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Systemic Immune-Inflammation Index Predicts Outcomes in Platinum-Resistant Relapsed Ovarian Cancer

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Abstract

We explored the prognostic impact of simple indices that reflect the immunological milieu (neutrophils to lymphocyte ratio [NLR] and systemic immune-inflammation [SII]) in 49 platinum-resistant relapsed ovarian cancer patients. The median progression-free survival (PFS) and overall survival (OS) were 4 and 8 months, respectively. Patients with a lower NLR ($\leq$2.89) had a better PFS (5 vs. 2 months [$p = 0.02$]) and OS (9 vs. 5 months [$p = 0.20$]). Factors associated with a worse PFS were NLR > 2.8 (hazard ratio [HR] =2.32, $p = 0.02$) and SII > 639 (HR =3.70, $p = 0.002$). SII > 639 independently predicted PFS (HR =4.13, $p = 0.03$). Future studies should study the validity of inflammatory markers and could consider incorporating it as a biomarker in clinical trials.

Keywords

- platinum-resistant ovarian cancer
- treatment
- outcomes
- systemic immune-inflammation index
- neutrophil to lymphocyte ratio

Majority (70–80%) of the epithelial ovarian cancers (EOC) recur with current therapy.[1] Patients who progress within 6 months of platinum-based chemotherapy are considered as having platinum-resistant ovarian cancer (PROC) disease and have a very poor prognosis. The median progression-free survival (PFS) in PROC is 3 to 4 months, and the median overall survival (OS) is 1 year.[2] Other than "platinum-refractory disease" (progression during or within 4 weeks of platinum-based therapy [median OS: 3–5 months]), few factors have been consistently associated with prognosis in PROC. We explored the prognostic impact of simple indices that reflect the immunological milieu (neutrophils to lymphocyte ratio [NLR] and systemic immune-inflammation [SII]) in patients with PROC. Inflammatory indices are prognostic in ovarian cancer (newly diagnosed and platinum-sensitive recurrence), but there are no reports in patients with PROC.[3,4] After obtaining approval from the Institutional Ethics Committee (EC Approval No: JIP/IEC/2019/558), data of patients diagnosed with PROC between January 1, 2015 and December 31, 2019 was collected. The diagnosis of relapse could be based on the elevation of CA-125 or symptoms/imaging findings. PFS was defined from the start of treatment of PROC until progression or death due to any cause. SII (platelet count $\times$ neutrophil count)/lymphocyte count and NLR (absolute neutrophil count/absolute lymphocyte count) were calculated. Their median values were used to divide patients into high and low categories.

Forty-nine patients who had started treatment for PROC ($n = 21$ with "refractory" disease) were included in this analysis (►**Fig. 1**). The median interval between the last platinum treatment to relapse was 3.2 (2.1–4.6) months. All had undergone surgery during initial treatment, either

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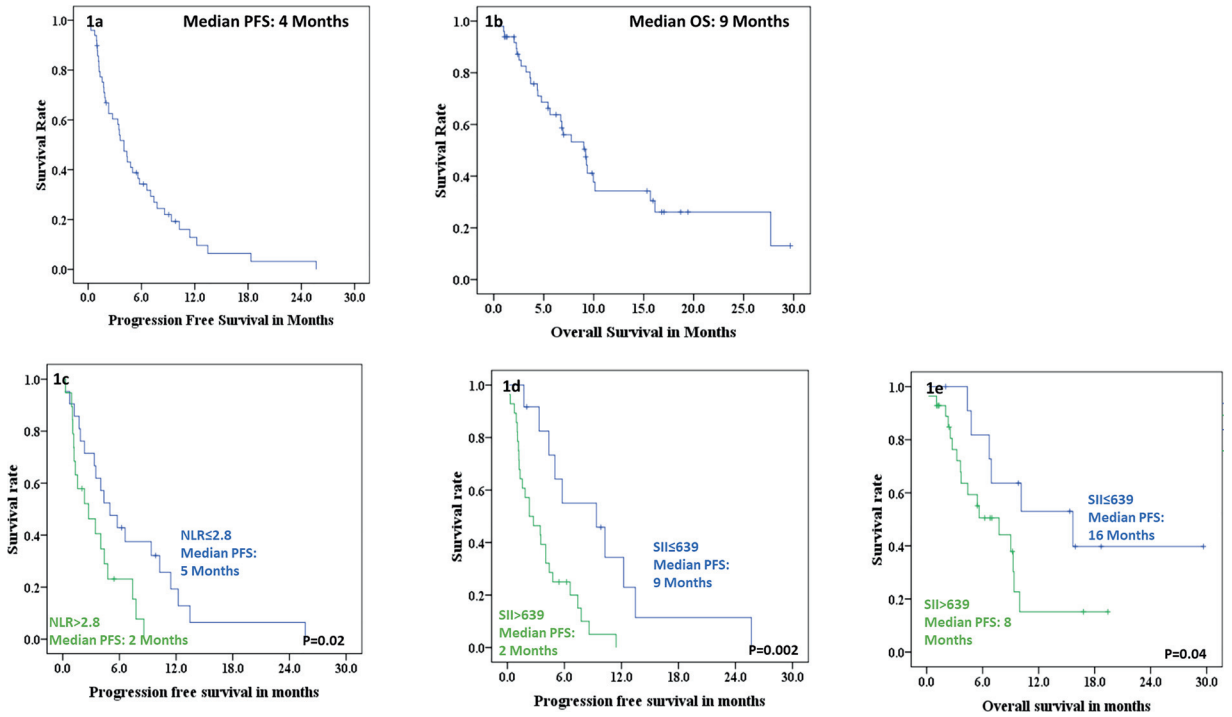

