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RESEARCH ARTICLE

COMPARISON OF DIAGNOSTIC ACCURACY BETWEEN THE RISK OF MALIGNANCY INDEX (RMI) AND THE RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA) TO ASSUME ANY MALIGNANCY IN OVARIAN TUMOR.

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Abstract

Malignancy of the ovary has a high incidence, however there are still many cases of undiagnosed ovarian malignancy. Many cases diagnosed as benign ovarian tumors during surgery show the results turned out to be malignant. The prognosis of ovarian malignancy is highly dependent on the results of the first surgery to achieve as much as possible cytoreduction. Currently to diagnose ovarian malignancy the Risk of Malignancy Index (RMI) score is used among other methods, however diagnostic capability for early detection of ovarian malignancy is still not good enough. Risk of Ovarian Malignancy Algorithm (ROMA) is an alternative diagnostic test in the early detection of ovarian malignancy. This study aimed to compare the diagnostic test capability between RMI and ROMA in suspected malignant ovarian tumors.

Subjects were all patients diagnosed with ovarian tumors and planned to undergo operation in the Hasan Sadikin Hospital. RMI and ROMA scores were calculated, then compared the results obtained with postoperative histopathology results. A statistical analysis of sensitivity and specificity calculations of both scores in detecting ovarian malignancy was performed.

Obtained 17 subjects research studies that met the inclusion criteria. Of the 17 there were 10 cases of malignancy and 7 cases of benign. There was no significant difference ($p>0.05$) on the characteristics of the study subjects by age and menopausal status. The results of the study showed that regarding the diagnostic test scores ROMA had a sensitivity of 80% and a specificity 85.5%, while the RMI had sensitivity of 30% and specificity of 71.4%.

In conclusion ROMA scores has better diagnostic test capability than RMI in suspected malignant ovarian tumors.

Introduction:-

Ovarian malignancies have a high incidence in the world. The United States is a developed country also has the incidence of malignant ovarian tumors with a high mortality rate of 57%.(1-5)In Indonesia, a malignant ovarian tumor ranks sixth highest of the 10 most common malignant tumor that occurs in people of Indonesia after cervical

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malignant tumor.(4) The high rate of relapse and low survival rate of ovarian malignancies caused by several things including due to late diagnosis, inaccurate diagnosis of pre-surgery, less optimal treatment or surgery, the still high cost of chemotherapy, as well as the factor of the tumor itself, namely the behavior of ovarian cancer in molecular biology is still much yet is known.(1-5)

Delay in treatment may be due to the ignorance of people, low levels of education, lack of social economy, the absence of early symptoms of malignancy when it started there, fault diagnosis when patients seek treatment at the first level, limited health facilities or diagnostic support facilities. Preoperative diagnosis error caused by underdeveloped scoring system that can be used as a method of prediction of malignant that has high sensitivity and specificity. While less than optimal treatment / surgery due to several things including the diagnosis of preoperative less precise, limited human resources, especially medical personnel, limited treatment technologies, lack of discipline patients, socioeconomic and education is low, and is likely due to the high cost of treatment is not affordable by the community.

Treatment of ovarian tumor is under the authority of a gynecologist, especially for cases of benign ovarian tumor. But often we get a doubt as to whether an ovarian tumor is a benign or malignant tumor. Various efforts have been made to conduct a more accurate preoperative diagnosis other than through good clinical examination, ultrasound and tumor marker tests. If it turns out Preoperative found suspicion of malignancy should be performed handled referral to adequate health care. Surgery should be performed by personnel skilled operators in the form of surgery maximumcytoreduction. Currently the diagnosis of ovarian malignancies efforts made other than through a clinical examination was also performed an ultrasound examination, tumor marker tests are CA125, and RMI score, with values> 200 to the reference as malignant ovarian tumors. From several studies, the sensitivity of RMI is still considered less despite having a fairly good specificity.(6-9)

