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ORIGINAL RESEARCH

Pre-Treatment CRP-Albumin-Lymphocyte Index (CALLY Index) as a Prognostic Biomarker of Survival in Patients with Epithelial Ovarian Cancer

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Background: The novel CRP–albumin–lymphocyte (CALLY) index is an improved immunonutritive scoring system, based on serum C-reactive protein (CRP), serum albumin, and the lymphocyte count. It has been determined as a prognostic index for patients with hepatocellular carcinoma. This study was conducted to explore the prognostic value of the CALLY index in patients with epithelial ovarian cancer (EOC) undergoing surgery.

Methods: Patients with EOC treated with surgery as an initial therapy were enrolled to form the training and validation cohorts. The effect of the CALLY index on overall survival (OS) and disease-free survival (DFS) was analyzed using Kaplan–Meier method and Cox proportional hazards model. The CALLY index was calculated as: (Albumin × Lymphocyte)/ (CRP × 10^4).

Results: There were 190 patients in the training cohort and 120 in the validation cohort, respectively. With a cut-off value of 3, patients were classified into the CALLY <3 and CALLY ≥3 groups. The CALLY index ≥3 was associated with better survival outcomes both in the training and validation cohorts. The univariate and multivariate COX analysis revealed that FIGO stage, lymphatic metastasis, and CALLY index were the prognostic factors for both OS and DFS.

Conclusion: The CALLY index is a novel prognostic biomarker for patients with EOC after surgery. The novel CALLY index could select appropriate patients with poor prognosis for postoperative adjuvant therapy.

Keywords: epithelial ovarian cancer, CALLY index, biomarker, survival

Introduction

Ovarian cancer is the eighth cause of cancer-related mortality among women and the leading cause of gynecological cancer-associated mortality worldwide.[1] It is estimated that approximately 193,811 deaths and 308,069 new cases of ovarian cancer will be reported worldwide during 2020.[2] Epithelial ovarian cancer (EOC) accounts for nearly 90% of all histological types of ovarian cancers.[3] Despite the great progress in treatment and diagnosis, over 70% of EOC was diagnosed at the advanced stage, resulting in poor prognosis with a 10-year survival rate of 5–21%.[4,5] Moreover, about 80% of patients with EOC will develop recurrence after initial standardised surgery and chemotherapy.[6] Given the poor prognosis, effective and easy-obtained methods to optimize risk stratification and predict survival outcomes are urgently required for patients with EOC after surgery.

Inflammatory reaction has been recognized as a vital factor relevant to ovarian cancer malignant progression and metastasis.[7] Currently, a series of studies have proposed several inflammation-based prognostic indices, including the Glasgow Prognostic Score (GPS),[8] neutrophil-to-lymphocyte ratio (NLR),[9] and platelet-to-lymphocyte ratio (PLR),[10] to be effective prognostic factors for ovarian cancer patients. The GPS is a system that evaluates nutritional status and inflammatory reactions using a combination of the serum C-reactive protein (CRP) and the serum albumin values.

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Moreover, the prognostic nutrition index (PNI) is a combination of the serum albumin value and total lymphocyte count, which indicates the remnant liver function and the immune system status, respectively.[11] PNI has been determined as a favorable immunonutritive biomarker for survival stratification in multiple cancers including ovarian cancer.[12–15] For example, Komura et al reported the superior ability of pre-treatment PNI for predicting disease-specific survival for patients with EOC.[16]

Based on two representative markers (GPS and PNI), we constructed the novel CRP–albumin–lymphocyte (CALLY) index, which is an improved immunonutritive scoring system. We reasoned that this unique combination of markers for liver function, immune system status, and inflammation might have a synergistic effect in predicting survival in patients with malignant tumours. Indeed, the CALLY index has only been reported as a novel prognostic index in hepatocellular carcinoma.[17,18] However, the prognostic value of CALLY index in patients with EOC after surgery is not well explored.

