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, a prevalent gynecologic malignancy, frequently presents challenges due to platinum therapy resistance. This study aims to investigate a monitoring approach for post-operative ovarian carcinoma and evaluate the immunohistochemical expression of PAX8 and CD117 in ovarian cancer tissues, assessing their association with platinum resistance development.

Materials and Methods: Employing a cross-sectional observational analytical design, this study utilized consecutive sampling of patients meeting predefined inclusion and exclusion criteria. Tissue samples, obtained from biopsy or surgical procedures and processed into representative paraffin blocks, underwent immunohistochemical analysis at the Anatomical Pathology Department of Saiful Anwar Hospital, Malang, Indonesia. Expressions of PAX8 and CD117 were evaluated using immunohistochemistry. Diagnostic performance was assessed through receiver operating characteristic (ROC) curves and Youden index calculations to determine sensitivity and specificity.

Results: The study findings revealed that the area under the curve (AUC) for PAX8 and CD117 was 0.785 and 0.809, respectively. PAX8 expression exhibited a positive predictive value of 53.125%, negative predictive value of 87.50%, sensitivity of 18.75%, specificity of 51.85%, and accuracy of 60.0%. For CD117 expression, the corresponding values were 71.4%, 72.73%, 70%, 72.73%, and 70% for positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, respectively.

Conclusion: The immunohistochemical expression of PAX8 and CD117 in ovarian cancer tissues may serve as prognostic biomarkers for platinum resistance. Despite these findings, the study acknowledges several limitations that warrant refinement in future research.

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Highlights:

1. Ovarian cancer, a prevalent gynecologic malignancy affecting women, poses a significant challenge due to the development of resistance to platinum-based therapy in its management.
2. PAX8 and CD117 have demonstrated potential as predictive biomarkers for platinum resistance in ovarian cancer; however, studies exploring their immunohistochemical expression in relation to platinum resistance in ovarian cancer patients remain limited.
3. This study aims to evaluate the immunohistochemical expression of CD117 and PAX8 in ovarian cancer tissues and investigate their association with the emergence of platinum resistance.

INTRODUCTION

Ovarian cancer, a significant gynecologic malignancy, ranks fourth among the most prevalent gynecological cancers globally, following cervical, breast, colorectal, and endometrial cancers. It is a major contributor to mortality, accounting for 47% of deaths related to gynecological malignancies.[1] Ovarian cancer is the fifth leading cause of cancer-related mortality among women, representing approximately 3% of all female malignancies. It predominantly affects older, post-menopausal women, with nearly 80% of cases diagnosed in individuals over 50 years of age.[2] In Indonesia, the precise prevalence and incidence of ovarian cancer remain uncertain. However, data from Dharmais Cancer Hospital in Jakarta, based on estimates from 2010 to 2013, indicate that ovarian cancer ranks as the fourth most common malignancy after breast, cervical, and lung cancers, with approximately 537 new cases and 126 reported deaths during that period.[3]

Alterations in the tumor microenvironment—including changes in extracellular matrix composition, matrix stiffness, hypervascularization, hypoxia, and paracrine signaling—are closely associated with cancer progression. Chemoresistance, a hallmark of aggressive malignancies, enables cancer cells to survive and adapt to chemotherapy. Components of the extracellular matrix may contribute to this resistance by activating signaling pathways that modify gene expression and protein activity, ultimately promoting therapeutic resistance. Understanding and overcoming chemoresistance remains a central goal of oncology research, as it is defined by the capacity of cancer cells to evade or withstand therapeutic interventions.[4]

PAX8 is recognized as a highly sensitive and specific immunohistochemical marker for identifying cancers originating from the ovary or fallopian tube. Its expression may provide valuable diagnostic and prognostic information, particularly in advanced-stage ovarian cancer, and may inform therapeutic strategies prior to neoadjuvant treatment.[5] Similarly, CD117 (c-Kit) is a transmembrane tyrosine kinase receptor essential for the development of several cell types, including melanocytes, germ cells, mast cells, erythrocytes, and interstitial cells.[6] CD117 plays a pathological role in various malignancies, including ovarian cancer. Recent studies have demonstrated that CD117 expression may influence responsiveness to targeted therapies such as imatinib, a tyrosine kinase inhibitor, thereby highlighting its potential clinical significance.[7]

Given this background, the present study aims to investigate a postoperative monitoring approach for ovarian carcinoma by evaluating the immunohistochemical expression of PAX8 and CD117 as potential predictive markers of platinum resistance in ovarian cancer patients at Saiful Anwar General Hospital, Malang, Indonesia.

