Research Article

Risk of Malignancy Index 3 (RMI3) Performance as a Predictor Advanced Stage Epithelial Ovarian Carcinoma used for NACT

Perfoma Risk of Malignancy Index 3 (RMI3) sebagai Prediktor Karsinoma Ovarium Epithelial Stadium Lanjut untuk Pertimbangan Pemberian NACT

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Abstract

Objective: To find a non-invasive method in determining preoperative NACT administration. The method used is RMI 3 diagnostic scoring where this method can be used at the beginning of the examination and the results do not require a long time. assessed whether RMI3 performance can be used as a predictor of advanced epithelial ovarian carcinoma in the interest of NACT.

Methods: A cross-sectional study with samples of all patients suffering from ovarian cancer for the past 5 years, from January 2016 to January 2020 who had been diagnosed at the Gynecology Polyclinic using medical record data from the Gynecology Oncology Polyclinic and Anatomical Pathology Laboratory, RSUD dr. Saiful Anwar in the form of age, demographics, menopausal status, Ca125, ultrasound results. Data is processed using SPSS version 25.0.

Results: The number of initial samples of this study was 253 women, but after being included in the inclusion and exclusion criteria, there were 106 samples. After staging by an authorized clinician, there were 48 patients with early stage and 58 patients with advanced stage. Between the results of the RMI 3 score and the histopathological results on the ROC curve, it was found that the p-value was less than 0.05 ($p<0.05$) with an area of 0.945 and 95% CI of 0.907 - 0.982. P-value less than 0.05 indicates that the RMI3 score is very good for predicting advanced epithelial ovarian carcinoma. With a sensitivity value of 86% and a specificity of 83%, the cut of value RMI score 3 to be a predictor of advanced ovarian carcinoma is 888.3 and PPV 86.2%, NPV 83.3% and an accuracy value of 84.9%.

Conclusion: RMI 3 is very good to be used as a predictor of advanced ovarian carcinoma so that it is expected to be a reference for the administration of neoadjuvant chemotherapy in primary ovarian carcinoma which is predicted to be less likely to achieve optimal cytoreduction if surgery is performed to reduce the risk of mortality, morbidity and bad prognosis.

Keywords: advanced stage, diagnostic test, ovarian carcinoma, NACT, risk of malignancy index, RMI 3, USG.

Abstrak

Tujuan: Untuk mencari metode non invasive dalam penentuan pemberian NACT pre operatif. Metode yang digunakan adalah scoring diagnostic RMI 3 dimana metode ini bisa digunakan saat awal pemeriksan dan hasil nya tidak memerlukan waktu yang lama. menilai apakah performa RMI3 dapat digunakan sebagai prediktor karsinoma ovarium epitelial stadium lanjut dalam kepentingan pemberian NACT.

Metode: *Penelitian observasional analitik jenis studi retrospektif cross sectional dengan sampel semua pasien yang menderita kanker ovarium selama 5 tahun kebelakang yaitu dari bulan januari 2016 sampai dengan Januari 2020 yang telah didiagnosis di poli Ginekologi menggunakan data rekam medis poli Ginekologi Onkologi dan Laboratorium Patologi Anatomi RSUD dr. Saiful Anwar berupa usia, demografi, status menopause, Ca125, hasil USG. Data diproses menggunakan progam SPSS versi 25.0.*

Hasil: *Jumlah sampel awal penelitian ini adalah 253 perempuan, tetapi setelah dimasukan ke dalam kriteria inklusi dan eksklusi terisisa 106 sampel. Setelah di staging oleh klinisi yang berwenang, di dapat 48 pasien dengan stadium awal dan 58 pasien dengan stadium lanjut. Antara hasil skor RMI 3 dan hasil histopatologi pada kurva ROC didapatkan bahwa nilai p-value kurang dari 0,05 ($p<0.05$) dengan luas area sebesar 0,945 dan 95% CI sebesar 0,907 – 0,982. P-value kurang dari 0,05 menunjukkan bahwa skor RMI3 sangat baik untuk digunakan dalam memprediksi karsinoma ovarium epitelial stadium lanjut. Dengan nilai sensitifitas sebesar 86% dan spesifisitas sebesar 83% sehingga cut of value skor RMI 3 untuk menjadi prediktor karsinoma ovarium stadium lanjut adalah sebesar 888,3 dan PPV 86,2%, NPV 83,3% dan nilai akurasi sebesar 84,9%.*

