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Bevacizumab as a mitigating factor for the impact of high systemic immune-inflammation index on chemorefractory in advanced epithelial ovarian cancer

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Abstract

Background Predicting chemorefractory disease in advanced epithelial ovarian cancer (EOC) remains challenging. This study aimed to identify clinicopathological factors and hemogram data as predictive markers for chemorefractory EOC and to explore potential therapeutic approaches that may mitigate these unfavorable conditions.

Methods We conducted a retrospective analysis of patients with advanced EOC treated with chemotherapy. Hemogram data and clinicopathological variables were collected. We employed logistic regression to assess factors associated with chemorefractory EOC and used the Kaplan–Meier method for survival analysis.

Results Among the 191 patients analyzed, suboptimal surgery, lymphocyte count < 1440/mm3, systemic immune-inflammation index (SII) ≥ 2350, and lack of bevacizumab therapy were independently associated with chemorefractory EOC (OR 19.30, 95% CI 7.01—53.12; OR 9.07, 95% CI 2.76—29.82; OR 12.45, 95% CI 3.87—40.07; OR 6.61, 95% CI 2.01—21.78, respectively). Elevated SII was also identified as a risk factor for poor progression-free (PFS) and overall survival (OS). Specifically, patients with high SII who did not receive bevacizumab had a significantly higher probability of chemorefractory EOC and poorer survival outcomes compared to those who received bevacizumab.

Conclusions Our findings suggest that hemogram parameters and clinicopathological factors such as suboptimal surgery, lymphocyte count, SII, and bevacizumab therapy status are predictive markers for chemorefractory disease in advanced EOC. Elevated SII emerged as a predictor for poorer PFS and OS outcomes, particularly in the absence of bevacizumab therapy.

Keywords Epithelial ovarian cancer, Systemic immune-inflammation index, Chemorefractory disease, Bevacizumab

Background

Ovarian cancer ranks as the third most prevalent gynecological malignancy globally. While it may not have the highest mortality rate, it is considered the most lethally. In 2022, approximately 320,000 new cases were reported worldwide, with nearly 210,000 deaths [1]. Ovarian cancer encompasses various histopathological subtypes, with epithelial ovarian cancer (EOC) being the most common,

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representing approximately 90% of all cases [2]. Diagnosis often occurs at an advanced stage, leading to a poor prognosis, with 5-year survival rates for stage III and IV EOC at 41% and 20%, respectively [3]. The primary treatment for EOC involves primary debulking surgery (PDS) followed by platinum-based chemotherapy. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is an alternative for selected patients, with adjuvant chemotherapy remaining crucial. The standard first-line chemotherapy for advanced EOC typically combines platinum (cisplatin or carboplatin) and paclitaxel, achieving complete clinical remission in around 80% of patients [4]. However, treatment poses challenges as up to 25% of patients are chemorefractory, and among those who initially respond well, 70% eventually experience disease relapse [5]. Therefore, identifying prognostic factors to evaluate chemotherapy response is vital for enhancing treatment strategies.

In cancer development and progression, inflammation has been identified as a significant factor [6]. Previous research has shown that certain inflammatory markers, including platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), can serve as valuable prognostic indicators in ovarian cancer [7–9]. Elevated levels of NLR and PLR have been linked to a worse prognosis. More recently, attention has been directed towards the systemic immune-inflammation index (SII), a novel marker derived from the calculation of neutrophils multiplied by platelets and then divided by lymphocytes, and its influence on the prognosis of ovarian cancer [10–12]. Higher SII values have been associated with a poorer prognosis in ovarian cancer patients. Nevertheless, there is a gap in the existing literature regarding the underlying reasons for the correlation between inflammatory indexes and the poor prognosis of EOC.

Prior research has indicated that chemorefractory status plays a crucial role in determining the prognosis of advanced ovarian cancer. This study aimed to evaluate the significance of different inflammatory markers, such as PLR, NLR, and SII, concerning chemorefractory status in advanced EOC. Furthermore, the study aims to explore the utility of these inflammatory markers as predictors of poor prognosis for EOC within our particular study population. Finally, our investigation aims to identify potential treatment strategies or clinical variables that could alleviate these unfavorable conditions.

Methods

In this study, we conducted a retrospective analysis of the medical records of ovarian cancer patients treated at Kaohsiung Chang Gung Memorial Hospital over a period of seven years, from January 2015 to December 2021. Patients with non-epithelial ovarian cancer, early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] I-II) coexisting malignancies, or those lacking regular follow-up were excluded from the study. Additionally, patients who did not receive surgical treatment or adjuvant chemotherapy at our hospital were also excluded.

