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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

IDENTIFYING OF PATIENTS WITH ADVANCED OVARIAN CANCER EXPERIENCING THE HIGHEST BENEFIT FROM BEVACIZUMAB IN THE FIRST-LINE SETTING ON THE BASIS OF KELIM SCORE

IDENTIFIKACIJA PACIJENATA SA UZNAPREDOVALIM KARCINOMOM JAJNIKA KOJI IMAJU NAJVEĆU KORIST OD PRIMENE BEVACIZUMABA U PRVOJ LINIJI NA OSNOVU PRIMENE KELIM SKORA

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Abstract

Introduction. Ovarian cancer represents the deadliest gynecological malignancy. The aim of this study is to validate the predictive value of Cancer antigen-125 Elimination rate constant K score regarding progression-free survival among patients with Stage IIIc-IV high-grade serous ovarian cancer according to the International Federation of Gynecology and Obstetrics, treated with bevacizumab. Additionally, the study aims to determine the significance of a score in the assessment of progression-free survival in relation to operation status and disease stage. **Material and Methods.** The retrospective study was conducted at the Oncology Institute of Vojvodina and included 56 patients treated for high-grade serous ovarian cancer. The treatment protocol consisted of chemotherapy with paclitaxel and carboplatin, followed by bevacizumab maintenance therapy. The Cancer Antigen-125 Elimination Rate Constant K score was calculated using three Cancer Antigen 125 tumor marker values. Based on this calculation, the score was dichotomized into favorabe (≥1) and unfavorable (<1) groups. **Results.** The analysis of the score's impact on progression-free survival revealed that patients with a score ≥1 had longer mean survival time compared to a score <1 (19.4 vs 17.0 months). This difference was not statistically significant (p=0.549). The operation status in relation to a score was the only statistically significant factor with progression-free survival benefit (p=0.002). **Conclusion.** In our study, Cancer antigen-125 Elimination rate constant K score did not emerge as a statistically significant prognostic factor for identifying patients most likely to benefit from bevacizumab. The operative status showed significant predictive value.

Key words: Ovarian Neoplasms; Bevacizumab; CA-125 Antigen; Poly(ADP-ribose) Polymerase Inhibitors; Treatment Outcome; Prognosis

Sažetak

Uvod. Karcinom jajnika predstavlja najletalniji ginekološki malignitet. Cilj rada je potvrditi prediktivnu vrednost *Cancer antigen-125 Elimination rate constant* K skora u odnosu na preživljavanje bez progresije kod pacijentkinja sa seroznim karcinomom jajnika visokog stepena, stadijuma IIIC-IV prema Internacionalnoj federaciji za ginekologiju i akušerstvo, koje su lečene primenom bevacizumaba; utvrditi značaj ovog skora u proceni preživljavanja bez progresije u odnosu na operacioni status i stadijum bolesti. **Materijal i metode.** Istraživanje predstavlja retrospektivnu studiju koja je sprovedena u Institutu za onkologiju Vojvodine. Studijom je obuhvaćeno 56 pacijentkinja koje su lečene od seroznog karcinoma jajnika visokog stepena primenom hemioterapije na bazi paklitaksela i karboplatine i biološkom terapijom održavanja bevacizumabom. Pacijentkinjama je na osnovu tri vrednosti tumorskog markera karcinom antigena 125 izračunat *Cancer antigen-125 Elimination rate constant* K skor koji je tumačen kao povoljan (≥ 1) ili nepovoljan (< 1). **Rezultati.** Ispitivanjem uticaja *Cancer antigen-125 Elimination rate constant* K skora na preživljavanje bez progresije utvrđeno je duže prosečno preživljavanje kod pacijentkinja sa skorom ≥ 1 u odnosu na skor < 1 (19,4 vs. 17 meseci), međutim ono nije bilo statistički značajno (p = 0,549). Operacioni status u odnosu na *Cancer antigen-125 Elimination rate constant* K skor pokazan je kao jedini statistički značajan faktor koji doprinosi preživljavanju bez progresije bolesti (p = 0,002), dok stadijum bolesti nije pokazao statističku značajnost. **Zaključak.** U našem istraživanju *Cancer antigen-125 Elimination rate constant* K skor nije pokazan kao značajan prognostički faktor u odabiru pacijentkinja koje bi imale najveću korist od primene bevacizumaba; operacioni status u odnosu na *Cancer antigen-125 Elimination rate constant* K skor jeste.

