



THE EFFICACY OF CA 125, RESISTANT MALIGNANCY INDEX (RMI) IN DIAGNOSING OVARIAN MALIGNANCIES AND ITS CORRELATION WITH HISTOPATHOLOGY

Gynaecology

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ABSTRACT

OBJECTIVE: To evaluate the ability of CA 125, Risk of malignancy indices (RMI 1 and RMI 2) to discriminate between benign, borderline or malignant ovarian tumors.

METHODS: This is a retrospective study conducted in tertiary care centre between May 2015 to April 2017. A total of 100 women with adnexal lesions were included in the study. The inclusion criteria included women who underwent surgical intervention and who had preoperative CA-125 testing and pelvic ultrasound in the work-up plan of their management. The surgical intervention was usually followed by a histopathological diagnosis, for the nature of the lesion, which was used as the gold standard for the evaluation of both CA-125 and RMI. The sensitivity, specificity and positive predictive (PPV) and negative predictive (NPV) values of CA 125 and two RMI were calculated.

RESULTS: This study included 100 women who had serum CA-125 and pelvic ultrasound prior to the surgical intervention of the adnexal lesion. Of these women, 35% had malignant ovarian lesions. Using the proposed cut-off 35 U/ml for CA-125 and 200 for RMI 1 and RMI 2, the CA-125 test was more sensitive for detecting the majority of malignant ovarian tumors compared to the RMI 1 and RMI 2 (73% vs 64% and 67%). However, specificity was better with RMI 1 and RMI 2 than CA 125 (98% and 97% vs 95%). Using a cut-off level of 200 to indicate malignancy, the RMI 1 gave sensitivity of 64.7%, specificity of 98.5 %, PPV of 69.2%, and NPV of 98%. The RMI 2 gave sensitivity of 67.6%, specificity of 97.1% %, PPV of 54%, and NPV of 98.3 %. The RMI 2 had better sensitivity in predicting malignancy than RMI 1.

CONCLUSION: Both CA-125 and RMI have good validity in the diagnosis of ovarian tumors. CA-125 has higher sensitivity; however, RMI has higher specificity. RMI 2 is more accurate in discriminating between malignant, borderline and benign ovarian masses. Differential use of these two tools will improve the triage of women with suspected ovarian tumors since both are measured in their work-up.

KEYWORDS

CA 125, RMI 1, RMI 2, usg score, ovarian tumors.

Ovarian cancer is the second most common gynaecological malignancy, the fifth most common cause of death due to cancer and has more mortality than other gynaecologic malignancies (1,2). A woman's risk of getting ovarian cancer during her lifetime is about 1 in 75. Her lifetime chance of dying from ovarian cancer is about 1 in 100. Due to the often asymptomatic nature of the early stage of disease, many cases of ovarian cancer present in the advanced stage for which the 5-year survival rate remains low (Benjamin et al., 2007). The quality of primary cytoreductive surgery is one of the most important prognostic factors.

Carbohydrate antigen 125 or cancer antigen 125 (CA-125), also known as mucin 16 (MUC16), is a member of mucin glycoproteins, which contains 22,000 amino acids. It is significantly expressed by most ovarian epithelial tumors but also by the normal epithelium of the female reproductive system, gastrointestinal mucosal cells, and the luminal surface of mesothelium lining the peritoneum, pleura, and pericardium (3,4).

The risk of malignancy index (RMI) is a scoring system of the combination of various clinical features. It has been developed to improve diagnostic accuracy for ovarian malignancy. Jacob et al. (1990) originally developed the RMI 1 based on ultrasonographic findings, menopausal status, and serum levels of CA 125. The RMI was modified by Tingstad et al. (5) in 1996 to the RMI 2.

In recent years, ultrasonography has been increasingly used for the assessment of women presenting with a wide range of gynecological complaints. During a pelvic scan an attempt is routinely made to identify the ovaries and to examine their morphological appearance. This has led to a substantial increase in the number of asymptomatic women diagnosed with ovarian abnormalities (6). Recent studies have shown that a detailed sonographic examination of an ovarian tumor by an expert in gynecological ultrasonography may be superior to all previously described diagnostic models for the noninvasive diagnosis of ovarian cancer (7).

