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Machine learning-enhanced immune signatures optimize cancer antigen 125 performance for epithelial ovarian carcinoma detection

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Abstract

Introduction: Ovarian cancer (OC) ranks as the fifth most common gynecologic malignancy among women worldwide.

Objective: The present study evaluates the diagnostic potential of hematological biomarkers for the early detection and differential diagnosis of OC.

Methods: A bioinformatic analysis was performed to compare immune cell profiles in blood and tissue samples from patients with OC using data from The Cancer Genome Atlas and Gene Expression Omnibus databases. Subsequently, a retrospective clinical study was conducted at Yichang Central People's Hospital between January 2015 and January 2021, including three cohorts: (i) Patients with benign ovarian tumors (n = 70), (ii) Patients with OC (n = 70), and (iii) Healthy controls (n = 60). A comprehensive analysis of routine blood parameters and the tumor marker cancer antigen 125 (CA125) was performed.

Results: The findings revealed that peripheral blood immune markers exhibited superior diagnostic utility compared with tissue-based indicators. The combination of CA125 with erythrocyte sedimentation rate (ESR) and neutrophil-to-lymphocyte ratio showed high accuracy in differentiating benign ovarian tumors from OC (area under the curve [AUC]: 0.87). Furthermore, a panel combining CA125 and platelet-to-neutrophil ratio showed enhanced diagnostic performance in distinguishing early-stage from advanced epithelial OC (sensitivity: 81.3%; specificity: 96.6%). Notably, the triad of CA125, ESR, and white blood cell count demonstrated strong screening performance for detecting epithelial OC (AUC: 0.941; p<0.001).

Conclusion: These results suggest that integrating CA125 with routine hematological parameters significantly enhances the diagnostic accuracy and early detection of epithelial OC compared to CA125 alone, providing a practical and cost-effective screening strategy for clinical implementation.

Keywords: Epithelial ovarian cancer; Hematological parameters; Screening, Cancer antigen 125; Bioinformatics

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1. Introduction

Ovarian cancer (OC), the most lethal malignancy of the female reproductive system, is the fifth most prevalent cancer among women.[1] A total of 240,000 female patients

worldwide are diagnosed with the condition each year.[2] This poor prognosis stems from diagnostic challenges associated with the lack of specific symptoms in early-stage disease and the limited therapeutic options for advanced-stage (stage III/IV) patients.[3] The 5-year overall survival rate drops from 90% in early-stage disease to 20–25% in advanced-stage disease. Notably, the majority of women are diagnosed at the advanced stage,[4] highlighting the critical importance of early detection to improve OC outcomes.

Current clinical screening protocols predominantly rely on transvaginal ultrasound combined with cancer antigen 125 (CA125) testing.[5] As a member of the mucin family (mucin-16), CA125 is elevated in 83% of patients with OC but exhibits a sensitivity of only 50–60% in early-stage disease.[6] The diagnostic utility of CA125 is constrained by its limited specificity. Elevated levels are observed in benign gynecological conditions (such as endometriosis), physiological states (such as menstruation and pregnancy), and hematologic malignancies, including Hodgkin's lymphoma.[7,8] With a sensitivity of 70% and a specificity of 87%,[9] CA125 alone exhibits insufficient reliability for population-based screening. Similarly, imaging modalities face specificity challenges, as large-scale randomized controlled trials have indicated that transvaginal ultrasound alone provides limited diagnostic efficacy for detecting disease before metastatic spread.[10-12] These limitations underscore the urgent need for novel multiplex biomarker panels to optimize early OC detection strategies.

The immunoregulatory mechanisms of the tumor microenvironment (TME) provide novel perspectives for biomarker development. Since Virchow's 1863 discovery of leukocyte infiltration in tumor tissues and his proposal of the "chronic inflammation–cancer hypothesis,"[13] extensive research has confirmed that immune cell infiltration influences tumor progression by regulating oncogenesis, proliferation, and metastasis.[14,15] Systemic inflammatory responses may foster a pro-tumorigenic microenvironment through mechanisms such as metabolic reprogramming,[16,17] suggesting that TME components could serve as critical regulators of cancer initiation, progression, and prognosis.[18] Clinical studies have validated the prognostic value of inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet count (PLT), in renal cell carcinoma and lung cancer.[19,20] A recent study utilizing a multiplex bead-based immunoassay system to analyze CA125, leptin, human epididymis protein 4, and four additional biomarkers achieved remarkable sensitivity (94.3%) and specificity (92.3%).[21] However, the potential of immune markers in early OC screening remains underexplored.