Ključne reči: tumori jajnika; bevacizumab; CA-125 antigen; poli adenozin-difosfat riboza polimeraza inhibitori; ishod lečenja; prognoza

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Abbreviations

PARP	– poly adenosine diphosphate-ribose polymerase
KELIM score	– Cancer Antigen-125 Elimination Rate Constant K
PFS	– progression free survival
FIGO	– The International Federation of Gynecology and Obstetrics
CA-125	– Cancer Antigen-125
VEGF	– vascular endothelial growth factor
VEGFR-1,2	– vascular endothelial growth factor receptor 1,2
BRCA gene	– Breast Cancer gene
GCIG	– Gynecologic Cancer Intergroup
OS	– overall survival

Introduction

Ovarian carcinomas rank as the eighth most common malignancy and the eighth leading cause of death among women worldwide, with a 5-year survival rate of 46% [1]. It is the most lethal gynecological malignancy and the second most common in developed countries after endometrial cancer. In Serbia, however, it ranks third, following endometrial and cervical cancers. Approximately 820 new cases are reported annually in Serbia, where it remains the leading cause of death among gynecological malignancies and ranks sixth in overall statistics [1, 2].

In terms of histological characteristics, ovarian cancers are divided into four major groups: epithelial tumors, germ cell tumors, stromal tumors of the genital cord, and sarcomas. The most common histological subtype is epithelial adenocarcinoma, which accounts for 95% of cases, with high-grade serous carcinomas comprising 70-80% of all ovarian cancers. Due to the lack of symptoms in earlier stages and the impossibility of screening, 80% of cases are diagnosed in advanced stages of the disease (International Federation of Gynecology and Obstetrics (FIGO) III-IV) [2–4].

Metastases typically occur on the omentum and peritoneum, while lymphogenous and hematogenous spread occurs in only 2-3% of cases. Once the disease spreads in the abdomen, often presenting as ascites, it progresses to the chest, causing malignant pleural effusions. The cytokine vascular endothelial growth factor (VEGF) plays a pivotal role in the development of ascites and malignant pleural effusions by promoting fluid extravasation from vascular spaces [2]. VEGF also contributes to tumor growth and metastasis, exacerbating the prognosis of ovarian cancer [5]. It exerts its effects by binding to two tyrosine kinase receptors on the surface of endothelial cells of tumor blood vessels: vascular endothelial growth factor receptor 1 (VEGFR1) and 2 (VEGFR2) [6]. Bevacizumab, a humanized monoclonal antibody, selectively binds to circulating VEGF, preventing its receptor binding. By reducing tumor microvascular angiogenesis, bevacizumab restricts the oxygen and nutrient supply to the tumor, decreases interstitial pressure, and enhances vascular permeability, thereby improving the flow and effect of chemotherapeutic agents in the tumor [7]. Despite its proven efficacy in prolonging progression-free survival (PFS), bevacizumab is associated with significant adverse effects, including gastrointestinal perforation, hypertension, proteinuria, thromboembolism, bleeding, and impaired wound healing, which can limit its use [6, 7]. Therefore, identifying patients who benefit most from bevacizumab is crucial.

