

Role of cancer antigen 125 and risk of malignancy index 3 to differentiate benign and malignant female pelvic masses followed by histopathological correlation

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Abstract

Introduction: Pelvic mass is a worldwide female health problem with serious consequences in mortality, morbidity, and cost to the society. The present study was designed to see the role of serum Cancer Antigen 125 (CA125) and Risk of Malignancy Index 3 (RMI3) to differentiate benign and malignant pelvic masses followed by histopathological correlation.

Materials and Method: In this prospective study 70 cases of female with pelvic mass were included. Serum CA125 with other clinical covariates were measured and RMI3 was calculated. The findings were histopathologically correlated. 70 normal healthy females served as controls. Statistical analysis was done by using unpaired t-test and Fisher's exact test.

Results: Serum CA125 and RMI3 were significantly elevated in 92.3% of malignant cases and only in 3.5% of benign cases. Mean of RMI3 and CA125 was 5191.6 and 608.1 U/mL in malignant cases, where 39.0 and 20.9 U/mL in benign cases respectively. The sensitivity and specificity of both CA125 (cutoff of 35U/mL) and RMI3 (cutoff of 200) for predicting malignancy was 96.49% and 92.31% respectively with 98.21% positive predictive and 85.71% negative predictive value.

Conclusion: Serum CA125 and RMI3 were increased significantly in females with malignant pelvic mass in comparison to benign cases. Value of CA125 >35 U/mL and RMI3 >200 in predicting malignancy revealed modest diagnostic accuracy. Therefore combining RMI3 and CA125 helps to assess pelvic masses pre-operatively and to refer patients to gynaecological oncology center for appropriate management.

Keywords: Cancer Antigen 125, pelvic mass, Risk of Malignancy Index

Received: 23rd May, 2017

Accepted: 29th August, 2017

Introduction

Pelvic mass is an enlargement or swelling in the lower abdomen or pelvic region found during physical examination or during the course of investigation including ultrasonography (USG) and radiology (X-ray). Female pelvic masses are mainly caused by gynaecological diseases such as ovarian cancer, follicular or corpus luteum cysts of the ovary, fibroid, adenomyosis, chocolate cyst, tubo-ovarian (TO) mass, polycystic ovary syndrome (PCOS), endometrial implants causing endometriosis, pelvic haematocele, pelvic abscess, pelvic kidney, encysted peritonitis, ectopic pregnancy or much less commonly trophoblastic disease.

A woman presenting with a pelvic mass is a very common clinical problem and a reason for referral to hospital. To differentiate between benign and malignant tumors is an important step in the clinical handling of such cases.⁽¹⁾ The majority of women are treated in a community hospital by a gynaecologist or general surgeon. Although this is appropriate for patients who have a benign mass, patients with a malignancy should be referred to a tertiary care center.

Jacobs et al. developed an objective tool known as Risk of Malignancy Index (RMI) which is calculated from menopausal status, ultrasound score, and serum CA125 levels. It helps to identify the high risk patients with ovarian masses and helpful for referral to cancer center.^(2,3) There are different risk of malignancy scores

which can be used to assess an ovarian mass. The RMI3 is the most effective among them.⁽²⁾

CA 125 is a protein which is encoded by the MUC16 gene. It is a membrane associated mucin with a single transmembrane domain. It contains about 22,000 amino acids and it the largest membrane associated mucin.⁽⁴⁾ CA 125 is mostly used as a tumor marker for ovarian cancer.⁽⁵⁾

With this background, the present study is designed to see the performance of RMI3 and serum CA125 to differentiate benign and malignant pelvic mass using histopathology as a gold standard.

Materials and Method

The present research work was a case control study of 70 women admitted in the Gynecology Department at Sir Takhtsinhji General Hospital, Bhavnagar for surgical exploration of pelvic masses and the study was conducted for a period of one year. The female with pelvic mass were primarily diagnosed by cardinal symptoms like lower abdominal pain and swelling, menstrual alteration and confirmed by USG (Ultrasonography). Serum CA125 level, ultrasound finding and menopausal status were assessed and RMI3 score was calculated. A group of 70 normal healthy females, from the same population served as control. Serum CA 125 estimation was done by enzyme-linked immunosorbent assay on Biorad iMark Elisa Reader. The study was reviewed and approved by Human

Ethics Committee of Institutional Review Board, Government Medical College, Bhavnagar. Informed consents were taken from all the participants in this study.

