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ORIGINAL ARTICLE

An Evaluation of the Applicability of the Risk of Malignancy Index for Adnexal Masses to Patients Seen at a Tertiary Hospital in Chandigarh, India

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Abstract

Back ground The discrimination between benign and malignant ovarian tumors is important considering to optimally plan for an appropriate surgical treatment.

Aims To determine the applicability of risk of malignancy index (RMI 2) for triaging patients with adnexal masses seen at tertiary care hospital in India.

Subjects and Methods A retrospective case note review of patients with adnexal masses admitted in Gynecology department was done. RMI 2 was calculated for each patient using ultrasound score, menopausal status, and CA-125 levels (U/ml), and the value of RMI was compared to the histological diagnosis. Statistical analyses were performed using SPSS version 17.0 by descriptive and inferential statistics. The p value ≤ 0.05 was considered significant.

Results The Mean age and SD of hundred patients was 52.8 (10) years. Most of the patients were postmenopausal (68/100). A significant relationship of ovarian malignancy was found with increasing age, high ultrasound score, and high serum CA-125. The average value of CA-125 in benign and malignant ovarian tumor was 7.4 and 625, respectively. The RMI 2 at a cut-off value of 200 had a sensitivity of 96.7 %, specificity of 84 %, positive predictive value of 85.5 %, and negative predictive value of 67.7 %.

Conclusion Our study confirms the applicability of RMI 2 >200 in diagnosing adnexal masses with high risk of malignancy. It can be easily introduced into clinical

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practice to facilitate the selection of the patients for surgery and also helpful in triaging patients to different treatment groups.

Keywords Ovarian cancer · Ultrasound score · Menopausal status · CA-125

Introduction

Ovarian cancer has emerged as one of the most common gynecological malignancies affecting women. In India, it is the fourth most common malignancy among females. The age-standardized incidence rates (ASR) for ovarian cancer varied from 0.9 to 8.4 per lac during the period 2001–2006. Age-specific incidence rate (ASIR) found that ovarian cancer increases from 35 years and reaches a peak between 55 and 64 years [1]. The factors associated with an increased risk include older age, race (white), nulliparity, and family history of ovarian, endometrial, or breast cancer [2].

As the symptoms of the ovarian cancer are very vague like bloating, pelvic or abdominal pain, poor appetite, feeling full quickly, and urinary urgency, it is also known as "silent killer." Thus, silent occurrence and slow progression, added to the fact that few effective methods for early diagnosis exist, make its mortality rate the highest among gynecologic malignancies [3]. The main challenge is to identify patients with high-risk adnexal masses preoperatively and this is compounded by the lack of definitive noninvasive diagnostic tests. Currently the conventional modalities like clinical examination, ultrasound assessment, and tumor marker assay are used to assess pelvic mass, but as been demonstrated by various studies, none is alone sufficiently sensitive and specific for detecting malignancy in ovarian masses [4]. The use of transvaginal ultrasound (TVS) and CA-125 for screening the general population was studied in Prostate, Lung, Colorectal, and Ovarian screening trial presented at American society of Cancer oncology in 2011. This study included 78,216 asymptomatic women from the general population aged 55–74 years between 1993 and 2001, who were randomized to undergo either annual screening with CA-125 and TVS or usual care and followed for diagnosis of ovarian cancer until 2010. The study concluded that screening with both CA-125 and TVS did not decrease the risk of ovarian cancer mortality and unnecessarily increase the number of false positives [5].

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. [6], which was termed as RMI 1. RMI 1 is a product of ultrasound findings (U), the menopausal status (M), and serum CA-125 levels (RMI = $U \times M \times$ CA-125). In 1996, RMI 1 was modified by Tingulstad et al. [7] and known as RMI 2. RMI 2 was again modified in 1999 and termed as RMI 3 [8]. The difference between three scores is based on how U and M are assigned.