The standard surgical procedure for these patients included total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, omentectomy, and debulking of any metastatic tumors. Following PDS, patients received platinum-based chemotherapy every three weeks for at least 6 cycles if presence of response. Patients with clinically unresectable advanced disease underwent 3–4 cycles of NACT followed by IDS, and then received an additional 4 to 6 cycles of chemotherapy. Treatment protocols adhered to the institute's guidelines, and the use of bevacizumab was based on the preference of attending physicians.

About the Ethics approval and consent to participate, the study was approved by the Institutional Review Board (IRB number: 202301253B0) of Chang Gung Memorial Hospital, and according to the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective nature of the analysis and individual patients was not affected. This research was funded by grants CORPG8M0391, CORPG8N0371, CMRPG8K1412, and CMRPG8P0261 from Kaohsiung Chang Gung Memorial Hospital.

Data on patient demographics, FIGO stage, histologic subtype, residual tumor burden, chemotherapy response, bevacizumab usage, and laboratory parameters including complete blood count (CBC) and cancer antigen 125 (CA-125) levels were collected. Serum CA-125 levels were measured using the Architect CA-125 II assay, while CBC and differential counts were obtained using automated hematology analyzers, the Sysmex 5 (XN-3000 (Sysmex Corporation, Kobe, Japan). Laboratory data were collected within one week prior to the diagnosis or treatment of ovarian cancer. Additionally, the NLR (ratio between the neutrophil and lymphocyte counts), PLR (ratio between the platele and lymphocyte counts), and SII (neutrophils × platelets/lymphocytes) were calculated.

Chemorefractory disease was defined as progression during primary chemotherapy or within one month of completing primary adjuvant chemotherapy [13], while objective response was defined according to the World Health Organization and Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and Gynecologic Cancer InterGroup (GCIG) criteria [14, 15]. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up, and progression-free survival (PFS) was

defined as the time from initial treatment to disease recurrence or progression.

Statistical analyses were performed to determine optimal cutoff values for predicting chemorefractory disease using receiver operating characteristic (ROC) curve analysis. Categorical variables were compared using the $\chi 2$ test, while continuous data were analyzed using the two-sample t-test or Mann–Whitney U test based on data distribution. A bivariate Pearson Correlation analysis was performed to evaluate the correlation of each variable. Logistic regression analysis was utilized to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to assess associations between clinical parameters and chemorefractory ovarian cancer. We also examined the independent risk factors for chemorefractory EOC and created a logistic regression predictive model. This model was developed through stepwise backward elimination, incorporating all factors that were identified as significant ($p < 0.05$). In this method, we initially included all variables found to be significant in the univariate analysis in the full model. Kaplan–Meier curves were employed to illustrate OS and PFS, with the log-rank test p-values utilized to evaluate statistical significance. A multivariate Cox proportional hazards model was employed to assess the clinical parameters for their significance in prognosis.

Results

The flowchart depicted in Fig. 1 delineates the enrollment procedure and patient figures at Kaohsiung Chang Gung Memorial Hospital spanning the years 2015 to 2021. Initially, a total of 601 patients diagnosed with ovarian cancers were enrolled in the investigation. Patients with non-epithelial ovarian cancers, double cancers, or those lacking consistent follow-up were excluded from the analysis. Specifically, only patients with FIGO stage III and IV diseases were considered for inclusion, resulting in a final cohort of 191 patients for further analysis.

The median follow-up duration was 40.5 months, ranging from 7.6 to 149.7 months. Patients with EOC were stratified based on their primary chemotherapy responses into non-chemorefractory group and a chemorefractory group. A comparison of baseline characteristics among these patient groups is detailed in Table 1. The mean age of the patients was 56.1 years. In our cohort, there was a higher percentage of patients at stage III (66.0%) compared to stage IV (44.0%) The majority of patients (56.0%) presented with serous-type tumors. Optimal debulking surgery (residual tumors < 1 cm) was conducted on 70.7% of patients, all of whom received platinum and paclitaxel chemotherapy as their primary treatment. Pretreatment or diagnosis blood tests were administered. A total of 80 patients underwent PDS, representing 41.9% of the overall patient cohort. Within this subset, 67 patients achieved optimal debulking, whereas 13 patients

