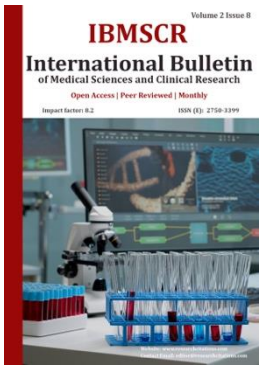


# INVESTIGATION OF THE ROLE OF IMMUNE SYSTEM FACTORS AND VASCULAR ANGIOGENESIS IN THE TUMOR MICROENVIRONMENT ON OVARIAN CANCER PROGRESSION

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**Abstract**

Ovarian cancer is a major contributor to cancer-related mortality among women worldwide. The poor prognosis is often due to its asymptomatic early stages, delayed diagnosis, and the high incidence of chemoresistant recurrences. Recent attention has shifted towards understanding the role of the tumor microenvironment (TME), particularly immune cells and vascular angiogenesis, in ovarian cancer progression. This study analyzes the structural and functional characteristics of immune cell populations ($CD4^+$ and $CD8^+$ T-lymphocytes, tumor-associated macrophages, NK cells) and evaluates the expression of key angiogenic and hypoxia-related markers (VEGF, CD31, HIF-1α) in both primary and metastatic ovarian tumors.

**Keywords:** ovarian cancer, tumor microenvironment, immune cells, angiogenesis, VEGF, PD-L1, HIF-1α, tumor-associated macrophages, hypoxia, immunotherapy.

**Introduction**

Ovarian cancer is frequently diagnosed at advanced stages (III-IV FIGO), by which time peritoneal dissemination, ascites, and carcinomatosis are already present [1,2]. Despite advances in surgical techniques and platinum-based chemotherapy, five-year survival rates remain below 30% for advanced stages [3]. This has led to the investigation of the tumor microenvironment (TME) as a major regulator of tumor behavior and treatment response.

The TME includes a complex interplay of immune cells, stromal elements, cytokines, extracellular matrix components, and blood vessels. Among immune components, cytotoxic $CD8^+$ T-cells are key effectors of anti-tumor immunity, while tumor-associated macrophages (TAMs), particularly the M2 phenotype, contribute to immune suppression, angiogenesis, and tumor invasion [4,5]. Hypoxia within the TME further exacerbates immunosuppression by upregulating hypoxia-inducible factor 1-alpha (HIF-1α), which promotes VEGF expression and pathological neovascularization.

This study aims to characterize the immune-vascular interactions within the ovarian cancer microenvironment and determine their impact on disease progression, with the goal of identifying potential prognostic markers and therapeutic targets.

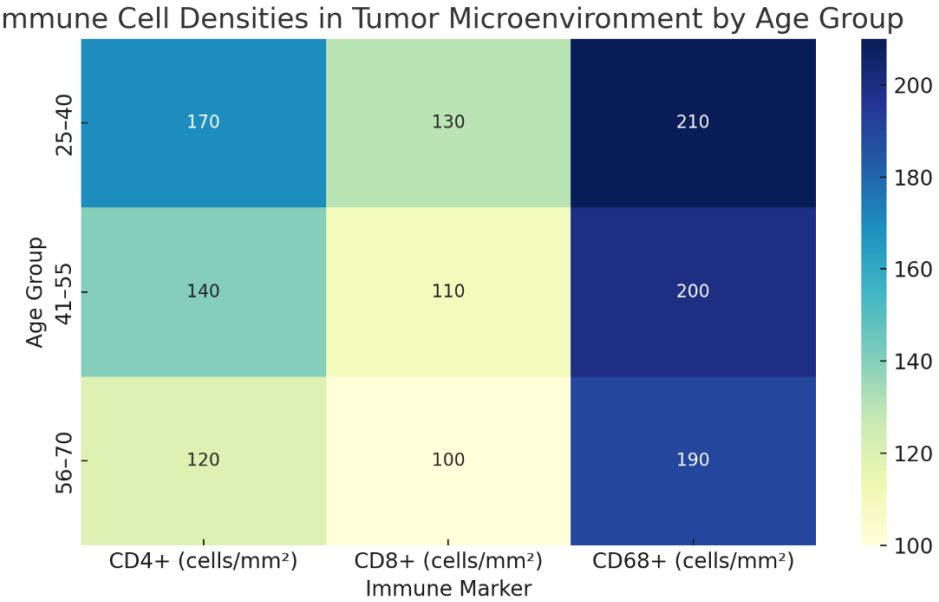
**Materials and Methods** A total of 135 female patients diagnosed with stage IIIA–IV epithelial ovarian cancer were prospectively enrolled between 2020 and 2025 at the Samarkand branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. Inclusion criteria involved confirmed histopathology, presence of peritoneal carcinomatosis, and availability of tumor and ascitic fluid samples.