MATERIALS AND METHODS

An analytical observational design with a cross-sectional study methodology was employed in this investigation. The research was conducted at the Gynecologic Oncology Outpatient Clinic, Medical Records Department, and the Anatomical Pathology Laboratory of Saiful Anwar General Hospital in Malang, Indonesia. The study period spanned from November 2022 to October 2023.

The sampling technique used in this study was non-probability sampling, specifically consecutive sampling, and adhered to the established inclusion and exclusion criteria. Tissue specimens obtained from biopsy or surgical procedures were processed into paraffin blocks, followed by immunohistochemical analysis at the Anatomical Pathology Department of Saiful Anwar General Hospital in Malang. Inclusion criteria comprised patients diagnosed with ovarian carcinoma by clinicians in the Obstetrics and Gynecology Department, who had received platinum-based chemotherapy and experienced recurrence within six months of their last chemotherapy session; patients who had undergone laparotomy for confirmation of clinical examination findings; and patients with paraffin blocks of ovarian cancer tissue available at the Anatomical Pathology Laboratory of Saiful Anwar General Hospital in Malang. Exclusion criteria included patients with adnexal masses not originating from the ovaries, those diagnosed with other malignancies, and those with infected adnexal masses.

The expressions of PAX8 and CD117 were evaluated from five distinct perspectives. Strong intensity of PAX8 and CD117 expression was identified under 400x magnification as dark brown nuclear staining. Moderate expression intensity was characterized by a lighter brown hue in the nuclei at the same magnification. In contrast, weak intensity was evidenced by a pale brown nuclear coloration under 400x magnification.

The expressions of CD117 and PAX8 were analyzed descriptively. Cut-off values for CD117 and PAX8 expression were determined by identifying the optimal threshold between sensitivity and specificity. This was accomplished through Receiver Operating Characteristic (ROC) curve analysis, supplemented by calculation of the Youden index. The cut-off corresponding to the

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highest Youden index was selected as the optimal threshold. Subsequently, specificity, sensitivity, positive predictive value, and negative predictive value were calculated using the established cut-off values. Statistical analysis of the data was performed using the SPSS software program, with a p-value of < 0.05 considered statistically significant.

This research received ethical approval from the Health Research Ethics Commission of Saiful Anwar General Hospital, Malang, Indonesia, under registration number 400/228/K.3/102.7/2022, issued on 21 September 2022.