In this study, we aimed to evaluate and validate the prognostic value of the CALLY index in patients with EOC after surgery using a retrospective training cohort and a prospective validation cohort.

Materials and Methods

Study Population

In the training cohort, clinical data from 190 patients with EOC was analyzed retrospectively at the Department of Obstetrics and Gynecology, Shijiazhuang Maternity and Child Health Care Hospital from January 2010 to December 2012. In the validation cohort, clinical data from 120 patients with EOC was reviewed prospectively at the same institution from January 2013 to December 2014. The study was approved by the Ethics Committees of Shijiazhuang Maternity and Child Health Care Hospital and conducted according to the Declaration of Helsinki. Written informed consent was obtained from each participant for their data to be used in this research.

Inclusion and Exclusion Criteria

In this study, the inclusion and exclusion criteria were consistent in the training and validation cohorts. The inclusion criteria were: 1) EOC was confirmed histologically; 2) underwent primary staging or debulking surgery; or 3) no coexisting cancers or prior cancers within 5 years. The exclusion criteria were: 1) with other preoperative anti-cancer treatments; 2) with incomplete follow-up data; or 3) with active infection, hematological or autoimmune disease.

Data Collection

The routine blood parameters, including neutrophil count, lymphocyte count, platelet count, albumin, and CRP, were obtained within 3 days before surgery. The following clinicopathologic variables were collected form medical records: age, Body Mass Index (BMI), menopausal status, fertility history, comorbidities, tumour size, pathological grade, International Federation of Gynecology and Obstetrics (FIGO) stage, histological type, and lymphatic metastasis. The overall survival (OS) was defined as the date of surgery to the date of death or last follow-up. The disease-free survival (DFS) was defined as the date of surgery to the date of EOC recurrence, death, or last follow-up. The CALLY index was defined as the preoperative albumin value multiplied by the lymphocyte count and divided by the CRP value multiplied by 10,000: (Albumin × Lymphocyte)/(CRP × 10^4).

Statistical Analysis

Continuous variables, reported as the mean ± standard deviation or the median with interquartile range, were compared using the Student's *t*-test or Mann–Whitney *U*-test, respectively. Categorical variables, reported as frequencies (%), were compared using the chi-square test or Fisher's exact test. The Kaplan-Meier curves were generated for OS or DFS and compared with the Log rank test in different groups. Factors associated with OS or DFS in EOC patients were assessed by both univariate and multivariate Cox regression analyses with forward step-wise approach. The cut-off value of CALLY index was selected by Receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed with SPSS statistical software (version 25.0) and GraphPad Prism (version 8.3.0). *P* values less than 0.05 were considered statistically significant. All tests were two-tailed.

Results

Baseline Characteristics

As shown in Figure 1, a consecutive of 232 patients with EOC who underwent surgery from January 2010 to December 2012 were enrolled. After excluding 42 patients with incomplete follow-up data, preoperative treatments, and active infection, hematological or autoimmune disease, the other 190 patients formed the training cohort. An independent cohort of 120 patients with EOC after initial surgery from January 2013 to December 2014 was prospectively recruited to constitute the validation cohort. Baseline characteristics of the patients in the training and validation cohorts are summarized in Table 1. All the variables were well balanced between two cohorts.