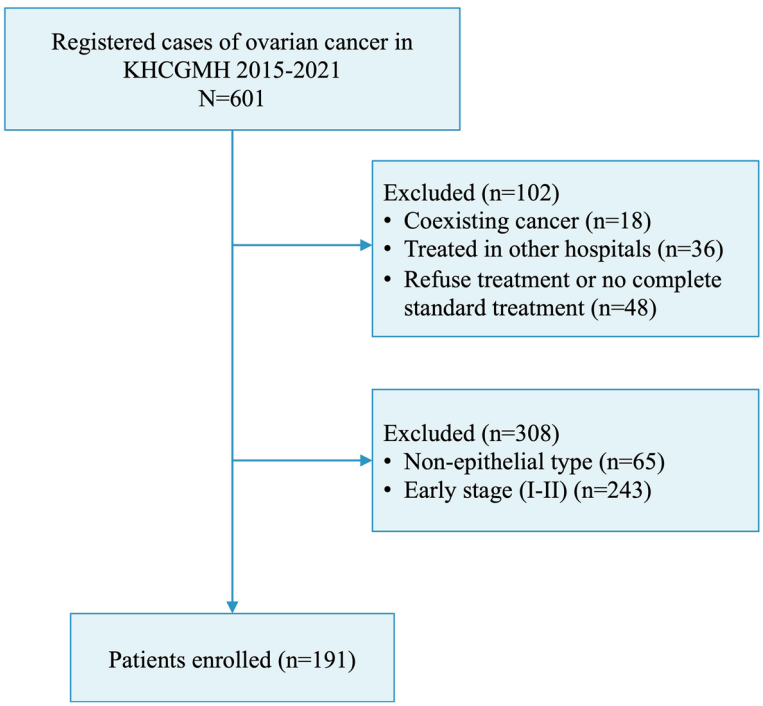

Fig. 1 Schematic representation illustrating the process of participant screening and enrollment within our cohort

Table 1 Clinicopathological characteristics of patients

	Total (191)	Non-Chemorefractory (148)	Chemorefractory (43)	*p* value
Variable				
Age (SD), y/o	56.1 (11.7)	56.5 (10.9)	55.4 (14.1)	< 0.001
Stage (%)				0.002
Stage 3	126 (66.0)	106 (71.6)	20 (46.5)	
Stage 4	65 (34)	42 (28.4)	23 (53.5)	
Histology (%)				0.005
Serous	107 (56.0)	91 (61.5)	16 (37.2)	
Non-serous	84 (44.0)	57 (38.5)	27 (62.8)	
Tumor residue (%)				< 0.001
Optimal	135 (70.7)	124 (83.8)	11 (25.6)	
Sub-optimal	56 (29.3)	24 (16.2)	32 (74.4)	
PDS (%)	80 (41.9)	71 (88.8)	9 (11.2)	0.002
CA-125 (SD), U/mL	1937.1 (2472.9)	1767.7 (2343.3)	2519.9 (2830.8)	0.117
WBC (SD), /μL	8641.2 (5280.1)	8266.6 (5738.8)	9932.2 (2941.9)	0.012
Hgb (SD), g/μL	11.4 (1.7)	11.6 (1.6)	10.9 (1.8)	0.021
ANC (SD), /μL	6350.5 (2846.2)	6001.3 (2813.7)	7552.3 (2651.4)	0.001
lymphocyte (SD), /μL	1366.2 (472.8)	1338.5 (422.4)	1461.3 (609.6)	0.221
Platelet (SD), 1000/μL	388.9 (127.2)	370.3 (123.6)	452.8 (119.7)	< 0.001
NLR, (SD)	5.4 (4.0)	5.2 (4.2)	6.1 (3.2)	0.021
PLR, (SD)	326.7 (176.3)	312.8 (165.2)	374.6 (205.4)	0.043
SII (SD)	2147.7 (1706.5)	1938.0 (1636.7)	2869.6 (1763.5)	0.003
Bevacizumab				0.005
Yes	65 (34.0)	58 (39.2)	7 (16.3)	
No	126 (66.0)	90 (60.8)	36 (83.7)	

Abbreviation: ANC absolute neutrophil count, *CA-125* cancer antigen 125, *CI* confidence interval, *CR* complete response, *Hgb* hemoglobin, *NLR* Neutrophil-to-Lymphocyte Ratio, *PDS* primary debulking surgery, *PLR* Platelet-to-Lymphocyte Ratio, *PR* partial response, *SD* standard deviation, *SII* Systemic Immune-Inflammation Index (neutrophil x platelet/lymphocyte counts.), *WBC* white blood cell

experienced suboptimal debulking. It is noteworthy that among the 67 patients who attained optimal debulking, only 5 (7.5%) subsequently developed chemorefractory disease. In contrast, 13 patients who underwent PDS with suboptimal debulking exhibited significantly higher rates of chemorefractory disease development, with 4 out of 13 patients (30.8%) affected. Additionally, 111 patients received NACT, of whom 14 patients experienced suboptimal debulking, 68 patients achieved optimal debulking, and 29 patients did not undergo interval debulking due to disease progression during NACT.

Table 1 reveals that 43 patients (22.5%) exhibited refractoriness to primary chemotherapy. These chemorefractory patients were notably older and displayed elevated levels of white blood cell (WBC) count, absolute neutrophil count (ANC), platelet count, NLR, PLR, and SII (Table 1). Conversely, they demonstrated lower levels of Hgb, as well as a lower percentage of stage III, serous histology, optimal debulking surgery, and bevacizumab therapy.

