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Systematic Review

Peripheral Blood Biomarkers in Non-Hodgkin Lymphoma: Evaluation of Classical Serological Markers and Emerging Liquid Biopsy Approaches

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Abstract:

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of lymphoid malignancies with varied clinical behavior, treatment response, and prognosis. While tissue biopsy remains the diagnostic gold standard, peripheral blood biomarkers have gained increasing importance as minimally invasive, cost-effective tools for diagnosis, prognostic stratification, treatment monitoring, and detection of minimal residual disease. Classical serological biomarkers such as lactate dehydrogenase (LDH), beta-2 microglobulin (β2-microglobulin), and carcinoembryonic antigen (CEA) are widely available and routinely used in clinical practice, particularly in resource-limited settings. Recent advances have further expanded the scope of peripheral blood biomarkers through liquid biopsy approaches, including circulating tumor DNA (ctDNA), circulating RNAs, and epigenetic markers. This review provides a comprehensive and simplified synthesis of global evidence on peripheral blood biomarkers in NHL, with particular emphasis on the evaluation of serum LDH, β2-microglobulin, and CEA, their biological basis, clinical utility, prognostic significance, and public health relevance, while also highlighting emerging molecular approaches and future directions.

Keywords: Non-Hodgkin lymphoma; LDH; beta-2 microglobulin; CEA; peripheral blood biomarkers; liquid biopsy; prognosis.

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Introduction

Non-Hodgkin lymphoma (NHL) comprises a diverse group of malignancies arising from B lymphocytes, T lymphocytes, or natural killer cells, accounting for a substantial proportion of hematological cancers worldwide. The global incidence of NHL has shown a steady increase over recent decades, making it an important public health concern, particularly in low- and middle-income countries where diagnostic and treatment resources are often limited. The disease exhibits marked heterogeneity in terms of histology, molecular characteristics, clinical presentation, and outcomes.

Advances in lymphoma classification have shifted diagnostic paradigms from purely morphological assessment to integrated clinicopathological approaches incorporating immunophenotyping, cytogenetics, and molecular profiling[1]. Despite these advances, tissue biopsy and radiological imaging remain central to diagnosis and staging. However, these modalities are invasive, expensive, and not well suited for repeated disease monitoring. In addition, they may fail to capture intratumoral heterogeneity and dynamic changes during treatment.

Peripheral blood biomarkers provide a minimally invasive window into tumor biology and host–tumor interactions. Classical serological markers such as LDH, β2-microglobulin, and CEA are inexpensive, widely available, and routinely measured in clinical settings. Numerous studies have demonstrated their association with tumor burden, disease stage, treatment response, and survival outcomes in NHL [1,10,13]. In parallel, advances in molecular biology have led to the development of liquid biopsy techniques, enabling detection of tumor-derived nucleic acids in peripheral blood. Nevertheless, the accessibility of such advanced technologies remains limited in many healthcare systems, underscoring the continued relevance of classical serum biomarkers.

This review aims to comprehensively evaluate peripheral blood biomarkers in non-Hodgkin lymphoma, with a specific focus on serum LDH, β2-microglobulin, and CEA, while situating these markers within the evolving landscape of liquid

biopsy technologies and highlighting their clinical and public health significance.

Biological Basis of Peripheral Blood Biomarkers in NHL: Peripheral blood biomarkers originate from multiple biological processes related to lymphoma pathogenesis. Rapid tumor cell proliferation and turnover result in the release of intracellular enzymes such as LDH into circulation. Activation and expansion of malignant lymphocytes lead to increased shedding of β2-microglobulin, while extensive tissue infiltration and systemic inflammation may contribute to elevated CEA levels [1,2]. Additionally, apoptosis and necrosis of tumor cells release fragmented DNA and RNA into the bloodstream, forming the basis of liquid biopsy approaches.

Evaluation of Classical Serological Biomarkers

Lactate Dehydrogenase (LDH): LDH is a cytoplasmic enzyme involved in anaerobic glycolysis and is released during cellular damage and hypoxia. Elevated serum LDH is a well-established marker of high tumor burden and aggressive disease biology in NHL. It is a key component of the International Prognostic Index and has consistently been associated with advanced disease stage, extranodal involvement, inferior response to therapy, and reduced overall survival [1,10].