Comparison of Baseline Characteristics Between the CALLY ≥3 and CALLY <3 Groups

After applying optimal stratification, the optimal cut-off for the median OS was 3 points for the CALLY index. With this cut-off value, 105 patients formed the CALLY <3 group and the other 85 patients constituted the CALLY ≥3 group in the training cohort. The comparison of clinical characteristics between the CALLY ≥3 and CALLY <3 groups were described in Table 2. The CALLY ≥3 group showed significantly higher lymphocyte counts (P <0.001) and albumin levels (P <0.001) but significantly lower neutrophil counts (P =0.001) and CRP values (P <0.001) compared to the CALLY <3 group. The mean tumor size was significantly larger in the CALLY <3 group than in the CALLY ≥3 group (7.1 vs 6.2 cm; P =0.025). In terms of FIGO stage, there were more patients with early stage (I–II) in the CALLY ≥3 group when compared to the CALLY <3 group (23.8% vs 43.5%; P =0.004). The percentage of positive lymphatic metastasis was higher in the CALLY <3 group than in the CALLY ≥3 group (66.7% vs 48.2%; P =0.010). No significant difference was found between two groups in age, BMI, menopausal status, fertility history, comorbidities, platelet counts, pathological grade, and histological type. In the validation cohort, patients were also classified into the CALLY <3 (n = 50) and CALLY ≥3 (n = 70) groups.

Survival Analysis

In the training cohort, the 1-, 3-, and 5-year OS rates were significantly higher in the CALLY ≥3 group (95%, 81%, and 59%, respectively; median OS: 69 months) compared to the CALLY <3 group (91%, 69%, and 47%, respectively; median OS: 56 months) (P = 0.015, Figure 2A). Similarly, the 1-, 3-, and 5-year DFS rates were significantly higher in the CALLY ≥3 group (94%, 75%, and 48%, respectively; median DFS: 58 months) compared to the CALLY <3 group (82%, 54%, and 27%, respectively; median DFS: 39 months) (P = 0.002, Figure 2B). In the validation cohort, the 1-, 3-,

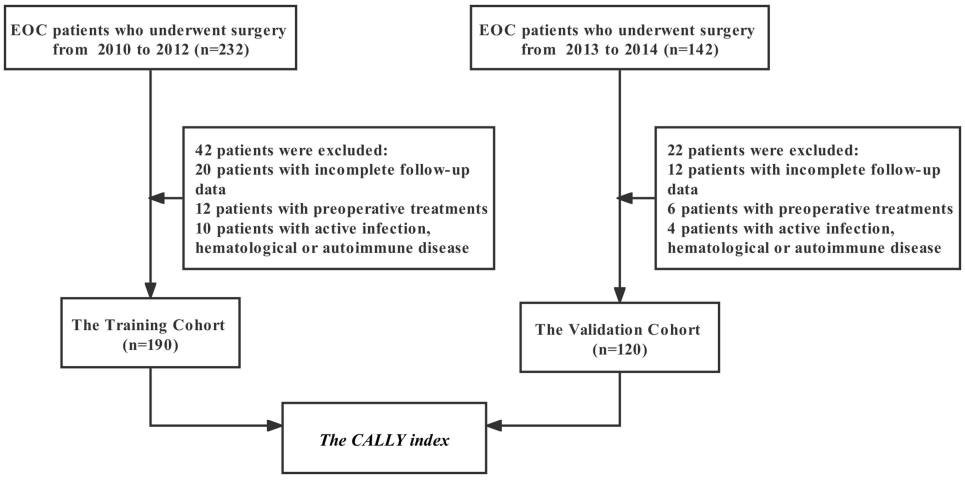

Figure 1 Flow chart showing the process of selection of EOC patients who underwent surgery in the training cohort (n = 190) and the validation cohort (n = 120).
Note: The definition of CALLY index was shown with italics.
Abbreviation: EOC, epithelial ovarian cancer.