In order to establish the most suitable threshold levels for WBC, Hgb, ANC count, lymphocyte count, platelet count, NLR, PLR, and SII, ROC curves were constructed with refractory response to therapy as the dependent variable. The optimal cutoff points for WBC, Hgb, ANC, lymphocyte count, platelet count, NLR, PLR, and SII were determined as 7500 /μL, 10 g/dL, 5800 /μL, 1440 /μL, $400*10^3$/μL, 3.7, 300, and 2350, respectively. These identified cutoff values were subsequently applied in binary logistic regression analysis.

In a univariate regression analysis examining chemorefractory, several of variables were found to be significant factors impacting chemorefractory, with the exceptions of age, Hgb level, and ANC. Subsequent multivariate analysis identified suboptimal surgery, lymphocyte count < 1440, SII ≥ 2350, and lack of bevacizumab therapy as independent factors associated with refractory to chemotherapy. The corresponding ORs and 95% CIs were calculated as 19.30 (7.01—53.12), 9.07 (2.76—29.82), 12.45 (3.87—40.07), and 6.61 (2.01—21.78), respectively (see Table 2 for details). We further

examined the relationship between the SII and various risk factors such as stage, histology, and residual disease. The Pearson correlation coefficient r values for SII concerning stage, histology, and residual disease were 0.137, 0.076, and 0.241, respectively. These values suggest a positive relationship, but the strength of the correlation is either weak or negligible.

The logistic regression analysis conducted in this study identified various risk factors associated with chemorefractory, as presented in Table 2. Among these risk factors were markers of inflammation, including levels of lymphocytes, platelets, SII, NLR, and PLR. The Kaplan–Meier survival analysis was performed to assess PFS and OS based on these prognostic factors, as illustrated in Fig. 2. While lymphocyte count was identified as a risk factor for chemorefractory, it did not show a significant association with poor PFS or OS (Fig. 2A and B). Platelet count, SII and suboptimal surgery were not only identified as risk factors for chemorefractory but also for PFS and OS (Fig. 2C, D, E, F, K and L). Although no relationship was observed between NLR and PLR and poor PFS, these factors were found to be significant factors of OS (Fig. 2G, H, I, and J). Cox regression analysis with stepwise backward elimination was utilized to determine the independent predictors of inflammation markers for PFS or OS. The study revealed that platelet count and SII were identified as independent factors affecting both PFS and OS (supplementary, Table S1).

A heightened SII index was identified as a risk factor associated with chemorefractory cases, PFS, and OS. Further investigation into this factor revealed that patients with a lower SII index displayed a similar incidence of chemorefractory cases, regardless of whether they received bevacizumab therapy or not (refer to Fig. 3A, # $p=0.087$). The occurrence of chemorefractory cases in patients treated with bevacizumab was comparable between those with low and high SII indices (refer to Fig. 3A, ## $p=0.072$). Patients who did not undergo bevacizumab treatment exhibited a significantly higher risk of developing chemorefractory cases in the high SII group compared to the low SII group (refer to Fig. 3A, ** $p<0.001$). Among patients in the high SII group, those who did not receive bevacizumab therapy had a notably increased likelihood of experiencing chemorefractory cases compared to those who received bevacizumab (refer to Fig. 3A, * $p=0.003$).

For patients with low SII levels, regardless of bevacizumab treatment, their rates of PFS and OS survival were similar. Conversely, in patients with high SII levels, those who underwent bevacizumab treatment demonstrated a significant enhancement in their PFS and OS survival rates (refer to Fig. 3B, $p=0.002$; Fig. 3C, $p<0.001$). The Kaplan–Meier survival curves for PFS and OS indicated that survival outcomes were poorest in patients within the high SII group who did not receive bevacizumab.

The administration of bevacizumab plays a crucial role in the prognosis and chemorefractoriness of EOC. In this study, the decision to use bevacizumab is influenced by the preferences of the attending physicians. To investigate possible biases in treatment selection, we compared the

Table 2 univariate and multivariate analysis of risk factors of ECO refractory to primary chemotherapy

