



Flow Cytometric Analysis of Immunophenotypic Characteristics of B-cell Lymphoproliferative Disorders: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Mature B cell neoplasm present a diverse group of disorders characterized by distinct clinical presentations, pathological features, and outcomes. These neoplasms originate from B-Cell lineages, exhibiting clonality along with morphological, immunophenotypic, and genetic characteristics. This review provides a detailed evaluation of global variations, diagnostic challenges, and prognostic significance of B cell non-Hodgkin lymphomas (B-NHL). It emphasizes the critical role of immunophenotypic markers, such as CD5, and CD10, and the application of advanced diagnostic technologies like flow cytometry in guiding personalized treatment strategies. The literature search was conducted using key terms like "B cell lymphoproliferative disorders", "BCLPDs", "B-NHL" and "Flow cytometric immunophenotyping of B-CLPDs" across multiple databases and google scholar. The review highlights the key findings from worldwide studies, offering insights into how these markers and technologies contribute to improved diagnostic accuracy and patient outcomes. Additionally, it discusses the implications of aberrant marker expression and bi-clonality, which further complicate diagnosis but hold significant prognostic value. This comprehensive analysis aims to assist clinicians and researches in refining diagnostic criteria and optimizing therapeutic approaches for B-NHL globally.

Keywords: Flow cytometry; immunophenotyping; lymphoma; BCLPD; B-NHL.

1. INTRODUCTION

Mature B cell neoplasms consists of a diverse group of disorders with distinct clinical presentations, pathology, and outcomes. They originate from B cell lineage, exhibit clonality, and possess morphological, immunophenotypic, and genetic features of mature B-cells [1]. Flow cytometric assessment categorizes mature B-cell lymphomas into four main groups based on CD5 and CD10 expression: They are: CD5+/CD10-, CD5-/CD10+, CD5+/CD10+, and CD5-/CD10-. The objective of the review is to explore the global variations, diagnostic challenges, and prognostic implications of B- Non-Hodgkin's lymphoma (B-NHL) subtypes, emphasizing the role of immunophenotypic markers and advanced diagnostic techniques in guiding personalized treatment strategies and improving patient outcomes worldwide. This article provides a comprehensive review of the immunophenotyping of BCLPDs, with a particular focus on diagnostic and prognostic markers. The significance of this work lies in its detailed evaluation of global variations and diagnostic challenges in BCLPDs, highlighting the importance of flow cytometry in personalized treatment strategies.

2. METHODOLOGY

The literature search was conducted across multiple databases, namely "PubMed," "HINARI" database, and the well-established academic

search engine "Google Scholar." To effectively narrow down the search, specific key terms were employed, including "B cell lymphoproliferative disorders," "B-CLPD," "B-NHL," and "Flow cytometric immunophenotyping of B-CLPD." These terms were strategically combined using "or" and "and" operators to enhance the precision of the search results.

Inclusion criteria were set to consider only published clinical studies, review papers, and related articles relevant to BCLPDs. Additionally, the search was confined to English-language publications to ensure consistency and accessibility. Each combination of keywords was systematically inputted into the databases to retrieve pertinent literature for the study.

3. RESULTS

3.1 CD5+/CD10-Group

This group includes Chronic Lymphocytic Leukaemia/ Small Lymphocytic Leukaemia (CLL/SLL), Mantle Cell Lymphoma (MCL), some B-cell prolymphocytic Leukaemia (B-PLL), and small percentages of Marginal Zone Lymphoma (MZL), Diffuse Large B-cell Lymphoma (DLBCL), and possibly Lymphoplasmacytic Lymphoma (LPL) [2].

CLL presents with small, mature lymphocytes with dense nuclei lacking discernible nucleoli and partially aggregated chromatin (1). Diagnosis

requires confirming monoclonal B cell count $>5 \times 10^9/L$ and demonstrating light chain restriction using flow cytometry [3].

These cells express CD5, CD23, CD19, CD20, CD43, and CD200. They are negative for CD10, and CD79b may be weak. FMC7 is typically negative or weak. Surface CD20, surface Ig, and CD79b levels are low compared to normal B cells [4]. Morphology is essential to distinguish CLL/SLL from DLBCL and B-PLL. Fluorescence in situ hybridization (FISH) can offer prognostic insight [5].

