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Original Article

Comparative Analysis of Bone Marrow Involvement in Pediatric and Adult Hodgkin and Non-Hodgkin Lymphomas

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Abstract

Background: Lymphomas, including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), are major hematologic malignancies. Bone marrow evaluation may provide important information for staging and disease assessment in selected patients. This study compared bone marrow involvement (BMi) and peripheral blood findings between pediatric and adult patients with HL and NHL and evaluated the factors associated with BMi.

Materials and Methods: This is a retrospective cross-sectional study conducted on 125 patients with histologically confirmed HL or NHL who underwent bone marrow biopsy (BMB), bone marrow aspiration (BMA), and peripheral blood smear (PBS) examination at Shahid Sadoughi Hospital, Yazd, Iran, during the study period. The patients were categorized into pediatric (< 18 years) and adult (≥ 18 years), and the lymphoma diagnoses were classified according to the 2016 WHO classification. The factors associated with BMi were assessed using binary logistic regression.

Results: A total of 125 patients were included, with a male predominance. HL and NHL were diagnosed in 64 (51.2%) and 61 (48.8%) patients, respectively. BMi was observed in 23 patients and was more frequent in NHL than in HL (16/61 vs. 7/64, P = 0.001). Peripheral blood lymphocytosis was observed exclusively in the patients with NHL (P = 0.001). In univariate logistic regression, adult age (OR = 2.77, P = 0.040) and lymphoma type (OR = 0.34, P = 0.029) were associated with BMi. However, none of the examined variables remained independently associated with BMi after multivariable adjustments.

Conclusion: BMi was more frequent in NHL than in HL. Although adult age and lymphoma type were associated with BMi in the univariate analyses, neither remained independently associated with BMi after multivariable adjustments. These findings should be interpreted cautiously given the retrospective nature of the study, single-center design, small pediatric sample, and small number of BMi events.

Keywords: Adult, Hodgkin lymphoma, Non-Hodgkin lymphoma, Pediatric

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Introduction

Cancer is a major global health concern, with significant geographical and age-related variations in incidence and outcomes (1, 2). Cancer incidence varies substantially across regions because of differences in population structure, environmental exposures, diagnostic capacity, and cancer registration systems (3, 4). Among hematologic malignancies, lymphomas, which are malignant neoplasms of the lymphatic and immune systems, constitute a substantial proportion of cases and primarily originate from B-cell and T-cell lymphoid lineages (5, 6). Although many lymphomas arise within lymph nodes, a substantial proportion originate primarily in extranodal sites, including the gastrointestinal tract, skin, central nervous system, testis, and other organs (7).

Lymphomas are broadly classified into Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL), which together account for more than half of all hematologic cancers. HL, characterized by Reed-Sternberg cells, typically affects young adults aged 15-35 years and older adults above 55 years, with a slight male predominance (8-10). NHL, approximately six times more common than HL, is the fifth most prevalent cancer worldwide and is associated with increased incidence in older adults. Importantly, survival outcomes differ by age; while pediatrics with lymphoma often achieve favorable prognoses with modern therapies, adults, especially the elderly, experience lower survival rates and higher relapse frequencies (9, 11).

Recent epidemiological studies have demonstrated important differences between pediatric and adult lymphomas in terms of subtype distribution and clinical characteristics. HL is more frequently observed in pediatrics, whereas NHL predominates in adults. These age-related variations may influence disease presentation and contribute to differences in the frequency and pattern of bone marrow involvement (BMi). Therefore, comparative evaluation across age groups is essential for a better understanding of lymphoma characteristics and bone marrow findings (9, 12-14).

Bone marrow evaluation may provide important pathological information through the assessment and staging of lymphoma, although its role varies according to the lymphoma subtype and the availability of contemporary imaging modalities. BMi patterns differ between pediatric and adult patients as well as among lymphoma subtypes. For example, bone marrow infiltration occurs in more than 90% of mantle cell and hepatosplenic T-cell lymphomas, which are predominantly adult diseases, while, in pediatric cases, marrow involvement is more frequently observed in Burkitt lymphoma and other aggressive NHL subtypes (15, 16). In HL, marrow infiltration is less common in pediatric patients but increases with age and advanced stage (16). Peripheral blood smears may provide supportive findings associated with marrow involvement, such as cytopenias or the presence of lymphoma cells. Bone marrow examination remains an important pathological method for assessing BMi in selected patients, while its findings should be interpreted in conjunction with clinical and imaging data (17). Despite these observations, the comparisons of pediatric and adult lymphoma patients in terms of BMi remain limited, particularly in Middle Eastern populations.

Therefore, the present study was designed to compare the clinicopathological characteristics, BMi, and peripheral blood findings between pediatric and adult patients with Hodgkin and non-Hodgkin lymphoma. In addition, the differences between HL and NHL were evaluated, and multivariable logistic regression analyses were performed to identify the factors independently associated with BMi.

Material and Methods

Study design and settings

This retrospective analytical cross-sectional study was conducted in the Department of Pathology at Shahid Sadoughi Hospital, Yazd, Iran. The medical records and archived pathological specimens of the patients diagnosed with Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) from 21 March 2016 to 20 March 2022 were retrospectively reviewed. The patients were enrolled consecutively, and all the

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eligible cases with complete pathological records available during the study period were included. They were then categorized into pediatric (< 18 years) and adult (≥ 18 years) groups.

Participants and eligibility criteria

The patients included in the study were those with a confirmed diagnosis of HL or NHL who had available records of BMB, bone marrow aspiration (BMA), and PBS examinations. A total of 13 cases were excluded because of missing or incomplete records of BMB, BMA, or PBS examinations, unavailable archived slides, or uncertain lymphoma classification. No missing data were identified for the study variables included in the final analysis, as only the patients with complete pathological records were enrolled (Figure 1).