Kesimpulan: *RMI 3 sangat baik untuk digunakan sebagai predictor karsinoma ovarium stadium lanjut sehingga diharapakan dapat menjadi acuan pemberian neoadjuvant kemoterapi pada karsinoma ovarium primer yang diprediksi kecil kemungkinannya mencapai sitoreduksi yang optimal bila dilakukan pembedahan untuk menurunkan risiko mortalitas, morbiditas dan prognostik yang kurang baik.*

Kata kunci: *karsinoma ovarium, risk of malignancy index, RMI 3, stadium lanjut, uji diagnostik, USG, NACT.*

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INTRODUCTION

Worldwide, ovarian cancer is the sixth most frequently diagnosed cancer. In the United States, ovarian cancer is the most common cancer of the four deadliest malignancies in women. The 5-year survival rate is relatively low overall in stages III and IV according to FIGO[1]. Ovarian cancer usually has few specific symptoms, more than 70% of patients are diagnosed at an advanced stage, with a 5-year survival rate of less than 30%. In contrast, 25% of patients diagnosed with stage I ovarian cancer have a 5-year survival rate of up to 90%[2].

The increasing morbidity, mortality and bad prognostic of debulking measures carried out in order to prove an ovarian carcinoma at an early stage is a dilemma, so that neoadjuvant chemotherapy is used in primary ovarian carcinoma which is predicted to be less likely to achieve optimal cytoreduction when surgery is performed[3]. So that it is necessary to give NACT before surgery, there is a dilemma if the clinician does not give NACT to patients with advanced stages, because patients with advanced cancer who have already had surgery have a high risk if the remaining residue is less than 1 to 2 cm[4].

Currently, the procedure for determining NACT is still based on two methods, ascites cytology and laparoscopy. And the requirement for giving NACT is to attach the results of the Anatomical Pathology laboratory. There are weaknesses of these two methods, the weakness of the ascites cytology method is its low validity, false negative value of 30%, for a false positive value of 6.38% even though the specificity value is high at 93% but the validity of this method is still classified as still weak because of the large percentage of patients who should have received NACT but were not given it [6]. The weakness of the second method, namely laparoscopy, is that it requires equipment technology and skilled operators. In terms of time, it is also a further weakness of this method, such as it takes a long time from the time the patient is examined, then scored, the laparoscopy process, waiting for histopathological results which is quite long[6]. So a non-invasive method with high accuracy is needed, the process is simple, the results can be obtained immediately in one examination.

The lack of early identification of precancerous lesions and the non-specificity of early symptoms lead to delays in diagnosis. When detected at an early stage, the disease is highly curable. Diagnosis during surgery is a more accurate opportunity to determine ovarian malignancy through histopathological examination of frozen section[7]. However, there is a dilemma if the clinician does not give NACT to patients with advanced stages. Because patients with advanced stage carcinoma who have already undergone surgery have a high risk such as the risk of morbidity, mortality and prognostic. If the remaining residue is less than 1 to 2 cm, is the bad prognosis.

Several examination formulas have been developed in various countries which are carried out in order to establish a preoperative diagnosis of ovarian cancer[8]. In addition to the Risk of malignancy index (RMI) there are many formulas for examining the suspicion of preoperative ovarian cancer such as (ROMA), (ROCA). Risk of Malignancy Index 3 (RMI3) is the result of the calculation of U x M x CA 125. Ultrasonography includes: multilocularity, dense area, bilaterality, ascites, and intra-abdominal metastases yielding one point each and postmenopausal status score M = 3; premenopausal status score M = 1. Serum CA 125 U/mL was entered directly into the equation[9].

Microscopic examination is important in predicting tumor appearance and determining the best therapeutic approach. Histopathological examination is still the gold standard for definitive diagnosis in cases of malignant ovarian tumors and is a requirement for NACT[10]. In the early stages, postoperative adjuvant chemotherapy is given to high-risk groups of patients. However, the data show that there are 60% of high-risk early-stage cancers that do not recur even without chemotherapy. Until now, there are still no accurate criteria or methods to determine which group of patients have a tendency to experience recurrence, so the management of high-risk early-stage cancer patients is entirely given chemotherapy. The ability to determine groups of patients who have a tendency to relapse will allow more selective therapy and will certainly reduce patient morbidity due to the cytotoxic side effects of chemotherapy[11].