- RMI 1 = $U \times M \times$ CA-125; ultrasound score of 0 is $U = 0$, score of 1 is $U = 1$, and a score of 2 is $U = 3$. Premenopausal is $M = 1$ and postmenopausal is $M = 3$.
- RMI II = $U \times M \times$ CA-125; ultrasound score of 0 or 1 is $U = 1$, and score of 2 is $U = 4$. Premenopausal is $M = 1$ and postmenopausal is $M = 4$.
- RMI III = $U \times M \times$ CA-125; ultrasound score of 0 or 1 is $U = 1$, and score of 2 is $U = 3$. Premenopausal is $M = 1$ and postmenopausal is $M = 3$.

Recently in 2009, Yamamoto et al. created their own model of a malignancy risk index. They added the parameter of the tumor size (S) to the RMI and have termed it the RMI 4. The formula used for calculating RMI 4 was $U \times M \times S$ (size in centimeters) $\times$ CA-125, A tumor size of <7 cm made $S = 1$, and ≥ 7 cm made $S = 2$. The serum level of CA-125 was applied directly to the calculation [9].

Several studies have compared these scoring indices. A retrospective study included 209 women of pelvic masses admitted for laparotomy, RMI 1 and RMI 2 at a cut-off level of 200 were calculated for each patient and compared. They found that RMI 2 gave sensitivity of 80 %, specificity of 92 %, and positive predictive value (PPV) of 83 % as compared to RMI 1 which gave 71 % sensitivity, 96 % specificity, and 89 % PPV [10]. In a prospective study, Aslam et al. enrolled sixty-one women of known adnexal masses that were examined preoperatively, using RMI 1, RMI 2, and Tailor's regression model. This study concluded that these diagnostic models were less accurate when applied prospectively than original reported [11]. Recent study published in 2011 compared the three indices and CA-125, retrospectively, in 182 women with pelvic masses and concluded that there was no statistically significant difference between three scoring algorithms and CA-125 levels in differentiating between benign and malignant adnexal masses [12].

The aim of this study was to evaluate the performance of RMI 2 as a predictive method to discriminate between benign and malignant adnexal masses and its applicability in our setting of a tertiary care hospital at Chandigarh. The study was planned in such a way that it did not affect the normal diagnostic guidelines followed by the doctors of the institute.

Subjects and Methods

This study was a retrospective case note review to evaluate the applicability of RMI in our Institute. The patients admitted with adnexal masses, in the department of

Obstetrics and Gynecology at Government Medical College Chandigarh, were studied between January 2007 and December 2008. The patients were selected and data related to age, menstrual history, symptoms at diagnosis, presence of ascites, CA-125 levels, and ultrasound findings were abstracted and coded into SPSS software. The exclusion criteria were the patients with incomplete medical records and which did not had their histopathology reports in spite of all the other parameters.

The histopathological reports from surgically removed ovarian tissues were retrieved, and the tumors were classified according to FIGO (International Federation of Gynecological Obstetrics) recommendations [13]. After calculating the RMI, the histopathological diagnosis was considered as the gold standard for comparing the outcomes.

Calculations of RMI 2 score

For our study group, we chose RMI 2 scoring system which was calculated for each patient using formula:

$$\text{RMI 2 score} = \text{Ultrasound score } (U) \times \text{Menopausal status } (M) \times \text{CA} - 125 \text{ levels } (\text{U/ml}).$$

Ultrasound scans were scored as one point for each of the following characteristics: multilocular cyst, evidence of solid areas, evidence of metastasis, presence of ascites, bilateral lesions using the scoring system. The total ultrasonography score of 0 gave $U = 0$, a score of 1 gave $U = 1$ and a score of ≥ 2 gave $U = 4$.

The score of premenopausal status $M = 1$ and for postmenopausal status $M = 4$. The classification of "postmenopausal" is a woman who had no period for more than 1 year or a woman over 50 who had a hysterectomy.

The serum levels of CA-125 were taken in U/ml and CA-125 were determined by using advanced chemiluminescence (ACS): 180 plus in the department of Biochemistry. The levels of <35 U/ml were considered to be normal.

The cut-off levels for RMI 2 score were taken as 200 for the study group. The patients with RMI 2 score <200 were labeled as benign and score >200 were labeled as malignant. The study was approved by the research ethical committee of the institute.

