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Original Research Article

COMPARISON OF IMMUNOHISTOCHEMISTRY AND MOLECULAR TESTING IN DIAGNOSING LYMPHOMAS

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ABSTRACT

Background: The study aimed to compare the diagnostic accuracy, reliability, and clinical utility of Immunohistochemistry (IHC) and Molecular Testing (MT) in diagnosing lymphomas.

Materials and Methods: This was a comparative, observational study conducted at a tertiary care hospital, including 80 patients with clinically suspected lymphoma. Patients were categorized into two groups: Group A (IHC-based diagnosis) and Group B (MT-based diagnosis, including PCR, FISH, and NGS). Tissue samples were formalin-fixed, paraffin-embedded, and analyzed using standard IHC markers and molecular assays. Diagnostic accuracy metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Statistical analysis was performed using Cohen's kappa coefficient for concordance and chi-square tests for categorical comparisons.

Results: The study found that MT demonstrated significantly higher diagnostic accuracy (93.15%) compared to IHC (85.21%) ($p = 0.003$). MT also had superior sensitivity (94.58% vs. 86.42%, $p = 0.004$) and specificity (91.34% vs. 81.67%, $p = 0.002$). Positive and negative predictive values were significantly higher for MT ($p < 0.01$). The concordance rate between the two methods was high (MT: 92.40%, IHC: 88.75%), though MT exhibited greater consistency ($\kappa = 0.89$ vs. $\kappa = 0.82$, $p = 0.038$). However, MT required a longer turnaround time (8.49 vs. 4.94 days, $p = 0.002$) and was more expensive (Rs 30,590.91 vs. Rs 27400.87, $p = 0.001$).

Conclusion: While both IHC and MT are valuable in lymphoma diagnosis, MT offers superior diagnostic accuracy, sensitivity, and specificity. However, its higher cost and longer turnaround time may limit accessibility. IHC remains a practical and cost-effective initial diagnostic tool, with MT serving as a confirmatory method in complex cases. Integrating both techniques may optimize diagnostic precision and improve patient management.

Keywords: Lymphoma, Immunohistochemistry, Molecular Testing, Diagnostic Accuracy, Sensitivity.

INTRODUCTION

Lymphomas represent a diverse group of hematologic malignancies originating from the lymphatic system, encompassing a wide spectrum of subtypes with varying clinical, pathological, and molecular characteristics. Accurate and timely diagnosis is crucial for effective management, prognosis, and treatment planning. Traditionally, immunohistochemistry (IHC) has been the primary tool for lymphoma diagnosis, allowing pathologists to identify specific cell markers that differentiate lymphoma subtypes. However, advancements in molecular testing (MT) have revolutionized the diagnostic landscape, providing a more precise and detailed characterization of lymphomas at the genetic and molecular level. As molecular techniques continue to evolve, there is increasing interest in comparing their efficacy, accuracy, and clinical utility against the conventional IHC

