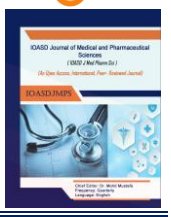
OPEN ACCESS

IOASD Journal of Medical and Pharmaceutical Sciences

IOASD J Med Pharm Sci, Vol-3, Iss-2, Apr-Jun., 2026
Frequency: Quarterly
ISSN: 3049-0294 (Online)
ISSN: 3049-3773 (Print)
Homepage: https://ioasdjmps.com



Hematologic Cytokine Storm: Immune Dysregulation in Advanced Ovarian Cancer

Emmanuel Ifeanyi Obeagu[1,2*]

[1]Division of Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe
[2]Department of Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding Author: Emmanuel Ifeanyi Obeagu
Division of Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe

DOI: 10.67224/ioasdjmps.2026.v03i02.006

ABSTRACT

Advanced ovarian cancer is frequently associated with profound immune dysregulation characterized by a hematologic cytokine storm, a hyperinflammatory state driven by excessive cytokine release. This dysregulated immune response contributes to tumor progression, systemic inflammation, and significant hematologic abnormalities including anemia, thrombocytosis, and leukocytosis. The cytokine storm reflects a complex interplay between tumor cells, immune cells, and the tumor microenvironment, resulting in the amplification of pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). The pathophysiology of the cytokine storm involves a feed-forward loop of immune activation where elevated cytokine levels disrupt normal hematopoiesis, induce endothelial dysfunction, and promote coagulation abnormalities. Clinically, patients exhibit systemic inflammatory symptoms and laboratory evidence of hematologic dyscrasia, which negatively impact treatment response and overall prognosis. Understanding the mechanisms underlying cytokine-driven hematologic dysfunction is crucial for improving patient management in advanced ovarian cancer.

Keywords: cytokine storm, immune dysregulation, ovarian cancer, hematologic inflammation, tumor microenvironment.

Original Research Article

Article History
Received: 07-05-2026
Accepted: 11-06-2026
Published: 15-06-2026

ABBREVIATIONS

CAR-T – Chimeric Antigen Receptor T-cell Therapy
CRP – C-reactive Protein
CXCR2 – C-X-C Chemokine Receptor Type 2
DOACs – Direct Oral Anticoagulants
ESR – Erythrocyte Sedimentation Rate
GM-CSF – Granulocyte–Macrophage Colony-Stimulating Factor
G-CSF – Granulocyte Colony-Stimulating Factor
IL-1β – Interleukin-1 Beta
IL-6 – Interleukin-6
IL-8 – Interleukin-8
IL-10 – Interleukin-10
LMWH – Low-Molecular-Weight Heparin
MDSCs – Myeloid-Derived Suppressor Cells
NETs – Neutrophil Extracellular Traps
NF-κB – Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NLR – Neutrophil-to-Lymphocyte Ratio
NK Cells – Natural Killer Cells
PAD4 – Peptidyl Arginine Deiminase 4
PD-1 – Programmed Cell Death Protein 1
PD-L1 – Programmed Death-Ligand 1
PLR – Platelet-to-Lymphocyte Ratio
STAT3 – Signal Transducer and Activator of Transcription 3
TGF-β – Transforming Growth Factor Beta
TNF-α – Tumor Necrosis Factor Alpha
VEGF – Vascular Endothelial Growth Factor

INTRODUCTION

Ovarian cancer is a leading cause of gynecologic cancer mortality worldwide, largely due to its diagnosis at advanced stages and the complex biology of its tumor microenvironment [1-2]. Despite advances in surgical techniques and chemotherapeutic regimens, long-term survival remains poor, particularly in patients with late-stage disease. A growing body of evidence implicates immune dysregulation as a central feature of ovarian cancer progression, with inflammatory processes and aberrant cytokine signaling playing critical roles in tumor development, metastasis, and resistance to therapy [3-4]. Among the diverse immune abnormalities observed in ovarian cancer, the phenomenon of a

cytokine storm—an excessive and uncontrolled release of pro-inflammatory cytokines—has emerged as a key driver of systemic inflammation and hematologic dysfunction. Originally described in infectious and autoimmune diseases, cytokine storms are increasingly recognized in malignancies where tumor-induced immune activation triggers a cascade of inflammatory mediators. In advanced ovarian cancer, this hematologic cytokine storm contributes not only to local tumor-promoting inflammation but also to systemic complications that adversely affect patient outcomes [5-6].

