8)	36.4% (19.7-57.1)	94% (83.8-97.9)	3.2% (2.5-3.9)	0.4% (0.2-0.7)
Menopausal score 3	54.6% (28-78.7)	80.3% (68.7-88.4)	33.3% (16.3-56)	90.7% (80.1-96)	2.7% (1.8-4.3)	0.5% (0.4-0.8)

* +LR = positive likelihood ratio # -LR = negative likelihood ratio.

Majority (75%) of the women were in premenopausal period. Fifty cases (69.4 %) had an ultrasound score of 1, (presence of one finding), while lesions of twenty-two (30.5%) cases were scored 3 (two or more findings). Of the 50 cases, with an ultrasound score of 1, 44 (61%) had benign disease, while 3 (4.2%) had borderline and three were malignant on histopathological diagnosis. Among twenty-two cases of ultrasound score of 3, 13 (18.1%) had benign disease, 1 (1.4%) had borderline, and 8 (11.1%) had malignant disease.

Mostly the lesions were multilocular in nature (61.1%). Bilateral cysts were seen in 6 (8.3%) patients, while 66 (91.7%) revealed unilateral cystic lesions. Nearly one-third of the patients 22 (30.6%) had evidence of solid foci on ultrasound. Ascites was present in only 5 patients (3.6%). Only 3 cases showed evidence of metastasis.

Most of the patients 57 (79.2%) patients had benign lesions, while 11 (15.2%) had a malignant disease. Malignant disease was reported in 6 (8.3%) patients in the age group of 40-59 years, and 2 (2.7%) cases occurred among patients aged ≥60 years. Forty-six (63.8%) of the 54 premenopausal women had benign disease, three (4.16%) had borderline lesions, and five (6.94%) patients had malignant disease. Among 18 postmenopausal women, 6 (8.3%) had malignant disease.

The serum CA125 levels in this study varied from 5.04 to 2530 U/ml. Out of 72 patients, 36 (50%) patients had CA125 levels ≥35 U/ml. In the higher (≥35 U/ml) level group, 23 (31.9%) patients had benign disease, 4 (5.55%) had borderline, and 9 (12.5%) had malignant disease. Nearly half of cases 34 (47.2%) with benign disease had CA125 level <35 U/ml, and 2 (2.7%) malignant cases, (uterine sarcoma and dysgerminoma) reported low serum CA125 levels (<35 U/ml). No borderline case was reported in this group.

The RMI was calculated as per the standard formula Jacobs et al. The RMI scores of the patients ranged from 5.04 to 7590. Of seventy-two cases, 14 (19.44%) patients had RMI scores of ≥250 of which 7 (9.7%) patients had malignant disease. Fifty-three (73.6%) patients with RMI ≤250 had benign disease, 1 (1.38%) had borderline and 4 (5.55%) cases had malignant disease in this study.

Histopathological diagnosis of pelvic mass is depicted in Table 3. Two patients had borderline serous, and two had borderline mucinous tumours. The majority of the women with malignant disease had ovarian cancer; of them two had metastatic (Kruckenberg) tumour, and one had non ovarian gynaecological malignant disease.

Table 5: ROC analysis of screening ability of CA-125 and RMI score.

	Cut-off value	AUC	P-value	95% CI	Sensitivity	Specificity
RMI score	205.8	0.829	0.001	0.66-0.99	81.8	85
CA-125	68.6	0.801	0.002	0.63-0.96	82	75

