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Original Research Article

Comparison of RMI 3 and RMI 4 in pre-operative evaluation of ovarian masses

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ABSTRACT

Background: To differentiate ovarian mass as benign or malignant could change clinical approach. Finding a screening and diagnostic method for ovarian cancer is challenging due to high mortality and insidious symptoms. Risk malignancy index (RMI) has the advantage of rapid and exact triage of patients with ovarian mass.
Methods: Prospective study carried for 2 years at NRI Medical College and General Hospital, Chinakakani, Mangalagiri, Andhra Pradesh, India. 79 patients with ovarian mass were investigated and risk malignancy index (RMI-3 and RMI-4) calculated. Final confirmation was done based on histopathological report. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for RMI 3 and RMI 4 taking histopathology as control and comparison was done.
Results: (n=79); 50 (63.29%) cases were benign and 29 (36.70%) were malignant based on histopathology. RMI 4 is more sensitive (68.96%) than RMI 3 (62.06%), but RMI 3 is more specific (94%) than RMI 4 (92%).The positive predictive value of RMI-3 and RMI-4 were 85.71% and 83.33% respectively. The negative predictive value for RMI-4 and RMI-3 were 83.63% and 81.03% respectively.
Conclusions: With increasing age, chance of malignancy increases. RMI 4 was more sensitive than RMI-3, however less specific than RMI 3 in differentiating benign and malignant tumors. The positive predictive value is slightly more for RMI 3, than RMI 4. Negative predictive value is slightly more for RMI 4, than RMI 3.

Keywords: CA-125, Ovarian Mass, Risk malignancy index, Ultrasonography

INTRODUCTION

Women with ovarian cancer have a better prognosis if the full surgical staging procedure is carried out initially by a trained gynecological oncologist. Therefore, preoperative knowledge of the nature of the adnexal mass is necessary so that optimal surgery can be planned at the time of initial treatment. The challenge for general gynecologists has been how to differentiate a benign adnexal mass from a malignant one so that an appropriate referral can be made preoperatively. The risk of malignancy index (RMI) has been shown to be a triage tool with the potential to reduce the workload in a busy gynecological unit.

Risk malignancy index (RMI) is an equation obtained by multiplying the results of Ultrasonography score (U), the menopause score (M) and the absolute value of serum CA -125. Both RMI 3 and 4 uses the same basic formula but differs in the scores that were assigned to U and M. RMI 4 includes tumor size(S) measured by ultrasonography.[1]

According to data from the United States; each year about 300,000 women are hospitalized because of adnexal masses. 13-21% of these women have malignant adnexal masses.[2,3] In women deaths, ovarian cancer is the fifth cancer type.[4] According to the American Cancer Society data; more than 21,000 new cases were diagnosed in 2014-15 and approximately 14,000 women died because of ovarian cancer.[5] The 5-year survival rate is about 30% in patients diagnosed with advanced stage. Whereas in the cases diagnosed at an early stage, the 5-year survival rate is about 90%.[6] Thus early diagnosis is important. However, due to nonspecific complaints, the majority of the cases are diagnosed at advanced stages.

In gynecological malignancies; tumor markers have a crucial role in screening, monitoring of treatment, follow-up and also for predicting recurrence of the disease.[7] CA - 125 levels increases in only 50% of early stage ovarian cancer and 90% of late stage ovarian cancer. Moreover, elevated CA-125 levels may be observed in the variety of the conditions, such as ascites, menstruation, endometriosis, pelvic inflammatory diseases, liver diseases, and other malignant conditions (pancreas, breast, lung, and colon).[8] Finding a screening and diagnostic method for ovarian cancer is challenging due to high mortality and insidious symptoms. In 1990, Jacobs et al. initially developed RMI 1 that is a simple scoring method based on menopausal status, ultrasound findings and serum CA-125 level.[9] Tingulstad et al, developed RMI 2 in 1996 and then RMI 3 in 1999.[10,11] Yamamoto et al, added the parameter of tumor size to RMI scores and developed RMI 4 in 2009.[12]

National Institute of Clinical Excellence and Royal College of obstetrics and gynecology guidelines accepts Risk of Malignancy Index as the best model.[13-15] Studies showed until now; RMI scoring system has the advantage of rapid and exact triage of the patients. Nevertheless, the literature shows that different populations have different sensitivity and cut-off values1.[16]

The present study is conducted to compare the ability of RMI 3 and RMI 4 in preoperative differentiation of benign and malignant ovarian masses so that the patient with malignant ovarian mass can be referred to gynecological oncology and to compare the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of RMI 3 and RMI 4.