The tumor microenvironment in ovarian cancer is composed of a heterogeneous population of immune cells, including tumor-associated macrophages, neutrophils, dendritic cells, and lymphocytes, all of which interact with malignant cells to modulate cytokine production. Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) have been consistently identified in both tumor tissue and peripheral blood of patients with advanced disease. These cytokines activate signaling pathways that promote tumor cell proliferation, angiogenesis, and immune evasion, while simultaneously disrupting normal hematopoietic processes in the bone marrow [7-8]. Hematologic abnormalities frequently accompany the cytokine storm in ovarian cancer and include anemia of chronic disease, thrombocytosis, and leukocytosis. These changes not only reflect underlying inflammation but also exacerbate clinical symptoms such as fatigue, increased thrombotic risk, and susceptibility to infection. The dysregulated immune environment impairs effective anti-tumor immunity and complicates the administration of standard therapies, highlighting the need for a better understanding of cytokine-mediated hematologic dysfunction [9-10].

In recent years, therapeutic approaches targeting components of the cytokine storm have gained attention. Agents such as IL-6 receptor antagonists and TNF-α inhibitors, widely used in autoimmune conditions, are being investigated for their potential to mitigate hyperinflammation and improve treatment tolerance in ovarian cancer patients. Moreover, immune checkpoint inhibitors and novel immunomodulatory therapies hold promise for restoring immune balance, although their efficacy may be limited by the immunosuppressive effects of chronic cytokine exposure [11-12].

AIM

This review aims to provide a comprehensive analysis of the hematologic cytokine storm as a key component of immune dysregulation in advanced ovarian cancer.

METHODS

This narrative review was conducted through a comprehensive search of the scientific literature to explore the role of hematologic cytokine storm and immune dysregulation in advanced ovarian cancer. The databases searched included PubMed, Scopus, Web of Science, and Google Scholar, covering publications from January 2000 to December 2025. Key search terms used were “ovarian cancer,” “cytokine storm,” “immune dysregulation,” “hematologic dysfunction,” “myeloid-derived suppressor cells,” “neutrophil extracellular traps,” “coagulopathy,” and “tumor microenvironment.”

The selection criteria focused on peer-reviewed original research articles, reviews, clinical studies, and mechanistic reports relevant to systemic inflammatory responses and hematologic alterations in ovarian cancer. Articles not published in English, preprints without peer review, and studies lacking clear mechanistic or clinical relevance were excluded. Data from the selected studies were synthesized thematically, emphasizing mechanistic insights, systemic hematologic consequences, biomarker profiles, clinical correlations, and therapeutic implications. The narrative approach allowed integration of preclinical findings, translational evidence, and clinical observations to provide a comprehensive understanding of cytokine-driven immune and hematologic dysregulation in advanced ovarian cancer.

Pathophysiology of Hematologic Cytokine Storm in Ovarian Cancer

The hematologic cytokine storm observed in advanced ovarian cancer represents a hyperactive and dysregulated immune response characterized by excessive secretion of pro-inflammatory cytokines that profoundly impact both the tumor microenvironment and systemic physiology. This phenomenon arises from complex interactions between malignant ovarian cells and various components of the host immune system, creating a self-perpetuating cycle of inflammation and immune dysregulation [13-14]. At the core of this process are tumor-associated immune cells, particularly macrophages, neutrophils, and dendritic cells, which become aberrantly activated within the tumor microenvironment. These cells secrete elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cytokines initiate and amplify inflammatory signaling cascades that not only promote tumor cell survival, proliferation, and invasion but also modulate hematopoietic function in the bone marrow [15-16].