The present study integrates OC omics data from The Cancer Genome Atlas (TCGA) and the Gene Expression Omnibus (GEO) databases, as well as retrospective clinical data from Yichang Central People's Hospital. Results of this study indicate that blood-derived immune components more accurately reflect diagnostic signatures of OC compared with tumor tissue samples. Moreover, distinct immune cell infiltration patterns can be observed in blood samples from patients with OC compared with healthy and benign controls. Combining CA125 with inflammatory biomarkers significantly enhances the diagnostic efficacy for detecting epithelial OC (EOC). The CA125 + erythrocyte sedimentation rate (ESR) + NLR panel demonstrates optimal performance in discriminating between malignant and benign tumors. The CA125 + platelet-to-neutrophil ratio (PNR) and CA125 + ESR + NLR panels effectively differentiate between early-stage and advanced-stage carcinomas. The CA125 + ESR + white blood cell count (WBC) triad exhibits remarkable potential for screening applications. These findings provide a critical theoretical foundation for establishing a stratified diagnostic framework for OC based on peripheral blood immune biomarkers.

2. Materials and methods

2.1. Bioinformatics analysis

The bioinformatics component of this study focused on exploring the relationship between immunity and OC. The gene expression profiles were retrieved from the GEO (https://www.ncbi.nlm.nih.gov/gds; accession numbers: GSE31682 and GSE14407) and TCGA (https://portal.gdc.cancer.gov/) databases (Table 1).

2.2. Immune infiltration analysis

This analysis integrated OC omics data from TCGA and GEO databases, employing Estimation of Stromal and Immune Cells in Malignant Tumors using Expression Data (ESTIMATE) and Cell Type Identification by Estimating Relative Subsets of RNA Transcripts (CIBERSORT) algorithms to systematically deconvolute the composition of tumor-infiltrating immune cells and

Table 1. Basic information on selected datasets acquired from the Gene Expression Omnibus database

Datasets	Platform	Species	Total	OC sample	Normal sample	Type
GSE31682	GPL2986	*Homo sapiens*	68	48	20	Blood
GSE14407	GPL570	*Homo sapiens*	24	12	12	Tissue

Abbreviation: OC: Ovarian cancer.

quantify immune/stromal component ratios. R version 4.4.2 software was employed to calculate ESTIMATE and CIBERSORT scores for the selected gene expression datasets. Subsequently, box plots were generated.[22]

2.3. Survival analysis

Overall survival was evaluated for 401 patients with OC (1 case with early-stage disease and 400 cases with advanced-stage disease) from the TCGA-OC cohort. Kaplan–Meier curves were generated using the "survival" (v3.5-7) and "survminer" (v0.4.9) packages. Optimal cutoff values for immune markers were determined via maximally selected rank statistics. Survival differences were assessed using log-rank analysis, with statistical significance defined as $p<0.05$.[22]

2.4. Study design and ethics

The present retrospective study included 70 patients with EOC and 70 patients with benign ovarian tumors, who underwent primary surgery at Yichang Central People's Hospital between January 2015 and January 2021. A cohort of 60 age-matched healthy individuals (41.9 ± 15.0 years) who underwent physical examinations at the same hospital was included as controls. The study protocol was reviewed and approved by the Medical Ethics Committee of Yichang Central People's Hospital, Hubei, China (ethics approval no. 2021-122-01). All procedures performed in this study were in full adherence to the ethical standards set forth by the Declaration of Helsinki. As the research involved a retrospective analysis of existing anonymized data, without any foreseeable risk to the participants, the Ethics Committee formally waived the requirement for obtaining individual informed consent.