In this study, we evaluated CA 125, risk of malignancy indices (RMI 1 and RMI 2) with the diagnosis of ovarian tumour to discriminate between benign, borderline or malignant tumor.

MATERIALS AND METHODS:

We conducted a retrospective study of medical records of 100 women with pelvic masses admitted for laparotomy in the tertiary care centre between May 2015 to April 2017.

We included patients who met the following criteria: 1) premenstrual or postmenstrual 2) having adnexal mass diagnosed by an ultrasound evaluation 3) having preoperative measurement of serum levels of CA 125 and 4) underwent laparotomy.

The exclusion criteria were the patients with incomplete medical records.

The presence of multilocular cystic lesions, solid areas, bilateral lesions, ascites, and intra-abdominal metastases scored 1 point for each. A total ultrasonographic score (U) was calculated for each patient.

Postmenopausal status (M) was defined as 1 year or more of amenorrhea. All other women were considered to be premenopausal. $RMI = U \times M \times \text{serum CA-125}$

RMI 1 (Jacobs et al.) (1990) - where a total ultrasonographic score of 0 gave U = 0, a score of 1 gave U = 1 and a score of ≥ 2 gave U = 3; premenopausal status gave M = 1, postmenopausal status M = 3.

RMI 2 (Tingstad et al.) where a total ultrasonographic score of 0 gave U = 0, a score of 1 gave U = 1 and a score of ≥ 2 gave U = 4; premenopausal status gave M = 1, postmenopausal status M = 4.

We used cut-off level of at least 200 for indicating malignancy.

RESULTS:

TABLE 1: AGE DISTURBUTION

AGE (YEARS)	NUMBER(n=100)	BENIGN(n=60)	MALIGNANT(n=35)	BODERLINE(n=05)
10-20	05	03	02	00
21-30	16	14	02	00
31-40	24	18	05	01
41-50	21	13	07	01
51-60	19	08	08	03
61-70	07	00	07	00
71-80	06	03	03	00
81-90	02	01	01	00

31-40 age group constituted the highest number of patients with ovarian tumors (24%) while least was seen before 20 years (05%) or after 80 years (02%).

TABLE 2: CLINICAL SYMPTOMS

SYMPTOMS	NUMBER
PAIN ABDOMEN	75
MASS PER ADOMEN	13
ABDOMINAL DISTENSION	33
LOSS OF APPETITE	09
LOSS OF WEIGHT	14
POST MENOPAUSAL BLEEDING	08
MENSTRUAL ABNORMALITY	03
ACCIDENTAL ULTRASOUND FINDING	05
BACKACHE	04

Pain abdomen was the most common mode of presentation (75%). While 33% came with complaints of abdominal distension.

TABLE 3: CLASSIFICATION OF OVARIAN MALIGNANCY

OVARIAN MALIGNANCY	NUMBER(n=100)	PERCENTAGE (%)
BENIGN	60	60%
MALIGNANT	35	35%
BODERLINE TUMOR	05	05%

Benign constituted 60% of the ovarian tumors.

TABLE 4: MENSTRUAL STATUS

MENSTRUAL HISTORY	NUMBER (n=100)	BENIGN (n=60)	MALIGNANT (n=35)	BODERLINE (n=05)
PRE MENSTRUAL	53	43	09	01
POST MENSTRUAL	47	17	26	04

Incidence of benign ovarian tumors was most common in premenopausal age group while malignant ovarian tumors were seen in postmenopausal age group

TABLE 5: PARITY

PARITY	NUMBER(n=100)	PERCENTAGE (100%)
NULLIPARITY	43	43%
PRIMIPARITY	15	15%
MULTIPARITY	42	42%

Ovarian tumors were more commonly found in nulliparity women.

TABLE 6: LEVEL OF CA 125

CA 125	NUMBER (n=100)	BENIGN (n=60)	MALIGNANT (n=35)	BODERLINE (n=05)
<35 UNITS/mL	70	55	10	05
>35UNITS/mL	30	05	25	00

Incidence of benign tumors was seen more in CA 125 <35 units/ml group and malignant tumors were found in CA 125 >35units/ml.