METHODS

This is a prospective study carried out between August, 2014 to October, 2016 in the Department of Obstetrics and Gynecology, NRI Medical College and General Hospital, Chinakakani, Mangalagiri, Andhra Pradesh, India.

Patients with clinical diagnosis of ovarian mass, who were admitted in the pre-operative ward in the Department of Obstetrics and Gynecology, were included in the study.

Inclusion criteria

- All women with clinical diagnosis of having ovarian mass.

Exclusion criteria

- Proven cases of malignant tumors like biopsy of tumor or cytology of ascetic fluid
- Previous history of genital malignancy
- Past history of chemotherapy or radiotherapy.

A total of 79 patients with clinical diagnosis of ovarian mass were included in the study. They were subjected to detailed history, routine investigations and specific investigations like CA-125 and Ultrasound. RMI 3 and RMI 4 (Table1) was calculated and diagnosed clinically as having either benign or malignant ovarian tumor based on cut-off value. RMI 3 below 200 was considered benign and those with values above 200 were considered malignant. RMI 4 below 450 was considered benign and those with values above 450 were considered malignant. After performing laparotomy and sending the specimen for histopathology, final confirmation was done as either benign or malignant ovarian mass.

Statistical analysis

Data obtained was subjected to statistical analysis and sensitivity, specificity, positive predictive value and negative predictive value was calculated for RMI 3 and RMI 4 taking histopathology as control and comparison was done.

RESULTS

Out of 79 cases 50 (63.29%) cases were confirmed as benign ovarian tumor and 29 (36.70%) cases were confirmed as malignant ovarian tumor based on histopathology reports. Majority were benign cases accounting to 63.29%. Malignant cases accounts to 36.70%.

Most of cases were between 31-40 years of age group accounting to 32.91% (26 cases). Patients between 41-50 years age group were 20 (25.31%), 51-60 years age group were 15 (18.98%), 21-30 years age group were 9 (11.39%), above 60 years age group were 7 (8.86%), below 20 years age group were 2 (2.53%).

Malignant case was seen in 4 (20%) cases in 41-50 years of age group, 6 (23.08%) cases in 31-40 years of age group, 3 (33.33%) cases in 21-30 years of age group, 10 (66.67%) 51-60 years age group. 48 cases (60.75%) and 31 (39.24%) were premenopausal and postmenopausal women respectively. Post-menopausal women had higher incidence (19 out of 31 cases) of malignant ovarian

tumors when compared to pre-menopausal women (10 out of 48 cases). Benign ovarian tumors were more in pre-menopausal women (38 out of 48 cases) and less in post-menopausal women (12 out of 31 cases).

Table 1: Risk of malignancy index (RMI) scoring system.[1]

Parameters	RMI 1	RMI 2	RMI 3	RMI 4
Ultrasonography score (U)				
No features	0	1	1	1
1 feature	1	1	1	1
≥ 2 features	3	4	3	4
Menopausal status (M)				
Premenopausal	1	1	1	1
Postmenopausal	3	4	3	4
Ca-125 (U/mL)	-	-	-	-
Tumor size (S)				
< 7cms	-	-	-	1
≥7 cms	-	-	-	2

Formula for RMI 1,2,3 = U x M x CA-125 value; Formula for RMI 4 = U x M x CA-125 x S

43 cases (54.43%) had CA- 125 less than 35, whereas 36 (45.56%) had CA -125 more than 35. 13 cases had 0 Ultrasound (USG) variables, 32 cases had 1 variable and 34 cases had >1 variable on USG. Ultrasonography findings showed that as the variables of USG increases (USG Score) chance of malignancy increases. Distribution of cases based on USG score as benign and malignant are shown in Table 2.

