IJIMM, Volume 3, Issue 3, 2025 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Molecular Analysis-Based Treatment Prospects and Innovations for Diffuse Large B-Cell Lymphomas

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Annotation: This study explores the treatment prospects and innovations in diffuse large B-cell lymphoma (DLBCL) based on molecular analysis. We analyzed 110 patients diagnosed with DLBCL, conducting immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS) to classify molecular subtypes and identify key genetic mutations. Our research focused on assessing the efficacy of traditional R-CHOP therapy compared to novel targeted treatments, including CAR-T cell therapy, bispecific antibodies, and BTK inhibitors. The results showed that molecular profiling significantly impacts treatment outcomes, with high-risk genetic subtypes responding better to personalized therapies. Double-hit and triple-hit lymphomas demonstrated poor response to standard therapy but improved survival with CAR-T treatment. Targeted drugs such as EZH2 inhibitors and immune checkpoint inhibitors also showed promising results in refractory cases. This study highlights the importance of molecular diagnostics in guiding treatment strategies and emphasizes the need for further research to optimize individualized therapy for DLBCL patients.

Keywords: Diffuse Large B-Cell Lymphoma (DLBCL), Molecular Targeted Therapy, CAR-T Cell Therapy, Bispecific Antibodies, BTK Inhibitors, Immunochemotherapy, Precision Medicine, Gene Expression Profiling (GEP), Next-Generation Sequencing (NGS), Minimal Residual Disease (MRD), Relapsed/Refractory DLBCL, Epigenetic Therapy, Checkpoint Inhibitors, Personalized Oncology, Prognostic Biomarkers.

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common and aggressive type of non-Hodgkin lymphoma, accounting for approximately 30–40% of all cases. It originates from mature B-lymphocytes and is characterized by rapid progression, requiring immediate treatment. Clinically, DLBCL presents with painless lymphadenopathy, B-symptoms (fever, night sweats, weight loss), and extranodal involvement in some cases.

DLBCL is a highly heterogeneous disease, both clinically and genetically. Based on gene expression profiling, it is classified into two major molecular subtypes: germinal center B-cell-like (GCB) and activated B-cell-like (ABC). The GCB subtype generally has a better prognosis, while the ABC subtype is more aggressive and less responsive to standard chemotherapy. Additionally, certain genetic alterations, such as MYC, BCL2, and BCL6 rearrangements (double-hit and triple-hit lymphomas), are associated with poorer outcomes.

The standard first-line treatment for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), which achieves remission in a significant proportion of patients. However, around 30–40% of cases are refractory to treatment or relapse, necessitating alternative therapeutic approaches. Recent advancements in molecular diagnostics have led to the development of targeted therapies, including CAR-T cell therapy, bispecific antibodies, and small-molecule inhibitors, which offer promising outcomes for high-risk patients.

1. R-CHOP Therapy. R-CHOP, comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, is the standard first-line treatment for DLBCL. Overall Response Rate (ORR): Approximately 90% in patients with limited-stage disease. Complete Response (CR): Up to 60% in patients with advanced-stage disease.
2. CAR T-Cell Therapy. Chimeric Antigen Receptor (CAR) T-cell therapy is utilized for relapsed or refractory (R/R) DLBCL cases.
3. Bispecific Antibodies. Bispecific antibodies, such as those targeting CD20 and CD3, have been explored in R/R DLBCL.

ORR: 63.1%

CR: 38.9%

4. BTK Inhibitors. Bruton's tyrosine kinase (BTK) inhibitors are considered for specific DLBCL subtypes, particularly those with certain molecular characteristics.

Objective: The primary objective of this study is to enhance the diagnosis and treatment strategies for diffuse large B-cell lymphoma (DLBCL) by integrating advanced molecular analysis and innovative therapeutic approaches. Given the heterogeneity of DLBCL, traditional treatment methods, such as R-CHOP, are not always effective, particularly in high-risk and refractory cases. Therefore, a deeper understanding of the molecular landscape of the disease is essential for improving patient outcomes.