IL-6 is a central mediator in the cytokine storm, acting through the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway to drive cancer cell growth, resistance to apoptosis, and angiogenesis. Elevated IL-6 levels also contribute to systemic manifestations by stimulating the hepatic acute

phase response, leading to increased production of C-reactive protein (CRP) and other inflammatory proteins. This cytokine further disrupts normal hematopoiesis by promoting myeloid lineage skewing, resulting in neutrophilia and thrombocytosis commonly seen in ovarian cancer patients [17-18]. TNF-α and IL-1β enhance vascular permeability and recruit additional immune cells to the tumor site, facilitating a pro-inflammatory microenvironment that supports tumor progression and metastasis. These cytokines can also induce endothelial activation and dysfunction, contributing to coagulopathy and increasing the risk of thromboembolic events—a significant cause of morbidity in ovarian cancer. Moreover, they suppress erythropoiesis and induce apoptosis in erythroid progenitors, contributing to anemia of chronic disease [19-20]. The persistent release of these cytokines triggers systemic immune activation, which overwhelms regulatory mechanisms designed to contain inflammation. This unchecked inflammation leads to hematologic derangements including anemia, leukocytosis, and thrombocytosis. In addition, chronic exposure to elevated cytokine levels induces immune exhaustion and senescence, impairing the capacity of lymphocytes to mount effective anti-tumor responses (Table 1) [20].

Table 1: Key Cytokines Involved in Hematologic Cytokine Storm and Their Roles in Ovarian Cancer

Cytokine	Primary Source	Functions in Ovarian Cancer	Hematologic Impact
Interleukin-6 (IL-6)	Tumor cells, macrophages, T cells	Promotes tumor growth, angiogenesis, immune evasion via JAK/STAT3	Induces thrombocytosis, anemia of chronic disease
Tumor Necrosis Factor-alpha (TNF-α)	Macrophages, neutrophils	Enhances inflammation, vascular permeability, tumor invasion	Suppresses erythropoiesis, promotes endothelial dysfunction
Interleukin-1 beta (IL-1β)	Activated macrophages, dendritic cells	Amplifies inflammatory signaling, recruits immune cells	Contributes to anemia, coagulopathy
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Tumor and stromal cells	Drives myeloid cell proliferation and differentiation	Causes leukocytosis, alters immune cell balance
Interleukin-10 (IL-10)	Regulatory T cells, macrophages	Immunosuppressive, limits excessive inflammation	May contribute to immune exhaustion

Clinical and Hematologic Manifestations

The hematologic cytokine storm in advanced ovarian cancer manifests clinically with a spectrum of systemic inflammatory symptoms and hematologic abnormalities that significantly impact patient morbidity and prognosis. Patients frequently present with constitutional symptoms such as persistent fever, fatigue, malaise, and weight loss, reflecting the systemic inflammatory burden driven by excessive cytokine release. These symptoms often complicate clinical management by masking or exacerbating cancer-related manifestations [21]. Hematologic abnormalities associated with the cytokine storm are common and include anemia of chronic disease, leukocytosis, and thrombocytosis. Anemia is primarily driven by chronic inflammation and cytokine-mediated suppression of erythropoiesis, along with shortened erythrocyte lifespan. Elevated levels of IL-6 and TNF-α inhibit erythroid progenitor proliferation and decrease erythropoietin production, contributing to hypoproliferative anemia that worsens fatigue and reduces quality of life [22-23].

Leukocytosis, especially neutrophilia, results from cytokine-induced myelopoiesis and the recruitment of neutrophils into circulation. This expansion of the myeloid compartment may paradoxically coincide with immune dysfunction, as neutrophils adopt pro-tumorigenic phenotypes that facilitate tumor growth, angiogenesis, and metastasis. Similarly, thrombocytosis is commonly observed and is mediated by inflammatory cytokines such as IL-6, which stimulate thrombopoietin production and megakaryocyte proliferation. Elevated platelet counts not only correlate with advanced disease stage but also increase the risk of thromboembolic complications, which remain a leading cause of death in ovarian cancer patients [24-25]. Beyond these hematologic changes, systemic inflammation induced by cytokine storms can disrupt endothelial integrity and coagulation pathways, resulting in a hypercoagulable state. This predisposes patients to venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, further complicating treatment and prognosis. Elevated D-dimer and fibrinogen levels often accompany these clinical events, reflecting ongoing coagulation and fibrinolysis [26]. Laboratory markers such as increased C-reactive protein (CRP), ferritin, and erythrocyte sedimentation rate (ESR) serve as indicators of systemic inflammation and correlate with cytokine storm severity. These biomarkers, combined with hematologic parameters like neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been proposed as prognostic tools for disease progression and survival in ovarian cancer patients (Table 2) [27].