First-line treatment of ovarian cancer includes primary or interval surgery and platinum- and taxane-based chemotherapy, which may be combined with maintenance therapies such as bevacizumab or poly adenosine diphosphate-ribose polymerase (PARP) inhibitors, where applicable [8]. In Serbia, bevacizumab is approved alongside standard chemotherapy with carboplatin and paclitaxel for patients with epithelial ovarian carcinomas (FIGO stage IIIC: suboptimally operated or inoperable cases, and FIGO stage IV), fallopian tube carcinomas, and primary peritoneal carcinomas. Eligible patients must be in good general condition (performance status 0-1), without significant comorbidities or intestinal infiltration. PARP inhibitors, such as olaparib, are indicated as maintenance therapy for newly diagnosed advanced (FIGO stages III-IV) serous/endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancers with high-grade tumors and Breast Cancer (BRCA) gene 1 or 2 mutations (germinal or somatic) that achieve complete or partial response after completing the first-line platinum-based chemotherapy [9].

Bevacizumab has shown greater activity of in patients with platinum-resistant recurrent ovarian cancer [10]. This highlights the importance of evaluating the role of intrinsic tumor chemosensitivity in determining the effectiveness of bevacizumab in first-line therapy. The Cancer Antigen-125 Elimination Rate Constant K (KELIM) is a score calculated based on at least three measurements of the Cancer Antigen-125 (CA-125) tumor marker during the first 100 days of chemotherapy. It reflects the clearance rate of CA-125, with higher values indicating faster elimination of CA-125, and greater chemosensitivity to the applied therapy [11]. CA-125 is primarily associated with ovarian cancer but may be elevated in other conditions. According to the Gynecologic Cancer Intergroup (GCIG) criteria, CA-125 is used to monitor treatment response in recurrent disease or to define progression after first-line chemotherapy. Assessing the prognostic value of CA-125 over time for recurrence poses statistical challenge, as its trajectory can be summarized in various ways (e.g., KELIM after three months, or CA-125 values or

decreases at three or six months), and its prognostic role has been analyzed in many studies. Measurement error and biological variation further complicate its use as a biomarker, prompting some researchers to advocate for modeling techniques to better estimate its evolution. The KELIM score, based on longitudinal CA-125 measurements and incorporating pharmacokinetic and pharmacodynamic parameters, has gained interest in multiple contexts, including recurrent disease and neoadjuvant or initial treatments. The prognostic role of the KELIM score after 100 days (approximately three months) in adjuvant and neoadjuvant treatments had been tested in several studies [8].

Material and Methods

Research Goals

The objectives of this research are:

1. To validate the predictive value of the KELIM score for PFS period in patients with high-grade serous ovarian cancer, FIGO stages IIIC-IV, treated with bevacizumab.

2. To assess the significance of the KELIM score in evaluating PFS in relation to surgical status and disease stage.

This retrospective study was conducted at the Oncology Institute of Vojvodina in Sremska Kamenica, utilizing data from the Oncology Institute's BirPis21 database. The study included patients treated for high-grade serous ovarian cancer, FIGO stage IIIC-IV, between January 2019 and December 2021. These patients received a chemotherapy regimen of paclitaxel/carboplatin administered every 21 days in six cycles, followed by biological maintenance therapy with bevacizumab. Out of 91 patients, 56 had documented values of at least three theca-125 tumor marker measurements within the first 100 days of chemotherapy, required for KELIM score calculation. CA-125 levels were measured in local laboratories. Patient follow-up continued until December 2023 to determine the time in months post-chemotherapy until disease progression occurred. Ethical approval was obtained from the Ethics Committee of the Oncology Institute of Vojvodina in Sremska Kamenica.

Data collected from the BirPis21 information system included: patient's year of birth, FIGO stage, operative status, dates of chemotherapy cycles, date of bevacizumab initiation, CA-125 values and corresponding dates, progression-free survival in months following the last chemotherapy cycle.

Calculation of the KELIM score

KELIM scores were computed using a validated online tool (Biomarker Kinetics) [12]. Three CA-125 values obtained during the first 100 days of chemotherapy, as along with the dates of chemotherapy cycles, were imputed into the calculator. The results were classified as either favorable (KELIM ≥ 1) or unfavorable (KELIM < 1).