	Univariate		Multivariate	
Parameter	**ORs ± 95% C.I**	***p* value**	**ORs ± 95% C.I**	***p* value**
Age ≥ 53	0.85 (0.43—1.68)	0.636		
Stage 4	2.90 (1.45—5.83)	0.003		
Non-serious type	2.69 (1.34—5.43)	0.006		
Suboptimal	15.03 (6.67—33.87)	< 0.001	19.30 (7.01 – 53.12)	< 0.001
PDS	0.28 (0.13 – 0.64)	0.002		
WBC ≥ 7500/μL	3.07 (1.44—6.54)	0.004		
Hb < 10 g/μL	1.13 (0.56—2.67)	0.723		
ANC ≥ 5800/μL	1.88 (0.81—4.39)	0.141		
Lymphocyte < 1440/μL	2.21 (1.11—4.42)	0.024	9.07 (2.76 – 29.82)	< 0.001
Platelet ≥ 400*10^3/μL	3.79 (1.82—7.87)	< 0.001		
NLR ≥ 3.7	3.38 (1.67—6.87)	0.006		
PLR ≥ 300	3.11 (1.50—6.45)	0.002		
SII ≥ 2350	4.88 (2.38—10.04)	< 0.001	12.45 (3.87 – 40.07)	< 0.001
No bevacizumab	3.31 (1.38—7.95)	0.007	6.61 (2.01 – 21.78)	0.002

Abbreviation: ANC Absolute neutrophil count, *CA-125* cancer antigen 125, *Hb* hemoglobin, *HR* hazard ratio, *NLR* Neutrophil-to-Lymphocyte Ratio, *PDS* primary debulking surgery, *PLR* Platelet-to-Lymphocyte Ratio, *PR* partial response, *SD* standard deviation, *SII* Systemic Immune-Inflammation Index (neutrophil x platelet/lymphocyte counts.), *WBC* white blood cell

