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ORIGINAL RESEARCH

Identification of a Novel Prognostic Classification Model in Epithelial Ovarian Cancer by Cluster Analysis

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Background: Heterogeneity plays an essential role in ovarian cancer. Patients with different clinical features may manifest diverse patterns in diagnosis, treatment, and prognosis. The aim of the present study was to identify a novel ovarian cancer–classification model through cluster analysis and assess its significance in prognosis.

Methods: Among patients diagnosed with ovarian cancer in the Women's Hospital School of Medicine, Zhejiang University between January 2014 and May 2019, 328 patients were included in a *K*-mean cluster analysis and 176 patients followed up. Major clinical indicators, overall survival, and recurrence-free survival in different subgroups were compared.

Results: Two clusters for ovarian cancer were identified and grouped as noninflammatory (n=247) and inflammatory subtypes (n=81). Compared with the noninflammatory subgroup, the inflammatory subgroup presented a statistically significantly higher level of median CRP (median (IQR) 20.4 [7.8–47.3] vs 1.2 [0.4–3.5], $p<0.001$), neutrophil percentage (median (IQR) 76.9 [72.6–81.3] vs 66.2 [61.0–72.0], $p<0.001$), leukocyte count (median (IQR) 8.9 [7.0–10.0] vs 6.0 [5.1–7.2], $p<0.001$), fibrinogen (median (IQR) 5.0 [4.4–6.0] vs 3.4 [2.9–3.9], $p<0.001$), and platelet count (median (IQR) 324 [270–405] vs 229 [181.5–269], $p<0.001$). During a median follow-up of 52 months, 21 participants (16.3%) died in the noninflammatory group, while 14 (29.8%) died in the inflammatory group (HR 2.15, 95% CI 1.09–4.23; $p=0.024$). Death/recurrence was observed in 38 (29.5%) patients from the noninflammatory group and 25 (53.2%) from the inflammatory group (HR 2.32, 95% CI 1.40–3.85; $p<0.001$).

Conclusion: Our study revealed a novel classification model of ovarian cancer that features inflammation. Inflammation predicts shorter survival and poorer prognosis, suggesting the significance of inflammation in the management of ovarian cancer.

Keywords: ovarian cancer, classification, heterogeneity, cluster analysis, inflammation, prognosis

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Introduction

Ovarian cancer is the fifth–most frequent cause of cancer death in women and the leading cause of death from gynecological cancer, accounting for 5% of estimated cancer deaths.[1–3] With most patients diagnosed at an advanced stage, the prognosis remains unsatisfactory.[1] In fact, ovarian cancer is a collective term for cancers of the ovaries, peritoneum, and fallopian tube. Ovarian cancer consists of heterogeneous subtypes classified by International Federation of Gynecology and Obstetrics (FIGO) stage, tissue of origin,[4–6] pathological grade,[7] clinical presentation,[8] molecular profiling,[9,10] and treatment.[6,11] These subtypes can vary from each other in

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initial symptoms, diagnosis, treatment protocol, and prognosis.[4,5] A practical classification of ovarian cancer is of great significance to differentiate specific subgroups, guide personalized treatment, and ultimately improve prognosis.

Several widely known models have been carried out to categorize ovarian cancers. The revised dualistic model, integrating histopathologic classification with molecular genetic features, classified ovarian cancers into two groups (type I and type II).[7] Type I was further divided into three subtypes. In general, type I tumors usually derived from benign extraovarian lesions, while many type II carcinomas developed from intraepithelial carcinomas in the fallopian tube.[7] Type I cancers were typically indolent, with a good prognosis. In contrast, type II cancers were more aggressive and accompanied worse outcomes.[7] Emphasizing the dramatic differences between the two groups, the dualistic model was expected to guide ovarian cancer screening, prevention, and treatment. Another two studies focusing on genomic and/or proteomic data based on The Cancer Genome Atlas identified different subtypes and cast a new light on the understanding of ovarian cancer.[9,10]

The aforementioned classification models rely on histopathological and molecular features obtained after invasive procedures and operation. More accessible and convenient classification paradigms would be beneficial to have a better understanding of the condition of patients prior to invasive procedures and provide additional information for clinical decision-making. Therefore, the current study aimed to identify preoperative ovarian cancer subtypes through cluster analysis of easily accessible variables, such as demographic data and laboratory results, and to evaluate the feasibility of our novel classification paradigm in the survival prediction of ovarian cancer patients.