RESULTS AND DISCUSSION

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

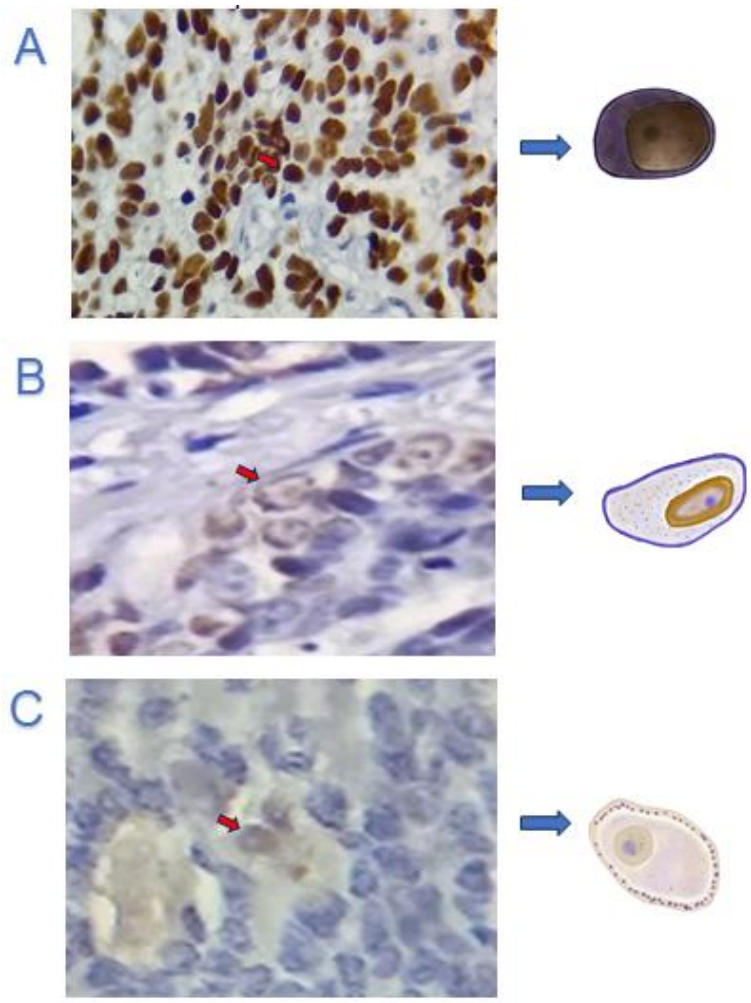

Figure 1. Immunohistochemical staining of PAX8 under the microscope. (A) Strong intensity of PAX8 expression observed under the microscope at 400x magnification; (B) Moderate intensity of PAX8 expression observed under the microscope at 400x magnification; (C) Weak intensity of PAX8 expression observed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

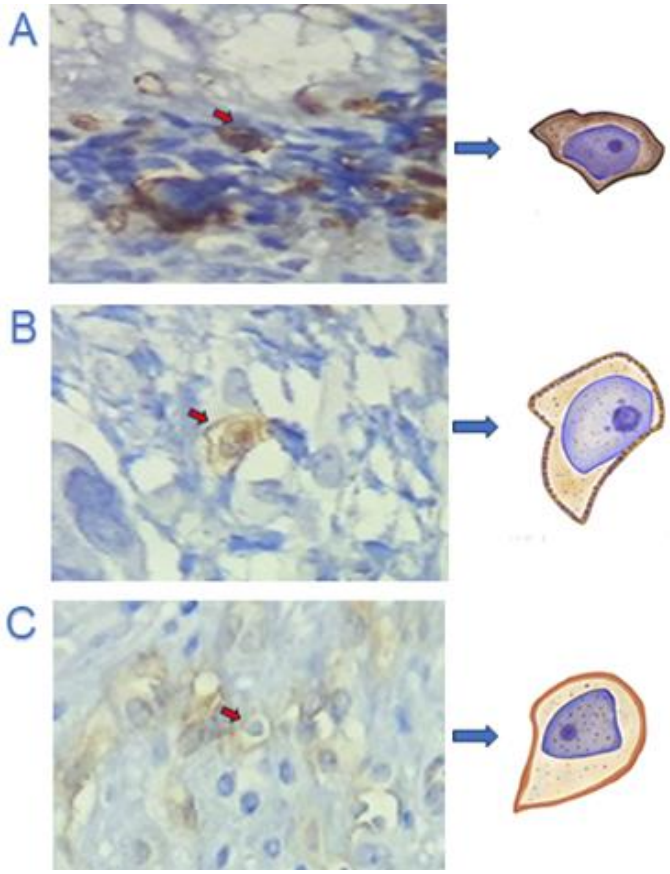

Figure 2. Immunohistochemical staining of CD117 under the microscope. (A) Strong intensity of CD117 expression observed under the microscope at 400x magnification; (B) Moderate intensity of CD117 expression observed under the microscope at 400x magnification; (C) Weak intensity of CD117 expression observed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

In this study, quantitative assessments were also performed in the form of percentage calculations based on the number of tumor cells exhibiting immunohistochemical staining for PAX8 and CD117 antibodies. A total of 32 samples were analyzed, divided into two groups consisting of 16 platinum-resistant samples and 16 platinum-sensitive samples for comparative purposes (Figure 3).

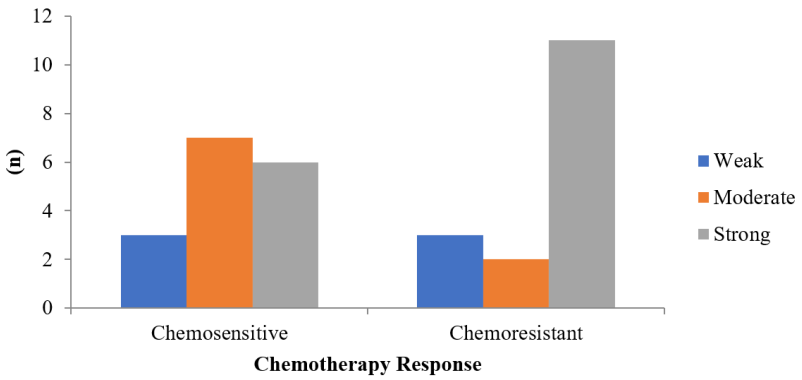

Figure 3. Distribution of PAX8 expression in relation to the occurrence of platinum resistance.

