Original Article

Assessment of Diagnostic Value of Serum Ca-125 and Risk of Malignancy Index Scoring in the Evaluation of Adnexal Masses

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Abstract

Introduction: Adnexal masses have a wide spectrum with respect to the age of presentation, signs and symptoms, imaging findings, and histopathology report. **Materials and Methods:** This is a cross-sectional diagnostic study, conducted at All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India. The data were collected from department of gynecology over a period of 1½ years from June 2017 to December 2018. All women who were diagnosed to have an adnexal mass irrespective to age, parity, and menopausal status were included in the study. Ultrasonography of the abdomen with the pelvis was ordered in all patients followed by contrast-enhanced computed tomography or magnetic resonance imaging in selective patients. Tumor markers such as Ca-125 was measured, and risk of malignancy index (RMI) was calculated for each tumor. The clinical and imaging findings were correlated with intra-operative findings and finally with the histopathology examination report. **Results:** A total of 171 women were included in the study who were diagnosed to have adnexal mass. A total of 137 women (80.1%) had benign tumor (Group B), whereas 34 women (19.9%) were found to have malignant tumor (Group M). Mean age in Group B was 35.85 ± 12.46 and in Group M was 46.12 ± 13.46 (P = 0.001). Ca-125 was significantly higher in Group M (1350 U/ml) than Group B (175 U/ml) (P = 0.008). The RMI score was also found to significantly increased in Group M than Group B (P = 0.007). **Conclusion:** With respect to adnexal masses, both Ca-125, as well as RMI scoring, are important diagnostic tools. RMI scoring has a better overall diagnostic performance than Ca-125 in predicting malignancy.

Keywords: *Adnexal mass, Ca-125, ovarian malignancy, risk of malignancy index*

Introduction

Adnexal masses have a wide spectrum with respect to the age of presentation, signs and symptoms, imaging findings, and histopathology report.

Preoperative differentiation of adnexal masses whether benign or malignant is important to determine the optimal mode of management. Nongynecological adnexal masses are rare but should be considered in the differential diagnosis. Metastatic cancers as the stomach, colon, and breast can also present as adnexal masses.[1] The focus of evaluation should be to rule out malignancy. According to data reported by surveillance, epidemiology, and end result program, 2009–2013, the median age for the diagnosis of ovarian cancer was 63 years of which 69.4% of patients were 55 years or older.[2] Although chances of malignant ovarian masses are more in postmenopausal women, most adnexal masses in postmenopausal women are benign.[3] The most important risk factor associated with ovarian malignancy is age, with sharp increase in the incidence after menopause.[2] Other risk factors related

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to ovarian malignancy are a strong family history of breast and ovarian cancer, nulliparity, early menarche, late menopause, white race, primary infertility, and endometriosis.[4]

Diagnosis making requires a thorough history regarding risk factors, comprehensive examination, and other diagnostic modalities. transvaginal sonography (TVS) is the recommended imaging modality for a suspected pelvic mass. There is no superiority of computed tomography (CT)/magnetic resonance imaging (MRI) over TVS to recommend its routine use.[1] Tumor markers, especially Ca-125 is helpful in determining the risk of malignancy in an ovarian mass, although its use is far from accurate.

No individual measure such as demographic data, pelvic examination, ultrasonography (USG), or tumor marker (Ca-125) has been found to have significantly better performance in differentiating malignant to the benign ovarian tumor. Risk of malignancy index (RMI) was developed to predict whether an adnexal mass is benign or malignant which is a combination of these modalities. RMI 1 was developed in 1990, further modified in RMI 2 in 1996, and in RMI 3 in 1999. Subsequently, RMI 4 was introduced which included tumor size as an additional parameter.[5] The best cutoff value of RMI for the distinction between benign and malignant masses has been proved to be 200.[5]

The aim of the study was to identify women with adnexal masses and to categorize them on the basis of their malignant potential. Furthermore, to assess the diagnostic value of Ca-125 and RMI scoring in the evaluation of adnexal masses.