Methods

Study Population and Data Collection

This study included patients who had been histopathologically diagnosed with epithelial ovarian cancer at the Women's Hospital School of Medicine, Zhejiang University between January 2014 and May 2019. Exclusion criteria were nonepithelial ovarian tumors, neoadjuvant chemotherapy before interval debulking surgery, suboptimal debulking, borderline tumors, metastatic ovarian cancer, previous surgery for ovarian cancer, recurrent ovarian cancer, history of malignant tumors, and scarce information to carry out our analysis. Results of laboratory tests taken prior to invasive operations were collected retrospectively from the electronic medical records. Age, BMI, histopathological subtype, FIGO stage, and grade were extracted as well. Patients diagnosed between January 2014 and December 2016 were followed up with telephone or hospital records until January 2020. The outcomes of interest were overall survival and recurrence-free survival. Overall survival was defined as the time between primary diagnosis and death. Recurrence-free survival was defined as the time from primary diagnosis to disease recurrence or progression or death from any cause, whichever occurred first. Disease progression was defined according to Response Evaluation Criteria in Solid Tumors version 1.1 or on the basis of CA125 level elevated from baseline. The present retrospective observational study was approved by the ethical committee of the Women's Hospital School of Medicine, Zhejiang University (decision 20,180,196). Informed consent was waived, due to the retrospective nature of the study and anonymous analyses of the data. All analyses were carried out with confidentiality. This study was performed in compliance with the ethical standards of the Declaration of Helsinki.

Design and Procedures

Variables selected for all participants (Table 1) to enter the cluster analysis were age, BMI, and laboratory results. Histopathological characteristics were compared between groups after clustering. The dualistic model of epithelial ovarian carcinogenesis was adopted to divide tumors into type I and type II.[7] Cluster analysis was validated by verifying its association with overall survival and recurrence-free survival. Patients diagnosed between January 2014 and December 2016 were included in the survival analysis.

Statistical Analysis

Cluster analysis was performed using *K*-mean cluster analysis after data standardization. Baseline characteristics were compared according to the group after clustering. Continuous and categorical variables are expressed as medians (interquartile range, IQR) and number (percentage), respectively. Rank-sum, Kruskal–Wallis and ANOVA *F* tests were employed for comparing continuous variables between groups. Fisher's exact or χ^2 tests were employed to compare categorical variables. The Kaplan–Meier method with log-rank testing was used in survival analysis. The Cox regression model was used to calculate HR and 95% CI. Two-tailed $p<0.05$ was

Table 1 Comparison of Baseline Characteristics Between Groups

	Cluster 1 (Noninflammatory)	Cluster 2 (Inflammatory)	*p*-value
Total	247	81	
Age, years	51 (42,57)	52 (46,58)	0.253
CRP	1.2 (0.4,3.5)	20.4 (7.8,47.3)	<0.001
Leukocyte count	6.0 (5.1,7.2)	8.9 (7.0,10.0)	<0.001
Neutrophil percentage	66.2 (61.0,72.0)	76.9 (72.6,81.3)	<0.001
Fibrinogen	3.4 (2.9,3.9)	5.0 (4.4,6.0)	<0.001
Platelet count	229 (181.5,269)	324 (270,405)	<0.001
Albumin	44.6 (42.7,46.5)	40.9 (38,43.7)	<0.001
Lymphocyte percentage	25.3 (19.9,30.4)	15.2 (11.7,19.7)	<0.001
CA125	111 (36.5,400.1)	697.1 (262.1,1785)	<0.001
BMI	22.9 (21.2,24.7)	23.4 (21,25.2)	0.757
GGT	14 (11,22)	19 (12,27)	0.012
ALT	18 (13,24.5)	14 (12,22)	0.028
AST	20 (17,24)	21 (17,25)	0.439
TBil	10.6 (7.8,14.2)	8.1 (6,11.5)	<0.001
DBil	4.1 (3.1,5.2)	3.5 (2.6,4.3)	0.002
IBil	6.6 (4.6,9.2)	4.7 (3.3,7.1)	<0.001
Creatinine	75.2 (66.2,81.2)	73.6 (64.5,80.8)	0.235
BUN	4.3 (3.5,5.2)	4.2 (3.2,5.3)	0.288
UA	247 (219.5,288.5)	244 (211,285)	0.348
HDL	1.3 (1.1,1.5)	1.1 (1,1.2)	<0.001
LDL	2.6 (2.2,3)	2.7 (2.3,3.1)	0.227
TG	1.2 (0.8,1.8)	1.3 (1.1,1.9)	0.099