2.5. Inclusion/exclusion criteria

Patients diagnosed with OC who underwent initial surgery at Yichang Central People's Hospital between January 2015 and January 2021 were included in this retrospective cohort study. All diagnoses were rigorously validated by pathological assessment and confirmed to be EOC. Comprehensive clinical and pathological data of these patients were systematically documented at the time of initial diagnosis using a standardized electronic medical record system. In addition, laboratory tests, including a complete blood count and tumor marker panels (such as CA125), were performed for all patients within 1 week before surgery to ensure an accurate pre-operative assessment. The exclusion criteria comprised patients who had received neoadjuvant chemotherapy or targeted therapy before their initial surgical procedure, as well as those who died during the perioperative period, to minimize potential confounding factors and ensure homogeneity of the study population. Furthermore, individuals with incomplete clinical data were excluded from the analysis. We also excluded samples from all individuals who were concurrently suffering from infectious diseases, hematologic disorders, thrombosis, or hemorrhage, as these conditions are known to have a substantial impact on hematological parameters and could thus introduce confounding effects into our study.

2.6. Data collection

The data extraction process involved systematically retrieving all relevant information from the medical records of the patient cohort, including initial symptoms, tumor dimensions, International Federation of Gynecology and Obstetrics (FIGO) stage, imaging findings, and tumor histology. These variables were collected to serve as the foundation for subsequent statistical analysis and outcome assessment.

Before surgery, inflammatory and biochemical marker levels of the patients were determined, including hematological parameters such as WBC, PLT, percentage of neutrophils (NEUT%), percentage of lymphocytes (LYMPH%), percentage of eosinophils (EO%), percentage of basophils (BASO%), percentage of monocytes (MONO%), neutrophil count (NEUT), lymphocyte count (LYMPH), eosinophil count (EO), basophil count (BASO), monocyte count (MONO), red cell distribution width-coefficient of variation (RDW-CV), red cell distribution width-standard deviation, platelet distribution width (PDW), mean platelet volume (MPV), procalcitonin (PCT), hematocrit, mean corpuscular volume, and ESR. In addition, the following markers were also tested: CA125, NLR, PLR, lymphocyte-to-monocyte ratio (LMR), platelet-to-monocyte ratio, PNR, red blood cell distribution width-to-lymphocyte ratio, and systemic immune-inflammation index (SII). For patients who had multiple pre-operative markers recorded, a single value was selected for analysis. The selection was based on the principle of temporal proximity, meaning the measurement taken closest to the time of surgery was deemed the most representative and was therefore chosen.

2.7. Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences software, version 25.0, and R, version 4.4.2. Bioinformatics data were analyzed using the non-parametric Wilcoxon rank-sum test. For normally distributed continuous variables, *t*-tests were employed, and results are presented as the mean ± standard deviation. When the continuous variables deviated from a normal distribution, the rank-sum test was used for statistical analysis, with the results presented as the median and

quartiles. The χ^2 test was applied to analyze differences between the categorical variables, and the results are presented as the number of cases and their corresponding percentages. Univariate and multivariate logistic regression analyses were performed, presenting results as odds ratios with corresponding 95% confidence intervals (CIs) and *p*-values. Diagnostic performance was evaluated via receiver operating characteristic curve analysis, with area under the curve (AUC) comparisons performed using DeLong's test.

All statistical tests conducted in this study were two-tailed. A $p<0.05$ was established as the threshold for a statistically significant difference, which is a conventional standard in biomedical research.

3. Results

3.1. Immune cell infiltration in OC and normal samples

Kaplan–Meier survival analysis was performed using the ImmuneScore and StromalScore to determine their association with overall survival. Higher ImmuneScore or StromalScore values indicate a greater abundance of immune or stromal components in the TME. The analysis revealed that these scores were significantly correlated with patient clinical outcomes, suggesting that the presence of immune infiltrates and stromal structures may play an important role in risk stratification and disease progression.

As shown in Figure 1A, the proportion of immune and stromal components in blood samples from patients with OC was lower than that in samples from healthy controls, with no significant differences observed in OC tissues (Figure 1B). In addition, the ImmuneScore and StromalScore showed no significant association with overall survival or tumor stage in OC tissues (Figure S1).