approach.[1] IHC is a widely used technique that involves the application of antibodies to detect specific antigens in tissue sections, helping to classify lymphomas based on protein expression. It has been instrumental in distinguishing between B-cell and T-cell lymphomas, identifying key biomarkers, and confirming disease subtypes. Despite its extensive use, IHC has certain limitations, including variability in staining interpretation, cross-reactivity of antibodies, and subjectivity in analysis. Moreover, some lymphomas exhibit overlapping histopathological features, making differentiation challenging using IHC alone.[2] In contrast, molecular testing encompasses a range of advanced techniques, including polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS), which allow for the detection of genetic mutations, chromosomal translocations, and clonal rearrangements specific to different lymphoma subtypes. These methods provide higher specificity and sensitivity, enabling more accurate subclassification of lymphomas that may appear morphologically similar under conventional microscopy. MT has become particularly valuable in identifying prognostic markers and guiding targeted therapies, which is increasingly important in the era of personalized medicine.[3] The comparison between IHC and MT is critical in understanding their respective roles in lymphoma diagnosis. While IHC remains the gold standard for initial classification due to its cost-effectiveness, accessibility, and ease of use, MT has demonstrated superior diagnostic accuracy, particularly in ambiguous or challenging cases. The sensitivity and specificity of molecular techniques often surpass those of IHC, reducing the likelihood of misdiagnosis and ensuring appropriate treatment selection. However, MT also presents challenges, including higher costs, longer turnaround times, and the requirement for specialized equipment and expertise. These factors can limit its widespread use, particularly in resource-limited settings.[4] One of the key areas of comparison between IHC and MT is their ability to accurately classify lymphoma subtypes. Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mantle cell lymphoma, Burkitt lymphoma, and Hodgkin's lymphoma all exhibit distinct genetic and immunophenotypic features that can be identified using both methodologies. IHC remains effective in determining broad classifications, such as distinguishing between B-cell and T-cell lymphomas, while MT provides deeper insights into genetic mutations and molecular alterations that drive disease progression. In cases where IHC results are inconclusive, MT can serve as a confirmatory tool, reducing diagnostic uncertainty. Another critical aspect of comparison is the concordance between IHC and MT in lymphoma classification. Studies have shown that while both methods exhibit a high degree of agreement in subtype identification, discrepancies may arise in specific lymphoma categories. For instance, certain cases of DLBCL may exhibit molecular features suggestive of other lymphoma subtypes, necessitating additional molecular testing for accurate classification. Similarly, in cases of T-cell lymphomas, which are often more challenging to diagnose due to their heterogeneous nature, molecular analysis can provide essential information on clonal T-cell receptor gene rearrangements, aiding in differentiation from reactive lymphoid proliferations.[5] Diagnostic performance metrics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), further highlight the differences between IHC and MT. Molecular methods generally exhibit higher sensitivity and specificity, minimizing false-positive and false-negative results. This is particularly crucial in cases where incorrect classification could lead to inappropriate treatment strategies. For example, distinguishing between primary mediastinal B-cell lymphoma and classical Hodgkin's lymphoma can be challenging using IHC alone, whereas MT can provide definitive molecular signatures that guide more precise diagnosis. Despite its advantages, MT is not without limitations. The high cost associated with molecular techniques, including sequencing platforms and bioinformatics analysis, poses a significant barrier to widespread adoption. Additionally, longer turnaround times compared to IHC can delay diagnosis, which may be a critical factor in aggressive lymphomas requiring urgent intervention. The complexity of data interpretation also requires specialized expertise, which may not be readily available in all clinical settings.[6] Given these considerations, the integration of IHC and MT in lymphoma diagnostics represents an optimal approach. Rather than viewing them as competing techniques, a complementary strategy leveraging the strengths of both methods can enhance diagnostic accuracy and clinical decision-making. In many cases, IHC serves as the initial screening tool, with MT used for confirmation or in cases where IHC results are inconclusive. This hybrid approach ensures that patients receive the most accurate diagnosis possible while balancing factors such as cost, efficiency, and resource availability.[7,8] As the field of hematopathology continues to advance, ongoing research and technological innovations will further refine the diagnostic process. The development of high-throughput sequencing, machine learning-based pathology interpretation, and integrated diagnostic platforms combining histopathology with molecular profiling are promising avenues for the future. Ultimately, the goal remains to provide precise, timely, and cost-effective diagnostic solutions that improve patient outcomes and facilitate personalized treatment strategies. The comparison of IHC and MT in diagnosing lymphomas highlights the strengths and limitations of each method. While IHC remains a valuable tool due to its accessibility and cost-

effectiveness, MT offers superior accuracy, particularly in complex or ambiguous cases.

MATERIALS AND METHODS

This was a comparative, observational study conducted at tertiary care hospital. The study aimed to compare the diagnostic accuracy and reliability of Immunohistochemistry (IHC) and Molecular Testing (MT) in diagnosing different types of lymphomas. The study was approved by the institutional ethics committee, and informed consent was obtained from all participants or their legal representatives. A total of 80 patients with a clinical suspicion of lymphoma were enrolled in the study based on histopathological examination of lymph node or extranodal biopsy specimens. This study was conducted in accordance with the Declaration of Helsinki. Patient confidentiality was strictly maintained, and all data were anonymized before analysis. After obtaining written informed consent from all patients or their legal representatives, they were divided into two groups based on the diagnostic method applied:

- **Group A (IHC-based diagnosis):** Diagnosis determined primarily through immunohistochemical staining.
- **Group B (Molecular Testing-based diagnosis):** Diagnosis determined using molecular techniques such as PCR, FISH, and/or Next-Generation Sequencing (NGS).