Note: Data presented as medians (IQR).

Abbreviations: CA125, cancer antigen 125; BMI, body-mass index; GGT, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; BUN, blood urea nitrogen; UA, uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

considered statistically significant. All statistical analyses were performed using R version 3.5.1.

Results

Among the 645 patients collected between January 2014 and May 2019, 23 duplicates were excluded and another 229 patients excluded according to the aforementioned exclusion criteria. A total of 65 patients were not able to be clustered because of missing data of at least one of the included variables. Finally, 328 patients were included in the present study. Characteristics of patients included were shown in Table 1. *K*-mean clustering identified two clusters of patients (Figure 1A): 247 patients in cluster 1 and 81 in cluster 2. Average silhouette width was 0.16 (Figure 1B).

As shown in Table 2, cluster 2 featured a higher death/recurrence rate ($p<0.001$) and a higher proportion of advanced patients ($p<0.001$). Interestingly, cluster 2 presented higher levels of inflammation biomarkers, as shown in Table 1 and Figure 2. Median CRP levels were 20.4 (7.8–47.3) and 1.2 (0.4–3.5) in cluster 2 and cluster 1, respectively ($p<0.001$). Median leukocyte counts were 8.9 (7.0–10.0) and 6.0 (5.1–7.2) in cluster 2 and cluster 1, respectively ($p<0.001$). Median neutrophil percentages were 76.9 (72.6–81.3) and 66.2 (61.0–72.0) in cluster 2 and cluster 1, respectively ($p<0.001$). Cluster 2 was also characterized by higher fibrinogen levels ($p<0.001$), higher platelet counts ($p<0.001$), lower albumin levels ($p<0.001$) and higher CA125 levels ($p<0.001$).

Concerning higher proportion of advanced tumors and higher levels of inflammation biomarkers in cluster 2, Table 3 shows associations between laboratory findings and FIGO stages. Table 3 indicates that CRP levels ($p<0.001$), neutrophil percentage ($p<0.001$), fibrinogen ($p<0.001$), platelet counts ($p<0.001$), and CA125 levels ($p<0.001$) ascended from stage I to stage IV, while albumin levels ($p<0.001$) and lymphocyte percentage ($p<0.001$) descended.

Survival Analysis

To further verify these results, survival analysis was carried out. Based on the elevated inflammation biomarkers,

