ORIGINAL RESEARCH

The expression of immunohistochemical biomarkers PAX8 and CD117 in platinum resistant ovarian cancer at Saiful Anwar General Hospital, Malang, Indonesia

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ABSTRACT

Objective: Ovarian cancer is a gynecological disease commonly encountered by women, and resistance to platinum therapy is a significant challenge in its management. This study aims explore a monitoring method for post-operative ovarian carcinoma also evaluate the immunohistochemical expression of PAX8 and CD117 in ovarian cancer and identify their association with the occurrence of platinum resistance.

Materials and Methods: A cross-sectional approach to an observational analytical design, utilizing consecutive sampling which have met the inclusion and exclusion criteria. Tissue resulting from biopsy/surgical procedure which was made into a representative paraffin block was then subjected to immuno-histochemical examination in the Anatomical Pathology Department of Saiful Anwar Hospital Malang. PAX8 and CD117 expressions were analyzed using immunohistochemistry. The results of this study were assessed using ROC curves accompanied by Youden index calculation, determining sensitivity and specificity levels.

Results: In this research, the results were obtained that the area under the curve (AUC) for PAX8 and CD117 is 0.785 and 0.809, respectively. PAX8 expression demonstrates the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy of 53.125%, 87.50%, 18.75%, 51.85%, and 60.0%, respectively. The expression of CD117 displays the following values: 71.4 percent, 72.73%, 70%, 72.73%, and 70% for the positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, respectively.

Conclusion: According to this study, PAX8 and CD117 immunohistochemistry expression in ovarian cancer may act as prognostic biomarkers for platinum resistance. In this study there are several limitations that can be revised in future research.

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Highlights:

1. Ovarian cancer is a gynecological disease commonly encountered by women, and resistance to platinum therapy is a significant challenge in its management
2. PAX8 and CD117 have shown potential as predictors of resistance in ovarian cancer. However, research on the expression of these biomarkers concerning platinum resistance in ovarian cancer patients
3. The objective of this research is to assess the immunohistochemistry expression of CD117 and PAX8 in ovarian cancer and determine whether these expressions are linked to the development of platinum resistance.

INTRODUCTION

Ovarian cancer is a malignancy in the field of gynecology that ranks fourth among the most common types of gynecological cancers worldwide, following cervical, breast, colorectal, and uterine corpus cancers. It is a leading cause of death, accounting for 47% of all gynecological cancer-related deaths.[1] Ovarian cancer holds the fifth position among cancer-related deaths, with an incidence of around 3% of all malignancies in women. Ovarian cancer is commonly found in older women, postmenopausal, with nearly 80% of cases occurring in women over the age of 50.[2] The exact prevalence and incidence of ovarian cancer in Indonesia are not precisely known. Based on estimated data of new cases at Dharmais Cancer Hospital in Jakarta from 2010 to 2013, ovarian cancer ranks as the fourth most common cancer after breast, cervical, and lung cancers. The number of new cases of ovarian cancer at Dharmais Cancer Hospital from 2010 to 2013 was approximately 537 patients, with a patient mortality rate of 126 cases.[3]

Tumor microenvironment modifications, such as those pertaining to extracellular matrix composition, matrix stiffness, hypervascularization, hypoxia, and paracrine variables, are linked to the advancement of cancer. The capacity to withstand chemotherapy is a crucial characteristic of malignant cancer cells. Components of the extracellular matrix can augment cancer cells' chemoresistance by activating different signaling pathways, resulting in modifications to gene expression and protein activity that facilitate resistance. Oncology research aims to comprehend and conquer chemoresistance, the capacity of cancer cells to elude or reject therapeutic therapies.[4]