Table 2: Common Hematologic Manifestations of Cytokine Storm in Advanced Ovarian Cancer

Hematologic Abnormality	Description	Underlying Mechanism	Clinical Consequences
Anemia of Chronic Disease	Hypoproliferative anemia with low reticulocytes	Cytokine-mediated suppression of erythropoiesis (IL-6, TNF-α)	Fatigue, reduced treatment tolerance
Thrombocytosis	Elevated platelet count	IL-6 induced thrombopoietin stimulation	Increased thrombotic risk, vascular complications
Leukocytosis	Increased white blood cell count, mainly neutrophils	Cytokine-driven myelopoiesis and neutrophil mobilization	Predisposition to infection and immune dysfunction
Coagulopathy	Hypercoagulable state with elevated D-dimer, fibrinogen	Endothelial activation by TNF-α and IL-1β	Venous thromboembolism, bleeding risk
Elevated Inflammatory Markers	Raised CRP, ESR, ferritin	Acute phase response driven by IL-6	Correlates with disease severity and prognosis

Therapeutic Approaches

Addressing the hematologic cytokine storm in advanced ovarian cancer requires a multifaceted strategy aimed at modulating the hyperinflammatory state while preserving effective anti-tumor immunity. Therapeutic interventions focus on controlling excessive cytokine production, mitigating systemic inflammation, and managing hematologic complications to improve patient outcomes and quality of life (Table 3) [28].

Anti-inflammatory and Cytokine-Targeted Therapies: One of the primary approaches to attenuate the cytokine storm involves the use of agents that directly inhibit key pro-inflammatory cytokines. Interleukin-6 (IL-6) receptor antagonists, such as tocilizumab, have shown promise in mitigating systemic inflammation by blocking IL-6 mediated signaling pathways responsible for tumor progression and hematologic abnormalities. Similarly, tumor necrosis factor-alpha (TNF-α) inhibitors have potential to reduce inflammation and vascular dysfunction, although their use in oncology remains investigational. These therapies aim to disrupt the cytokine-driven feedback loop, thus limiting further immune dysregulation [29-30].

Immunomodulatory and Checkpoint Inhibitor Therapies: Immune checkpoint inhibitors (ICIs), targeting molecules such as PD-1, PD-L1, and CTLA-4, have revolutionized cancer treatment by reactivating exhausted T cells. However, their efficacy in ovarian cancer is often hampered by the immunosuppressive milieu created by chronic cytokine exposure and myeloid-derived suppressor cells (MDSCs). Combining ICIs with cytokine-targeting agents or myeloid cell modulators may enhance immune responses by alleviating cytokine-induced immunosuppression. Additionally, therapies aimed at reversing immune senescence and exhaustion, including senolytics and adoptive cell transfers, represent emerging modalities that warrant further exploration [31-32].

Supportive Hematologic Management: Managing hematologic abnormalities is critical in patients experiencing cytokine storms. Anemia may be treated with erythropoiesis-stimulating agents and transfusions, whereas thrombocytosis and leukocytosis require careful monitoring to prevent thrombotic and infectious complications. Anticoagulants, including low-molecular-weight heparin, are frequently employed to reduce venous thromboembolism risk, particularly in patients with elevated inflammatory markers and platelet counts. Growth factors such as granulocyte colony-stimulating factor (G-CSF) can be used to support neutrophil recovery during chemotherapy-induced myelosuppression [33-34].

Combination and Personalized Therapy: Given the complexity of immune dysregulation in ovarian cancer, personalized therapeutic approaches that integrate cytokine modulation, immune checkpoint blockade, and conventional chemotherapy hold the greatest promise. Biomarker-driven patient stratification—utilizing cytokine profiles, inflammatory markers, and immune cell phenotyping—can guide therapy selection and optimize efficacy while minimizing toxicity. Multidisciplinary care involving oncologists, hematologists, and immunologists is essential for tailoring interventions to individual patient needs [35-36].