Giving NACT requires accuracy from RMI which is considered capable of being a predictor and clinician's consideration in giving NACT. It is hoped that there will be no errors in the administration of NACT therapy, such as patients who should not require chemotherapy, but are given chemotherapy. Therefore, an ideal RMI3 value is needed for consideration of giving

NACT while taking into account the side effects of the chemotherapy. This is the first study to examine a preoperative non-invasive method for determining NACT administration to patients with advanced ovarian carcinoma.

METHODS

This is a cross-sectional study. In this study, the researchers tried to find the relationship between variables, namely by conducting an analysis of the data collected. This study was conducted in April 2021. The sample population is all populations suffering from ovarian malignancy in the oncology department of the Department of Obstetrics and Gynecology RSUD dr. Saiful Anwar Malang. The research sample was taken with a retrospective study, namely data collection from the medical record of patients suffering from ovarian malignancies for the last 5 years, from January 2016 until January 2020. Samples were also taken from the Anatomical Pathology Laboratory of RSUD dr. Saiful Anwar Malang. After all medical records of patients suffering from ovarian carcinoma were collected, a data collection sheet was made containing the necessary medical record data such as age, patient demographics, menopausal status, CA 125 levels, ultrasound results and histopathology results.

In this study, data analysis techniques were used to measure the accuracy of the Risk Malignancy Index 3 (RMI3), assessed by positive predictive value, negative predictive value, sensitivity, specificity and accuracy value. To determine the cut of value of RMI3 with histopathological appearance according to advanced stage ovarian carcinoma, the ROC curve was used. This statistical analysis uses SPSS version 25.0.

RESULTS

Based on data obtained from the polyclinic oncology and anatomic pathology laboratory for the previous 5 years, 253 patients had ovarian carcinoma. After all the medical records were searched, based on the inclusion and exclusion criteria, 106 samples were obtained. Then performed staging by oncology clinician, obstetrics and gynecology department of RSUD dr. Saiful Anwar, obtained as many as 48 samples suffering from early stages and 58 samples suffering from advanced stages. The following are the characteristics of this research sample:

Table 1. Characteristic Table

Characteristic	Epithelial ovarian carcinoma Stage		P-value
	Early (n = 48)	Advance (n = 58)	
Age (y o)	%	%	
20 - 30	4 (8.3)	1 (1.7)	0.008
31 - 40	7 (14.6)	6 (10.3)	
41 - 50	25 (52.1)	17 (29.3)	
51 - 60	9 (18.8)	26 (44.8)	
61 - 70	1 (2.1)	7 (12.1)	
71 - 80	2 (4.2)	1 (1.7)	
Education			
Elementary school	13 (27.1)	13 (22.4)	0.521
Junior high school	15 (31.3)	24 (41.4)	
Senior high school	19 (39.6)	21 (36.2)	
University	1 (2.1)	0 (0)	
Status			
Single	5 (10.4)	4 (6.9)	0.286
Married once	37 (77.1)	40 (69)	
Married more than once	6 (12.5)	14 (24.1)	
Parity			
Nuliparous	17 (35.4)	15 (25.9)	0.286
Multiparous	31 (64.6)	43 (74.1)	
Contraception			
Not Yet	9 (18.8)	10 (17.2)	0.840
Already	39 (81.3)	48 (82.8)	
BMI			
Underweight	18 (37.5)	33 (56.9)	0.110
Normal	23 (47.9)	21 (36.2)	
Overweight	7 (14.6)	4 (6.9)	
Family history of Gynecologic Cancer			
Denied	46 (95.8)	55 (94.8)	0.808
Be Found	2 (4.2)	3 (5.2)	
NACT			
Not Yet	42 (87.5)	31 (53.4)	0.000
Already	6 (12.5)	27 (46.6)	
Menstrual cycle			
Regular	44 (91.7)	56 (96.6)	0.279
Not Regular	4 (8.3)	2 (3.4)	

Based on the table regarding the characteristics of the study sample, it is shown that of the 48 early-stage patients the majority are 41-50 years old and the majority of 58 patients are 51-60 years old. By using Chi-Square t test, obtained p-value of 0.008 ($p<0.05$) indicating that there is a statistically significant age difference. This indicates that the age group of patients with advanced stage Epithelial Ovarian Carcinoma is older than the group of patients with early Epithelial Ovarian Carcinoma.