Matutes et al. proposed a scoring system (smlg density, CD5, CD79b, CD23, and FMC7) to differentiate CLL from other B-Cell Lymphoproliferative Disorders (B-CLPDs). A score $>3/5$ indicates "typical" CLL, while in other diseases, it is 0-2 [6]. In terms of immunophenotype, atypical CLL can be distinguished from classic CLL by the absence of one or fewer surface antigens, typically CD5 and CD23. Additionally, the patient does not fulfill the diagnostic criteria for any other B-cell lymphoid malignancy [7].

Delgado J et al. discovered a link between CD20 and FMC7 expression in patients with B-cell NHL (P.001) but not in CLL. Further, this study compared the current scoring system with a scoring system in which FMC7 was replaced by CD20, and the accuracy of differentiating CLL from other non-CLL disorders fell from 94.4% to 81.5% [8]. Also some CD5+, and CD10-neoplasms are challenging to classify using flow cytometry [9,10].

CD200 overexpression distinguishes CLL and HCL from MCL, aiding in prognosis [11]. Sorigue et al. found CLL and CLL-like Monoclonal B cell lymphocytosis (MBL) cases were CD200 positive, but MBL showed lower CD200 levels than CLL [12].

CD38 is a prognostic marker in CLL, with $>30\%$ CD38-positive cells indicating shorter survival [13]. Semanaj et al. (2014) noted 70% of CD5+CD19+CD23+ patients with CD38+ belonged to CLL stages III-IV, contrasting with 75% without CD38 belonging to stages 0-I-II [14].

CLL and SLL are related diseases. "SLL" denotes cases with $5 \times 10^9/L$ circulating lymphocytes and documented nodal, splenic, or extra medullary involvement [15,16]. CLL/SLL comprises 7% of NHL [17].

MCL is a B-cell neoplasm with small-to-medium-sized lymphoid cells with irregular nuclear contours [15]. These cells express intense smlg lambda over smlg kappa, CD19, CD5, CD20, CD79b, FMC7, BCL2, and CD43, and are negative/weak for CD23 and negative for CD10, CD200 [18].

MCL has a more variable phenotype than CLL/SLL, overlapping with other CD5+ mature B-cell neoplasms. Additional tests like immunohistochemistry for cyclin-D1 protein and cytogenetic for t(11;14) are recommended for diagnosis [19–21]. Distinguishing features include lack of CD23 expression and presence of plasmacytic differentiation with bright CD38 expression in MZL [2].

B-cell polymphocytic Leukaemia (B-PLL) is a neoplasm of B-cell polymphocytes affecting peripheral blood, bone marrow, and spleen. Polymphocytes must account for $\geq 55\%$ of lymphoid cells in peripheral blood [15]. The key factor distinguishing B-PLL from CLL lies in the proportion of polymphocytes present in the bloodstream. The FAB (French American British) classification system, widely acknowledged in the medical community, delineates this differentiation as follows: (i) CLL is identified when polymphocytes constitute equal to or less than 10% of lymphoid cells; (ii) Conversely, B-PLL is diagnosed when polymphocytes surpass 55% of lymphoid cells [22]. B-PLL express bright smlg lambda/kappa, CD19, CD5 (20-30% cases), CD20, CD79b, FMC7, and CD38 (50% cases), and are dimly positive/negative for CD200 and negative for CD10 [23].

Approximately 5% of LPLs are CD5+ (23,24). CD23 is usually negative, and if positive, it's weak. LPL doesn't have CLL/SLL phenotype [24]. Distinguishing LPL from other CD5+ B-cell lymphomas requires morphologic and clinical features.

Some DLBCLs are CD5+ but larger than small CD5+ B-cell lymphomas. Exclusion of the blastoid variant of MCL is recommended through testing for cyclin-D1 overexpression and t(11;14) (q13; q32) gene rearrangement [2].

3.2 CD5-/CD10+ Group

DLBCL and Follicular Lymphoma (FL) are common CD10+ and CD5- mature B-cell

neoplasms. Swerdlow et al. (2016) suggest CD10+ DLBCL might resemble BL and FL due to their large cell count.

DLBCL and Burkitt Lymphoma (BL) feature large lymphoid cells with moderate to abundant cytoplasm, round nuclei with one to many nucleoli, and fine chromatin. They express pan B cell markers. BL shows bright CD38, positive CD43, and negative CD200 [15].