Beta-2 Microglobulin (β2-Microglobulin): Beta-2 microglobulin is a low-molecular-weight protein that forms part of the major histocompatibility complex class I molecule. Elevated serum β2-microglobulin levels reflect increased tumor mass and immune activation. Several studies have demonstrated its independent prognostic value in both aggressive and indolent NHL, with higher levels correlating with advanced stage, bone marrow involvement, and poorer survival outcomes [10,13].

Carcinoembryonic Antigen (CEA): CEA is a glycoprotein commonly used as a tumor marker in epithelial malignancies. Although it lacks specificity for lymphoma, elevated CEA levels have been reported in a subset of patients with NHL, particularly those with advanced-stage disease, bulky tumors, and extranodal involvement. When interpreted alongside LDH and β2-microglobulin, CEA may provide additional prognostic information regarding disease extent and biological aggressiveness [13].

Combined Prognostic Value: Combined evaluation of LDH, β2-microglobulin, and CEA enhances risk stratification compared to single-marker assessment. Patients with simultaneous elevation of LDH and β2-microglobulin consistently demonstrate poorer outcomes, while CEA may add supplementary prognostic insight in selected cases. This combined serological approach offers a simple, cost-effective strategy for baseline assessment and follow-up.

Summary Table: Classical Serological Biomarkers in Non-Hodgkin Lymphoma

Parameter	LDH	β2-Microglobulin	CEA
Biological source	Cytoplasmic enzyme	MHC class I component	Glycoprotein
Key significance	Tumor burden, aggressiveness	Tumor mass, immune activation	Disease extent, inflammation
Prognostic value	Strong; part of IPI	Independent prognostic marker	Supplementary prognostic marker
Clinical utility	Prognosis, monitoring	Prognosis, monitoring	Adjunct marker
Limitations	Low specificity	Affected by renal function	Low specificity

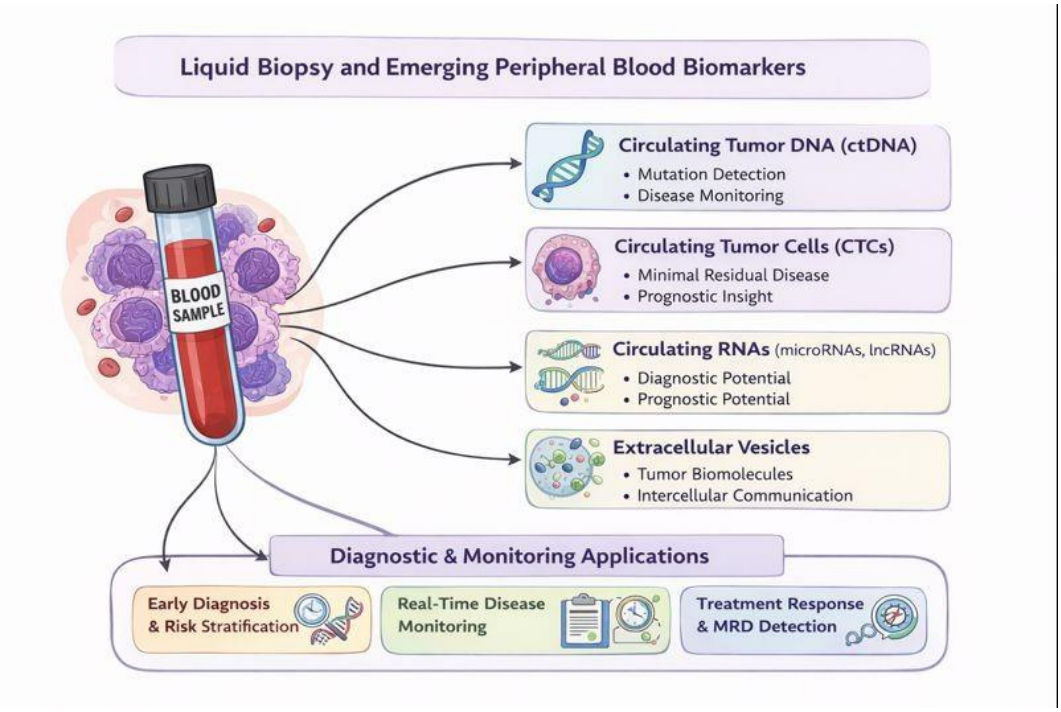
Immunophenotypic and Molecular Biomarkers: Flow cytometric immunophenotyping enables identification of circulating lymphoma cells, particularly in leukemic presentations and indolent subtypes. Molecular alterations such as chromosomal translocations involving BCL2, CCND1, and MYC, as well as TP53 mutations, can be detected in peripheral blood and have diagnostic and prognostic implications [1,12].