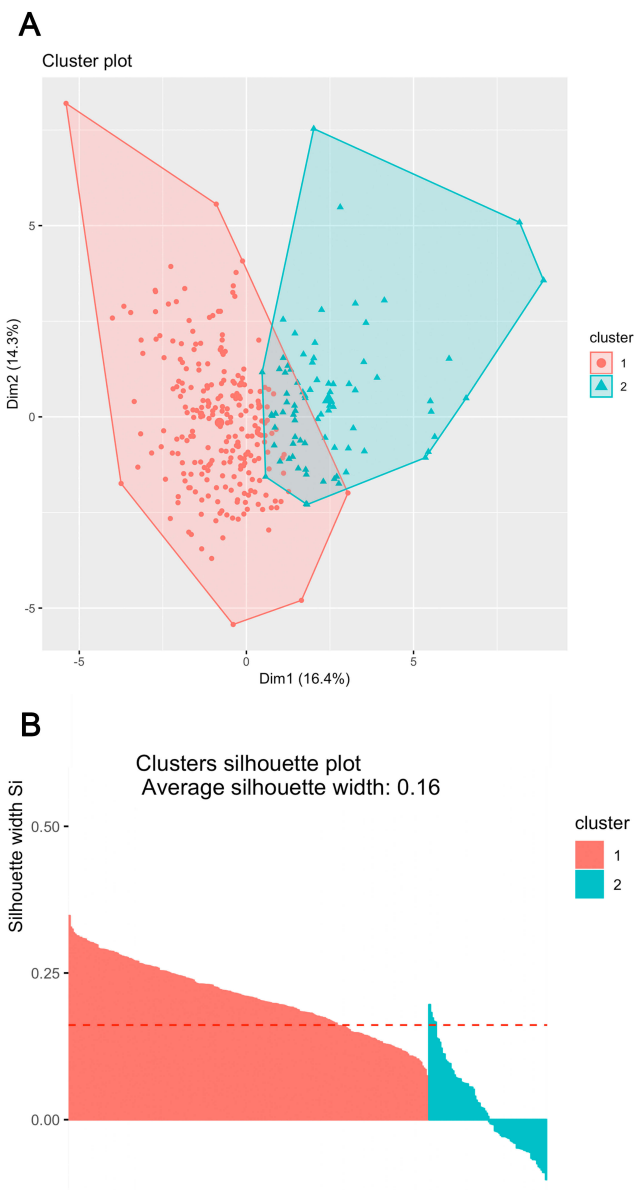


Figure 1 Results of *k*K-mean clustering. (**A**) Results from cluster analysis; (**B**) silhouette information from clustering.

cluster 1 and cluster 2 were classed as noninflammatory and inflammatory subtypes of ovarian cancer, respectively. Median follow-up was 52 months, at which 21 (16.3%) patients in the noninflammatory group had died compared to 14 (29.8%) in the inflammatory group (p=0.076), as shown in Table 2. Cox regression analysis indicated an HR of 2.15 (95% CI 1.09–4.23, p=0.024 by log-rank test), as shown in Figure 3A. Death or recurrence was observed in 38 (29.5%) patients in the noninflammatory group and 25 (53.2%) in the inflammatory group (HR 2.32, 95% CI 1.40–3.85; p<0.001 by log-rank test) as shown in Figure 3B.

Table 2 Comparison of Death Rate and Histopathological Characteristics Between Groups

	Cluster 1 (Noninflammatory)	Cluster 2 (Inflammatory)	*p*-value
Total	247	81	
Deaths (2014–2016)			0.076
Not observed	108 (83.7)	33 (70.2)	
Observed	21 (16.3)	14 (29.8)	
Deaths/recurrence (2014–2016)			0.006
Not observed	91 (70.5)	22 (46.8)	
Observed	38 (29.5)	25 (53.2)	
Grade			0.019
I	36 (20.1)	6 (8.5)	
II	14 (7.8)	2 (2.8)	
III	129 (72.1)	63 (88.7)	
Stage			<0.001
I	114 (46.2)	11 (13.6)	
II	33 (13.4)	9 (11.1)	
III	98 (39.7)	55 (67.9)	
IV	2 (0.8)	6 (7.4)	
Histological subtype			0.022
Serous	150 (60.7)	63 (77.8)	
Mucinous	32 (13)	2 (2.5)	
Endometrioid	21 (8.5)	4 (4.9)	
Clear cell	43 (17.4)	11 (13.6)	
Seromucinous	1 (0.4)	1 (1.2)	

Note: Data presented as n (%).

As one of the most important parameters of inflammation, CRP was selected to verify the association between inflammation and prognosis. CRP was dichotomized into two groups according to the median. The results in Table 4 indicate that CRP was an independent risk factor of overall survival (HR 3.79, 95% CI 1.54–9.33; p=0.001) and recurrence-free survival (HR 1.99; 95% CI 1.13–3.50; p=0.014). Subgroup analysis indicated that higher CRP was associated with poorer survival at both stage I–IIA (p=0.0094) and stage IIIB–IVB (p=0.026), as shown in Figure 4.

