Signatory of DORA
https://doi.org/10.56183/iberojhr.v4is.614
Ibero-American Journal of Health Science Research
OPEN ACCESS
BY-NC-ND
**Received**: 20/04/2024
**Accepted**: 13/05/2024
**Published**: 15/05/2024

# Predictive biomarkers in lymphoma: a systematic research review

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## ABSTRACT

Lymphoma is a diverse group of blood cancers originating in the lymphatic system, with varying clinical presentations and prognoses. Identifying and utilizing predictive biomarkers in lymphoma can significantly impact the management and outcome of patients. For instance, the presence of the BCL2 gene rearrangement in follicular lymphoma is associated with a poorer prognosis, while the expression of the CD20 protein in diffuse large B-cell lymphoma is a predictor of response to rituximab. These biomarkers are molecular or cellular indicators that can help forecast disease progression, therapeutic response, and patient prognosis. This abstract provides an overview of the current landscape of predictive biomarkers in lymphoma, focusing on their role which can help physicians to build personalized treatment strategies. We explore key types of biomarkers, including genetic mutations, protein expressions, and cellular markers, that have shown potential in predicting treatment response and survival outcomes across different lymphoma subtypes. Furthermore, we delve into recent advancements in biomarker discovery through high-throughput technologies such as next-generation sequencing and their strategic integration into clinical practice. The use of predictive biomarkers not only enhances the precision of treatment regimens but also contributes to better risk stratification and patient monitoring. The future of this field involves the refinement of biomarker panels for improved predictive accuracy and the exploration of novel targets for therapy. The strategic application of predictive biomarkers in lymphoma presents promising opportunities for optimizing patient care and advancing precision medicine in hematological malignancies.

**Keywords**: lymphoma. biomarkers. epigenetics. genetics. miRNA. lncRNA. immunophenotype. diagnosis. prognosis. therapeutic targeting.

## INTRODUCTION

Lymphoma is a cancer that originates from the lymphatic system, a vital part of the body's immune system. The lymphatic system contains lymphatic vessels, lymph nodes, tonsils, thymus, spleen, and other organs, and all these components work together to filter waste and fight infections. Lymphoma occurs when lymphocytes, a type of white blood cell, begin to grow and multiply uncontrollably, forming tumors. Tumors can develop in lymph nodes, the spleen, bone marrow, the thymus, or others at any part of the body. The 2008 World Health Organization Classification of Tumors of the Hematopoietic and Lymphoid Tissues delineated over 50 types of lymphoma (Swerdlow ., 2008). There are two main categories of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphoma is a more frequent type of cancer. NHL has diverse groups of lymphoma cancers, differing in cell type with behavior and even prognosis. Subtypes of NHL include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, Burkitt lymphoma, T-cell lymphomas, and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Symptoms may include painless swelling of lymph nodes, fatigue, fever, night sweats, weight loss, shortness of breath, and itchy skin. The cause is unclear, but it begins with genetic mutations in disease-fighting white blood cells called lymphocytes, leading to their rapid multiplication and accumulation in lymph nodes. Risk factors include age and gender (males are slightly more susceptible), compromised immune system, and certain infections like the Epstein-Barr virus. Diagnosis involves physical exams, blood tests, imaging scans, and lymph node biopsy. Treatment depends on the subtype and severity and may include chemotherapy, immunotherapy, radiation therapy, or bone marrow transplant (Lymphoma - Symptoms and Causes - Mayo Clinic, 2022). The heterogeneity of lymphoma subtypes manifests in variations in cell type, genetic mutations, clinical behavior, and treatment response,. This heterogeneity poses challenges in treatment while influencing theinfluencing progression and aggressiveness of the disease on the other hand (Iqbal., 2015). Current approaches often adopt a one-size-fits-all strategy, leading to treatment resistance and suboptimal outcomes for certain

subtypes. While biomarkers, particularly protein markers identified predominantly through immunohistochemistry and flow cytometry, have found extensive use and significantly contributed to the diagnosis, classification, and prognostication of lymphomas, there remains a need for novel, clinically applicable, reliable, and reproducible biomarkers. These would enhance the supervision of clinical trials for improved management (Sadida et al., 2024).

### Statistics

In 2023, an estimated 8,830 people in the United States, including 4,850 men and boys and 3,980 women and girls, are expected to be diagnosed with Hodgkin lymphoma. Worldwide, approximately 83,087 people were diagnosed with Hodgkin lymphoma in 2020. The disease is most common in two age groups in the U.S.: early adulthood, particularly in people in their 20s, and individuals older than 55, with the average age of diagnosis being 39. Though rare in children younger than 5, Hodgkin lymphoma is the most commonly diagnosed cancer in teens ages 15 to 19, accounting for 11% of all cancer cases in this age group. The estimated number of deaths from Hodgkin lymphoma in the U.S. in 2023 is 900, with 540 occurring in men and boys and 360 in women and girls. The survival rate has been increasing since around 1975 due to treatment improvements, with the 5-year relative survival rate in the U.S. being 89%. This rate varies based on factors such as cancer subtype, stage, age, general health, and treatment efficacy. For localized Hodgkin lymphoma, the 5-year relative survival rate is 93%, while for regional spread it is 95%, and for distant spread it is 83%. These statistics are based on data from people diagnosed between 2012 and 2018 and may not reflect recent advancements in diagnosis or treatment (Lymphoma - Hodgkin - Statistics, 2023).

