RESEARCH ARTICLE

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Prognostic Value of The Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Platelet Count for Platinum-Sensitive Recurrent Epithelial Ovarian Cancer

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Abstract

Objective: To study the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and platelet count in patients with platinum-sensitive recurrent epithelial ovarian cancer (PS-ROC). **Methods:** This was a retrospective study on a database of platinum-sensitive recurrent epithelial ovarian cancer patients who received treatment at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) between January 2010 and December 2020. The patients' demographic data, surgical factors, pathological factors, laboratory findings, and response to treatment were reviewed from the patients' medical records. Survival analysis was conducted using the Kaplan–Meier survival estimate and Cox regression model. **Results:** In total, 56 patients were recruited in this study. The median overall survival (OS) and progression-free survival (PFS) were 33 (95%CI 23–43) and 11 (95%CI 8–16) months, respectively. Survival analysis showed a high PLR was associated with decreased OS compared with low value but no significant difference in PFS. High NLR was associated with poor OS and PFS. There was no association between the platelet count and survival outcome (OS and PFS). In the multivariable Cox regression analysis, the NLR, PLR, and platelet count were not significant prognostic factors for survival outcome. However, low hemoglobin and a decreased disease-free interval were significantly associated with poor PFS. A white blood cell count (WBC) ≥ 8,000 cells/mm^3 was a poor prognostic factor for overall survival (Adjusted HR 7.64; 95%CI: 2.21–26.42; p-value = 0.001). **Conclusions:** The NLR, PLR, and platelet count were not associated with both the OS or PFS in patients with PS-ROC. However, the WBC level is an easy, readily available, and economical way to predict survival outcomes in PS-ROC patients and may help physicians to tailor therapeutic interventions in the future.

Keywords: Ovarian cancer- neutrophil-to-lymphocyte ratio (NLR)- platelet-to-lymphocyte ratio (PLR)- platelet count

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Introduction

Ovarian cancer is the sixth-most prevalent cancer among female cancer patients globally. In Thailand, ovarian cancer ranks third in gynecological patients, trailing only cervical and uterine cancer. Furthermore, this cancer has the second-highest mortality rate after cervical cancer, with up to 4,475 new patients per year and 2,941 deaths per year (Sung et al., 2021). Due to the lack of effective, accurate, and cost-effective screening methods, epithelial ovarian cancer is frequently diagnosed at an advanced stage. Also, its symptoms frequently occur in the advanced stage of the disease. Consequently, ovarian cancer is a cancer with a high relapse risk, as high as 70%, with a high death rate too, while a small number of patients can recover from the disease without experiencing a relapse (Berek et al., 2021). Even in early-stage patients, the prognosis for late-stage epithelial ovarian cancer is 29% with only a 5-year survival rate (Lheureux et al., 2019). Also, a 20%–25% chance of recurrence after treatment has also been reported (Berek et al., 2021). After more than six months of treatment, the majority of epithelial ovarian cancer patients treated with surgery and platinum-based chemotherapy drugs still relapse. This group is referred to as patients with epithelial ovarian cancer who respond to platinum-based chemotherapy. When monitoring this group of patients, it was discovered that their survival rate and prognosis are quite variable. Understanding the prognostic factors may tailor therapeutic intervention in the future.

The occurrence of cancer, particularly solid tumors, is associated with inflammatory responses in the body (Singh et al., 2019). This is the reason for using the erythrocyte sedimentation rate (ESR) in the body to observe and monitor disease progression in patients with various types of cancer. The values that can be obtained include the number of multiple types of white blood cells and platelets (Zhou et al., 2018; Hu et al., 2020). These

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values can be considered as the baseline values for blood tests commonly observed in hospitalized patients with chronic diseases. A correlation was found between a high number of neutrophil white blood cells, low number of lymphocytes, high number of platelets, and the death rate of patients with various types of solid cancers (Singh et al., 2019). According to additional studies, the blood test values mentioned above can indicate inflammation in the body, and may be associated with a poorer prognosis for epithelial ovarian cancer patients (Vano et al., 2018).