Discussion

Via *K*-mean clustering with preoperative laboratory results, we divided ovarian cancer patients into noninflammatory and inflammatory subtypes. The inflammatory subtype showed higher CRP, leukocyte counts, neutrophil percentage, fibrinogen, platelet counts, CA125, a higher proportion of patients in advanced stages, and lower levels of albumin. The inflammatory subtype was significantly associated with poor overall survival and recurrence-free survival.

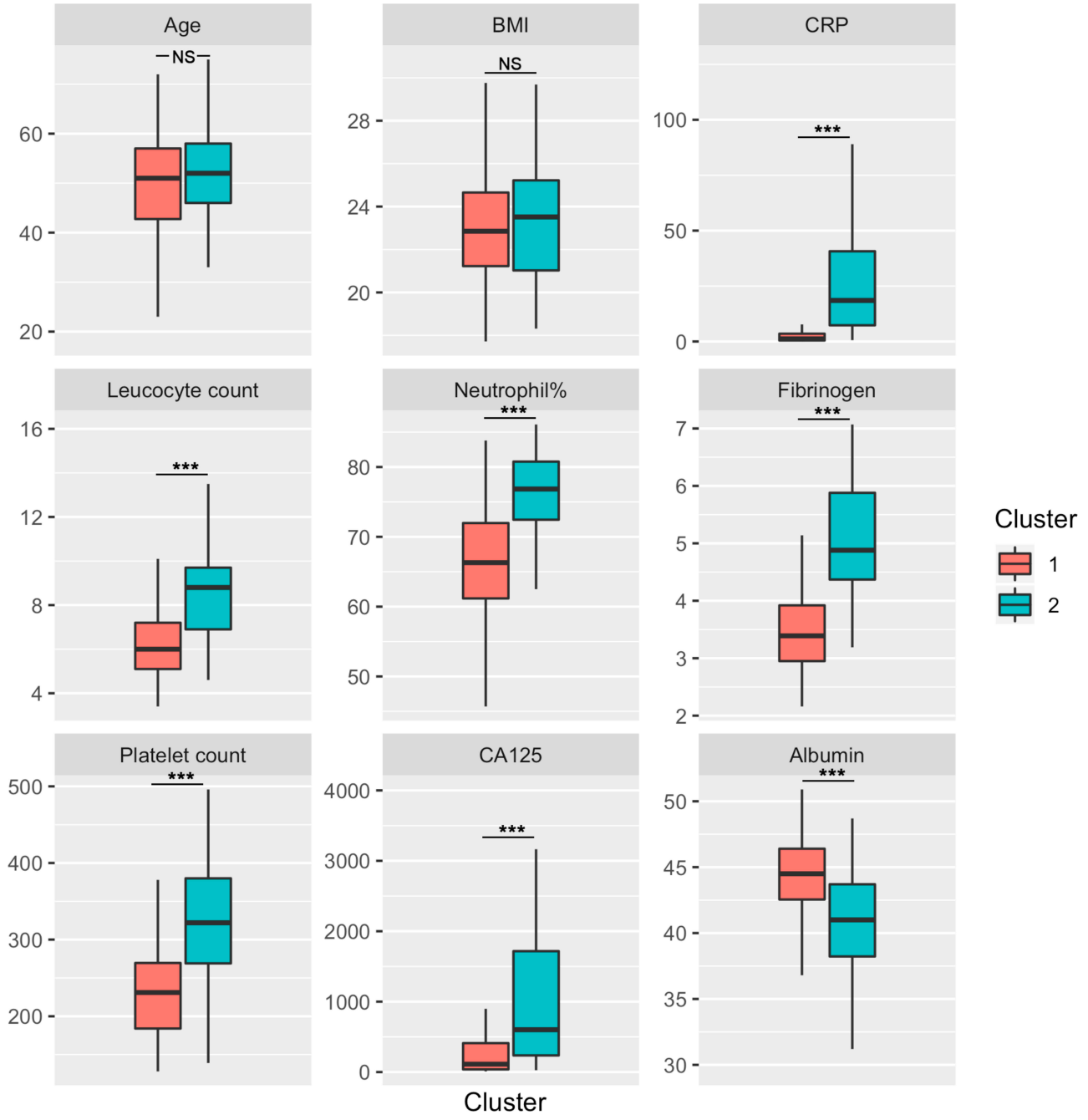


Figure 2 Box plot of inflammatory biomarkers between two clusters. CRP, leukocyte count, neutrophil percentage, fibrinogen, platelet count, and CA125 were significantly higher in cluster 2.
Note: ***$p<0.001$.
Abbreviation: NS, not significant.

Elevated fibrinogen and platelet counts were observed along with elevated inflammatory markers in the inflammatory subtype. Inflammation is well recognized as a regulator of coagulation and fibrinolytic activity, which are context-dependent.[12] In inflammatory conditions, hemostatic balance may be shifted toward prothrombotic and antifibrinolytic states, with an increase in circulating serum factors.[12] Meanwhile, the proinflammatory effect of fibrinogen has been reported, either by stimulating macrophages to release inflammatory cytokine or leading the cascade of tissue repair and inflammatory responses.[13,14] In addition to hemostatic mechanisms, platelet-derived molecules have been found to mediate inflammation.[15—17] This evidence justifies the classification model in the present study, which

Table 3 Associations Between Laboratory Findings and FIGO Stages

	Stage I	Stage II	Stage III	Stage IV	p-value
CRP*	1.1 (0.4,3.4)	1.5 (0.4,10.2)	3.7 (1.1,13.6)	32.6 (13.4,76.8)	<0.001
Leukocyte count*	6.4 (5.3,7.7)	6.2 (5,7.4)	6.7 (5.4,8.4)	6.7 (6.1,9.5)	0.204