PAX8 is a sensitive and specific marker that identifies cancers originating from the ovaries or fallopian tubes. Patients with advanced-stage ovarian cancer might benefit greatly from the use of PAX8 staining in the proper therapeutic context prior to neoadjuvant treatment.[5] Additionally, CD117 is a protein which is crucial in the development of various cell types, including melanocytes, germ cells, mast cells, erythrocytes, and interstitial cells.[6] The expression of CD117 (c-kit) plays a pathological role in various malignancies, including ovarian cancer. Recent research indicates the relevance of response to imatinib (a kinase inhibitor) in ovarian cancer patients.[7]

Based on the background mentioned above, the researcher intends to explore a monitoring method for post-operative ovarian carcinoma by examining the immunohistochemical expression of PAX8 and CD117 as predictors for the occurrence of platinum resistance in ovarian cancer cases at Dr. Saiful Anwar Regional General Hospital in Malang.

MATERIALS AND METHODS

An analytical observational design and a cross-sectional study methodology were used in this investigation. The research was conducted at the Gynecologic Oncology Outpatient Clinic, Medical Records, and Pathology Anatomy Laboratory of Dr. Saiful Anwar Regional General Hospital in Malang. The study was carried out from November 2022 to October 2023.

The sampling method in this study was chosen using non-probability sampling, specifically consecutive sampling, and met the inclusion and exclusion criteria. Tissue samples from biopsy/surgery were processed into paraffin blocks, followed by immunohistochemical examination at the Pathology Anatomy Department of Dr. Saiful Anwar Regional General Hospital in Malang. Criteria for inclusion consist of patients diagnosed with ovarian carcinoma by clinicians in the Obstetrics and Gynecology department who have undergone platinum-based chemotherapy and experienced recurrence within less than 6 months after the last chemotherapy session. Patients who have undergone laparotomy for confirmation of clinical examination results. Patients with Paraffin Blocks of ovarian cancer tissue available in the Pathology Anatomy Laboratory of Dr. Saiful Anwar Regional General Hospital in Malang. Criteria for exclusion consist of patients with adnexal masses not originating from the ovaries, suffering from other malignancies, and infected adnexal masses.

The expression of PAX8 and CD117 were examined from five perspectives. Strong intensity of PAX8 and CD117 expression was observed under the microscope at 400x magnification, revealing a dark brown color in the cell nuclei. In cases of moderate intensity of PAX8 and CD117 expression, a faint coloration was observed in the cell nuclei, appearing light brown under the microscope at 400x magnification. Conversely, weak intensity showed a pale brown coloration in the cell nuclei when examined under the microscope at 400x magnification.

The expressions of CD117 and PAX8 are presented descriptively. Cut-off values for CD117 and PAX8 expression are determined by selecting the best threshold between sensitivity and specificity values. This process is determined through Receiver Operating Characteristic (ROC) analysis, accompanied by Youden index calculation. The highest Youden index value is considered the optimal cut-off. Afterwards, specificity,

sensitivity, positive predictive value, and negative predictive value are ascertained using the computed ideal cut-off values. Statistical analysis of the obtained data was conducted using the SPSS program, and a p-value < 0.05 was considered statistically significant.

This research has received a legal approvement of ethical feasibility issued by the Health Research Ethics Commission of the General Hospital Dr. Saiful Anwar Malang with registration number 400/228/K.3/102.7/2022 which was issued on September 21st, 2022.

RESULTS AND DISCUSSION

Figure 1 and 2 display the features of the results obtained from the immunohistochemistry staining of PAX8 and CD117, respectively.