There is currently no definitive database on whether the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and platelet count obtained from a complete blood count test influence the prognosis in platinum-sensitive recurrent epithelial ovarian cancer (PS-ROC). Therefore, the aim of this study was to study the intercepts in these parameters that could be used to predict the overall survival rate and disease-free survival rate of patients with platinum-sensitive recurrent epithelial ovarian cancer for use as a guideline to improve the care and monitoring of future patients.

Materials and Methods

This study was conducted as a retrospective cohort study on a database of platinum-sensitive recurrent ovarian cancer (PS-ROC) patients who received treatment at the gynecologic out-patient department at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) between January 2010 and December 2020. The study population was platinum-sensitive recurrent ovarian cancer patients (disease-free interval from last chemotherapy of more than 6 months). The criteria for the presence of recurrence were determined based on imaging methods (ultrasound or computed tomography) and CA125 values, and included all patients who received platinum-based chemotherapy, including Carboplatin and Paclitaxel, and who had a complete blood count test before receiving chemotherapy. The exclusion criteria included a suspicious of infection or infected patients within weeks before a complete blood count test was performed, patients who had underlying diseases that could affect the white blood cell count or platelet count, such as leukemia, autoimmune disease, and acquired immune deficiency syndrome, and post-splenectomy patients.

The sample size was calculated based on the results from Ceran et al., (2019). The minimum number of patients needed to determine the prognostic values of these parameters on the survival outcome was calculated to be 58. This study was approved by the institute's ethics committee (registration number SWUEC/E-039/2564).

We used complete blood counts that were obtained closest to or on the day of the first cycle of second-line chemotherapy and recorded as the white blood cell count (WBC), neutrophil count, lymphocyte count, and platelet count. Then, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated and recorded separately. In addition to the complete blood count of the patients, the patients' age, parity, symptoms, ECOG score, size of pre-treatment disease, stage of the disease, histopathological diagnosis and the degree of differentiation of the tumor, pre-treatment cancer antigen 125 (CA125), disease-free interval (DFI), and number of metastatic sites were recorded. Progression-free survival (PFS) was defined as the period that had elapsed between the date of the last cycle of chemotherapy of second-line treatment and the date of diagnosis of any of the above criteria. Overall survival (OS) was defined as the period that had elapsed between the date of the last cycle of chemotherapy of second-line treatment and death. Survivors without these conditions were censored at the time of the last analysis.

All the analyses were done using Stata version 15.1 (Stata Corp. Stata statistical software: Release 15.1. College Station, TX: Stata Corporation, Texas, USA, 2017). Descriptive statistics were used for analyzing patients characteristic and presented as the frequency with percentage, mean with standard deviation, or median with interquartile range depending on the distribution of data. The relationship between the determined classification, which was determined by the cut-off value calculated according to the variables of the patient groups, and the actual classification was established using the sensitivity, specificity, positive predictive value, and negative predictive value. These values were analyzed by a receiver operating characteristic (ROC) curve and Youden method and were then expressed. The respective probability of PFS and OS was estimated according to the Kaplan–Meier survival analytic method and compared with the survival outcome using the log-rank test. In the univariable Cox regression analysis, the variables associated with survival outcomes (p-value < 0.1) were included in the multivariable Cox regression analysis to determine which had any significant association with the prognostic associations and were presented as adjusted hazard ratios (HRs), 95% confidence intervals (CI), and p-values. A statistically significant outcome was defined at p-value < 0.05.

Results

Patient and disease characteristics

Overall, 56 patients in the whole database between January 2010 and December 2020 of our hospital were determined to be eligible for participation. The clinicopathological characteristics of the included patients are shown in Table 1. The mean age was 54.52 ± 10.07 years old. Most of the patients were diagnosed with a serous histological subtype (High-grade serous carcinoma (HGSCA) 51.8%, low-grade serous carcinoma (LGSCA) 3.6%), and almost 75% were in the advanced stage (51.8% in stage III, 25% in stage IV). At the time of recurrence, the median (IQR) of PLR was 139.39 (111.76, 184.13) and NLR was 2.23 (1.635, 3.28). The median follow-up duration of study, as determined by the reverse Kaplan–Meier method, was 40 months.