Neutrophil percentage#	66.2 (10.4)	68.2 (8.7)	70.3 (8.2)	75.5 (5.1)	<0.001
Fibrinogen*	3.4 (2.9,3.9)	3.6 (3.2,4.4)	3.9 (3.2,4.8)	5 (4,6.5)	<0.001
Platelet count*	236 (193,280)	203 (170.5,268.2)	259 (205,319)	438 (321.2,455.8)	<0.001
Albumin*	44.9 (42.9,46.6)	43.7 (42.5,46.2)	43.3 (40.9,45.1)	37.4 (31.9,38.6)	<0.001
Lymphocyte percentage#	25.8 (9)	23.8 (7.6)	21.3 (7.1)	16.4 (4.3)	<0.001
CA125*	49 (21.4,111.2)	136.3 (49.9,399.3)	480.3 (186.2,1,179)	822.2 (428.6,1,668.5)	<0.001

Notes: *Data expressed as medians (IQR); #data expressed as means (SD).

emphasizes inflammation and interacting networks with various physiological processes.

The present study demonstrated that the ovarian cancer inflammatory subtype was linked to poor prognosis through cluster analysis. Similar results have been identified in previous studies. Neutrophil:lymphocyte ratio and platelet:lymphocyte ratio have been well investigated as inflammatory parameters closely related to ovarian cancer prognosis.[18—26] A meta-analysis verified the prognostic value of inflammatory markers in ovarian cancer patients.[27] With a novel method, *K*-mean cluster analysis, our study showed results consistent with previous research. Clustering is an unsupervised technique to classify a group of objects without prespecified labels into subgroups based on the similarity measure between objects.[28] In the present study, leukocyte count, neutrophil percentage, and platelet count were higher in the inflammatory subgroup, which was related to poorer prognosis. In contrast, lymphocyte percentage was lower. Under the circumstances, both neutrophil:lymphocyte and platelet:lymphocyte ratios in the inflammatory subgroup were higher, and thus expected to be related to worse outcomes.