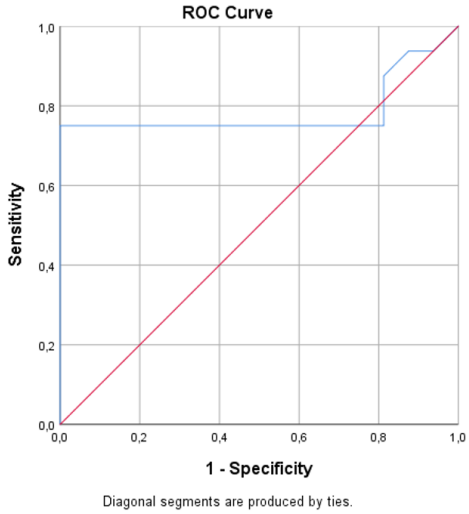

Figure 4. ROC curve of PAX8 expression in relation to the incidence of platinum resistance.

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 be significantly utilized as a predictor of platinum resistance incidence ($p = 0.006$; $p < 0.05$). The area under the PAX8 expression curve is 0.785, with an upper confidence limit of 0.973 and a lower limit of 0.598. The Youden index indicates that a PAX8 expression level ≥ 3.5 yields a sensitivity of 0.875. This cutoff point is selected because its sensitivity closely approximates the area under the curve for PAX8 expression. The results obtained from this cutoff point are subsequently subjected to sensitivity, specificity, positive predictive value, and negative predictive value testing (Figure 4). The outcomes of these diagnostic evaluations are presented in Table 2. Based on the calculations in this table, the overall accuracy is determined to be 53.125%, with a sensitivity of 87.50% and a specificity of 18.75%. The positive predictive value and negative predictive value are 51.85% and 60.0%, respectively. These findings suggest that PAX8 expression is more suitable for screening purposes due to its higher sensitivity relative to its specificity.

Table 2. Diagnostic test of PAX8 expression for platinum resistance

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

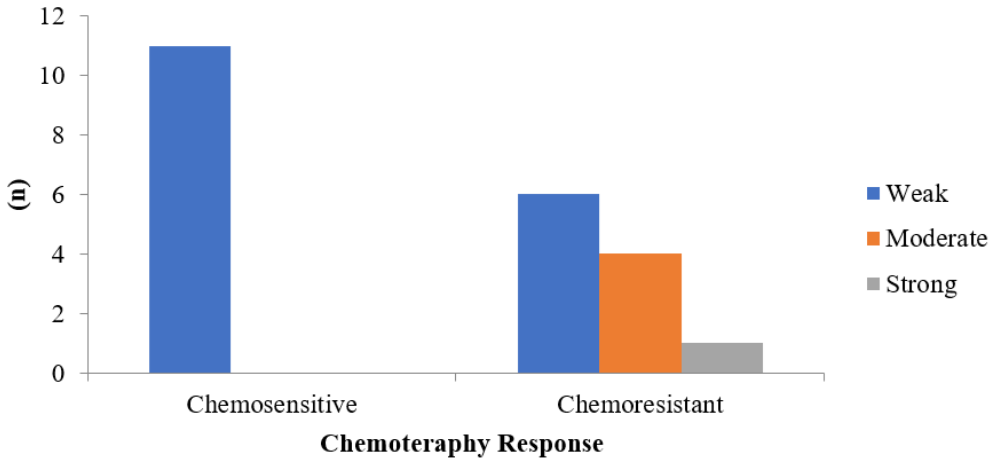

Figure 5. Distribution of CD117 expression in relation to the occurrence of platinum resistance.

Based on Figure 5, the distribution of CD117 expression in relation to the occurrence of platinum resistance is illustrated. Strong CD117 expression is observed in a small proportion of ovarian cancer patients exhibiting chemoresistance. In contrast, weak CD117 expression is more commonly found in ovarian cancer patients who are chemosensitive. According to the ROC curve analysis 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).