Table 3: Therapeutic Strategies Targeting Hematologic Cytokine Storm in Ovarian Cancer

Therapeutic Approach	Mechanism of Action	Examples/Agents	Clinical Considerations
Cytokine Inhibition	Blocks specific cytokine signaling to reduce inflammation	Tocilizumab (IL-6R antagonist), Infliximab (TNF-α inhibitor)	Potential immunosuppression; currently under clinical evaluation

Therapeutic Approach	Mechanism of Action	Examples/Agents	Clinical Considerations
Immune Checkpoint Blockade	Restores T cell function by inhibiting PD-1/PD-L1, CTLA-4	Pembrolizumab, Nivolumab	Efficacy may be limited by cytokine-induced immunosuppression
Hematologic Supportive Care	Corrects anemia, reduces thrombosis risk	Erythropoiesis-stimulating agents, anticoagulants, G-CSF	Requires monitoring to balance benefits and risks
Combination Immunotherapy	Combines cytokine inhibitors with ICIs or chemotherapy	Clinical trial combinations	Personalized therapy guided by biomarkers preferred
Emerging Therapies	Targets senescent immune cells or metabolic pathways	Senolytics, JAK/STAT inhibitors	Experimental; promising preclinical data

Future Perspectives

The hematologic cytokine storm in advanced ovarian cancer represents a formidable challenge in both understanding and clinical management. Future research directions must focus on elucidating the complex molecular and cellular networks driving this hyperinflammatory state, with an emphasis on identifying novel biomarkers and therapeutic targets. Advances in high-throughput technologies, such as single-cell RNA sequencing and proteomics, will facilitate deeper insights into the heterogeneity of immune cell populations and their dynamic interactions within the tumor microenvironment [37-38]. Emerging evidence suggests that the integration of multi-omics approaches, combining genomic, transcriptomic, and metabolomic data, can uncover key regulators of cytokine production and immune dysregulation. This systems biology perspective is essential for developing precision medicine strategies that tailor interventions based on individual patient profiles, including cytokine signatures, immune cell phenotypes, and genetic predispositions. Such personalized approaches hold promise for improving the efficacy of cytokine-targeted therapies and minimizing adverse effects [39].

Immunotherapeutic advancements, particularly in immune checkpoint blockade and adoptive cell therapies, are poised to benefit from concurrent modulation of the cytokine storm. Combinatorial regimens that simultaneously inhibit pro-inflammatory cytokines and rejuvenate exhausted T cells may enhance anti-tumor immunity. Furthermore, emerging modalities such as senolytic agents targeting senescent immune cells and metabolic reprogramming of immune subsets offer novel avenues to reverse immune dysfunction and restore homeostasis [40]. Clinical trials incorporating biomarker-driven patient selection will be pivotal in validating new therapeutic combinations and identifying predictors of response. Additionally, the development of non-invasive monitoring tools—such as circulating cytokine panels and liquid biopsies—will facilitate early detection of cytokine storm onset and guide timely intervention, potentially preventing severe systemic complications [41].

Addressing the hematologic complications of the cytokine storm, including anemia and thrombosis, remains a critical area of focus. Innovative supportive care protocols integrating anti-inflammatory agents, hematopoietic growth factors, and anticoagulants need to be optimized and individualized to balance efficacy with safety. Moreover, understanding the impact of standard chemotherapeutic and targeted agents on immune and hematologic parameters will inform combination strategies that mitigate exacerbation of cytokine-driven pathology [42]. Fostering interdisciplinary collaboration among oncologists, immunologists, hematologists, and bioinformaticians will accelerate the translation of basic scientific discoveries into clinical applications. By bridging gaps between laboratory research and patient care, future efforts can transform the management of hematologic cytokine storms and improve the prognosis for patients with advanced ovarian cancer [43].

CONCLUSION

The hematologic cytokine storm in advanced ovarian cancer represents a critical axis of immune dysregulation that profoundly influences disease progression, systemic inflammation, and hematologic abnormalities. This hyperinflammatory state, driven by excessive release of cytokines such as IL-6, TNF-α, and IL-1β, not only fosters a tumor-promoting microenvironment but also contributes to debilitating clinical manifestations including anemia, thrombocytosis, leukocytosis, and increased thrombotic risk. Understanding the complex interplay between tumor cells, immune effectors, and hematopoietic processes is essential for improving patient outcomes. Therapeutic strategies targeting key cytokines and inflammatory pathways, combined with immunomodulatory treatments and supportive hematologic care, hold promise for mitigating the detrimental effects of the cytokine storm. However, challenges remain in balancing immune suppression with the restoration of effective anti-tumor responses. Personalized approaches guided by biomarker profiling and integrated multi-omics analyses will be pivotal in tailoring therapies to individual patient needs.