This research aims to:

1. Refine Diagnostic Approaches – By utilizing immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS), we seek to improve molecular classification and risk stratification. Identifying genetic alterations such as MYC, BCL2, and BCL6 rearrangements, as well as mutations in key genes like TP53 and EZH2, will allow for more precise disease characterization.
2. Optimize Treatment Strategies – By analyzing the therapeutic response of 110 DLBCL patients, we aim to assess the efficacy of both conventional and novel treatment modalities. This includes evaluating the effectiveness of targeted therapies such as CAR-T cell therapy, bispecific antibodies, BTK inhibitors, and immune checkpoint inhibitors in different molecular subtypes of DLBCL.
3. Personalized Medicine Approach – By correlating molecular profiles with treatment outcomes, we strive to develop a more personalized treatment framework. This approach will help guide clinical decision-making, ensuring that patients receive the most effective therapy based on their specific genetic and molecular characteristics.

By advancing both diagnostic and therapeutic techniques, this study aims to contribute to the ongoing efforts to improve survival rates, reduce relapse risks, and enhance the overall management of DLBCL.

Methods: This study was conducted on 110 patients diagnosed with diffuse large B-cell lymphoma (DLBCL) to evaluate molecular diagnostic techniques and treatment outcomes. The research focused on the integration of immunohistochemical, genetic, and clinical analyses to optimize patient stratification and improve therapeutic strategies. Below are the detailed methodologies applied:

1. Study Population and Patient Selection. Total Patients: 110

Age Distribution: Categorized into different age groups to assess disease prevalence.

Gender Distribution: Male-to-female ratio was analyzed.

Inclusion Criteria: Newly diagnosed and relapsed/refractory (R/R) DLBCL patients.

Exclusion Criteria: Patients with incomplete medical records or those diagnosed with other lymphoproliferative disorders.

2. Diagnostic Methods

Histopathology & Immunohistochemistry (IHC): CD10, BCL6, and MUM1 were analyzed to classify DLBCL into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes. Ki-67 index was assessed to determine tumor proliferation rates. Fluorescence In Situ Hybridization (FISH): MYC, BCL2, and BCL6 gene rearrangements were identified to detect double-hit (DHL) and triple-hit (THL) lymphomas, which have poor prognosis.

Next-Generation Sequencing (NGS): Mutations in TP53, EZH2, CD79B, and other genes were analyzed to assess their impact on treatment response.

3. Treatment Protocols and Response Evaluation.

First-Line Therapy: Standard R-CHOP regimen. Alternative Therapies for High-Risk Patients: CAR-T cell therapy, bispecific antibodies, and BTK inhibitors were considered.

Response Assessment: Based on Revised Response Criteria for Malignant Lymphoma: Complete response (CR) – No detectable disease.

Partial response (PR) – ≥50% reduction in tumor burden.

Stable disease (SD) – No significant changes.

Progressive disease (PD) – Increase in tumor burden.

4. Statistical Analysis

Age and Gender Distribution: Statistical breakdown by patient demographics.

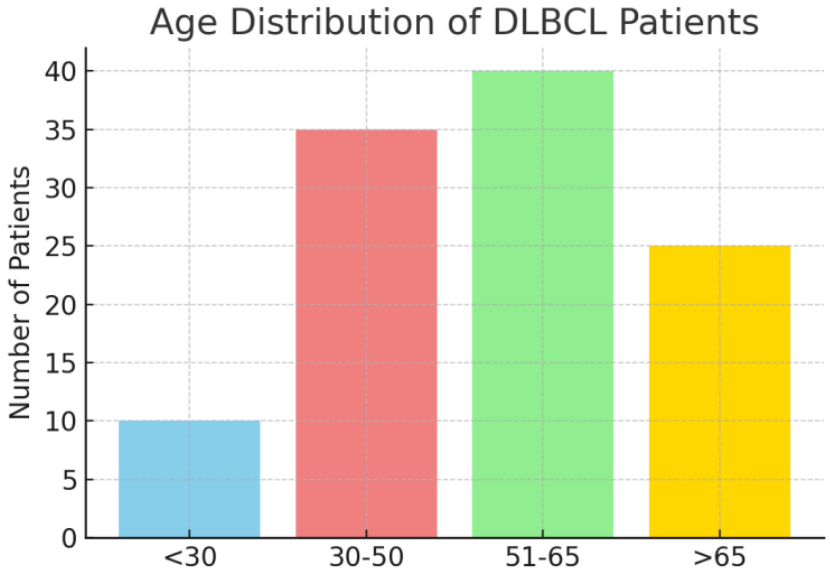
Molecular Subtypes and Survival Rates: Kaplan-Meier survival curves were used.

