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E-Cadherin Expression and KELIM Score as Predictive and Prognostic Factors for Platinum Sensitivity in Locally Advanced Epithelial Ovarian Cancer.

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Abstract
Background:
Success of treatment in stage III: IV epithelial ovarian cancer depends on chemotherapy (CTH) sensitivity and complete cyto-reductive surgery (CRS). There is a need for predictors of the tumor-primary chemosensitivity and the risk of subsequent platinum-resistant relapse. The predictive values of CA-125 decline percentages during treatments were area of ongoing investigations with inconsistent outcomes.
Methods:
The CA-125 serum concentrations and E-cadherin immunohistochemical expression were prospectively evaluated in locally advanced epithelial ovarian cancer planned for neo-adjuvant chemotherapy followed by interval debulking surgery. The CA-125 elimination rate constant K (KELIM) score and E-cadherin predictive value in relation to the tumor response rate, likelihood of complete IDS, risk of subsequent platinum-resistant relapse, and overall survival (OS) were assessed using univariate and multivariate tests.
Results:
The data from 86 patients were analyzed. KELIM was an independent and major predictor of subsequent platinum resistant relapse risk, and of survivals. In patients with highly chemo-sensitive diseases, the patient prognosis was driven more by the chemotherapy-induced antitumor effects than by the surgery.
CA125 normalization at the end of the neo-adjuvant CTH had a strong impact on OS (p=0.004). Notably favorably KELIM score had better numerical OS (p=0.061).
Conclusion:
KELIM score is a crucial predictor of platinum resistance and OS in chemo-sensitive patients. The presence of ascites and CA125 normalization after neo-adjuvant CTH significantly impact OS. Favorable KELIM score is associated with better survival outcomes.

Keywords:
Ovarian cancer, KElIM score, Platinum sensitivity, E-cadherin, prognostic factor.

Introduction

Globally, ovarian cancer (OC) is the eighth most common cancer in women, accounting for an estimated 3.7% of cases of women's cancer (1). Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. Less than one-half of patients survive for more than five years after diagnosis (2
). Lower survival in ovarian cancer can chiefly be attributed to the fact that many new cases of ovarian cancer are diagnosed in the advanced stage of the disease with intra-peritoneal metastasis. While the early stages mostly are asymptomatic or present with vague symptoms (3).

CA 125 is an antigenic determinant on a high molecular weight glycoprotein recognized by a monoclonal antibody. (4). Cancer antigen 125 (CA 125) is the commonest tumor marker recommended for clinical use in the diagnosis and

management of ovarian cancer. Its upper limit is 35 U/mL in pre and post-menopausal patients (4). It has been used in the early 1980's when Bast et al., specifically isolated the monoclonal antibody OC125 in cancerous ovarian tissue compared to healthy ovarian tissue (5).
CA 125 is expressed by more than 80% of non-mucinous epithelial ovarian carcinomas and is found in most carcinomas of Müllerian origin, including Fallopian tube and primary serous peritoneal carcinoma. However, this measurement is not very sensitive in the early phases of ovarian cancer; only reported to be elevated in 23 to 50% of stage I cases (5). The specificity of CA125 for detecting ovarian cancer was 78% (95%CI 76–80) (6).
CA 125 is the commonest tumor marker recommended for clinical use in the diagnosis and management of ovarian cancer. There are 5 main indications in which the determination of CA 125 levels is recommended (7).
Up to 80% of women with ovarian cancer of epithelial origin have elevated serum CA 125 levels, with the frequency of elevation correlating with the clinically detected stage (6). The degree of elevation has also been shown to correlate with tumor burden and International Federation of Obstetrics and Gynecologic (FIGO) pathologic stage.
Surgery remains the cornerstone for treatment in ovarian cancer yet irresectable advanced stages benefits of three to four cycles of neo-adjuvant chemotherapy (NACT) after which resectability is assessed radiological or by laparoscopic assessment. Interval cyto-reduction is performed for those who are operable, followed by further cycles of chemotherapy in the adjuvant setting. The goal of NACT is to reduce perioperative morbidity and mortality and increase the chance of a complete resection of disease at the time of cyto-reductive surgery. Despite the potentially improved surgical outcomes that result from NACT, clinical studies have shown that survival is not improved with NACT followed by surgery vs. standard surgery followed by adjuvant chemotherapy (13).