Comprehensive immune-stromal profiling revealed compartment-specific alterations in OC. Quantitative deconvolution demonstrated significantly decreased peripheral immune-stromal fractions in patients with OC compared with healthy controls (Figure 1A; $p<0.05$),

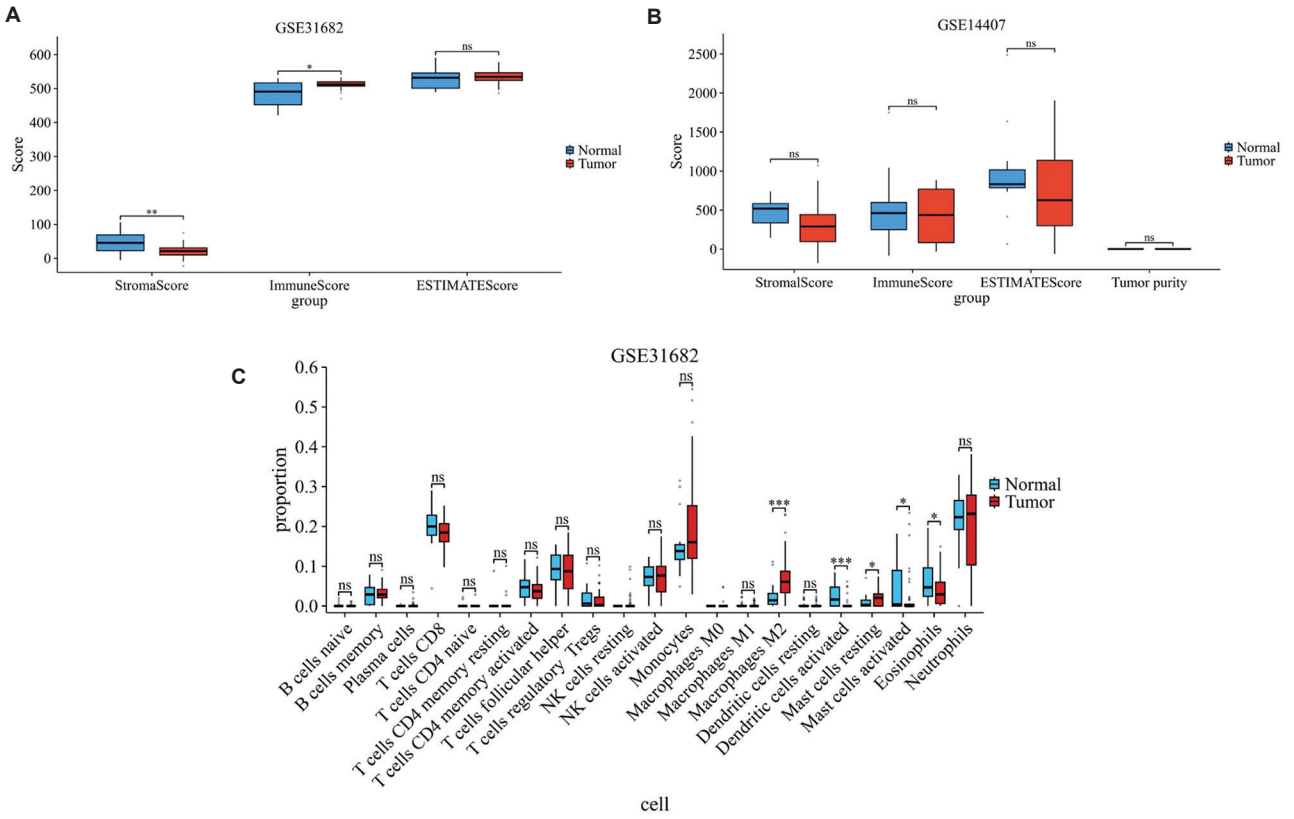

Figure 1. Box plot of immune and stromal scores. Blue represents the scores for normal blood, and red represents the scores for tumor blood. (A) ESTIMATE scores in the GSE31682 dataset from blood. (B) ESTIMATE score in the GSE14407 dataset from tissue. (C) CIBERSORT scores in the GSE31682 dataset from blood.

Note: Statistical significance determined at $*p<0.05$, $**p<0.01$, and $***p<0.001$; ns: not significant ($p>0.05$).