In our study, the inflammatory subgroup presented a higher proportion of advanced ovarian cancer patients. Inflammation and advanced stages are likely to be closely related. However, no causal relationship can be inferred from the results. Inflammation is well recognized as a hallmark of cancer.[29,30] Cross-talk between inflammation and cancer is quite complicated. Chronic inflammation predisposes tumor formation, while tumors elicit inflammation by reshaping the tumor microenvironment.[31] On one hand, inflammation takes part in tumor progression and metastasis.[31] Several signaling

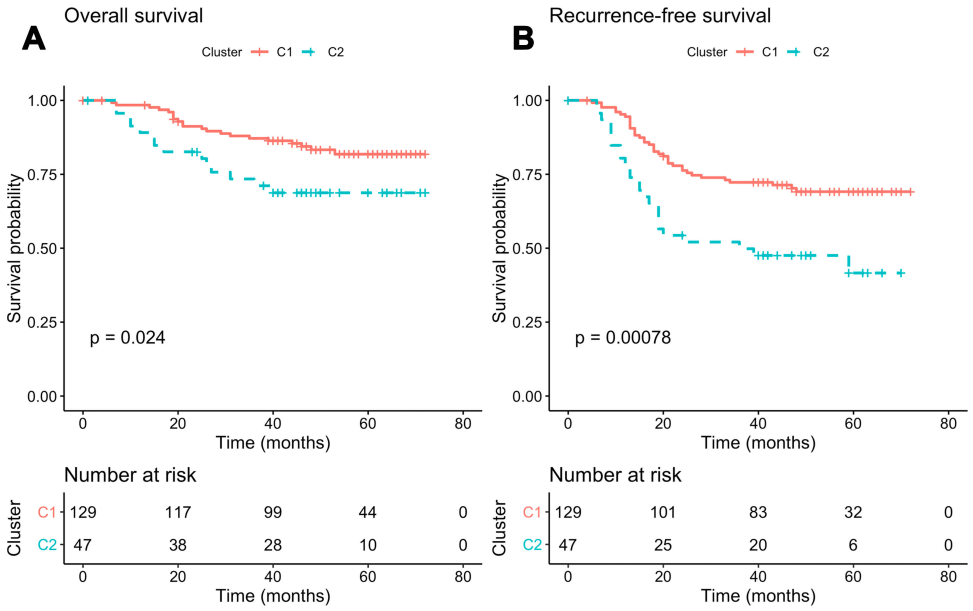


Figure 3 Kaplan–Meier curves with log-rank tests. (**A**) Kaplan–Meier curves showed cluster 2 (inflammatory group) showed poorer overall survival; (**B**) cluster 2 (inflammatory group) was associated with poorer recurrence-free survival.

Table 4 Univariate and Multivariate Analyses for overall Survival and Recurrence-free Survival

	Univariate Analysis			Multivariate Analysis		
	Crude HR	**95% CI**	**p-value**	**Adjusted HR***	**95% CI**	**p-value**
Overall survival						
CRP (high vs low)	5.84	2.42–14.09	<0.001	3.79	1.54–9.33	0.001
Stage	3.27	2.04–5.27	<0.001	3.02	1.80–5.07	<0.001
Type II	2.18	0.99–4.79	0.053	0.40	0.16–1.02	0.072
Age	1.05	1.02–1.09	0.001	1.04	1.00–1.08	0.037
Recurrence-free survival						
CRP (high vs low)	3.26	1.89–5.64	<0.001	1.99	1.13–3.50	0.014
Stage	3.44	2.40–4.93	<0.001	2.99	1.99–4.48	<0.001
Type II	3.49	1.82–6.70	<0.001	0.84	0.39–1.79	0.652
Age	1.04	1.02–1.07	<0.001	1.02	0.99–1.04	0.209

Note: *HRs adjusted by CRP, stage, type, and age.

pathways involved in the inflammatory response play important roles in ovarian cancer progression and metastasis. As a widely studied proinflammation cytokine, IL6 has been found to enhance expression of MMP9, which promoted tumor expansion and tumor-cell invasion in SKOV3 cells.[32] IL6 produced by M2 macrophages also stimulates the proliferation of SKOV3 cells via STAT3 activation.[33] In addition, it has been reported that IL6 *trans*-signaling on endothelial cells contributed to ovarian cancer progression by activating ERK.[34] These findings suggest the close relationship between inflammation and progression of ovarian cancer. On the other hand, tumors reshape the tumor microenvironment.[31] One pathway is that tumors promote inflammation in a hypoxia-dependent manner,[35,36] especially in advanced cancers.[37] Compared with the normal nondiseased controls, ROS concentration has been reported at 96% higher in malignant ovarian tissue.[38] Although more studies are expected to elucidate the complexity, promising cancer treatment through inflammation manipulation is on the way.[39,40] The findings of the present study validated the impact of preoperative inflammation on ovarian cancer survival, which would provide more possibilities in ovarian cancer management.