Table 1 Comparison Between Training Cohort and Validation Cohort

Variables	Training (n=190)	Validation (n=120)	*P*-value
Age (years)	57.5±9.8	57.8±8.4	0.563
BMI (kg/m^2)	22.2±0.8	21.6±0.9	0.436
Menopausal status (%)			0.370
Pre/peri-menopause	29 (15.3)	23 (19.2)	
Post-menopause	161 (84.7)	97 (80.8)	
Fertility history (%)			0.403
0	11 (5.8)	8 (6.7)	
1	86 (45.3)	45 (37.5)	
≥2	93 (48.9)	67 (55.8)	
Comorbidities (%)			0.166
Yes	35 (18.4)	30 (25.0)	
No	155 (81.6)	90 (75.0)	
Neutrophil (/μL)	4120 (3150–4860)	4240 (3160–4980)	0.156
Lymphocyte (/μL)	1320 (910–1630)	1380 (930–1520)	0.263
Platelet (x10^3/mL)	169 (129–212)	178 (125–218)	0.109
Albumin (g/dL)	3.9 (3.6–4.2)	3.8 (3.5–4.1)	0.234
C-reactive protein (mg/dL)	0.15 (0.09–0.42)	0.19 (0.10–0.57)	0.186
Tumor size (cm)	7.1±5.5	7.3±4.8	0.356
Pathological grade (%)			0.319
G1-2	49 (25.8)	25 (20.8)	
G3	141 (74.2)	95 (79.2)	
FIGO stage (%)			0.266
Early (I–II)	62 (32.6)	32 (26.7)	
Advanced (III–IV)	128 (67.4)	88 (73.3)	
Histological type (%)			0.236
Serous	119 (62.6)	65 (54.2)	
Mucinous	24 (12.6)	13 (10.8)	
Endometrioid	20 (10.5)	15 (12.5)	
Others	27 (14.2)	27 (22.5)	
Lymphatic metastasis (%)			0.079
Negative	79 (41.6)	38 (31.7)	
Positive	111 (58.4)	82 (68.3)	

Abbreviations: BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics.

and 5-year OS rates were significantly higher in the CALLY ≥3 group (100%, 84%, and 62%, respectively; median OS: NA) compared to the CALLY <3 group (87%, 70%, and 37%, respectively; median OS: 52 months) (P = 0.004, Figure 3A). Similarly, the 1-, 3-, and 5-year DFS rates were significantly higher in the CALLY ≥3 group (96%, 78%, and 46%, respectively; median DFS: 57 months) compared to the CALLY <3 group (81%, 53%, and 30%, respectively; median DFS: 44 months) (P = 0.028, Figure 3B).

Prognostic Factors for the OS and DFS

In the training cohort, univariate and multivariate analyses of the factors affecting OS and DFS were determined in Tables 3 and 4. As shown in Table 3, neutrophil, FIGO stage, lymphatic metastasis, and CALLY index found to be significant in the univariate analysis were included in the multivariate regression analysis. The results revealed that neutrophil (hazard ratio [HR] with 95% confidence interval [CI] = 1.212 [1.164–1.396]; P = 0.036), FIGO stage (HR with 95% CI = 1.516 [1.216–2.103]; P = 0.005), lymphatic metastasis (HR with 95% CI = 1.412 [1.311–1.796]; P = 0.016), and CALLY index (HR with 95% CI = 0.599 [0.391–0.896]; P <0.001) remained as significant predictors of OS. In addition, we also found that neutrophil, FIGO stage, lymphatic metastasis, and CALLY index were also significant

Table 2 Clinical Characteristics of the Patients According to CALLY Index in the Training Cohort