Conflicts of Interest

The author declares no conflict of interest

Sources of Funding

No fund was received to write this review paper

Ethical Approval

Not applicable

Consent

Not applicable

REFERENCES

1. Lukanović, D., Kobal, B., & Černe, K. (2022). Ovarian cancer: treatment and resistance to pharmacotherapy. *Reproductive Medicine*, *3*(2), 127-140. https://doi.org/10.3390/reprodmed3020011
2. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. (2016). Ovarian cancer. Nat Rev Dis Primers., 2:16061. doi: 10.1038/nrdp.2016.61.
3. Obeagu, E. I. (2025). Clear Cell Ovarian Carcinoma and Its Distinct Coagulopathy Profile: Molecular Drivers and Clinical Implications. *Cancer Management and Research*, 2459-2467. doi: 10.2147/CMAR.S555874.
4. Obeagu, E. I. (2025). Venous thromboembolism in ovarian cancer: pathophysiology, risk, and management. *Annals of Medicine and Surgery*, *87*(12), 8587-8596. doi: 10.1097/MS9.0000000000004192.
5. Obeagu, E. I. (2025). Modulation of chronic cytokine dysregulation in cervical cancer: potential biomarkers and therapeutic targets. *Cancer Management and Research*, 1113-1126. doi: 10.2147/CMAR.S527913.
6. Tisoncik, J. R., Korth, M. J., Simmons, C. P., Farrar, J., Martin, T. R., & Katze, M. G. (2012). Into the eye of the cytokine storm. *Microbiology and molecular biology reviews*, *76*(1), 16-32. doi: 10.1128/MMBR.05015-11.
7. Cheng, K. C., Lin, Y. H., Wu, D. S., Shih, I. M., & Wang, T. L. (2025). Macrophages and neutrophils in ovarian cancer microenvironment. *Frontiers in immunology*, *16*, 1677441. doi: 10.3389/fimmu.2025.1677441.
8. Blanc-Durand, F., Clemence Wei Xian, L., & Tan, D. S. (2023). Targeting the immune microenvironment for ovarian cancer therapy. *Frontiers in immunology*, *14*, 1328651. doi: 10.3389/fimmu.2023.1328651.
9. Lian, C., Fan, Y., & Li, J. (2025). Clarifying blood indices in patients with ovarian cancer. *JMIR Mhealth Uhealth*, *13*, e70895. doi: 10.2196/70895.
10. Chen, Y., Zhang, L., Liu, W. X., & Liu, X. Y. (2015). Prognostic significance of preoperative anemia, leukocytosis and thrombocytosis in chinese women with epithelial ovarian cancer. *Asian Pacific journal of cancer prevention*, *16*(3), 933-939. doi: 10.7314/apjcp.2015.16.3.933.
11. D'Elia, R. V., Harrison, K., Oyston, P. C., Lukaszewski, R. A., & Clark, G. C. (2013). Targeting the "cytokine storm" for therapeutic benefit. *Clinical and Vaccine Immunology*, *20*(3), 319-327. doi: 10.1128/CVI.00636-12.
12. Tang, X. D., Ji, T. T., Dong, J. R., Feng, H., Chen, F. Q., Chen, X., ... & Ma, W. T. (2021). Pathogenesis and treatment of cytokine storm induced by infectious diseases. *International Journal of Molecular Sciences*, *22*(23), 13009. https://doi.org/10.3390/ijms222313009