Fig. 1 The Kaplan–Meier analysis of progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) in patients with platinum-resistant ovarian cancer (PROC). Comparison of PFS between patients with high and low neutrophils to lymphocyte ratio (NLR) (**C**) and systemic immune-inflammation index (SII) (**D**). Comparison of the OS between patients with high and low SII (**E**).

upfront ($n = 9$, 18%) or interval ($n = 40$, 82%). At the time of diagnosis of PROC, 19 (39%) patients were symptomatic, 2 (4%) had isolated elevation of CA-125, and 28 (57%) had elevated CA-125 with abnormal imaging. For resistant disease, the majority received only chemotherapy ($n = 45$ [91%]), while few underwent additional surgery ($n = 4$ [8%]). Most received single-agent chemotherapy ($n = 27$), while a few received doublets ($n = 22$). The median number of chemotherapy cycles was 4 (range: 2–6). The overall response rate (ORR) was 21%. After a median follow-up of 3 (range: 2–7) months, 33 (67%) patients progressed, and 25 (57%) had died. During secondary progression, 25 patients (76%) were symptomatic, 4 (12%) had an elevation of CA-125, and 4 (12%) had both elevations of CA-125 and radiological imaging (►**Supplementary Table S1** [online only]).

The median PFS and OS were 4 (95% confidence interval [CI]: 2.44–4.55) and 9 months (95% CI: 4.77–10.76), respectively (►**Fig. 1A** and **1B**). Patients with a lower NLR (≤2.89) had a better PFS (5 vs. 2 months [$p = 0.02$]) and OS (9 vs. 5 months [$p = 0.20$]) when compared with patients with higher NLR (>2.89) (►**Fig. 1C**). Patients with lower SII≤639 had a better PFS (9 vs. 2 months [$p = 0.002$]) and OS (16 vs. 8 months [$p = 0.04$]) in comparison to patients with higher SII (►**Fig. 1D** and **1E**). On univariate analysis, the following factors were associated with a worse PFS: NLR > 2.8 (hazard ratio [HR] =2.32, $p = 0.02$) and SII > 639 (HR =3.70, $p = 0.002$) (►**Table 1**). On multivariate analysis (including NLR and SII), SII > 639 was the only factor that predicted survival (HR =4.13, $p = 0.03$) for PFS.

Even though PROC has a poor prognosis, this group has recognized heterogeneity.[5] Identifying patients with PROC who may benefit from subsequent therapy is currently based on clinical judgment (performance status, rapidity of progression, number of previous lines, and patient wish to continue potentially toxic treatment with a low expectation of benefit). There is a need for more objective markers to determine prognoses. This may help us tailor more intense therapies and stratify patients included in clinical trials in this segment. This is one of the first studies looking at the impact of inflammatory indices in PROC. We demonstrated that SII calculated at the time of diagnosis of PROC is a powerful independent predictor of outcomes (HR of 4.1 for PFS) among patients with PROC undergoing second/third line of chemotherapy.