However, there is data suggest that for selected women with stage III or IV epithelial ovarian cancer (EOC), NACT and interval cytoreduction, followed by adjuvant chemotherapy despite are similar to primary cytoreduction and adjuvant chemotherapy, with respect to OS and PFS, but are associated with less perioperative morbidity and mortality (13).
Cochrane review including three randomized trials enrolling 1521 women with stage III/IV ovarian cancer, showed that NACT followed by debulking surgery or primary debulking surgery followed by chemotherapy both approaches provided
similar OS (hazard ratio [HR] 0.95, 95% CI 0.84-1.07) (14).
Another four randomized trials evaluating PFS in such cases, resulted in similar PFS between the two groups (HR 0.97, 95% CI 0.87-1.07). However NACT was associated with lower postoperative mortality (relative risk 0.18, 95% CI 0.06-0.54), in form of lower rates of infection, less need for stoma formation, and much less need for bowel resection. Similar results were seen in the phase III SCORPION trial (15). NACT also permits in-vivo test and assessment of the effectiveness of chemotherapy prior to surgery, which may help to inform subsequent treatment. Patients who progress on NACT are unlikely to benefit from surgery because of intrinsically chemo-resistant disease.

Patients and Methods

This prospective cohort study included 86 female patients newly diagnosed with locally advanced epithelial ovarian carcinoma who received neoadjuvant chemotherapy (NACT). Serial follow-up of CA-125 levels was conducted at diagnosis and before each chemotherapy session. Tumor tissue samples underwent E-cadherin staining using an autoimmunostainer. Immunoreactivity was classified as positive/preserved, reduced, or negative. Abnormal E-cadherin expression (reduced/negative) was statistically analyzed.
Our primary objective was to assess CA-125 kinetics (KELIM score) as a predictive factor for platinum sensitivity, treatment response and to study E-cadherin expression in locally advanced epithelial ovarian cancer.
Results:

The statistical analysis of our prospective study included 86 locally advanced epithelial ovarian cancer patients revealed the following demographic and clinical characteristics. In terms of age distribution, the mean age was 55 years old (Range 24-80 years), 53.5% of participants were under 55 years old. The sample predominantly comprised of married individuals (100%) with a high proportion reporting parity (91.9%). Post-menopausal status was slightly more prevalent (54.7%) of the patient (47/86). Body mass index (BMI) varied, but the main character was towards obesity side (93% of the cases) with 24.4% classified as morbidly obese (BMI >35), 36.0% as obese (BMI 30:34.9), 32.6% as overweight (BMI 25:29.9), and only 7.0% falling within the normal range (BMI 18.5:24.9). Performance status (PS) assessment indicated that the majority (74.4%) had a PS score of 1 (64 out of the 86 patients). Family history of other malignant diseases were positive in 31.4% of cases. Table (1)

Table (1): Demographic data of the total 86 locally advanced ovarian cancer patients.

		Frequency	Percent %
Age (years)	<55	46	53.5
	≥55	40	46.5
Marital status	Single	0	0
	Married	86	100.0
Parity	Yes	79	91.9
	No	7	8.1
Menopausal status	Post	47	54.7
	Pre	39	45.3
BMI (kg/m2)	Normal	6	7.0
	Overweight	28	32.6
	Obese	31	36.0
	Morbid obesity	21	24.4
Performance status	PS 1	64	74.4
	PS 2	18	20.9
	PS 3	4	4.7
Family history of other malignancies	Negative	59	68.6
	Positive	27	31.4
	Total	86	100.0

Most patients (73.3%) achieved CA125 normalization at the end of the course of neo-adjuvant chemotherapy, with 50% showing favorable KELIM score (above or equal to KELIM score 1). Fifteen patients showed progressive disease after the neo-adjuvant TC protocol necessitating second line chemotherapy. Out of the 15 patients with initial platinum resistance, 40.0% experienced progressive disease (PD) after evaluation post 2nd line CTH, while another 40.0% showed a response to treatment (RD). The remaining 20.0% had stable disease (SD).

Pathological assessment of the IDS specimen showed positive omentum and peritoneum in (55 %, 30 % respectively). Lymph node pathological involvement was seen positive in 10 % of the cases Table (2).

Table (2). Clinicopathological criteria of the operable cases of locally advanced ovarian carcinoma (n= 64).

		Number	Percentage
Laterality	**Bilateral**	50	78.1
	Left	2	3.1
	Right	12	18.8
Ovarian capsule	**Infiltrated**	10	15.4
	Intact	54	84.6
Peritoneal deposit	**Negative**	45	70.3
	Positive	19	29.7
Omental deposit	**Negative**	28	44.6
	Positive	36	55.4
	Total	64	100.0

E-cadherin immunohistochemical staining was done in 71 cases out of 86 cases of the total study, whose formalin-fixed paraffin embedded tissue were available at the Pathology Department and contained enough or representative tumor tissue.

The results showed preserved stain 59 out of 71 patient (83.1%), negative in one patient, and reduced in the other 11 patient (15.5%). Table (3) the remaining 15 cases out of 86 cases showed either CPR or no enough viable tumor tissue in the specimen for evaluation.

