Received: 15 January 2023 | Revised: 2 July 2023 | Accepted: 10 July 2023

DOI: 10.1002/ijgo.15014

CLINICAL ARTICLE

Gynecology

Searching for prognostic markers for Stage I epithelial ovarian cancer: A role for systemic inflammatory markers

Fulvio Borella[1] | Luca Bertero[2] | Giorgio Valabrega[3,4] | Stefano Fucina[1] | Paola Cassoni[2] | Chiara Benedetto[1]

[1]Gynecology and Obstetrics Unit 1, Department of Surgical Sciences, City of Health and Science University Hospital, University of Turin, Turin, Italy

[2]Pathology Unit, Department of Medical Sciences, University of Turin and City of Health and Science University Hospital, Turin, Italy

[3]Department of Oncology, University of Turin, Turin, Italy

[4]Struttura Complessa a Direzione Universitaria Oncologia, Azienda Ospedaliera Ordine Mauriziano-Ospedale Umberto I, University of Turin, Turin, Italy

Correspondence
Fulvio Borella, Division of Gynecology and Obstetrics 1, Department of Surgical Sciences, City of Health and Science University Hospital, University of Turin, 10126 Turin, Italy.
Email: fulvio.borella@unito.it

Abstract

Objective: To determine the prognostic role of systemic inflammatory markers for Stage I epithelial ovarian cancer (EOC).

Materials and Methods: We performed a retrospective, single-center, observational study. We included patients with Stage I EOC cancer undergoing primary surgery between 1993 and 2016. Inflammatory markers were assessed by analyzing blood samples collected at initial diagnosis before EOC surgery. We evaluated these markers' association with disease-free survival (DFS) and cancer-specific survival (CSS).

Results: We included 176 women in our study. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) were related to both DFS and CSS in the univariate analysis. In the multivariate Cox analysis, adjuvant chemotherapy (hazard ratio [HR] 0.17, 95% confidence interval [CI] 0.04–0.71, $P=0.02$) and SII ≥730 (HR 6.84, 95% CI 1.30–35.9, $P=0.023$) were independent predictors of DFS, while FIGO Stage IB–IC (HR 7.91, 95% CI 1.04–59.8, $P=0.04$), NLR ≥3 (HR 56.8, 95% CI 7.46–433, $P<0.001$) and PLR ≥169 (HR 49.1 95% CI 11.1–217.8, $P=0.005$) were independent predictors of CSS.

Conclusions: Systemic inflammatory markers are easily obtainable from patients' routine blood analyses and may represent inexpensive and reproducible prognostic markers in early-stage EOC.

KEYWORDS
early stage, neutrophil-to-lymphocyte ratio, ovarian cancer, platelet-to-lymphocyte ratio, prognosis, stage I epithelial ovarian cancer, systemic inflammatory index

1 | INTRODUCTION

Epithelial ovarian cancer (EOC) represents the most lethal gynecologic cancer. Over 70% are diagnosed at an advanced stage (FIGO [International Federation of Gynecology and Obstetrics] Stage III–IV) and, despite the promising results of new targeted therapies (e.g., inhibitors of the enzyme poly-ADP ribose polymerase—PARPi), the overall survival (OS) remains low.[1] However, about 30% of patients are diagnosed with early-stage EOC (FIGO Stage I–II) with a risk of relapse ranging between 10% and 50% and a 5-year OS greater than 70% in most studies.[2,3]

The standard treatment for FIGO Stage I EOC is total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and aortic lymph node dissection, omentectomy, peritoneal biopsies, and

washing.[4] For adjuvant treatment, platinum-based chemotherapy improves both recurrence-free survival and OS and it is usually recommended, especially in high-risk patients (Stage IA grade 3, IB or IC grade 2 or 3, clear cell histology);[2] however, a Cochrane systematic review found that the survival benefits in women with high-risk tumors are based on low-quality evidence and there is still uncertainty for lower/intermediate-risk early-stage disease.[5] Several efforts have been made to stratify patients based on different prognostic factors to achieve more personalized risk estimations.[3,6,7] Stage I EOC is characterized by subtype-specific molecular alterations that affect tumor aggressiveness,[8–10] so tumor molecular profiling is an option, but there is also a need for inexpensive, easy, and reproducible markers to help predict the long-term behavior of these tumors. In recent years, the prognostic role of several inflammatory markers from the patient's blood count before starting treatment has been evaluated in different cancers, including EOC.[11] However, the prognostic role of systemic inflammatory markers has not been clarified in the specific subgroup of Stage I EOC. Based on this background, this study aims to evaluate the potential prognostic role of systemic inflammatory markers for Stage I EOC.

