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Original Article

Enhanced prognostic stratification in early-stage epithelial ovarian cancer: multi-histological analysis of neutrophil-to-lymphocyte ratio with particular emphasis on clear cell histology

En-Ling Sung[1], Hao Lin[1], Yu-Che Ou[1], Hung-Chun Fu[1], Mei-Yi Lin[1], Chien-Hsiang Kao[1], Chen-Hsuan Wu[1,2], Chan-Chao Changchien[1,3]

[1]Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan; [2]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan; [3]Department of Obstetrics and Gynecology, Kaohsiung Municipal Feng Shan Hospital - Under The Management of Chang Gung Medical Foundation, Kaohsiung 830025, Taiwan

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Abstract: In Asian populations, early-stage ovarian cancers account for approximately half of cases, substantially exceeding proportions observed in Western cohorts, with clear cell carcinoma (CCC) and endometrioid carcinoma (EMC) demonstrating markedly higher prevalence in Asian women. The tumor immune microenvironment critically influences oncological progression, and systemic inflammatory biomarkers can serve as surrogates of host immunological responses. This study evaluated the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), an established index of systemic inflammation and immune dysregulation, across histologic subtypes in early-stage epithelial ovarian cancer. We retrospectively analyzed patients with FIGO stage I-II epithelial ovarian cancer diagnosed between 2011 and 2018. Pretreatment NLR was calculated to reflect the balance between neutrophil-driven inflammation and lymphocyte-mediated immunity. Among 217 enrolled patients, CCC (28.1%) and EMC (34.6%) constituted the predominant histotypes, consistent with Asian demographic patterns. In univariable analyses, elevated NLR and advanced stage significantly correlated with diminished progression-free survival (HR 5.04, P<0.001; HR 3.81, P<0.001) and overall survival (HR 4.54, P=0.013; HR 3.91, P=0.003). In multivariable models, NLR remained an independent prognostic factor for both endpoints (PFS: HR 5.38, P=0.001; OS: HR 4.27, P=0.048). Histology-stratified analyses revealed distinctive immunological signatures, with elevated NLR in CCC patients exhibiting exceptionally strong prognostic value (univariable PFS: HR 8.14, P=0.001; OS: HR 22.42, P=0.005; multivariable PFS: HR 8.00, P=0.007; OS: HR 32.43, P=0.025), providing information beyond FIGO stage. Conversely, NLR demonstrated no prognostic relevance in EMC patients, indicating heterogeneous immune microenvironments across histological variants. Elevated pre-treatment NLR independently predicts adverse outcomes in early-stage epithelial ovarian cancer, with particularly pronounced prognostic utility in CCC. These findings may be especially relevant in Asian populations, in which CCC is more common, and could inform personalized risk stratification.

Keywords: Ovarian cancer, clear cell carcinoma, early stage, NL ratio, prognosis

Introduction

Ovarian cancer is the ninth leading cancer in Taiwan [1]. Unlike Western countries, approximately half of epithelial ovarian cancer are diagnosed at an early stage [1]. Most women with early-stage ovarian cancer have an excellent prognosis, and previous studies have demonstrated that stage and histology are the major prognostic factors for disease outcome [2-4]. Nevertheless, a subset of these patients still experience poor clinical outcome [2, 5]. Therefore, reliable biomarkers are needed to better predict outcomes in early-stage ovarian cancer.

Over the past decade, interest in tumor-immune interactions has grown. Tumor-related inflam-

matory responses - both local and systemic - as well as altered myelopoiesis contribute to the development and progression of malignancies [6, 7]. Different kinds of immune cells contribute can either promote or suppress tumor growth, and numerous studies have been conducted to explore the prognostic value of NLR in cancer patients [8, 9]. However, it is still difficult to verify the prognostic role of NLR in early-stage ovarian cancer. This study aimed to evaluate the association between clinical characteristics, including NLR, and clinical outcome in early-stage ovarian cancer, and to assess the prognostic value of NLR across histologic subtypes.

Material and methods

Study population

Clinical parameters of patients who had the diagnosis of stage I and II epithelial ovarian cancer and received further treatment or follow-up between 2011 and 2018 in Kaohsiung Chang Gung Memorial Hospital were collected for a retrospective review. The clinicopathological characteristics collected in the study included age at diagnosis, FIGO stage, histology, adjuvant chemotherapy regimen, progression free survival (PFS), overall survival (OS) and complete blood count (CBC). Pretreatment CBCs were obtained preoperatively when available. The availability of NLR measurements reflected routine practice by attending physicians rather than a study-specific protocol. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count in the pretreatment CBC. All patients achieved optimal cytoreduction, defined as no gross residual disease, as documented in operative reports. In cases without standard staging surgery, postoperative imaging was utilized to confirm the absence of residual disease. Patients who received adjuvant chemotherapy were treated every three weeks with either paclitaxel (175 mg/m^2) plus carboplatin (AUC 5), or cyclophosphamide (750 mg/m^2) plus cisplatin (75 mg/m^2), based on physician and patient preference. FIGO stage I patients received three to six cycles depending on histologic risk, while all stage II patients received six cycles. To assess the potential impact of missing data, we compared baseline characteristic between patients with and without available NLR data. For subgroup analyses of prognostic factors, patients were categorized by histologic subtype - clear cell carcinoma, endometrioid carcinoma, and others. Patients without a confirmed subtype or without follow-up at our institution were excluded. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (No. 202400936B0) and was executed in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was carried out with SPSS statistical package, Version 25.0 (IBM Corporation). The cut-off value of NLR was determined using receiver operating characteristic (ROC) curve. Correlations between PFS, OS and the possible prognostic factors, including age, FIGO stage, histologic subtype, platelet, CA-125, and NLR were computed using univariable analysis. Independent associations were evaluated using multivariable Cox models, and results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Survival analysis associated with NLR was presented with Kaplan-Meier survival plots. For all analyses, the significance level was specified as $P<0.05$.