In FL, >40% of lymphocytes display cleaving, scanty cytoplasm, high N/C ratio, and condensed chromatin. They're usually CD5- and CD10+, with positive CD19, FMC7, CD79b, and bright CD20. Most cases show Kappa or Lambda restriction, with variable CD23 expression [15].

3.3 CD5+/CD10+ Group

Mature B-cell lymphoid neoplasms co-expressing CD5 and CD10 are rare [25,26]. This group includes DLBCL, FL, MCL, CLL/SLL, BL [27], and rare other B-cell malignancies.

A study found 42 cases with simultaneous expression of CD5 and CD10: DLBCL was reported in 14 (33%), FL in 10 (24%), MCL in 9 (21%), CLL in 4 (10%), acute precursor B-cell lymphoblastic leukemia/lymphoma in 2 (5%), and other low-grade B-cell lymphomas in 3 (7%) cases. All FLs had the expected morphology, were bcl-2+ and bcl-6+, but were CD43- [27].

3.4 CD5-CD10-Group

Mature B-cell neoplasms without CD5 and CD10 include DLBCL, MZL, Hairy Cell Leukaemia (HCL), LPL, CD10-FL, and CD5-MCL. HCL consists of small mature lymphoid cells with oval nuclei and abundant cytoplasm with hairy

projections in blood and marrow. Most lack CD5 and CD10 but express bright surface immunoglobulin, CD11c, CD103, CD25, CD123, and CD200. The BRAF V600E mutation is a molecular marker of classic HCL, not found in the hairy cell variant (HCL-v) [17,28].

Splenic Marginal Zone Lymphoma (SMZL) comprises small to medium-sized lymphoid cells with regular nuclei, clumped chromatin, and small nucleoli in 20–40% of cells, often with localized cytoplasmic villi. They are typically CD5 and CD10 negative but express CD19, CD20, FMC7, CD79b, and bright smlg lambda/kappa. Some cases lack CD23, CD43, CD200, CD103, CD123, and CD25 [15,29].

LPL consists of small mature B lymphocytes, plasmacytoid lymphocytes, and plasma cells, expressing CD19, CD20, FMC7, CD79b, and CD25. CD23 is positive in 30–60% of cases. Plasma cells express CD19 and CD138 [1].

CD10- FL and CD5- MCL are recognized and fit into the CD5- CD10- group. Identifying these variants typically involves combining morphological and immunophenotypic methods.

3.5 Global Variations in B-NHL Subtypes

A study in Sri Lanka revealed, common WHO lymphoma sub types were DLBCL and FL by immunohistochemistry using biopsy specimens of patients [30]. The frequencies of lymphoma subtypes in the Sri Lankan sample (Table 1) were in accordance with the globally observed variations and similar to those observed in other South Asian countries (Table 2). In this study, all lymphomas were sub classified according to WHO 2007 revised classification of haematopoietic and lymphoid neoplasms [1].

Table 1. B-CLPDs WHO subtypes in Sri Lanka

Lymphoma sub type	Frequency	Mean age in years (SD)	Number of Males (M)	Number of Females (F)
Diffuse large B cell lymphoma	87 (58.8%)	53.68 (16.9)	52 (59.8%)	35 (40.2%)
SLL/CLL	11(7.4%)	49.08 (17.15)	6 (54.5%)	5 (55.5%)
Follicular lymphoma	26 (17.6%)	54.7 (13.09)	11 (42.3%)	15 (57.7%)
Mantle cell lymphoma	10 (6.8%)	52.56 (11.94)	7 (70%)	3 (30%)
Marginal zone lymphoma	6 (4%)	61.83 (13.03)	3 (50%)	3 (50%)
Burkitt lymphoma	1 (0.7%)		1(100%)	-
Unclassifiable	7 (4.7%)	55.4 (17.11)	6 (85%)	1 (15%)

