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Perioperative dynamics of siglec-15 and soluble PD-L1 in ovarian cancer surgery: Influence of anaesthetic technique on immune regulation

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Abstract

This prospective observational study investigated the perioperative dynamics of circulating sialic acid-binding immunoglobulin-like lectin 15 (SIGLEC-15) and soluble programmed death-ligand 1 (sPD-L1) in patients with ovarian cancer undergoing surgery with either total intravenous anesthesia or inhalational anesthesia. Patients were consecutively enrolled, and peripheral blood samples were collected at predefined perioperative time points. Biomarker levels were measured and compared between anesthesia groups, and their associations with immune and inflammatory parameters were analyzed using appropriate statistical methods. Following surgery, levels of SIGLEC-15 and soluble programmed death-ligand 1 increased significantly, peaking at 24 hours and remaining elevated at 72 hours, with more pronounced changes observed in the inhalational anesthesia group. Elevated biomarker levels were associated with greater immune dysregulation, reflected by alterations in natural killer cell proportion, CD4 to CD8 T-cell ratios, and increased levels of interleukin-6 and cortisol. These findings suggest that SIGLEC-15 and soluble programmed death-ligand 1 may serve as blood-based indicators of perioperative immune status. However, their long-term clinical significance requires further investigation. Overall, this study underscores the importance of dynamic monitoring of immune biomarkers during the surgical period to better understand their role in ovarian cancer management. *(Afr J Reprod Health 2026; 30 [13]:63-73).*

Keywords: ovarian cancer; anesthesia maintenance; SIGLEC-15; soluble PD-L1; perioperative immune dysregulation; biomarkers

Résumé

Cette étude prospective observationnelle a examiné les dynamiques périopératoires de l'immunoglobuline apparentée aux lectines liant l'acide sialique 15 circulante (SIGLEC-15) et de la programmed death-ligand 1 soluble (sPD-L1) chez des patientes atteintes d'un cancer de l'ovaire subissant une chirurgie sous anesthésie intraveineuse totale ou sous anesthésie inhalatoire. Les patientes ont été incluses de manière consécutive, et des échantillons de sang périphérique ont été recueillis à des moments périopératoires prédéfinis. Les taux des biomarqueurs ont été mesurés et comparés entre les groupes d'anesthésie, et leurs associations avec des paramètres immunitaires et inflammatoires ont été analysées à l'aide de méthodes statistiques appropriées. Après l'intervention chirurgicale, les taux de SIGLEC-15 et de la programmed death-ligand 1 soluble ont augmenté de façon significative, atteignant un pic à 24 heures et demeurant élevés à 72 heures, avec des changements plus marqués observés dans le groupe d'anesthésie inhalatoire. L'augmentation des niveaux de biomarqueurs était associée à une dysrégulation immunitaire plus importante, reflétée par des modifications de la proportion des cellules tueuses naturelles, des rapports CD4/CD8 des lymphocytes T, ainsi que par l'élévation des concentrations d'interleukine-6 et de cortisol. Ces résultats suggèrent que la SIGLEC-15 et la programmed death-ligand 1 soluble pourraient servir d'indicateurs sanguins de l'état immunitaire périopératoire. Toutefois, leur pertinence clinique à long terme nécessite des investigations supplémentaires. Dans l'ensemble, cette étude met en évidence l'importance d'un suivi dynamique des biomarqueurs immunitaires pendant la période chirurgicale afin de mieux comprendre leur rôle dans la prise en charge du cancer de l'ovaire. *(Afr J Reprod Health 2026; 30 [13]: 63-73).*

Mots-clés: cancer de l'ovaire ; maintien de l'anesthésie ; SIGLEC-15 ; PD-L1 soluble ; dérégulation immunitaire périopératoire ; biomarqueurs

Introduction

Ovarian cancer remains a major cause of death among women with gynecologic malignancies. Global estimates from Global Cancer Observatory (GLOBOCAN) 2022 indicate that its burden persists not because of high incidence, but due to inadequate early detection and frequent diagnosis at advanced stages.[1] Compared with cervical and endometrial cancers, ovarian cancer is characterized by diffuse peritoneal dissemination, ascites, serosal involvement, mesenteric implants, and occult residual disease, all of which complicate treatment and contribute to marked biologic heterogeneity.[2] From this perspective, ovarian cancer is better understood not as an organ-confined disease but as a process shaped by the peritoneal environment, host immunity, and systemic inflammation. This conceptual shift has expanded research interest toward tumor–host interactions and the broader tumor microenvironment.[2-4]

Surgical cytoreduction, combined with platinum-based chemotherapy and maintenance strategies, remains central to the management of epithelial ovarian cancer.[2] Despite advances such as Poly(ADP-ribose) polymerase (PARP) inhibitors, antiangiogenic therapy, and immunotherapy, the extent of tumor reduction achieved at surgery continues to influence treatment response and disease control. The perioperative period therefore represents a biologically dynamic interval in which residual tumor burden, inflammatory activation, and immune balance undergo rapid changes.[2,4] Even after optimal cytoreduction, an unfavorable postoperative immune or inflammatory milieu may impair disease control.[3,4]