Survival outcome

The median overall survival (OS) and progression-free survival (PFS) were 33 (95%CI: 23–43) and 11 (95%CI: 8–16) months, respectively. The optimal cut-off values

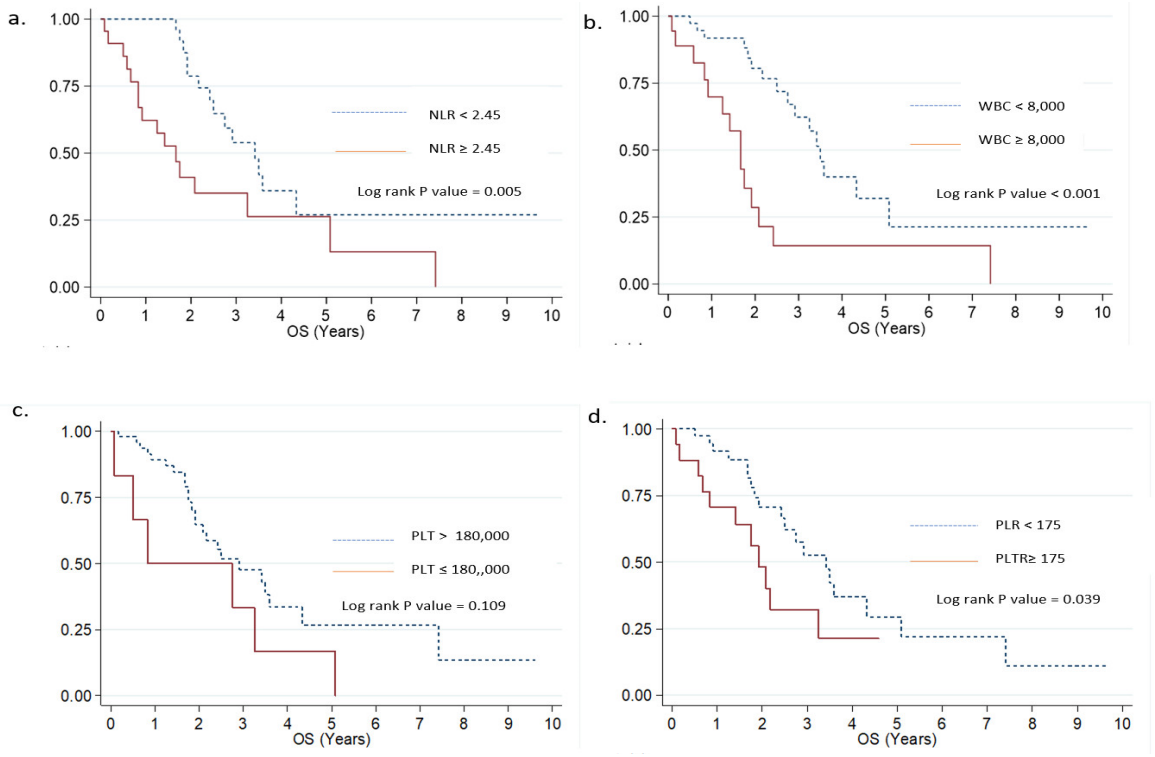

Figure 1. Kaplan-Meier Curves for OS Based on the NLR level (a), WBC count (b), PLT count (c), and PLR (d).