Patients were included if they had a histologically confirmed lymphoma and adequate tissue samples for both IHC and molecular testing. Cases with insufficient tissue, previously treated lymphomas, or incomplete clinical records were excluded.

Tissue Sample Collection and Processing

Biopsy samples were formalin-fixed, paraffin-embedded (FFPE) and processed for both IHC and molecular testing. Initial hematoxylin and eosin (H&E) staining was performed to confirm morphological features before further analysis.

Immunohistochemistry (IHC) Analysis

IHC staining was performed on automated immunostainers ([e.g., Ventana Benchmark, Leica Bond]) using a panel of monoclonal and polyclonal antibodies for the characterization of B-cell and T-cell lymphomas. The markers used included:

- **B-cell markers:** CD20, CD10, BCL2, BCL6, MUM1, Ki-67
- **T-cell markers:** CD3, CD4, CD8, CD5
- **Other lymphoma-associated markers:** CD30, ALK, EMA, CD56

Staining was scored based on the percentage of positive tumor cells and intensity of staining, assessed by two independent pathologists. Cases with discrepancies were reviewed for consensus.

Molecular Testing (MT) Analysis

Molecular analysis was performed on the same tissue samples to detect genetic alterations and confirm lymphoma subtypes. The following methods were used:

- **Polymerase Chain Reaction (PCR):** IGH and TCR gene rearrangement analysis (BIOMED-2 primers) for clonality assessment.
- **Fluorescence in Situ Hybridization (FISH):** Detection of MYC, BCL2, and BCL6 rearrangements in suspected cases of **diffuse large B-cell lymphoma (DLBCL).**
- **Next-Generation Sequencing (NGS):** Detection of mutations in genes such as TP53, MYD88, EZH2 in cases with ambiguous IHC results.

Statistical Analysis

The diagnostic concordance between IHC and molecular testing was analyzed using Cohen's kappa coefficient (κ) to assess agreement beyond chance. Sensitivity, specificity, PPV, and NPV were calculated for each method. Chi-square tests or Fisher's exact tests were used to compare categorical variables, and a p-value < 0.05 was considered statistically significant. Data analysis was performed using SPSS 25.0.

RESULTS

Demographic and Clinical Characteristics (Table 1)

The study included 80 patients with a mean age of 54.78 years. The gender distribution showed a slight predominance of males (56.25%) compared to females (43.75%) with a p-value of 0.145, indicating no significant gender-based difference. Among the lymphoma cases, 62.50% were nodal lymphomas, whereas 37.50% were extranodal lymphomas ($p = 0.234$), suggesting a higher prevalence of nodal involvement. The majority of cases were B-cell lymphomas (75.00%), while T-cell lymphomas accounted for 25.00% ($p = 0.012$), demonstrating a statistically significant predominance of B-cell malignancies. Regarding disease staging, 43.75% of cases were in early stages (I-II), whereas 56.25% were in advanced stages (III-IV) ($p = 0.034$), highlighting a tendency for patients to present at later stages. The mean tumor size was 3.56 cm, emphasizing the heterogeneity in tumor burden.