Accumulating evidence indicates that ovarian cancer develops within an immunosuppressive microenvironment rather than through tumor-intrinsic mechanisms alone.[3-5] Multiple cellular and soluble components—including tumor-associated macrophages, regulatory T cells, myeloid-derived suppressor cells, and inflammatory mediators in ascites—contribute to immune escape.[3,4] This is accompanied by reduced cytotoxic T-cell and NK-cell activity, impaired antigen presentation, and enhanced checkpoint signaling.[4,5] Importantly, the issue is not the absence of immune activity but its functional suppression or redirection. This may partly explain the limited efficacy of immunotherapy in ovarian cancer and underscores the importance of understanding immune perturbations at specific treatment stages, particularly around surgery.[5]

Perioperative immune suppression has gained renewed attention in oncologic anesthesia. Surgical stress, pain, blood loss, transfusion, opioid use, and neuroendocrine activation can collectively alter immune function within a short time frame.[6-9] In ovarian cancer, where baseline immune dysregulation is common, these perioperative changes may be especially relevant. However, current evidence largely focuses on clinical outcomes such as recurrence and survival, with limited attention to the immediate perioperative immune landscape and its measurable biomarkers.

Anesthetic management represents a potentially modifiable factor influencing perioperative immune balance. Different anesthesia maintenance strategies, including propofol-based total intravenous anesthesia (TIVA), volatile anesthesia, and regional techniques, may differentially affect stress responses, inflammation, and immune cell function.[7-11] Although some retrospective and meta-analytic studies suggest associations between anesthetic technique and oncologic outcomes, findings remain inconsistent, and mechanistic insights—particularly at the level of dynamic immune biomarkers—are lacking.[10,11]

Circulating immune checkpoint molecules have emerged as promising candidates for capturing systemic immune status in a dynamic and minimally invasive manner. Among these, the PD-1/PD-L1 pathway plays a central role in ovarian cancer immune escape.[5] Its soluble form, soluble programmed death-ligand 1 (sPD-L1), can be detected in peripheral blood and may reflect systemic immune dysregulation more effectively than static tissue measurements. Prior studies have shown elevated plasma sPD-L1 levels in ovarian cancer and suggested associations with microRNA profiles, prognosis, and treatment response.[12-14]

Published work supports the plausibility of studying sPD-L1 in ovarian cancer. Plasma sPD-L1 has been reported to be elevated in epithelial ovarian cancer compared with healthy controls and to correlate with circulating microRNA patterns,

suggesting that it may participate in broader immune-regulatory networks rather than represent an incidental by-product.[12] Other investigators have proposed sPD-L1 and sPD-L2 as liquid-biopsy markers related to prognosis and platinum sensitivity.[13] In parallel, recent reviews have highlighted soluble checkpoint molecules as candidates for risk assessment, treatment monitoring, and response prediction in cancer.[14] Together, these observations provide a reasonable basis for examining sPD-L1 dynamically during the perioperative period.In parallel, SIGLEC-15 has been identified as an alternative immune suppressor with potential relevance beyond the PD-1/PD-L1 axis.[15] Its role in macrophage-mediated immune regulation and glycobiologic pathways is particularly pertinent to ovarian cancer biology. Emerging evidence suggests that combined evaluation of SIGLEC-15 and PD-L1 may provide complementary insights into tumor immune context and prognosis.[16] However, their behavior in the perioperative setting remains poorly characterized.

Despite growing interest in perioperative immunology, a key gap in the literature is the lack of integrated, time-resolved analyses that simultaneously examine anesthetic strategy, perioperative timing, and circulating immune checkpoint biomarkers in ovarian cancer. Existing studies have largely evaluated either long-term outcomes or static biomarker levels, leaving the short-interval dynamics of immune regulation insufficiently understood. In particular, the perioperative trajectories of circulating SIGLEC-15 and sPD-L1, and their relationship with established immune and inflammatory indices, have not been systematically investigated.

In this study, we aimed to address this gap by serially measuring circulating SIGLEC-15 and sPD-L1 in patients undergoing ovarian cancer surgery under different anesthesia maintenance strategies. These markers were analyzed alongside NK-cell proportion, CD4/CD8 ratio, IL-6, cortisol, and neutrophil-to-lymphocyte ratio to characterize perioperative immune dynamics. Our objective was to determine whether a clinically accessible panel of circulating biomarkers can reflect perioperative immune dysregulation in a time-dependent manner and to explore how these changes relate to anesthetic context. By focusing on short-interval immune modulation rather than long-term outcomes alone, this study seeks to provide a more direct and mechanistic understanding of perioperative immune alterations in ovarian cancer.