Table 1. Clinicopathological Characteristics of the Platinum-Sensitive Recurrent Epithelial Ovarian Cancer Patients (n = 56)

Variables	n (%)
age, mean ± SD, (year)	54.52 ± 10.07
Parity	
Nulliparous	24 (42.9)
Multiparous	32 (57.1)
ECOG score	
0	
1	9 (16.1)
FIGO stage n (%)	
I	11(19.6)
II	2 (3.6)
III	29 (51.8)
IV	14 (25)
Histology type, n (%)	
Serous carcinoma	31 (55.4)
Mucinous carcinoma	3 (5.4)
Endometrioid carcinoma	5(8.8)
Clear cell carcinoma	12 (21.4)
Adenocarcinoma	5 (8.9)
Tumor markers at recurrence, median (IQR)	
CA125	80.24 (54.57, 163.18)
CA19-9	34.73 (12.8, 64.74)
Number of recurrent lesions, n (%)	
Single site	28 (50%)
Multiple sites	28 (50%)
Disease-free interval (months), median (IQR)	13 (9, 27.5)

for the prognostic factors that maximized the sum of the sensitivity and specificity in the ROC curve are shown in Table 2. The cut-off values for the NLR, PLR, and platelet count were ≥2.45, ≥175, and ≤180,000, respectively. The platelet count had the highest specificity, namely 100%. The associations between the survival outcomes (OS, PFS) and complete blood count (CBC) parameters are presented in Figures 1 and 2. A high value of PLR was associated with a decreased median OS compared with a low value, significantly (23 months (95%CI: 8–39) versus 41 months (95%CI: 29–61), log rank p-value = 0.039); however, there was no significant difference for a median PFS value (10 months (95%CI: 3–16) versus 11 months (95%CI: 8–17), log rank p-value = 0.314). A high value of NLR showed significant differences for both the median OS (20 months (95%CI: 10–39) versus 41 months (95%CI: 20–52), log rank p-value = 0.005) and median PFS (6 months (95%CI: 3–12) versus 12 months (95%CI: 9–22) months, log rank p-value = 0.001), respectively. There was no significant difference in the platelet value cut-off point for both the median OS (10 months (95%CI: 1–39) versus 30 months (95%CI:23–52), log rank p-value = 0.109) and median PFS (4 months (95%CI: 3–9) versus 12 months (95%CI: 9–16), log rank p-value = 0.052). We also found that an increased WBC count was a significant poor prognostic factor for OS (HR 1.01; 95%CI: 1.000019–1.000287; p-value = 0.025) and PFS (HR 1.01; 95%CI: 1.000034–1.000297; p-value = 0.014). Due to its convenience in real clinical practice, we evaluated the optimal cut-off value of WBC count using the ROC curve and found a WBC level of ≥8,000 was associated with a lower median OS (20 months (95%CI: 10–25) versus 42 months (95%CI: 33–61), log rank p-value < 0.001), and median PFS (9 months (95%CI: 3–12) versus 12 months (95%CI: 9–22),

Table 2. Cut-off value, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy According to the Survival Statistics

Overall survival (OS)						
Variables	Cut-off level	AUC*	Sensitivity	Specificity	PPV	NPV
PLT	180,000	0.54	20.00%	100.00%	100%	52.00%
PLR	175	0.503	36.70%	76.90%	64.70%	51.30%
NLR	2.45	0.607	53.30%	76.90%	72.70%	58.80%
WBC	8,000	0.672	46.70%	84.60%	77.80%	57.90%
Progression-free survival (PFS)						
Variables	Cut-off level	AUC*	Sensitivity	Specificity	PPV	NPV
PLT	180,000	0.484	13.30%	100.00%	100%	22.00%
PLR	175	0.527	31.10%	72.70%	82.40%	20.50%
NLR	2.45	0.669	44.40%	81.80%	90.90%	26.50%
WBC	8,000	0.675	35.60%	81.80%	88.90%	23.70%

* AUC, Area under the receiver operating characteristic curve.

log rank p-value = 0.004), respectively, with significance.

Univariable and multivariable Cox regression analysis

The results of the univariable and multivariable Cox regression analyses for the OS and PFS are shown in Table 3. Based on the results of the univariable analysis, the disease-free interval (DFI), absolute neutrophil count (ANC), WBC count, PLR, and NLR were all factors that were associated with both OS and PFS, although PLR was not significantly associated with PFS. The platelet count was not associated with either PFS or OS. We found that the Hb level was associated with PFS significantly.

