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ORIGINAL RESEARCH

Predictive Value of the KELIM Index for Progression-Free Survival in Ovarian Cancer Under Current Treatment Modalities

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Background: The KELIM index, a dynamic biomarker derived from CA125 kinetics, has shown prognostic value in ovarian cancer. However, its predictive role under contemporary treatment paradigms incorporating bevacizumab and PARP inhibitors remains underexplored.

Objective: To evaluate the predictive value of the KELIM index for progression-free survival (PFS) in ovarian cancer patients treated with current therapeutic modalities.

Methods: A total of 52 patients with ovarian cancer who underwent surgical treatment in the Affiliated Hospital of Jiaxing University from January 1, 2020 to September 30, 2023 were retrospectively analyzed. Clinicopathological data, treatment details (including bevacizumab/PARPi use), and serial CA125 values were collected. The KELIM index was calculated using the online biomarker kinetics tool (https://www.biomarker-kinetics.org/CA125). Cox regression and Kaplan-Meier analyses assessed prognostic factors.

Results: The mean age of the 52 patients was 55.17±13.57 years, and the mean body mass index (BMI) was 22.95±3.62kg/m^2. There were 35 cases (67.3%) in the KELIM index ≥1 group and 17 cases (32.7%) in the KELIM index < 1 group. Multivariate analysis identified KELIM index (HR=0.25, 95% CI 0.077–0.818, P<0.05) and treatment approach (direct surgery vs NACT+IDS) as independent PFS predictors. Patients with KELIM<1 had a median PFS of 38.3 months, while those with KELIM≥1 did not reach median PFS (P<0.05).

Conclusion: The KELIM index is expected to be another high quality index for predicting OC under the current treatment model, potentially guiding personalized treatment intensification.

Keywords: ovarian cancer, progression-free survival, KELIM index

Introduction

Ovarian Cancer (OC) is one of the most common malignant tumors of the female reproductive system. According to the National Cancer Center,[1] there are 57000 new cases of ovarian cancer in China in 2022, ranking the third among malignant tumors of the female reproductive system, and the mortality rate ranks the first. Due to the lack of specific clinical manifestations, 70% of patients are found in the advanced stage, resulting in poor treatment effect and seriously affecting women's life and health. Therefore, how to prolong the survival time of ovarian cancer is an urgent problem to be solved by all gynecological oncologists. Over the past decade, the treatment paradigm has shifted significantly with the introduction of maintenance therapies, including anti-angiogenic agents and poly ADP-ribose polymerase inhibitors (PARPi). These advances have substantially prolonged PFS, yet the lack of dynamic biomarkers to predict therapeutic response under contemporary regimens remains a critical challenge. Previous studies[2] have found that tumor marker carbohydrate antigen 125 (CA125), histological type, residual lesion size and gene mutation status can effectively predict the prognosis of patients with ovarian cancer. However, these indicators mostly rely on static data at the time of treatment, and it is difficult to dynamically reflect the patient's response to treatment. In 2013, You et al developed a CA125 clearance model based on the

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principles of pharmacokinetics and pharmacokinetics, which calculated a value based on at least three CA125 values within the first 100 days after the initiation of chemotherapy.[3] The modeled CA-125 ELIMination rate constant K (KELIM) was used to assess the sensitivity of patients to chemotherapy, and CALYPSO trial[3] data were retrospectively evaluated. The KELIM index was found to be significantly associated with PFS. Thereafter, Colomban et al reviewed the data from several studies and found that KELIM index was closely related to PFS and OS in ovarian cancer.[4–7]KELIM, developed as a pharmacokinetic model of CA125 kinetics during chemotherapy, has demonstrated prognostic value for PFS in historical cohorts. However, its predictive utility has not been adequately validated in patients receiving modern first-line therapies incorporating PARPi and bevacizumab. Therefore, this study aimed to evaluate the KELIM index as a predictor of PFS in ovarian cancer patients under current treatment modalities, addressing a key evidence gap in personalized treatment optimization.