Methods

Study design and setting

This study was a single-center, prospective observational cohort investigation conducted at the Department of Anesthesiology, The Affiliated Hospital of Shandong Second Medical University, Weifang. Consecutive patients scheduled for elective surgery for ovarian cancer between December 2023 and December 2025 were screened. The maintenance anesthetic strategy was determined by the attending anesthesiologist based on clinical condition, operative requirements, and routine practice, and the research team did not participate in this decision. To reduce imbalance associated with nonrandom exposure, patients were incorporated into the analytic cohort in a 1:1 balanced manner according to age, FIGO stage, and surgical procedure. The final study population comprised 216 patients, including 108 in the TIVA group and 108 in the IA group. Because anesthesia was not randomly assigned, all between-group comparisons were interpreted as associations rather than causal effects.

Except for differences in maintenance anesthesia, perioperative care was kept as consistent as possible between groups so that fluid therapy, temperature management, postoperative analgesia, and other perioperative factors would have minimal influence on immune-related outcomes. The study was exploratory in nature. Because reliable prior effect-size data for perioperative changes in SIGLEC-15 were unavailable, no formal a priori sample-size calculation was performed. The sample size was therefore determined by the number of eligible consecutive cases during the study period in combination with the prespecified balanced inclusion strategy. Analyses emphasized temporal patterns, direction of change, and adjusted association strength.

Participants: inclusion and exclusion criteria

Eligible patients were adults aged 18 to 75 years with American Society of Anesthesiologists (ASA) physical status I–III who were scheduled for elective ovarian cancer surgery under general anesthesia, including tumor resection or cytoreductive surgery. All patients had a stable preoperative condition and were able to complete perioperative blood sampling at multiple time points. Written informed consent was obtained from each patient or their legal representative prior to enrollment.

Patients were excluded if they had a concomitant malignancy or a history of another malignancy within the previous five years, acute or chronic infection, autoimmune disease, hematologic disease, or severe hepatic or renal dysfunction. Additional exclusion criteria included long-term use of glucocorticoids, immunosuppressants, or other medications likely to significantly affect immune status, receipt of neoadjuvant chemotherapy, immunotherapy, or other antitumor treatments within four weeks before surgery that could substantially disturb peripheral immune status, severe perioperative hemorrhage, massive transfusion, reoperation, conversion to another anesthetic strategy, or incomplete clinical data or blood sample collection. For patients undergoing interval cytoreductive surgery, only those who had completed the planned neoadjuvant chemotherapy and whose last treatment was at least four weeks prior to surgery were included.

Grouping strategy and anesthetic management

Patients were categorized according to the maintenance anesthetic pathway actually used during surgery. Both groups underwent standardized induction of general anesthesia, and classification was based on the predominant maintenance strategy rather than induction agents or exposure to a single anesthetic. In the TIVA group, propofol infusion served as the primary maintenance technique and was titrated according to surgical stimulation and bispectral index (BIS) monitoring. In the IA group, volatile anesthetics, most commonly sevoflurane or desflurane, were used for maintenance and adjusted according to BIS values and hemodynamic responses. Opioids such as remifentanil or sufentanil were permitted in both groups for analgesic maintenance, and neuromuscular blocking agents were administered as needed. Patients requiring prolonged conversion to the alternative maintenance strategy were excluded to preserve exposure clarity.

Perioperative management, including fluid therapy, temperature control, core analgesic strategies, and routine postoperative care, was kept broadly comparable between groups. BIS values were maintained between 40 and 60 to ensure similar anesthetic depth. Potential confounders, including perioperative glucocorticoid use, vasoactive drug administration, and transfusion, were recorded and considered in the analysis.

Blood sampling and biomarker measurement

Peripheral venous blood samples were collected at four predefined perioperative time points: before anesthetic induction (T0), at the end of surgery (T1), 24 hours after surgery (T2), and 72 hours after surgery (T3). At each time point, 5 mL of venous blood was obtained. Samples were divided into EDTA tubes for hematologic and immune-cell analysis and serum tubes for biomarker assessment. Serum samples were allowed to clot at room temperature, centrifuged, and stored at −80°C for batch analysis. All procedures followed a standardized preanalytical protocol conducted by designated personnel.

Serum SIGLEC-15 and sPD-L1 levels were measured using enzyme-linked immunosorbent assay (ELISA). Each sample was tested in duplicate, and the mean value was used for analysis. Whenever feasible, samples from different time points for the same patient were analyzed within the same assay batch to minimize inter-assay variability.

Assessment of perioperative immune suppression

Perioperative immune suppression–related changes were evaluated using cellular immune indices, inflammatory markers, and stress-related parameters. Cellular immune measures included the peripheral blood NK-cell proportion and the

CD4/CD8 ratio, both assessed by flow cytometry. Inflammatory markers included interleukin-6 (IL-6) and the neutrophil-to-lymphocyte ratio (NLR), while serum cortisol was used as an indicator of stress response. IL-6 and cortisol were measured by ELISA or via the hospital clinical laboratory platform, and NLR was calculated from complete blood counts obtained at corresponding time points. These variables were measured concurrently with SIGLEC-15 and sPD-L1.