Systemic inflammation induced by cancer cells may aid tumor progression by several mechanisms.[6] These indices have also been identified as powerful independent prognostic factors in various cancers. In patients with newly diagnosed EOC, SII, NLR, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio have been shown to predict outcomes. Recently, predictive abilities have been demonstrated in patients with platinum-sensitive relapsed ovarian cancer.[3,7] Neutrophil infiltration of the tumor is associated with tumor growth (release of proinvasive factors, angiogenesis)[8] while less amount of CD8+ tumor-infiltrating lymphocytes is associated with poorer prognosis.[9,10] Thus, the combination of high neutrophil and low lymphocytes in the peripheral blood reflects an immunological milieu that favors tumor growth which explains the predictive ability of the SII. Earlier studies have also demonstrated that SII could predict therapeutic benefit.[3] Patients with higher SII (≥730) levels did not show any benefit with the addition of

Table 1 Univariate analysis of survival outcomes in platinum resistant/refractory patients

Variable	*n*	Median PFS	95% CI	HR	*p*-Value	Median OS	95% CI	HR	*p*-Value
Duration from last platinum									
3–6 mo	28	4	1.47–6.59	1	0.88	9	6.67–12.05	1	0.59
< 3 mo	21	3	1.19–6.00	1.04		6	0.00–13.41	1.22	
ECOG[a]									
0,1	13	9	0.00–13.64	1	0.10	27	0.00–63.14	1	0.04
2,3	24	3	2.23–4.88	2.01		7	2.60–10.79	2.93	
Type of therapy for PROC[b]									
IV chemotherapy doublet									
Yes	22	4	1.57–5.36	1	0.60	5	8.49–11.73	1	0.08
No	27	5	2.39–7.60	0.85		9	3.55–7.31	0.52	
IV chemotherapy single agent									
Yes	5	4	0.00–11.45	1	0.63	4	0.00–9.37	1	0.40
No	44	4	2.86–5.19	1.29		9	7.31–11.24	1.59	
Oral etoposide									
Yes	22	6	2.22–8.97	1	0.82	10	3.23–8.02	1	0.02
No	27	4	1.93–6.13	1.07		5	8.75–9.78	2.31	
Number of previous lines of treatment									
1	38	4	2.40–4.95	1	0.96	7	3.95–9.91	1	0.69
2	11	4	3.61–5.18	1.02		6	3.86–9.73	1.25	
NLR									
≤2.8	19	5	2.40–7.59	1	0.02	10	6.11–13.81	1	0.11
> 2.8	21	2	0.23–5.23	2.32		5	0.95–9.90	1.94	
SII									
≤639	12	9	2.94–15.79	1	0.002	16	3.95–27.38	1	0.04
> 639	28	2	0.22–4.37	3.70		8	3.25–12.27	2.49	
LMR									
> 6.7	20	4	2.24–6.48	1	0.09	9	6.45–12.08	1	0.75
≤6.7	20	2	0.12–5.51	1.77		7	2.62–11.24	1.13	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival; SII, systemic immune-inflammation index; HR, hazard ratio.
[a]At the time of platinum resistance.
[b]The chemotherapy regimens used were paclitaxel/carboplatin ($n = 7$, 14%), lipodox/carbo ($n = 4$, 8%), single-agent lipodox ($n = 5$, 10%), oral etoposide ($n = 22$, 45%), and gemcitabine/epirubicin/carbo ($n = 11$, 22%).

bevacizumab to chemotherapy (when compared with those with lower SII who benefited from the addition of bevacizumab).

Other studies attempting to develop prognostic nomograms in PROC have not incorporated SII in their models.[11,12] Also, there is a paucity of real-world studies on PROC; most data are from trials or analysis of specific treatments such as bevacizumab or oral metronomic chemotherapy. Although this study is limited by the small sample size and its retrospective nature, ours is the first data showing that SII could be a useful prognostic predictor in patients with platinum-refractory/resistant disease. The treatment undergone by the patients was uniform—all our patients received chemotherapy, and there were no patients treated with bevacizumab or other targeted agents. Though several studies in different types of cancers have shown the usefulness of this index, it is yet to be incorporated into practice. Future studies should study the validity of inflammatory markers in PROC and could consider incorporating it as a biomarker in clinical trials.

Ethical Approval

The study was approved by JIPMER IEC (EC Approval No: JIP/IEC/2019/558).

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Conflicts of Interest/Disclosure
None of the authors have any relevant conflicts of interest to declare.

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