All statistical analyses were performed using the Statistical Package for the Social Sciences version (SPSS Inc) 17.0 windows. The Chi-square test was used to compare the differences in distribution of age, menopausal status and ultra-sonographic score of benign, borderline and malignant patients. A probability value of $p \leq 0.05$ was considered to be statistically significant. The sensitivity, specificity, positive (PPV), and negative (NPV) predictive values with reference to the presence of malignant and benign disease were calculated.

Results

Of 950 patients admitted with pelvic masses during the 2 year period, only 100 patients with complete medical and histological records were included and studied. The age of the patients ranged from 30 to 74 years with mean (SD) was 52.8 (10). Out of hundred patients included in the study, thirty-two were premenopausal and sixty-eight were postmenopausal. Table 1 shows the distribution of ultrasound score (U), menopausal status (M), and serum CA-125 levels in women with pelvic masses. Preoperative levels of CA-125 showed a varied range from 6 to 11,225 U/ml. The comparison of U score in between three groups was statistically extremely significant ($p \leq 0.0001$).

The results obtained after calculation of RMI 2 are summarized in Table 2.

The sensitivity of the RMI 2 for diagnosing malignant lesion was 96.7 % (59/61) and the specificity was 84 % (21/25). The PPV was 85.5 % (59/69) and negative predictive value (NPV) was 67.7 % (21/31) for the study group. Table 3 shows sensitivity, specificity, PPV, and NPV done by various previous studies and compared their results with the present study.

Out of the hundred patients, 25 patients had benign disease (endometrioma, serous cystadenoma, mucinous cystadenoma, dermoid cyst, follicular cyst, etc.), 14 had borderline (serous borderline tumor and mucinous borderline tumor), and 61 had advanced malignant disease (serous cystadenocarcinoma, mucinous cystadenocarcinoma, serous-mucinous cystadenocarcinoma, endometrioid carcinoma, etc.). Table 4 shows the distribution of ovarian pathologies that give rise to false-positive and false-negative results.

Discussion

The present study observed that the ovarian cancer was more prevalent in women of postmenopausal age group and more than 60 % came with advanced stage of ovarian malignancy. This observation was consistent with previous studies, which showed that the disease was more prevalent in age group of 41–60 years (mean 50 years) [18]. In this study, we evaluate the RMI 2 in our study population and found that at a cut-off value of 200, this method was able to correctly identify 96.7 % of women with malignant ovarian cancer. It could possibly be due to

Table 1 The distribution of ultrasound score (U), menopausal status (M), and serum CA-125 levels in women with pelvic masses

Variables	Benign ($n = 25$)	Malignant ($n = 61$)
Ultrasound score (*U*)		
0	16 (64 %)	0
1	7 (28 %)	3 (0.0 %)
>2	2 (0.1 %)	58 (95 %)
Menopausal status (*M*)		
Pre-menopausal	22 (88 %)	2 (0.0 %)
Postmenopausal	3 (12 %)	59 (96.7 %)
CA-125(U/ml)		
Mean	7.4 (6–34)	625 (100–11,225)

n number of patients

Table 2 Calculated RMI in the study group

Parameters	Benign ($n = 25$)	Malignant ($n = 61$)
RMI <200	21	2
RMI >200	4	59

n number of patients

Table 3 Comparison of the present study results with previous studies

Study	RMI (cut-off value)	*N*	Sensitivity (%)	Specificity (%)	PPV	NPV
Jacobs et al [6]	200	143	85.4	96.9		
Tingulstad et al [7]	200	173	71.0	96.0	89	88
Tingulstad et al [8]	200	365	71.0	92.0	69	92
Morgante et al [14]	125	124	81.0	90.0	74	–
Andersen et al [15]	200	180	70.6	89.3	66	91
Obeidat et al [16]	200	100	90.0	89.0	96	78
Ulusoy et al. [17]	153	296	76.4	80.0	66	85.5
Our study	200	100	96.7	84.0	85.5	67.7

N number of subjects involved in the study

Table 4 Distribution of pathologies that gave false-positive and false-negative results

False-positive ($n = 4$)	Number of patients (*n*)
Endometrioma	2
Dermoid cyst	1
Mucinous cystadenoma	1
False-negative (n = 10)	
Borderline tumor	6
Serous cystadenocarcinoma	2
Adenocarcinoma	1
Granulosa cell carcinoma	1

the significantly high levels of CA-125. It can be seen that high levels of CA-125 directly and significantly affects the RMI 2. The higher sensitivity of the present study as compared to the other similar studies (Table 3) was in favor of the use of RMI 2 in early identification and better prognosis of the ovarian cancer patients.