Variables	CALLY <3 (n=105)	CALLY ≥3 (n=85)	*P*-value
Age (years)	58.8±9.1	56.9±10.6	0.612
BMI (kg/m^2)	22.1±0.7	21.3±0.8	0.165
Menopausal status (%)			0.107
Pre/peri-menopause	20 (19.0)	9 (10.6)	
Post-menopause	85 (81.0)	76 (89.4)	
Fertility history (%)			0.764
0	6 (5.7)	5 (5.9)	
1	50 (47.6)	36 (42.4)	
≥2	49 (46.7)	44 (51.8)	
Comorbidities (%)			0.613
Yes	18 (17.1)	17 (20.0)	
No	87 (82.9)	68 (80.0)	
Neutrophil (/μL)	4420 (3200–5200)	3980 (2900–4500)	**0.001**
Lymphocyte (/μL)	1230 (899–1450)	1520 (1210–1890)	**<0.001**
Platelet (x10^3/mL)	171 (131–214)	162 (127–210)	0.098
Albumin (g/dL)	3.7 (3.4–4.0)	4.2 (3.8–4.3)	**<0.001**
C-reactive protein (mg/dL)	0.28 (0.16–0.71)	0.07 (0.03–0.10)	**<0.001**
Tumor size (cm)	7.1±5.4	6.2±5.2	**0.025**
Pathological grade (%)			0.759
G1-2	28 (26.7)	21 (24.7)	
G3	77 (73.3)	64 (75.3)	
FIGO stage (%)			**0.004**
Early (I–II)	25 (23.8)	37 (43.5)	
Advanced (III–IV)	80 (76.2)	48 (56.5)	
Histological type (%)			0.423
Serous	61 (58.1)	58 (68.2)	
Mucinous	16 (15.2)	8 (9.4)	
Endometrioid	13 (12.4)	7 (8.2)	
Others	15 (14.3)	12 (14.1)	
Lymphatic metastasis (%)			**0.010**
Negative	35 (33.3)	44 (51.8)	
Positive	70 (66.7)	41 (48.2)	

Note: The bold values denote *P*-value less than 0.05 with statistical significance.
Abbreviations: BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics.

prognostic factors for DFS (Table 4). In the validation cohort, univariate and multivariate analyses of the factors affecting OS and DFS were determined in Tables S1 and S2. We identified neutrophil, tumor size, FIGO stage, lymphatic metastasis, and CALLY index as prognostic factors for OS (Table S1). Moreover, FIGO stage, lymphatic metastasis, and CALLY index were still independent prognostic factors for DFS (Table S2).

Discussion

To our knowledge, this study is the first to report and validate the CALLY index to predict survival in patients with EOC treated with surgery. The inflammatory, immunological, and nutritional condition are commonly reported to be highly involved in carcinogenesis.[19] The CALLY index based on CRP, lymphocyte, and albumin combines markers of inflammation, the immune response, and nutritional status. CRP is a critical acute phase response protein produced by the hepatocytes in response to inflammation.[20] Several studies have confirmed that high circulating CRP levels were associated with poor survival in patients with ovarian cancer.[21–23] The underlying mechanism is that CRP can accelerate

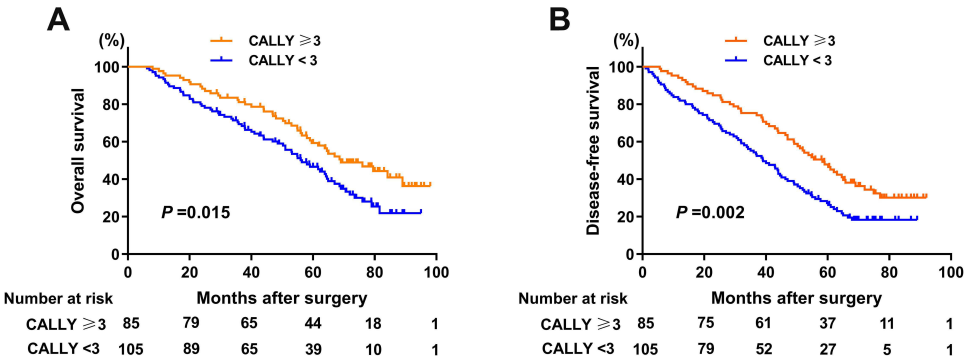

Figure 2 Kaplan-Meier curves for overall survival (**A**) and disease-free survival (**B**) of the CALLY ≥3 and CALLY <3 groups in the training cohort.