Abbreviations: ESTIMATE: Estimation of Stromal and Immune Cells in Malignant Tumors using Expression Data; CIBERSORT: Cell Type Identification by Estimating Relative Subsets of RNA Transcripts.

whereas tumor tissues exhibited comparable infiltration levels to normal ovarian stroma (Figure 1B; $p>0.05$). Survival analysis further confirmed the lack of prognostic association for the tissue-based ImmuneScore and StromalScore across FIGO stages (Figure S1).

The proportions of tumor-infiltrating immune cell subsets were analyzed using the CIBERSORT algorithm. Five of the 21 immune cell subsets in OC blood showed significantly altered proportions compared with healthy controls (Figure 1C). These results collectively indicate that peripheral blood immune profiles, rather than tissue-based assessments, better reflect systemic and OC-specific immunological alterations. This suggests that a blood-based approach provides substantial diagnostic utility and may serve as a minimally invasive liquid biopsy in clinical practice.

3.2. Diagnostic performance of blood immune cell infiltration in OC

The present case–control study enrolled 70 treatment-naïve patients with EOC, 70 patients with benign ovarian tumors, and 60 age-matched healthy controls between January 2015 and January 2021. The detailed clinical information of patients is provided in Tables S1 and S2. There were no significant differences in age at menarche, number of pregnancies, or number of births among the subjects ($p>0.05$; Table S1). Table S2 summarizes the clinicopathological characteristics of patients with malignant and benign ovarian tumors.

3.3. Diagnostic performance of blood-based immune and biochemical markers

3.3.1 Malignant versus benign differentiation

Comparisons of hematologic parameters between the malignant (EOC; $n = 70$) and benign ovarian tumor ($n = 70$) groups revealed distinct inflammatory profiles (Table S3). A preliminary analysis revealed statistically significant differences in several hematological parameters between the two groups, with statistically significant differences observed for WBC, PLT, NEUT%, LYMPH%, BASO%, MONO%, NEUT, BASO, MONO, ESR, CA125, NLR, PLR, LMR, PNR, and SII ($p<0.05$). However, no significant differences were observed for hematocrit, mean corpuscular volume, EO%, LYMPH, EO, RDW-CV, red cell distribution width-standard deviation, PDW, MPV, PCT, platelet-to-monocyte ratio, and red blood cell distribution width-to-lymphocyte ratio ($p>0.05$).

Univariate logistic regression analysis indicated that NLR, SII, ESR, and CA125 were significant discriminators of EOC versus benign ovarian tumors (Table S4). In addition, the AUC for CA125 alone was 0.852 ($p<0.001$), indicating a higher diagnostic capability than that of ESR at 0.772 ($p<0.001$), SII at 0.720 ($p<0.001$), and NLR at 0.713 ($p=0.001$) (Table S5). The AUC for the combined markers CA125 + ESR + NLR was the highest, with a Youden index of 0.711, a sensitivity of 0.794, and a specificity of 0.917 (95% CI: 0.783–0.950; $p<0.001$), suggesting that integrating inflammatory markers with CA125 significantly improves diagnostic precision for distinguishing malignant from benign ovarian lesions (Table 2).

3.3.2. Stratification of OC stages versus benign lesions

The cohort comprised 32 early-stage (45.7%; FIGO I–II) and 38 advanced-stage (54.3%; FIGO III–IV) EOC cases. Comparative analysis revealed significant differences ($p<0.05$) in inflammatory profiles between the EOC and benign ovarian tumor groups, including in NEUT%, LYMPH%, BASO%, NEUT, MONO, ESR, CA125, NLR, LMR, PNR, and SII (Table S6).

Logistic regression analysis identified CA125, SII, and PNR as independent predictors for early-stage EOC versus benign ovarian tumors (Table S7). Furthermore, the AUC for CA125 was 0.727 ($p<0.001$), which was higher than that of SII and PNR. The cutoff value for CA125 was established at 132.85 U/mL, with a sensitivity of 0.500

Table 2. Diagnostic performance of cancer antigen 125 and inflammatory markers in differentiating malignant from benign ovarian tumors