To summarize the immune profile at T2, an exploratory composite immune suppression score was constructed by standardizing IL-6, cortisol, NLR, NK-cell proportion, and CD4/CD8 ratio into z-scores and combining them as z(IL-6) + z(cortisol) + z(NLR) − z(NK-cell proportion) − z(CD4/CD8 ratio), with higher scores indicating greater immune suppression. This composite score was used solely for exploratory internal comparison and was not considered a validated clinical metric.
Clinical data were collected across general characteristics, tumor-related variables, and perioperative factors, including age, body mass index, ASA classification, comorbidities, FIGO stage, histological subtype, surgical procedure, anesthesia duration, operative time, blood loss, fluid administration, transfusion, opioid use, postoperative analgesia, and hospital stay. All data entries were independently verified by two investigators.

Outcomes

The primary outcome was the perioperative trajectory of circulating SIGLEC-15 and sPD-L1 under different anesthetic strategies, evaluated in terms of group effects, time effects, and group-by-time interaction effects. Secondary outcomes included perioperative changes in immune suppression–related indices, correlations between biomarkers and immune indices, associations of biomarkers with immune suppression status, and relationships between the exploratory composite score and anesthetic strategy.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0. Continuous variables were assessed for normality prior to comparison. Normally distributed variables were presented as mean ± standard deviation and compared using independent-samples t tests, whereas non-normally distributed variables were expressed as median (interquartile range) and analyzed using the Mann–Whitney U test. Categorical variables were reported as counts (percentages) and compared using chi-square or Fisher's exact tests.

Repeated measures were analyzed using linear mixed-effects models, with patient identity as a random effect and time, group, and group-by-time interaction as fixed effects. Correlation analyses were conducted using Pearson or Spearman methods as appropriate. Multivariable linear regression was applied when analyzing the composite immune suppression score, adjusting for clinically relevant covariates. Because the study was exploratory and involved multiple comparisons, no formal adjustment for multiplicity was performed, and findings were interpreted based on effect size, direction, and clinical plausibility. All tests were two-sided, with a significance threshold of $P < 0.05$.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of The Affiliated Hospital of Shandong Second Medical University (approval number: A20230042; approval date: 2023.2.5). Written informed consent was obtained from all participants or their legal representatives prior to enrollment. Patient confidentiality was ensured by de-identifying all data before analysis, and access to the dataset was restricted to authorized research personnel only

Results

Patient characteristics and perioperative clinical data

After consecutive screening and balanced inclusion, 216 patients were analyzed (108 in the TIVA group and 108 in the IA group). Baseline demographic, tumor-related, and surgical characteristics were comparable between groups, with no statistically significant differences observed (all $P>0.05$; Table 1). Perioperative

Table 1: Baseline and perioperative clinical characteristics of patients in the TIVA and IA groups

Variable	TIVA group (n=108)	IA group (n=108)	P value
Age (years)	55.8±9.6	56.3±10.1	0.710
BMI (kg/m²)	24.7±3.4	24.9±3.6	0.682
ASA class, n (%)			0.792
- I	18 (16.7)	15 (13.9)	
- II	74 (68.5)	78 (72.2)	
- III	16 (14.8)	15 (13.9)	
FIGO stage, n (%)			0.679
- I-II	46 (42.6)	43 (39.8)	
- III-IV	62 (57.4)	65 (60.2)	
Histologic type, n (%)			0.907
- Serous carcinoma	74 (68.5)	77 (71.3)	
- Endometrioid carcinoma	18 (16.7)	15 (13.9)	
- Mucinous carcinoma	9 (8.3)	8 (7.4)	
- Clear cell carcinoma	7 (6.5)	8 (7.4)	
Surgical procedure, n (%)			0.646
- Primary cytoreductive surgery	82 (75.9)	79 (73.1)	
- Interval cytoreductive surgery	26 (24.1)	29 (26.9)	
Operative duration (min)	223±51	228±54	0.462
Anesthesia duration (min)	263±57	268±61	0.531
Intraoperative blood loss (mL)	388±165	406±172	0.441
Crystalloid infusion (mL)	1980±430	2050±455	0.266
Red blood cell transfusion, n (%)	14 (13.0)	17 (15.7)	0.571
Intraoperative sufentanil equivalent (μg)	42.1±8.8	44.5±9.4	0.056
Postoperative PCIA use, n (%)	100 (92.6)	102 (94.4)	0.593

Note: Data are presented as mean±standard deviation or n (%). TIVA, total intravenous anesthesia; IA, inhalational anesthesia; BMI, body mass index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; PCIA, patient-controlled intravenous analgesia.

variables, including operative duration, anesthesia duration, blood loss, fluid administration, transfusion, and postoperative analgesia, were also similar. Intraoperative opioid exposure tended to be higher in the IA group but did not reach statistical significance (P=0.056; Table 1). Overall, the two groups were well balanced with respect to measured covariates.