Statistical data processing

Statistical analyses were performed using SPSS Statistics version 25.0 software package. Statistically significant differences were observed between suboptimally operated FIGO stage IIIC and non-operated FIGO stage IIIC-IV patients regarding KELIM scores and the benefit of bevacizumab for PFS. Kaplan-Meier analysis and Cox regression were employed to examine correlations between the studied parameters. Statistically significant difference was defined as $p<0.05$ (p – level of statistical significance).

Results

A total of 91 patients with high-grade serous ovarian cancer (FIGO stage IIIC-IV) were included in this study. Of these, 32 were excluded due to insufficient CA-125 data (fewer than three documented values within the first 100 days of chemotherapy, required to calculate the KELIM score), and three patients were excluded due to the endometrioid subtype of epithelial ovarian cancer. All patients were treated with a standard chemotherapy protocol comprising paclitaxel and carboplatin, followed by maintenance therapy with bevacizumab. Data from the remaining 56 patients were analyzed using univariate and multivariate methods. The average patient age was 62 years (range: 36-79). The average progression-free survival (PFS) from the last chemotherapy cycle was 13.4 months (range: 2-51). Key patient characteristics included FIGO stage, operative status, and KELIM score. Among the participants, 39 (69.6%) had FIGO stage IIIC and 17 (30.4%) had stage IV. Regarding the operative status, 34 (60.7%) underwent surgery, while 22 (39.3%) did not. Based on KELIM scores, 48 patients (85.7%) had an unfavorable score (KELIM < 1), while 8 (14.3%) had a favorable score (KELIM ≥ 1).

Univariate analysis of PFS relative to KELIM scores i summarized in **Table 1.** Patients with KELIM ≥ 1 had a longer PFS compared to those with KELIM<1 (19.4 vs. 17.0). However, the difference was not statistically significant (p=0.549), likely due to the small proportion of patients with KELIM ≥ 1 (14.3%). **Graph 1** illustrates differences between these groups.

The multivariate analysis, detailed in **Table 2**, assessed the effect of operative status and FIGO stage on PFS in patients with an unfavorable KELIM score (KELIM < 1).

Table 1. Analysis for progression-free survival (PFS) in relation to KELIM score

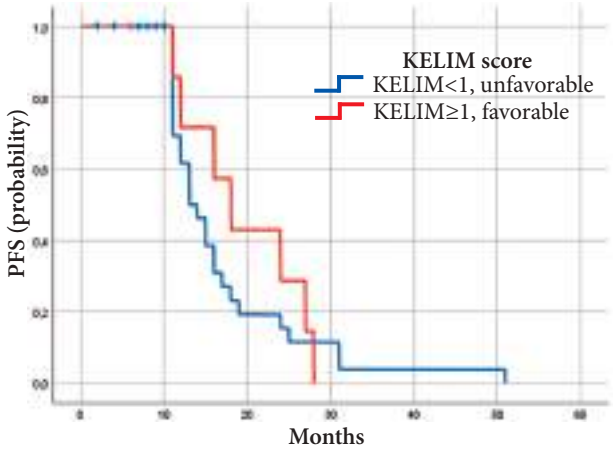
	PFS				
	n	Mean value (months)	95% CI (month)	Median (months)	p
Favorable KELIM≥1	8	19.4	14.3-24.6	18.0	0.549
Unfavorable KELIM<1	48	17.0	13.5-20.5	13.0	

n – number of patients 95%; CI – 95% confidence interval; p – statistical level significance; PFS – progression-free survival

Table 2. Multivariate analysis for progression-free survival (PFS) vs operative status and FIGO disease stage in patients with KELIM<1

		n	Mean value PFS (month)	Estimate	OR	95% CI	p
Operation status for KELIM<1	Unoperated	18	9.8	Ref	Ref	Ref	0.002
	Operated	30	14.4	-1.624	0.20	0.07-0.55	
FIGO stage for KELIM<1	IIIC	35	14.2	Ref	Ref	Ref	0.166
	IV	13	8.6	0.696	2.01	0.75-5.37	