Liquid Biopsy and Emerging Peripheral Blood Biomarkers

Circulating Tumor DNA (ctDNA): ctDNA consists of fragmented tumor-derived DNA released into the bloodstream. Studies have demonstrated high concordance between ctDNA mutational profiles and tissue biopsy findings. Serial ctDNA monitoring correlates with tumor burden, treatment response, and minimal residual disease, often predicting relapse earlier than conventional imaging in aggressive NHL, particularly diffuse large B-cell lymphoma [4-6,11].

Circulating RNAs: Circulating microRNAs such as miR-21, miR-155, and the miR-17-92 cluster are dysregulated in NHL and play key roles in B-cell proliferation, apoptosis, and oncogenic signaling. These microRNAs are stable in plasma and show promise as diagnostic and prognostic biomarkers [7]. Long non-coding RNAs and circular RNAs are emerging as additional regulatory layers, although their clinical utility remains under investigation.

Epigenetic Signatures: Aberrant DNA methylation patterns detectable in peripheral blood have been associated with lymphoma risk, prognosis, and treatment response. These epigenetic biomarkers may reflect early oncogenic changes and hold promise for early detection strategies [8].



Epidemiological Evidence and Immune Activation Markers: Strong epidemiological evidence supports a role for chronic B-cell activation in NHL pathogenesis. In a large nested case–control study within the Women's Health Initiative, elevated prediagnostic levels of soluble CD23, CD27, CD30, CD44, and CXCL13 were associated with a significantly increased risk of B-cell NHL, detectable up to a decade before diagnosis [2]. Risk increased with the number of elevated biomarkers, supporting a cumulative effect of immune activation.

Clinical Applications: Peripheral blood biomarkers contribute across the continuum of NHL care, including diagnosis, prognostic stratification, treatment monitoring, MRD detection, and early relapse prediction. Integration of classical serological markers with immunophenotypic and molecular liquid biopsy approaches enables more personalized and dynamic disease management [1,4-6,11].

Limitations and Challenges: Despite promising advances, several challenges limit routine clinical implementation, including lack of assay standardization, biological heterogeneity among NHL subtypes, limited prospective validation, and high costs of advanced molecular techniques.

Future Perspectives: Future research is expected to focus on multi-analyte biomarker panels, integration of liquid biopsy data with imaging and clinical indices, and application of artificial intelligence for risk prediction. Large prospective studies are essential to translate emerging biomarkers into routine clinical practice.

Conclusion

Peripheral blood biomarkers have evolved from simple indicators of tumor burden to sophisticated molecular tools capable of reflecting the dynamic biology of non-Hodgkin lymphoma. Classical serological markers such as lactate dehydrogenase (LDH) and beta-2 microglobulin (β2-microglobulin) continue to play a pivotal role in prognostic stratification and therapeutic decision-making and remain especially valuable in routine clinical practice. Alongside these, rapid advances in liquid biopsy technologies—including circulating tumor DNA, circulating RNAs, and extracellular vesicles—have transformed the landscape of disease monitoring by enabling non-invasive, real-time assessment of tumor burden, treatment response, minimal residual disease, and early relapse.

Public Health Significance: From a public health perspective, non-Hodgkin lymphoma constitutes a significant and growing global health burden, with increasing incidence across both high-income and low- and middle-income countries. Peripheral blood–based biomarkers offer a minimally invasive, cost-effective, and scalable strategy for improving early detection, prognostic assessment, and longitudinal follow-up of patients at the population

level. The use of readily available serological markers can support timely risk stratification, optimize referral pathways, and guide treatment intensity in settings where access to advanced imaging, molecular diagnostics, or repeated tissue biopsies is limited. Furthermore, liquid biopsy approaches have the potential to reduce diagnostic delays, minimize patient discomfort, enable decentralized monitoring, and promote equity in access to precision oncology across diverse healthcare systems.

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