TABLE 7: RESULTS OF EVALUATION RISK OF MALIGNANT INDEX

RMI 1	BENIGN(n=60)	MALIGNANT(n=35)	BODERLINE(n=05)
<200	59	13	05
≥200	01	22	00
RMI 2	BENIGN(n=60)	MALIGNANT(n=35)	BODERLINE(n=05)
<200	59	11	05
≥200	01	24	00

There was a difference of 2 patients in RMI 2 in malignant group than RMI 1. Both the patients had histopathological report of malignant tumor.

TABLE 8: ULTRASOUND SCORE

ULTRASOUND SCORE	NUMBER(n=100)	BENIGN (n=60)	MALIGNANT (n=35)	BODERLINE (n=05)
0	26	24	2	00
1	42	25	14	03
3 (RMI 1) or 4 (RMI 2)	32	11	19	02

Ultrasound score of 0 or 1 diagnosed most of the benign tumors while ultrasound score of 3 or 4 was observed more with malignant ovarian masses.

TABLE 9: HISTOPATHOLOGY REPORT

HPR-BENIGN		NUMBER
EPITHELIAL TUMOR	SEROUS CYSTADENOMA	26
	MUCINOUS CYSTADENOMA	10
	ENDOMETRIAL CYST	05
SEX CORD TUMOR	FIBROMA	06
	FIBROTHERCOMA	01
GERM CELL TUMOR	TERATOMA	03
OTHERS	SIMPLE CYST	05
	CORPUS HAEMORRHAGICUM	05
HPR-MALIGNANT		
EPITHELIAL TUMOR	SEROUS CYSTADENOCARCINOMA	13
	MUCINOUS CYSTADENOCARCINOMA	07
	ENDOMETRIOID CARCINOMA	02
SEX CORD TUMOR	GRANULOSA CELL TUMOR	09
GERM CELL TUMOR	DYSGERMINOMA	02
	IMMATURE TERATOMA	01
HPR-BORDERLINE		
EPITHELIAL TUMOR		
	SEROUS BORDERLINE TUMOR	01
	MUCINOUS BORDERLINE TUMOR	04

Benign tumors were more in this study, with serous cystadenoma (26%) being the most common benign tumor. Serous cystadenocarcinoma (13%) is the most common malignant tumor.

TABLE 10: DIAGNOSTIC PERFORMANCE OF CA 125, RMI 1 AND RMI 2 WITH CUTOFF VALUE OF 200 TO INDICATE MALIGNANCY

	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
CA 125	73.5%	95.4%	46%	98.6%
RMI 1	64.7%	98.5%	69.2%	98.1%
RMI 2	67.6%	97.1%	54%	98.3%

With cut off value of 200, the sensitivity and specificity of RMI 1 and RMI 2 are 64.5%, 67.5% and 98.5%, 97.01% respectively. The sensitivity and specificity of CA125 is 73.5%, 95.4%.

DISCUSSION

Ovarian cancer is a common gynecological cancer in women and has a poor prognosis with a five-year survival rate less than 35%. About 20% of ovarian cancers are found at an early stage. When ovarian cancer is found early at a localized stage, about 94% of patients live longer than 5 years after diagnosis. International health organizations including NICE, the European Society for Medical Oncology (ESMO)⁸, and other bodies have set clinical guidelines on the recognition and management of women with ovarian cancer. Early cancers of the ovaries often cause no symptoms. When ovarian cancer causes symptoms, they tend to be symptoms that are more commonly caused by other things. These symptoms include abdominal swelling or bloating (due to a mass or a build-up of fluid), pelvic pressure or abdominal pain, difficulty eating or feeling full quickly, and/or urinary symptoms (having to go urgently or often). Most of these symptoms can also be caused by other less serious conditions. By the time ovarian cancer is considered as a possible cause of these symptoms, it usually has already spread beyond the ovaries. Also, some types of ovarian cancer can rapidly spread to the surface of nearby organs. Still, prompt attention to symptoms may improve the odds of early diagnosis and successful treatment.