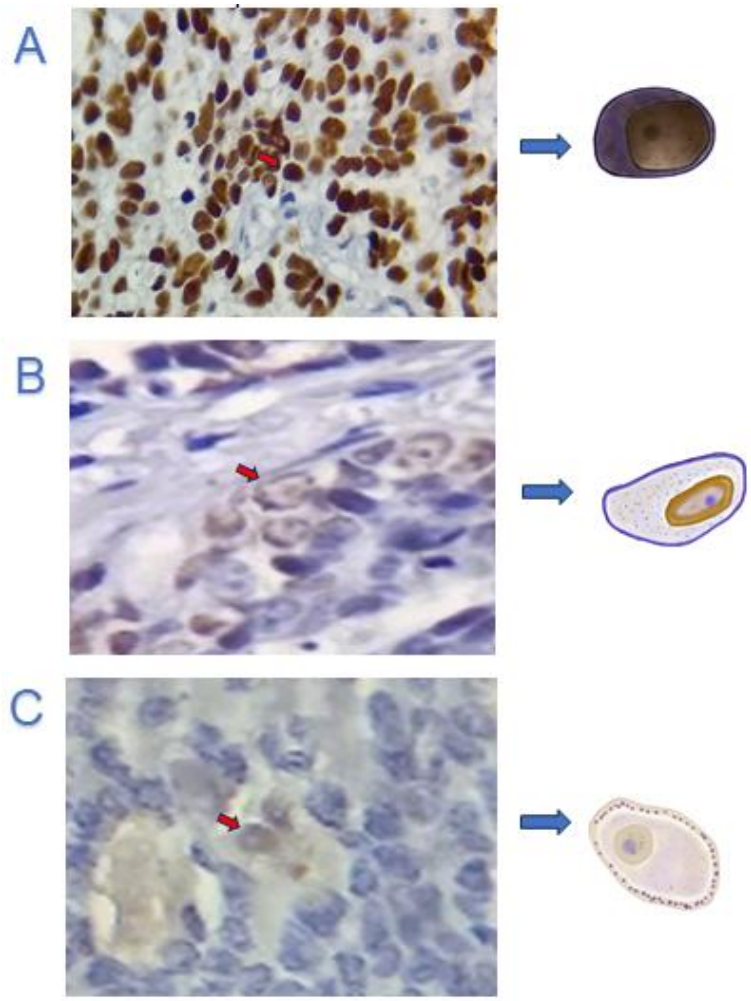

Figure 1. Immunohistochemical staining of PAX8 under the microscope. (A) Strong intensity of PAX8 expression observed under the microscope at 400x magnification; (B) Moderate intensity of PAX8 expression observed under the microscope at 400x magnification; (C) Weak intensity of PAX8 expression observed under the microscope at 400x magnification.

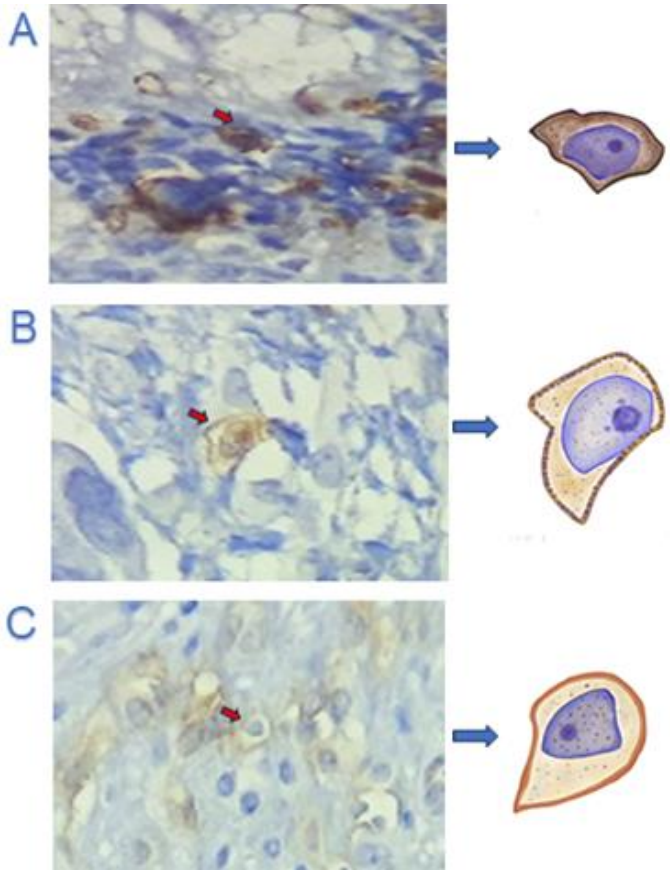

Figure 2. Immunohistochemical staining of CD117 under the microscope. (A) Strong intensity of CD117 expression observed under the microscope at 400x magnification; (B) Moderate intensity of CD117 expression observed under the microscope at 400x magnification; (C) Weak intensity of CD117 expression observed under the microscope at 400x magnification.