Results

Patient characteristics and study population

A total of 217 patients were enrolled in this study. The clinical and pathologic characteristics of these patients were summarized in **Table 1**. The mean age at diagnosis was 48.8±12.2 years, and the median follow-up duration was 63 months. By FIGO stage, 89 (41.0%) had stage IA/IB disease, 89 (41.0%) had stage IC disease, and 39 (18.0%) had stage II disease. Histologic subtypes included endometrioid carcinoma in 75 (34.6%), clear cell carcinoma in 61 (28.1%), mucinous carcinoma (MUC) in 41 (18.9%), and high-grade serous carcinoma (HGSC) in 21 (9.7%); other subtypes accounted for 19 patients (8.7%). As for the post-operative treatment, 136 patients (60.4%) received chemotherapy and the remaining 89 patients (39.6%) did not.

Biomarker distribution and NLR cutoff determination

Among patients with available data, pre-treatment platelet count was ≥400,000 in 173

Table 1. Clinicopathological characteristics of all patients (N=217)

Age, years, mean (SD)	48.8 (12.2)
Follow-up, months, median (range)	63 (0-139)
FIGO stage, n (%)	
IA, IB	89 (41)
IC	89 (41)
II	39 (18)
Histology, n (%)	
HGSC	21 (9.7)
Clear cell carcinoma	61 (28.1)
Endometrial carcinoma	75 (34.6)
Mucinous carcinoma	41 (18.9)
Others	19 (8.7)
Pre-treatment platelet, n (%)	
<40 10^4/uL	173 (79.7)
≥40 10^4/uL	28 (12.9)
missing	16 (7.4)
Pre-treatment CA-125, n (%)	
<35 U/mL	48 (22.1)
≥35 U/mL	137 (63.1)
Missing	32 (14.7)
OP method	
Complete staging	173 (79.7)
Unilateral/bilateral salpingo-oopherectomy	29 (13.4)
Hysterectomy + bilateral salpingo-oopherectomy	11 (5.1)
Cystectomy	4 (1.8)
Post-op C/T, n (%)	
Yes	138 (63.6)
No	79 (36.4)
Pre-treatment N/L, mean (SD)	4.0 (3.53)
Missing, n (%)	67 (30.9)
Post-treatment N/L, mean (SD)	2.3 (2.35)
Missing, n (%)	85 (39.2)

(79.7%) patients, and <400,000 in 28 (12.9%) patients. Elevated pre-treatment CA-125 was detected in 137 (63.1%) patients, while 48 (22.1%) patients had value within the normal range. Pre-treatment NLR data were available for 150 (70%) patients, with a mean value of 3.9 (SD: 3.45). The cut-off value of NLR determined by ROC curve (**Figure 1**) was 4.7, and patients were accordingly categorized as high and low NLR accordingly. Among the 150 patients with available NLR, 121 patients had high pre-treatment NLR, which was defined as NLR ≥4.7 and low NLR (defined as <4.7) was observed in 29 patients. There was no difference in age, stage, histology type, pre-treatment CA-125 and the percentage of receiving post-operation chemotherapy between both groups (**Table 2**).

Survival analysis in the entire cohort

Patients with high NLR had higher pre-treatment platelet counts (P=0.012) than those with low NLR. In the univariable analyses of the entire cohort (**Table 3**), high NLR (≥4.7) was significantly associated with shorter PFS (HR, 5.04; 95% CI, 2.13-11.93; P<0.001) and OS (HR, 4.54; 95% CI, 1.38-15.01; P=0.013). Patients without NLR measurements did not differ significantly from the low-NLR group for either PFS (HR 1.75, P= 0.181) or OS (HR 2.13, P= 0.146), indicating that the association between high NLR and worse outcomes was robust to inclusion of cases with missing NLR. FIGO stage II was also significantly associated with poor outcomes for both PFS (HR, 3.81; 95% CI, 1.88-7.70; P<0.001) and OS (HR, 3.91; 95% CI, 1.59-9.62; P= 0.003). By histological subtypes, CCC showed a trend toward shorter PFS compared with non-CCC (HR, 2.03; 95% CI, 1.02-4.04; P=0.045), while endometrioid carcinoma (EMC) demonstrated better OS compared to non-EMC (HR, 0.20; 95% CI, 0.05-0.85; P=0.030).