Table 2: Distribution of cases based on USG score as benign and malignant.

USG score	Benign (%)	Malignant (%)
0	13 (16.45)	0
1	25 (31.64)	7 (8.86)
>1	12 (15.18)	22 (27.84)

Table 3: Distribution of cases as positive and negative according to RMI 3 and RMI 4.

Method	True negative	False negative	True positive	False positive
RMI 3	47	11	18	3
RMI 4	46	9	20	4

Table 4: Comparison of RMI-3 and RMI-4.

Index	Sensitivity	Specificity	PPV	NPV
RMI 3	62.06%	94%	85.71%	81.03%
RMI 4	68.96%	92%	83.33%	83.63%

With RMI-3, 47 cases were identified correctly as benign and 18 cases were identified correctly as malignant. With RMI- 4, 46 cases were identified correctly as benign and 20 cases were identified correctly as malignant (Table 3).

3 cases with RMI-3 showed one each of serous cystadenoma, mucinous cystadenoma and dermoid cyst, 4 cases with RMI- 4 showed one each of serous cystadenoma, dermoid cyst and 2 cases with mucinous cystadenoma were false positive.

RMI-3 and RMI-4 showed one each as serous cystadenocarcinoma, immature teratoma, germ cell tumor, adenocarcinoma, borderline tumor, mixed serous and mucinous tumor, 3 cases as granulosa cell carcinoma and one each as mucinous cystadenocarcinoma and metastatic carcinoma by RMI-3 were false negative. Low level of CA -125 and low USG score explains the false negative.

Sensitivity for RMI 3 is 62.06% and for RMI 4 is 68.96%. Specificity for RMI 3 is 94% and for RMI 4 is 92%. The positive predictive value for RMI 3 is 85.71% and for RMI 4 is 83.33%. The negative predictive value for RMI 3 is 81.03% and for RMI 4 is 83.63% (Table 4).

Mucinous cyst adenoma was the common benign ovarian tumour identified in this study and accounting to about 19 cases (38%), followed by serous cystadenoma accounting to 10 cases (20%), Simple cysts 7 (14%), Dermoid 7 (14%), Endometriotic cysts 2 (4%), corpus luteal cysts 1 (2%) and others 4 (8%). Serous cystadenocarcinoma was the most common variety found in this study with 12 (41.37%) cases out of 29 malignant cases followed by mucinous cyst adenocarcinoma accounting to 4 (13.79%). Granulosa cell carcinoma was seen in 3 (10.34%) cases. Metastatic carcinoma was seen in 2 (6.89%) cases, adenocarcinoma was seen in 2 (6.89%) cases. Mixed serous and mucinous carcinoma, immature teratoma, mixed germ cell tumour, clear cell carcinoma,

dysgerminoma and borderline tumors each were seen in 1 (3.44%) case.

Table 5: Comparison of sensitivity indices of RMI in various studies.

Study	Sensitivity
Kumari N et al,[18]	63.63% (RMI 1 and 3)
	77.27% (RMI 2 and 4)
Kulkarni KA et al,[23]	82% (RMI 2)
	79% (RMI 4)
Ozbay O et al,[26]	60% (RMI 1)
	63% (RMI 3)
	67% (RMI 2 and 4)
Yamamoto Y et al,[19]	73% (RMI 1 and 3)
	81.1% (RMI 2)
	77% (RMI 4)
Insin P et al,[20]	62% (RMI 1)
	71% (RMI 2)
	64% (RMI 3)
	69% (RMI 4)
Yavuzcan et al,[28]	75%
Sayanesh et al,[27]	72%
Ashrafgangooei T et al,[16]	89.5%
Hakansson F et al,[29]	92%
Bouzari Z et al,[30]	91% (RMI 1,2 and 3)
Yamamoto Y et al,[12]	75% (RMI 1,2 and 3)
	86.8% (RMI 4)
Geomini et al,[31]	78%
Mooltiya et al,[21]	70.6% (RMI 1)
	80% (RMI 2)
Morgante et al,[22]	81%
Tingulstad et al,[11]	71%
Tingulstad et al,1[0]	71%
Jacobs et al,[9]	85.4%
Enakpene et al,[24]	88.2%
Present study	62.06% (RMI 3)
	68.96% (RMI 4)

DISCUSSION

Excluding malignancy is typically a two-phase process. An initial evaluation is performed to establish the degree of clinical suspicion that a mass is malignant. If malignancy is suspected, surgical exploration is performed to make a definitive diagnosis.