Table (3): E-cadherin expression of the 71 ovarian cancer patients with adequate tissue sample for evaluation.

E-cadherin		Number	Percentage
	Preserved	59	83.1
	Reduced	11	15.5
	Negative	1	1.4
	Total	71	100.0

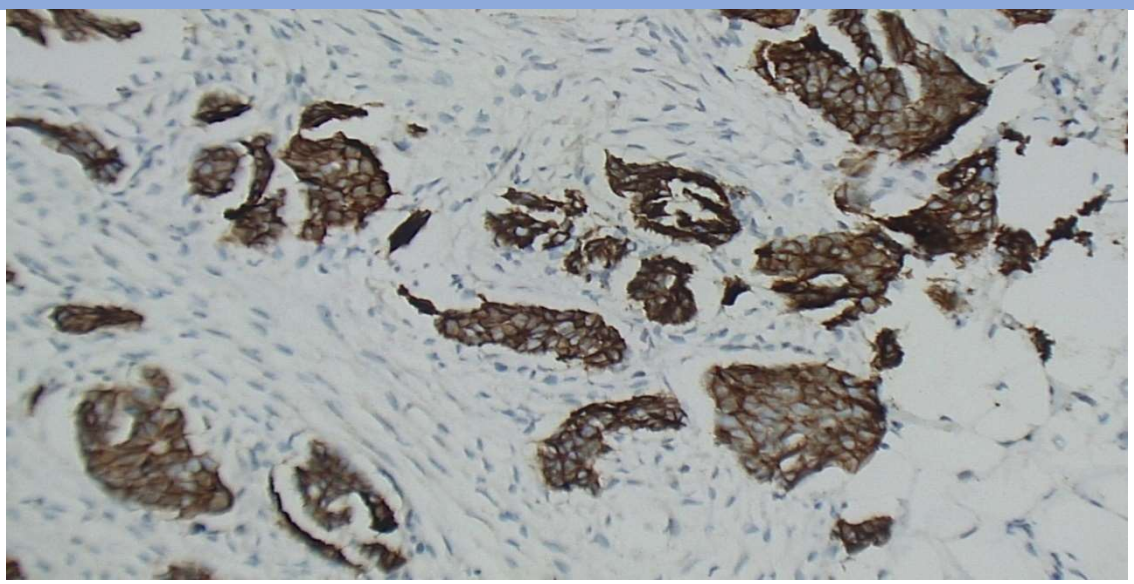

Figure (1): A case of serous carcinoma exhibited strong and continuous cell membranous immunostaining reaction to E-cad monoclonal antibody and classified as positive or preserved E-cad expression (DAB, original magnification x2 00).

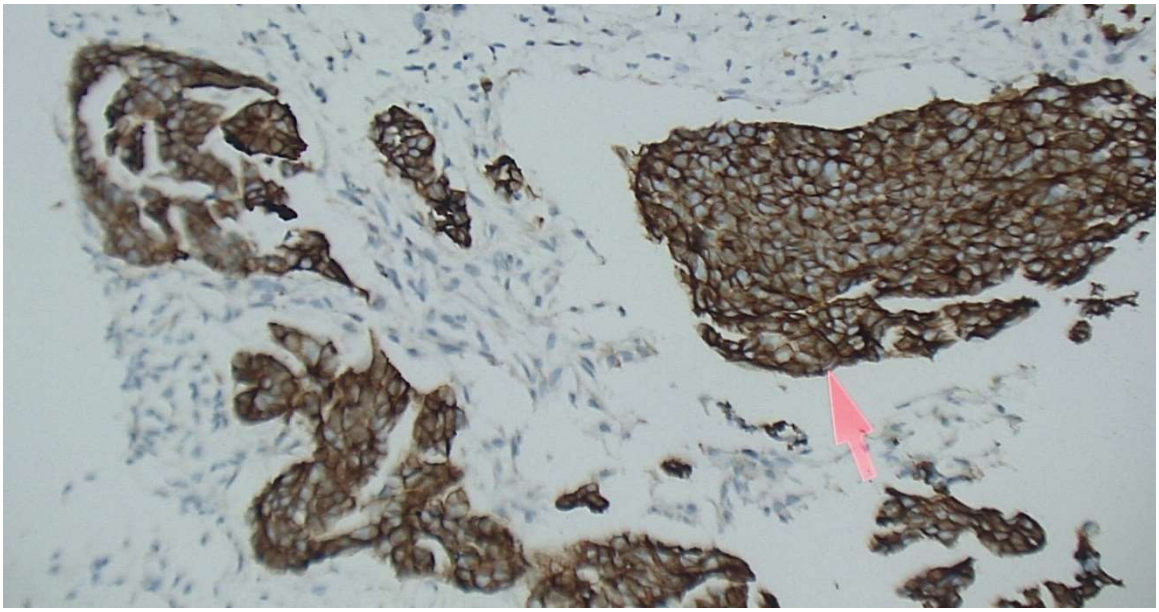

Figure (2): another field of the same previous case illustrating the homogenous strong E-cad immunoreactivity throughout the tumor section. The arrow points to a sheet of tumor where all tumor cells positively expressing E-cad (DAB, original magnification X200).