RMI is the weakness of the examination CA125 levels can be influenced by several other factors. Tumor marker have to specific, content conforms to numbers of cancer cell and is able to detect malignancy before clinical symptoms appear.(1, 10)Increased CA125 occurred in 82% of malignant ovarian tumors showed with above normal (> 35 U / mL), in advanced ovarian malignant tumors 90% CA125 levels rise above normal limits. But it was only less than 50% increase above normal values occur in malignant ovarian tumor stage I. In addition, other diseases that are not a malignancy can demonstrate increased CA125 values such as uterine fibroids, pelvic inflammatory disease, endometriosis and pregnancy. Positive results were also found in cases of peritonitis, pancreatitis, kidney disease and alcoholic hepatitis.(8, 11, 12)

Ultrasound examination of the RMI also has the disadvantage of their subjectivity factor of ultrasound operator, which can cause different results when performed calculations score RMI. Although ultrasound examination performed by a gynecologist who has good skills, but because there is the factor of subjectivity and different standards would lead to a different result. Human epididymis protein 4 (HE4) has demonstrated excellence as a marker of malignant ovarian tumors compared with CA125. HE4 has the ability to distinguish benign from malignant disease better than CA125. HE4 showed excessive expression in serous ovarian malignancy of 93%, the type of epithelium by 100% and clear cell (not mucinous) by 50%. HE4 also have good sensitivity in cases of ovarian malignancies, especially early-stage (stage I and II).(6, 7, 13) 19-26.

The combination of the use of tumor marker CA125 and HE4 of several studies shown to increase the sensitivity and specificity as a marker of malignant ovarian tumors. ROMA is a test that combines examination of CA125 and HE4 is associated with a woman's menopausal status. With this test by looking at a woman's menopausal status whether premenopausal or postmenopausal ovarian tumors can be distinguished by whether the tumor has a tendency to malignancy or not.(6-8, 13, 14)

With good diagnostic capability is expected to reduce the incidence of ovarian cancer treatment is inadequate, especially at the primary and secondary health care, so that it can be done if the referral system obtained an ovarian tumor has a tendency malignant after diagnostic examination before surgery.

Methods:-

The subjects were patients with ovarian tumors who came to the Hasan Sadikin Hospital from December 2013. Exclusion criteria were *Duranteoperationum* found that the tumor is not from the ovary and histopathological results cannot be checked.

Clinical examinations:-
The physical examination includes the general state of awareness, weight and height and cardiorespiratory examination. Gynecological examination to determine the state of ovarian tumors. Ultrasound examination to determine the state of an ovarian tumor and surrounding tissue.

Laboratory examinations:-
The level of CA 125 and HE4 conducted using ELISA method.

Calculation of ROMA:-
From research algorithm formula determined by regression analysis:
Premenopausal women:
Predictive index (PI) = -12.0 + 2.38*LN[HE4] + 0.0626*LN[CA125]
Postmenopausal women:
Predictive index (PI) = -8.09 + 1.04*LN[HE4] + 0.732*LN[CA125]

Data analysis:-
The analysis used is univariate to describe the characteristics of the research subjects. Bivariate analysis was conducted to see the relationship between the two variables are independent variables and the dependent relationship. Multivariate analysis performed to control for confounding variables.

Results:-

In this research, diagnostic tests on 17 patients with a diagnosis of ovarian tumors dating surgery at Hasan Sadikin Hospital and meet inclusion criteria. The study was conducted from December 2013 to January 2014. Prior to surgery, performed the calculation of the value of RMI and ROMA, then do histopathology. From the histopathological results is then created two groups and do a comparison between the RMI and the diagnostic accuracy for alleged ROMA ovarian malignancy of the tumor. Table 1 presents the data characteristics of the two study groups, include age and histopathologic results. Of the 17 samples, based on histopathology obtained as many as 10 samples of malignant (58.9%) and 7 benign samples (41.1%).

Tabel 1:- Subject Characteristics.

Characteristic	Benign Histopathology (n=7)	Malignant Histopathology (=10)	Significance
Age			
Mean	36,71	41,40	t=1,001
SD	7,477	10,637	p=0,333

Notes: Independent T test

According to the table 1 for normally distributed data using unpaired t test. Visible to the characteristics of age by unpaired t test (p value of 0.333) of the variable is greater than 0.05% means that no significant or not statistically significant.