2 | MATERIALS AND METHODS

We performed a retrospective study of all patients surgically treated for FIGO Stage I EOC at the Department of Surgical Sciences, S. Anna Hospital, University of Turin, from January 1993 to December 2016.

We excluded patients with borderline tumors, non-epithelial ovarian cancer, age younger than 18 years, and incomplete clinical data and/or follow up. We also excluded patients with concurrent infection, immunosuppressive therapy, or hematologic disorders at the time of the surgery.

For the selected patients, we collected the following clinical and histopathologic data: (1) age at diagnosis; (2) histopathologic features of ovarian cancer including tumor histotype, grade, and FIGO Stage; (3) type of surgical treatment, (4) preoperative total count of neutrophil, lymphocyte, platelets, and CA125 U/mL, and (5) date of death or last follow up.

All patients had preoperative complete physical and gynecologic examinations, gynecologic ultrasound examination, chest X-ray, computed tomography scan, and routine blood and urine analysis.

Surgical treatment consisted of total hysterectomy with bilateral salpingo-oophorectomy, careful abdominal and pelvic palpation and exploration, random peritoneal sampling biopsies, omentectomy, and peritoneal washing. Para-aortic and pelvic lymph node dissection were performed according to the patient and tumor characteristics. Preservation of the uterus and of one ovary was performed in young patients who wanted to preserve fertility. Adjuvant treatment was platinum-based chemotherapy according to the tumor and patient's clinical characteristics.

All cases were revised by a dedicated pathologist (LB) according to the WHO[12] Classification of Tumors of Female Reproductive Organs, while the stage of the disease was determined with the FIGO staging system.[13]

We calculated inflammatory markers as follows: neutrophil-to-lymphocyte ratio (NLR) by dividing the absolute neutrophil count by the absolute lymphocyte count, platelet-to-lymphocyte ratio (PLR) by dividing absolute platelet count by absolute lymphocyte count, and systemic immune inflammation index (SII) was estimated as (platelet count × neutrophil count)/ lymphocyte count.

We chose the following cut-off values for serum biomarkers based on the literature data: NLR: 3,[14,15] PLR: 169,[15] SII: 730,[14,15] and CA125: 30 U/mL.[16]

The study was submitted to and approved by the Ethics Institutional Review Board for "Biobanking and use of human tissues for experimental studies" of the Department of Medical Sciences of the University of Turin, protocol n. DSM-ChBU no. 6/2020.

Due to the retrospective nature of this study, no written informed consent from the patients was necessary, as stated by our Ethics Institutional Review Board. All the cases were recorded in a dedicated database and pseudonymized.

Time for OS was stopped at the time of death or the last follow up with a cut-off date in December 2021. We obtained disease status or cause of death from clinical charts and/or cancer registry data of our region (Piedmont Cancer Registry, Centre for Epidemiology and Prevention in Oncology in Piedmont). For cancer-specific survival (CSS), we counted only cancer-associated deaths, whereas other deaths unrelated to Stage I EOC were noted. Disease-free survival (DFS) was defined as the time interval from the date of the Stage I EOC diagnosis to the date of first recurrence or last follow up.

Statistical analyses were performed using IBM SPSS version 25 (IBM, Armonk, NY, USA) software. Continuous variables were reported as mean and range, and categorical variables as frequency and percentage. Differences among different survival groups were tested using Pearson's χ^2 test or Fisher exact test, as appropriate. For the variable "age", the Shapiro–Wilk test was used to test the normality of distribution, and the Mann–Whitney *U* test was used for the comparison. Survival outcomes (CSS and DFS) were analyzed by the Kaplan Meier method and by univariate and Cox proportional hazards models. Significant variables (*P* values less than 0.05) were included in the multivariate analysis. Analyses were conducted with a 95% confidence interval (CI), and a two-sided *P* value of 0.05 was considered statistically significant.

3 | RESULTS

One hundred and seventy-six women treated for apparent Stage I EOC in our center met the inclusion criteria. The mean age of the whole cohort was 57 years (20–85 years). Most of the patients had an FIGO Stage IC EOC ($n = 99$, 56%).

The most common histotypes were endometrioid ($n = 59$, 33.5%) and mucinous ($n = 43$, 24%), and most cases a histologic grade 1 ($n = 72$, 41%).

Abdominal laparotomy was performed in 150 women (85%), whereas laparoscopic surgery was used in 26 women (15%).

Forty-five patients (25%) had a fertility-sparing procedure, and lymphadenectomy was performed in 110 patients (63%). Adjuvant chemotherapy was administered in 77 patients (43%).