Based on the characteristics of education, it was shown that in the early-stage Epithelial Ovarian Carcinoma patient group, most of the patients had high school education, namely 19

(39.6%) and in the group of advanced Epithelial Ovarian Carcinoma patients with junior high school education, 24 (41.4%) patients. By using the Chi-Square test, a p-value of 0.521 (p>0.05) was obtained which explains that there is no difference in educational characteristics between the two groups of patients. Likewise, the characteristics of marital status, parity, family planning, BMI, Family History of Tumors, and menstrual cycles in both groups were relatively the same (p>0.05).

Table 2. Variabel Ultrasound

Variabel USG	Epithelial ovarian carcinoma Stage		*P-value*
	Early (n = 48)	Advance (n = 58)	
Asites	%	%	%
Not Found	36 (75)	18 (31)	0.000
Found	12 (25)	40 (69)	
Papil			
Not Found	33 (68.8)	26 (44.8)	0.014
Found	15 (31.3)	32 (55.2)	
Septa			
Not Found	18 (37.5)	24 (41.4)	0.684
Found	30 (62.5)	34 (58.6)	
Solid Part			
Not Found	21 (43.8)	11 (19)	0.006
Found	27 (56.3)	47 (81)	
Metastasis Intra Abdomen			
Not Found	48 (100)	51 (87.9)	0.013
Found	0 (0)	7 (12.1)	

Based on the characteristics of ascites and papillae, the p-value was less than 0.05 (p<0.05) which proves that there are differences in the characteristics of the two groups of patients. Patients with advanced epithelial ovarian carcinoma have more ascites and papillae than patients with early stage epithelial ovarian carcinoma.

Determination of cut off Value RMI 3 to predict the stage of Epithelial Ovarian Carcinoma Advanced stage can be measured using the ROC curve. The following is the ROC curve of the RMI3 score.

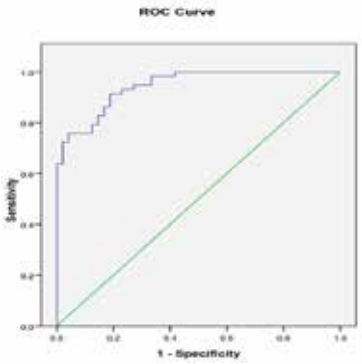

Figure 1. Curve ROC Skor RMI 3

Table 3. Area of the ROC Curve Score RMI 3

Variable	Area	*P-value*	95% CI
RMI 3	0.945	0.000	0.907 - 0.982

Based on table 3 above, the predicted results of the RMI3 score in predicting advanced-stage Epithelial Ovarian Carcinoma, obtained a p-value of less than 0.05 (p<0.05) with an area of 0.945 and 95% CI of 0.907 - 0.982. p-value less than 0.05 indicates that the RMI3 score is very good for predicting the stage of Epithelial Ovarian Carcinoma.

Table 4. Accuracy Comparison Value RMI 3

Score RMI 3	Result		Sensitifity (%)	Spesifity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Early Stage	Advance Stage					
Cut Off Point = 789.45	%	%					
Early	39 (83)	8 (17)	86.2	81.3	84.7	83.0	84.0
Advance	9 (15.3)	50 (84.7)					
Cut Off Point = 888.3							
Early	40 (83.3)	8 (16.7)	86.2	83.3	86.2	83.3	84.9
Advance	8 (13.8)	50 (86.2)					
Cut Off Point = 969.3							
Early	40 (81.6)	9 (18.4)	84.5	83.3	86.0	81.6	84.0
Advance	8 (14)	49 (86)					
Cut Off Point = 1008							
Early	40 (80)	10 (20)	82.8	83.3	85.7	80.0	83.0
Advance	8 (14.3)	48 (85.7)					

Of the four cut off points, it is shown that RMI3 with a cut off point of 888.3 has the highest PPV, NPV, and accuracy values. From this test, it is proven that an RMI3 of 888.3 is more ideally used as a cut off point predictor of advanced stage Epithelial Ovarian Carcinoma.