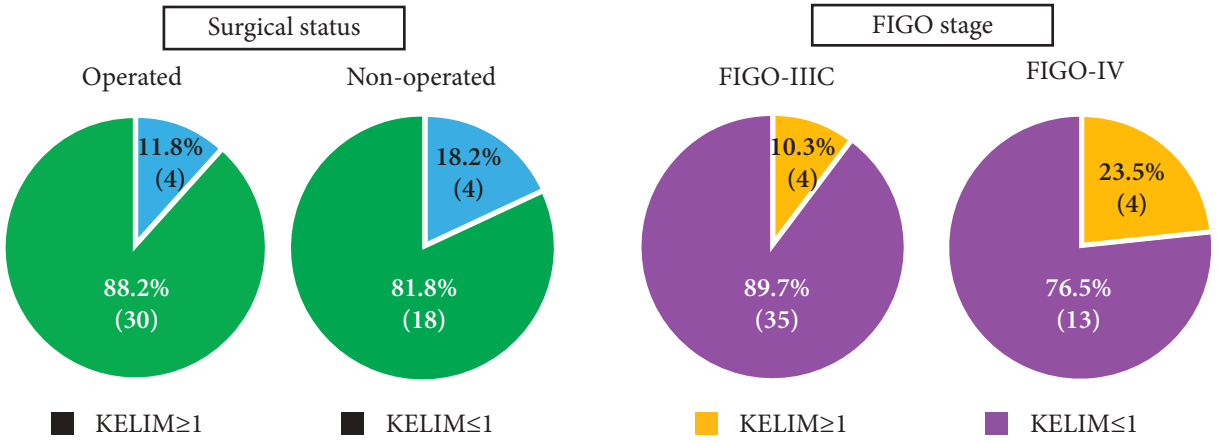
n – number of patients; PFS – progression free survival; Estimate – evaluation; OR – odd ratio; 95% CI – 95% confidence interval; p – level of statistical significance; Ref – reference



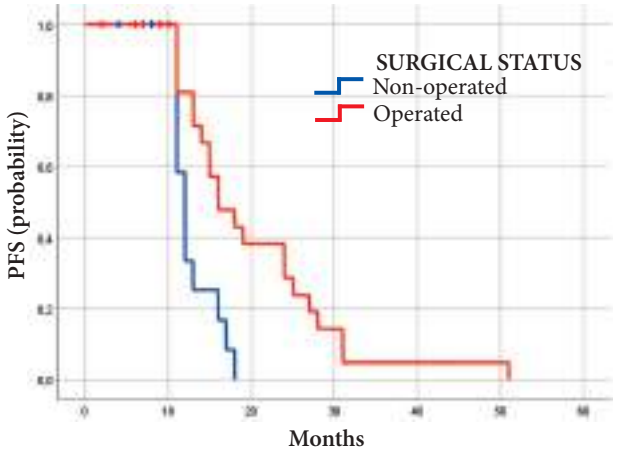
KELIM<1	48	64.6% (31)	10.4% (5)	6.25% (3)	2.1% (1)	2.1% (1)	0
KELIM≥1	8	87.5% (7)	37.5% (3)	0	0	0	0