The values of the analyzed serum biomarkers were elevated, according to the chosen cut-offs, as follows: CA125 > 30 in 122 (69%) women, NLR ≥3 in 52 (30%) women, PLR ≥169 in 32 (18%) women, and SII ≥730, in 53 (30%) women.

The median follow-up duration was 126 months (6–289 months). Disease recurrence occurred in 22 patients (12.5%), and the median time of recurrence was 54 months (8–63 months).

TABLE 1 Distribution of the clinical and pathologic features according to recurrence and cancer-specific death.

Clinical characteristics	Total (*N* = 176)	No recurrence (*N* = 154)	Recurrence (*N* = 22)	*P* value	Alive (*N* = 159)	DOD (*N* = 17)	*P* value
Age, year[a]	57 (20–85)	58 (24–85)	64 (20–77)	0.34	57 (24–85)	58 (20–77)	0.58
FIGO stage							
IA	67 (38%)	65 (97%)	2 (3%)	0.011	66 (99%)	1 (1%)	0.013
IB	10 (6%)	8 (80%)	2 (20%)		8 (80%)	2 (20%)	
IC	99 (56%)	81 (82%)	18 (18%)		85 (86%)	14 (14%)	
Histology							
LG-S	22 (13%)	21 (96%)	1 (4%)	0.097	21 (93%)	1 (7%)	0.37
HG-S	25 (14%)	18 (72%)	7 (28%)		20 (80%)	5 (20%)	
Endometrioid	59 (34%)	51 (86%)	8 (14%)		53 (90%)	6 (10%)	
Clear cell	27 (15%)	25 (93%)	2 (7%)		25 (93%)	2 (7%)	
Mucinous	43 (24%)	39 (91%)	4 (9%)		40 (93%)	3 (7%)	
Grade							
1	72 (41%)	69 (96%)	3 (4%)	0.013	69 (96%)	3 (4%)	0.08
2	47 (27%)	40 (85%)	7 (15%)		42 (89%)	5 (11%)	
3	57 (32%)	45 (79%)	12 (21%)		48 (84%)	9 (16%)	
Surgical procedure							
Hysterectomy + BSO	131 (75%)	115 (88%)	16 (12%)	0.844	118 (90%)	13 (10%)	0.839
Fertility sparing surgery	45 (25%)	39 (87%)	6 (13%)		41 (91%)	4 (9%)	
Surgical approach							
Laparotomy	150 (85%)	134 (89%)	16 (11%)	0.08	134 (89%)	16 (11%)	0.47
Laparoscopy	26 (15%)	20 (77%)	6 (23%)		25 (96%)	1 (4%)	
Pelvic bilateral lymphadenectomy							
Yes	110 (63%)	93 (84%)	17 (16%)	0.126	96 (87%)	14 (13%)	0.112
No	66 (37%)	61 (92%)	5 (8%)		63 (95%)	3 (5%)	
Chemotherapy							
Yes	77 (43%)	75 (97%)	2 (3%)	<0.001	75 (97%)	2 (3%)	0.005
No	99 (57%)	79 (80%)	20 (20%)		84 (85%)	15 (15%)	
CA125							
≤30	54 (31%)	53 (98%)	1 (2%)	0.003	54 (100%)	0 (0%)	0.002
>30	122 (69%)	101 (82%)	21 (18%)		105 (86%)	17 (14%)	
NLR							
<3	124 (70%)	121 (98%)	3 (2%)	<0.001	123 (99%)	1 (1%)	<0.001
≥3	52 (30%)	33 (64%)	19 (36%)		36 (69%)	16 (31%)	
PLR							
<169	144 (82%)	138 (96%)	6 (4%)	<0.001	142 (99%)	2 (1%)	<0.001
≥169	32 (18%)	16 (50%)	16 (50%)		17 (53%)	15 (47%)	
SII				<0.001			<0.001
<730	123 (70%)	120 (98%)	3 (2%)		123 (100%)	0 (0%)	
≥730	53 (30%)	34 (64%)	19 (36%)		36 (68%)	17 (32%)	

Abbreviations: BSO, bilateral salpingo-oophorectomy; DOD, dead of disease; FIGO, International Federation of Gynecology & Obstetrics; HG-S, high-grade serous; LG-S, low-grade serous; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

[a]Data are presented as median (range) or as number (percentage).

The OS was 68%, but only 17 patients died of disease (CSS 90.4%).

Table 1 shows the characteristics of the whole cohort and the comparisons between patients who experienced recurrence and those who remained disease-free and between patients who died of disease and patients who did not.

The following variables had a significantly different distribution according to recurrence and CSS: FIGO Stage, tumor grade

TABLE 2 Univariate analysis of variables associated with DFS and CSS.