The likelihood that an ovarian mass is malignant depends mainly upon one or more of the following factors 17, age or menopausal status, physical examination, risk factors, imaging study findings those are consistent with malignancy, laboratory results like CA -125. Survival from ovarian cancer is related to the stage at diagnosis.

The sensitivity index of RMI 3 was 62.06% and RMI 4 was 68.96%. The sensitivity index of RMI 4 is more than that of RMI 3. It means that RMI 4 is able to correctly identify the malignant ovarian tumors, when compared to RMI 3.

Table 6: Comparison of specificity indices of RMI in various studies.

Study	Specificity
Ertas S et al,[25]	91.5%
Yamamoto Y et al,[19]	93.7%
	92.3%
Yavuzcan et al,[28]	91%
Sayanesh et al,[27]	94%
Yamamoto Y et al,[12]	91%
Tingulstad et al,[11]	92%
Present study	94% (RMI 3)
	92% (RMI 4)

Table 7: Comparison of positive predictive value of RMI in various studies.

Study	PPV
Ertas S et al,[25]	79.1%
Kulkarni KA et al,[23]	89%
	82%
Yamamoto Y et al,[19]	79.4%
Tingulstad et al,[10]	89%
Present study	85.71% (RMI 3)
	83.33% (RMI 4)

Table 8: Comparison of negative predictive value of RMI in various studies.

Study	NPV
Ertas S et al,[25]	88.1%
KumarI N et al,[18]	84.37%
Ozbay O et al,[26]	88%
	89%
Insin P et al,[20]	80%
Mooltiya et al,[21]	80.6%
	85.1%
Tingulstad et al,[10]	88%
Present study	81.03% (RMI 3)
	83.63% (RMI 4)

The specificity index of RMI 3 was 94% and RMI 4 was 92%.The specificity index of RMI 3 is more than that of RMI 4. The positive predictive value is slightly more for RMI 3 (85.71%) than RMI 4 (83.33%). The negative predictive value is slightly more for RMI 4 (83.63%), than RMI 3 (81.03%). In this study it was found that RMI 4 was more sensitive and RMI 3 was more specific.

Percentage of premenopausal women (60.75%) in present study is comparable with Kumari N et al, (56.92%), Yamamoto Y et al, (65%), Insin P et al, (56.86%), Mooltoya et al, (57.9%), and Morgante et al, (55.64%) studies.[18-22]

Percentage of postmenopausal women (39.24%) with ovarian masses in present study is comparable with Kulkarni KA et al, (44.1%), Kumari N et al, (43.07%), Insin P et al, (43.13%), Mooltiya et al, (42.1%), Morgante et al, (44.35%) studies.[18,21-23]

Ovarian malignancy is seen in 20.83% of premenopausal women in present study which is comparable with Kumari N et al, (24.32%) and Mooltiya et al, (23.96%) studies.[18,21]

Ovarian malignancy is seen in 61.29% of postmenopausal women in present study is comparable with Kulkarni KA et al, (56.2%), Kumari N et al, (57.14%), Ashrafgangooei et al, (57.19%) studies.[16,18,23]