Non-Hodgkin lymphoma (NHL) is a prevalent cancer in the United States, constituting about 4% of all cancers. The American Cancer Society estimates that in 2024, approximately 80,620 individuals (44,590 males and 36,030 females) will be diagnosed with NHL, including both adults and children. About 20,140 people are expected to succumb to this cancer, with 11,780 males and 8,360 females among them. The likelihood of developing NHL is around 1 in 42 for men and 1 in 52 for women over their lifetimes, with individual risk influenced by various factors. While NHL can manifest at any age and is among the more common cancers in children, teens, and young adults, the risk escalates with age, with over half of patients being 65 or older at initial diagnosis. Incidence rates have seen a decline of approximately 1% per year since 2015, and the death rate has dropped by 2% annually from 2012 to 2021 (How Common Is Lymphoma? | Key Statistics for Non-Hodgkin Lymphoma, n.d.).

## METHODOLOGY

Inclusion criteria: In lymphoma research, epigenetic biomarkers scrutinize genes like P16/INK4A, MGMT, KLF4, MLL2, MEF2, plus EZH2, bypassing alterations including hypermethylation or mutation. The gene function, the clinical correlations, prognostic implications, and those found in lymphoma types are among the many other features that will be considered in diagnosis, prognosis, and for treatment planning. Genetics biomarkers in lymphoma studies include BC6, TP53, MYC, BCL2, MYD88, SPIB, TNFAIP3, CIITA, MLL, IRF4, LMO2, FOXP1, EZH2, BCL11A, CDKN2A as well as MSH6 and documented roles in the Classification of genetic variations to determine the genes functions, associations with unspecified type of lymphoma and prognostic value. That help in patient's stratification and the development of targeted therapy. MicroRNA (miRNA) and long noncoding RNA (lncRNA) biomarkers in lymphoma research encompass molecules such as miR-155, miR-17-92 cluster, miR-15a/16-1, miR-18b, miR-29 family, miR-127-3p, miR-615-3p, miR-222, miR-181a, miR-129-5p, miR-138-5p, miR-147a, miR-147b, miR-511-5p, miR-34s, miR-512-3p, miR-886-5p, miR-886-3p, miR-708, miR-135b, miR-146a, miR-210, miR-197, miR-191, miR-451, miR-22, miR-455-3p, miR-455-5p, miR-143, miR-494, MIR155HG, and PVT1. Comprehending's comprise their enzyme actions, function, involvement in lymphoma pathogenesis, lymphoma subtype's affiliation and the prognostic significance in assisting diagnostics, prognosis and so targeting the disease. Immunophenotyping is the analysis of surface and intracellular molecules and the subsequent separation of cancer cells, which is the method used in detection of lymphoma and identification of its biomarkers which includes: CD15, CD30, MDM2, p53, SOX-11, Bcl-6, cyclin D1, Bcl-2, Myc,Such markers are considered as diagnostic tools since they give information pertaining to subtype determination in addition to prognosis and therapeutic response assessment. Point and case are here with the diagnostic role, relevance to different lymphoma categories, and prognostic influence which in turn informs of personalized treatment for lymphoma patients. Data is extracted from peer reviewed websites such as PubMed, Nature, ScienceDirect and Google scholar. Latest papers published after 2013 are included in English language.

Search strategy

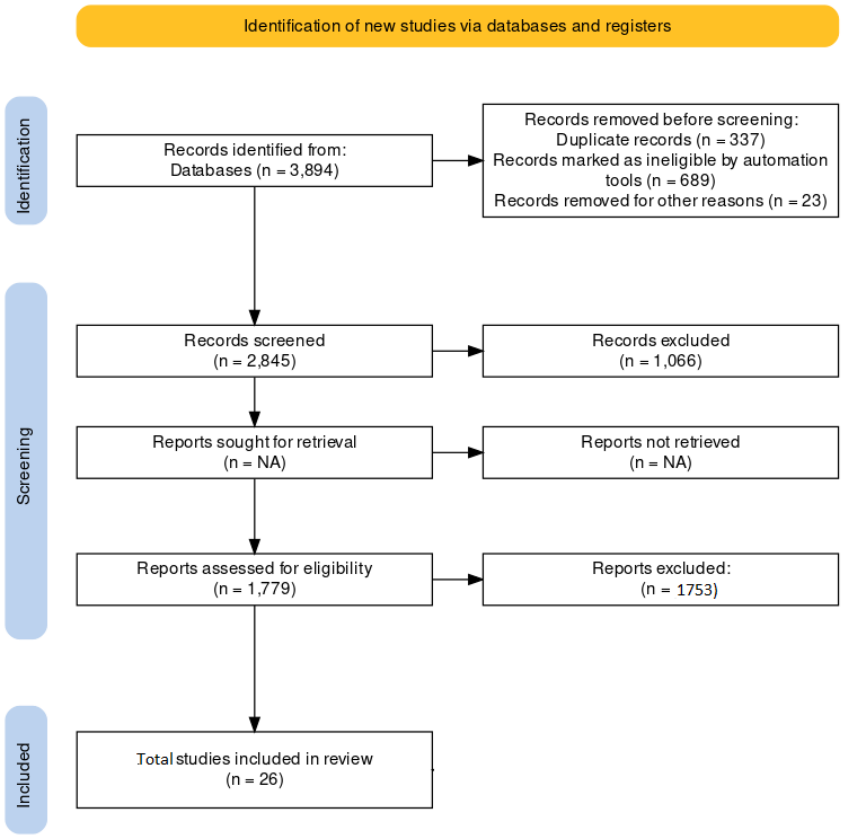
This study was designed to search papers through a certain way which was based on systematic literature review approach and covered the main aspects of epigenetic, genetic, microRNA (miRNA), long noncoding RNA (lncRNA), and immunophenotypic biomarkers in lymphoma. The investigations of the search terms lived through combining a number of

the key phrases like "lymphoma", "biomarkers", "epigenetics", "genetics", "microRNA", "long noncoding RNA", and "immunophenotype". " Articles dated [write time frame], published in English, were used. Searches were made with PubMed, Scopus, and Web of Science databases.