Materials and Methods

This study was a cross-sectional diagnostic study, conducted at a tertiary care center (All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India). The data were collected from gynecology department over a period of 1½ years from June 2017 to December 2018. All women who were diagnosed to have an adnexal mass, irrespective of age, parity and menopausal status were included in the study. The diagnosis of adnexal mass was made on the basis of the clinical examination and imaging findings. A thorough history followed by detailed clinical examination was done in all the women. All of them were evaluated using transvaginal or transabdominal USG for morphological features that would raise the clinician's level of concern regarding malignancy, like cyst size >10 cm, papillary or solid components, irregularity, presence of ascites, and high color Doppler flow, laterality, presence, and thickness of septations. USG Doppler, CT scan, or MRI were used selectively, only in cases of doubtful origin or suspicious malignancy. Tumor markers such as CA-125, CEA, CA-19-9, alpha fetoprotein (AFP), beta-human chorionic gonadotropin, and lactate dehydrogenase were done according to age and other tumor characteristics. RMI score (Ca-125 ×USG score ×menopausal score) was calculated for all the patients. USG score was measured on the basis of five criteria-bilateral, multilocular, presence of solid areas, ascites, and intra-abdominal metastasis. If none or one of the five criteria was present, a score of 1 was given, and a score of 3 was given if the 2–5 criteria were present. Similarly, menopausal score was calculated for each patient based on menstrual status. A score of 1 was given for premenopausal women and a score of 3 was given for postmenopausal women (more than 1 year of amenorrhea or age older than 50 years in women who had hysterectomy). All patients underwent surgical management. Laparoscopy was the preferred mode of treatment for presumed benign adnexal masses. Laparotomy was performed in patients with suspected malignancy. Fertility conservative approach was considered in adolescents and premenopausal women who had not completed childbearing. Clinical, imaging findings and RMI scoring were correlated with intraoperative findings and finally with the histopathology examination (HPE) report.

Data were tabulated and analyzed using IBM SPSS Statistics version 23, SPSS South Asia Pvt Limited, Bangalore, India. To elucidate the associations and comparisons between different categorical variables, Chi-square test was used as nonparametric test. Receiver operator characteristic (ROC) analysis was carried out, and the ROC curve was drawn to conclude on the sensitivity and specificity of Ca-125 and RMI scoring. $P < 0.05$ at 95% confidence interval (CI) was considered statistically significant.

Results

A total of 171 women were included in the study who were diagnosed to have adnexal mass. They were divided into two groups, benign (B) and malignant (M) on the basis of final HPE diagnosis for the purpose of the analysis. A total of 137 women (80.1%) had a benign tumor (Group B), while 34 women (19.9%) were found to have malignant tumor (Group M). The overall mean age in both the groups was 37.9 ± 13.3 years, ranging from 15 to 87 years. The mean age in Group B was 35.85 ± 12.46 years and in Group M was 46.12 ± 13.46 years. Distribution of adnexal mass was further evaluated in various age groups, and the differences were observed to be significant [Table 1]. Most of the women (63.7%) with adnexal masses were 21–40 years of age. Most

of the participants with benign tumors (56.7%) fell in the age category of 21–40 years, whereas malignant tumors (8.2%) were commonly observed in 41–60 years' old participants.

Menopausal status was observed to be significantly associated with the type of adnexal lesions [Table 2]. The proportion of benign lesions was much higher (67.8%) in the premenopausal state than malignant lesions (9.9%).

Four of 34 women in Group M (2.3%) were nulligravida. Symptoms were variable in all the women. The most common symptom was pain abdomen followed by abdominal distension.

Out of all benign lesions, most common was endometriotic cysts followed by ectopic pregnancy. The most common malignant lesion was serous carcinoma of the ovary. Table 3 depicts the various causes of benign and malignant lesions.

Ca-125 and RMI scoring was not done for patients with ectopic pregnancy (n = 24) and they were excluded from the analysis.

Table 4 shows bivariate analysis of Ca-125 values, USG score, menopausal score, and a composite RMI score with respect to types of adnexal mass and all were observed to be significantly associated.

Ascites was present in 16/34 (47%) women in Group M, while 9/113 (8%) women in Group B. The difference was statistically significant (P = 0.000). Tumors were bilateral in 26.5% cases in Group M, while 15.9% in Group B (P = 0.16).

Table 1: Age distribution of respondents with respect to the benign and malignant adnexal mass

Age by group (years)	Group B, *n* (%)	Group M, *n* (%)	Total, *n* (%)
≤20	6 (3.5)	1 (0.6)	7 (4.1)
21-40	97 (56.7)	12 (7)	109 (63.7)
41-60	28 (16.4)	14 (8.2)	42 (24.6)
>60	6 (3.5)	7 (4.1)	13 (7.6)
Total	137 (80.1)	34 (19.9)	171 (100)

Pearson χ^2: 20.421, df: 3, P: 0.000

Table 2: Association of menopausal status with types of adnexal masses

Menopausal status	Group B, *n* (%)	Group M, *n* (%)	Total, *n* (%)
Premenopausal	116 (67.8)	17 (9.9)	133 (77.7)
Postmenopausal	18 (10.5)	14 (8.2)	32 (18.7)
Surgical menopause	3 (1.8)	3 (1.8)	6 (3.6)