	DFS			CSS		
Variable related to survival	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.021	0.987–1.056	0.238	1.015	0.977–1.055	0.44
FIGO stage						
IA	1			1		
IB	7.44	1.05–52.9	0.045	15.03	1.36–166	0.027
IC	6.51	1.51–28.1	0.012	10.1	1.33–77.1	0.025
Histology						
LG-S	1			1		
HG-S	2.96	1.21–5.99	0.015	1.455	0.29–7.22	0.64
Endometroid	1.31	0.61–2.85	0.49	2.85	0.55–14.7	0.21
Clear cell	0.58	0.20–2.29	0.54	0.66	0.06–7.12	0.72
Mucinous	0.44	0.09–2.25	0.33	1.01	0.17–6.08	0.99
Grade						
1	1			1		
2	3.59	0.92–13.9	0.06	2.59	0.62–10.8	0.19
3	5.08	1.43–18.01	0.012	3.80	1.02–14.0	0.045
Surgical procedure						
Hysterectomy + BSO	1					
Fertility sparing surgery	1.23	0.48–3.14	0.67	1.23	0.48–3.14	0.67
Surgical approach						
Laparotomy	1			1		
Laparoscopy	0.30	0.04–2.25	0.24	0.40	0.53–30.3	0.38
Pelvic bilateral lymphadenectomy						
No	1				1	
Yes	0.51	0.19–1.59	0.19	0.38	0.11–1.30	0.12
Chemotherapy						
No	1			1		
Yes	0.12	0.03–0.55	0.006	0.17	0.04–0.74	0.018
CA125						
<30	1			1		
≥30	10.01	1.35–74.6	0.001	37.5	0.52–2668	0.096
NLR						
<3	1			1		
≥3	22.1	6.46–75.5	<0.001	56.8	7.46–433	<0.001
PLR						
<169	1			1	1	
≥169	16.5	6.40–42.8	<0.001	49.1	11.1–217.8	<0.001
SII						
<730	1			1		
≥730	23.1	6.57–80.8	<0.001	576	1.9–1707	0.03

Abbreviations: BSO, bilateral salpingo-oophorectomy; CI, confidence interval; CSS, cancer-specific survival; DFS, disease-free survival; FIGO, International Federation of Gynecology & Obstetrics; HG-S, high-grade serous; HR, hazard ratio; LG-S, low-grade serous; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

(only for recurrence), adjuvant chemotherapy, CA125, NLR, PLR, and SII.

Table 2 shows the univariate Cox regression model comparing the DFS and CSS for each analyzed prognostic variable: FIGO Stages IB and IC, high-grade serous histology, tumor grade 3, adjuvant chemotherapy, CA125, NLR, PLR, and SII were associated with DFS. All variables associated with DFS, except for high-grade serous histology, also correlated with CSS.

The prognostic role of NLR, PLR, and SII was confirmed by Kaplan–Meier curves for DFS (Figure 1) and CSS (Figure 2).

By multivariate Cox analysis, adjuvant chemotherapy (hazard ratio [HR] 0.17, 95% confidence interval [CI] 0.04–0.71, $P=0.02$) and SII ≥730 (HR 6.84, 95% CI 1.30–35.9, $P=0.023$) were independent predictors of DFS, whereas FIGO Stage IB–IC (HR 7.91, 95% CI 1.04–59.8, $P=0.04$), NLR ≥730 (HR 56.8, 95% CI 7.46–433, $P<0.001$), and PLR ≥169 (HR 49.1 95% CI 11.1–217.8, $P=0.005$) were independent predictors of CSS (Table 3).

4 | DISCUSSION

The aim of this study was to search for risk factors that affect recurrence and CSS in a large number of consecutive patients with Stage I EOC who received surgical treatment in a referral center. The main finding of our study was that serum biomarkers such as NLR, PLR, and SII are associated with survival outcomes in this setting. It is known that immune system cells can affect all stages of tumor development by releasing pro inflammatory cytokines.[17] In particular, neutrophils may promote genomic instability by releasing reactive oxygen species and favor extracellular matrix remodeling and cancer cell invasion by the production of proteases, growth factors, and oncostatins.[18] Moreover, neutrophils may stimulate tumor angiogenesis and suppress anti-tumor adaptive immunity.[18] Similarly, platelets may support cancer progression in different ways: secreting pro-inflammatory factors (CXCL1, CXCL4, CXCL5, CXCL7, CXCL12, and interleukin-8), contributing to thrombosis and vascular inflammation, and promoting the recruitment of neutrophils and monocytes.[19] On the other hand, tumor-infiltrating T lymphocytes may have antitumor activities in immunogenic tumors, including EOC.[20] Because of the role of inflammatory cells in cancer development, the prognostic significance of these biomarkers has also been evaluated in EOC. Nie et al.[21] investigated the role of several prognostic factors related to progression-free survival (PFS) and OS in a retrospective cohort of 553 EOC patients and found that preoperative high-values of NLR and SII were independent factors related to poor survival in both groups, whereas PLR did not show