Subgroup analysis by NLR data availability

Baseline characteristics were compared between patients with available NLR data (n= 150) and those without NLR data (n=67). The groups were well balanced for most variables, including age, histologic subtype, FIGO stage, and performance status (Supplementary Table 1). However, chemotherapy use was lower in the missing-NLR group than in the available-NLR group (52.2% vs. 68.7%, P=0.020). Given this differential missing pattern, separate mul-

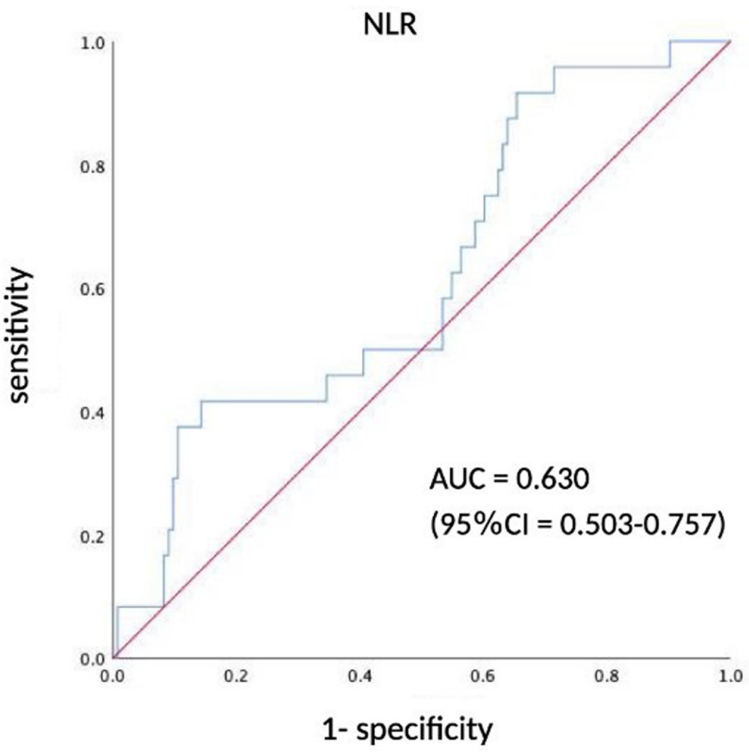

Figure 1. ROC curve drawn at different cut-off values of pretreatment NLR.

Table 2. Factors associated with pre-treatment N/L ratio in patients of stage I-II EOC with available NLR data (N=150)

Pre-treatment N/L ratio	<4.7 n=121	≥4.7 n=29	*p* value
Age, years mean (SD)	50 (12.2)	48.5 (9.4)	0.550
Stage, %			0.155
IA/IB	48 (39.7)	6 (20.7)	
IC	52 (43.0)	17 (58.6)	
II	21 (17.4)	6 (20.7)	
Histology, %			0.653
HGSC	12 (9.9)	1 (3.4)	
Clear cell carcinoma	35 (28.9)	9 (31.0)	
Endometrioid cancer	37 (30.6)	11 (37.9)	
Others	37 (30.6)	8 (27.6)	
Pre-Platelet*, 10^4/uL			0.012
mean (SD)	29.0 (9.6)	35.5 (12.3)	
Pre-CA-125**, U/ml			0.322
mean (SD)	538.1 (2115.2)	964.7 (1130.3)	
C/T, %			0.169
Yes	80 (66.1)	23 (79.3)	
No	41 (33.9)	6 (20.7)	

*total N=145, **total N=136.

tivariable Cox regression analyses were conducted within each subgroup. Among patients with available NLR data (n=150), multivariable analysis adjusting for age, histologic subtype, FIGO stage, and chemotherapy status showed that high NLR remained independently associated with shorter PFS (HR 5.33, 95% CI 2.20-12.88, P<0.001) and OS (HR 5.51, 95% CI 1.61-18.90, P=0.007) (**Table 4**). In patients without NLR data (n=67), FIGO stage was the only independent prognostic factor for PFS (HR 5.53, P=0.017), whereas histologic subtype and chemotherapy status were not significantly associated with outcomes (Supplementary Table 2).

Dynamic changes in NLR following treatment

To evaluate the effect of chemotherapy on systemic inflammation and the prognostic value of post-treatment NLR, we analyzed 131 patients with posttreatment NLR measured after completion of chemotherapy. Chemotherapy significantly reduced NLR from 4.0±3.5 pre-treatment to 2.4±2.6 post-treatment (mean reduction: 1.6±4.2, P<0.001), consistent with decreased systemic inflammation. ROC analysis identified a post-chemotherapy NLR cut-off value of 1.68 for predicting recurrence (AUC=0.63, 95% CI: 0.506-0.761, P=0.041). However, in multivariate Cox regression analysis adjusting for FIGO stage and histology, post-chemotherapy NLR ≥1.68 was not significantly associated with PFS (HR 1.95, 95% CI: 0.78-4.87, P=0.154) or OS (HR 1.19, 95% CI: 0.40-3.51, P=0.754), in contrast to the strong prognostic value of pre-treatment NLR (Supplementary Tables 3, 4).

