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Short-Communication

Immune-Inflammatory Crosstalk in Cancer Progression: Translational Insights from Neutrophil-to-Lymphocyte Ratio Studies

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Abstract:
The interplay between the immune system and cancer is a fundamental determinant of disease progression, therapeutic response, and patient survival. Among various systemic inflammatory markers, the **Neutrophil-to-Lymphocyte Ratio (NLR)** has emerged as a robust, cost-effective, and readily accessible prognostic tool. An elevated NLR reflects a shift in the immune-inflammatory balance: a dominance of pro-tumorigenic innate responses (neutrophilia) over anti-tumor adaptive immunity (lymphopenia). This manuscript provides a comprehensive review of the translational mechanisms linking NLR to cancer progression, its role as a prognostic biomarker across various solid tumors, and its emerging utility in predicting responses to modern therapies, including immune checkpoint inhibitors.
Keywords: Immune–Inflammatory Crosstalk, Cancer Progression, Neutrophil-to-Lymphocyte Ratio

1. Introduction

Cancer development is not solely an autonomous genetic process but is deeply integrated with the host's immune-inflammatory landscape (Mosca et al., 2023). While the immune system's primary role is to eliminate transformed cells, chronic inflammatory responses often foster a microenvironment conducive to tumor growth, angiogenesis, and metastasis (Mosca et al., 2023).

The **Neutrophil-to-Lymphocyte Ratio (NLR)**—calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a standard full blood count—serves as a peripheral mirror of this systemic inflammatory status (Mosca et al., 2023; Zhou et al., 2021). Its clinical appeal lies in its simplicity and universal availability (Mosca et al., 2023).

2. Pathophysiological Mechanisms of NLR

2.1. The Role of Neutrophils: From Defense to Tumor Promotion

Historically viewed as simple "foot soldiers," neutrophils are now recognized as dynamic orchestrators of the **tumor microenvironment (TME)** (Frontiers, 2026). They exhibit significant plasticity, often categorized into two polar phenotypes:

- **N1 Neutrophils:** Anti-tumorigenic cells that activate innate and adaptive immune responses (Mosca et al., 2023).
- **N2 Neutrophils:** Pro-tumorigenic cells that promote neo-angiogenesis, stroma remodeling, and immunosuppression (Mosca et al., 2023).

High NLR values often correlate with an increased concentration of **tumor-associated neutrophils (TANs)** and pro-inflammatory cytokines such as IL-6, IL-8, and IL-17 (Mosca et al., 2023). These cells facilitate metastasis by trapping circulating tumor cells via **neutrophil extracellular traps (NETs)** and producing matrix metalloproteinases (e.g., MMP9) that degrade the extracellular matrix (Mosca et al., 2023).

2.2. Lymphopenia and the Failure of Adaptive Immunity

Conversely, the denominator of the NLR—the lymphocyte count—represents the adaptive immune system's ability to mount an anti-tumor response. Low lymphocyte levels often signify T-cell dysregulation or apoptosis, a common counter-regulatory response to chronic stress and tumor-

induced inflammation (Chee et al., 2025). This functional exhaustion allows tumors to evade immune surveillance (Frontiers, 2026).

3. Clinical Utility as a Prognostic Biomarker

3.1. Solid Tumors and Metastasis

Extensive research has demonstrated that a high baseline NLR is an independent risk factor for poor outcomes in various cancers:

- **Lung Cancer:** Elevated NLR is strongly associated with an increased risk of brain metastasis, particularly in small cell lung cancer (SCLC) (Frontiers, 2026).
- **Breast Cancer:** Meta-analyses show that a high NLR predicts lower disease-free survival (DFS) and overall survival (OS) in patients receiving neoadjuvant chemotherapy (Zhou et al., 2021).
- **Nasopharyngeal Carcinoma (NPC):** High pre-treatment NLR values are linked to chemoresistance and poor short-term prognosis (Asian Pacific Journal of Cancer Biology, 2026).

3.2. Predictive Role in Immunotherapy

In the era of **Immune Checkpoint Inhibitors (ICIs)**, NLR has gained prominence as a predictive marker. Patients with an upward trend in NLR after starting ICI treatment typically experience worse clinical outcomes (Guo et al., 2022). Furthermore, NLR is being investigated as a biomarker for **hyperprogressive disease (HPD)**—a phenomenon where ICIs paradoxically accelerate tumor growth (Pei et al., 2024).

Marker	Clinical Significance	Prognostic Impact
High NLR	Systemic inflammation, N2 neutrophil dominance	Poor Survival, Higher Metastasis Risk
Low NLR	Robust adaptive immunity, N1 neutrophil presence	Favorable Prognosis, Better Therapy Response

4. Translational Insights and Future Directions

The dynamic nature of NLR makes it a valuable tool for monitoring treatment response. Studies show that a significant decrease in NLR following chemotherapy (e.g., in NPC patients) correlates with improved outcomes (Asian Pacific Journal of Cancer Biology, 2026).

Future research is moving toward integrating NLR with other biomarkers, such as **PD-L1 expression** and **tumor mutational burden (TMB)**, to create more accurate patient stratification models (Mosca et al., 2023). Spatial transcriptomics and single-cell resolution studies will be essential to fully map the neutrophil signaling pathways that drive these systemic changes (Frontiers, 2026).

5. Conclusion

The Neutrophil-to-Lymphocyte Ratio is more than just a numerical value; it is a clinical proxy for the complex immune-inflammatory crosstalk that dictates cancer progression. While its ease of use is a major advantage, its integration into daily clinical practice requires standardized cut-off values and further prospective validation across diverse populations.

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