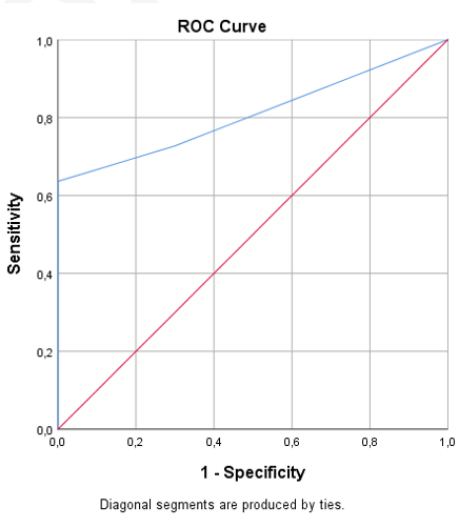

Figure 6. ROC curve of CD117 expression in relation to the incidence of platinum resistance

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

As shown in Table 3, CD117 expression demonstrates significant potential as a predictive marker for the incidence of platinum resistance ($p = 0.017$; $p < 0.05$). The area under the receiver operating characteristic (ROC) curve for CD117 expression is 0.809, with a maximum value of 1.000 and a minimum of 0.613.

According to the Youden index, a CD117 expression threshold of ≥ 0.55 yields a sensitivity of 0.827. This cutoff point was selected because its sensitivity closely approximates the area under the CD117 curve. This selected cutoff was then evaluated for its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The detailed outcomes of these analyses are presented in Table 4.

From the diagnostic assessment in Table 4, the calculated accuracy is 71.4%, with a sensitivity of 72.73% and a specificity of 70%. The values for the positive predictive and negative predictive tests are 72.73% and 70%, respectively. These results indicate that CD117 expression may be better suited for screening applications due to its relatively higher sensitivity compared to specificity.

The entirety of this study was conducted at Saiful Anwar General Hospital, Malang. Patient samples were collected from cases diagnosed with ovarian cancer at the Gynecologic Oncology Outpatient Clinic and through the Medical Records Department of the same hospital. A blind sampling method was employed to mitigate research bias. The identity information labeled on paraffin-embedded tissue blocks remained concealed from the investigator. The investigator subsequently evaluated PAX8 and CD117 expression levels in the coded specimens and documented the corresponding results.

This investigation reveals that PAX8 expression is elevated in platinum-resistant ovarian cancer. PAX8 is a well-established biomarker in high-grade serous ovarian carcinomas (HGSC), being expressed in nearly 90% of these cases. Di Palma (2022) found that reducing PAX8 expression in HGSC cells leads to apoptosis, and inhibits both migration and invasion. The depletion of PAX8 also downregulates critical extracellular matrix components and lowers the secretion of TGFbeta, a cytokine pivotal to tumor microenvironment re-modeling. Internally, loss of PAX8 compromises spheroid cohesion and diminishes extracellular matrix protein levels.[8]

The work by Adler (2017) aimed to clarify the function of the transcription factor PAX8 in epithelial ovarian cancer (EOC) pathogenesis. Their results showed that PAX8 is commonly overexpressed in primary EOC, supporting its potential role as an oncogene. Knockdown of PAX8 significantly reduced cellular proliferation and tumorigenic potential.

Despite its cell-type-specific expression, the study also identified novel therapeutic avenues for EOC by examining downstream genes and molecular partners regulated by PAX8.[9] Additionally, PAX8 contributes significantly to cell migration and adhesion in both uterine epithelial and ovarian cancer cells. Pharmacological inhibition of PAX8 leads to reduced motility and adhesion, particularly on extracellular matrix substrates such as fibronectin and collagen.[10]

In our own study involving 32 female patients diagnosed with ovarian carcinoma at Saiful Anwar General Hospital, Malang, the ROC analysis demonstrated that PAX8 expression is associated with platinum resistance, with a statistically significant p-value of less than 0.006 ($p < 0.05$). Analysis using the contingency coefficient revealed an accuracy of 53.125%, with a positive predictive value of 51.85% and a negative predictive value of 60%.

These findings confirm the utility of PAX8 expression as a potential marker for predicting platinum resistance in ovarian cancer. This is consistent with earlier literature. Chai (2017) reported that the positive predictive value of PAX8 for identifying primary epithelial ovarian carcinoma was 92%, while for benign ovarian tumors, it was 85%. Moreover, prior studies have also indicated that elevated PAX8 expression is associated with increased mortality.[11] Therefore, besides evaluating resistance, increased PAX8 expression may also serve as a prognostic indicator of patient survival.