Materials and Methods

Research Subjects

From January 1, 2020 to September 30, 2023, 52 patients with ovarian cancer who were treated and operated in the Affiliated Hospital of Jiaxing University First Hospital of Jiaxing were selected as the research objects. The inclusion criteria were as follows: 1) ovarian malignant tumor diagnosed by surgical treatment and pathology and standardized chemotherapy; 2) complete clinical data; Exclusion criteria: 1) without standardized treatment; 2) combined with other malignant tumors; This study has been approved by the Medical Ethics Committee of the First Hospital of Jiaxing (Ethics number: 2025-KY-154).

Sample Size Calculation

Sample size was calculated using PS Power software. Based on historical data from the ICON7 trial, we assumed a hazard ratio (HR) of 0.35 for PFS between high/low KELIM groups. Target power = 80% (β=0.20), α=0.05 (two-sided) using Cox regression. Attrition rate: Anticipated dropout rate = 10% (loss to follow-up, treatment discontinuation). 52 patients would provide 82% power to detect the assumed HR.

Data Collection

Data collection Clinical and pathological data such as age, height, weight, treatment method, pathological type, use of bevacizumab and PARP inhibitors were collected. The disease progression of patients was followed up through out-patient service or telephone. The deadline for follow-up was December 31, 2024, with recurrence or the deadline for follow-up as the end point.

Measurement of Std KELIM

The KELIM index was calculated by collecting CA125 values at the time of onset, before each chemotherapy, after each chemotherapy, and during the perioperative period. KELIM values were calculated based on at least three CA125 values within the first 100 days after starting chemotherapy (https://www.biomarker-kinetics.org/CA125).

Statistical of Analysis

Statistical processing SPSS 26.0 software was used to analyze the data. Measurement data conforming to normal distribution were expressed as mean ± standard deviation. The measurement data not in accordance with the normal distribution were expressed as the median ± interquartile range, and the count data were expressed as the rate (%). Kaplan-Meier method was used for survival analysis, and Log Rank test was used for univariate analysis. Cox regression analysis was used for multivariate analysis. $P < 0.05$ was considered statistically significant.

Results

General Information of the Study Subjects

The average age of the enrolled patients was 55.17±13.57 years, the average body mass index was 22.95±3.62kg/m^2, 35 patients (67.3%) were postmenopausal, 17 patients (32.7%) were still menstruating at the time of onset. Postoperative

pathological results showed that 46 patients (88.5%) were epithelial cancer, and 6 patients (11.5%) were non-epithelial cancer. Forty-six cases (88.5%) were treated by direct surgery, and 6 cases (11.5%) were treated by NACT+IDS. According to the pathological results, the final staging was determined, including 9 cases (17.3%) in stage I, 8 cases (15.4%) in stage II, 27 cases (51.9%) in stage III, and 8 cases (15.4%) in stage IV. Seven patients (13.5%) were treated with bevacizumab, 45 patients (86.5%) were not treated with bevacizumab, 42 patients (80.8%) were not treated with PARP inhibitor after chemotherapy, 4 patients (7.7%) were treated with olaparib after chemotherapy, and 6 patients (11.5%) were treated with niraparib after chemotherapy. According to the official website of KELIM index, 35 cases (67.3%) had KELIM index ≥1 and 17 cases (32.7%) had KELIM index <1, as shown in Table 1.

Analysis of Influencing Factors of PFS in Patients with Ovarian Cancer

Multivariate COX regression analysis of PFS in imaging patients showed that treatment methods and KELIM index were independent risk factors for PFS (P<0.05), as shown in Table 2. Bootstrap test (b=2000) showed that KELIM index significantly predicted PFS (β=−1.18, P<0.05).

Table 1 General Data and Pathological Data of 52 Patients

Clinical Data	Segmentation Criteria	Example (%)
Menopausal status	Already menopausal	35 (67.3)
	Pre-menopausal	17 (32.7)
Type of pathology	Epithelial carcinoma	46 (88.5)
	Non-epithelial carcinoma	6 (11.5)
Methods of treatment	Direct surgery	46 (88.5)
	NACT	6 (11.5)
FIGO staging	Phase I	9 (17.3)
	Phase II	8 (15.4)
	Phase III	27 (51.9)
	Phase IV	8 (15.4)
Whether to use bevacizumab	Yes	7 (13.5)
	Not used	45 (86.5)
Whether to use PARP inhibitors	Not used	42 (80.8)
	Olaparib	4 (7.7)
	Nirapali	6 (11.5)
Kelim index	≥1	35 (67.3)
	<1	17 (32.7)