Table 3. Univariate analysis of factors associated with progression-free survival (PFS) and overall survival (OS) in patients with available NLR data (N=150)

Factors	PFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years (≥50 vs. <50)	1.442	0.72-2.89	0.301	1.88	0.76-4.65	0.17
FIGO stage (II vs. I)	3.81	1.88-7.70	<0.001	3.91	1.59-9.62	0.003
Histology						
EMC vs. non-EMC	0.677	0.32-1.46	0.319	0.20	0.05-0.85	0.030
CCC vs. non-CCC	2.03	1.02-4.04	0.045	2.24	0.93-5.41	0.073
HGSC vs. non-HGSC	1.82	0.70-4.71	0.219	2.57	0.86-7.74	0.092
Platelet, 10^4/uL (≥40 vs. <40)	1.47	0.60-3.62	0.398	1.42	0.47-4.29	0.536
CA-125, U/ml (≥35 vs. <35)	3.26	0.99-10.78	0.053	32.80	0.35-3115.66	0.133
N/L ratio						
(≥4.7 vs. <4.7)	5.04	2.13-11.93	<0.001	4.54	1.38-15.01	0.013
(missing vs. <4.7)	1.75	0.77-3.98	0.181	2.13	0.77-5.90	0.146

Table 4. Multivariate Cox regression analyses of factors associated with progression-free survival (PFS) and overall survival (OS) in patients with available NLR data (N=150)

Variable	Comparison	PFS			OS		
		HR	95% CI	*P* value	HR	95% CI	*P* value
FIGO	I	1	1.39-8.87	0.008	1	1.37-15.96	0.014
	II	3.52			4.67		
Histology	Non-CCC	1	0.78-6.35	0.138	1	0.46-5.54	0.466
	CCC	2.22			1.59		
	Non-EMC	1	0.33-3.33	0.937	1	0.02-1.62	0.127
	EMC	1.05			0.18		
Chemotherapy	No	1	0.33-3.40	0.933	1	0.25-6.76	0.757
	Yes	1.05			1.30		
NLR	<4.7	1	2.20-12.88	<0.001	1	1.61-18.90	0.007
	≥4.7	5.33			5.51		

Histology-specific analysis

Notably, histology-specific analyses (**Figure 2**; **Table 5**) revealed marked differences in the prognostic value of NLR. Among patients with CCC, high NLR demonstrated e strong prognostic value in univariable models, with HR 8.14 (95% CI, 2.26-29.34; P=0.001) for PFS and HR 22.42 (95% CI, 2.50-201.3; P=0.005) for OS. After multivariate adjustment (**Table 6**), NLR remained highly significant in CCC patients for both PFS (HR, 8.00; 95% CI, 1.77-36.1; P=0.007) and OS (HR, 32.43; 95% CI, 1.53-685.6; P=0.025), whereas FIGO stage was not significantly associated with outcomes in this subgroup (PFS: HR, 2.08; P=0.340; OS: HR, 0.78; P=0.869). In contrast, for EMC patients (**Table 5**), NLR showed no significant association with PFS in either univariate (P=0.250) or multivariate (P=0.224) analysis (**Tables 5**, **6**). For overall survival in EMC patients, Cox regression could not be performeddue to very few events - no deaths occurred among stage I patients and the overall number of deaths was insufficient for meaningful analysis.

Discussion

Inflammatory processes have long been recognized as crucial contributors to cancer development [7], and the neutrophil-to-lymphocyte ratio (NLR) has emerged as a useful marker of systemic inflammation across malignancies [11, 12]. In our analysis of 217 patients with early-stage EOC, we demonstrated that NLR exhibits remarkable histology-specific prognostic significance. Notably, in ovarian clear