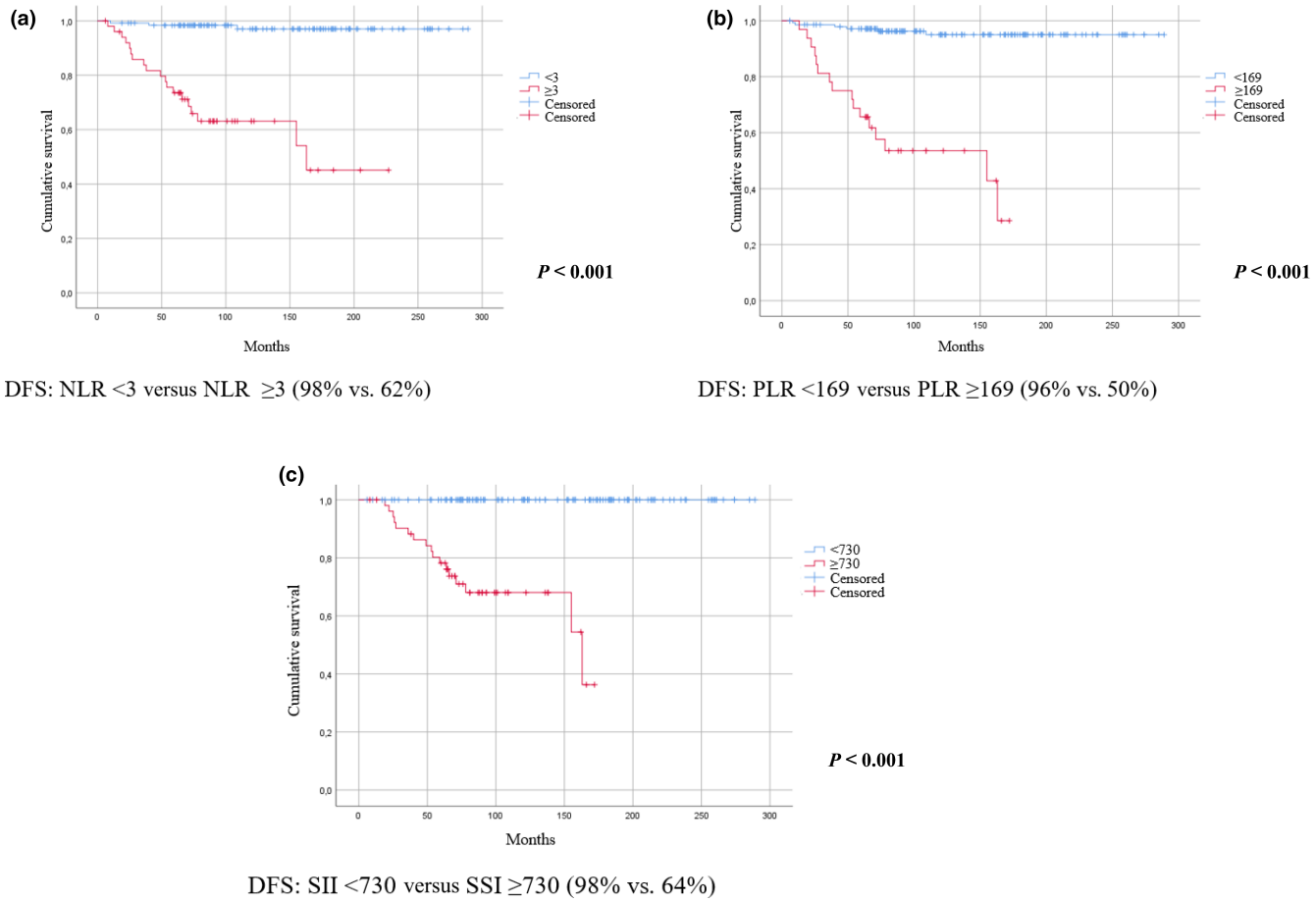

FIGURE 1 Kaplan–Meier curves for DFS according to (a) NLR, (b) PLR, and (c) SSI. DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

