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MALIGNANCY RISK INDEX 4 (RMI 4) IS BETTER THAN RMI 3 AS A PREDICTOR ADVANCED EPITHELIAL OVARIAN CARCINOMA WAS USED FOR NACT

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Abstract

Of the 4 cancers in women, ovarian carcinoma is the first cause of death. The low survival rate in patients with advanced stages requires early detection to improve treatment outcomes. The methods currently used to determine whether a patient can be given neoadjuvant chemotherapy are ascites cytology and laparoscopy.This study aims To compare RMI 4 and RMI 3 as a non-invasive method in determining preoperative NACT administration. The method used is RMI 3 and RMI 4 diagnostic scoring where this method can be used as a predictor of advanced epithelial ovarian carcinoma in the interest of NACT. An analytical observational study with a retrospective cross sectional type 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 RSUD dr. Saiful Anwar. The number of initial samples of this study was 253 women, but after being included in the inclusion 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 score and the histopathological results on the ROC curve, it was found that the accuracy value of RMI 3 is 84.9% and the accuracy value of RMI 4 is 86.8%. It can be concluded that RMI 4 is better than RMI 3 as a predictor of advanced ovarian carcinoma to determining preoperative NACT administration.

Keywords: *Risk of malignancy index, RMI4, RMI3, ovarian carcinoma, advanced stage, diagnostic test, NACT*

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INTRODUCTION

Worldwide, ovarian carcinoma has the highest mortality rate of all gynecologic malignancies [1]. According to WHO/IARC (International Agency for Research on Cancer) it is stated that the incidence of ovarian carcinoma in Indonesia ranks second after cervical carcinoma with an incidence rate of 9664 cases in 2008 [2]. The high rate of morbidity and mortality is related to the complications found in the operation of patients with advanced ovarian carcinoma who underwent surgery without neoadjuvant chemotherapy, including adhesions, organ injury and bleeding[3].

Currently, the standard primary therapy for patients with advanced ovarian carcinoma is primary debulking surgery followed by adjuvant chemotherapy with Carboplatin and Paclitaxel [4]. Debulking is considered optimal if the residue left is 1cm in size. The increasing morbidity and mortality of debulking performed in the context of proving an ovarian carcinoma at an early stage is a dilemma. Therefore, neoadjuvant chemotherapy is used for primary ovarian carcinoma, which is predicted to be less likely to achieve optimal cytoreduction if surgery is performed [5]. Patients with poor performance status, who are at high risk for morbidity and mortality if cytoreduction surgery is performed, can also be given multiple cycles and standard chemotherapy before surgery, so that subsequent cytoreduction surgery will be safer [6].

The multiparametric Risk of Malignancy Index (RMI) score can be a useful tool in predicting ovarian malignancy in areas with limited resources. The Risk of Malignancy Index (RMI), which takes into account serum CA-125 levels, menopausal status, and ultrasound findings in predicting malignant pelvic masses, is widely used in developed countries [7]. Yamamoto in 2009, who confirmed that RMI 4 is more reliable than RMI 1, RMI 2, and RMI 3 [8].

RMI3 score 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. [9] In other study RMI4 score is very good to be used in predicting the stage of Epihteal Ovarian Carcinoma. The best cut off point RMI 4 that can be used as a reference limit to determine advanced stage Epithelial Ovarian Carcinoma is 2982. [10] However, there are no studies that discusses the comparison of the performance of Risk Of Malignancy Index 3 (RMI3) and Risk Of Malignancy Index 4 (RMI4) as predictors advanced epithelial ovarian carcinoma used for NACT

METHODS

1) The design of this research is an analytical observational cross sectional study, in this study the researcher tried to compare 2 variables between the performance of RMI 3 and RMI 4 by analyzing the data collected. This research was conducted in April 2021. The sample population was the entire population of patients with ovarian malignancy in the oncology section of the Department of Obstetrics and Gynecology RSUD dr. Saiful Anwar Malang Indonesia. The research sample was taken by retrospective study, collecting data from the medical records of patients suffering from ovarian malignancy for the last 5 years, from January 2016 to January 2020.
2) Samples were also taken from the Anatomical Pathology Laboratory of RSUD dr. Saiful Anwar Malang. After all data on patients suffering from ovarian carcinoma were collected, a data collection sheet was made containing medical record data needed for RMI scoring such as age, patient demographics, menopausal status, CA 125 levels, ultrasound results and histopathological results.
3) In this study, data analysis techniques were used to measure the accuracy of Risk Malignancy Index 3 (RMI3) and RMI4 which were assessed with positive predictive value, negative predictive value, sensitivity, specificity and accuracy value. To determine the truncation of RMI3 and RMI4 values with histopathological features according to advanced ovarian carcinoma, the ROC curve was used. We then compare the accuracy values, which between the 2 variables have the best accuracy values. This statistical analysis uses SPSS version 25.0.