13. Liu, C., Yin, Q., Wu, Z., Li, W., Huang, J., Chen, B., ... & Wang, J. (2025). Inflammation and immune escape in ovarian cancer: pathways and therapeutic opportunities. *Journal of Inflammation Research*, 895-909. doi: 10.2147/JIR.S503479.
14. Mielczarek-Palacz, A., Sikora, J., Kondera-Anasz, Z., Mickiewicz, P., & Mickiewicz, A. (2016). Effect of Th1/Th2 cytokine administration on proinflammatory SKOV-3 cell activation. *Archives of Medical Science*, *12*(6), 1337-1347. doi: 10.5114/aoms.2015.53143.
15. Shen, M., Du, Y., & Ye, Y. (2021). Tumor-associated macrophages, dendritic cells, and neutrophils: biological roles, crosstalk, and therapeutic relevance. *Medical Review*, *1*(2), 222-243. doi: 10.1515/mr-2021-0014. PMID: 37724296; PMCID: PMC10388790.
16. Turlej, E., Domaradzka, A., Radzka, J., Drulis-Fajdasz, D., Kulbacka, J., & Gizak, A. (2025). Cross-talk between cancer and its cellular environment—A role in cancer progression. *Cells*, *14*(6), 403. https://doi.org/10.3390/cells14060403
17. Huang, B., Lang, X., & Li, X. (2022). The role of IL-6/JAK2/STAT3 signaling pathway in cancers. *Frontiers in oncology*, *12*, 1023177. doi: 10.3389/fonc.2022.1023177.
18. Johnson, D. E., O'Keefe, R. A., & Grandis, J. R. (2018). Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nature reviews Clinical oncology*, *15*(4), 234-248. doi: 10.1038/nrclinonc.2018.8.
19. Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., & Li, Y. (2021). Inflammation and tumor progression: signaling pathways and targeted intervention. *Signal transduction and targeted therapy*, *6*(1), 263. doi: 10.1038/s41392-021-00658-5.
20. O'Carroll, S. J., Kho, D. T., Wiltshire, R., Nelson, V., Rotimi, O., Johnson, R., ... & Graham, E. S. (2015). Pro-inflammatory TNFα and IL-1β differentially regulate the inflammatory phenotype of brain microvascular endothelial cells. *Journal of neuroinflammation*, *12*(1), 131. doi: 10.1186/s12974-015-0346-0.
21. Jammal MP, Martins-Filho A, Silveira TP, Murta EF, Nomelini RS. (2016). Cytokines and Prognostic Factors in Epithelial Ovarian Cancer. Clin Med Insights Oncol., 10:71-76. doi: 10.4137/CMO.S38333.
22. Nie, J., Zhou, L., Tian, W., Liu, X., Yang, L., Yang, X., ... & Wei, J. (2025). Deep insight into cytokine storm: from pathogenesis to treatment. *Signal Transduction and Targeted Therapy*, *10*(1), 112. doi: 10.1038/s41392-025-02178-y.
23. Wiciński, M., Liczner, G., Cadelski, K., Kołnierzak, T., Nowaczewska, M., & Malinowski, B. (2020). Anemia of chronic diseases: wider diagnostics—better treatment?. *Nutrients*, *12*(6), 1784. doi: 10.3390/nu12061784.