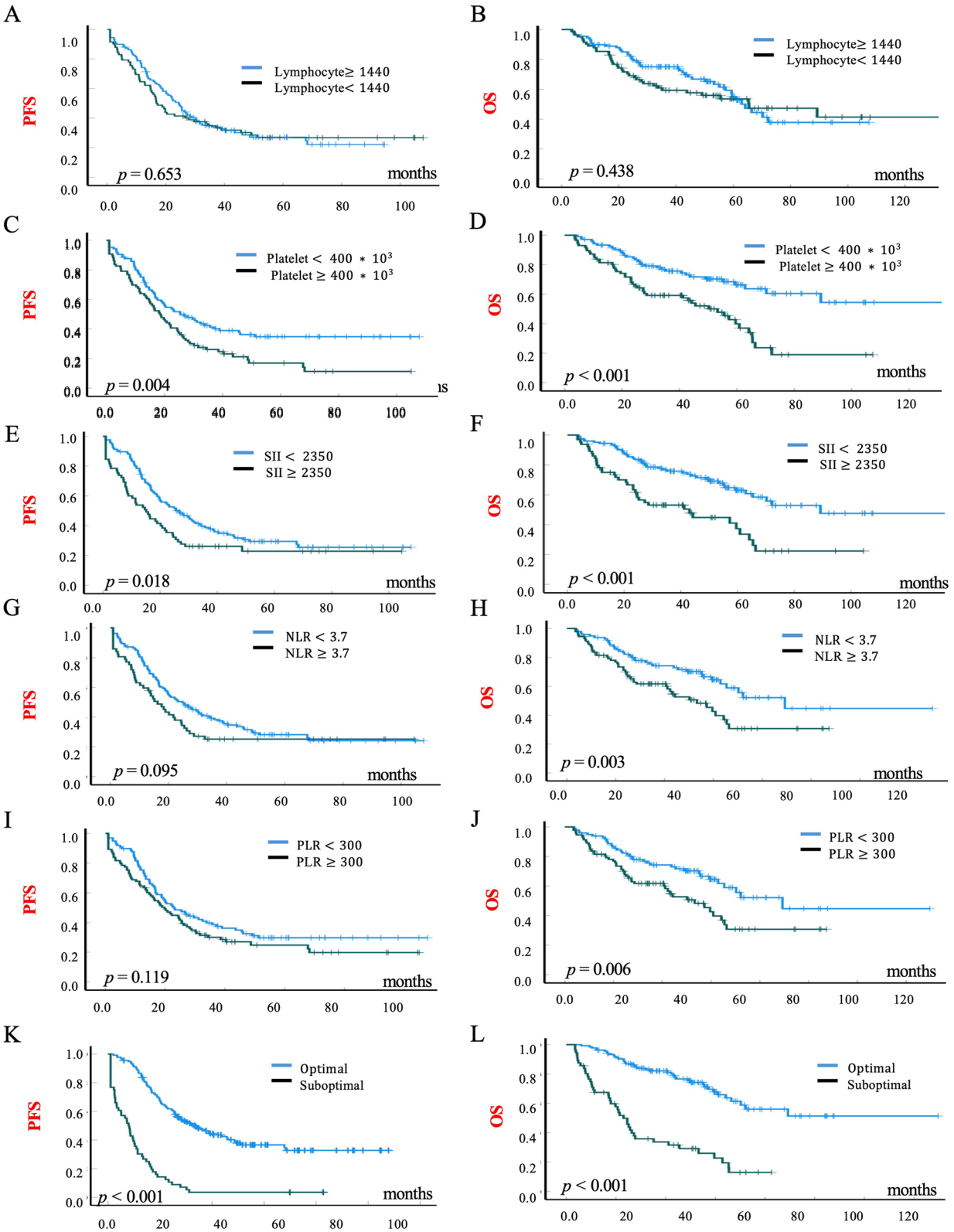

Fig. 2 Kaplan–Meier curves were utilized to analyze progression-free survival and overall survival rates among patients, with consideration given to pretreatment levels of lymphocytes (**A**, **B**), platelets (**C**, **D**), systemic immune-inflammation index (SII) (**E**, **F**), neutrophil-to-lymphocyte ratio (NLR) (**G**, **H**), platelet-to-lymphocyte ratio (PLR) (**I**, **J**) and optimal/suboptimal debulking surgery (**K**, **L**). If the *p*-value is below 0.05, it is considered statistically significant

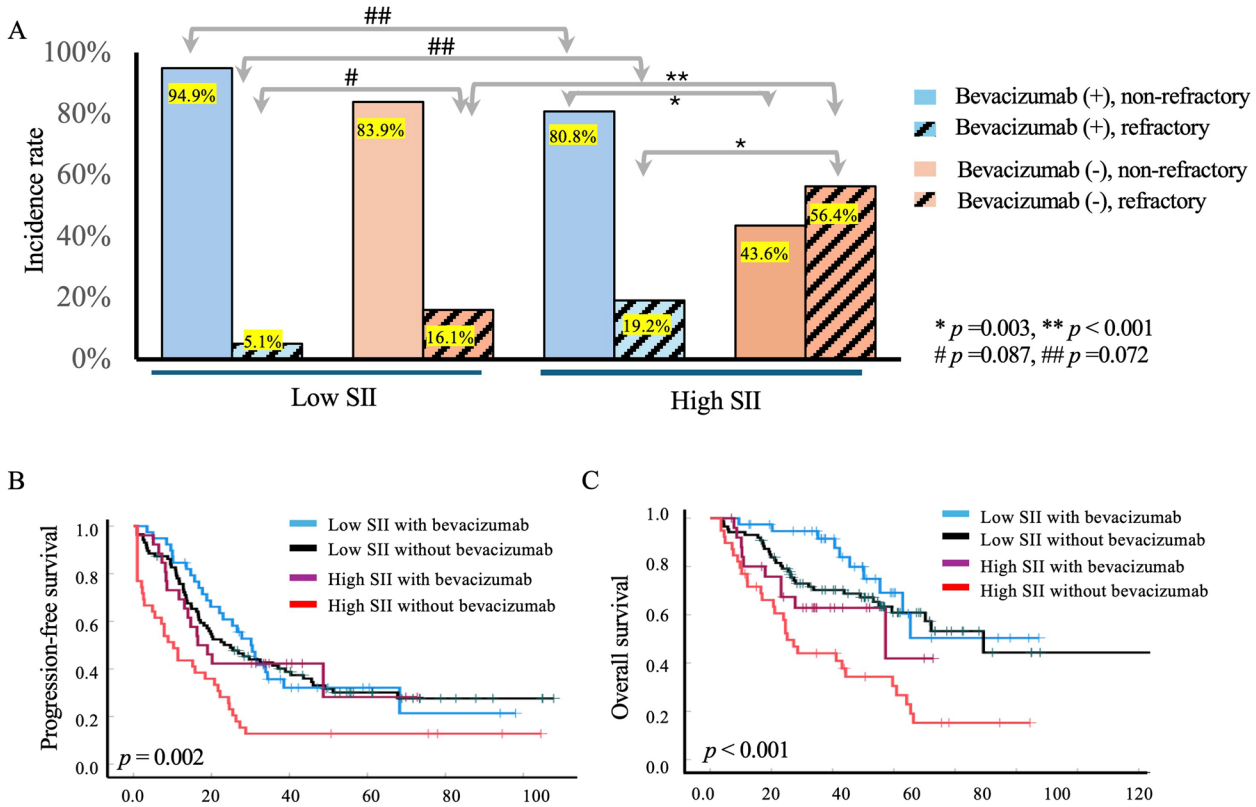

Fig. 3 The patients were categorized into two groups based on their SII levels: a low SII group and a high SII group. The incidence of chemorefractory cases was then observed in patients receiving bevacizumab treatment compared to those not receiving it (**A**). Kaplan–Meier curves was utilized to analyze the variations in progression-free survival and overall survival rates across the distinct groups (**B**, **C**). If the *p*-value is below 0.05, it is considered statistically significant

clinicopathologic characteristics of patients who received bevacizumab with those who did not. Our results show that a higher percentage of serous type ovarian cancer is present in the bevacizumab group, while no other significant differences in clinicopathologic features were found between the two groups. This information is provided in Supplementary Table 2.