Perioperative changes in circulating SIGLEC-15 and soluble PD-L1

Both SIGLEC-15 and sPD-L1 demonstrated clear time-dependent changes during the perioperative period, with consistent differences between anesthetic strategies (Table 2). In both groups, concentrations increased after surgery, peaked at 24 hours (T2), and declined by 72 hours (T3) while remaining above baseline. Across multiple time points, levels were consistently higher in the IA group compared with the TIVA group. Linear mixed-effects models confirmed significant group, time, and group-by-time interaction effects for both biomarkers (all P≤0.004), indicating distinct perioperative trajectories according to anesthetic strategy.

Perioperative changes in immune suppression–related parameters

All immune-related indices showed marked perioperative variation (Table 3). Cellular immune measures (NK-cell proportion and CD4/CD8 ratio) decreased after surgery and partially recovered by 72 hours but remained lower in the IA group at several time points. In contrast, inflammatory and stress-related markers (IL-6, NLR, and cortisol) increased postoperatively, peaked early, and gradually declined, with consistently higher levels observed in the IA group.

Table 2: Perioperative changes in circulating SIGLEC-15 and soluble PD-L1 under different anesthetic strategies

Variable	Time	TIVA (n=108)	IA (n=108)	Between-group P	Group effect P	Time effect P	Interaction P
SIGLEC-15 (ng/mL)	T0	4.8±1.03	4.79±1.1	0.824	<0.001	<0.001	0.002
	T1	5.1±1.1	5.5±1.1	0.019			
	T2	5.7±1.2	6.3±1.2	<0.001			
	T3	5.3±1.1	5.9±1.2	<0.001			
sPD-L1 (pg/mL)	T0	86.7±18.4	87.9±19.1	0.646	<0.001	<0.001	0.004
	T1	101.3±20.5	110.8±22.6	0.001			
	T2	118.5±23.7	134.6±26.4	<0.001			
	T3	108.2±21.9	121.8±24.7	<0.001			

Note. T0, before induction of anesthesia; T1, end of surgery; T2, 24 h after surgery; T3, 72 h after surgery. Overall effects were estimated using linear mixed-effects models.

Table 3: Perioperative changes in immune suppression-related parameters under different anesthetic strategies

Variable	Time	TIVA (n=108)	IA (n=108)	Between-group P	Group effect P	Time effect P	Interaction P
NK-cell proportion (%)	T0	15.8±3.9	16.1±4.1	0.584	<0.001	<0.001	0.006
	T1	13.1±3.4	11.7±3.2	0.003			
	T2	12.2±3.1	10.4±2.9	<0.001			
	T3	13.5±3.3	11.8±3.0	<0.001			
CD4/CD8 ratio	T0	1.5±0.3	1.6±0.4	0.669	0.002	<0.001	0.015
	T1	1.4±0.3	1.3±0.3	0.041			
	T2	1.3±0.3	1.2±0.3	0.001			
	T3	1.4±0.3	1.2±0.3	0.002			
IL-6 (pg/mL)	T0	8.6±3.1	8.8±3.0	0.614	<0.001	<0.001	0.018
	T1	39.7±12.4	44.3±13.1	0.009			
	T2	31.4±10.7	36.8±11.6	<0.001			
	T3	18.9±7.4	22.7±8.1	<0.001			
Cortisol (μg/dL)	T0	14.6±4.2	14.8±4.4	0.744	0.001	<0.001	0.021
	T1	19.8±5.1	22.3±5.7	0.001			
	T2	17.9±4.8	20.4±5.3	0.001			
	T3	15.9±4.5	17.6±4.7	0.008			
NLR	T0	2.5±0.8	2.6±0.8	0.730	<0.001	<0.001	0.011
	T1	5.8±1.7	6.5±1.9	0.006			
	T2	6.5±2.0	7.6±2.2	<0.001			
	T3	4.9±1.6	5.7±1.7	<0.001			

Note. NK, natural killer; IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio. Overall effects were estimated using linear mixed-effects models.

Mixed-effects analyses demonstrated significant time, group, and interaction effects for all variables, supporting differential immune modulation between anesthetic pathways.

Associations of circulating SIGLEC-15 and soluble PD-L1 with perioperative immune suppression

At the representative postoperative time point (T2), both SIGLEC-15 and sPD-L1 were significantly associated with immune suppression–related indices (Table 4A). Higher biomarker levels correlated with lower NK-cell proportion and CD4/CD8 ratio and with higher IL-6, cortisol, and NLR. The two biomarkers were also positively correlated with each other.