Variable	AUC	Youden index	95% CI	*p*-value	Sensitivity	Specificity
CA125+ESR	0.862	0.682	0.776–0.948	<0.001	0.765	0.917
CA125+SII	0.830	0.606	0.735–0.926	<0.001	0.706	0.900
CA125+NLR	0.846	0.639	0.759–0.932	<0.001	0.706	0.933
CA125+ESR+SII	0.856	0.677	0.768–0.945	<0.001	0.794	0.883
CA125+ESR+NLR	0.867	0.711	0.783–0.950	<0.001	0.794	0.917
CA125+SII+NLR	0.821	0.626	0.720–0.922	<0.001	0.676	0.950
CA125+ESR+SII+NLR	0.854	0.677	0.762–0.946	<0.001	0.794	0.883

Abbreviations: AUC: Area under the curve; CA125: Cancer antigen 125; CI: Confidence interval; ESR: erythrocyte sedimentation rate; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index.

and a specificity of 0.900 (95% CI: 0.618–0.836; $p<0.001$). The diagnostic efficacy of SII and PNR was somewhat restricted individually. The present biomarker validation study demonstrated significant diagnostic improvement through the use of combinatorial biomarker strategies. A multimarker panel combining CA125 and PNR achieved superior performance (AUC: 0.768; 95% CI: 0.673–0.863; $p<0.001$) compared with CA125 alone (AUC: 0.727; 95% CI: 0.618–0.836), representing a 5.4% increase, with a sensitivity of 81.3% at a specificity threshold of 91.6% for early-stage EOC identification (Table 3).

The comparative analysis of immune and biochemical markers between advanced-stage EOC and benign ovarian tumors is summarized in Table S8. Logistic regression modeling identified ESR, CA125, SII, and NLR as independent predictive factors for advanced EOC diagnosis, with detailed statistical outcomes presented in Tables S9 and S10. The CA125 + ESR + NLR triad demonstrated unprecedented diagnostic precision (AUC: 0.977; 95% CI: 0.951–1.000; $p<0.001$), representing a 4.1% improvement compared with CA125 alone (ΔAUC: +0.038; $p<0.001$), achieving a sensitivity of 96.0% at a specificity of 94.0% for advanced EOC identification (Table 4).

3.3.3. Comparison between the EOC group and healthy controls

The comparative analysis of inflammatory and biochemical markers between the EOC group and healthy control group revealed that there were significant differences in several indicators, including WBC, PLT, NEUT%, LYMPH%, MONO%, NEUT, EO, BASO, MONO, PCT, ESR, CA125, NLR, PLR, LMR, PNR, and SII (Table S11). Logistic regression analysis identified ESR, WBC, and CA125 as independent predictors of the presence of EOC versus healthy status (Table S12).

The diagnostic performance analysis demonstrated that CA125 achieved an AUC of 0.912 ($p<0.001$), significantly surpassing ESR (AUC: 0.856; $p<0.001$) and WBC (AUC: 0.755; $p<0.001$). At an optimal cutoff value of 130.25 U/mL, CA125 exhibited a sensitivity of 70.0% and a specificity of 96.7% (95% CI: 0.863–0.969; $p<0.001$), showing superior diagnostic accuracy compared with ESR or WBC alone (Table S13). Notably, multimarker panels combining CA125 with WBC (AUC: 0.915) and CA125 with ESR (AUC: 0.927) outperformed single-marker assessments. The tripartite combination of CA125 + ESR + WBC achieved the highest discriminative power (AUC: 0.941; 95% CI: 0.904–0.978; $p<0.001$), with optimized sensitivity (80.0%) and specificity (98.3%), as detailed in Figure S2 and Table 5.

4. Discussion

OC is the eighth most prevalent malignancy worldwide, with an age-standardized incidence rate of 6.6/100,000 women.[23] Notably, 67% of patients present with advanced-stage disease at diagnosis, correlating with a dismal 5-year

Table 3. Diagnostic performance of cancer antigen 125 combined with inflammatory markers in epithelial ovarian cancer and benign ovarian tumors

Variable	AUC	Youden index	95% CI	*p*-value	Sensitivity	Specificity
CA125+PNR	0.768	0.399	0.673–0.863	<0.001	0.813	0.916
CA125+SII	0.718	0.369	0.602–0.835	<0.001	0.469	0.900
CA125+PNR+SII	0.754	0.429	0.654–0.855	<0.001	0.500	0.929

Abbreviations: AUC: Area under the curve; CA125: Cancer antigen 125; CI: Confidence interval; PNR: Platelet-to-neutrophil ratio; SII: Systemic immune-inflammation index.