Selection Criteria

Papers were chosen according to their suitability of the topic under the study include those of studies investigating potential biomarkers such as CDKN2 proteins (p16/INK4A, p15 and p21 (CCND1), BCL6, miR-155) in lymphoma. Inclusion criteria referred to the original research articles, reviews and meta-analyses on the functions, clinical connections, prognostic implications and therapeutic relevance of the specified markers in the different types of lymphomas. Articles are not considered if a major emphasis in not on the lymphoma (lymphoproliferative disorders) or if the information about biomarkers use was not significant.

**Figure 1. Identification of new studies via databases and registers**




Source: the authors.

A total of 3,894 studies were initially identified through database searches. We screened titles of 2845 papers. Following duplicate removal and screening of titles and abstracts, 1,066 studies were excluded. Of the remaining reports, 1,779 underwent eligibility assessment and we readied abstracts, leading to the inclusion of 26 studies in the final systematic review.

## RESULTS AND DISCUSSION

### 1. Epigenetic Biomarkers in Lymphoma

The biomarkers related to epigenetic alterations in lymphomas encompass various functions and clinical correlations across different lymphoma types. P16/INK4A hypermethylation in DLBCL and MCL is linked to worse prognosis. KLF4 hypermethylation, prevalent in FL, DLBCL, BL, and HL, shows potential prognostic value. EZH2 hypertrimethylation in GCB-DLBCL and FL correlates with gene mutation. MLL2/KMT2D reduced trimethylation in DLBCL and FL indicates therapeutic potential. MGMT hypermethylation in DLBCL suggests a favorable prognosis. CREBBP/EP300 reduced acetylation in DLBCL and FL aids in chemotherapy failure risk stratification. Other biomarkers like JMJD2C, SOX9, HOXA9, AHR, NR2F2, ROBO1,

SNCA, SPG20, CNRIP1, TET2, IDH2, DNMT3A, and SMAD1 exhibit diverse epigenetic patterns and clinical correlations across various lymphoma types, offering insights into diagnosis, prognosis, and therapeutic strategies. (Lai & Wang, 2021) (Sermer et al., 2019).

**Table 1. List of Epigenetic Biomarkers, functions, their prognostic implications in Lymphoma Cancer**

| Biomarker | Alteration/Function | Lymphoma Types | Prognostic Implications |
|---|---|---|---|
| **P16/INK4A** | Homozygous deletion; methylation | All lymphoma types | Inconsistent prognostic importance; associated with poorer prognosis in some studies |
| **MGMT** | Promoter hypermethylation | Diffuse large B-cell lymphoma | Favorable prognosis |
| **KLF4** | Aberrantly hypermethylated; acts as a tumor suppressor | T- and B-cell lymphomas | Potential benefit to patients; subtype-independent mechanism of lymphomagenesis |
| **MLL2 (KMT2D)** | Inactivated by mutations | Follicular lymphoma, Diffuse large B-cell lymphoma | No difference between lymphoma subtypes; frequent mutations |
| **MEF2** | Mutations linked to lymphoma; somatic mutations in germinal center B-cell-like diffuse large B-cell lymphoma and follicular lymphoma | Germinal center B-cell-like diffuse large B-cell lymphoma, Follicular lymphoma | Role in enhancing malignant transformation; potential alternative for inhibition of BCL6 activity |
| **EZH2** | Mutated in follicular lymphoma and diffuse large B-cell lymphoma; mutations enhance H3K27 trimethylation activity; protein expression may be a better prognostic indicator | Follicular lymphoma, Diffuse large B-cell lymphoma | No observed prognostic impact; combination with demethylating agents may be useful |
| **SOX9** | Hypermethylation | Mantle cell lymphoma | Correlates with higher proliferation, increased chromosomal abnormalities, and poorer survival |
| **HOXA9** | Hypermethylation | Mantle cell lymphoma | Correlates with higher proliferation, increased chromosomal abnormalities, and poorer survival |
| **AHR** | Hypermethylation | Mantle cell lymphoma | Correlates with higher proliferation, increased chromosomal abnormalities, and poorer survival |
| **NR2F2** | Hypermethylation | Mantle cell lymphoma | Correlates with higher proliferation, increased chromosomal abnormalities, and poorer survival |
| **ROBO1** | Hypermethylation | Mantle cell lymphoma | Correlates with higher proliferation, increased chromosomal abnormalities, and poorer survival |
| **CNRIP1** | Promoter methylation | Diffuse large B-cell lymphoma | Associated with poorer overall survival |
| **FBN1** | FBN1 promotes DLBCL cell migration, possibly through activating the Wnt/β-catenin signaling pathway and regulating TIMP1 expression. Hypermethylation of FBN1 may contribute to its downregulation, potentially impacting cell migration and DLBCL progression. | FBN1 is associated with promoting diffuse large B-cell lymphoma (DLBCL) progression, especially in advanced stages and non-GCB subtypes. | Wang et al 2020 suggests that FBN1 activates the Wnt/β-catenin signaling pathway and regulates TIMP1, which could potentially contribute to DLBCL progression (wang., 2020) |
| **MAL** | Methylation | methylation of MAL may have prognostic implications for patients with non-Hodgkin lymphomas. | The MAL biomarker is associated with lymphoma detection and monitoring. Its methylation status can help distinguish lymphoma from healthy controls with high sensitivity and specificity. |
| **SNCA** | Methylation | non-Hodgkin lymphomas | SNCA, or α-synuclein, is a protein primarily associated with neuronal function, particularly in synaptic vesicle trafficking and neurotransmitter release. Mutations or abnormal aggregation of SNCA are linked to neurodegenerative diseases like Parkinson's disease and multiple system atrophy. In the context of lymphoma, its methylation status, as mentioned earlier, is used as a biomarker for distinguishing lymphoma from healthy controls. |
| **SPG20** | SPG20 (spastic paraplegia 20) is a gene that codes for a protein associated with reduced mitochondrial cytochrome c oxidase activity. Mutations in SPG20 have been linked to Troyer syndrome, a form of autosomal recessive hereditary spastic paraplegia. In the context of lymphoma, SPG20 has been identified as a methylated target, suggesting epigenetic dysregulation in lymphoid cells. | Diffuse large B cell lymphoma (DLBCL), which is a common type of Non-Hodgkin lymphoma (NHL). SPG20 methylation status was investigated in DLBCL-derived cell lines. | SPG20 methylation's prognostic implications in lymphoma aren't specified, but such gene methylation is linked to cancer progression and treatment response. It may offer insights into lymphoma development and serve as a biomarker for prognosis and therapy. Further research is required to clarify SPG20 methylation's prognostic significance in lymphomas. |
| **TNF alpha pathway biomarkers** | Methylation | Diffuse large B-cell lymphoma | Helpful in distinguishing lymphoma subtypes |
| **SMAD1** | Hypermethylation | Diffuse large B-cell lymphoma | Predicts chemotherapy resistance; potential for inducing chemotherapy responsiveness |