Table 2 Multivariate COX Regression Analysis of Influencing Factors on PFS of Patients

	B	SE	Wald	Degrees of Freedom	P	Exp (B)	95% CI	
							Lower Limit	Upper Limit
Age	−0.019	0.062	0.091	1	0.763	0.982	0.870	1.108
BMI	0.041	0.079	0.272	1	0.602	1.042	0.892	1.217
Menopausal status	0.066	1.135	0.003	1	0.954	1.068	0.115	9.879
Pathological type	−13.464	404.300	0.001	1	0.973	0.000	0.000	–
Treatment modalities	2.707	0.744	13.238	1	0.000	14.989	3.487	64.441
Bevacizumab	0.494	0.877	0.317	1	0.573	1.639	0.294	9.149
FIGO staging	−0.130	0.333	0.154	1	0.695	0.878	0.457	1.685
PARP inhibitors	0.422	0.339	1.550	1	0.213	1.526	0.785	2.967
KELIM index	−1.385	0.604	5.254	1	0.022	0.250	0.077	0.818

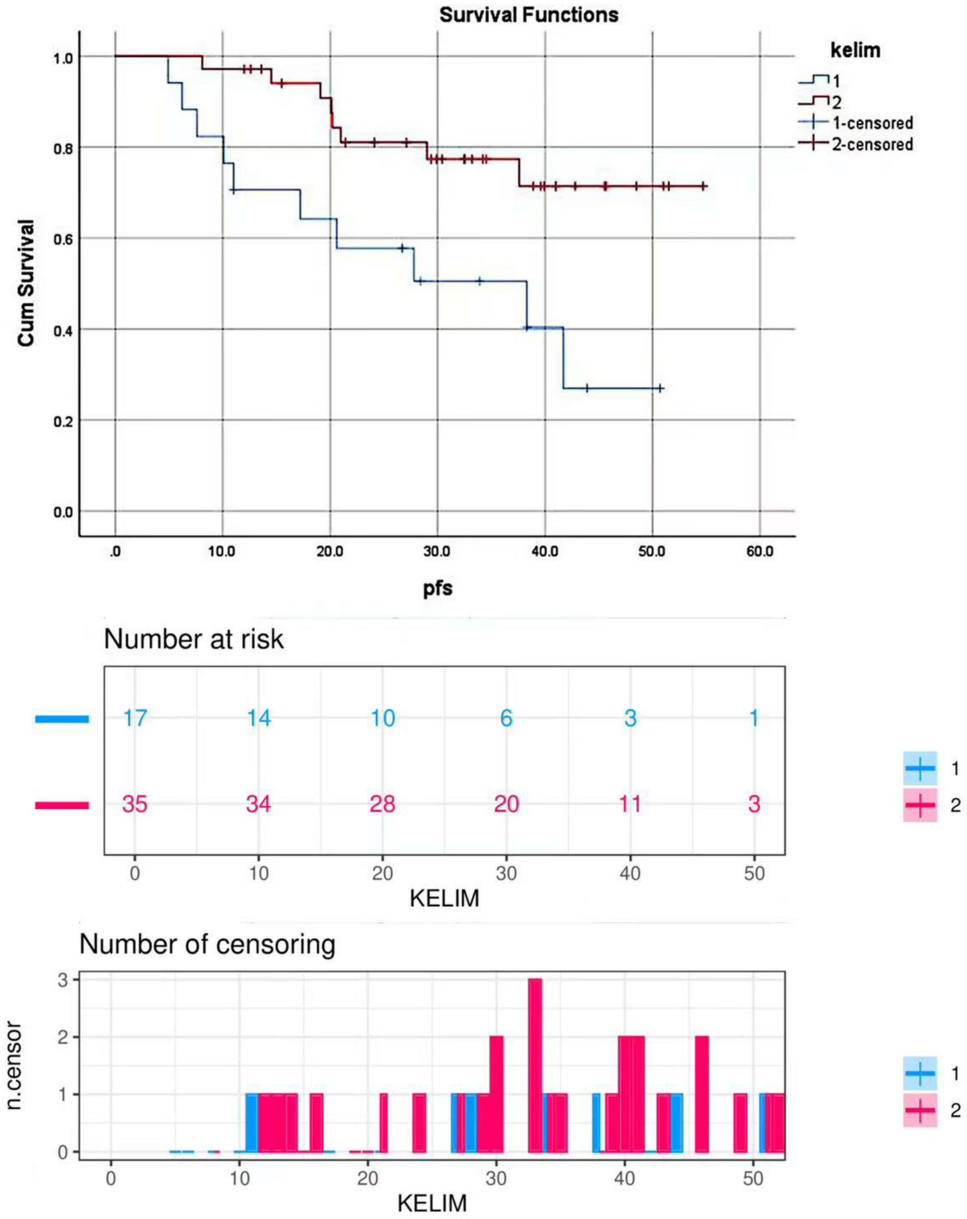

Figure 1 Survival curves of PFS in patients with different KELIM index.

PFS of Patients with Different KELIM Index

Kaplan-Meier survival analysis showed that the median survival time of patients with KELIM index <1 (assigned 1) was 38.3 months, while the median survival time of patients with KELIM index ≥1 (assigned 2) still did not reach the median survival time. The PFS of patients with KELIM index ≥1 was higher than that of patients with KELIM index <1. The difference between the two groups was statistically significant (P<0.05), as shown in Figure 1.

Discussion

It is well known that CA125 is one of the sensitive indicators to monitor the progression, efficacy and recurrence of ovarian cancer, but due to its susceptibility to a variety of factors, its diagnostic specificity is not strong.[8] On this basis, You et al developed the KELIM index to indirectly predict the sensitivity of chemotherapy through the elimination rate of CA125, which once became a research hotspot at that time.[3,9–11] CHIVA Phase II trial[12] results showed that patients with a good KELIM index had a higher PFS and OS. A recent meta-analysis[13] included 14444 ovarian cancer patients. The