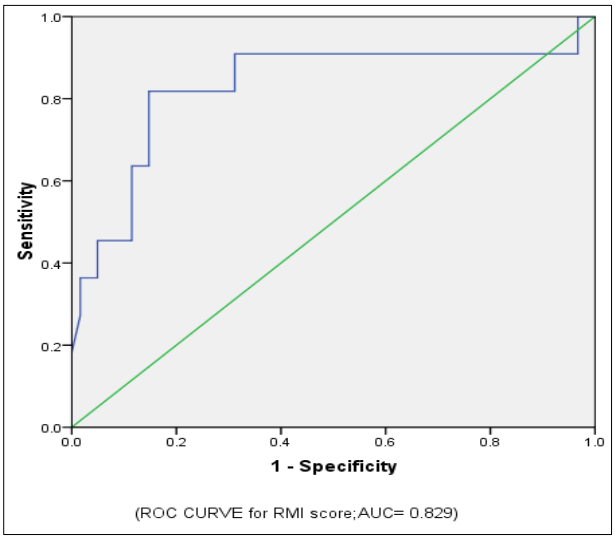

Figure 1: ROC curve for RMI score.

The sensitivity, specificity and positive and negative likelihood ratios of serum CA125 ≥35 u/ml, USG score 3, menopausal score 3, and RMI (≥250) is reported in Table 4. The ultrasound score 3 had the highest sensitivity 72.7% (CI; 43.4-90.2), while an RMI score ≥250 had the highest specificity 88.5% (CI; 78.1-94.3).The latter also had the highest positive predictive value of 50% (CI; 26.8-73.2), while negative predictive value was highest for an USG score of 3 as 94% (CI; 83.8-97.9). The positive likelihood ratio was highest for RMI score of ≥250.

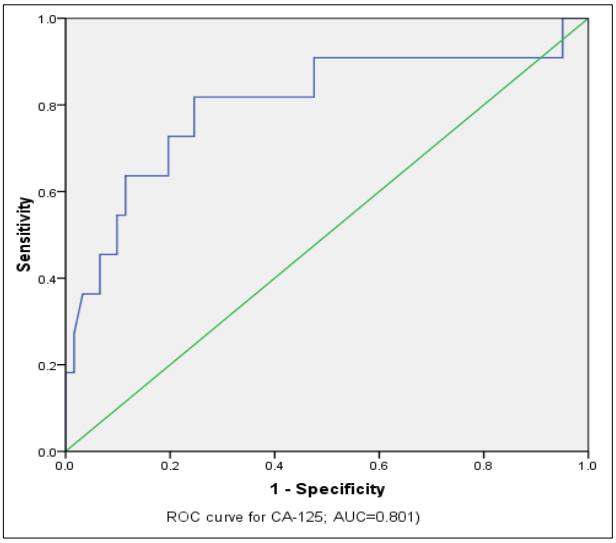

Figure 2: ROC curve for CA-125.

A receiver operating curve (ROC) was plotted for RMI and CA-125 (Figure 1 and Figure 2). The area under the

curve (AUC) value, p-value and cut off points estimated for sensitivity and specificity are reported in Table 5. The cut-off points based on ROC analysis demonstrates significant predictive ability for ovarian cancer for both RMI and CA 125 with AUC to the tune of 82.9% and 80.1% respectively.

DISCUSSION

When an ovarian tumor is identified, it is important to establish its risk of malignancy to properly inform the patient and to plan the most appropriate surgical approach. A thorough preoperative evaluation is done to determine the anatomic location, size, and morphology of the ovarian tumor by transvaginal ultrasound which is the most accurate test for assessing size and morphology. Serum biomarker levels are obtained and used independently and in conjunction with sonographic findings as a means to differentiate benign from malignant disease. The proposed parameter, risk of malignancy index (RMI) is a simple and practical tool with acceptable sensitivity and specificity that can be used to predict malignant ovarian disease especially in settings with resource constraints this study aimed at determining the role of RMI in preoperative evaluation and prediction of malignant ovarian disease. In this study conducted in the 700 bedded tertiary care hospital, seventy-two patients who underwent surgery due to pelvic mass/adnexal mass over a period of two years were included for analysis. Eleven patients had histopathological diagnosis of malignant disease, and four reported to have borderline malignancy on histopathology. Preoperative RMI scores were then compared with the final pathological results.