Source: the authors.

La Summary: The molecular alterations of several genes, including P16/INK4A, MGMT, KLF4, MLL2, MEF2, and EZH2, play significant roles in lymphoma development and prognosis. P16/INK4A is often affected by homozygous deletion or methylation, with inconsistent prognostic implications. MGMT's function is frequently lost due to epigenetic alterations, correlating with better outcomes in certain lymphoma cases. KLF4 acts as a tumor suppressor and is hypermethylated in various lymphoma types, indicating a subtype-independent mechanism of lymphomagenesis. MLL2 mutations are prevalent in follicular and diffuse large B-cell lymphomas. MEF2 mutations, mainly detected in germinal center B-cell-like diffuse large

B-cell lymphoma and follicular lymphoma, enhance malignant transformation. EZH2 mutations, common in follicular and diffuse large B-cell lymphomas, have implications for prognosis and potential therapeutic targeting (Sun et al., 2016). Other epigenetic gene signatures, such as hypermethylation of SOX9, HOXA9, AHR, NR2F2, and ROBO1, have been linked to poorer outcomes in mantle cell lymphoma. Methylation status of specific genes like SNCA and SPG20 could aid in lymphoma detection and monitoring. Methylation of CNRIP1 may serve as a prognostic factor in diffuse large B-cell lymphoma. Hypermethylation of SMAD1 predicts chemotherapy resistance in diffuse large B-cell lymphoma. Mutations in genes like TET2, DNMT3A, IDH2, and RHOA are prevalent in peripheral T-cell lymphoma, with implications for disease progression and prognosis (Sun et al., 2016).

## 2. Genetic biomarkers

Advancements in genomic technologies have greatly enhanced our understanding of lymphomagenesis by enabling the identification of genetic alterations and associated biomarkers. Microarray-based studies such as gene expression profiling have also significantly contributed to the attempt. Similarly, the rapid emergence of next-generation sequencing methods is another vital component. These techniques have deducted some novel biomarkers, implying how the molecular mechanisms behind lymphomagenesis operate. These discoveries lead to enhanced and more tailored diagnostic methods and precision of patient stratification, therefore increasing the possibility of developing therapeutic interventions targeting specific genetic aberrations.

Using these new technologies, we were able to find genome and molecular markers associated with different types of lymphoma, from B-cell types to NK cell ones. Besides, myeloid, lymphoid, and genome-wide mutations have been recognized using a large population in diffuse large B-cell lymphoma. These data sets, as a whole, describe the complicated fitness for genetic alterations that give rise to lymphomagenesis and highlight the role of this clinical setting in offering a framework for targeted therapy and prognostication (Kos et al., 2021).