RESULTS

Based on the data we have collected from the oncology and anatomical pathology polyclinic laboratory for the past 5 years, 253 patients had ovarian carcinoma. We grouped all searchable medical records, based on inclusion and exclusion criteria, the final result was 106 samples. Then performed staging by specialists oncology, obstetrics and gynecology RSUD dr. Saiful Anwar, obtained as many as 48 samples suffering from early stages and 58 samples suffering from advanced stages. The following is a description of each assessment variable from RMI

Table 1. 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%)	
Tumor Size			
< 7	0 (0%)	2 (3.4%)	0.194
>= 7	48 (100%)	56 (96.6%)	

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.

Based on the characteristics of the solid section and intra-abdominal metastases, p-value <0.05 was obtained, which proves that there are differences in characteristics between the two groups of patients. Solid sections and intra-abdominal metastases were more common in patients with advanced-stage epithelial ovarian carcinoma than in early-stage epithelial carcinoma. Based on the characteristics of the septa and tumor size, a p-value of > 0.005 was obtained, which means that there was no significant difference in patients with early and advanced epithelial ovarian carcinoma compared to the characteristics of the ultrasound septa and tumor size.

Curve ROC RMI 3

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

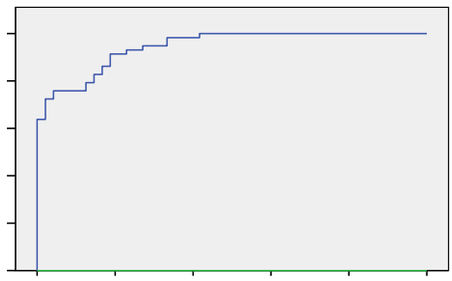


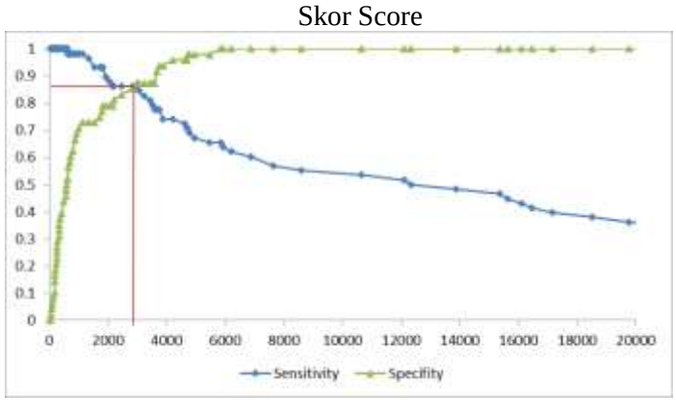
Table 2. Area of the ROC Curve Score RMI3

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

Based on table 2 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.

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 RMI3 score:

Figure 2. Sensitivity and Specificity Plot of RMI3 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 3. 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%.

Curve ROC RMI 4

Determination of Cut Off Value RMI4 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 RMI4 score:

Figure 3. Curve ROC Skor RMI 4

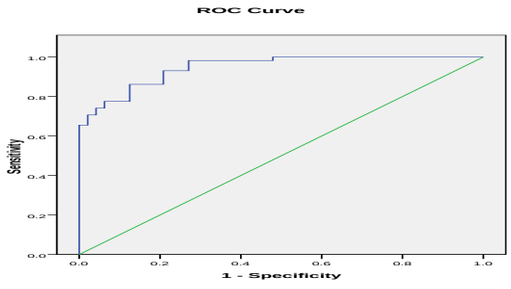
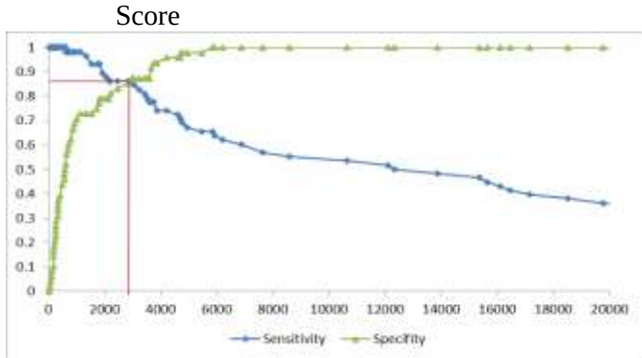


Table 4. Area of the ROC Curve Score RMI4

Variable	Area	p-value	95% CI
RMI 4	0.948	0.000	0.912 - 0.984

Based on table 4 above, the predicted results of the RMI4 score in predicting advanced-stage Epithelial Ovarian Carcinoma, obtained a p-value of less than 0.05 ($p<0.05$) with an area of 0.948 and 95% CI of 0.912 - 0.984. P-value less than 0.05 indicates that the RMI4 score is very good to be used in predicting the stage of Epithelial Ovarian Carcinoma.