In the multivariable Cox regression analysis, the included variables were the NLR, PLR, PLT, WBC, disease-free interval (DFI), absolute neutrophil count, and hemoglobin value (Hb). The PLR, NLR, and platelet count were not associated with OS or PFS. The WBC count was the only independent variable for OS, whereby a WBC count ≥ 8,000 showed a significant decrease in OS (Adjusted HR 7.64; 95%CI: 2.21–26.42, p-value = 0.001). The Hb level and DFI remained the factors associated with PFS. An increased Hb level significantly improved PFS (Adjusted HR 0.72; 95%CI: 0.56–0.91; p-value = 0.006), while an increased DFI also improved PFS (Adjusted HR 0.97; 95%CI: 0.94–0.99; p-value = 0.02).

Discussion

In the present study, the pre-treatment levels of PLR and NLR were elevated in patients with low overall

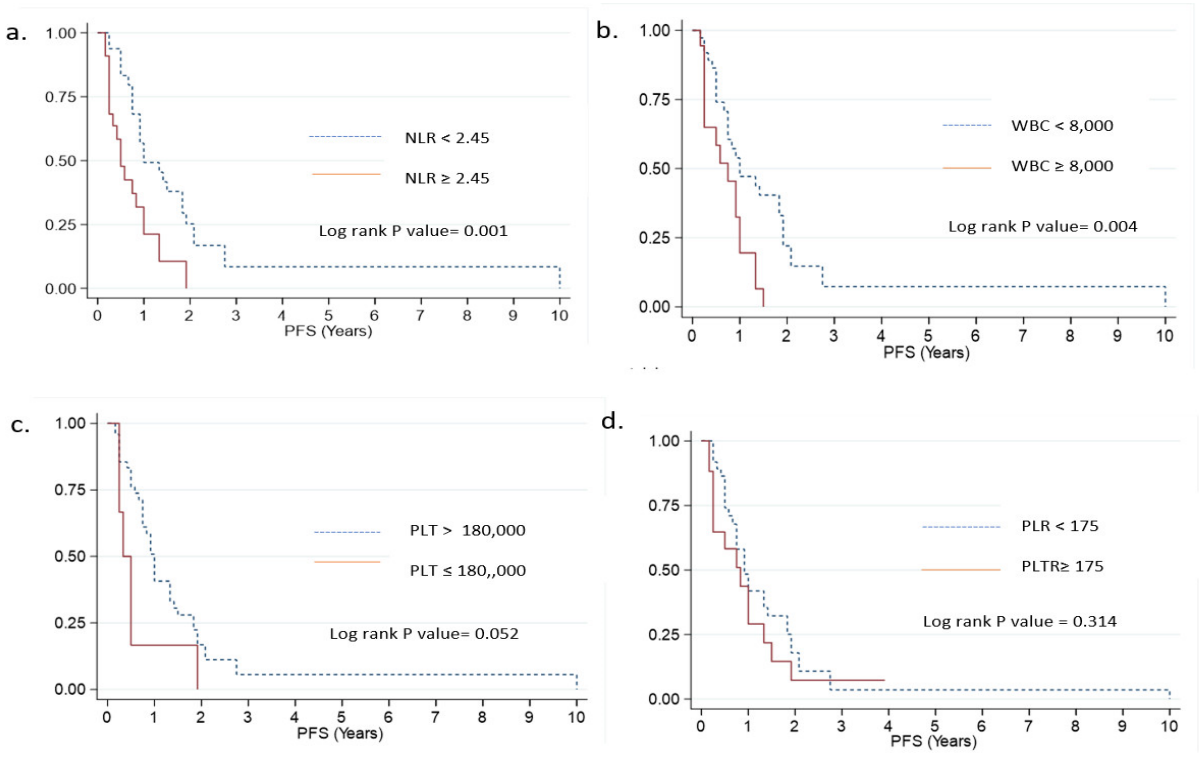

Figure 2. Kaplan–Meier Curves for PFS based on the NLR level (a),WBC count (b), PLT count (c), and PLR (d).