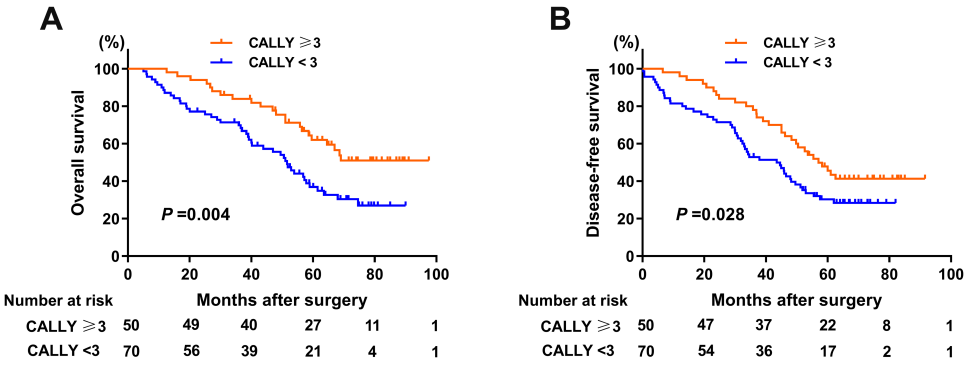

Figure 3 Kaplan-Meier curves for overall survival (**A**) and disease-free survival (**B**) of the CALLY ≥3 and CALLY <3 groups in the validation cohort.

angiogenesis via increasing the circulating levels of vascular growth factors and interleukin in cancer patients.[24] Albumin is also synthesized by the liver, which is now widely used as an indicator of malnutrition and liver function. Albumin values are closely related to prognosis in patients with cancer.[25] Several studies demonstrated that pre-surgery low serum albumin levels are an independent poor prognostic factor in patients with ovarian cancer.[26,27] The lower lymphocyte count is related to the existence of a primary immunodeficiency, as lymphocytes play a part in tumour immunity to suppress tumorigenesis.[28]

In this study, with the CALLY index cut-off value set to 3 using ROC analysis, we designed a simple score system which showed promising results in predicting prognosis for patients with EOC after surgery. The survival stratification ability of the CALLY index was further confirmed in the validation cohort with the same cut-off value as 3. Moreover, univariate and multivariate analysis revealed that CALLY index was an independent prognostic factor for both OS and DFS, along with other prognostic factors including neutrophil, FIGO stage, and lymphatic metastasis. The neutrophil count, a critical inflammatory mark, has been reported as a prognostic index in multiple cancers including EOC.[29] The FIGO stage is a commonly used staging system that can provide prognostic information and guidance on personalized management of ovarian cancer,[30] the prognostic value of which was also validated in this study. Moreover, the presence of lymphatic metastasis represents the aggressive characteristics of tumors and may lead to suboptimal prognosis in EOC patients,[31] which was also confirmed in the current study.

Table 3 Univariate and Multivariate Analysis of Overall Survival in the Training Cohort

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.002 (0.942–1.097)	0.631		
BMI (kg/m^2)	0.995 (0.727–1.209)	0.372		
Menopausal status (%)				
Pre/peri-menopause	Reference	-		
Post-menopause	0.836 (0.496–1.243)	0.265		
Fertility history (%)				
0	Reference	-		
1	0.923 (0.836–1.174)	0.531		
≥2	1.104 (0.719–1.394)	0.631		
Comorbidities (%)				
Yes	Reference	-		
No	1.825 (0.698–1.120)	0.289		
Neutrophil (/μL)	1.249 (1.184–1.426)	**0.010**	1.212 (1.164–1.396)	**0.036**
Platelet (x10^3/mL)	1.000 (0.991–1.008)	0.815		
Tumor size (cm)	1.303 (0.958–1.632)	0.516		
Pathological grade (%)				
G1-2	Reference	-		
G3	0.769 (0.465–1.312)	0.364		
FIGO stage (%)				
Early (I–II)	Reference	-	Reference	-
Advanced (III–IV)	1.564 (1.234–2.131)	**0.001**	1.516 (1.216–2.103)	**0.005**
Histological type (%)				
Serous	Reference	-		
Mucinous	0.978 (0.814–1.125)	0.635		
Endometrioid	0.997 (0.789–1.097)	0.125		
Others	1.004 (0.912–1.164)	0.231		
Lymphatic metastasis (%)				
Negative	Reference	-	Reference	-
Positive	1.495 (1.326–1.896)	**0.008**	1.412 (1.311–1.796)	**0.016**
CALLY index				
CALLY <3	Reference	-	Reference	-
CALLY ≥3	0.542 (0.321–0.746)	**<0.001**	0.599 (0.391–0.896)	**<0.001**