There were major limitations of our study. Only some of the included patients were followed, and the follow-up might not have been long enough. This might have resulted in underestimated prognosis differences; however, according to the significantly different prognoses in the

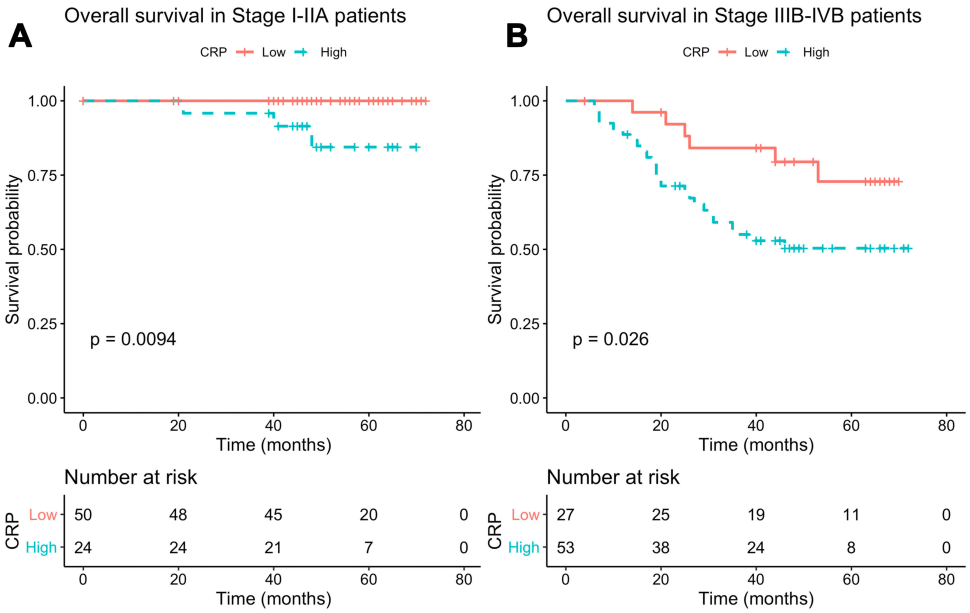


Figure 4 Subgroup survival analysis. Kaplan–Meier curves showed higher CRP was associated with poorer overall survival in (**A**) stage I–IIA and (**B**) stage IIIB–IVB.

results, our follow-up duration might be sufficient to demonstrate prognosis differences. With further analysis of patient data and longer follow-up in future, it will be intriguing to explore more potential effects of our novel classification model in the clinical management of ovarian cancer. Another potential limitation is subjectivity in selection of variables to include and determination of the optimal number of clusters. Although the clustering was validated with survival analysis, the possibility still exists that other variables and other number of clusters might lead to a better classification paradigm.

Conclusion

Our cluster analysis identified two subtypes of ovarian cancer: noninflammatory and inflammatory. The inflammatory group featured higher CRP, leukocyte counts, neutrophil percentage, fibrinogen, platelet counts, CA125, and proportion of patients in advanced stages, with lower albumin levels and lymphocyte percentage. The inflammatory group was associated with poorer prognosis. The results of the present study should lead to further investigation into the cross-talk between inflammation and cancer.

Abbreviations

CA125, cancer antigen 125; CRP, C-reactive protein; BMI, body-mass index; GGT, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; BUN, blood urea nitrogen; UA, uric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; HR hazard ratio; CI, confidence interval; IQR, interquartile range; FIGO, International Federation of Gynecology and Obstetrics.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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