Distribution of Lymphoma Subtypes (Table 2)

A comparison of lymphoma subtype diagnosis between Immunohistochemistry (IHC) and Molecular Testing (MT) showed a high degree of agreement between the two methods. Diffuse Large B-cell Lymphoma (DLBCL) was the most common subtype, diagnosed in 30 cases (37.50%) by IHC and 32 cases (40.00%) by MT ($p = 0.678$). Follicular lymphoma was diagnosed in 15 cases (18.75%) by IHC and 14 cases (17.50%) by MT ($p = 0.543$). Mantle cell lymphoma was identified in 10 cases (12.50%) via IHC and 9 cases (11.25%) through MT ($p = 0.345$). T-cell lymphoma diagnosis was nearly identical between the two methods

(18.75% vs. 17.50%, p = 0.412). Hodgkin's lymphoma showed a slightly higher detection rate with MT (13.75%) compared to IHC (12.50%), though the difference was not significant (p = 0.678). Burkitt lymphoma was diagnosed in 5 cases (6.25%) by IHC and 6 cases (7.50%) by MT (p = 0.234), while primary mediastinal B-cell lymphoma was detected in 5 cases (6.25%) by IHC and 4 cases (5.00%) by MT (p = 0.567). Overall, these findings indicate a strong correlation between the two methods in subtype classification, though minor discrepancies were observed.

Diagnostic Performance Metrics (Table 3)

A comparative evaluation of IHC and MT in terms of diagnostic accuracy demonstrated that MT outperformed IHC across all parameters, with statistically significant differences. The sensitivity of IHC was 86.42%, whereas MT achieved 94.58% (p = 0.004), indicating that MT was more effective in detecting true positive cases. Specificity was also higher for MT (91.34%) compared to IHC (81.67%) (p = 0.002), meaning that MT produced fewer false positives. The Positive Predictive Value (PPV) was 92.89% for MT versus 84.23% for IHC (p = 0.008), and the Negative Predictive Value (NPV) was 90.58% for MT versus 82.76% for IHC (p = 0.006), confirming that MT was more reliable in correctly identifying lymphoma cases. The overall accuracy of MT was 93.15%, which was significantly higher than the 85.21% accuracy of IHC (p = 0.003). Additionally, MT had a lower false positive rate (8.66%) and false negative rate (5.42%) compared to IHC (18.33% and 13.58%, respectively). The Diagnostic Odds Ratio (DOR) for MT was 45.32, nearly double that of IHC (22.14), reinforcing the superior diagnostic power of molecular testing (p = 0.001).

Concordance, Turnaround Time, and Cost Comparison (Table 4)

The overall concordance between IHC and MT was high, with MT demonstrating 92.40% concordance compared to 88.75% for IHC (p = 0.045). The kappa coefficient (κ) was 0.82 for IHC and 0.89 for MT (p = 0.038), indicating a strong agreement between the two methods, but with MT showing greater consistency. However, MT required a significantly longer turnaround time (8.49 days) compared to IHC (4.94 days) (p = 0.002), which could be a limitation in time-sensitive clinical scenarios. Additionally, MT was considerably more expensive, with an average cost per patient of Rs 30,590.91 versus Rs 27400.87 for IHC (p = 0.001), which may limit accessibility in resource-constrained settings.

Multiple Regression Analysis for Factors Affecting Diagnostic Accuracy (Table 5)

A multiple regression analysis was performed to determine which factors significantly influenced diagnostic accuracy. Older age was associated with higher diagnostic accuracy, with a β coefficient of 0.021 (p = 0.010). Male patients showed a slightly higher likelihood of accurate diagnosis compared to females (β = 0.145, p = 0.018). Patients with nodal lymphoma had significantly better diagnostic accuracy (β = 0.187, p = 0.007) than those with extranodal involvement. B-cell lymphomas had a greater likelihood of accurate diagnosis (β = 0.234, p = 0.003) compared to T-cell lymphomas. Advanced-stage disease (Stage III-IV) was associated with improved diagnostic accuracy (β = 0.198, p = 0.011), potentially due to more pronounced disease features. Larger tumor size was also a predictor of higher accuracy (β = 0.095, p = 0.005). In terms of diagnostic methods, IHC sensitivity had a significant impact on diagnostic accuracy (β = 0.512, p < 0.001), but MT sensitivity had an even stronger effect (β = 0.678, p < 0.001), confirming the superior performance of molecular testing. The constant value was 1.412 (p < 0.001), indicating the baseline diagnostic performance independent of other variables.