Table 4. Discriminatory power of cancer antigen 125 combined with inflammatory markers in distinguishing advanced epithelial ovarian cancer from benign ovarian tumors

Variable	AUC	Youden index	95% CI	*p*-value	Sensitivity	Specificity
CA125+NLR	0.937	0.815	0.869–1.000	<0.001	0.882	0.933
CA125+ESR	0.974	0.874	0.944–1.000	<0.001	0.941	0.933
CA125+SII	0.931	0.782	0.846–1.000	<0.001	0.882	0.900
CA125+ESR+NLR	0.977	0.900	0.951–1.000	<0.001	0.960	0.940
CA125+NLR+SII	0.924	0.832	0.821–1.000	<0.001	0.882	0.950
CA125+ESR+SII	0.971	0.858	0.939–1.000	<0.001	0.941	0.917
CA125+NLR+SII+ESR	0.975	0.874	0.946–1.000	<0.001	0.941	0.933

Abbreviations: AUC: Area under the curve; CA125: Cancer antigen 125; CI: Confidence interval; ESR: erythrocyte sedimentation rate; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index.

Table 5. Screening efficacy of cancer antigen 125 combined with inflammatory markers in discriminating epithelial ovarian cancer from healthy individuals

Variable	AUC	Youden index	95% CI	*p*-value	Sensitivity	Specificity
CA125+WBC	0.915	0.700	0.896–0.961	<0.001	0.800	0.900
CA125+ESR	0.927	0.769	0.883–0.971	<0.001	0.786	0.983
CA125+ESR+WBC	0.941	0.783	0.904–0.978	<0.001	0.800	0.983

Abbreviations: AUC: Area under the curve; CA125: Cancer antigen 125; CI: Confidence interval; ESR: erythrocyte sedimentation rate; WBC: White blood cell count.

survival rate of 30%.[24] This epidemiological pattern highlights the urgent need for enhanced early detection strategies to improve clinical outcomes.

The TME undergoes dynamic remodeling during carcinogenesis, characterized by aberrant cytokine/chemokine signaling that drives tumor initiation, invasion, and metastatic dissemination.[18] Emerging evidence has highlighted the diagnostic potential of systemic inflammatory biomarkers, including neutrophils, lymphocytes, platelets, and circulating immune cell profiles, which reflect alterations in the TME and are associated with oncogenesis across multiple malignancies, such as ovarian and lung carcinomas.[25,26] While the pre-operative NLR has demonstrated prognostic value in various cancer types, including head and neck squamous cell carcinoma,[27,28] the clinical utility of peripheral blood-derived immune biomarkers for differential diagnosis and population screening of EOC remains underexplored. The present bioinformatics investigation revealed that peripheral blood immune signatures exhibited superior diagnostic performance compared with tissue-based biomarkers, suggesting a paradigm shift toward liquid biopsy approaches. Notably, the integration of CA125 with routine hematological parameters significantly enhanced the diagnostic accuracy for early detection of EOC.

The present retrospective cohort analysis identified 17 significantly dysregulated pre-operative biomarkers between patients with EOC and healthy controls, encompassing WBC, PLT, NEUT%, LYMPH%, MONO%, NEUT, EO, BASO, MONO, PCT, ESR, CA125, NLR, PLR, LMR, PNR, and SII. Multivariate modeling identified NLR, ESR, SII, and CA125 as independent predictors of ovarian malignancy ($p<0.05$).

The integration of CA125 with hematological inflammatory biomarkers exhibited marked diagnostic improvement in OC detection. Notably, the CA125 + ESR + NLR triad achieved excellent discriminative performance (AUC: 0.867; 95% CI: 0.783–0.950; $p<0.001$), exhibiting a sensitivity of 79.4% and a specificity of 91.7% for distinguishing between malignancy and benign conditions. This multi-analyte approach reduced false-negative rates compared with CA125 alone, particularly in lesions with borderline or indeterminate imaging features. For early-stage EOC, the CA125 + PNR combination improved sensitivity by 31.3% (81.3% vs. 50.0% for CA125 alone; $p<0.001$), while maintaining specificity at 91.6%. This panel demonstrated superior accuracy for discriminating early-stage disease from benign ovarian tumors and offers high specificity for excluding benign lesions, which is critical for reducing unnecessary invasive procedures in clinical practice. In advanced-stage EOC evaluation, the CA125 + ESR + NLR panel demonstrated superior discriminative capacity (AUC: 0.977 vs. 0.939 for CA125 alone; ΔAUC: +0.038; $p<0.01$), with a sensitivity of 96.0% at a specificity of 94.0%, supporting its use as a reliable tool for the diagnosis of advanced EOC.