Table 2. Comparison of B-CLPDs WHO subtypes

Lymphoma WHO sub type	Sri Lanka Waravita T S e al. [31]	India Naresh K N et al. [32]	Pakistan Mushtaq S et al. [33]	USA Morton LM et al. [17]	Japan Aoki R et al. [34]	S. Korea Yoon SO et al [35]	China Yang QP et al, [36]
Sample size	148	2027	151	57975	1521	3482	3862
Diffuse large B cell lymphoma	87 (58.7%)	937 (46.2%)	119 (78.8%)	24246 (41.8%)	746 (49%)	1650 (47.2%)	2288 (59.2%)
SLL/CLL	11 (7.4%)	155 (7.6%)	4 (2.6%)	16984(29.2%)	32 (21%)	97 (2.7%)	256 (6.6%)
Follicular lymphoma	26 (17.5%)	350 (17.2%)	9 (5.9%)	10705 (18.4%)	413 (27.1%)	91 (2.6%)	327 (8.4%)
Mantle cell lymphoma	10 (6.75%)	95 (4.6%)	4(2.6%)	1691 (2.9%)	61 (4.0%)	98 (2.8%)	175 (4.5%)
Marginal zone lymphoma	6 (4%)	220 (10.8%)	4(2.6%)	3247 (5.6%)	127 (8.3%)	720 (20.6%)	355 (9.1%)
Nodal	2 (1.35%)	52(2.05%)	0	0	32 (1.5%)	54 (1.5%)	5 (0.1%)
Extra nodal	4 (2.7%)	168 (8.2%)	4(2.6%)	0	95 (6.2%)	661 (18.9%)	350 (9.0%)
Burkitt lymphoma	1 (0.6%)	50 (2.4%)	7 (4.6%)	1102 (1.9%)	15 (0.98%)	111 (3.18%)	106 (2.7%)

Another study done in China revealed, CLL was the most common B-CLPD, but the overall incidence was lower compared to the West [36]. Proportions of CLL (55.9%), FL (2.6%), and HCL (0.2%) were lower, while LPL (5.4%) was higher in China. CD23 expression in MCL (31.7%) was higher compared to Western cohorts [36,37]. CD200 showed better diagnostic performance (94.6% accuracy) than CD23 in distinguishing CLL from MCL. Some cases remained unclassified as CD5+ BCPLDs (7.7%) and CD5 - BCPLDs (15.8%)[36]. HCL was rare in this cohort, with only 1 patient among 653 BCLPD cases [36]. Similarly, Yi et al. found CD5+ BCLPD unclassified (10%) in their study. CD5+ BCLPD unclassified and MCL shared similar immunophenotype, with CD11c more frequent in CD5+ BCLPD unclassified. However, CD200, usually absent in MCL, was expressed in most CD5+ BCLPD unclassified cases. A USA study proposed non-BM tissue biopsy for definitive diagnosis in CD5+B-CLPD [38].

Miao et al. found a lower proportion of CLL (compared to Gujral et al.) at 68.3%, while LPL was higher at 5.4 % (37). Gujral et al. studied mature B-cell NHL at Tata Memorial Hospital, reporting CLL (68.5%), FL (8.5%), MCL (5.5%), SMZL (5%), and HCL (5%). CD5+/CD23+ had 93% PPV for CLL diagnosis, while CD5+/CD23- had 99% NPV for MCL. Some cases (4%) were labeled B NHL Unclassifiable, not fitting WHO categories [39].

In an Albanian study, 2 out of 84 individuals (2.4%) had abnormal T-cells, while 82 (97.6%) showed a pathological B-cell line. 58 (69.1%) had typical CLL markers (CD19+CD5+CD23+), 5 (5.9%) had a non-typical CLL profile (CD19+CD5+CD23-), and 19 (22.6%) had abnormal CD19+CD5- B cells. CD38 positivity correlated significantly with the CLL clinical stage ($p = 0.04$) [14].

In India, Dwivedi et al. (2019) stressed the importance of immunophenotyping, with a 79.17% concordance rate between morphological and immunophenotypic diagnoses. Flow cytometry confirms diagnoses and classifies unclassifiable CLPD cases by morphology [40].

A Brazilian study recommends shifting from traditional four-color to more color (>8) assays for accurate diagnoses, using fewer tubes and markers, and analyzing small cell samples effectively. FL and DLBCL may show reduced

CD19 expression, affecting B-cell identification. Neoplastic B-cells are first gated on CD19+/FSC low/SSC low cells, followed by evaluating other antigens [41].

Another study done in Brazil to study the CD5 expression in leukemic cells from 42 patients with chronic B-cell malignancies by flow cytometry revealed CD5 expression was present in all B-CLL and MCL, and low expression of CD5 was observed in one patient with B-PLL and was negative in all cases of HCL. They demonstrated that CD5 expression can help distinguish between B-CLL from HCL and B-PLL, but it is similarly expressed in MCL [42].