RMI3 was calculated for all patients using the following formula

$$\text{RMI3} = \text{M} \times \text{U} \times \text{serum CA 125}^{(2)}$$

Serum CA 125 is the assayed level expressed in U/mL and its value was entered directly into the equation. "M" refers to the patient's menopausal status. Postmenopausal status is defined as more than 1 year of amenorrhea. A score of M=3 is given to postmenopausal women and M=1 for premenopausal women. "U" refers to the ultrasonography score. Multilocularity, solid areas, bilaterality, ascites and intraabdominal metastasis score 1 point each. A total of 2 or more points is recalculated into U=3, fewer than 2 points into U=1.

Final diagnosis is based on the histopathological report of the surgical specimen.

The statistical analysis was performed using unpaired t-test and Fisher's exact test and Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) were calculated.

Result

In this study, 70 patients with a palpable or ultrasonographically demonstrated pelvic mass were considered as cases (Group II) and evaluated for serum CA125 level and RMI3. The patients were operated and histopathological examination revealed malignancy in 13 cases (18.57%) and benign in 57 cases (81.43%). 70 apparently healthy females were also included as control (Group I)

Table 1 represents level of biochemical parameters like CA 125, SGPT and SGOT in cases and controls. CA 125 levels were significantly elevated in cases than controls, whereas levels of SGPT and SGOT showed no significant difference between the two groups.

Table 1: Distribution serum CA 125, SGPT, SGOT level in Group I and Group II

Parameter		Group I: (N=70)	Group II:		
			Total (N=70)	Malignant (N=13)	Benign (N=57)
CA 125 (U/mL)	Mean	17.7	129.9	608.1	20.9
	Minimum	8	7	20	7
	Maximum	31	966	966	70
	Standard deviation	5.4	254.0	473.0	9.7
SGPT (IU/L)	Mean	17.9	17.2	18.8	16.8
	Minimum	8	10	10	10
	Maximum	39	47	32	47
	Standard deviation	7.1	6.4	7.1	6.2
SGOT (IU/L)	Mean	22.6	20.9	22.4	20.5
	Minimum	11	11	12	11
	Maximum	38	40	35	40
	Standard deviation	7.0	6.7	8.6	6.2

As evident from Table 2, mean of age, Ultrasonography score, RMI3, Serum CA 125 and Menopausal status differ significantly (<0.0001) between Benign and Malignant cases. In this study the malignancy was found to be associated with increasing age and increasing ultrasound score. Incidence of malignancy was higher in postmenopausal women (92.3%) than premenopausal women (7.7%). The mean of CA125 (608.1 U/mL Vs 20.9 U/mL) and RMI3

(5191.6 Vs 39) were significantly elevated in women with malignancy compared to benign cases.

Table 3 and 4 showed performance level of CA 125 at 35 U/mL had a sensitivity and specificity of 96.49% and 92.31% respectively to differentiate malignancy from benign cases. The performance obtained for the RMI3 at cut off point 200 had a same sensitivity and specificity like CA 125.

Table 2: Distribution of age, menopausal status, ultrasonography score, RMI3 and serum CA125 levels between benign and malignant cases

Variables		Malignant (N=13)	Benign (N=57)	P value
Age	Mean	59	39.9	<0.0001
	Minimum	41	20	
	Maximum	85	65	
	Standard deviation	9.6	8.1	

Menopausal status (M)	Premenopausal	1	46	<0.0001
	Postmenopausal	12	11	
Ultrasonography score (U)	U=1	0	48	<0.0001
	U=3	13	9	
RMI3	Mean	5191.6	39	<0.0001
	Minimum	180	7	
	Maximum	8694	216	
	Standard deviation	2511.4	42.5	
Serum CA 125 (U/mL)	Mean	608.1	20.9	<0.0001
	Minimum	20	7	
	Maximum	966	70	
	Standard deviation	473.0	9.7	

Table 3: Serum CA 125 (at cut off level 35 U/L) and RMI3 (at cut off level 200) cross tabulation with histopathological result

		Histopathology result		Total
		Benign tumor	Malignant tumor	
CA 125 (U/mL)	<35	55 (79%)	1 (1%)	56 (80%)
	>35	2 (3%)	12 (17%)	14 (14%)
Total		57 (81%)	13 (19%)	70 (100%)
RMI3	<200	55 (79%)	1 (1%)	56 (80%)
	>200	2 (3%)	12 (17%)	14 (14%)
Total		57 (81%)	13 (19%)	70 (100%)

Table 4: Performance of CA 125 at cut off level 35 U/L and RMI3 at cut off level 200

Parameter	CA 125	RMI3
Sensitivity	96.49%	96.49%
Specificity	92.31%	92.31%
Positive Predictive Value	98.21%	98.21%
Negative Predictive Value	85.71%	85.71%

Discussion

Approximately 20% of women develop pelvic mass at some time in their lives and is one of the common contributor of morbidity and mortality worldwide.⁽⁶⁾ Gynaecologist are often confronted with the dilemma to differentiate malignant tumors from benign in patients presenting with pelvic mass and also most of women present at advanced stage with poor prognosis.^(3,7)

The present study aimed to investigate the usefulness of serum CA125 and RMI3 to differentiate benign and malignant female pelvic masses preoperatively followed by histopathological correlation.