In this study, quantitative measurements were also conducted in the form of percentages based on the number of immunohistochemical staining findings on tumor cells for PAX8 and CD117 antibodies. There was a total of 32 samples divided into two groups, comprising 16 platinum-resistant samples and 16 platinum-sensitive samples for comparison (Figure 3).

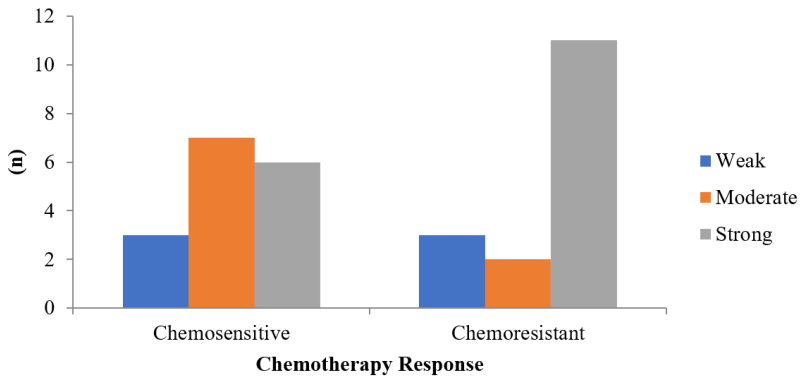

Figure 3. Distribution of PAX8 expression in relation to the occurrence of platinum resistance.

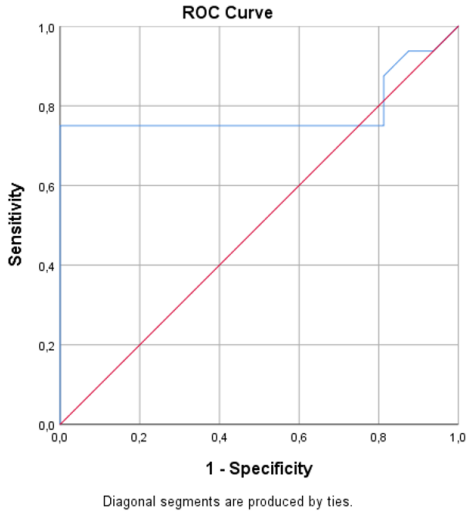

Figure 4. ROC curve of PAX8 expression in relation to the incidence of platinum resistance.

Table 1. Area under the curve for PAX8 expression and incidence of resistance

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.785	.096	.006	.598	.973

The test result variable(s): PAX_Num has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Based on Table 1, it is evident that PAX8 expression can significantly be utilized as a predictor of platinum resistance incidence ($p = 0.006$; $p < 0.05$). The area under the PAX expression curve is 0.785, with an upper limit value of 0.973 and a lower limit of 0.598. The Youden index indicates that PAX8 expression ≥ 3.5 has a sensitivity level of 0.875. This cutoff point is chosen because it has sensitivity values close to the PAX8 area. The results of this cutoff point are then subjected to sensitivity, specificity, positive predictive, and negative predictive testing (Figure 4). The outcomes of these tests are presented in Table 2. Based on the diagnostic test calculations in this table, the accuracy value is found to be 53.125%, with sensitivity value of 87.50% and specificity value of 18.75%. The positive predictive value and negative predictive value are calculated to be 51.85% and 60.0%, respectively. These findings suggest that PAX8 expression tends to be more suitable for screening purposes, given its higher sensitivity compared to its specificity.