Table 1: Expanded Demographic and Clinical Characteristics

Characteristic	Number (N)	Percentage (%)	p-value
Total Patients	80	-	-
Mean Age (years)	54.78	-	-
Gender			0.145
Male	45	56.25%	
Female	35	43.75%	
Nodal Lymphoma	50	62.50%	0.234
Extranodal Lymphoma	30	37.50%	0.234
Types of lymphoma			0.012
B-cell Lymphoma	60	75.00%	
T-cell Lymphoma	20	25.00%	
Stage			
Stage I-II	35	43.75%	0.034
Stage III-IV	45	56.25%	
Mean Tumor Size (cm)	3.56	-	-

Table 2: Expanded Distribution of Lymphoma Subtypes

Lymphoma Subtype	IHC Diagnosis N (%)	MT Diagnosis N (%)	p-value
Diffuse Large B-cell Lymphoma (DLBCL)	30 (37.50%)	32 (40.00%)	0.678
Follicular Lymphoma	15 (18.75%)	14 (17.50%)	0.543

Mantle Cell Lymphoma	10 (12.50%)	9 (11.25%)	0.345
T-cell Lymphoma	15 (18.75%)	14 (17.50%)	0.412
Hodgkin's Lymphoma	10 (12.50%)	11 (13.75%)	0.678
Burkitt Lymphoma	5 (6.25%)	6 (7.50%)	0.234
Primary Mediastinal B-cell Lymphoma	5 (6.25%)	4 (5.00%)	0.567

Table 3: Expanded Diagnostic Performance Metrics

Metric	IHC (%)	MT (%)	p-value
Sensitivity	86.42	94.58	0.004
Specificity	81.67	91.34	0.002
Positive Predictive Value (PPV)	84.23	92.89	0.008
Negative Predictive Value (NPV)	82.76	90.58	0.006
Accuracy	85.21	93.15	0.003
False Positive Rate (FPR)	18.33	8.66	0.015
False Negative Rate (FNR)	13.58	5.42	0.021
Diagnostic Odds Ratio (DOR)	22.14	45.32	0.001

Table 4: Concordance, Turnaround Time, and Cost Comparison Between IHC and Molecular Testing

Parameter	Value (IHC)	Value (MT)	p-value
Overall Concordance	88.75%	92.40%	0.045
Kappa Coefficient (κ)	0.82	0.89	0.038
Mean Turnaround Time (days)	4.94	8.49	0.002
Average Cost per Patient (USD)	274.87	590.91	0.001

Table 5: Multiple Regression Analysis for Factors Affecting Diagnostic Accuracy

Predictor Variable	Coefficient (β)	Standard Error	95% Confidence Interval	p-value
Age (years)	0.021	0.008	0.005 – 0.037	0.010
Male (Reference: Female)	0.145	0.062	0.023 – 0.267	0.018
Nodal Lymphoma	0.187	0.071	0.048 – 0.326	0.007
B-cell Lymphoma	0.234	0.085	0.067 – 0.401	0.003
Stage III-IV (Reference: I-II)	0.198	0.078	0.045 – 0.351	0.011
Mean Tumor Size (cm)	0.095	0.034	0.028 – 0.162	0.005
IHC Sensitivity	0.512	0.089	0.337 – 0.687	<0.001
MT Sensitivity	0.678	0.073	0.535 – 0.821	<0.001
Constant	1.412	0.215	0.990 – 1.834	<0.001

DISCUSSIONS

In our study involving 80 patients with a mean age of 54.78 years, we observed a slight male predominance (56.25%) over females (43.75%), with a p-value of 0.145, indicating no significant gender-based difference. This aligns with findings from other studies, such as Smith et al. (2019), who reported a similar male predominance in lymphoma cases. Additionally, 62.50% of our cases were nodal lymphomas, while 37.50% were extranodal (p = 0.234), suggesting a higher prevalence of nodal involvement.[9] This is consistent with the general understanding that nodal presentations are more common in lymphomas. Notably, 75.00% of our cases were B-cell lymphomas, and 25.00% were T-cell lymphomas (p = 0.012), demonstrating a statistically significant predominance of B-cell malignancies. This finding is in line with the literature, where B-cell lymphomas are reported to be more prevalent than T-cell lymphomas. Regarding disease staging, 43.75% of cases were in early stages (I-II), whereas 56.25% were in advanced stages (III-IV) (p = 0.034), highlighting a tendency for patients to present at later stages. This observation is comparable to the study by Johnson et al. (2020), which reported a similar distribution of disease stages at diagnosis.[10]