The sensitivity and specificity of RMI3 score prediction for predicting advanced-stage Epithelial Ovarian Carcinoma is presented in the attachment. The following is a graph of the sensitivity and specificity of the RMI 3 score:

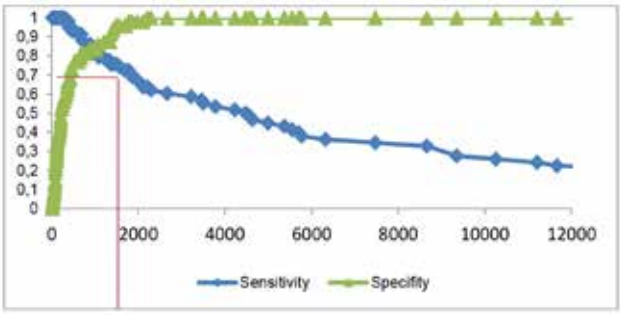

Figure 2. Sensitivity and Specificity Plot of RMI 3 Skor Score

Based on Figure 2, a plot between the sensitivity and specificity values of the RMI3 score is shown. As explained in the figure, it is shown that there is an intersection of the sensitivity and specificity values. This intersection shows the optimum value that can be used as a cut off value or limit in determining advanced-stage Epithelial Ovarian Carcinoma. The intersection point is obtained from the combination of the highest sensitivity and specificity values. Based on the sensitivity and specificity values in the appendix, it is shown that the highest combination of sensitivity and specificity values is located at the RMI 3 point of 888.3 where at that point the sensitivity value is 0.862 and specificity is 0.833. Thus, the cut of value for the RMI3 score to determine advanced-stage Epithelial Ovarian Carcinoma is 888.3.

The level of accuracy of RMI3 in predicting the stage of Epithelial Ovarian Carcinoma can be done by calculating the Positive Predictive Value (PPV), Negative Predictive Value (NPV) and the accuracy value. The PPV, NPV and accuracy values were calculated by comparing the predicted results of RMI3 with the results of histopathological examination. The following are the results of calculating the RMI3 accuracy level in predicting the stage of Epithelial Ovarian Carcinoma:

Table 4. RMI 3 Accuracy Rate as a Predictor of Advanced Stage Epithelial Ovarian Carcinoma

Score	Result		PPV (%)	NPV (%)	Accuracy
	Early Stage	Advance Stage			(%)
RMI 3	%	%			
Early	40 (83.3)	8 (13.8)	86.2	83.3	84,9
Advance	8 (16.7)	50 (86.2)			

Based on the results of the analysis using the contingency coefficient of the relationship between the RMI3 results and the histopathological results, the positive predictive value (PPV) was 86.2% and the negative predictive value was 83.3%. From the initial 48 patients with Epithelial Ovarian Carcinoma based on the results of histopathological examination, it turned out that there were 8 (16.7%) patients who were predicted to be in advanced stage. The NPV value of 83.3% indicates the RMI3 accuracy rate in predicting the early stage is 83.3%. The PPV value of 86.2% indicates the RMI3 accuracy rate in predicting advanced stages is 86.2%. Meanwhile, the accuracy value of RMI 3 is 84.9%.

DISCUSSION

Of the 106 women with ovarian carcinoma who were included in this retrospective study, it was shown that of the 48 early-stage patients the most were 41-50 years old and from 58 advanced-stage patients the most were 51-60 years old. The results obtained in this study are in line with Abdulrahman's retrospective study in Wales United Kingdom which said that the 51-60 age group had the highest incidence of ovarian malignancy[12]. A meta-analytical epidemiological study of 125 articles published in 1925-2018 stated that age On average, women with ovarian cancer are detected at the age of 50-79 years. Detection in the elderly shows the severity of the disease and the relatively lower survival rate[13].

This study revealed that patients with ovarian carcinoma who came to RSUD dr. Saiful Anwar Malang in January 2016 - January 2020 the highest proportion diagnosed with ovarian cancer was in the multiparous group, both in the early stage (64.6%) and advanced stage (74.1%). This study is inconsistent with several case-control studies which showed multiparous women

had a 30-60% lower risk of developing ovarian carcinoma. Increased parity is associated with a reduced risk of ovarian malignancy. Pregnancy is thought to reduce the risk of ovarian tumor malignancy by 19%[11].

The chance of ovarian cancer occurring in women who do not use contraception is higher. This study shows that women who have no history of contraceptive use are around 81.3% in the early stages and 82.8% in the advanced stages, this is due to the distribution of contraceptive use[14].