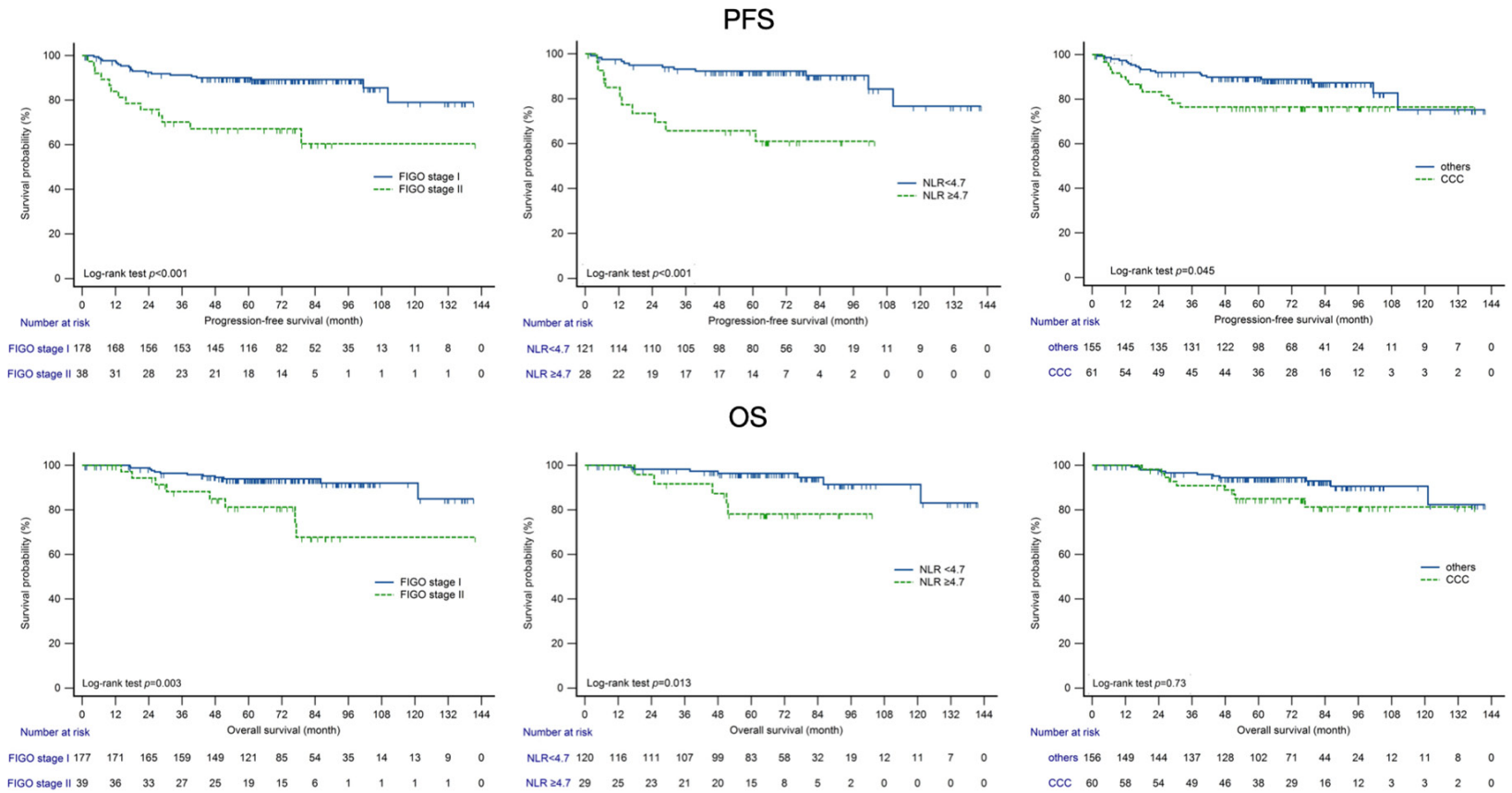

Figure 2. Kaplan-Meier survival curves for PFS and OS stratified by clinicopathological characteristics.

Table 5. Univariate analyses of clinical factors associated with progression-free survival (PFS) and overall survival (OS) in early-stage CCC and EMC patients

CCC		PFS			OS	
Factors	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years (≥50 vs. <50)	1.33	0.47-3.80	0.593	0.72	0.18-2.87	0.637
FIGO stage (II vs. I)	3.20	1.07-9.60	0.037	4.90	1.32-18.28	0.018
Platelet, 10^4/uL (≥40 vs. <40)	0.45	0.06-3.44	0.441	0.65	0.08-5.24	0.689
CA-125, U/ml (≥35 vs. <35)	4.16	0.54-32.00	0.171	32.76	0.04-25.4×10^3	0.304
N/L ratio (≥4.7 vs. <4.7)	8.14	2.26-29.34	0.001	22.42	2.50-201.3	0.005
EMC		PFS			OS	
Factors	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years (≥50 vs. <50)	0.65	0.15-2.71	0.551	1.06	0.07-16.93	0.968
FIGO stage (II vs. I)	3.71	0.92-15.01	0.066	NA*	NA*	NA*
Platelet, 10^4/uL (≥40 vs. <40)	2.41	0.47-12.50	0.295	NA*	NA*	NA*
CA-125, U/ml (≥35 vs. <35)	1.13	0.21-6.00	0.883	NA*	NA*	NA*
N/L ratio (≥4.7 vs. <4.7)	2.90	0.47-17.74	0.250	NA*	NA*	NA*

*No case died at stage I.

Table 6. Multivariate Cox regression analyses of clinical factors associated with progression-free survival (PFS) and overall survival (OS) in early-stage CCC and EMC patients

CCC			PFS			OS	
Variable	Comparison	HR	95% CI	*P* value	HR	95% CI	*P* value
FIGO	I	1	0.46-9.36	0.340	1	0.04-14.50	0.869
	II	2.08			0.78		
NLR	<4.7	1	1.77-36.1	0.007	1	1.53-685.6	0.025
	≥4.7	8.00			32.43		
EMC			PFS			OS	
Variable	Comparison	HR	95% CI	*P* value	HR	95% CI	*P* value
FIGO	I	1	0.51-16.00	0.235	NA*	NA*	NA*
	II	2.85					
NLR	<4.7	1	0.50-19.56	0.224	NA*	NA*	NA*
	≥4.7	3.12					

*No case died at stage I.

cell carcinoma (CCC), elevated pretreatment NLR (≥4.7) was a stronger predictor of poor outcomes than FIGO stage, with hazard ratios of 6.91 for progression-free survival (PFS) (P=0.004) and 17.79 for overall survival (OS) (P=0.011). This pronounced effect persisted among stage I CCC patients, where NLR remained highly predictive of recurrence and mortality. By contrast, in endometrioid and other histological subtypes, NLR had limited prognostic value, and FIGO stage was the principal determinant of survival. These findings highlight the distinctive immune microenvironment of CCC and position NLR as a simple and widely available prognostic marker that can outperform traditional staging in this histologic subtype, which is particularly prevalent in Asian populations.