Note: The bold values denote *P*-value less than 0.05 with statistical significance.
Abbreviations: CI, confidence interval; HR, hazard ratio; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics.

The CALLY index has four significant advantages in clinical practice. First, the CALLY index showed stability and accuracy in predicting survival in EOC patients treated with surgery using the cut-off score ≥3. Second, the CALLY index is easily available in clinical practice and the calculation method used for the CALLY index was simple. Third, the CALLY index ≥3 can be used to select suitable patients for surgery. Finally, for the subgroup of patients with the CALLY index <3 who have poor prognosis after surgery, some postoperative adjuvant therapies such as chemotherapy or targeted therapy can be applied to improve long-term survival outcomes. However, this study had some limitations. First, this is a retrospective study with its inherent defects. Second, this study was conducted at one institution in China, which needs to be validated in more independent institutions with a sufficient number of patients.

In conclusion, the CALLY index, which are calculated using the CRP value, albumin level, and lymphocyte count, could be an effective and efficient predictive biomarker for postoperative prognosis in patients with EOC. The CALLY index may provide a novel paradigm for personalized application of postoperative adjuvant therapy for patients with the CALLY index <3.

Table 4 Univariate and Multivariate Analysis of Recurrence-Free Survival in the Training Cohort

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.013 (0.891–1.213)	0.396		
BMI (kg/m^2)	1.002 (0.845–1.312)	0.293		
Menopausal status (%)				
Pre/peri-menopause	Reference	-		
Post-menopause	0.901 (0.632–1.296)	0.293		
Fertility history (%)				
0	Reference	-		
1	1.008 (0.863–1.197)	0.741		
≥2	1.002 (0.767–1.376)	0.511		
Comorbidities (%)				
Yes	Reference	-		
No	1.010 (0.728–1.321)	0.536		
Neutrophil (/μL)	1.369 (1.203–1.513)	**0.004**	1.298 (1.193–1.501)	**0.008**
Platelet (x10^3/mL)	1.004 (0.912–1.014)	0.853		
Tumor size (cm)	1.598 (1.132–1.862)	**0.013**	1.341 (0.931–1.697)	0.113
Pathological grade (%)				
G1-2	Reference	-		
G3	0.863 (0.531–1.473)	0.642		
FIGO stage (%)				
Early (I–II)	Reference	-	Reference	-
Advanced (III–IV)	1.763 (1.364–2.362)	**<0.001**	1.637 (1.117–2.009)	**0.001**
Histological type (%)				
Serous	Reference	-		
Mucinous	0.956 (0.846–1.193)	0.572		
Endometrioid	0.912 (0.812–1.052)	0.255		
Others	1.001 (0.942–1.185)	0.113		
Lymphatic metastasis (%)				
Negative	Reference	-	Reference	-
Positive	1.526 (1.293–1.783)	**0.005**	1.318 (1.131–1.631)	**0.012**
CALLY index				
CALLY <3	Reference	-	Reference	-
CALLY ≥3	0.563 (0.334–0.764)	**<0.001**	0.612 (0.423–0.856)	**0.001**

Note: The bold values denote *P*-value less than 0.05 with statistical significance.
Abbreviations: CI, confidence interval; HR, hazard ratio; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

No potential conflicts of interest are disclosed.

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