Table 2:- Comparison of Ca 125, HE4, RMI and ROMA based on the results of histopathology.

Examination	Combination (n=17)	PA Examination		p-value *)
		Malignant (n=10)	Benign (n=7)	
RMI	101.78	92.28	154.12	1.000
	(5.9-6604.8)	(5.9-6604.8)	(8.85-774.66)	
ROMA	14.2	25.9	2.4	0.005
	(1.9-98.7)	(2.7-98.7)	(1.9-21.7)	

Notes: *) Based on Mann-Whitney test; **) median and range value

Using data from this study, the results obtained as listed in Table 2, that the RMI good at detecting ovarian tumors are benign, but it cannot properly detect malignant ovarian tumors. To ROMA, showed a positive test for the detection of benign and malignant ovarian tumors. This data is also supported by the results of the ROMA p is close to zero.

Table 3:- Correlation of RMI and ROMA based on histopathology.

Variables	Histopathology results					
	Total Sample (n=17)		Malignant (n=10)		Benign (n=7)	
	r_s	p value	r_s	p value	r_s	p value
RMI v.s ROMA	0.463	0.061	0.527	0.117	0.821	0.023

Notes: r_s = coefficient of rank Spearman correlation

From Table 3, it can be seen that between RMI and ROMA has a good correlation to assess the data from benign ovarian tumors, and poor correlation scores to assess the combined data and malignant ovarian. Furthermore, to determine the validity of test results ROMA and RMI in the diagnosis of malignancy of an ovarian tumor were made tables 2x2, by first determining the cutoff point of the examination results ROMA and RMI in accordance with the criteria of the cutoff point ROMA for pre-menopausal> 7.4% and in patients with menopause > 25.3%. While the cutoff point RMI is> 200, and then calculated the diagnostic test (table 4).

Table 4:- Correlation between histopathology result and ROMA score.

Scoring System	Histopathology results		p value
	Malignant (n=10)	Benign (n=7)	
ROMA *)			0.015
Malignant	8	2	
Benign	2	5	

Notes: analyzed using Exact-Fisher test. Cut off point value for ROMA of pre menopause was ≥7.4% and of menopause was ≥25.3%.

Table 5:- Correlation between histopathology result and RMI score.

Scoring System	Histopathology results		p value
	Malignant (n=10)	Benign (n=7)	
RMI *)			1.000
Malignant	3	2	
Benign	7	5	

Notes: analyzed using Exact-Fisher test. Cut off point value for RMI was ≥200.

Based on table 4 and 5 appear only ROMA test results that show significant correlation with the results of the PA. Furthermore, the comparison of the ability of a diagnostic test both systems score in determining malignancy of an ovarian tumor with assessing the sensitivity, specificity, PPV and NPV accuracy (table 6).

Table 6:- Comparison of the accuracy of diagnosis ROMA and RMI to suspect malignancy in ovarian tumors.

Scoring system	Sensitivity (%)	Specificity (%)	Accuration (%)	PPV (%)	NPV (%)
ROMA	80	85.5	82.3	89	75.2
RMI	30	71.4	47.0	60	41.7

Discussion:-

Chamim(15) doing research on 242 women with ovarian tumors, 100 (41.3%) benign tumors and 142 (58.7%) malignant tumor, by taking a cutoff point of age 36 years; apparently showing a significant relationship ($p < 0.05$), where the mean benign tumor patients younger (35.13 years) than patients with malignant tumors (39.91). Alcazar doing research on 38 patients with ovarian tumors, by taking a cutoff point of 40 years of age; it turns out the average age group of malignant ovarian tumors 47.44 ± 13.83 years compared with 34.65 ± 9.01 years in the group of benign ovarian tumor ($p = 0.003$).