Table 3. Univariable and Multivariable Cox Regression Model Results for OS and PFS

Variables	Overall survival				Progression-free survival			
	Univariable		Multivariable		Univariable		Multivariable	
	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
Age	0.98 (0.94, 1.01)	0.129	-	-	1 (0.98, 1.03)	0.787	-	-
Histology								
Serous type	0.74 (0.35, 1.53)	0.411	-	-	1.12 (0.61,2.03)	0.72	-	-
Non-serous type	Reference		-	-	Reference		-	-
Stage								
Early stage	Reference	0.349	-	-	Reference	0.713	-	-
Advance stage	0.67 (0.3, 1.54)		-	-	1.15 (0.55,2.42)		-	-
Size (cm)	1.01 (0.93, 1.1)	0.83	-	-	0.97 (0.9, 1.05)	0.468	-	-
CA125 at recurrence	1 (1, 1)	0.806	-	-	1 (1, 1)	0.685	-	-
Number of lesions								
Single site	Reference	0.859	-	-	Reference	0.509	-	-
Multiple sites	0.94 (0.45, 1.95)		-	-	1.23 (0.66,2.28)		-	-
DFI	0.97 (0.95, 1)	0.034*	0.97 (0.94–1.01)	0.068	0.97 (0.94, 0.99)	0.006*	0.97 (0.94–0.99)	0.02*
ECOG score	1.4 (0.57, 3.45)	0.466	-	-	1.7 (0.75,3.89)	0.206	-	-
WBC parameters								
Neutrophil	1.01 (1.01, 1.02)	0.013*	0.99 (0.99–1.01)	0.12	1.01 (1.01, 1.02)	0.002*	0.99 (0.99–1.01)	0.989
Hemoglobin	0.81 (0.64, 1.02)	0.075	0.99 (0.76–1.40)	0.82	0.66 (0.52, 0.82)	<0.001*	0.72 (0.56–0.91)	0.006*
Lymphocyte	1 (0.99, 1.01)	0.86			1 (0.99, 1)	0.377		
WBC		0.001*		0.015*		0.009*		0.41
< 8,000	Reference		Reference		Reference		Reference	
≥ 8,000	3.68 (1.74, 7.78)		7.64 (2.21, 26.42)		2.47 (1.26, 4.86)		1.53 (0.55, 1.35)	
PLT		0.119		0.086		0.05		0.16
≤ 180,000	Reference		Reference		Reference		Reference	
> 180,000	0.48 (0.19, 1.2)		0.36 (0.12, 1.15)		0.42 (0.17, 1.0)		0.47(0.14, 1.57)	
PLR		0.045*		0.069		0.345		0.892
< 175	Reference		Reference		Reference		Reference	
≥ 175	2.2 (1.02, 4.77)		2.54 (0.93, 6.93)		1.36 (0.72, 2.57)		0.94 (0.42, 2.14)	
NLR		0.07*		0.695		0.003*		0.427
< 2.45	Reference		Reference		Reference		Reference	
≥ 2.45	2.72 (1.31, 5.63)		1.25 (0.40–3.92)		2.57 (1.37, 4.81)		1.52 (0.54–4.31)	

DFI, disease-free interval; WBC, white blood cell count; PLT, platelet count; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; * Variables included in multivariable analysis were the NLR, PLR, PLT, WBC, disease-free interval, neutrophil, hemoglobin.

survival, and a high level of NLR was associated with a decreased progression-free survival. The platelet count was not associated with the survival outcomes of patients with PS-ROC. In the Cox regression analysis, these count factors were not associated with survival outcomes, significantly. Previous studies revealed that inflammatory markers from CBC (PLR, NLR, platelet count) were associated with the prognosis of patients (Zhou et al., 2018; Ceran et al., 2019; Nomelini et al., 2019; Zhang et al., 2019). However, all these previous studies evaluated the parameters from the CBC at the time of first diagnosis (preoperative treatment), which was different from the case with the patients in our study. A possible explanation for this difference is that patients receiving previous frontline chemotherapy could develop residual or long-term bone marrow injury. Wang et al., (2006) reported that following subsequent cycles of cancer treatment, residual bone marrow injury can deteriorate to become a hypoplastic or myelodysplastic syndrome. From the result of our study, the PLR, NLR, and platelet count might not be appropriate markers to predict the prognosis in PS-ROC. Nevertheless, one study conducted in recurrent ovarian cancer patients showed that an NLR less than 3 was a prognostic factor in PS-ROC patients (Farolfi et al., 2018). However, the small sample size of our study may preclude its prognostic significance after the multivariate analysis.