**Table 2. Genetic Biomarkers Implicated in Lymphomagenesis: Roles, Associations, and Prognostic Implications**

| Biomarker | Role/Function | Lymphoma Association | Prognostic Implications |
|---|---|---|---|
| **B-Cell Lymphoma 6 (BCL6)** | Transcriptional factor involved in B-cell differentiation and lymphomagenesis | Dysregulation via translocation or mutation; associated with better prognosis in diffuse large B-cell lymphoma (DLBCL) | High expression of BCL6 mRNA and protein associated with better prognosis in DLBCL |
| **Tumor Protein 53 (TP53)** | Tumor suppressor gene | Mutation associated with poorer prognosis in DLBCL, follicular lymphoma, and mantle cell lymphoma; particularly impactful in certain DLBCL subtypes | TP53 mutation, especially in specific DNA-binding domains, correlates with poorer prognosis in DLBCL |
| **V-Myc Avian Myelocytomatosis Viral Oncogene Homolog (MYC)** | Oncogene involved in cell biology and oncology | Translocations associated with poorer prognosis in aggressive B-cell lymphomas; especially impactful when involving immunoglobulin (IG) genes | MYC translocations, particularly with IG partners, are associated with poorer prognosis in DLBCL |
| **B-Cell Lymphoma 2 (BCL2)** | Apoptosis regulator | Translocations and amplifications associated with lymphoma development; controversial prognostic impact in DLBCL | BCL2 alterations, especially in conjunction with MYC translocations, associated with poorer prognosis in DLBCL |
| **Myeloid Differentiation Primary Response 88 (MYD88)** | Adaptor protein involved in signaling pathways | Mutation linked to lymphoplasmacytic lymphoma, activated B-cell-like DLBCL; protein expression associated with recurrence and shorter survival | MYD88 mutation status not prognostic in DLBCL; protein expression linked to recurrence and shorter disease-free survival |
| **Spi-B Transcription Factor (SPIB)** | Transcription factor involved in oncogenesis | Overexpressed in activated B-cell-like DLBCL; implicated in oncogenesis via chromosomal aberrations | Elevated SPIB expression linked to activated B-cell-like DLBCL; role in oncogenesis suggested by chromosomal aberrations |
| **Tumor Necrosis Factor α-Induced Protein 3 (TNFAIP3)** | NF-κB pathway regulator | Mutations, deletions, or epigenetic silencing in various lymphomas; involvement in NF-κB dysregulation | Inactivation of TNFAIP3 associated with NF-κB dysregulation |
| **Major Histocompatibility Complex Class II Transactivator (CIITA)** | Coactivator of MHC class II promoter | Chromosomal translocations associated with primary mediastinal B-cell lymphoma; potential as a diagnostic biomarker | CIITA translocations as a potential diagnostic marker for primary mediastinal B-cell lymphoma; uncommon in DLBCL |
| **Other Genetic Biomarkers/Gene Expression Models** | Various roles in lymphomagenesis | Several genes implicated in survival prediction, molecular sub-classification, and risk stratification; diverse implications across lymphoma subtypes | Models incorporating gene expression profiles or specific gene mutations provide insight into survival, sub-classification, and risk stratification |
| **Myeloid/Lymphoid or Mixed-Lineage Leukemia (MLL) gene** | Transcriptional regulator | Involved in chromosomal translocations in lymphomas such as Burkitt lymphoma; associated with aggressive clinical course and poorer prognosis | MLL translocations often indicate aggressive lymphoma phenotype with poor prognosis |
| **Interferon Regulatory Factor 4 (IRF4)** | Transcription factor implicated in lymphocyte activation | Overexpression linked to lymphomagenesis, particularly in DLBCL subtypes; associated with poorer prognosis | Elevated IRF4 expression associated with aggressive DLBCL subtypes and poorer prognosis |
| **LIM Domain Only 2 (LMO2)** | Transcriptional regulator involved in hematopoietic development | Overexpression associated with lymphomagenesis and poorer prognosis in DLBCL | LMO2 overexpression correlates with aggressive DLBCL subtypes and poorer prognosis |
| **Forkhead Box P1 (FOXP1)** | Transcription factor involved in lymphocyte development | Overexpression associated with lymphomagenesis and poorer prognosis in DLBCL | FOXP1 overexpression correlates with aggressive DLBCL subtypes and poorer prognosis |
| **Enhancer of Zeste Homolog 2 (EZH2)** | Histone methyltransferase involved in gene silencing | Mutations associated with lymphomagenesis, particularly in DLBCL subtypes; linked to aggressive | EZH2 mutations correlate with aggressive DLBCL subtypes and poorer prognosis |

| | | | |
|---|---|---|---|
| | | disease phenotype | |
| **B-Cell CLL/Lymphoma 11A (BCL11A)** | Transcriptional regulator involved in B-cell development | Overexpression associated with lymphomagenesis and poorer prognosis in DLBCL | BCL11A overexpression correlates with aggressive DLBCL subtypes and poorer prognosis |
| **Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A)** | Cell cycle regulator and tumor suppressor | Deletions or mutations associated with lymphomagenesis and poorer prognosis in DLBCL | CDKN2A alterations linked to aggressive DLBCL subtypes and poorer prognosis |
| **MutS Homolog 6 (MSH6)** | DNA mismatch repair protein | Mutations associated with lymphomagenesis and potentially with chemoresistance in DLBCL | MSH6 mutations may contribute to lymphoma development and resistance to chemotherapy |

Source: the authors.

Summary: Genetic biomarkers related to lymphomagenesis take on different regulatory cleavages, and such a role depends on the clinical outcomes of the patients. Time and time again, the BCL6, TP53, MYC, and BCL2 are crucial in B-cell lymphomas, with some translocations and mutations marvelously predicting the prognosis. The potentially oncogenic effects of MYD88, SPIB, and TNFAIP3 are assessed through the modulation of signaling pathways, and consequently, they affect the recurrence and survival of individuals. Through its ability to diagnose primary mediastinal B-cell lymphoma, CIITA serves as a diagnostic marker. Other biomarkers, including MLL, IRF4, and EZH2, depict aggressive lymphoma phenotypes, whereas LMO2, FOXP1, and BCL11A are gloomy prognoses. Frequently, mutations in CDKN2A and MSH6 suggest the development of chemoresistance in cancer cells. These biomarkers give an overview of the lymphoma process, allowing subtypes to be classified and a basis for targeted treatments to be formed in a process where patient outcomes are the priority (Sun et al., 2016) (Akay et al., 2014)

## 3. MicroRNA and lncRNA in Lymphomas

MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs) serve as valuable biomarkers in lymphomas, aiding in diagnosis and prognosis. The miR-17-92 cluster, miR-155, and miR-127-3p are associated with various lymphoma subtypes, influencing proliferation, apoptosis, and angiogenesis. While miR-615-3p's role remains unclear, miR-222 and miR-29 promote cell proliferation and survival in specific lymphoma types. Additionally, miR-18b, miR-181a, and miR-296-3p have prognostic implications, affecting overall survival and progression-free survival. Other miRNAs, including miR-21, miR-150, and miR-34a, contribute to lymphoma pathogenesis by modulating cellular functions. Furthermore, lncRNAs like MIR155HG and PVT1 are associated with lymphoma subtypes, potentially impacting gene regulation and oncogenesis. These biomarkers offer promising avenues for personalized treatment approaches and improved management of lymphoma patients (Sun et al., 2016) (Ratti et al., 2020).