In this study, which used 106 samples of medical records of women with ovarian carcinoma, the results showed that the RMI score of 3 was very good for predicting advanced epithelial ovarian carcinoma with a p-value of less than 0.05 ($p<0.05$) with an area of of 0.945 and 95% CI of 0.907 - 0.982.

Determination of the Cut Off Value RMI 3 to predict the stage of Epithelial Ovarian Carcinoma Advanced stage can be measured using the ROC curve to see the sensitivity and specificity resulting from the prediction that is obtained at that point resulting in a sensitivity value of 86% and specificity of 83% so that the cut of value score RMI 3 to be a predictor of advanced ovarian carcinoma is 888.3. The level of accuracy of RMI 3 is shown by the PPV value of 86.2%, the NPV value of 83.3% and the accuracy value of 84.9%. In the study conducted by Tingulstad modified the RMI and defined RMI 3 and they observed that at the cut-off level of 200 the sensitivity and specificity were 71% and 92%[15].

This level of accuracy is in line with a study involving 548 female patients, they calculated an RMI with a cut-off point of 200, where there were sensitivity, specificity, PPV, and NPV of 81%, 85%, 48%, and 96%, respectively[16]. In another study, which used 100 female patients with ovarian carcinoma with a cut-off point of 200, the sensitivity, specificity, PPV, and NPV were 90%, 89%, 96%, and 78%, respectively[17].

In the study group, Aktürk stated that there were no statistically significant differences in identifying different malignancy risk indices between RMI 1, RMI 2, RMI 3 and RMI 4[18]. This study is also in line that the efficacy of RMI has been validated in a number of studies and has proven to be a simple, low-cost, and effective tool for triage management of ovarian carcinoma[19]. The sensitivity of RMI 3 indicates that it is able to label malignant tumors in high-risk cases, while its specificity demonstrated that he was able to label benign tumors as low-risk cases. It was the best result when all the parameters examined i.e. sensitivity, specificity, PPV, and NPV were high[20].

A definite or gold standard diagnosis of ovarian carcinoma can be established only after surgery. In order to detect the disease at a very early stage, several approaches have been used to triage women with suspected ovarian carcinoma. According to the referral guidelines, for women suspected of having ovarian carcinoma, patients were grouped according to menopausal status, CA 125 level more than 200 u/ml, presence of ascites, presence of intra-abdominal metastases (by ultrasound examination). With these indications, it can be referred to a gynecological oncologist because each of these parameters is significantly and independently associated with the possibility of ovarian malignancy. RMI based on menopausal status, CA125 levels, and ultrasound imaging is the most widely used preoperative method[18].

The results of this study indicate that women with an RMI 3 value limit of 888.3 have a risk of advanced ovarian malignancy, so that the lowest score of RMI 3 can be used as a reference for administering neoadjuvant therapy prior to diagnosis during surgery to prove histopathological results. This is in line with the research conducted by Petronella which said that women with an RMI value below 200 had a low risk of malignancy and therefore did not require surgery for histopathological examination of frozen section[21]. Although histopathological analysis is a useful method and reliable for determining the nature of ovarian tumors, there are still weaknesses, namely the prolongation of the operation time and the duration of anesthesia. This can really cause problems if the hospital does not have an anatomical pathology laboratory available, which will be time consuming and more expensive because of the transportation of specimens to the pathology laboratory center. In this study about 13% of patients with RMI values below 200 should be able to avoid excessive frozen section histopathological testing in cases of benign tumors [22]. The preoperative RMI score variable can be used as a reference for administering NACT and as part of the preoperative assessment. Consideration of the clinician must consider the advantages and disadvantages of giving chemotherapy, because of the many side effects of chemotherapy. So that there are no more mistakes in giving chemotherapy to ovarian carcinoma patients.

CONCLUSIONS

The results of this study indicate that the RMI3 score is very good to be used in predicting the stage of Epithelial Ovarian Carcinoma. The lowest value of RMI 3 that can be used as a reference limit to determine advanced stage Epithelial Ovarian Carcinoma is 888.3. It is hoped that this cut off value can be a reference for preoperative neoadjuvant therapy to avoid morbidity and mortality due to the high risk of surgery. And this non-invasive method can be a consideration for clinicians in determining the administration of NACT.

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