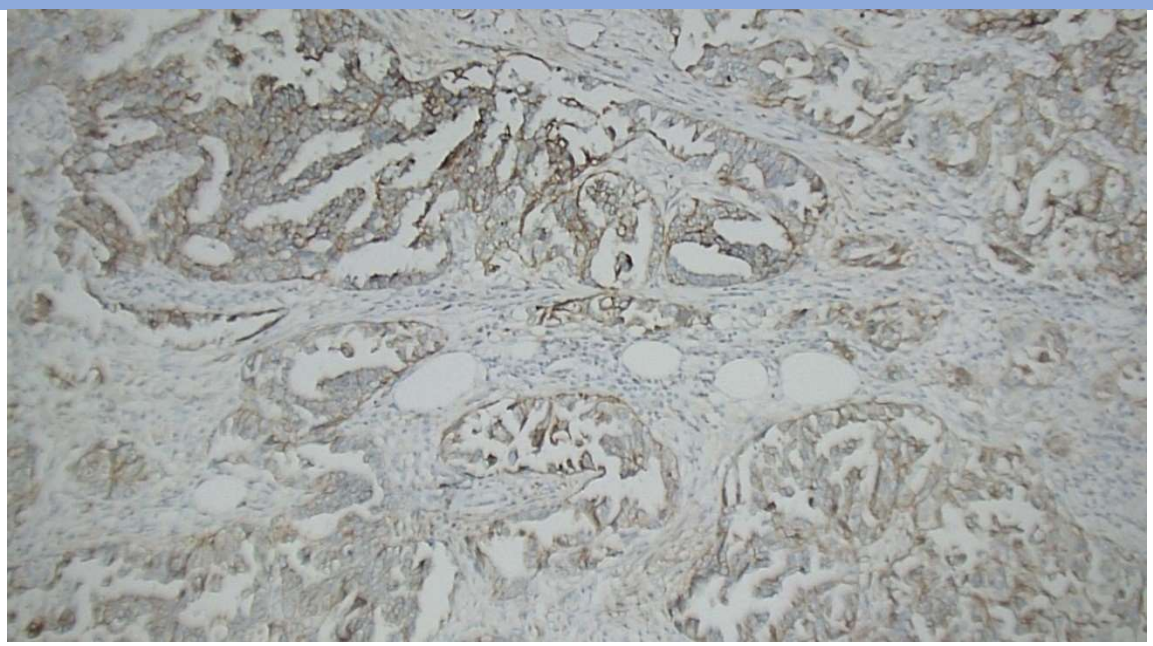

Figure (3): Higher magnification of previous case showing positive strong E-cad immunostaining reaction in all tumor cells (DAB, original magnification X400).