**Table 3. MicroRNA and lncRNA in Lymphomas**

| Biomarker | Function | Role in Lymphoma | Prognostic Implications |
|---|---|---|---|
| **miR-155** | Acts as an onco-miR in the pathogenesis and aggressiveness of diffuse large B-cell lymphoma (DLBCL). | Levels of miR-155 are significantly higher in activated B-cell-like DLBCL compared to germinal center B-cell-like DLBCL, contributing to poor prognosis in the former. | Correlation observed between miR-155 expression and resistance to R-CHOP therapy in DLBCL patients. |
| **miR-17-92** | Overexpressed due to locus amplification in various lymphoma types, including germinal center B-cell-like DLBCL, follicular lymphoma, mantle cell lymphoma, anaplastic large cell lymphoma, and Burkitt lymphoma. | Correlates with poorer overall survival in mantle cell lymphoma. | High expression of miR-18b and downregulation of the miR-29 family predict poor outcome in mantle cell lymphoma patients. |
| **miR-15a/16-1** | Deregulation due to deletion of chromosome 13q14, implicated in the pathogenesis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). | Deletion of 13q14 and consequent low expression of miR-15a/16-1 associated with favorable prognosis in CLL/SLL patients. | Deletion of 13q14 and low miR-15a/16-1 expression correlate with better prognosis in CLL/SLL, contrasting with poorer prognosis linked to other chromosomal abnormalities. |
| **miR-18b** | Overexpression predicts poor outcome in mantle cell lymphoma patients. | Associated with unfavorable prognosis in mantle cell lymphoma patients. | High expression of miR-18b predicts poor outcome in mantle cell lymphoma. |
| **miR-29 family** | Downregulation predicts poor outcome in mantle cell lymphoma patients. | Associated with poor prognosis in mantle cell lymphoma patients. | Downregulation of miR-29 family members is associated with poorer prognosis in mantle cell lymphoma. |
| **miR-127-3p** | Combination with Ki67 provides a prognostic model for mantle cell lymphoma. | Prognostic marker for mantle cell lymphoma. | Combination of miR-127-3p with Ki67 provides a novel prognostic model for mantle cell lymphoma. |
| **miR-615-3p** | Combined with Mantle Cell Lymphoma International Prognostic Index, holds prognostic value in mantle cell lymphoma. | Predictive of prognosis in mantle cell lymphoma patients. | The combination of miR-615-3p and the Mantle Cell Lymphoma International Prognostic Index has prognostic value in mantle cell lymphoma. |
| **miR-222** | Associated with an inferior overall survival in lymphoma patients. | Indicates poor prognosis in lymphoma patients. | miR-222 expression is consistently associated with an inferior overall survival in lymphoma patients. |
| **miR-181a** | Shown prognostic value for DLBCL patients. | Implicated in determining prognosis | miR-181a has been identified as a |

| | | | |
|---|---|---|---|
| | | in DLBCL patients. | prognostic marker in DLBCL patients. |
| **miR-129-5p** | Shown prognostic value for DLBCL patients. | Implicated in determining prognosis in DLBCL patients. | miR-129-5p has been identified as a prognostic marker in DLBCL patients. |
| **miR-138-5p** | Associated with longer overall survival in hepatitis C virus-associated DLBCL patients. | Indicates favorable prognosis in hepatitis C virus-associated DLBCL patients. | miR-138-5p expression is associated with longer overall survival in hepatitis C virus-associated DLBCL patients. |
| **miR-147a** | Associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. | Indicates poor prognosis in hepatitis C virus-associated DLBCL patients. | miR-147a expression is associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. |
| **miR-147b** | Associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. | Indicates poor prognosis in hepatitis C virus-associated DLBCL patients. | miR-147b expression is associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. |
| **miR-511-5p** | Associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. | Indicates poor prognosis in hepatitis C virus-associated DLBCL patients. | miR-511-5p expression is associated with shorter overall survival in hepatitis C virus-associated DLBCL patients. |
| **miR-34s** | Downregulated by promoter hypermethylation in DLBCL, particularly in TP53/MIR34A 'double hit' subtype, associated with poorer overall survival. | Indicative of aggressive DLBCL subtype with poorer overall survival. | Downregulation of miR-34s due to promoter hypermethylation is associated with poorer overall survival in DLBCL patients, particularly in the TP53/MIR34A 'double hit' subtype. |
| **miR-512-3p miR-886-5p, miR-886-3p, miR-708, miR-135b, miR-146a, miR-210, miR-197, miR-191, miR-451, miR-22, miR-455-3p, miR-455-5p, miR-143, miR-494** | Implicated in ALK+ anaplastic large cell lymphoma. | Diagnostic marker for ALK+ anaplastic large cell lymphoma. | miR-512-3p is mainly implicated in ALK+ anaplastic large cell lymphoma. |

Source: the authors.

Summary: Various microRNAs (miRNAs) serve as biomarkers for lymphoma detection and prognosis. miR-155, prevalent in diffuse large B-cell lymphoma (DLBCL), aids subtype differentiation and predicts poor prognosis. The miR-17-92 cluster, overexpressed in multiple lymphoma types, correlates with worse survival in mantle cell lymphoma. Deregulated miR-15a/16-1, linked to chromosome 13q14 deletion, signifies a favorable prognosis in chronic lymphocytic leukemia/small lymphocytic lymphoma. Additionally, miR-18b and the miR-29 family predict poor outcome in mantle cell lymphoma. Unique miRNA signatures distinguish ALK+ anaplastic large cell lymphoma and ALK− peripheral T-cell lymphomas. These miRNAs offer diagnostic insights, prognostic value, and potential therapeutic targets, enhancing lymphoma management (Sun et al., 2016) (Bertoli et al., 2015) (Mazan-Mamczarz & Gartenhaus, 2013)

## 4. Microenvironment-related in Lymphoma

The tumor microenvironment plays a critical role in the progression and treatment response of lymphomas. Comprising a complex interplay of malignant cells, non-malignant cells, and extracellular matrix components, the microenvironment influences tumor behavior through dynamic interactions mediated by various cytokines and chemokines. Understanding these interactions has led to the identification of microenvironment-related biomarkers that hold promise for prognostication and guiding immunotherapy in lymphomas.