Figure 4. Sensitivity and Specificity Plot of RMI3 Score



Based on Figure 4, a plot between the sensitivity and specificity values of the RMI 4 score is shown. As explained in the figure, it is shown that there is an intersection of the sensitivity and specificity values. 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 4 point of 2982 where at that point the sensitivity value is 86,2 % and specificity is 87,5%. Thus, the cut off value of the RMI4 score to determine advanced epithelial ovarian carcinoma is 2982.

The level of accuracy of RMI 4 in predicting the stage of epithelial ovarian carcinoma can be done by calculating the Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Accuracy value. These coefficients were calculated by comparing the predicted results of RMI 4 with the results of histopathological examination. In this study, the accuracy level was measured by comparing 4 RMI 4 cut-off points. The following are the results of calculating the RMI 4 accuracy level in predicting advanced-stage epithelial ovarian carcinoma at 4 cut-off points:
Of the four cut off points, it is shown that RMI 4 with a cut off point of 2982 has the highest PPV, NPV, and accuracy values. From this test, it was proven that RMI 4 of 2982 was more appropriate to be used as a cut off point predictor of advanced epithelial ovarian carcinoma.

RMI 4 Accuracy Level as a Predictor of Advanced Epithelial Ovarian Carcinoma

The level of accuracy of RMI4 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 RMI4 with the results of histopathological examination. The following are the results of calculating the RMI4 accuracy level in predicting the stage of Epithelial Ovarian Carcinoma:

Table 5. RMI 4 Accuracy Rate as a Predictor of Advanced Stage Epithelial Ovarian Carcinoma

Score	Gold Standart		PPV (%)	NPV (%)	Accuracy (%)
	Early Stage	Advance Stage			
RMI 4					
- Early	42 (87.5%)	8 (13.8%)	89.2	84.0	86,8
- dvance	6 (12.5%)	50 (86.2%)			

Based on the results of the analysis using the contingency coefficient of the relationship between the results of RMI 4 and histopathological results, the positive predictive value (PPV) was 89.3% and the negative predictive value was 84.0%. From 48 patients with early-stage epithelial ovarian carcinoma based on histopathological examination results, it turned out that there were 6 (12.5%) patients who were predicted to be in advanced stage. The NPV value of 84.0% indicates the RMI4 accuracy rate in predicting early-stage epithelial ovarian carcinoma is 84.0%. Meanwhile, out of 58 patients with advanced epithelial ovarian carcinoma based on histopathology, there were 8 (13.8%) patients who were predicted to have early stage epithelial ovarian carcinoma. The PPV value of 89.3% indicates the RMI4 accuracy rate in predicting advanced stage epithelial ovarian carcinoma is 89.3%.

DISCUSSIONS

The International Agency for Research on Cancer (IARC) states that the incidence of ovarian carcinoma in Indonesia ranks second most after cervical carcinoma with an incidence rate of 9664 cases in 2008 with the age group suffering from ovarian carcinoma the most being the age group 41 to 50 years, which is 62.7%. and at least 31 to 40 years, which is as much as 10.8%[2]. IARC also stated that in 2020 there were 14.896 cases of ovarian cancer in women at all age levels that occurred in Indonesia. Ovarian cancer is still one of the top 10 deadliest cancers in the world.

Based on the results obtained data for the last 5 years, there were 253 patients suffering from ovarian carcinoma. This data is grouped from all searchable medical records, based on inclusion and exclusion criteria, the final result is 106 samples. Then performed staging by specialists oncology, obstetrics and gynecology RSUD dr. Saiful Anwar, obtained as many as 48 samples suffering from early stages and 58 samples suffering from advanced stages.

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. 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. [9] 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. [22]

RMI 4 can be used as a predictor of advanced epithelial ovarian carcinoma with a p-value <0.05 and a positive predictive value (PPV) of 89.3% and a negative predictive value of 84.0%. The best cut off point value as a predictor of advanced epithelial ovarian carcinoma was found at 2982, with a sensitivity value of 0.082, specificity 0.875, positive predictive value (PPV) of 89.3%, and negative predictive value (NPV) of 84%. %. [10] In the study conducted by Tingulstad modified the RMI and defined RMI 4 and they observed that at the cut-off level of 450 the sensitivity and specificity were 71% and 92%[16]. 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 [17]. In another study, which used 100 female patients with ovarian carcinoma with a cut-off point of 450, the sensitivity, specificity, PPV, and NPV were 90%, 89%, 96%, and 78%, respectively [18].

In this study RMI4 has an accuracy of 86.8% as a predictor of advanced stage epithelial ovarian carcinoma while RMI3 has an accuracy of 84.9% as a predictor of advanced stage epithelial ovarian carcinoma. This shows that RMI4 is better used as a predictor of advanced stage epithelial ovarian than RMI3.

CONCLUSION

In conclusions our results of this study indicate that RMI4 has an accuracy of 86.8% as a predictor of advanced stage epithelial ovarian carcinoma while RMI3 has an accuracy of 84.9% as a predictor of advanced stage epithelial ovarian carcinoma. This shows that RMI4 is better used as a predictor of advanced stage epithelial ovarian than RMI3.

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