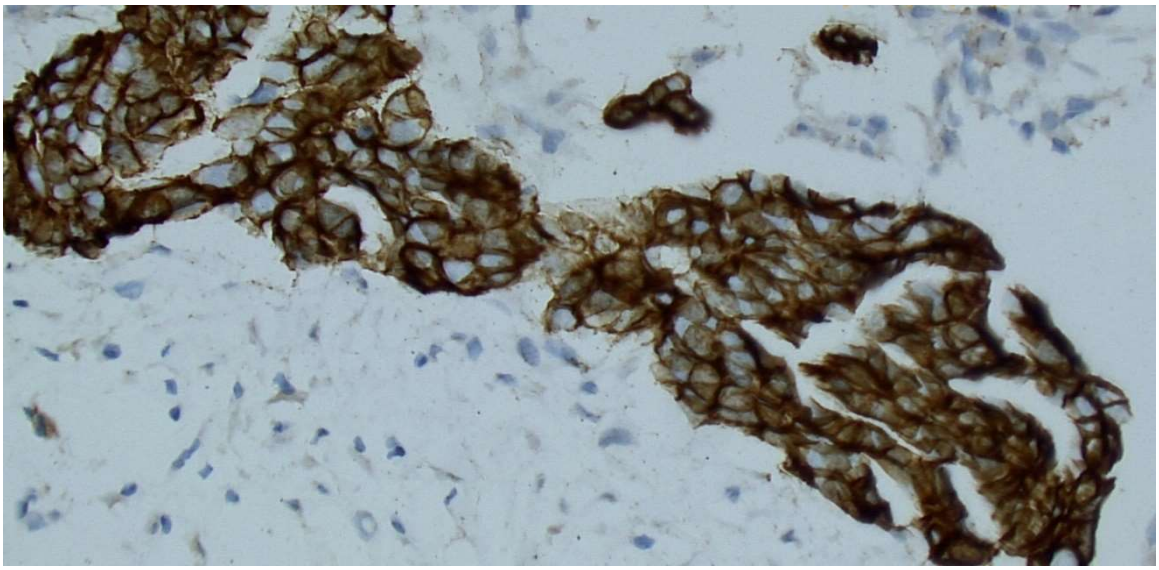

Figure (4): a case of serous carcinoma showing reduced E-cadherin expression in the form of heterogenous and indistinct cell membranous immunoreaction (DAB, original magnification x 100).

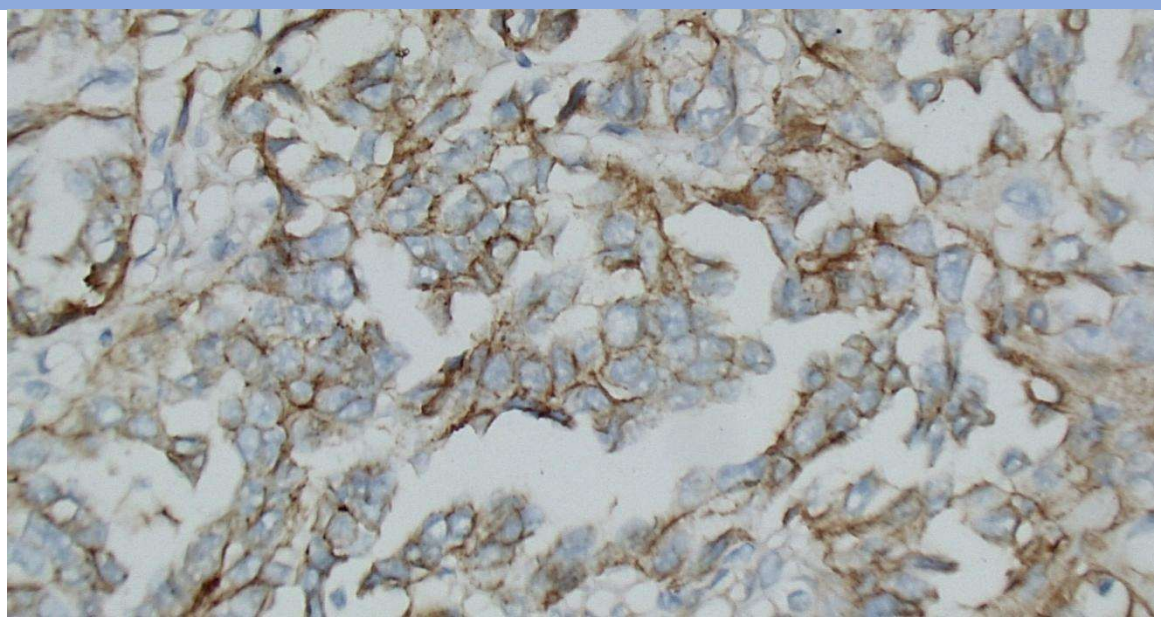

Figure (5): Higher magnification of previous case showing the discontinuous cell membrane reaction to E-cadherin monoclonal antibody in most of tumor cells (DAN, original magnification x 400).