Prognostic limitations in early-stage ovarian cancer and NLR as an emerging biomarker

Ovarian cancer is the ninth most cancer in Taiwan [1], and nearly half of epithelial ovarian cancer cases are detected at an early stage [1]. Results of prior studies indicate that only disease stage and histology are associated with prognostic outcomes in these cases [2-4]. Although most women diagnosed with early-stage ovarian cancer have a promising prognosis, a subset experiences unfavorable clinical

outcome. Consequently, there exists a demand for prognostic biomarkers for patients with early-stage ovarian cancer. Ovarian cancer is recognized as an immunogenic tumor, and previous studies reported the association between NLR and prognosis. In a retrospective study, Agnieszka et al. found that higher pretreatment value of NLR was an independent negative prognostic factor for PFS in patients across all stages [10]. Furthermore, Yin et al. reported that higher NLR was associated with worse OS and shorter PFS in a meta-analysis including ten retrospective studies and 2,919 patients [11]. Some of these studies focused solely on advanced stages, whereas others included patients across all stages. To minimize the impact of multiple known prognostic factors of advanced ovarian cancer, only patient with FIGO stage I and II were involved in our study.

Biological basis of NLR prognostic value: tumor-immune microenvironment interactions

There are some plausible explanations for the association between NLR and cancer prognosis. Neutrophils are the a major component of the leukocyte population, and the degree of neutrophil infiltration correlates with the increased vascular endothelial growth factor (VEGF) expression, which plays a critical role in tumor-associated angiogenesis, growth, and metastasis [7, 12]. Besides, neutrophils also produce and release numerous proinflammatory cytokines, such as tumor interleukin 1, interleukin 6, and matrix metalloprotease 9 (MMP9) [13], thereby modulating the tumor microenvironment in ways that promote tumor progression. By contrast, lymphocytes are known to be critical in tumor defense by inhibiting tumor cell proliferation [14]. Increased lymphocytic infiltration within tumors correlates with improved clinical outcome [14]. Taken together, NLR could reflect an interaction between host's immune system and tumor. Prior studies reported an association between NLR, survival and tumor progression in cancer patients. Elevated NLR is linked to poor prognosis in various types of cancer, including colorectal cancer, gastric cancer, hepatocellular carcinoma, bladder cancer, breast cancer, endometrial cancer, and esophageal cancer [15-21].

Differential NLR prognostic value across histological subtypes

The epidemiological landscape of ovarian cancer demonstrates notable geographic variation, with clear cell carcinoma showing markedly elevated incidence rates in Asian populations compared to Western cohorts [22, 23]. This regional disparity, combined with the tendency for CCC to present predominantly at an early stage, creates a unique clinical scenario particularly relevant to Asian healthcare settings. Our institutional analysis of 217 patients revealed that CCC and EMC accounted for 28.1% and 34.6% of early-stage epithelial ovarian cancers respectively, with a mean age of 48.8 years and 82% presenting with stage I disease. These proportions substantially exceed those typically reported in Western populations, highlighting the distinct tumor biology patterns characteristic of Asian patients. Most prior NLR research in ovarian cancer has either focused on single histologic subtypes - often single-institution studies of early-stage CCC with limited sample sizes [24], - or pooled mixed populations without histotype-specific analyses [25] In contrast, our cross-histology comparison demonstrates histology-specific differences in the prognostic relevance of inflammatory markers. Building upon previous early-stage CCC findings [24], our study expands the investigation to include multiple histological subtypes simultaneously, revealing that NLR significance varies dramatically between CCC and EMC within the same early-stage population. In our cohort, patients with elevated NLR had significantly higher platelet counts (mean 35.5×10^4/μL vs. 29.0×10^4/μL, P=0.012), consistent with systemic inflammatory activation. However, the prognostic impact varied by histological subtype: NLR demonstrated strong prognostic significance in CCC but failed to reach significance in EMC. Notably, the hazard ratio for NLR in CCC overall survival was large (HR 32.43, P=0.025), but the wide 95% CI (1.53-685.6) reflects the rarity of death events in small early-stage subgroups, indicating the need for validation in larger CCC cohorts.

This differential response suggests that the underlying tumor microenvironment characteristics, particularly the highly immune-infiltrated nature of CCC with prominent immunosuppres-

sive signaling pathways [26, 27], may modulate the clinical relevance of systemic inflammatory markers. Our findings suggest that the distinct molecular and immunological characteristics of CCC, compared to other histological subtypes, may create a microenvironment where systemic inflammatory responses have enhanced prognostic influence.