Serum CA 125 level was significantly higher in females with pelvic mass in comparison to healthy subjects (Table 1). But the prevalence of SGPT and SGOT of the cases and controls did not differ and their levels were within normal level, which rules out existence of any liver disease in both cases and controls.

In the cases malignancy was found with increasing age and increasing ultrasound score (Table 2).

Incidence of malignancy was higher in postmenopausal women compared to premenopausal women. The mean of CA125 and RMI3 was significantly higher among women with malignancy than benign cases (Table 2).

It was shown that CA 125 at a cut off of 35 U/L and RMI3 at a cut off of 200 both had a sensitivity of 96.49%, specificity of 92.31%, Positive Predictive Value of 98.21% and Negative Predictive Value 85.71% for the prediction of malignancy.

In another study by Farnaz and coworkers on 86 women, the sensitivity and specificity of CA125 (cutoff of 35U/mL) for predicting ovarian cancer was 96.49% and 92.31% respectively.⁽⁸⁾ Study by Jyothi H Rao on 158 women concluded Sensitivity of RMI (cutoff of 200) was 84%, Specificity was 89%, PPV was 93% and NPV was 71%.⁽³⁾

From above findings it is indicated that serum CA 125 and RMI3 increases significantly in females with malignant pelvic mass. So both this parameters can be used to investigate in a woman with suspected malignant pelvic mass and provides earlier referral to a gynaecological oncology center specialized in its

management. CA125 and RMI seems to be simple, easy and reliable method as shown in our study also.

Conclusion

Serum CA125 level and RMI3 were significantly higher in females with malignant pelvic mass in comparison to benign cases. CA125 >35 U/mL in predicting malignancy revealed modest diagnostic accuracy. RMI3 is a convenient method to investigate the probability of malignancy in suspected patients with pelvic mass. RMI3 can be calculated by CA125 levels, menopausal status and ultrasound characteristics. RMI3 >200 in predicting malignancy has the same sensitivity and specificity like CA125. Therefore present study concludes that combining RMI3 and CA125 helps in assessment of pelvic mass pre-operatively and earlier referral of patients to gynaecological cancer center for appropriate management.

Reference

1. Erik Soegaard Andersen, Aage Knudsen, Per Rix, Birger Johansen. Risk of Malignancy Index in the preoperative evaluation of patients with adnexal masses. *Gynecologic Oncology*. 2003;90:109-112.
2. Zinatossadat Bouzari, Shahla Yazdani, Mahmoud Haji Ahmadi, Shahnaz Barat, Ziba Shirkhani Kelagar, Maryam Javadian Kutenaie, Nargeuss Abbaszade and Fateme Khajat. Comparison of three malignancy risk indices and CA-125 in the preoperative evaluation of patients with pelvic masses. *BMC Research Notes* 2011;4(206):1-4.
3. Jyothi H Rao. Risk of malignancy index in assessment of pelvic mass. *International Journal of Biomedical Research*. 2014;05(03):184-86.
4. <https://en.wikipedia.org/wiki/CA-125> accessed on September 25, 2016.
5. T Van Gorp, I Cadron, E Despierre, A Daemen, K Leunen, F Amant, D Timmerman, B De Moor, I Vergote. HE4 and CA125 as a diagnostic test in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. *British Journal of Cancer*. 2011;1-8.
6. Yasmin A, Lyons, Pamela T. Soliman, Michael M. Frumovitz. The pelvic mass workup. *Contemporary Ob/Gyn Obstetrics-Gynecology & Women's Health BRCA mutations*. 2014;1-8.
7. Safia Sultana Munir, Misbah Sultana, Dawood Amin. The evaluation of pelvic mass. *Biomedica Vol. 26*. 2010:70-75
8. Farnaz, Samdana Wahab, Lubna Hassan. The diagnostic validity of pre-operative serumca125 level in women with ovarian masses. *J Postgrad Med Inst* 2012;26(1):73-78.