Table 2. Diagnostic test of PAX8 expression for platinum resistance

PAX8 Expression	Platinum resistance		Total
	Yes	No	
PAX8 $\geq$ 3.5	14	13	27
PAX8 < 3.5	2	3	5
Total	16	16	32

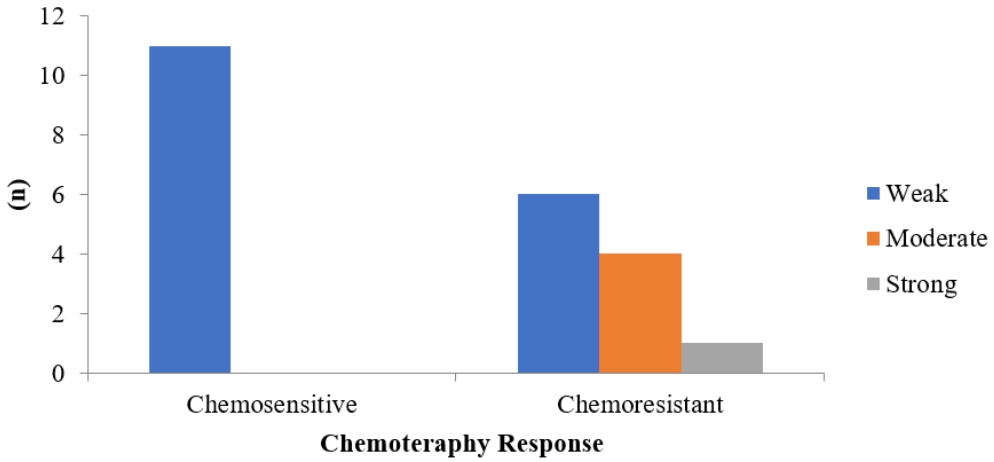

Figure 5. Distribution of CD117 expression in relation to the occurrence of platinum resistance.

Based on Figure 5, it illustrates the distribution of CD117 expression concerning the occurrence of platinum resistance. Strong CD117 expression is observed in a small proportion of ovarian cancer patients with chemoresistance. The distribution of weak CD117 expression is more prevalent in ovarian cancer patients with chemosensitive. Based on the ROC curve between CD117 expression and the occurrence of platinum resistance, it is evident that the sensitivity area is lower compared to the 1-specificity area (Figure 6).

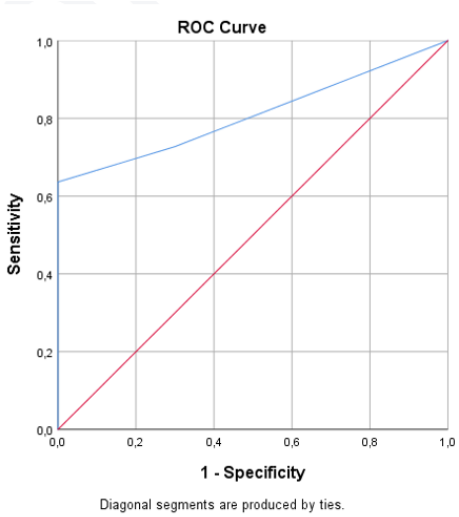

Figure 6. ROC curve of CD117 expression in relation to the incidence of platinum resistance

Table 3: Area under the curve for CD117 expression and incidence of resistance

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.809	.100	.017	.613	1.000

The test result variable(s): CD17_Num has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Table 4. Diagnostic test of CD117 expression for platinum resistance

CD117 expression	Platinum resistance		Total
	Yes	No	
CD117 ≥ 0.55	8	3	11
CD117 < 0.55	3	7	10
Total	11	10	21

According to Table 3, it is evident that CD117 expression can significantly be utilized as a predictor of platinum resistance incidence ($p = 0.017$; $p < 0.05$). The area under the CD117 expression curve is 0.809, with an upper limit value of 1.000 and a lower limit of 0.613.

The Youden index suggests that CD117 expression ≥ 0.55 has a sensitivity level of 0.827. This cutoff point is chosen because it has sensitivity values close to the CD117 area. The results of this cutoff point are then subjected to sensitivity, specificity, positive predictive, and negative predictive testing. The outcomes of these tests are presented in Table 4.