results showed that higher KELIM index was associated with better PFS (HR=0.53,95% CI 0.45–0.62) and OS (HR=0.51,95% CI 0.43–0.62). The results of another meta-analysis[14] showed that KELIM index was an independent prognostic marker for ovarian cancer and one of the determinants of the success of first-line treatment. Most of the above studies focused on ovarian cancer patients with NACT, and the data sources were relatively early, and there was a lack of data on maintenance therapy. The innovation of this study was to focus on all patients with ovarian cancer treated by surgery, regardless of stage, maintenance therapy, and neoadjuvant chemotherapy. In this study, patients with KELIM≥1 had a higher PFS (HR=0.25, 95% CI 0.077–0.818), basically consistent with the results of Kim et al,[13] but due to the short follow-up time, these patients still did not reach the median PFS, which may predict that under the current treatment model of ovarian cancer, patients with Kelim ≥1 had a higher PFS. The KELIM index can still be used as an indicator to predict platinum-sensitive status and PFS in the early stage, which may be helpful for clinicians to adjust the treatment plan as soon as possible. The KELIM index can be calculated during the third chemotherapy cycle (median: 63 days), offering a considerably earlier dynamic assessment of chemotherapy sensitivity compared to traditional methods, such as CT evaluation of efficacy in the sixth cycle. In our cohort, patients with a low KELIM value (<1) exhibited a significantly shortened PFS (median: 38.3 months), highlighting the urgency of early identification. We propose incorporating the KELIM index into the routine clinical workflow of the third cycle to guide preemptive interventions, for instance:Early transition to Metronomic Chemotherapy[15] or Dose-Dense Chemotherapy[16] to increase the sensitivity of chemotherapy and improve the prognosis of patients, or Enrollment in clinical trials exploring novel agents for chemoresistant disease.