More than 80% of epithelial ovarian cancers are found in postmenopausal women(6, 16). Alcazar who did research on 38 patients with ovarian tumors, 18 patients with malignant tumors and 20 benign tumors; there are 14 postmenopausal patients and 10 patients (71.43%) of them suffer from malignant ovarian tumors ($p = 0.023$).(12)Research conducted by Chamim in 242 women with ovarian tumors showed that subjects who had

menopause is more prevalent on the subject of malignant tumors (22.54%) compared with benign tumors (10%) (p = 0.008); by taking a cutoff point menopause age of 48 years, patients with malignant ovarian tumors (71.88%) occurred in the age over 48 years; whereas in benign ovarian tumors, only 2.0% occurred in the age over 48 years.(15)

From this research it appears that the subject's age and menopausal status did not have a statistically significant difference in the incidence of ovarian malignancy. This is contrary to existing research that shows that age and menopausal status can be one variable in the incidence of ovarian malignancy. This can happen because of the distribution of the patients in this study was uneven and the number of small sample.

Research Moore et al stated ROMA had a sensitivity of 94.3% compared with 84.6% in the RMI distinguishing benign ovarian tumor with malignant. In the same study revealed ROMA has better sensitivity (85.3%) in differentiating early-stage ovarian cancer (stage I and II) as compared to RMI (64.7%).(6)

From the research showed ROMA has a diagnostic test capability that is better than RMI at all stages of ovarian cancer both clinically and statistically. From research conducted found that ROMA has the ability to better diagnostic test than the RMI in suspected ovarian tumor malignancy, this can be seen in Table 6 to the determination of the cutoff point ≥200 for suspected malignancy, the RMI has an accuracy rate of 47%, with sensitivity by 30%, while the cutoff point ROMA ≥7,4% in premenopausal subjects and ≥ 25.3% for suspected malignancies have an accuracy of 82.3% with a sensitivity of 80%, so it is much better compared to RMI in diagnosing a malignancy of the tumor ovary. Specificity of the RMI in this study also was lower (71.4%) compared ROMA (85.5%). In this study, the results of RMI has a very low diagnostic capabilities may be caused by one of the parameters for RMI here, that ultrasound has a weakness, that is the factor of subjectivity from the ultrasound operator, which can cause different results when performed calculations score RMI. Although ultrasound examination performed by a gynecologist who has good skills, but because there is the factor of subjectivity, and a different standard would lead to a different result. In this research CA125 levels can be influenced by several other factors. The ideal tumor marker should be specific, the levels are in accordance with the number of cancer cells and is able to detect malignancy before clinical symptoms arise.(1, 10)

Increased CA125 occurred in 82% of malignant ovarian tumors is shown with a value above normal (> 350 / ml), in advanced ovarian malignant tumors 90% CA125 levels rise above normal limits. But it was only less than 50% increase above normal values occur in malignant ovarian tumor stage I. In addition, other diseases, which is not a malignancy, may show increased CA125 values such as; myoma uteri, pelvic inflammatory disease, endometriosis, and pregnancy. Positive results were also found in cases of peritonitis, pancreatitis, kidney disease, and alcoholic hepatitis.

RMI with a score of ≥200 become a reference as malignant ovarian tumors. RMI sensitivity of some of the research is still lacking despite the specificity pretty good. With less good sensitivity is obtained weaknesses in detecting ovarian malignancies.

Human Epididymis Protein-4 (HE4) has demonstrated excellence as a marker of malignant ovarian tumors compared with CA125. HE4 has the ability to distinguish benign from malignant disease better than CA125. HE4 showed excessive expression in serous ovarian malignancy of 93%, amounting to 100% of epithelial type, and clear cell (not mucinous) by 50%. HE4 also have good sensitivity in cases of ovarian malignancies, especially early-stage (stage I and II), HE4 was also no increase in cases of endometriosis or infection, so it is better specificity. But if the HE4 and CA125 combined will improve both sensitivity and specificity in diagnosing malignancy in ovarian tumors.

Although this research has been carried out effort to remove the confounding factor by making the criteria for inclusion and exclusion criteria but not entirely perfect. In addition to the cost factor both ROMA examination or RMI is high enough.

Conclusions:-

Based on the results of this study concluded that ROMA has better diagnostic accuracy compared to RMI in suspected ovarian tumor malignancy. ROMA can be used as an alternative parameter in order to reduce the incidence of under treatment in cases of ovarian malignancies.

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