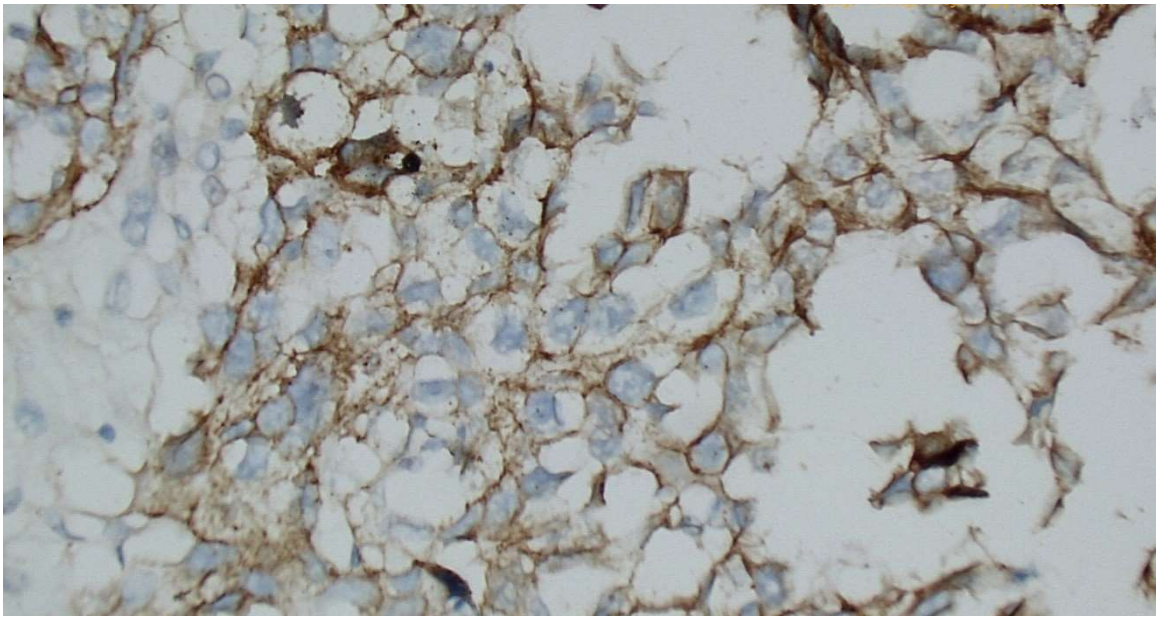

Figure (6): Another case showing reduced E-cadherin immune-staining reaction (DAB, original magnification x 400).

Multivariate analysis was done to evaluate the E-cadherin status and the pathology tumor grade at the tumor tissue in relation to response to CTH as evaluated radiological but wasn't statistically significant (p= 0.77). For statistical purposes pathology tumor grade I&II was grouped together.

Patients who were platinum-sensitive had a higher proportion of favorable KELIM scores (61.2%) compared to those who were platinum-refractory (35.1%), with a statistically significant p-value of 0.017. This suggests that platinum sensitivity is strongly associated with favorable KELIM scores, indicating better treatment outcomes.

Table (4): Relation between platinum sensitivity and KELIM score favorability.

			Favorability		p value
			Favorable	**Unfavorable**	
Platinum sensitivity(n=86)	**Refractory**	no	13	24	0.017
		%	35.1%	64.9%	
	Sensitive	no	30	19	
		%	61.2%	38.8%	

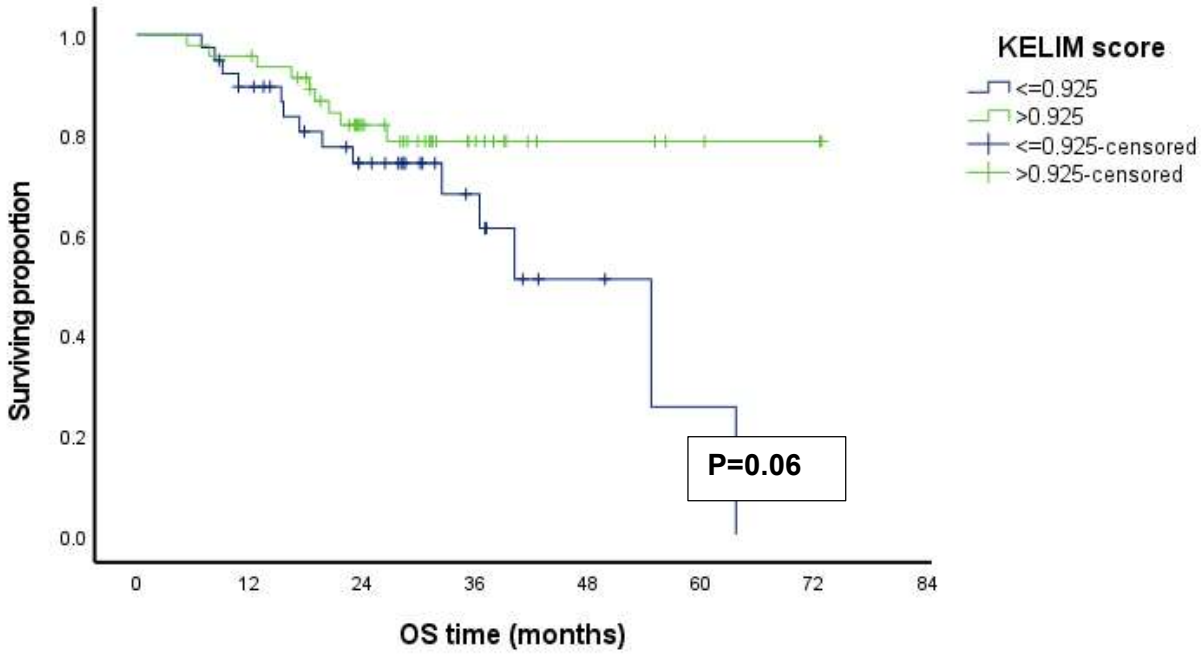

Figure (7): The relation between KELIM score favorability and OS.