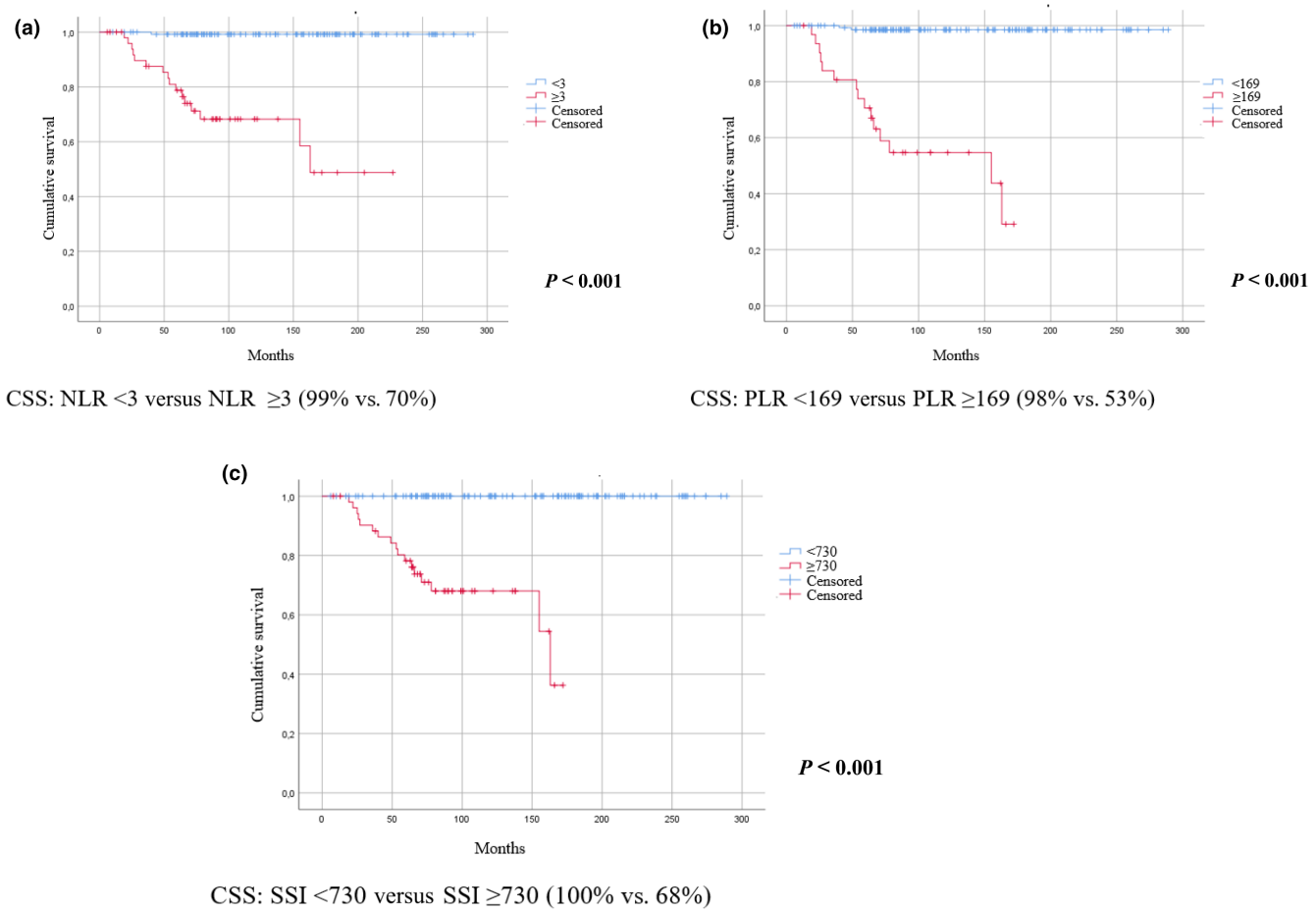

FIGURE 2 Kaplan–Meier curves for CSS according to (a) NLR, (b) PLR, and (c) SSI. CSS, cancer-specific survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

prognostic value. Also, a multicenter, retrospective analysis by the MITO Group on 375 patients with FIGO Stage III–IV EOC showed a correlation between low inflammatory markers (NLR, PLR, SII) and better survival. Moreover, the authors observed that NLR could be a predictive factor of bevacizumab efficacy and bevacizumab seems to be detrimental in patients with a high SII.[14] The same study group also showed that NLR ≥3 and SII ≥730 are significantly associated with worse OS in platinum-sensitive EOC.[15] A high NLR value was related to worse survival in another retrospective analysis on 397 EOC regardless of BRCA-mutation status.[22] More recently, the role of preoperative systemic inflammatory markers was investigated in early-stage EOC. In a study including 359 patients (248 Stage I, 69%; 81 Stage II, 22.5%, 30 Stage IIIA1, 8.5%) an NLR ≥3 and an SII ≥1000 were associated with worse 3-year DFS, and an SII ≥1000 was associated with worse 3-year OS.[23] The unfavorable prognostic role in terms of PFS and OS for NLR and PLR has also been confirmed in a meta-analysis including 2919 patients with EOC.[11]