Graph 1. PFS curves according to KELIM score

Among the 56 patients, 34 (60.7%) underwent surgery, of whom 4 (11.8%) had a favorable KELIM score (KELIM ≥ 1) and 30 (88.2%) had an unfavorable score (KELIM < 1). Among the 22 (39.3%) non-operated patients, 4 (18.2%) had a favorable score (KELIM ≥ 1), while 18 (81.8%) had an unfavorable score (KELIM <1) (**Graph 2**). Comparisons were not made in the KELIM ≥1 subgroup due to the small portion of patients. In the KELIM < 1 subgroup, surgery was associated with significantly longer average PFS compared to non-operated patients (14.4 vs. 9.8 months) (p=0.002). Operated patients had an 80% lower likelihood of disease progression (OR=0.20). **Graph 3** illustrates PFS comparisons between operated and non-operated patients with an unfavorable KELIM score. Regarding FIGO stage, 39 patients (69.6%) were stage IIIC, and 17 (30.4%) were stage IV. In the stage IIIC group, 4 patients (10.3%) had KELIM ≥ 1, and 35 (89.7%) had KELIM <1. In the stage IV group, 4 patients (23.5%) had KELIM ≥1, while 13 (76.5%) had KELIM < 1 **(Graph 2)**. Due to the small portion of patients with KELIM ≥1, comparisons were made in the KELIM <1 group only. Among the patients with KELIM < 1, those with stage IIIC had longer average PFS than stage IV (14.2 vs. 8.6). However, this difference was not statistically significant. A high odds ratio (OR=2.01) indicated a two-fold increased risk of disease progression in stage IV disease, but the wide

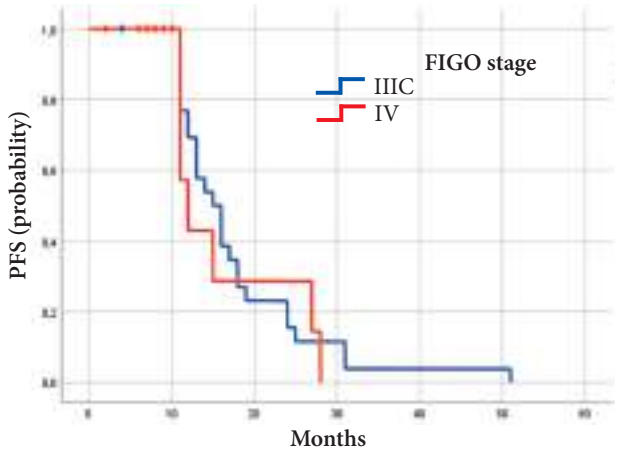


Graph 2. Patient distribution based on KELIM score in relation to surgical status and FIGO stage



Non-operated with KELIM<1	18	50% (9)	0	0	0	0	0
Operated with KELIM<1	30	56.7% (17)	16.7% (5)	10% (3)	3.3% (1)	3.3% (1)	0

Graph 3. PFS curves of patients with KELIM < 1 according to surgical status



IIIC with KELIM<1	32	62.9% (22)	14.3% (5)	8.6% (3)	2.9% (1)	2.9% (1)	0
IV with KELIM<1	13	30.8% (4)	0	0	0	0	0

Graph 4. PFS curves of patients with KELIM < 1 according to FIGO stage

confidence interval (95% CI: 0.75-5.37) suggests further validation is needed. **Graph 4** compares PFS across FIGO stages in the KELIM < 1 subgroup.

Discussion

Substantial efforts have been made to identify reproducible markers predicting bevacizumab efficacy in first-line therapy in advanced ovarian cancer [13, 14]. The KELIM score has recently emerged as a promising prognostic and predictive factor, identifying patients likely to benefit most from bevacizumab.

In our study, the KELIM score was not proven to be a statistically significant predictor of response to bevacizumab in the first-line therapy, based on PFS (p=0.549). Nonetheless, graphical representation suggested improved PFS in patients with KELIM ≥ 1. Multivariate analysis demonstrated statistically significantly longer PFS in operated patients compared to non-operated patients within the KELIM < 1 group (p=0.002), whereas FIGO stage did not prove to be a statistically significantly influence PFS in this population.