United Kingdom Collaborative Trial of Ovarian Cancer (UKCTOCS) has done a prospective cohort study in 2012. They enrolled 48,053 postmenopausal women and estimate the risk of primary epithelial ovarian cancer (EOC) and slow growing borderline or type I and aggressive type II EOC with adnexal abnormalities on ultrasound. Ultrasound was used as a screening module to detect abnormal adnexal mass followed by postal questionnaires. Study concluded that asymptomatic women, who had ultrasound-detected adnexal abnormalities, have an 1 in 22 risk for EOC. Despite the higher prevalence of Type II EOC, the risk of borderline or type I cancer in women with ultrasound abnormalities seems to be higher than does the risk of type II cancer. This has important immediate implications for patients with incidental adnexal findings as well as for any future ultrasound-based screening [19].

We observed four false-positive cases in this study. They were histopathologically diagnosed as endometrioma, dermoid cyst, and mucinous cystadenoma. The solid parts found in dermoid cyst and multilocular cystic lesions found in mucinous cystadenomas may have given higher ultrasound scores which resulted to false-positive results [20]. In cases of endometrioma, probably the irritation of peritoneum produced high levels of CA-125 levels which gave a higher RMI [21].

Yazbek et al, conducted a study in 2006 which compared the use of RMI score versus ultra-sonographically detected OCS (ovarian crescent sign). OCS is a rim of visible healthy ovarian tissue in the affected ovary. They found that seven patients of endometriomas, all had RMI score >200 and therefore false-positives, were accurately detected by the presence of the OCS, and did not have ovarian cancer [22]. The disadvantage of this method is that, it is difficult to detect OCS during menopause. The diagnostic performance and training skill of an ultrasonologists are important for OCS and RMI.

In any scoring system to exclude malignancy, the false negative rate should ideally be zero or close to zero [23]. The present study observed ten false-negative patients. Out of the ten patients, two patients had stage I malignant ovarian disease but RMI was <200, six patients were diagnosed with mucinous borderline ovarian disease, one patient was histologically diagnosed as stage I cystic granulosa cell carcinoma, and the tenth patient had metastatic adenocarcinoma. Gadducci et al. [24] reported that mucinous tumors expressed CA-125 less than non-mucinous type. The low levels of CA-125 in mucinous borderline tumor and stage I malignant ovarian tumor can explain the false-negative results. The low level of CA-125 and the low ultrasonographic score are likely to explain the false-negative results in these patients. Previous studies have similarly demonstrated a reduced sensitivity of the RMI 2 score in borderline disease [15]. This appears to be a limitation of the RMI 2 score in not only detecting patients with borderline and early stage tumor and large study are needed to fully understand this relationship. The Thai gynecologic cancer society conducted a study in 2009. They recommend the use of RMI developed by Jacob et al., in tertiary care hospital as a diagnostic tool to aid in selecting the patients of ovarian cancer for referral to cancer centers for surgery and early interventions [25]. Thus, in order to reduce the burden on the surgeons to some extent and for better prognosis of the patients RMI can be used as an effective index. This study also guides primary and secondary health care centers to refer patients at an early stage so that their risk of malignancy is assessed at the earliest.

Conclusion

In conclusion, the present study demonstrated that RMI 2 (at a cut-off value of 200) was a simple, easy, and useful method to apply in our tertiary care hospital. Our study reconfirms its accuracy in diagnosing adnexal masses with high risk of malignancy and highlights its limitations in excluding benign and borderline tumors. RMI 2 is the best screening method with higher sensitivity, but more studies are required to fully understand its relation with benign and borderline ovarian malignancy so as to decrease the false-positive and false-negative cases.

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Sunny Chopra, Richa Vaishya, and Jasbinder Kaur declare that they have no conflict of interest.

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