The microenvironment of lymphomas is characterized by a multitude of biomarkers reflecting the diverse cellular and molecular components interacting within the tumor milieu. Key biomarkers include CD21+ follicular dendritic cells, granzyme B+ tumor-infiltrating cytotoxic T cells, CD117+ mast cells, CD68+ or CD163+ macrophages, FOXP3+ regulatory T cells, PD-1 and PD-L1, CD58 and TNFRSF14, as well as microenvironment-related gene expression profiling signatures (García-Domínguez et al., 2022).

Each biomarker serves a specific function within the microenvironment, influencing immune responses, tumor growth, and therapy response. Importantly, these biomarkers have prognostic implications, with their expression levels or presence correlating with patient outcomes in various lymphoma subtypes (Sun et al., 2016) (Fowler et al., 2016).

**Table 4. Microenvironment-related in Lymphoma**

| Biomarker | Function | Role in Lymphoma | Prognostic Implications |
|---|---|---|---|
| **CD21+ Follicular Dendritic Cells** | Support antigen presentation to B cells | Presence indicates a functional immune response in lymph nodes | Absence predicts unfavorable outcome in classical Hodgkin lymphoma. Destruction of normal lymph node architecture correlates with prognosis. |
| **Granzyme B+ Tumor-Infiltrating Cytotoxic T Cells** | Induce apoptosis in target cells | Reflects cytotoxic immune response against tumor cells | Correlates with clinical outcome in classical Hodgkin lymphoma and anaplastic large cell lymphoma, indicating a more favorable prognosis when present in higher numbers. |
| **CD117+ Mast Cells** | Modulate immune responses and angiogenesis | Variable effects depending on lymphoma subtype | Unfavorable outcome in classical Hodgkin lymphoma, while promising outcome in diffuse large B-cell lymphoma. |
| **CD68+ or CD163+** | Phagocytosis, cytokine | Influence tumor growth, | Increased levels of a specific biomarker are linked to a worse prognosis in |

| | | | |
|---|---|---|---|
| **Macrophages** | production | invasion, and response to therapy | classical Hodgkin lymphoma and follicular lymphoma. In diffuse large B-cell lymphoma, however, the impact of this biomarker on prognosis can vary depending on the treatment approach. |
| **FOXP3+ Regulatory T Cells** | Suppress immune responses | Maintain immune tolerance, potentially inhibiting neoplastic cells | Increased numbers associated with better prognosis in follicular lymphoma, Hodgkin lymphoma, and NK/T-cell lymphomas. Role in diffuse large B-cell lymphoma prognosis is debatable. |
| **PD-1 and PD-L1** | Regulate T cell activation and tolerance | Modulate anti-tumor immune responses | High numbers of PD-1+ T cells and PD-L1 expression predict inferior overall survival in classical Hodgkin lymphoma. Immunotherapy targeting PD-1/PD-L1 axis shows promise in lymphoma treatment. |
| **CD58 and TNFRSF14** | Mediate cell-cell interactions and immune responses | Impact immune escape and regulation of tumor microenvironment | Decreased expression of CD58 and inactivation of TNFRSF14 associated with poorer outcomes in certain lymphoma subtypes. |
| **EBV and Other Viruses** | Infect and modulate host immune responses | Implicated in lymphomagenesis and tumor microenvironment | EBV positivity associated with variable outcomes depending on lymphoma type and patient age. Other viruses like hepatitis B and C may influence clinical outcomes in specific lymphoma subtypes. |
| **Microenvironment-Related Gene Expression Profiling Signatures** | Reflect gene expression patterns in the tumor microenvironment | Provide insights into immune cell composition and activity | Gene expression signatures associated with macrophages, cytotoxic T cells, and stromal cells have prognostic implications and may guide treatment decisions in lymphoma. |

Source: the authors.

Summary: Considering microenvironmental biomarkers, researchers can receive valuable information about the complicated interplay of tumor cells with the surrounding milieu in lymphoma. Through such an inquiry, physicians will acquire the capacity to diagnose a poor patient prognosis with greater precision and operate more effectively in developing new treatment strategies. In addition, further research into molecular mechanisms operating behind these biomarkers is needed to improve their utility and, finally, for phase III clinical trials to determine their use as personalized medicine tools in lymphoma management (Medeiros et al., 2016) (Ingravallo et al., 2022)

## 5. Immunophenotypic biomarkers

Properly diagnosing and classifying lymphomas is vital for pointing the way toward the correct treatment approach and prognosis for individual patients (Sun et al., 2016). This process uses a histopathological examination and an immunophenotypic analysis for the determination of several specific biomarkers, including CD15, CD30, murine double minute 2 (MDM2), p53, SOX-11, Bcl-6, cyclin D1, Bcl-2, Myc, CIP2A, and p63. They are equivalent sources of knowledge on the molecular characteristics of lymphomas, which prove useful in subtype determination and prognosis. Moreover, biomarkers of therapeutic impact such as CD30 will determine responses toward specific treatment, such as brentuximab vedotin. It is important to understand the role of the biomarkers in improving diagnostic strategies, patient care, and patient outcomes for lymphoma.