In 2022, You et al. [15] published a paper examining the relationship between intrinsic tumor chemosensitivity and the benefits of bevacizumab as the first-line treatment. This retrospective confirmatory analysis of the GOG-0218 trial, an international, multicenter, double-blind, placebo-controlled phase III clinical study, involved 1662 patients. The study demonstrated a statistically significant improvement in PFS OS with bevacizumab compared to placebo in patients with an unfavorable KELIM score (KELIM < 1). Conversely, no such benefit was observed in patients with a favorable KELIM score (KELIM ≥ 1). The most pronounced benefit was seen in patients with KELIM <1 and high-risk disease, specifically those with suboptimal surgical outcomes in FIGO stage IIIC and those in FIGO stage IV. Unlike their study, which compared bevacizumab and placebo groups, all patients in our study received bevacizumab. We observed that patients with KELIM ≥1 had longer PFS, as did those with KELIM <1 who underwent surgical treatment.

In 2020, You et al. [16] presented findings from the CHIVA study, a phase II clinical trial involving 134 patients treated with neoadjuvant chemotherapy, interval surgical treatment, and nintedanib or placebo. This study validated the independent predictive value of the KELIM score for tumor response rate, likelihood of complete surgical resection after neoadjuvant chemotherapy, risk of platinum-resistant relapse, PFS, and OS. Similar results were reported by Van Wagensveld et al. [17] in 2021. Their study, which analyzed 1,582 patients receiving neoadjuvant chemotherapy, identified the KELIM score as the most significant predictive factor for tumor response rate, complete surgical resection, PFS, and OS. Piedimonte et al. [18] conducted a 2022 study involving 217 patients with platinum-resistant tumor treated with neoadjuvant chemotherapy. They found that KELIM ≥1 was associated with statistically significantly longer PFS (p < 0.001) and OS (p = 0.014) compared to KELIM <1. Similarly, in 2023, Liontos et al. [19] evaluated the predictive value of the KELIM score on PFS and OS in real-world clinical settings among 99 patients receiving neoadjuvant chemotherapy. Their result confirmed a statistically significant correlation between the KELIM score and both PFS and OS. Moreover, they demonstrated adding

bevacizumab after neoadjuvant chemotherapy increased the statistical significance in regard to PFS and OS only in patients with an unfavorable KELIM score.

Our study is limited by the small sample size. Tumor marker CA-125 levels were measured in local laboratories, potentially introducing variability in the KELIM score due to non-standardized immunoassays. However, this variability is likely minimized by the scoring method, which utilizes multiple CA-125 measurements over time. Additionally, some patients were excluded from the final analysis due to insufficient CA-125 data, as the findings were self-reported by female patients. Another limitation is the small proportion of patients with a positive KELIM score (14.3%), which reduced statistical power and precluded their inclusion in the final multivariate analysis. Furthermore, surgeries were performed by different surgeons at various institutions, potentially affecting the quality of surgical resection and its influence on PFS in the operated group. Finally, since the patients were not prospectively monitored, OS data are unavailable, limiting this study to PFS evaluation.

Given that the KELIM score is a relatively new prognostic tool, primarily studied in controlled clinical trials with homogeneous patient populations, further research is required to validate its applicability in real-world clinical settings. Further studies should include diverse patient populations and explore its use across various therapeutic regimens, including bevacizumab and/or PARP inhibitors. These treatments, especially among of patients with BRCA 1/2 mutations, have shown a positive impact on survival and are increasingly used in the first-line therapy [20, 21].

Conclusion

Although our study did not find a statistically significant correlation between the Cancer Antigen-125 Elimination Rate Constant K score and progression-free survival in bevacizumab-treated patients, the findings has one significant limitation that is reflected in the small sample of patients, primarily those with a favorable the Cancer Antigen-125 Elimination Rate Constant K score. Certainly, the Cancer Antigen-125 Elimination Rate Constant K score calculator remains an accessible prognostic tool, and its utility in identifying patients who would benefit most from bevacizumab in the first-line therapy warrants further investigation. The patient operative status, on the other hand, proved to be the most significant factor contributing to survival, which is in line with the literature.

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