Our results agree with previous studies suggesting a significant prognostic role for neutrophils, lymphocytes, and platelet counts also for Stage I EOC: at multivariate analysis, SII was found to be associated with shorter PFS, while NLR and PLR were associated with CSS. Moreover, our study is the first to evaluate the association between systemic inflammatory markers and CSS instead of OS. CSS was analyzed because we considered it a more accurate outcome for evaluating a potential prognostic variable as it removes competing causes of death[24] and this is especially important considering the long median follow up of our study and the low mortality of Stage I EOC. Therefore, analysis of OS in this specific setting could be affected by significant biases preventing a correct assessment of the analyzed prognostic factors.

Systemic inflammatory markers may change in the presence of infections, hematologic disorders, or some immunosuppressive or immunomodulatory drugs, so they may not be reliable in these situations. Regarding other gynecologic inflammatory conditions such as endometriosis, one study measured the NLR in these patients and found it higher than in controls, but the patients were younger (mean age 33 years) and the NLR values were lower than in our study (mean 2.66, range 2.43–2.89), so this condition should not affect the prognostic role of these biomarkers in EOC.[25]

The main limitation of this study is related to its retrospective design and to the potential differences in terms of patient management over the years due to the time range used to collect the study cohort.

TABLE 3 Multivariate analysis of variables associated with DFS and CSS.

	DFS			CSS		
Variable related to survival	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
FIGO stage						
IA	NS			1		
IB–IC				7.91	1.04–59.8	0.04
Histology						
Other histotypes	NS			NS		
HG-S						
Grade						
1–2	NS			NS		
3						
Chemotherapy						
No	1			NS		
Yes	0.17	0.04–0.71	0.02			
CA125						
<35	NS			Not included		
≥35						
NLR						
<3	NS			1		
≥3				56.8	7.46–433	<0.001
PLR						
<169	NS			1		
≥169				49.1	11.1–217.8	0.005
SII						
<730	1			NS		
≥730	6.84	1.30–35.9	0.023			

Abbreviations: CI, confidence interval; CSS, cancer-specific survival; DFS, disease-free survival; HG-S, high grade serous; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; NS, not significant; PLR, platelet-lymphocyte ratio; SII, systemic inflammatory index.

The main strength of this study is that, as far as we know, this is the first study that evaluates the prognostic role of inflammatory markers in Stage I EOC.

Overall, Stage I EOC is characterized by a relatively good prognosis, but as a subset of patients shows an unfavorable outcome, there is a strong need to define novel and effective prognostic markers to promptly identify them and tailor their adjuvant treatments. Recently, a prognostic score based on the genome distribution of somatic copy number variations in a retrospective cohort of Stage I EOC was proposed;[9] however, systemic inflammatory indices are easily obtainable from patients' routine blood samples and may represent an inexpensive and reproducible marker for prognostic stratification and treatment tailoring. For example, systemic inflammatory indices could help to identify patients who are more likely to benefit from adjuvant chemotherapy or targeted therapies, such as bevacizumab or PARPi, also for high-risk Stage I EOC. Moreover, systemic inflammatory indices could be used to monitor the response to treatment and the risk of recurrence, as well as to guide the frequency and duration of follow up. Systemic inflammatory markers should be interpreted with caution in the presence of concurrent events that can alter the immune response, as they could lead to false results and hence invalidate their prognostic value. Even though increasing evidence is emerging on the prognostic role of these biomarkers in EOC, their validation in large prospective studies is needed for their implementation into clinical practice. These studies should also define the optimal cut-off values and time points for measuring these biomarkers, as well as their interaction with other prognostic factors.

AUTHOR CONTRIBUTIONS

Fulvio Borella, Luca Bertero, and Giorgio Valabrega conceived and designed the study; Fulvio Borella and Luca Bertero wrote the original draft and performed the statistical analyses; Luca Bertero revised the pathologic slides; Stefano Fucina collected the data; Paola Cassoni and Chiara Benedetto performed the project administration and supervision; writing—review and editing were performed by Fulvio Borella, Luca Bertero, Giorgio Valabrega, and Paola Cassoni. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Fulvio Borella https://orcid.org/0000-0001-8398-7557