This study also found that different treatment methods were also independent risk factors for PFS of ovarian cancer, and patients with direct surgery had longer PFS than those with NACT. A large meta-analysis[17] of 1,774 patients randomized to PDS or NACT+IDS showed no significant difference in PFS or OS, while NACT+IDS even reduced the risk of serious adverse events. Onda et al,[18] randomized 301 patients with stage III/IV ovarian cancer to PDS (n=149) and NACT+IDS (n=152). The median OS for PDS and NACT+IDS was 49.0 and 44.3 months, respectively, but the difference was not statistically significant. All the patients enrolled in the above studies were advanced patients, while in this study, 17 patients belonged to stage I/II patients, which had earlier stage, relatively limited tumor location, and relatively good prognosis. There were only 6 patients in the NACT group. The sample size was too low, and there may be a certain selection bias.

Maintenance treatment refers to the use of drugs to delay the recurrence of ovarian cancer after complete or partial remission is achieved by surgery and chemotherapy. The ICON7 study[19] included patients with early-stage high-risk and advanced ovarian cancer. The median PFS was 19.8 months and 17.4 months for chemotherapy plus bevacizumab followed by bevacizumab maintenance therapy and chemotherapy alone, respectively, but there was no significant difference in OS. Similarly, the GOG-0218 study[20] also showed that chemotherapy combined with bevacizumab maintenance therapy had a PFS benefit. In addition, the PRIMA[21] trial, a multicenter, randomized, double-blind, Phase III trial of niraparib monotherapy as first-line maintenance treatment in ovarian cancer, without a primary endpoint of PFS, involving 733 patients with advanced disease, showed that 5-year PFS was 22% in the niraparib group and 12% in the placebo group (HR 0.66; 95% CI, 0.55–0.78), confirming the superior ability of lenilaparib to delay disease recurrence and prolong PFS in the overall population. The PAOLA-1 study[22] also demonstrated a significantly longer PFS with olaparib plus bevacizumab compared with placebo (46.8 vs 17.6 months), and the above studies all showed a significant PFS improvement with PARP inhibitors and bevacizumab. Although PARPi (HR=1.53, P=0.213) and bevacizumab (HR=1.64, P=0.57) demonstrated a trend towards a benefit in PFS, which aligns with the findings from related ovarian cancer studies and is mechanistically plausible, these differences did not reach statistical significance due to the small number of patients in subgroups (n<10) and the crossover use of PARPi and bevacizumab in some patients. On the one hand, selection bias may occur due to the inclusion of patients with early ovarian cancer and the lack of supplemental maintenance therapy after chemotherapy. Further expansion of the sample size is necessary, accompanied by rigorous control over the maintenance treatment regimen for verification.

The primary limitation of this study lies in its small sample size, comprising only 52 cases, and the relatively short follow-up period, with the KELIM ≥ 1 group yet to reach median PFS. Furthermore, several potential biases in this study merit consideration. Firstly, selection bias may arise due to the retrospective nature and single-center cohort design of the

study. Although we enrolled consecutive patients who met the eligibility criteria, the exclusion of patients with incomplete CA125 data may have influenced the results. Secondly, variations in the timing of CA125 measurements during chemotherapy could impact the calculation of KELIM, introducing bias into the results. Thirdly, there is potential confounding from treatment heterogeneity, given the variations in maintenance treatment regimens (such as PARP inhibitor type and bevacizumab dosage).

Conclusion

This study confirmed that the kelim index is still a powerful predictor of progression free survival in patients with ovarian cancer under the contemporary treatment mode. However, due to the small sample size of this study, subgroup analysis is limited; The short follow-up time may underestimate the long-term results, and large sample prospective verification is still needed in the follow-up, especially for those patients who receive parpi/bevacizumab treatment, which is very important for the development of clinical algorithm guided by kelim. Future research should integrate dynamic biomarkers (such as ctDNA) and cost-benefit analysis to improve the treatment strategy for individual risk.

Ethics Statement

This study exempted informed consent through the ethics committee of Jiaxing first hospital for the following reasons: Minimal Risk to Patients:The research involved only de-identified historical data extracted from electronic health records, with no physical, psychological, or social risks to participants. Protection of Confidentiality: All personally identifiable information (eg, names, IDs, contact details) was permanently removed before analysis. Data were accessible only to authorized researchers via encrypted hospital servers, with results aggregated to prevent re-identification. Alignment with Ethical Guidelines: This waiver complies with Article 32 of the Declaration of Helsinki, permitting retrospective exemption when research poses negligible risk and consent is impracticable.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors disclosed no relevant relationships.

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