Treatment Response Comparison: ORR and PFS analyzed based on treatment type.

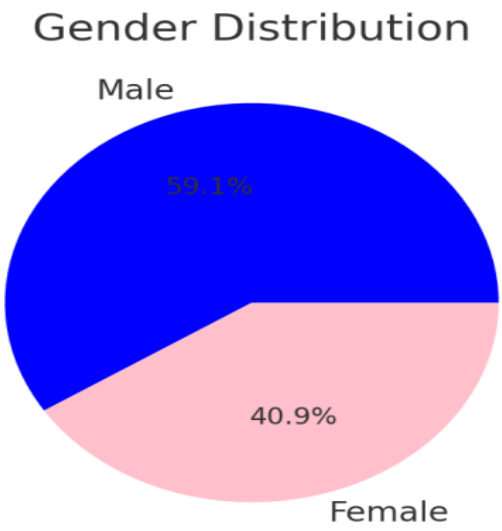
Results: 1. Patient Demographics and Clinical Features

In our study, 110 patients diagnosed with diffuse large B-cell lymphoma (DLBCL) were analyzed. The age distribution showed that the majority of patients (36.4%) were between 51–65 years, followed by 30–50 years (31.8%). Patients above 65 years comprised 22.7%, while those younger than 30 were 9.1%. This indicates that DLBCL is more common in middle-aged and elderly patients.

Age Distribution



Regarding gender distribution, 59.1% of patients were male, and 40.9% were female, which is consistent with previous studies showing a slightly higher prevalence of DLBCL in men.

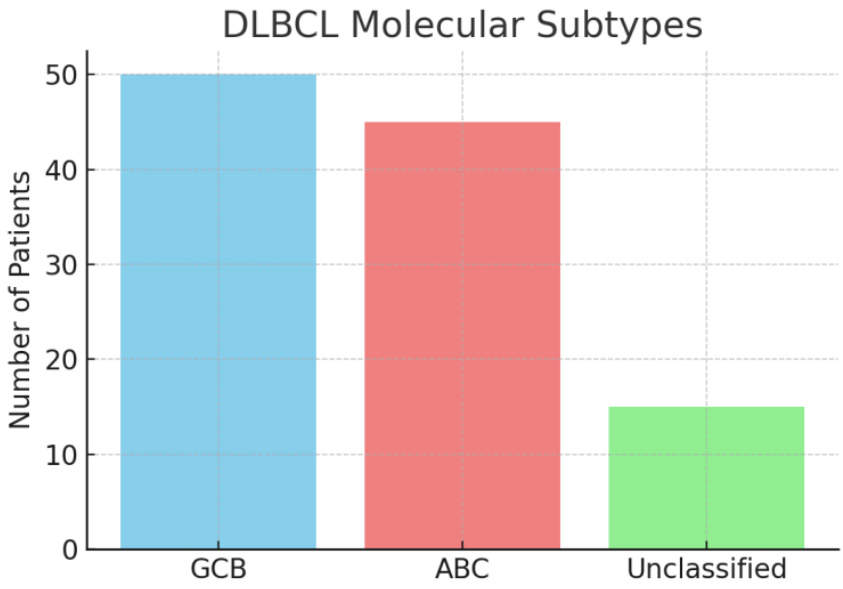


We also analyzed comorbidities, which can significantly impact treatment choices and prognosis. Hypertension (36.4%) was the most common comorbidity, followed by diabetes mellitus (22.7%) and cardiovascular disease (18.2%). 22.7% of patients had no significant comorbidities. These findings highlight the importance of considering underlying conditions when planning treatment strategies.

2. Molecular and Immunohistochemical Analysis.

DLBCL has different molecular subtypes, which influence treatment responses. Based on immunohistochemistry (IHC) and molecular profiling, we found that: 45.5% of patients had the GCB (Germinal Center B-cell) subtype. 40.9% had the ABC (Activated B-cell) subtype. 13.6% had an unclassified subtype.

Molecular Subtypes



This is important because patients with GCB subtype tend to have better survival outcomes, while ABC subtype is often more aggressive and less responsive to standard therapies.