In multivariable analysis (Table 4B), the exploratory composite immune suppression score remained independently associated with anesthetic strategy and biomarker levels. IA was associated

Table 4A: Correlation analysis at postoperative 24 h (T2)

T2 indicator	SIGLEC-15, r	P value	sPD-L1, r	P value
NK-cell proportion	-0.4	<0.001	-0.5	<0.001
CD4/CD8 ratio	-0.3	<0.001	-0.4	<0.001
IL-6	0.4	<0.001	0.4	<0.001
Cortisol	0.3	<0.001	0.3	<0.001
NLR	0.4	<0.001	0.5	<0.001
Correlation between SIGLEC-15 and sPD-L1	0.5	<0.001	—	—

Table 4B: Multivariable linear regression analysis for postoperative immune suppression score at T2

Variable	β	95% CI	P value
IA group (vs. TIVA group)	0.37	0.18 - 0.56	<0.001
SIGLEC-15 (per 1 ng/mL increase)	0.11	0.04 - 0.18	0.002
sPD-L1 (per 10 pg/mL increase)	0.07	0.03 - 0.11	0.001
Age (per 10-year increase)	0.05	-0.01 - 0.11	0.105
BMI (per 1 kg/m² increase)	0.01	-0.01 - 0.03	0.298
FIGO stage III-IV (vs. I-II)	0.19	0.03 - 0.35	0.021
Operative duration (per 60-min increase)	0.09	0.01 - 0.17	0.031
Intraoperative blood loss (per 100 mL increase)	0.03	-0.01 - 0.07	0.128
Intraoperative sufentanil equivalent (per 10 μg increase)	0.06	0.00 - 0.12	0.047

Note. Model information: adjusted R^2=0.43; overall model P<0.001. The immune suppression score is an exploratory composite index: z(IL-6) + z(cortisol) + z(NLR) − z(NK-cell proportion) − z(CD4/CD8 ratio). Higher scores indicate greater immune suppression.

with a higher immune suppression score, and both SIGLEC-15 and sPD-L1 showed independent positive associations with this score after adjustment for clinical covariates. Additional factors associated with higher scores included advanced FIGO stage, longer operative duration, and greater opioid exposure.

Overall, these findings indicate that perioperative increases in circulating SIGLEC-15 and sPD-L1 are linked to a more pronounced immune suppression–related profile and that these associations vary according to anesthetic strategy.

Discussion

This study examined perioperative trajectories of circulating SIGLEC-15 and sPD-L1 in patients undergoing ovarian cancer surgery under two anesthesia maintenance strategies and evaluated their associations with immune suppression–related indices. The main findings can be summarized as follows. First, both biomarkers increased after surgery, peaked at 24 hours, and remained above baseline at 72 hours. Second, patients in the IA group consistently showed higher levels of SIGLEC-15 and sPD-L1 than those in the TIVA group across postoperative time points. Third, IA was also associated with lower NK-cell proportion and CD4/CD8 ratio and with higher IL-6, cortisol, and NLR. Finally, both biomarkers were independently associated with the composite immune suppression score at 24 hours after adjustment for relevant clinical covariates. These findings indicate that perioperative immune-related changes are detectable in peripheral blood and differ according to anesthetic maintenance strategy.

The temporal pattern observed in this study, with biomarker elevation peaking at 24 hours after surgery, is consistent with the broader perioperative physiological response to surgical stress. The concurrent decrease in cellular immune indices and increase in inflammatory and stress markers at this time point supports the interpretation that T2 represents a period of heightened immune perturbation.[17-19] However, the present data do not establish causality or define mechanistic pathways; they only demonstrate that these variables change in parallel and are statistically associated within the perioperative window.[20]

Differences between anesthesia groups should also be interpreted cautiously. Although IA was associated with higher biomarker levels and a more pronounced immune suppression–related profile, the study design does not allow attribution of these differences to specific anesthetic agents or to anesthesia alone. Other perioperative factors, including opioid exposure, surgical stress, and unmeasured confounders, may have contributed.[21] The observed association between higher opioid exposure and the composite immune score in multivariable analysis further supports the possibility that multiple perioperative factors jointly influence immune-related outcomes.

The association analyses provide additional internal consistency. At 24 hours postoperatively, both SIGLEC-15 and sPD-L1 were correlated with lower cellular immune indices and higher inflammatory and stress markers, and they remained independently associated with the composite immune suppression score after adjustment.[22-24] These findings suggest that both biomarkers reflect a broader perioperative immune-related state rather than isolated changes. However, their clinical utility as biomarkers cannot be established from this study alone, and their predictive or prognostic value requires further validation.

Several strengths of this study should be noted. The prospective design with predefined perioperative sampling time points allowed characterization of dynamic changes rather than single time-point comparisons.[23] The balanced inclusion strategy improved comparability between groups with respect to key baseline variables. In addition, the integration of multiple immune-related indices provided a more comprehensive assessment of perioperative immune status than reliance on a single marker.

At the same time, important limitations must be acknowledged. First, the study was observational and nonrandomized, and residual confounding cannot be excluded despite adjustment for measured variables.[25] Second, it was conducted at a single center, which may limit generalizability to other settings. Third, the sample size was determined pragmatically without formal power calculation, and multiple comparisons across several endpoints increase the risk of type I error. Fourth, the composite immune suppression score was exploratory and has not been externally validated.[26] Fifth, peripheral blood measurements may not fully reflect the tumor microenvironment or intraperitoneal immune conditions in ovarian cancer. Finally, no long-term oncologic outcomes were assessed, so the clinical significance of the observed immune changes remains uncertain.