Based on the diagnostic test calculations in Table 4, the accuracy value is found to be 71.4%, with a sensitivity of 72.73% and specificity of 70%. The positive predictive value and negative predictive value are calculated to be 72.73% and 70%, respectively. These findings suggest that CD117 expression tends to be more suitable for screening purposes, given its higher sensitivity compared to its specificity.

This research was entirely conducted at Dr. Saiful Anwar Malang Regional General Hospital. The samples were obtained from patient data diagnosed with Ovarian Cancer at the Gynecologic Oncology Outpatient Clinic and Medical Records of Dr. Saiful Anwar Malang Regional General Hospital. The sample management in this study was conducted through blind sampling to minimize the occurrence of bias in the research. Patient identities indicated on the paraffin blocks were kept confidential from the researcher. The researcher then assessed the expression of PAX8 and CD117 in the numbered samples and recorded the findings.

This study indicates that the expression of PAX8 increases in platinum-resistant ovarian cancer conditions. PAX8 is a biomarker widely used in high-grade serous ovarian carcinomas (HGSC) and is expressed in approximately 90% of cases. Research by Di Palma (2022) demonstrates that reduced levels of PAX8 result in cell death, decreased migration, and invasion in HGSC cells. The loss of PAX8 also leads to a decrease in key components of the extracellular matrix and a reduction in the secretion of TGFbeta, a cytokine crucial for remodeling the tumor environment. Within cells, the loss of PAX8 weakens spheroid integrity and reduces extracellular matrix proteins.[8]

The study by Adler (2017) aimed to investigate the role of the transcription factor PAX8 in the development of epithelial ovarian cancer (EOC). They found that PAX8 is frequently overexpressed in primary EOC, indicating its potential as an oncogene. Reduction in PAX8 levels decreases cell proliferation and tumorigenesis.

Although PAX8 shows cell-type specificity, the research identified potential therapeutic targets for EOC through the analysis of PAX8 target genes and associated factors.[9] While, PAX8 plays a crucial role in the migration and adhesion of uterine epithelial cells and ovarian cancer cells. Inhibiting PAX8 results in a reduced ability of ovarian cancer cells to migrate and adhere, especially on fibronectin and collagen substrates.[10]

From our research results, we conducted a study on 32 women diagnosed with ovarian carcinoma at Dr. Saiful Anwar Malang Regional General Hospital. The ROC curve shows the results of PAX8 expression and the occurrence of resistance, with a p-value of less than 0.006 ($p < 0.05$). Based on the analysis results using the contingency coefficient for the relationship between PAX8 results and the occurrence of resistance, an accuracy value of 53.125% was obtained, with a positive predictive value (PPV) of 51.85% and a negative predictive value of 60%.

This study demonstrates that PAX8 can be utilized to predict platinum resistance in ovarian cancer. These findings are consistent with previous research. In a study by Chai (2017), positive predictions of PAX8 for primary epithelial ovarian cancer were 92%, while positive predictions for benign ovarian tumors were 85%. Furthermore, earlier research also indicated that an increase in PAX8 expression correlates with an elevated mortality rate.[11] This suggests that besides evaluating resistance, the increased expression of PAX8 can also be used to predict mortality rates.

From the research results, we conducted a study involving 32 women diagnosed with ovarian carcinoma at Dr. Saiful Anwar Malang Regional General Hospital.

The ROC curve indicates the results of CD117 expression and the occurrence of resistance, with a p-value of less than 0.017 ($p < 0.05$). Based on the analysis results using the contingency coefficient for the relationship between CD117 results and the occurrence of resistance, an accuracy value of 71.4% was obtained, having a 70 percent negative predictive value and a 72.73 percent positive predictive value (PPV).