In a study done in Canada, cases of B-cell lymphoproliferation with two B-cell populations were reported. Forty-one of 790 samples (5.1%), from 22 male and 19 female patients, showed two monoclonal B-cell populations that differed in immunophenotype. From that, 13 samples had two co-existing aberrant B-cell populations that showed restriction of different sIg, one kappa-positive and one lambda-positive. In 10 of these 13 cases, one population had a B-CLL-related phenotype and two cases also showed a difference in CD38 expression between two populations. In four of the 13 cases [43], an abnormal plasma cell population was accompanied by B-CLPD [44]. It was revealed that patients with positive expression of CD38 had significantly shorter overall survival (mean, 81 months) than patients without CD38 expression (mean, 179 months) ($P = 0.015$) in a study on the Chinese population [44]. A cohort of 413 subsequent patients with de novo leukemic B-cell chronic lymphoproliferative disorders diagnosed in Croatian institutions during 30 months revealed bi-clonality in 16 (3.9%) patients with composite lymphoma. The vast majority (88%) of the cases had one of the clones phenotypically corresponding to CLL or SLL. Bi-clonal cases had an overall B-cell membrane lambda-to-kappa ratio within the normal range, making recognition of malignancy somewhat challenging. For composite lymphoma, the analysis strategy was based on the detection of aberrant B-cell phenotypes, with subsequent confirmation of the monoclonal nature of neoplastic clones about light chain restriction analysis [45].

In a Canadian study [46], they developed a composite diagnostic predictor called the "combined ratio score" (CRS) to distinguish between MCL and SLL. CRS integrated three

discriminative ratios (CD20/CD23, FMC7/CD23, CD20/CD11c) using machine-based algorithms. While conventional criteria correctly identified 64% of MCL and 69% of SLL cases, the novel approach accurately assigned 100% of MCL and 97% of SLL cases. The CD20/CD23 ratio was the most discriminating feature, with 100% sensitivity, specificity, and accuracy. Interestingly, including FMC7 expression reduced diagnostic accuracy (FMC7/CD23-96%, FMC7 alone 80%).

In a Danish study, 503 CD5+ and 37 CD5- B-cell CLL cases were identified. CD5- patients had a slightly shorter survival than CD5+ patients. Most CD5- cases were FMC7+ and CD23+, with strong IgM fluorescence and splenomegaly. However, age, clinical stage, and lymphocyte count didn't differ between CD5+ and CD5- cases [47].

In an Egyptian study on CLL and MCL, 80% of MCL cases showed small cell morphology, with the remaining 20% showing the blastoid variant. Immunophenotypic differences weren't detected between the morphologic variants of MCL. CLL cases were positive for CD19 (100%), CD20 (90%), and CD22 (47%). CD79b negativity was observed in 63% of cases, with low expression in positive cases. CD200 was expressed in 100% of CLL cases with moderate intensity compared to only 10% of MCL cases with low intensity [18].

In 20% of confirmed MCL cases, CD5 expression is absent [48]. In Iraq, CD200 was expressed in 94.9% of 39 CLL patients, while all MCL cases

were negative. A significant association between CD200 expression and B-CLL was observed ($p = 0.001$), with only 5.1% of advanced disease cases showing negative expression [49].

The reported frequency of CLL from studies in Hong Kong was variable, ranging from 6.5% to 12%. In a study by Ho et al [50]. on malignant lymphomas, only 12 CLL cases out of 267 cases were observed over 8 years [50]. For instance, in Kwong's study, up to 20% of CLL cases were retrospective series of CLL cases from Chinese people in Hong Kong, which were CD5-negative [51].

Jain M et al. reported a case of a 50-year-old male with CLL with aberrant CD8 expression. The CD19-gated B cell showed co-expression of CD8 and CD19. Other T cell markers (CD4, CD2, CD3, and CD7) were not expressed by B cells [52]. Inaba et al. [53] and Kampalath et al. [54] have similarly reported CD2 and CD7 expression in CLL or B-NHL to be associated with poor prognosis and shorter overall survival.