Pearson χ^2: 11.635, df: 2, P: 0.003

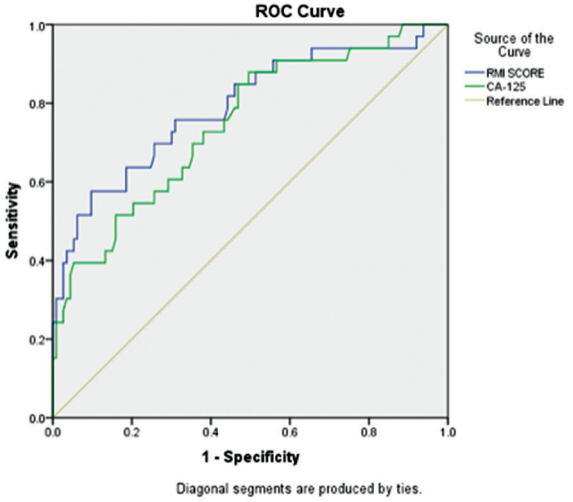
Mean age, Ca-125 value, and RMI score were found to be significantly higher in Group M than Group B as shown in Table 5.

Figure 1 shows area under the curve, which is a combined measure of sensitivity and specificity. It was reported to be 0.790 (95% CI 0.694–0.886) for RMI levels and 0.747 (95% CI 0.650–0.843) for Ca-125 levels, which indicate a good performance of both the tests. The P value was also reported to be significant for both the variables. RMI scoring was found to have a better overall diagnostic performance than Ca-125 in predicting malignancy.

In postmenopausal women, RMI score were highly predictive of malignancy. Almost 93% women had a RMI score of >200 (χ^2 = 13.55; P = 0.00).

Discussion

Adnexal masses have a wide spectrum of etiology from benign to malignant tumors which include both gynecological or nongynecological causes (e.g., functional cyst, paraovarian cyst, hemorrhagic cyst, tubo-ovarian mass, hydrosalpinx, ectopic pregnancy, broad ligament fibroid, benign and malignant ovarian



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
RMI	.790	.049	.000	.694	.886
CA-125	.747	.049	.000	.650	.843

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1: Receiver operator characteristic curve for Ca-125 and risk of malignancy index scoring

Table 3: Distribution of various types of benign and malignant tumors

Types of tumours	*n* (%)
Benign tumours	137
Endometrioma	39 (28.5)
Ectopic pregnancy	24 (17.5)
Serous cystadenoma	16 (11.7)
Mature cystic teratoma	14 (10.2)
Follicular cyst	11 (8.0)
Mucinous cystadenoma	10 (7.3)
Broad ligament fibroid	6 (4.4)
Tuberculosis	5 (3.6)
Hemorrhagic cyst	3 (2.2)
Serous adenofibroma	2 (1.5)
Fibroma	2 (1.5)
Hydrosalpinx	2 (1.5)
Struma ovarii	2 (1.5)
Sex cord stromal tumor	1 (0.7)
Malignant tumors	34
Serous carcinoma of ovary	12 (35.3)
Adenocarcinoma of ovary	6 (17.6)
Endometriod adenocarcinoma of ovary	3 (8.8)
Mucinous carcinoma of ovary	3 (8.8)
Krukenberg's tumor	2 (5.9)
Brenner's tumor	1 (2.9)
Clear cell carcinoma	1 (2.9)
Dysgerminoma	1 (2.9)
Granulosa cell tumor	1 (2.9)
immature teratoma	1 (2.9)
Brenner's tumor	1 (2.9)
Clear cell carcinoma	1 (2.9)
Dysgerminoma	1 (2.9)
Granulosa cell tumor	1 (2.9)
immature teratoma	1 (2.9)
Mixed seromucinous tumor	1 (2.9)
Serous carcinoma of fallopian tube	1 (2.9)
Sertoli leydig-sex cord tumor	1 (2.9)

Table 4: Bivariate analysis of various scores and types of adnexal mass

	Group B (*n*=113), *n* (%)	Group M (*n*=34), *n* (%)	*P*
Ca-125 U/ml			
<35	66 (58.4)	9 (26.5)	0.001
>35	47 (41.6)	25 (73.5)	
USG score			
1	96 (85)	12 (35.3)	0.00
3	17 (15)	22 (64.7)	
Menopausal score			
1	94 (83.2)	20 (58.8)	0.003
3	19 (16.8)	14 (41.2)	
RMI scoring			
<200	99 (87.6)	14 (41.2)	0.000
>200	14 (12.4)	20 (58.8)	

RMI: Risk of malignancy index, USG: Ultrasonography

tumors, carcinoma of fallopian tube, colonic malignancy). Such a wide range presents as a diagnostic dilemma. The primary modality for the detection and characterization of the adnexal mass is USG and the gold standard is HPE for which the tissues are available only after surgery. Accurate preoperative assessment to differentiate benign or malignant nature of an adnexal mass is essential for the optimum management. The analysis of data related to patient demographics, tumor morphology by USG, serum Ca-125, and calculation of RMI helps in estimating the risk of malignancy in a woman with adnexal mass.