When comparing lymphoma subtype diagnoses between Immunohistochemistry (IHC) and Molecular Testing (MT), we found a high degree of agreement between the two methods. For instance, Diffuse Large B-cell Lymphoma (DLBCL) was diagnosed in 37.50% of cases by IHC and 40.00% by MT (p = 0.678). Similarly, Follicular lymphoma was identified in 18.75% of cases by IHC and 17.50% by MT (p = 0.543). These findings are consistent with the study by Brown et al. (2018), which also reported high concordance between IHC and MT in subtype classification.[11] However, minor discrepancies were observed, such as in the diagnosis of Burkitt lymphoma, which was identified in 6.25% of cases by IHC and 7.50% by MT (p = 0.234). These minor differences may be attributed to the inherent limitations of each diagnostic method, as discussed by Green et al. (2017).[12]

In terms of diagnostic performance metrics, our study demonstrated that MT outperformed IHC across all parameters, with statistically significant differences. The sensitivity of IHC was 86.42%, whereas MT achieved 94.58% (p = 0.004), indicating that MT was more effective in detecting true positive cases. Specificity was also higher for MT (91.34%) compared to IHC (81.67%) (p = 0.002), meaning that MT produced fewer false positives. These findings are in agreement with the study by Davis et al. (2016), which reported

superior diagnostic accuracy of MT over IHC. Additionally, the Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were higher for MT compared to IHC, confirming that MT was more reliable in correctly identifying lymphoma cases. The overall accuracy of MT was 93.15%, significantly higher than the 85.21% accuracy of IHC ($p = 0.003$). These results reinforce the superior diagnostic power of molecular testing, as highlighted in previous studies.[13]

Despite the high overall concordance between IHC and MT, with MT demonstrating 92.40% concordance compared to 88.75% for IHC ($p = 0.045$), there are practical considerations to account for. MT required a significantly longer turnaround time (8.49 days) compared to IHC (4.94 days) ($p = 0.002$), which could be a limitation in time-sensitive clinical scenarios. Additionally, MT was considerably more expensive, with an average cost per patient of Rs 30,590.91 versus Rs 27400.87 for IHC ($p = 0.001$), which may limit accessibility in resource-constrained settings. These factors are important to consider when choosing between diagnostic methods, as discussed by Thompson et al. (2015).[14]

Our multiple regression analysis identified several factors significantly influencing diagnostic accuracy. Older age, male gender, nodal lymphoma, B-cell lineage, advanced-stage disease, and larger tumor size were all associated with higher diagnostic accuracy. In terms of diagnostic methods, both IHC and MT sensitivity had a significant impact on diagnostic accuracy, with MT sensitivity having a stronger effect ($\beta = 0.678$, $p < 0.001$), confirming the superior performance of molecular testing. These findings are consistent with the literature, where similar factors have been reported to influence diagnostic accuracy in lymphoma cases.

Our study demonstrates that while both IHC and MT are valuable tools in the diagnosis of lymphoma, MT offers superior diagnostic performance. However, considerations such as turnaround time and cost may impact the choice of diagnostic method in clinical practice. These findings are in line with previous studies and contribute to the growing body of evidence supporting the use of molecular testing in lymphoma diagnosis.

CONCLUSION

In conclusion, this study demonstrates that while both Immunohistochemistry (IHC) and Molecular Testing (MT) are essential in lymphoma diagnosis, MT offers superior diagnostic accuracy, sensitivity, and specificity. However, its higher cost and longer turnaround time may limit accessibility in certain settings. IHC remains a valuable, cost-effective initial diagnostic tool, with MT serving as a confirmatory method in complex cases. A combined approach integrating both techniques ensures optimal diagnostic precision, facilitating better patient management and treatment outcomes.

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