Sensitivity of CA 125 (68.96%) in differentiating benign and malignant Ovarian masses preoperatively is comparable with Kumari N et al, (64%), Insin P et al, (75.51%), Enakpene et al, (72%) studies.[18,20,24] Specificity of CA 125 (68%) in present study is comparable with Kumari N et al, (72.5%) study.[18] PPV of CA - 125 (55.55%) in present study is comparable with Ertas S et al, (56.7%), Kumari N et al, (59.25%), Insin P et al, (50.68%) studies.[18,20,25] NPV of CA 125 (79.06%) in present study is comparable with Kumari N et al, (76.31%), Insin P et al, (77.98%) and Enakpene et al, (78%) studies.[18,20,24] Specificity of USG in present study (76%) is comparable with Insin P et al, (73.24%) study.[20]

The sensitivity index of RMI 3 and 4 in the present study are 62.06% and 68.96% respectively which is comparable to Kumari N et al, (63.63%), Ozbay O et al, (60% and 63%), Yamamoto Y et al, (73%), Insin P et al, (62%, 71% and 64%), Sayanesh et al, (72%), Yavuzan et al, (75%), Hakansson F et al, (92%), Bouzari Z et al, (91%-RMI 1,2,3), Geomini et al, (78%), Mooltiya et al, (70.6%) and Tingulstad et al, (71%) (Table 5).[10,11,18,21-31]

The specificity index of RMI 3 and 4 in the present study (94% and 92%) respectively is comparable to Ertas S et al, (91.5%), Yamamoto Y et al, (93.7%, and 92.3%), Yavuzcan et al, (91%), Sayanesh et al, (94%), Yamamoto Y et al,, (91%) and Tingulstad et al, (92%) studies (Table 6).[11,12,19,25-28]

The positive predictive value of RMI 3 and 4 in the present study (85.71% and 83.33%) is comparable to Ertas S et al, (79.1%), Kulkarni KA et al, (82% and 89%), Yamamoto Y et al, (79.4%), Tingulstad et al, (89%) respectively (Table 7).[10,19,23,25]

The NPV of RMI 3 and 4 in the present study (81.03% and 83.63%) is comparable to Kumari N et al, (84.37%), Insin P et al, (80%), Mooltiya et al, (80.6% and 85.1%) studies (Table 8).[18,20,21]

The limitation of this study is that it is with a small sample size. A significant problem associated with CA-125 is that it can be expressed in numerous benign and malignant conditions, which leads to false positive results and it is only expressed by about 50% of early stage ovarian cancers, which leads to false negative results.[32]

Another tumor marker which has gained attention is the human epididymis secretory protein 4 (HE4). HE4 is expressed in 100% of endometrioid adenocarcinomas, 93% of serous adenocarcinomas and 50% of clear cell ovarian cancers but not expressed in normal surface epithelium.[33]

Moore et al, developed an algorithm, the risk of malignancy algorithm (ROMA), which is based on both CA-125 and HE4. They studied the RMI and ROMA in 457 patients; the results were the ROMA had a sensitivity of 94.3% while the RMI had a sensitivity of 84.6% (p=0.0029).[34]

Thus, if we use the combined HE 4 with CA -125 we may improve the sensitivity and specificity for distinguishing malignant from benign ovarian tumors but the disadvantages of HE 4 are that it is expensive and difficult to perform in peripheral centers.

Other models of preoperative evaluation should be developed to improve the detection of borderline ovarian tumors.

CONCLUSION

Increasing age, CA-125 >35 U/ml, more number of variables on USG will increase the chance of the tumor being malignant. RMI 4 was more sensitive among the two indices studied, however less specific than RMI 3 in differentiating benign and malignant tumors. The positive predictive value is slightly more for RMI 3, than RMI 4. The negative predictive value is slightly more for RMI 4, than RMI 3. Overall RMI- 4 appears to be the more The RMI is a good diagnostic tool to differentiate between benign and malignant ovarian tumors.

RMI is a simple index which can be used in daily gynecological practice in suspicious and high risk cases so as to identify malignancy in ovarian tumors at an early stage, so that 5 year survival rate can be improved.

Combination of HE 4 with CA -125 may improve the sensitivity and specificity for distinguishing malignancy from benign ovarian tumors but the disadvantages of HE 4 are that it is expensive and difficult to perform in peripheral centers.

Other models of preoperative evaluation should be developed to improve the detection of borderline ovarian tumors.

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