Discussion

Our study revealed that suboptimal debulking surgery, decreased lymphocyte count, elevated SII, and absence of bevacizumab administration were identified as independent predictive factors for chemorefractory disease in advanced EOC. Furthermore, suboptimal debulking surgery, elevated SII and platelet count were correlated with inferior PFS and OS rates. Patients who received bevacizumab treatment showed a reduction in the risk linked to high SII in relation to chemorefractory, leading to improved PFS and OS. However, the use of bevacizumab did not show significant benefits in patients with a low SII. Consequently, from a clinical perspective, SII may serve as a predictive marker to identify the subset of patients who would derive advantages from bevacizumab therapy.

Chemorefractory ovarian cancer presents a notable obstacle to therapeutic interventions. Our findings indicate that 22.5% of patients with advanced EOC in our cohort were classified as chemorefractory disease, a proportion consistent with previous studies reporting rates of up to 25% in cases of high-grade serous ovarian carcinoma [5]. Previous studies showed residual tumor, elder age, cell types, NACT and inflammation related indexes were biomarkers related chemotherapy responses of EOC [16]. In our study, we found that suboptimal debulking surgery is an independent factor for chemorefractory disease. Patients undergoing suboptimal debulking surgery are more likely to develop chemoresistance. This may be due to the persistence of residual bulky tumor cells, which could increase the probability of housing resistant clones by enriching cancer stem cells (CSCs) when subjected to subsequent platinum-based treatment [17]. Bryant et al. assessed the prognostic significance of residual tumor following debulking surgery on survival outcomes in patients

with advanced EOC [18]. Their analysis enclosed 46 studies, which included a total of 22,376 women who underwent primary debulking surgery and 3,697 who underwent interval debulking surgery. In the primary debulking surgery group, they identified that the extent of residual tumor post-surgery serves as a prognostic indicator for both overall survival and progression-free survival in women diagnosed with advanced ovarian cancer. Although a similar phenomenon was observed in the interval debulking group, the robustness of the evidence was found to be less compelling compared to that of the primary debulking group. In our investigation, we did not differentiate between patients based on whether they underwent primary or interval debulking surgery. Overall, our findings indicated that patients with residual tumor following debulking surgery faced nearly a fivefold increased risk of recurrence (OR 4.82, 95% CI 3.56 to 6.92) (Fig. 2K) and mortality (OR 4.52, 95% CI 2.91 to 7.02) (Fig. 2L). Thus, the presence of residual tumor is a critical determinant of survival outcomes and chemorefractoriness.

Many factors contributing to the chemoresistance of EOC have been previously documented. These factors include changes in secretome profiles of chemoresistant cells that induce resistance in neighboring cells [5], disruptions in cytokine and type I interferon signaling pathways [19], the presence of ovarian CSCs with heightened tumorigenicity and resistance to chemotherapy [17], as well as the inflammatory status and mediators [20]. Inflammation is a complex and dynamic system that plays a crucial role in cancer progression, angiogenesis, and metastasis, involving a variety of cellular and molecular components such as immune cells (neutrophils, lymphocytes, macrophages, T cells, and B cells), endothelial cells, extracellular matrix, and numerous cytokines [21]. Various indices are available for assessing inflammation status such as WBC count, ANC, lymphocyte count, platelet count, NLR, PLR, and SII. In the present study, we demonstrated that lymphocyte count and SII serve as significant independent inflammatory markers associated with chemorefractory status. However, only high SII translated to poorer PFS and OS compared to low SII. Previous studies have reported that high SII levels are linked to unfavorable clinical characteristics, such as advanced stage and lymph node metastasis, and are independently correlated with reduced 5-year survival rates [12, 22]. Additionally, high SII can predict NACT inefficacy in stage III EOC. Notably, the optimal cutoff values of SII are conflicting, ranging from 612 to 1000 across different study cohorts [23]. Our current study found that the best cutoff value for SII was 2350 for predicting chemorefractory status. This discrepancy might be due to differences in hematology analyzers, study cohorts, and target definitions.

Platelet count was associated with both PFS and OS, but it was not an independent predictor of chemorefractory. Pretreatment thrombocytosis has been reported as a factor predicting both chemorefractory and poorer prognosis [24, 25]. In our research, platelet count emerged as a notable indicator of chemorefractory status in the initial univariate analysis; however, its significance diminished in the subsequent multivariate analysis. This attenuation of significance could be attributed to multicollinearity, a condition wherein multiple independent variables within the model exhibit strong correlations, thereby complicating the differentiation of individual variable effects. The existence of multicollinearity has the potential to elevate the standard errors of coefficients, consequently leading to the statistical insignificance of platelet count. The observed correlations among platelet count, SII, and PLR are inevitable, as both SII and PLR are derived from platelet measurements.