This study also indicates that CD117 can be detected and used to predict platinum resistance. The results of this research are supported by previous studies. Shnaider's study (2023) aimed to evaluate the relationship between CD117 expression and histological tumor types in ovarian cancer cell lines and extracellular vesicles from ovarian cancer patients. Shnaider's study (2023) demonstrated that high CD117 expression in cells and extracellular vesicles correlated with tumor grade and resistance status to therapy. Additionally, the research showed that recurrent ovarian cancer is characterized by a significantly higher increase in CD117 compared to primary tumors.[12] Another study also indicated that CD117 expression is associated with residual tumors and treatment choices, and survival outcomes vary depending on the ovarian cancer subtype, with poorer outcomes observed in cases of mucinous and endometrioid ovarian cancer.[7]

The findings of this study are referred by previous meta-analyses. The results of the meta-analysis indicate a significant correlation between CD117 expression and patient age, disease stage, tumor differentiation level, and histological type. Patients with epithelial ovarian cancer (EOC) expressing high levels of CD117 have an overall worse survival rate.[13]

The determination of the cut-off values for PAX8 and CD117 expression to predict platinum resistance in ovarian carcinoma can be based on the sensitivity and also specificity levels generated from the predictions. Based on the obtained sensitivity and specificity values, it appears that the combination of the highest sensitivity and specificity values for PAX8 is at the point 3.5, where it yields a sensitivity value of 0.875 and a specificity value of 0.813. Meanwhile, for CD117, it is at the point 0.55, where it produces a sensitivity value of 0.827 and a specificity value of 0.300. From these cut-off points, PAX8 has a positive predictive value (PPV) of 51.85% and a negative predictive value (NPV) of 60.0%. On the other hand, CD117 has a PPV of 72.73% and an NPV of 70.0%. This indicates that the predictive value of CD117 is higher than that of PAX8. A PPV of 72.73% means that out of 100 individuals evaluated as positive, approximately 73 individuals truly positive experienced platinum resistance. Meanwhile, an NPV of 70% means that out of 100 individuals evaluated as negative, approximately 70 individuals did not experience platinum resistance.

The assessment of the cut-off points, as indicated above, also considers the sensitivity and specificity values of PAX8 and CD117 expression as predictors of platinum resistance in ovarian carcinoma. This study demonstrates that the expression of PAX8 and CD117 has sensitivities of 87.50% and 72.73%, respectively, while their specificities are lower at 18.75% and 70%, respectively. These results suggest that both biomarkers have the potential to be used as screening tools for ovarian cancer that is resistant to platinum.

Immunohistochemical examinations such as PAX8 and CD117 are expected to assist clinicians in understanding the tendency of ovarian cancer patients toward developing resistance to platinum-based chemotherapy. This is anticipated to aid as a consideration in planning the patient's therapy for optimal results.[14-16] There are several alternative therapy options for platinum-resistant ovarian cancer, including Taxanes (paclitaxel), PARP inhibitors (niraparib), and Bevacizumab (Avastin).[17-20]

In this study, there are several limitations. Firstly, clinical characteristics of patients were not evaluated. Secondly, the research was conducted at only one study site, necessitating further investigation at various research centers. Thirdly, survival evaluation of patients was not performed in this study, thus preventing the determination of the prognosis for platinum-resistant ovarian cancer patients.

CONCLUSION

When ovarian cancer patients express PAX8, it can be used as a screening tool for platinum resistance; its accuracy, sensitivity, specificity, positive predictive value, and negative predictive value rates are as follows 53.125%, 87.50%, 18.75%, 51.85%, and 60.0%, respectively. The expression of CD117 can serve as a screening tool for predicting platinum resistance in ovarian cancer patients, with accuracy, sensitivity, specificity, positive predictive value, and negative predictive value rates of 71.4%, 72.73%, 70%, 72.73%, and 70%, respectively.

DISCLOSURES

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Conflict of interest

There are no conflicts of interest among the authors.

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Author contribution

All authors participated to all aspects of this study, including preparation, data collection and analysis, drafting, and approval for publishing.

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