REFERENCES

1. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. *Lancet*. 2019;393(10177):1240-1253.
2. Collinson F, Qian W, Fossati R, et al. Optimal treatment of early-stage ovarian cancer. *Ann Oncol*. 2014;25(6):1165-1171.
3. Wei W, Li N, Sun Y, Li B, Xu L, Wu L. Clinical outcome and prognostic factors of patients with early-stage epithelial ovarian cancer. *Oncotarget*. 2017;8:23862-23870.
4. Garcia-Soto AE, Boren T, Wingo SN, Heffernen T, Miller DS. Is comprehensive surgical staging needed for thorough evaluation of early-stage ovarian carcinoma? *Am J Obstet Gynecol*. 2012;206(3):242.e1-242.e5.
5. Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2015;2015(12):CD004706.
6. Leskela S, Romero I, Cristobal E, et al. The frequency and prognostic significance of the histologic type in early-stage ovarian carcinoma: a reclassification study by the Spanish Group for Ovarian Cancer Research (GEICO). *Am J Surg Pathol*. 2020;44(2):149-161.
7. Ditto A, Leone Roberti Maggiore U, Bogani G, et al. Predictive factors of recurrence in patients with early-stage epithelial ovarian cancer. *Int J Gynaecol Obstet*. 2019;145(1):28-33.
8. Calura E, Ciciani M, Sambugaro A, et al. Transcriptional characterization of stage I epithelial ovarian cancer: a multicentric study. *Cell*. 2019;8(12):1554.
9. Pesenti C, Beltrame L, Velle A, et al. Copy number alterations in stage I epithelial ovarian cancer highlight three genomic patterns associated with prognosis. *Eur J Cancer*. 2022;171:85-95.
10. Velle A, Pesenti C, Grassi T, et al. A comprehensive investigation of histotype-specific microRNA and their variants in stage I epithelial ovarian cancers. *Int J Cancer*. 2023;152(9):1989-2001.
11. Zhu Y, Zhou S, Liu Y, Zhai L, Sun X. Prognostic value of systemic inflammatory markers in ovarian cancer: a PRISMA-compliant meta-analysis and systematic review. *BMC Cancer*. 2018;18(1):443.
12. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. *WHO Classification of Tumours of Female Reproductive Organs*. International Agency for Research on Cancer; 2014.
13. Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2014;124(1):1-5.
14. Farolfi A, Petrone M, Scarpi E, et al. Inflammatory indexes as prognostic and predictive factors in ovarian cancer treated with chemotherapy alone or together with bevacizumab. A multicenter, retrospective analysis by the MITO group (MITO 24). *Target Oncol*. 2018;4:469-479.
15. Farolfi A, Scarpi E, Greco F, et al. Inflammatory indexes as predictive factors for platinum sensitivity and as prognostic factors in recurrent epithelial ovarian cancer patients: a MITO24 retrospective study. *Sci Rep*. 2020;10(1):18190.
16. Obermair A, Fuller A, Lopez-Varela E, et al. A new prognostic model for FIGO stage 1 epithelial ovarian cancer. *Gynecol Oncol*. 2007;104(3):607-611.
17. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity*. 2019;51(1):27-41.
18. Galdiero MR, Varricchi G, Loffredo S, Mantovani A, Marone G. Roles of neutrophils in cancer growth and progression. *J Leukoc Biol*. 2018;103(3):457-464.
19. Palacios-Acedo AL, Mège D, Crescence L, Dignat-George F, Dubois C, Panicot-Dubois L. Platelets, thrombo-inflammation, and cancer: collaborating with the enemy. *Front Immunol*. 2019;10:1805.
20. Li J, Wang J, Chen R, Bai Y, Lu X. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. *Oncotarget*. 2017;8(9):15621-15631.
21. Nie D, Gong H, Mao X, Li Z. Systemic immune-inflammation index predicts prognosis in patients with epithelial ovarian cancer: a retrospective study. *Gynecol Oncol*. 2019;152(2):259-264.
22. Marchetti C, D'Indinosante M, Bottoni C, et al. NLR and BRCA mutational status in patients with high grade serous advanced ovarian cancer. *Sci Rep*. 2021;11(1):11125.
23. Bizzarri N, D'Indinosante M, Marchetti C, et al. The prognostic role of systemic inflammatory markers in apparent early-stage ovarian cancer. *Int J Clin Oncol*. 2023;28(2):314-320.
24. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst*. 2010;102(20):1584-1598.
25. Cho S, Cho H, Nam A, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. *Fertil Steril*. 2008;90(6):2073-2079.

How to cite this article: Borella F, Bertero L, Valabrega G, Fucina S, Cassoni P, Benedetto C. Searching for prognostic markers for Stage I epithelial ovarian cancer: A role for systemic inflammatory markers. *Int J Gynecol Obstet*. 2023;00:1-8. doi:10.1002/ijgo.15014