In India, a study found CD3 positive in 10% of CLL cases and CD10 positive in 5%. CD38 was positive in 40% of CLL cases. All atypical CLLs showed CD22 positivity, with two cases negative for CD5. CD20 was expressed in 85% of CLL cases, while CD79b and FMC7 were expressed in 57.5% and 12.5% of cases, respectively [55]. In Iran, Maljaei et al. showed that lower CD45 density was associated highly with typical CLL ($P < 0.001$) and non-CLL cases had brighter CD45 expression than atypical CLL ($P = 0.014$) [56].

Table 3. The immunophenotypes of B-NHL, (Kaleem, 2006)

The immunophenotypes of B-NHL with respect to CD5, CD10, and CD23			
Lymphoma	Typical Pattern	Less common pattern	Unusual pattern
SLL/CLL	CD5+, CD23+, CD10-	CD5+, CD23-, CD10-	CD5-, CD23+, CD10-
MCL	CD5+, CD23-, CD10-	CD5+, CD23+, CD10-	CD5+, CD23-, CD10+
FL	CD5-, CD23-, CD10+	CD5-, CD23+, CD10+	CD5+, CD23-, CD10+
DLBCL	CD5-, CD23-, CD10-	CD5-, CD23-, CD10+	CD5-, CD23+, CD10-
MZL	CD5-, CD23-, CD10-	CD5-, CD23+, CD10-	CD5+, CD23-, CD10-
B-PLL	CD5-, CD23-, CD10-	CD5-, CD23+, CD10-	CD5+, CD23+, CD10-
HCL	CD5-, CD10- CD11c+, CD103+, CD25+	CD5-, CD10- CD11c+, CD103+, CD25-	CD5-, CD10- CD11c+, CD103-, CD25-
BL	CD5-, CD23-, CD10+	CD5-, CD23-, CD10-	CD5-, CD23+, CD10-
LPL	CD5-, CD23-, CD10-	CD5-, CD23-, CD10-	CD5-, CD23+, CD10-

Aberrant expression of immunophenotypic markers is seen in patients with blood cancers. An interesting biological feature is that T-cell antigen expression in B-cell non-Hodgkin's lymphoma (B-NHL) on neoplastic B cells. CD5 is normally expressed by B-CLL and MCL and is considered a diagnostic feature of such diseases [57]. A study revealed that among chronic leukemia patients, aberrant expressions were seen in cases of B-CLL (10/28) with CD11c, CD3, and CD10 as the aberrantly expressed markers [58].

A review article that was written by Zahid Kaleem reported different types of immunophenotypes of B-cell non-Hodgkin's Lymphoma concerning CD5, CD10, and CD23. The following table (table 1) shows these findings [59].

4. DISCUSSION

Studies from different regions and populations across the world reveal significant variations in the incidence and distribution of B-NHL subtypes. Among them, DLBCL remains the most prevalent subtype across many regions, while others, such as CLL, FL, MCL, SMZL, and BL, exhibit distinct frequency patterns. For instance, studies from India and Pakistan show relatively higher frequencies of DLBCL compared to CLL, whereas studies from the USA and Japan demonstrate more balanced distributions. These discrepancies may reflect regional differences in genetic predisposition, environmental factors, or healthcare infrastructure affecting disease diagnosis and reporting [60].

The immunophenotypic markers play a crucial role in subtype classification and diagnosis. CD5 expression, traditionally associated with CLL and MCL, exhibits regional variations and diagnostic implications. Studies from China highlight differences in CD5 expression patterns compared to Western cohorts, influencing disease classification and diagnostic algorithms. Additionally, aberrant expression of markers like CD11c, CD200, and CD38 further complicates subtype identification, emphasizing the need for comprehensive immunophenotyping techniques for accurate diagnosis and prognosis assessment.

However, aberrant marker expression, bi-clonality, and composite lymphoma cases highlight the prognostic significance of immunophenotypic characteristics in B-NHL.

Understanding these implications is critical for personalized treatment strategies and patient management.

Moreover, the emergence of novel diagnostic approaches, such as machine-based algorithms and composite diagnostic predictors like the combined ratio score (CRS), showcases advancements in disease classification and subtype differentiation [61]. These innovative methodologies improve diagnostic accuracy and streamline patient management by effectively distinguishing between closely related BCLPD subtypes like MCL and SLL [62].

5. CONCLUSION

Overall, the data underscores the complex nature of BCLPDs, influenced by both geographical factors and immunophenotypic characteristics. Understanding these nuances is crucial for refining diagnostic strategies, optimizing treatment approaches, and ultimately improving patient outcomes.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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