In the present study, 81% adnexal masses were originated from ovary. Approximately 76% of ovarian tumor were benign and 24% were malignant. Most of the ovarian malignancies present in the age ranges from 41 to 60 years. In our study, 26% (9 out of 34) patients with malignant adnexal masses had bilateral tumors. Seventy four percent (25/34) patients had a raised value of Ca-125 (>35 U/L). RMI Score was >200 in 59% (20/34) of the malignant adnexal masses.

Most adnexal masses in postmenopausal women are benign neoplasms, such as cystadenomas, but the risk of malignancy is much greater than in premenopausal women.[1] In our study, 19 out of 34 women with malignant adnexal mass were found in premenopausal patient. Hence, there should be a high index of suspicion in women with complex or heterogeneous mass on USG and a high Ca-125 value even in premenopausal women.

Ca-125 is the most extensively studied tumor marker for predicting the risk of malignancy. It is raised in 80% of epithelial ovarian cancer but efficacy is comparatively low in Stage 1 malignancy.[6] In differentiating benign to malignant disease, it has a sensitivity of 61%–90%, specificity of 71%–93%, positive predictive value of 35%–91%, and negative predictive value of 67%–90%.[7] Although the ability of Ca-125 to predict cancer risk in premenopausal women is less as compared to in postmenopausal women, its extreme value should raise the suspicion for malignancy. According to recent American college of obstetricians and gynecologist 2016 practice Bulletin[1] there is no higher threshold for Ca-125 for referral to a gynecological oncologist which earlier was 200 U/ml.

McDonald *et al.*[8] reported the association of Ca-125 >35U/ml and complex solid mass on USG with either borderline and malignant ovarian cancer in more than three fourth of patients. In our study, a total 72 out of 147 patients (49%) had raised Ca-125 (>35U/ml), of which, 25 were found to have malignancy on final HPE. Only nine patients with Ca-125 value of <35U/ml had malignancy.

Table 5: Mean age, cancer antigen-125 and risk of malignancy index score distribution between benign and malignant cases

Variables	Mean±SD		*t*	*P*
	Group B (*n*=113)	Group M (*n*=34)		
Age	37.3±12.9	46.1±13.5	−3.47	0.001
Ca-125	75.1±175.4	737.3±1350.0	−2.81	0.008
RMI score	152.2±538.9	4167.2±8175.6	−2.86	0.007

P<0.05 is considered significant. SD: Standard deviation, RMI: Risk of malignancy index

The best cutoff value of RMI for the distinction between benign and malignant masses has been proved to be 200.[5] In the present study, of 147 cases, 34 cases had elevated RMI (>200), of which, 20 cases were malignant. The remaining 14 cases who had false polite results were 7 cases of endometriosis, 3 case of tuberculosis, 2 cases of fibroma, and 2 cases of serous cystadenoma. Of 113 cases with RMI <200, 14 cases turned out to be malignant (granulosa cell tumor, clear-cell carcinoma, Krukenberg tumor, Sertoli-Leydig cell tumor, serous carcinoma of fallopian tube, and serous cystadenocarcinoma). RMI has got better diagnostic performance for predicting malignancy in our study which is comparable to other studies.[5,9-11] The diagnostic performance of RMI further improved in postmenopausal women (χ^2 = 13.55, *P* = 0.00). Of 33 postmenopausal women, 18 had RMI >200, of which 13 were malignant and 15 had RMI of <200, of which only one women had malignancy.

The possible limitation of the study is that the data were collected from a single institution, which might have bias in relation to different regions. Therefore, studies which involve multiple centers and with large sample size is required.

Conclusion

With respect to adnexal masses, both Ca-125 and RMI scoring are important diagnostic tools. RMI scoring has a better overall diagnostic performance than Ca-125 in predicting malignancy. RMI scoring improves the prognosis of patient with ovarian malignancy and it provides the general gynecologist an option to refer patient with suspected malignancy to oncologist.

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Conflicts of interest

There are no conflicts of interest.

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