Another inflammatory marker, lymphocyte count, has not been previously reported to be associated with chemosensitivity of EOC. Nevertheless, peripheral lymphopenia has been recognized as an unfavorable prognostic indicator in ovarian cancer [26], possibly attributed to the capacity of tumor-infiltrating lymphocytes to efficiently combat and eliminate tumor cells [27]. Our study is the first to show that a low lymphocyte count is associated with chemorefractory disease. The major concern is the unresolved question of how the severity of lymphopenia affects the ability of tumor-infiltrating lymphocytes to attack tumor cells. A global consensus suggests that a lymphocyte count of at least less than $1000/mm^3$, a cutoff value much lower than ours, could impact prognosis in several malignancies [28].

The relationship between other inflammatory markers, such as the NLR and PLR, and chemotherapy response and disease prognosis remains inconclusive. For instance, Miao et al. reported that an NLR > 3.02 and a PLR > 207 could predict platinum resistance [29], with elevated levels of NLR and PLR observed in the platinum-resistant group in their study. Conversely, Winarno et al. found that increased NLR and PLR were associated with a better response to platinum-based chemotherapy [30]. These conflicting results may stem from differences in methodology, such as the utilization of pre-treatment (Miao et al. and our study) versus post-operation (Winarno et al.) CBC data.

Interestingly, we discovered that bevacizumab serves as a protective factor for patients who exhibit refractory to chemotherapy, leading to an extension in PFS and OS durations. Farolfi et al. conducted a study which indicated that bevacizumab could enhance survival rates in

patients with EOC who have a NLR but not a high SII (≥730) [31]. Our unique finding is that bevacizumab has the potential to alleviate the negative effects of elevated SII in chemorefractory cases. Previous studies have demonstrated that bevacizumab, an anti-VEGF antibody, has the ability to modulate the tumor microenvironment to combat tumors [32]. Consequently, this may elucidate why patients with high SII levels who receive bevacizumab exhibit improved survival outcomes and chemotherapy sensitivity compared to those who do not receive this treatment. Further exploration into the immunological implications of bevacizumab is warranted.

Limitations present in our study include its retrospective design, the relatively modest sample size of patients who received bevacizumab treatment and the inevitable presence of multicollinearity among the inflammatory markers. Prior to 2020, a limited number of patients received treatment with bevacizumab due to lack of health insurance coverage, resulting in potential bias. It is imperative to conduct extensive prospective studies to confirm the validity of our results.

In conclusion, our research demonstrated that a high SII is a significant predictor of chemorefractory status and poorer OS and DFS in advanced EOC. This research is considered to be the first investigation to recognize the SII as a factor in both the assessment of chemorefractory disease and the prognosis in EOC. Additionally, our findings suggest that SII could serve as a potential indicator for the effectiveness and benefits of bevacizumab treatment. Stratifying patients based on their SII levels may offer a personalized medicine approach, allowing healthcare providers to tailor individualized treatment plans and enhance surveillance strategies.

Abbreviations

ANC	Absolute neutrophil count
CA-125	Cancer antigen 125
CBC	Complete blood count
CI	Confidence interval
CSC	Cancer stem cell
EOC	Epithelial ovarian cancer
FIGO	International Federation of Gynecology and Obstetrics
GCIG	Gynecologic Cancer InterGroup
Hgb	Hemoglobin
IDS	Interval debulking surgery
IRB	Institutional Review Board
NACT	Neoadjuvant chemotherapy
NLR	Neutrophil-to-lymphocyte ratio
OR	Odds ratio
OS	Overall survival
PDS	Primary debulking surgery
PFS	Progression-free survival
PLR	Platelet-to-lymphocyte ratio
RECIST	Response Evaluation Criteria in Solid Tumours
ROC	Receiver operating characteristic
SII	Systemic immune-inflammation index
WBC	White blood cell

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
Yan-Ping Fu: drafted the work, acquisition, analysis. Hao Lin: acquisition, analysis. Yu-Che Ou: interpretation of data. Chen-Hsuan Wu: interpretation of data. Hung-Chun Fu: conception, funding, design of the work, drafted the work and substantively revised it.

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Data availability
The data that support the findings of this study are available from [Kaohsiung Chang Gung Memorial Hospital] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Kaohsiung Chang Gung Memorial Hospital].

Declarations

Ethics approval and consent to participate
About the ethics approval and consent to participate, the study was approved by the Institutional Review Board (IRB number: 202301253B0) of Chang Gung Memorial Hospital, and according to the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective nature of the analysis and individual patients was not affected.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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