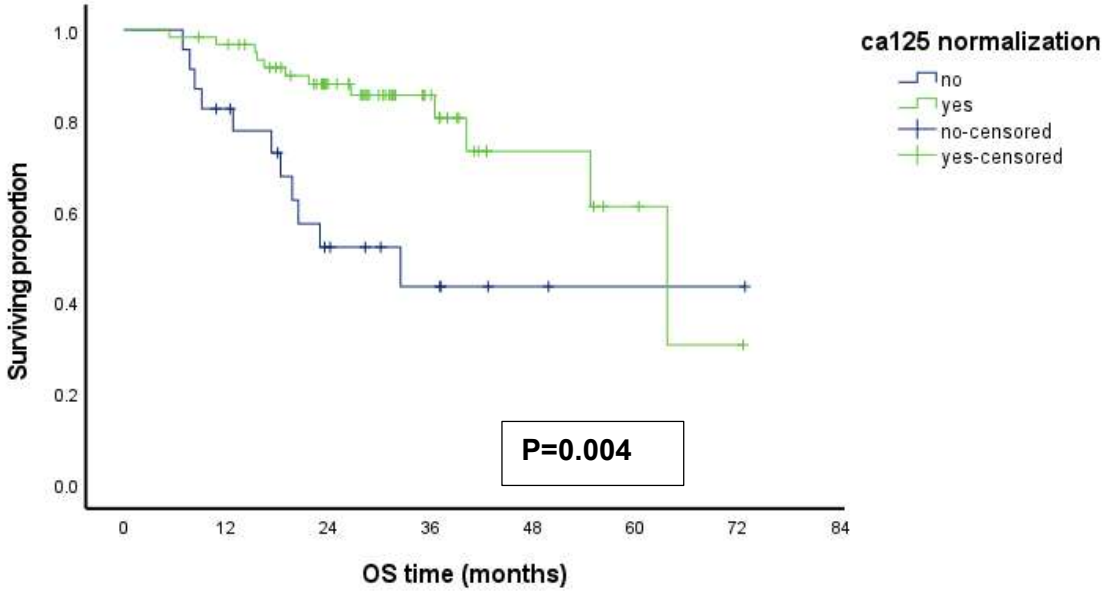

Figure (8): The relation between CA 125 normalization and OS.

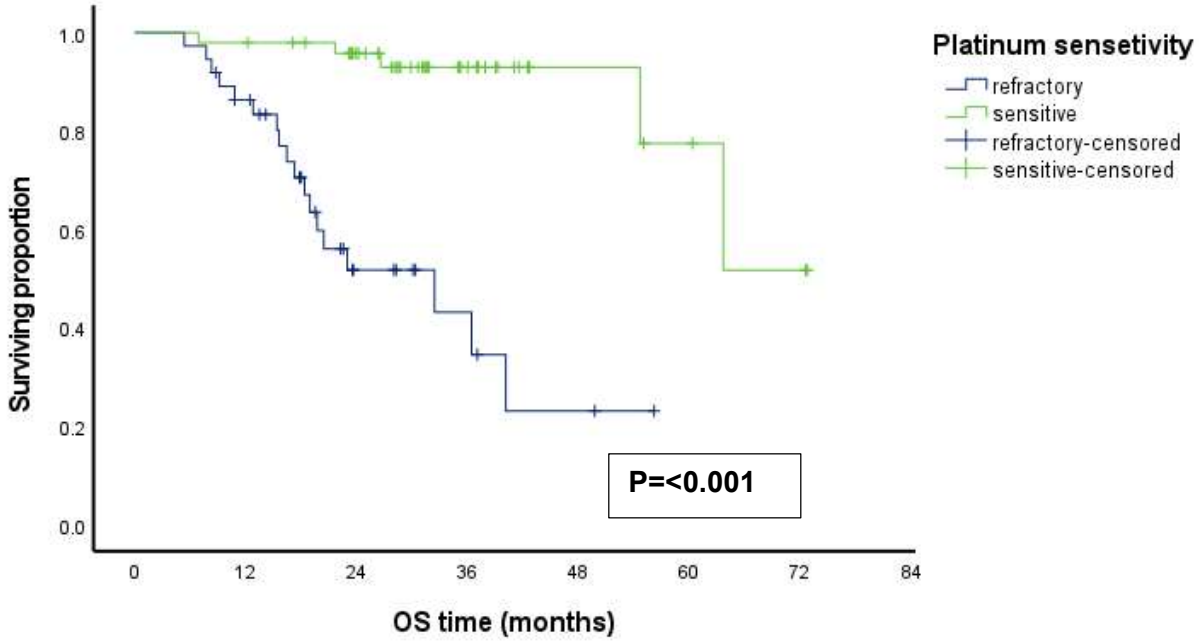

Figure (9): The relation between platinum sensitivity and OS.