24. Polymeris, A., Kogia, C., Ioannidis, D., Lilis, D., Drakou, M., Maounis, N., ... & Tseleni-Balafouta, S. (2020). Excessive leukocytosis leading to a diagnosis of aggressive thyroid anaplastic carcinoma: a case report and relevant review. *European Thyroid Journal*, *9*(3), 162-168. doi: 10.1159/000506767.
25. Sturgeon, R., Goel, P., Molczyk, C., Bhola, R., Grandgenett, P. M., Hollingsworth, M. A., & Singh, R. K. (2025). Neutrophil Dynamics Contribute to Disease Progression and Poor Survival in Pancreatic Cancer. *Cancers*, *17*(21), 3541. https://doi.org/10.3390/cancers17213541
26. Savla, S. R., Prabhavalkar, K. S., & Bhatt, L. K. (2021). Cytokine storm associated coagulation complications in COVID-19 patients: Pathogenesis and Management. *Expert review of anti-infective therapy*, *19*(11), 1397-1413. doi: 10.1080/14787210.2021.1915129.
27. Gündüz, Ö., Seven, B., Ozgu-Erdınc, A. S., Ayhan, S. G., Sahin, D., Tekin, O. M., & Keskin, H. L. (2023). Correlation of systemic inflammation biomarkers and disease severity in pregnant women with COVID-19. *Revista da Associação Médica Brasileira*, *69*(6), e20221614. doi: 10.1590/1806-9282.20221614.
28. Scarlett, U. K., & Conejo-Garcia, J. R. (2012). Modulating the tumor immune microenvironment as an ovarian cancer treatment strategy. *Expert review of obstetrics & gynecology*, *7*(5), 413-419. doi: 10.1586/eog.12.41.
29. Morgulchik, N., Athanasopoulou, F., Chu, E., Lam, Y., & Kamaly, N. (2022). Potential therapeutic approaches for targeted inhibition of inflammatory cytokines following COVID-19 infection-induced cytokine storm. *Interface focus*, *12*(1). 20210006. doi: 10.1098/rsfs.2021.0006.
30. Mohammed, M. A. (2023). Fighting cytokine storm and immunomodulatory deficiency: By using natural products therapy up to now. *Frontiers in Pharmacology*, *14*, 1111329. doi: 10.3389/fphar.2023.1111329.
31. Chen, H., Yang, H., Guo, L., & Sun, Q. (2025). The role of immune checkpoint inhibitors in cancer therapy: mechanism and therapeutic advances. *MedComm*, *6*(10), e70412. doi: 10.1002/mco2.70412.
32. Almawash, S. (2025). Revolutionary cancer therapy for personalization and improved efficacy: strategies to overcome resistance to immune checkpoint inhibitor therapy. *Cancers*, *17*(5), 880. https://doi.org/10.3390/cancers17050880
33. Bryer, E. J., Kallan, M. J., Chiu, T. S., Scheuba, K. M., & Henry, D. H. (2020). A retrospective analysis of venous thromboembolism trends in chemotherapy-induced anemia: Red blood cell transfusion versus erythrocyte stimulating agent administration. *EJHaem*, *1*(1), 35-43. doi: 10.1002/jha2.18.
34. Muhammed, Z. A. E., Alfatih, M., Babiker, A. S. H., Aldau, K. M. A., Hajali, H. E., Gharbawi, M. E. S., ... & Ahmed, A. (2022). Extreme thrombocytosis with severe anemia and infection in a Sudanese patient: A case report. *Annals of Medicine and Surgery*, *84*, 104927. doi: 10.1016/j.amsu.2022.104927.
35. Butterfield, L. H., & Najjar, Y. G. (2024). Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations. *Nature Reviews Immunology*, *24*(6), 399-416. doi: 10.1038/s41577-023-00973-8.
36. Yang, C., Xia, B. R., Zhang, Z. C., Zhang, Y. J., Lou, G., & Jin, W. L. (2020). Immunotherapy for ovarian cancer: adjuvant, combination, and neoadjuvant. *Frontiers in immunology*, *11*, 577869. doi: 10.3389/fimmu.2020.577869.
37. Worzfeld, T., Pogge von Strandmann, E., Huber, M., Adhikary, T., Wagner, U., Reinartz, S., & Müller, R. (2017). The unique molecular and cellular microenvironment of ovarian cancer. *Frontiers in oncology*, *7*, 24. doi: 10.3389/fonc.2017.00024.
38. Karki, R., & Kanneganti, T. D. (2021). The 'cytokine storm': molecular mechanisms and therapeutic prospects. *Trends in immunology*, *42*(8), 681-705. doi: 10.1016/j.it.2021.06.001.
39. Ivanisevic, T., & Sewduth, R. N. (2023). Multi-omics integration for the design of novel therapies and the identification of novel biomarkers. *Proteomes*, *11*(4), 34. doi: 10.3390/proteomes11040034. PMID: 37873876; PMCID: PMC10594525.
40. Manzano, S., & Caffarel, M. M. (2025). Cytokine-centered strategies to boost cancer immunotherapy. *Molecular Oncology*, *19*(3), 579-583. doi: 10.1002/1878-0261.13818.
41. Passaro, A., Al Bakir, M., Hamilton, E. G., Diehn, M., André, F., Roy-Chowdhuri, S., ... & Peters, S. (2024). Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. *Cell*, *187*(7), 1617-1635. doi: 10.1016/j.cell.2024.02.041.
42. Savla, S. R., Prabhavalkar, K. S., & Bhatt, L. K. (2021). Cytokine storm associated coagulation complications in COVID-19 patients: Pathogenesis and Management. *Expert review of anti-infective therapy*, *19*(11), 1397-1413. doi: 10.1080/14787210.2021.1915129.
43. Mäurer, M., Staudacher, J., Meyer, R., Mäurer, I., Lazaridis, L., Müther, M., ... & Young Oncologists United (YOU). (2023). Importance of interdisciplinarity in modern oncology: results of a national intergroup survey of the Young Oncologists United (YOU). *Journal of Cancer Research and Clinical Oncology*, *149*(12), 10075-10084. doi: 10.1007/s00432-023-04937-2.