The diagnostic algorithm developed to distinguish patients with EOC from healthy controls demonstrated substantial improvement through biomarker integration. Multivariate analysis revealed that combining CA125 with hematological inflammatory biomarkers, specifically the CA125 + ESR + WBC triad, achieved superior discriminative capacity (AUC, 0.941; 95% CI: 0.904–0.978) compared with CA125 alone (ΔAUC: +0.029; $p<0.001$). This optimized panel exhibited a sensitivity of 80.0% and a specificity of 98.3%.

These findings can be contextualized within the broader framework of OC pathobiology. The elevated systemic inflammatory state captured by panels such as CA125 + ESR + NLR may reflect underlying immune activation and oxidative stress processes that characterize OC progression.[29] For instance, neutrophil activity and acute-phase reactants such as ESR are known to be influenced by reactive oxygen species and cytokine cascades originating from the TME. Similarly, platelet activation, reflected in metrics such as PNR and SII, may be linked to stromal crosstalk and pro-thrombotic shifts that facilitate tumor growth and dissemination. Thus, the diagnostic superiority of these multi-parameter panels likely stems from their ability to capture complementary aspects of OC-associated systemic dysregulation, including inflammation, immune evasion, and tumor-stroma interactions.

As a ubiquitous and readily available diagnostic tool, peripheral blood analysis serves as a cost-effective cornerstone in assessing systemic inflammatory and immune activity. Notably, parameters derived from the complete blood count have exhibited particular clinical utility in oncological screening and prognostication, providing valuable insights from a simple blood draw.

Notwithstanding the potential multifactorial influences on peripheral blood analysis results, the present study systematically addressed selection bias by excluding subjects with pre-existing conditions known to affect inflammatory markers, such as autoimmune disorders, acute infections, and hematological malignancies. Specifically, all participants underwent comprehensive cervical cancer screening during the 3-month pre-enrollment window, which included human papillomavirus genotyping and cervical ThinPrep cytology as per standard clinical protocols.

5. Conclusion

In summary, the present study established hematological biomarkers as pivotal tools in OC management, demonstrating triple clinical utility across differential diagnosis, early detection, and population screening. In particular, the CA125 + ESR + NLR triad achieved superior diagnostic accuracy in differentiating malignancy and benign conditions, thereby reducing the incidence of false-negative diagnoses. Furthermore, the CA125 + PNR panel improved discrimination of early-stage disease from benign ovarian tumors, whereas the CA125 + ESR + NLR panel enhanced identification of advanced-stage carcinomas. The CA125 + ESR + WBC panel exhibited cost-effective screening potential for distinguishing EOC from healthy individuals. These findings underscore the clinical potential of combining inflammatory and immune biomarkers with CA125 to improve diagnostic precision, better reflect underlying TME dynamics, and ultimately contribute to earlier and more accurate detection of OC.

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Conflict of interest

The authors declare that they have no competing interests.

Author contribution

Conceptualization: Yuanhong Zhou, Qiang Liu
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Investigation: Xuehui Chen, Jia Liu, Qianwen Zhang, Youzheng Luo
Methodology: All authors
Writing–original draft: Xuehui Chen, Jia Liu
Writing–review & editing: Yuanhong Zhou, Jia Liu, Qiang Liu

Ethics approval and consent to participate

The retrospective cohort study was conducted in accordance with the ethical principles of the Declaration of Helsinki and received approval from the hospital's Ethics Committee. After a comprehensive review, the ethics committee granted a waiver of informed consent due to the retrospective nature of the research, which involved minimal risk to participants and utilized anonymized patient data (serial number: 2021- 122-01).

Consent for publication

Not applicable.

Availability of data

The data generated in this study are available upon reasonable request to the corresponding author.

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