Biological mechanisms and dynamic prognostic value of NLR in CCC

The biological mechanisms underlying the prognostic relevance of NLR in CCC likely involve interconnected pathways, including IL-6/STAT3 signaling that promotes neutrophil recruitment and lymphocyte apoptosis [28], metabolic reprogramming-induced formation of neutrophil extracellular traps (NETs) [29], and chronic inflammation associated with an endometriosis background [30]. Together, these processes may create a tumor microenvironment in which NLR serves as a sensitive prognostic indicator in CCC. While our study focused on pretreatment NLR, emerging evidence indicates that dynamic NLR monitoring enhances prognostic assessment. Post-treatment declines in NLR have been associated with improved survival; in some studies, a >50% reduction predicted significantly longer PFS [31]. This dynamic assessment may be especially informative in chemoresistant CCC, where early NLR changes (about 6 weeks after therapy initiation) can forecast long-term outcomes and help identify patients who may benefit from alternative therapies [31, 32]. Conversely, persistently elevated or rising NLR after treatment initiation may indicate inadequate therapeutic response and warrant early treatment modification [32]. However, optimal monitoring protocols for CCC, including timing intervals and threshold values, require prospective validation.

Differential prognostic value of pre- versus post-treatment NLR

Our extended analysis showed that while chemotherapy significantly reduced NLR from 4.0±3.5 to 2.4±2.6 (P<0.001), post-treatment NLR was not significantly associated with either PFS (HR 1.95, P=0.154) or OS (HR 1.19, P=0.754), in contrast to the strong prognostic value of pre-treatment NLR. This apparent paradox may reflect the complex effects of chemotherapy on inflammatory indices. Chemotherapy-induced neutropenia has been linked to improved survival across solid tumors, likely as a proxy for adequate dosing rather than direct tumor control [33]. The dual effects of neutropenia (potentially favorable) and lymphopenia (immunosuppressive) after chemotherapy may decouple post-treatment NLR from underlying disease biology. Furthermore, heterogeneous treatment responses mean that normalized NLR values can occur in both chemosensitive and chemoresistant tumors, obscuring prognostic relationships. These findings emphasize that pre-treatment NLR, which captures the unmodified tumor-host inflammatory interaction, serves as a more reliable prognostic biomarker in early-stage EOC, particularly in CCC, and supports obtaining NLR before therapy initiation for optimal risk stratification.

Novel insights into traditional biomarker limitations

Our study highlights important limitations of traditional prognostic markers in early-stage ovarian cancer. Despite their established roles in advanced disease [34], both CA-125 and platelet counts showed limited prognostic utility in our early-stage cohort. Pre-treatment CA-125 was only marginally significant in univariable analysis (HR=3.26, P=0.053 for PFS; HR=2.80, P=0.133 for OS) and lost prognostic value in multivariable models. Platelet counts was not prognostic (HR=1.47, P=0.398 for PFS; HR=1.42, P=0.536 for OS), aligning with prior observations in early-stage CCC that platelet-based markers have limited impact compared with neutrophil-lymphocyte ratios [24]. This pattern suggests that platelet-related inflammatory responses may be less clinically relevant in early-stage disease than neutrophil-lymphocyte dynamics. In CCC specifically, neither CA-125 (HR=4.16, P=0.171 for PFS; HR=2.76, P=0.304 for OS) nor platelet count (HR=0.45, P=0.441 for PFS; HR=0.65, P=0.689 for OS) was prognostic. To our knowledge, this is among the first analyses to represent that traditional biomarkers lose prognostic utility in early-stage disease within Asian populations. Unlike NLR, which demonstrates histotype-specific significance, these traditional biomarkers have limited utility across early-stage subtypes, likely reflecting distinct biological mechanisms in early-stage tumors [35, 36]. The overall adju-

vant chemotherapy rate was 63.6%, with no difference between NLR groups (79.3% vs. 66.1%, P=0.169), consistent with current clinical practice in which inflammatory markers are not yet used to guide adjuvant treatment.

Clinical implications and future therapeutic directions

Our data indicate that NLR ≥4.7 provides prognostic information beyond traditional FIGO staging in patients with CCC. This finding extends previous meta-analyses [25, 37] by demonstrating histotype-specific differences in early-stage disease. The limited utility of traditional biomarkers, together with the prognostic strength of NLR, suggests that risk stratification in early-stage CCC should evolve. Given that early-stage CCC exhibits distinctive immunologic features, including overexpression of immune checkpoint molecules [38], NLR likely reflects underlying immune dysregulation. The high recurrence rate in early-stage CCC patients with elevated NLR, despite standard adjuvant chemotherapy, indicates this subgroup requires alternative approaches. Emerging evidence - including multiple meta-analyses - shows that elevated pretreatment NLR is consistently associated with shorter survival in patients receiving immune checkpoint inhibitors [39, 40]. In view of the frequent ARID1A mutations (approximately 50%) in CCC and their influence on the tumor immune microenvironment [41, 42], together with reports that advanced CCC can respond to immune checkpoint inhibitors [43], pre-treatment NLR could serve as a stratification variable for selecting early-stage CCC patients for adjuvant immunotherapy trials.