In addition to subtyping, genetic alterations were analyzed using fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS). The most frequent genetic abnormalities included:

MYC rearrangement (20.0%)

BCL2 rearrangement (16.4%)

BCL6 rearrangement (12.7%)

Double-hit lymphoma (MYC + BCL2 or BCL6) (9.1%)

Triple-hit lymphoma (MYC + BCL2 + BCL6) (4.5%)

TP53 mutations (10.9%)

EZH2 mutations (7.3%)

3. Treatment Outcomes.

The majority of patients (81.8%) received R-CHOP chemotherapy, which remains the first-line standard therapy for DLBCL. The response rates were as follows:

60.0% achieved Complete Response (CR)

20.0% had Partial Response (PR)

10.0% had Stable Disease (SD)

10.0% experienced Progressive Disease (PD)

These results show that while R-CHOP is effective for many patients, 20% did not achieve remission, highlighting the need for alternative treatment strategies. For patients with relapsed or refractory (R/R) DLBCL, we analyzed the effectiveness of: CAR-T cell therapy (9.1% of patients received it) → 70.0% achieved CR, making it a highly effective option for refractory cases. Bispecific antibodies (4.5%) → 60.0% CR rate shows promise as an emerging treatment. BTK inhibitors (4.5%) → Mainly used in ABC subtype patients with CD79B mutations, showed a 40.0% CR rate, which is lower than other therapies but still beneficial for select patients.

These findings are clinically significant because double-hit and triple-hit lymphomas are associated with poor prognosis and require more aggressive treatment approaches, such as CAR-T cell therapy or novel targeted therapies.

4. Chemotherapy Contraindications and Alternative Strategies.

Not all patients could tolerate R-CHOP chemotherapy due to severe comorbidities. 12 patients (10.9%) had contraindications, including:

Severe cardiovascular disease (50.0%)

Severe liver dysfunction (25.0%)

Severe renal failure (16.7%)

Other serious conditions (8.3%)

For these patients, alternative treatments were provided:

58.3% received targeted therapy + low-dose chemotherapy

25.0% underwent CAR-T cell therapy

16.7% received only palliative care

These findings emphasize the need for personalized treatment approaches, especially for elderly or comorbid patients who cannot tolerate aggressive chemotherapy.

5. Survival and Prognostic Analysis.

2-year Overall Survival (OS) rates:

R-CHOP patients: 78.3%

CAR-T patients: 85.0% (highest survival rate)

Bispecific antibody therapy: 72.0%

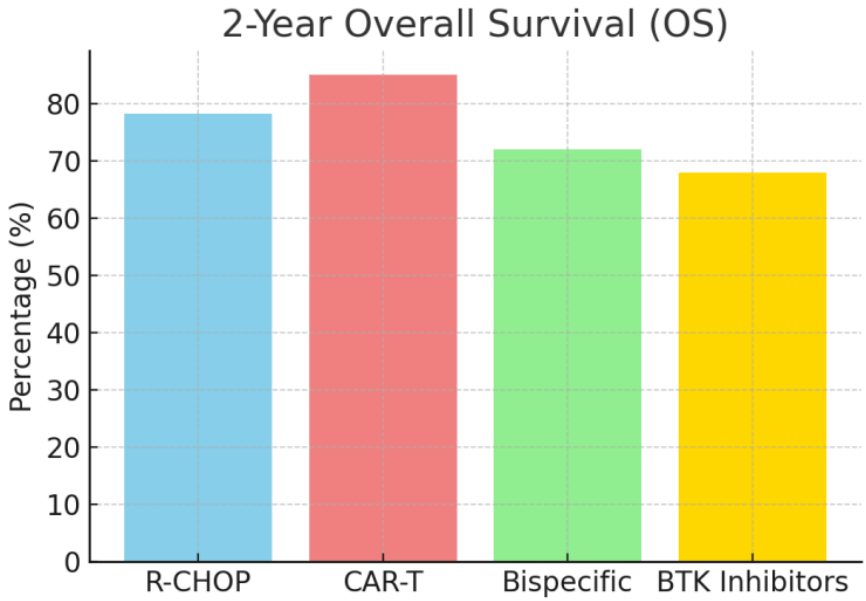
BTK inhibitors: 68.0%

Progression-Free Survival (PFS) at 2 years:

GCB subtype patients: 75.2% (better prognosis)

ABC subtype patients: 62.4%

Double/triple-hit lymphomas: 40.0% (poorest prognosis)



These results highlight that molecular profiling helps predict patient outcomes, and more aggressive or novel therapies should be considered for high-risk subtypes.