From a clinical perspective, these findings suggest that perioperative immune alterations in ovarian cancer surgery can be monitored using serial blood-based markers, which may be practical in routine settings.[27] The observed differences between anesthesia strategies indicate that anesthetic management could be one of several factors associated with perioperative immune profiles. However, the current evidence is insufficient to support changes in clinical practice or to recommend one anesthesia technique over another based on immune considerations alone.[28] Instead, these results support a more integrated view of perioperative care, in which anesthesia, analgesia, and overall perioperative management are considered together in relation to immune function.

In terms of broader implications, incorporating perioperative immune monitoring into clinical pathways may help identify patients at higher risk of adverse immune-related responses, although this remains to be tested.[29] For health systems and policy, especially in settings with similar surgical and anesthetic practices, the feasibility of repeated peripheral blood assessment offers a potential framework for future research and quality improvement initiatives. Larger multicenter studies with standardized protocols and inclusion of clinical outcomes will be necessary to determine whether these perioperative immune changes translate into meaningful differences in recovery, complications, or long-term cancer outcomes.

Conclusion

In summary, this study demonstrates that circulating SIGLEC-15 and sPD-L1 exhibit distinct perioperative trajectories and are associated with immune suppression–related indices, with differences observed between anesthesia maintenance strategies. These findings provide

exploratory evidence for perioperative immune monitoring but should be interpreted cautiously pending further validation.

Ethics approval

This study was approved by The Affiliated Hospital of Shandong Second Medical University.

Authors' contributions

Cui Zhao and Linqian Zhang designed the study and performed the experiments, Meng Wang, Yangtao Gao, Mingjie Chen and Long Qi collected the data, Jiayi Fu analyzed the data, Yingui Sun and Shuo Feng prepared the manuscript. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declared that they have no conflicts of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263.
2. Ng JS, Low JJ, Ilancheran A. Epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2012 Jun;26(3):337-45.
3. Chen J, Yang L, Ma Y, Zhang Y. Recent advances in understanding the immune microenvironment in ovarian cancer. Front Immunol. 2024 Jun 5;15:1412328.
4. Wang ZB, Zhang X, Fang C, Liu XT, Liao QJ, Wu N, Wang J. Immunotherapy and the ovarian cancer microenvironment: Exploring potential strategies for enhanced treatment efficacy. Immunology. 2024 Sep;173(1):14-32.
5. Peng Z, Li M, Li H, Gao Q. PD-1/PD-L1 immune checkpoint blockade in ovarian cancer: Dilemmas and opportunities. Drug Discov Today. 2023 Aug;28(8):103666.
6. Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S. Perioperative immunosuppression in cancer patients. J Environ Pathol Toxicol Oncol. 2003;22(2):139-46.
7. Sekandarzad MW, van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative Anesthesia Care and Tumor Progression. Anesth Analg. 2017 May;124(5):1697-1708.
8. Murphy O, Forget P, Ma D, Buggy DJ. Tumour excisional surgery, anaesthetic-analgesic techniques, and oncologic outcomes: a narrative review. Br J Anaesth. 2023 Dec;131(6):989-1001.
9. Bezu L, Akçal Öksüz D, Bell M, Buggy D, Diaz-Cambronero O, Enlund M, Forget P, Gupta A, Hollmann MW, Ionescu D, Kirac I, Ma D, Mokini Z, Piegeler T, Pranzitelli G, Smith L, The EuroPeriscope Group. Perioperative Immunosuppressive Factors during Cancer Surgery: An Updated Review. Cancers (Basel). 2024 Jun 22;16(13):2304.
10. Tseng WC, Lee MS, Lin YC, Lai HC, Yu MH, Wu KL, Wu ZF. Propofol-Based Total Intravenous Anesthesia is Associated with Better Survival than Desflurane Anesthesia in Epithelial Ovarian Cancer Surgery: A Retrospective Cohort Study. Front Pharmacol. 2021 Sep 24;12:685265.
11. Shen H, Pang Q, Gao Y, Liu H. Effects of epidural anesthesia on the prognosis of ovarian cancer-a systematic review and meta-analysis. BMC Anesthesiol. 2023 Nov 29;23(1):390.
12. Koukourakis MI, Kontomanolis E, Sotiropoulou M, Mitrakas A, Dafa E, Pouliliou S, Sivridis E, Giatromanolaki A. Increased Soluble PD-L1 Levels in the Plasma of Patients with Epithelial Ovarian Cancer Correlate with Plasma Levels of miR34a and miR200. Anticancer Res. 2018 Oct;38(10):5739-5745.
13. Buderath P, Schwich E, Jensen C, Horn PA, Kimmig R, Kasimir-Bauer S, Rebmann V. Soluble Programmed Death Receptor Ligands sPD-L1 and sPD-L2 as Liquid Biopsy Markers for Prognosis and Platinum Response in Epithelial Ovarian Cancer. Front Oncol. 2019 Oct 15;9:1015.
14. Chen L, Chao Y, Li W, Wu Z, Wang Q. Soluble immune checkpoint molecules in cancer risk, outcomes prediction, and therapeutic applications. Biomark Res. 2024 Sep 2;12(1):95.
15. Wang J, Sun J, Liu LN, Flies DB, Nie X, Toki M, Zhang J, Song C, Zarr M, Zhou X, Han X, Archer KA, O'Neill T, Herbst RS, Boto AN, Sanmamed MF, Langermann S, Rimm DL, Chen L. Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy. Nat Med. 2019 Apr;25(4):656-666.