We found that a WBC count of more than 8,000 was associated with poor OS, while the Hb level and DFI were associated with PFS, significantly. Tomita et al., (2009) reviewed patients with leukocytosis (WBC count > 10,000/mm3), anemia (Hb < 13 g/dL in men and < 12 g/dL in females), and thrombocytopenia (platelet count > 320000) in non-small cell lung cancer, and found that these patients were associated with poor prognosis. Leukocytosis may be caused by infection, bone marrow metastases, or corticosteroids. Consequently, we excluded patients with infection and none of the patients had bone

marrow metastasis. Tumor-related leukocytosis may be caused by the unregulated production of hematopoietic cytokines. Leukocytosis and anemia might be regarded as paraneoplastic phenomena. Previous studies have proved that anemia is associated with poor prognostic factors for survival in cancer patients (Caro et al., 2001; Shasha et al., 2001). The result in our study for DFI was similar to in the prior study of Goenka et al., (2021), who found that for PS-ROC patients, a low lymphocyte–monocyte ratio, platinum-free interval of less than 12 months, and no secondary cytoreduction were associated with poor survival outcomes. Canaz et al.. (2019) reported that DFI had prognostic significance only with high-grade epithelial ovarian cancers, but not for low-grade ones. However, we did not conduct a subgroup analysis of patients with high- and low-grade epithelial ovarian cancer.

While hematological indices based on NLR, PLR, and platelet count have been studied as prognostic factors in newly diagnosed epithelial ovarian cancer, there are limited data on these markers in recurrent disease. The strength of this study is that we focused on PS-ROC patients which no accurate predictive markers for this specific group. The major limitation of our study was its retrospective study nature and small sample size. We might find other significant results if we had a greater number of databases to investigate. The retrospective nature of the study may have led to bias in the data analysis. Almost all our patients were treated with combined platinum-based chemotherapy and paclitaxel. None of the patients received first-line maintenance with bevacizumab or a PARP-inhibitor, both of which have become new treatments to improve survival outcome (NCCN, version 1.2023). This could have affected the results of the inflammatory markers. Another limitation was that we had no data about BRCA mutation and the homologous recombination status, which are now recognized predictive markers, especially in high-grade serous epithelial ovarian cancer (Cadoo et al., 2022). Any future study should increase the sample size and include patients who are treated with the maintenance of new therapies. It would be interesting if the WBC count would still be useful to predict survival for these patients.

In conclusion, we found that a high PLR was associated with a worse OS, and a high NLR was associated with a worse OS and PFS from the survival analysis. However, the PLR, NLR, and platelet count were not statistically significant factors for predicting survival outcomes in the multivariable analysis. Recently, it has been reported BRCA gene mutation or homologous recombination deficiency (HRD) is associated with better survival outcomes in PS-ROC patients (Cadoo et al., 2022). However, genetic testing is not available in most hospitals and is still expensive. Pretreatment for leukocytosis, anemia, and DFI may provide a simple method to use when considering the treatment decision and predicting the survival outcome.

Author Contribution Statement

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Akrapat Sowannakul, Nopporn Rodpenpear Polsiri Ekbhum, and Tanitra Tantitamit. The first draft of the manuscript was written by Tanitra Tantitamit and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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General

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Ethical Declaration

Approval was obtained from the ethics committee of Srinakharinwirot University. The procedure used in this study adheres to the tenets of the Declaration of Helsinki.

Availability of data

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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