The mean age of the patients was 37.6±12.3 years. In this study 15.2% of the patients had malignant disease and 33.3% of malignancies occurred in postmenopausal patients and 9.2% were reported among the premenopausal patients. This data is comparable to other study where 35% of malignancies occurred in postmenopausal and 7.9% among premenopausal patients.[8]

Ultrasonography (USG) is widely used as the best method for evaluation of ovarian pathology. In the present study, USG score of 3 had a high sensitivity of 72.7% and negative predictive value of 94% and a low negative likelihood ratio (0.4; CI 0.2-0.7) among the parameters evaluated. Sensitivity to the tune of 78.3%, negative predictive value of 96.1% and least likelihood ratio (0.26) for similar method has been reported by other studies.[8,9]

Various biomarkers and their combinations have been employed for assessing the risk of ovarian cancer, among which serum CA-125 is widely appreciated. However other gynecological conditions like endometriosis, pelvic inflammatory disease can also increase its levels in premenopausal women. Earlier reports have shown sensitivity and specificity of less than 80% for this marker in prediction of ovarian cancers.[10] Authors reported a sensitivity of 81.8% and a specificity of 55.7%, a positive predictive value of 25%, a negative predictive value of 94.4%, and positive and negative likelihood ratio of 1.8 and 0.3 respectively for CA-125. A sensitivity of 78.6% and specificity of 63.5% for a CA 125 at cut off of 35U/m have been reported by others.[8,11] The ROC analysis plotted from this study shows a high sensitivity 82% and a specificity 75%, at a cut off value of 68.6 for CA 125 demonstrating significant predictive ability. It is suggested that moderately elevated CA125 in this study patients are also contributed by higher prevalence of inflammatory and non-specific uterine and ovarian pathology, like endometriosis, benign cysts and pelvic infection.

Both higher sensitivity, specificity, and positive and negative predictive values for a postmenopausal score of 3 and higher specificity and negative predictive value, but lower sensitivity and positive predictive value in assessing malignancy risk for this parameter has been reported by some.[8,12] Their findings are comparable to this study with a sensitivity and specificity of 54.6% and 80.3% respectively. Authors also had a high negative predictive value of 90.7% for this parameter.

Risk of malignancy index (RMI) has proven its success in discriminating benign and malignant adnexal masses compared with individual parameters such as USG score, CA125 and menopausal status. All versions of RMI (RMI, 1, 2, 3) were validated by many retrospective and prospective studies, and the best cut off value for RMI was found to be 200, with a sensitivity of 81-92%, a specificity of 82-85%.[5,6,13,14]

The RMI cut-offs in many studies ranged from 25 to 250.[15] The most accurate cut-off value for the RMI has been investigated and a value of >200 was found to be best with a sensitivity, specificity, a positive predictive value and a negative predictive value of 89-92%, 82-96%, 62-98% and 77-98% respectively.[7,16] A study on 143 patients reported a sensitivity of 85.4% and specificity 96.9% for this method at a cut off value of 200.[5] Other study found a sensitivity of 76% and specificity of 82% in 1996, and 74% and 91% respectively in 1999.[6] The ROC analysis for RMI at a cut off value of 205.8, exhibited the sensitivity and specificity of 81.8% and 85% respectively for predicting ovarian malignancy. A recent study reported an increased diagnostic accuracy and performance with an RMI cut off of 238 with a higher sensitivity of 89.5%, specificity 96.2%, positive predictive value of 77.3% and negative predictive value of 98.4%.[17] At a cut off of 250 in this study, authors reported a sensitivity of 63.4%, specificity of 88.5%, positive predictive value 50% (CI 26.8-73.2)and a negative predictive value NPV of 93.1% (CI 83.6-97.3), which are comparable to the majority of earlier reports employing similar cut off.[5,6,9,18-22]

CONCLUSION

Authors conclude, the risk of malignancy index is apparently able to identify the probability of malignant pelvic disease, by incorporating serum CA125 levels, USG morphology and menopausal status, performed individually in women with ovarian masses. This index is a simple score system which can be applied directly into clinical practice and might be of value in preoperative assessment, and their prompt triage and referral to expert care.

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