Based on the study findings, we conducted research involving 32 women diagnosed with ovarian carcinoma at Saiful Anwar General Hospital, Malang. The ROC curve demonstrates the association between CD117 expression and the presence of platinum resistance, with a p-value of less than 0.017 ($p < 0.05$). Analysis using the contingency coefficient to evaluate the relationship between CD117 expression and resistance yielded an accuracy of 71.4%, with a negative predictive value (NPV) of 70% and a positive predictive value (PPV) of 72.73%.

This investigation also indicates that CD117 is a detectable biomarker that can be utilized to predict platinum resistance. These findings are in alignment with earlier studies. Research by Shnaider (2023) explored the relationship between CD117 expression and histological tumor subtypes in ovarian cancer cell lines and extracellular vesicles obtained from patients. Shnaider's study (2023) reported that elevated CD117 expression in both cells and extracellular vesicles was positively correlated with tumor grade and resistance to therapy. Furthermore, the study found that recurrent ovarian cancer exhibited a significantly greater increase in CD117 expression compared to primary tumors.[12] Another investigation revealed that CD117 expression is associated with residual tumor presence, therapeutic decisions, and survival outcomes, which vary based on the ovarian cancer subtype, with the poorest prognosis found in mucinous and endometrioid histologies. [7]

The findings of this study are referred previous meta-analyses. These analyses identified a significant correlation between CD117 expression and patient age, disease stage, tumor differentiation status, and histolo-gical subtype. In patients with epithelial ovarian cancer (EOC), high CD117 expression was consistently associated with poorer overall survival outcomes. [13]

Determination of the cut-off points for PAX8 and CD117 expression in predicting platinum resistance in ovarian carcinoma can be guided by analyzing their respective sensitivity and specificity. Based on these measures, the optimal cut-off point for PAX8 expression appears to be 3.5, providing a sensitivity of 0.875 and specificity of 0.813. In comparison, the optimal cut-off for CD117 expression is 0.55, yielding a sensitivity of 0.827 and specificity of 0.300. At these thresholds, the PPV and NPV for PAX8 are 51.85% and 60.0%, respectively, whereas CD117 shows a PPV of 72.73% and an NPV of 70.0%. These findings suggest that CD117 has a stronger predictive capacity compared to PAX8. A PPV of 72.73% implies that out of 100 individuals identified as positive, approximately 73 truly experienced platinum resistance. Conversely, an NPV of 70% indicates that out of 100 individuals identified as negative, approximately 70 were correctly classified as not experiencing resistance.

Evaluation of the cut-off points described above also incorporates the sensitivity and specificity values of PAX8 and CD117 as predictors of platinum resistance in ovarian carcinoma. This study demonstrates that the sensitivity values of PAX8 and CD117 expression are 87.50% and 72.73%, respectively, while their specificity values are lower, at 18.75% and 70%, respectively. These data indicate that both PAX8 and CD117 possess potential as screening biomarkers for platinum-resistant ovarian cancer.

Immunohistochemical markers such as PAX8 and CD117 may support clinicians in assessing the likelihood of ovarian cancer patients developing resistance to platinum-based chemotherapy. This predictive capability may serve as a basis for tailoring individualized treatment strategies aimed at improving clinical outcomes.[14-16] Several alternative therapies are available for patients with platinum-resistant ovarian cancer, including taxanes (paclitaxel), poly (ADP-ribose) polymerase (PARP) inhibitors (niraparib), and the anti-angiogenic agent bevacizumab (Avastin). [17-20]

This study presents several limitations. First, the clinical characteristics of the patients were not included in the analysis. Second, the research was conducted at a single institution, thereby warranting validation through multicenter studies. Third, the study did not evaluate patient survival, limiting its ability to draw conclusions regarding prognosis in platinum-resistant ovarian carcinoma.

CONCLUSION

When PAX8 is expressed in ovarian cancer patients, it may function as a screening marker for platinum resistance, with corresponding values for accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 53.125%, 87.50%, 18.75%, 51.85%, and 60.0%, respectively. Similarly, CD117 expression may also be employed as a screening marker to predict platinum resistance in ovarian cancer patients, demonstrating accuracy, sensitivity, specificity, positive predictive value, and negative predictive value 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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