Discussion

There is a need for a triage tool that can identify the patients that will benefit from platinum containing neo-adjuvant chemotherapy protocols, but also the patients that will need further cycles of neo-adjuvant chemotherapy and a delayed interval debulking surgery. The association between the KELIM score and survival rates was studied as a secondary result, in order to establish KELIM score as a prognostic factor. We conducted a prospective study to evaluate whether the CA-125 elimination rate constant K (KELIM) score serves as an independent prognostic index

in the neo-adjuvant chemotherapy setting for patients with advanced ovarian cancer. These patients typically present with a high tumor burden and primary unresectable disease, which are associated with poorer outcomes. In recent trials, such as the CHIVA trial, KELIM has emerged as a significant predictor of chemotherapeutic response and prognosis in ovarian cancer patients undergoing NACT. (16)

Building on this evidence, our study enrolled 86 patients who were stratified into two groups based on KELIM scores. KELIM was calculated using at least three serial CA-125 measurements at specific intervals during chemotherapy cycles. Group A consisted of patients with favorable KELIM scores (≥1), while Group B included patients with unfavorable scores (<1).

Consistent with findings from previous trials like those by (17). Which highlighted the predictive value of KELIM for platinum sensitivity, our study found a significant association between KELIM scores and the likelihood of achieving complete cytoreductive surgery (CRS). Patients with favorable KELIM scores had better surgical outcomes, aligning with the results from the AGO DESKTOP III study, which also demonstrated improved resectability in patients with favorable AGO score . However, in some cases, KELIM did not accurately predict residual disease after interval debulking surgery, suggesting the need for further refinement in the application of this marker. (18)

Regarding overall survival (OS), higher KELIM scores were associated with superior outcomes. These results are in line with the findings of (19) who showed that a favorable KELIM score was an independent prognostic factor for both PFS and OS. Echoing findings from the ICON8 trial that emphasized the utility of early CA-125 dynamics in response prediction. Moreover, patients who achieved CA-125 normalization by the third chemotherapy cycle demonstrated a higher radiological response rate (93.7% vs. 70%, P = 0.003) (20).

The KELIM score's numerical association with OS (p=0.061) reflects a growing interest in its utility as a prognostic marker. While it did not reach statistical significance, this trend is consistent with previous research suggesting that KELIM may have potential as a predictor of survival, warranting further investigation

Overall, our study supports the prognostic and predictive value of KELIM scores in ovarian cancer patients receiving NACT, further validated by similar findings in recent clinical trials.

The predictive accuracy of KELIM, particularly for surgical outcomes and platinum sensitivity, highlights its potential utility in tailoring treatment strategies for this high risk population. Our study supports this idea, showing that the CA-125 elimination rate constant K (KELIM) serves as a reliable and independent predictor of tumor chemosensitivity. It demonstrated strong correlations with tumor response rates, the likelihood of achieving complete interval debulking surgery (IDS), and OS. This evidence aligns with the hypothesis that chemosensitivity plays a dominant prognostic role in first-line treatment success (19).

Moreover, KELIM could help identify poor-prognosis patients who may benefit from experimental treatments aimed at overcoming chemoresistance, such as immunotherapy or cell-cycle checkpoint inhibitors. The role of KELIM in differentiating between chemo-sensitive and chemo-resistant tumors becomes even more relevant with the increasing use of PARP inhibitors in both first-line and recurrent ovarian cancer. The marked difference in OS between platinum-sensitive and refractory groups (p<0.001) underscores the established role of platinum sensitivity as a pivotal prognostic factor in ovarian cancer. This finding aligns with extensive research indicating that platinum-sensitive patients have significantly better outcomes compared to those with platinum-resistant disease, who often face a median survival of less than 20 months (21). Our results reaffirm the critical importance of effective initial treatment and highlight the need for innovative approaches to manage platinum-resistant ovarian cancer.

Overall, our study contributes to the growing body of evidence on the prognostic factors influencing survival in ovarian cancer patients. While certain factors, such as the presence of ascites and platinum sensitivity, align well with existing literature, the nuances of other findings (e.g., KELIM score, significance of adjuvant chemotherapy) suggest avenues for future research to enhance understanding and treatment strategies for this patient population.

Continued investigation into the implications of treatment protocols and the integration of novel biomarkers could provide additional insights into improving patient outcomes in ovarian cancer.

Conclusion:

Our study reinforces the KELIM score's predictive and prognostic value in advanced ovarian cancer treated with NACT, particularly in relation to surgical outcomes, platinum sensitivity, and survival rates. The findings support KELIM's potential utility in tailoring treatment strategies and identifying patients at risk for chemoresistance. Further research is needed to refine KELIM's predictive accuracy, particularly in conjunction with other biomarkers like BRCA mutations and homologous recombination deficiency (HRD).

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