Tissue specimens from primary tumors and metastatic foci were collected during cytoreductive surgery. Histological analysis was conducted to assess tumor subtype and differentiation grade. Immunohistochemical staining was performed using antibodies against

CD4, CD8, CD68, VEGF, CD31, HIF-1α, PD-L1, and CTLA-4. Quantitative evaluation included cell density measurements (cells/mm$^2$), scoring of staining intensity (0 to 3+), and semi-quantitative analysis of angiogenic marker expression.

Ascitic fluid was analyzed cytologically and immunologically to determine immune cell composition, cytokine levels, and expression of immune checkpoints. Clinical data, including age, tumor histology, disease stage, and survival outcomes, were recorded. Statistical analysis involved chi-square tests, Spearman correlation coefficients, and Kaplan–Meier survival estimates using SPSS and Statistica software.

**Results** The majority of patients (62%) had high-grade serous carcinoma, followed by endometrioid, mucinous, and clear cell subtypes. Immunohistochemical analysis revealed that CD4$^+$ T-helper cells had the highest density in patients aged 25–40 years (mean 170 ± 20 cells/mm$^2$), declining with age. CD8$^+$ T-cell infiltration was significantly lower in G3 tumors (mean 100 ± 10 cells/mm$^2$) compared to G1 tumors (mean 140 ± 15 cells/mm$^2$, $p < 0.05$), indicating impaired cytotoxic immunity in poorly differentiated cancers.




CD68$^+$ TAMs were abundant in hypoxic tumor regions, with densities up to 250 ± 35 cells/mm$^2$. These areas also demonstrated elevated HIF-1α and VEGF expression, supporting the link between hypoxia and pro-tumorigenic angiogenesis. CD31 expression indicated high microvessel density in metastatic lesions, confirming increased neovascularization.

A significant inverse correlation was observed between CD8$^+$ T-cell density and HIF-1α expression ($r = -0.65$, $p = 0.01$). PD-L1 was co-expressed with VEGF in 41% of patients with stage IV disease and was associated with shorter overall survival (median 12.3 months vs. 20.7 months, $p < 0.01$). Multivariate analysis identified VEGF/PD-L1 co-expression as an independent predictor of poor prognosis.

**Discussion**

The findings of this study emphasize the immunosuppressive and angiogenic profile of the ovarian cancer microenvironment. Declining T-cell infiltration, coupled with increased TAMs and hypoxia-related markers, reflects a hostile milieu for anti-tumor immune activity. The dominance of M2-polarized macrophages and reduced CD8$^+$ cytotoxic response facilitate tumor immune escape, while VEGF-driven angiogenesis sustains tumor growth and metastasis [6].

HIF-1α emerges as a central mediator linking hypoxia to immune evasion and vascular proliferation. The observed co-expression of PD-L1 and VEGF strengthens the rationale for dual blockade using immune checkpoint inhibitors and anti-angiogenic agents. These insights are crucial for developing personalized treatment strategies, especially in patients with platinum-resistant or recurrent disease.

Furthermore, quantifying immune and angiogenic markers may assist in stratifying patients by risk and therapy responsiveness. This could inform clinical decision-making and optimize outcomes by tailoring therapy based on TME features.

**Conclusion**

Ovarian cancer progression is significantly influenced by the tumor microenvironment, where hypoxia, angiogenesis, and immune suppression act synergistically. The co-expression of VEGF and PD-L1 represents a powerful prognostic marker and therapeutic target. This study contributes valuable evidence supporting the integration of immunotherapy and anti-angiogenic therapy in personalized treatment regimens for advanced ovarian cancer.

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