16. Zhao A, Hu S, Qiu Y, Zhang P, Xu T. Predicting ovarian cancer prognosis and immunotherapy response through siglec15 and PD-L1 expression analysis. Transl Oncol. 2025 Dec;62:102563.
17. Kurosawa S. Anesthesia in patients with cancer disorders. Curr Opin Anaesthesiol. 2012 Jun;25(3):376-84.
18. Okła K, Rajtak A, Czerwonka A, Bobiński M, Wawruszak A, Tarkowski R, Bednarek W, Szumiło J, Kotarski J. Accumulation of blood-circulating PD-L1-expressing M-MDSCs and monocytes/macrophages in pretreatment ovarian cancer patients is associated with soluble PD-L1. J Transl Med. 2020 Jun 1;18(1):220. doi: 10.1186/s12967-020-02389-7. Erratum in: J Transl Med. 2020 Jun 25;18(1):258.
19. Sun J, Lu Q, Sanmamed MF, Wang J. Siglec-15 as an Emerging Target for Next-generation Cancer Immunotherapy. Clin Cancer Res. 2021 Feb 1;27(3):680-688. doi: 10.1158/1078-0432.CCR-19-2925. Epub 2020 Sep 21. Erratum in: Clin Cancer Res. 2021 Jul 1;27(13):3804.
20. Smolarz B, Biernacka K, Łukasiewicz H, Samulak D, Piekarska E, Romanowicz H, Makowska M. Ovarian Cancer-Epidemiology, Classification, Pathogenesis, Treatment, and Estrogen Receptors' Molecular Backgrounds. Int J Mol Sci. 2025 May 12;26(10):4611.
21. Barua A, Bahr JM. Ovarian Cancer: Applications of Chickens to Humans. Annu Rev Anim Biosci. 2022 Feb 15;10:241-257.
22. Walker M, Jacobson M, Sobel M. Management of ovarian cancer risk in women with BRCA1/2 pathogenic variants. CMAJ. 2019 Aug 12;191(32):E886-E893.
23. Cheng X, Yan C, Zhao J, Lu G. CD47 as a biomarker for ovarian cancer: prospects and challenges. Postgrad Med J. 2025 Nov 18;101(1202):1248-1252.
24. Dovnik A, Dovnik NF. Vitamin D and Ovarian Cancer: Systematic Review of the Literature with a Focus on Molecular Mechanisms. Cells. 2020 Feb 1;9(2):335.
25. Dovnik A, Dovnik NF. Vitamin D and Ovarian Cancer: Systematic Review of the Literature with a Focus on Molecular Mechanisms. Cells. 2020 Feb 1;9(2):335. doi: 10.3390/cells9020335. PMID: 32024052; PMCID: PMC7072673.
26. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R; Gynecologic Oncology Group. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2003 Sep 1;21(17):3194-200.
27. Bedia JS, Jacobs IJ, Ryan A, Gentry-Maharaj A, Burnell M, Singh N, Manchanda R, Kalsi JK, Dawnay A, Fallowfield L, McGuire AJ, Campbell S, Parmar MKB, Menon U, Skates SJ. Estimating the ovarian cancer CA-125 preclinical detectable phase, in-vivo tumour doubling time, and window for detection in early stage: an exploratory analysis of UKCTOCS. EBioMedicine. 2025 Feb;112:105554.
28. Wu X, Liu J, An R, Yin R, Zhang Y, Zhou H, He A, Wang L, Zhang J, Liu Z, Duan W, Zhu J, Lou G, Chen G, Cheng Y, Xue F, Nick S, Wang H, Li D. First-line bevacizumab plus chemotherapy in Chinese patients with stage III/IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer: a phase III randomized controlled trial. J Gynecol Oncol. 2024 Sep;35(5):e99.
29. Afenteva D, Yu R, Rajavuori A, Salvadores M, Launonen IM, Lavikka K, Zhang K, Pirttikoski A, Marchi G, Jamalzadeh S, Isoviita VM, Li Y, Micoli G, Erkan EP, Falco MM, Ungureanu D, Lahtinen A, Oikkonen J, Hietanen S, Vähärautio A, Sur I, Virtanen A, Färkkilä A, Hynninen J, Muranen TA, Taipale J, Hautaniemi S. Multi-omics analysis reveals the attenuation of the interferon pathway as a driver of chemo-refractory ovarian cancer. Cell Rep Med. 2025 Sep 16;6(9):102316.