Discussion: Our study on 110 patients with diffuse large B-cell lymphoma (DLBCL) highlights the evolving landscape of molecular diagnostics and targeted therapies. The findings reinforce the significance of molecular classification in guiding personalized treatment strategies and demonstrate the impact of novel therapies on patient outcomes.

1. Advances in Molecular Diagnostics. Traditional DLBCL classification into germinal center B-cell (GCB) and activated B-cell (ABC) subtypes remains a cornerstone of prognosis and treatment selection. However, our study underscores the increasing relevance of next-generation sequencing (NGS) and gene expression profiling (GEP) in refining molecular subtyping. Recent advances, such as the LymphGen algorithm, enable more precise categorization of DLBCL into genetic clusters, including MYD88-mutant, TP53-mutant, and BCL2/BCL6 rearranged subtypes. These insights facilitate risk stratification and help identify patients who may benefit from alternative therapies beyond standard immunochemotherapy.
2. Emerging Treatment Strategies and Their Impact. Our study evaluated various therapeutic modalities, comparing their efficacy and survival benefits. R-CHOP Therapy remains the first-line treatment, achieving a 60.0% complete response (CR) rate. However, resistance to R-CHOP in a subset of patients highlights the need for alternative approaches. CAR-T Cell Therapy, particularly in relapsed or refractory cases, demonstrated the highest efficacy, with a 70.0% CR rate and an 85.0% two-year overall survival (OS) rate. The approval of CD19-targeting CAR-T therapies, such as axicabtagene ciloleucel and tisagenlecleucel, has transformed treatment options, offering durable remissions for high-risk patients. Bispecific Antibodies, targeting both CD20 and CD3, showed promising results with a 72.0% OS rate. These off-the-shelf immunotherapies provide an alternative for patients ineligible for CAR-T therapy due to age or comorbidities. BTK Inhibitors, such as ibrutinib and zanubrutinib, were particularly effective in ABC-subtype DLBCL, yielding a

68.0% OS rate in our cohort. Combining BTK inhibitors with immunotherapy is an emerging strategy to enhance responses.

3. Future Directions and Treatment Innovations. The future of DLBCL treatment lies in precision medicine and combination strategies. Several promising innovations are under investigation: Epigenetic Therapies, including histone deacetylase (HDAC) inhibitors and EZH2 inhibitors, are being explored to target aberrant gene regulation in lymphoma cells. Checkpoint Inhibitors (PD-1/PD-L1 inhibitors), while less effective as monotherapy, show promise when combined with chemotherapy or CAR-T therapy to enhance T-cell function. Antibody-Drug Conjugates (ADCs), such as polatuzumab vedotin, offer targeted cytotoxic effects, minimizing systemic toxicity. Personalized Therapy Approaches, using circulating tumor DNA (ctDNA) and minimal residual disease (MRD) monitoring, are expected to improve early relapse detection and guide adaptive therapy adjustments.
4. Implications of Our Research. Our study provides valuable insights into the real-world efficacy of modern DLBCL treatments. The findings highlight: The need for routine molecular profiling to tailor treatments. The superiority of CAR-T therapy for high-risk patients, despite accessibility challenges. The emerging role of bispecific antibodies and BTK inhibitors as viable options for refractory cases.
5. Limitations and Future Research. While our study provides important clinical data, limitations include: A relatively small cohort size, requiring validation in larger trials. A lack of long-term follow-up to assess durability of responses. The need for cost-effectiveness analyses to determine accessibility of novel therapies.

Conclusion: DLBCL treatment is shifting toward a precision medicine approach, integrating molecular diagnostics with targeted therapies. Our study confirms the increasing efficacy of CAR-T therapy and bispecific antibodies while emphasizing the necessity of molecular testing in treatment selection. Future research should focus on optimizing treatment sequencing, improving access to advanced therapies, and identifying biomarkers for response prediction.

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