Limitation

This retrospective, single-center study has several inherent limitations. Various factors including infection, inflammation, underlying diseases, and lifestyle habits may affect blood cell counts and cannot be fully excluded. NLR data were missing for 30% of patients owing to variations in clinical practice, and missingness was more common among patients who did not receive chemotherapy (P=0.020); however, separate multivariable analyses confirmed that NLR's remained independently prognostic, and this real-world pattern of missingness may enhance generalizability to routine practice. As a single-institution study, external validity may be limited for populations with different genetic backgrounds or treatment protocols. Additionally, we lacked molecular profiling (e.g., ARID1A mutations) that might clarify relationships between genetic alterations and NLR in CCC, and we did not compare NLR with other inflammatory indices such as the platelet-to-lymphocyte ratio (PLR) or lymphocyte-to-monocyte ratio (LMR), which could provide complementary information. The small number of stage II patients also limited subgroup analyses. Future prospective multi-center studies incorporating molecular profiling and comprehensive inflammatory marker panels are needed to validate our findings and establish optimal clinical cutoff values.

Conclusion

This multi-histological study of 217 Asian patients reveals three key findings in early-stage ovarian cancer management. First, traditional biomarkers CA-125 and platelet counts showed limited prognostic utility in early-stage disease. Second, NLR demonstrates histotype-specific prognostic value - superior in CCC but ineffective in EMC - reflecting distinct immunological landscapes between subtypes. Third, elevated pretreatment NLR identified a high-risk subset of early-stage CCC despite standard adjuvant chemotherapy, suggesting the need to explore alternative strategies. Collectively, these findings establish NLR as a promising biomarker for personalized treatment approaches and support investigating immunotherapy in early-stage CCC. Prospective validation of NLR-guided treatment algorithms is warranted to transform management of this treatment-resistant subtype.

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Disclosure of conflict of interest

None.

Address correspondence to: Chen-Hsuan Wu, Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan. Tel: +886-9-75056430; Fax: +886-7-732-2915; E-mail: chenhsuan5@gmail.com; Chan-Chao Changchien, Kaohsiung Municipal Feng Shan Hospital - Under The Management of Chang Gung Medical Foundation, No. 42, 42-1, Ching-Wu Road, Feng-Shan District, Kaohsiung 830025, Taiwan. Tel: +886-9-75056430; Fax: +886-7-7322915; E-mail: chanchao@cgmh.org.tw

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Supplementary Table 1. Comparison between baseline characteristics between patients with available NLR data (N=150) and those with missing NLR data (N=67)

Pre-treatment N/L ratio data	Missing n=67	Available n=150	*p* value
Age, years mean (SD)	47.0 (13.0)	49.7 (11.7)	0.131
Stage, %			0.052
IA/IB	35 (52.2)	54 (36.0)	
IC	20 (29.9)	69 (46.0)	
II	12 (17.9)	27 (18.0)	
Histology, %			0.446
HGSC	8 (11.9)	13 (8.7)	
Clear cell carcinoma	17 (25.4)	44 (29.3)	
Endometrioid cancer	27 (40.3)	48 (32.0)	
Others	15 (22.4)	45 (30.0)	
Pre-Platelet*, 10^4/uL mean (SD)	30.0 (7.6)	30.3 (10.8)	0.801
Pre-CA-125**, U/ml mean (SD)	527.1 (1106.9)	619.0 (1970.2)	0.760
C/T, %			
Yes	35 (52.2)	103 (68.7)	
No	32 (47.8)	47 (31.3)	0.020

*total N=145, **total N=136.

Supplementary Table 2. Multivariate Cox regression analyses of factors associated with progression-free survival (PFS) and overall survival (OS) in NLR missing patients (N=67)

Variable	Comparison	PFS			OS		
		HR	95% CI	*P* value	HR	95% CI	*P* value
FIGO	I	1	1.36-22.4	0.017	1	0.40-10.67	0.386
	II	5.53			2.07		
Histology	Non-CCC	1	0.42-7.52	0.431	1	0.19-4.67	0.950
	CCC	1.78			0.95		
	Non-EMC	1	0.16-3.76	0.761	1	0.03-2.43	0.236
	EMC	0.78			0.26		
Chemotherapy	No	1	0.13-3.07	0.578	1	0.21-8.95	0.738
	Yes	0.64			1.38		

Supplementary Table 3. Difference between before and after chemotherapy in NLR

Variable	Pre	Post	Difference	*P* value
NLR	4.0±3.5	2.4±2.6	1.6±4.2	<0.001

Supplementary Table 4. Multivariate Cox regression analyses of factors associated with progression-free survival (PFS) and overall survival (OS) in patients with available post-chemotherapy NLR data (N=131)

Variable	Comparison	PFS			OS		
		HR	95% CI	*P* value	HR	95% CI	*P* value
FIGO	I	1	1.28-7.35	0.012	1	0.97-9.11	0.056
	II	3.06			2.98		
Histology	Non-CCC	1	0.67-4.65	0.251	1	0.55-5.70	0.335
	CCC	1.76			1.78		
	Non-EMC	1	0.13-1.96	0.316	1	0.03-2.18	0.210
	EMC	0.50			0.25		
NLR*	<1.68	1	0.78-4.87	0.154	1	0.40-3.51	0.754
	≥1.68	1.95			1.19		

*The cut-off value of post-chemotherapy NLR calculated by ROC curve is 1.68.