Immunophenotypic algorithms, developed as substitutes for gene expression profiling, classify diffuse large B-cell lymphoma (DLBCL) into germinal center B-cell-like and activated B-cell-like subtypes. These algorithms utilize markers like Bcl-2, Bcl-6, CD10, MUM-1/IRF4, FOXP1, and GCET1. The Hans algorithm, primarily based on CHOP-treated patients, is commonly used despite variable concordance rates with gene expression profiling. Other algorithms, such as Choi and Visco/Young algorithms, show higher concordance (~90%). Despite limitations, these immunohistochemical algorithms are favored for their accessibility and simplicity. Certain biomarkers within these classifiers, such as LMO2 and GCET1, correlate with better survival, while others like MUM-1/IFR4 and FOXP1 indicate poorer prognosis. Additionally, markers of oncogenic signaling pathways, including cyclin D2, cyclin D3, protein kinase c-B, caspase-9, and survivin, are linked to worse outcomes. NF-κB pathway activation is implicated in lymphomagenesis, with components like p50 and p65 associated with poorer prognosis in activated B-cell-like DLBCL. Conversely, p52/RelB may indicate a better prognosis in germinal center B-cell-like DLBCL.. Immunohistochemical biomarkers aid in the differential diagnosis of peripheral T-cell lymphomas, such as distinguishing classical Hodgkin lymphoma from angioimmunoblastic T-cell lymphoma using markers like CD10, PD-1, and CXCL13. Biomarkers like TIA-1, granzyme B, perforin, and clusterin assist in diagnosing specific lymphoma types like NK/T lymphomas and anaplastic large cell lymphomas. The Jun family proteins, notably c-Jun and JunB, show potential as diagnostic tool and therapeutic targets in certain lymphomas (Sun et al., 2016) (Syrykh et al., 2020).

**Table 5. Immunophenotypic biomarkers**

| Biomarker | Diagnostic Significance | Associated Lymphoma Subtypes |
|---|---|---|
| **CD30** | - This marker is highly expressed by tumor cells in classical Hodgkin lymphoma (cHL), anaplastic large cell lymphoma (ALCL), a subset of diffuse large B-cell lymphoma (DLBCL), and Epstein-Barr virus-driven lymphoproliferative disorders.<br>- It serves as a valuable biomarker for the diagnosis of cHL and ALCL. | Classical Hodgkin lymphoma, Anaplastic large cell lymphoma, Subset of diffuse large B-cell lymphoma |

| | | |
|---|---|---|
| **Bcl-6** | - Plays a crucial regulatory role in germinal center B cells.<br>- Its expression is not limited to germinal center B-cell-like DLBCL.<br>- Additionally, it is expressed by neoplastic T-cells in angioimmunoblastic T-cell lymphoma (AITL). | Germinal center B-cell-like DLBCL, Angioimmunoblastic T-cell lymphoma |
| **Bcl-2** | - Overexpression due to chromosomal translocations, diagnostic for follicular lymphoma. - Overexpression may occur in other lymphomas without translocations. | Follicular lymphoma, Various lymphomas |
| **Myc** | - Overexpression attributable to chromosomal translocations, diagnostic for Burkitt lymphoma. - Overexpression may occur in lymphomas without translocations. - Coexpression with Bcl-2 indicates aggressive clinical features. | Burkitt lymphoma, Various lymphomas |
| **Cyclin D1** | - Overexpressed due to t(11;14)(q13;q32), diagnostic for mantle cell lymphoma (MCL). - Rare cases of cyclin D1-negative MCL exist. | Mantle cell lymphoma, Subset of diffuse large B-cell lymphoma |
| **SOX-11** | - Marker of mantle cell lymphoma independent of cyclin D1 expression. - Useful for cyclin D1-negative MCL cases. | Mantle cell lymphoma |
| **p53** | - Overexpression may indicate poor prognosis in diffuse large B-cell lymphoma (DLBCL) patients treated with R-CHOP. - Combined expression with MDM2 may predict significantly poorer survival. | Diffuse large B-cell lymphoma |
| **MDM2** | - Expression combined with mutated-type p53 may predict significantly poorer survival in DLBCL patients. | Diffuse large B-cell lymphoma |
| **p63** | - Expressed in primary mediastinal B-cell lymphoma (PMBCL) but not in classical Hodgkin lymphoma (cHL), useful for distinguishing between them. | Primary mediastinal B-cell lymphoma, Classical Hodgkin lymphoma |
| **CIP2A** | - Expression associated with proliferation rate and disease stage in diffuse large B-cell lymphoma (DLBCL). | Diffuse large B-cell lymphoma |

Source: the authors.

Summary: Lymphoma diagnosis relies on histopathology and immunophenotypic analysis using various biomarkers like CD15, CD30, ALK-1, cyclin D1, SOX-11, p53, Bcl-6, Bcl-2, Myc, MDM2, p63, and CIP2A. These markers aid in subtype classification and prognostication. CD30 has therapeutic implications, evidenced by brentuximab vedotin efficacy. Overexpression of certain markers predicts outcomes and guides personalized therapy. Thus, these markers play pivotal roles in refining diagnosis, predicting outcomes, and guiding therapy in lymphoma patients. Immunophenotypic algorithms aid in categorizing diffuse large B-cell lymphoma (DLBCL) subtypes, correlating certain markers with prognosis. Biomarkers within these algorithms and oncogenic signaling pathways offer insights into DLBCL prognosis and potential therapeutic targets, while immunohistochemical markers assist in the differential diagnosis of various peripheral T-cell lymphomas (Sun et al., 2016) (Ali et al., 2022) (Xu-Monette et al., 2016).

## CONCLUSION

Condensing the diverse landscape of lymphoma biomarkers, epigenetic markers like DNA methylation patterns and histone modifications offer insights into disease development and progression. Genetic biomarkers, including translocations and mutations, elucidate molecular mechanisms and guide targeted therapies. MicroRNA, long non-coding RNA (lncRNA), and immunophenotypic markers aid in subtype classification and prognosis. Moreover, microenvironment-related biomarkers shed light on tumor-host interactions and therapeutic resistance. Future therapies are poised to harness these biomarkers for precision medicine interventions, utilizing immunotherapy advancements, targeted agents, and combination approaches to optimize treatment outcomes in lymphoma patients.

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