The risk of developing ovarian cancer gets higher with age. Ovarian cancer is rare in women younger than 40. Most ovarian cancers develop after menopause. In our study, maximum number of cases was found above 40 years. Benign tumors were more commonly found below 40 years while malignant tumors were more between 51-60 years.

In our study, we observed that there were 60% of benign cases, 35% were malignant cases and 5% was borderline epithelial ovarian tumors. In benign masses, the largest group constituted serous cystadenoma (43%) followed by mucinous cystadenoma (16%). In malignant ovarian masses, serous cystadenocarcinoma was most common (37%) followed by granulosa cell tumor (25%). Serous borderline tumor was most common borderline epithelial tumor.

Pain abdomen was the most common complaint which was seen in 75% of patients followed by abdominal distension (33%). Also, it was the most common mode of presentation in benign tumors. Abdominal distension, loss of weight and appetite was the main presentation in malignant tumors. Our studies were similar to Farzaneh F et al⁹ who also observed weight loss is more commonly associated with malignant ovarian masses.

Women who have used oral contraceptives have a lower risk of ovarian cancer. The lower risk is seen after only 3 to 6 months of using the pill, and the risk is lower the longer the pills are used. This lower risk continues for many years after the pill is stopped. In our study, ovarian tumors were found more in nulligravida (43%).

In our study, we observed that 53% and 47% patients were premenopausal and postmenopausal respectively. Malignant tumors were more common in postmenopausal women. Similar to studies conducted by Shuiqing MA et al¹⁰, Jung W P et al¹¹ and zinatossada B¹² observed that overall incidence of ovarian masses were less in postmenopausal women.

The recent advance development of ultrasound techniques and the better characterization of malignant tumours by this method have led to better performance of ultrasound as a predictor of malignancy especially in those cases with metastasis. Ultrasound can be the primary investigation which can be employed for diagnosing any ovarian mass. In the present study, we observed that ultrasonography with a score of more than 3 (RMI 1) or 4 (RMI 2) diagnosed correctly 19 (54%) malignant ovarian tumors and falsely diagnosed 11 cases (18%) of benign masses as malignant. This can be explained by fact that multilocular cyst may be found in cystadenoma and solid parts in dermoid cyst. The absence of all components of ultrasound score were associated with benign ovarian masses while presence of maximum features with malignancy.

CA-125 was raised (>35 U/ml) in 83% of women with malignant ovarian cancers and 17% of women with benign ovarian cancers. The CA-125 test was more sensitive for detecting the majority of malignant ovarian tumors compared to the RMI 1 and RMI 2 (73% vs 64% and 67%). Our study is similar to the study conducted by Khawla Al-Musallhi et al¹³, which also showed that CA-125 test was more

sensitive for detecting the majority of malignant ovarian tumors compared to the RMI (69% vs. 57%). Currently, CA-125 is still the most widely used tumor biomarker for the detection of ovarian cancer. However, its poor specificity is considered to be the main drawback that has limited its use alone, and its incorporation in the RMI has improved its specificity. It is known that CA-125 levels can be elevated in benign gynecological conditions particularly endometriosis and fibroids, and other medical disorders such as congestive heart failure and cirrhosis.

For this study, the RMI 2 provided better diagnostic accuracy than the RMI 1. This is in accordance with the studies done by Watcharada M et al¹⁴. At the cut-off level of 200, RMI 1 and 2 gave the sensitivity and specificity, 64.5%, 67.5% and 98.5%, 97.01% respectively. These findings are important for the clinical applicability of the RMI as a tool for referral of patients with ovarian cancer to gynecological cancer centers.

CONCLUSION:

Both CA-125 and RMI have good validity in the diagnosis of ovarian tumors. The RMI is able to discriminate between benign and borderline or malignant ovarian tumor. CA-125 has higher sensitivity; however, RMI has higher specificity. RMI 2 is more accurate in discriminating between malignant, borderline and benign ovarian masses. In combination, CA-125 might be more valid for the diagnosis of malignant ovarian cancer while RMI is more valid for excluding the diagnosis of these tumors. Differential use of these two tools will improve the triage of women with suspected ovarian tumors since both are measured in their work-up. We recommended the use of both tools in primary care to reduce referral to gynecology or oncology units.

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