Outcomes and data collection

The primary outcome of this study was the frequency and pattern of BMi among the patients with HL and NHL. The secondary outcomes included PBS findings and the distribution of lymphoma subtypes according to demographic characteristics. The demographic data, including age and sex, along with lymphoma subtype, BMi status, infiltration pattern, and peripheral blood findings, were extracted from the pathology records using a structured data collection form.

Histopathological and immunohistochemical evaluation

The diagnosis and classification of HL and NHL were performed according to the 2016 revision of the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues. Archived hematoxylin and eosin (H&E), BMA, and previously performed IHC slides from bone marrow biopsy paraffin blocks were independently reviewed by two experienced pathologists. For HL, an IHC panel including CD30, CD15, PAX5, CD20, and other markers when indicated, was used for diagnostic confirmation. The NHL cases were classified using morphology in conjunction with an appropriate subtype-specific IHC panel according to the suspected lymphoma subtype. These panels included B-cell markers (e.g., CD20, CD79a, PAX5, CD10, BCL2, BCL6, MUM1) , T-cell markers (e.g., CD3, CD5), precursor lymphoid markers (TdT), and additional subtype-specific markers such as cyclin D1, CD23, ALK, CD30, and Ki-67 proliferation index, when appropriate. In cases of disagreement between the two pathologists, the slides were reviewed jointly to reach a consensus on diagnosis.

BMi was defined as the presence of morphologically identifiable lymphoma infiltration within the bone marrow biopsy specimen, characterized by infiltration of atypical lymphoid cells with an abnormal distribution and/or replacement of normal marrow elements. For the purposes of this study, a simplified histopathological classification of bone marrow infiltration was adopted based on the dominant pattern of involvement. Accordingly, infiltration was categorized as diffuse, focal, or interstitial. A diffuse pattern was defined as extensive infiltration replacing a large proportion of normal hematopoietic tissue. A focal pattern was defined as discrete nodular or localized aggregates of lymphoma cells within otherwise preserved marrow. An interstitial pattern was defined as the scattered infiltration of lymphoma cells among normal hematopoietic elements without discrete nodules or diffuse marrow replacement (18).

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA). The continuous variables were expressed as mean ± standard deviation (SD), whereas the categorical variables were reported as frequencies and percentages. The independent samples t-test was used to compare the continuous variables, while the categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. To evaluate the factors associated with BMi, binary logistic regression analyses were performed. Bone marrow involvement (positive/negative) was considered the dependent variable. Age group (adult vs. pediatric), sex, and lymphoma type (Hodgkin vs. non-Hodgkin) were selected a priori as candidate independent variables based on their clinical relevance and biological plausibility. Univariate

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logistic regression analyses were initially performed to estimate the crude odds ratios (ORs) with 95% confidence intervals (CIs). Subsequently, these variables were entered simultaneously into a multivariable logistic regression model using the enter method to estimate the adjusted ORs and 95% CIs. Histological lymphoma subtypes were not included in the multivariable model because several subtype categories contained a small number of patients, which could have resulted in unstable estimates and excessively wide confidence intervals. Bone marrow infiltration pattern was excluded because it is only defined in patients with confirmed BMi, thus representing a consequence rather than an independent predictor of the outcome. PBS lymphocytosis was not included in the multivariable model because no positive cases were observed in the pediatric group, resulting in complete separation and potentially unreliable parameter estimates. The model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. A two-sided P-value of < 0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1400.403). The study was conducted in accordance with ethical standards, and patient confidentiality was maintained throughout the data collection and analysis. Informed consent was also obtained from the individual patients or their relatives to use their data for educational or research purposes. No personal information was used at the time of the data extraction.

Results

Patient characteristics

A total of 125 patients with lymphoma were included, comprising 96 adults (≥ 18 years) and 29 pediatric patients (< 18 years). Overall, HL was diagnosed in 64 patients (51.2%) and NHL in 61 patients (48.8%). The male-to-female ratio was 2.2:1. The demographic and clinical characteristics of the HL and NHL groups are summarized in Table I. A comparison of the pediatric and adult patients is presented in Table II. Among the adults, 67 (69.8%) were male and 29 (30.2%) were female. Among the pediatric patients, there were 19 males (65.5%) and 10 females (34.5%). No significant differences were observed between the two age groups regarding sex distribution (P = 0.663), lymphoma type (P = 0.362), or BMi (17.2% vs. 18.8%, P = 0.854). However, PBS lymphocytosis was observed exclusively in the adult patients (12.5% vs. 0.0%), representing a statistically significant difference (P = 0.022).

Lymphoma subtype distribution

In the HL group (n = 64), classical Hodgkin lymphoma (CHL) was the dominant subtype (58 cases, 90.6%), with nodular sclerosis being the most frequent variant. Nodular lymphocyte-dominant HL accounted for the remaining cases. In the NHL group (n = 61), mature B-cell lymphomas were the most common category (49 cases, 80.3%), with diffuse large B-cell lymphoma representing the dominant subtype. The other NHL subtypes, including mature T-cell and precursor lymphoblastic lymphomas, were less frequent (Table III, Figure 2).

Bone marrow involvement

BMi was observed in 23 patients (18.4%) and was more frequent in NHL than in HL (16/61 vs. 7/64, respectively; P = 0.001). It was also observed in both age groups, including 18 adults (12 NHL and 6 HL cases) and 5 pediatric patients (4 NHL and 1 HL case) (Tables I and 3). The pattern of bone marrow infiltration differed significantly between HL and NHL (P = 0.001) (Tables I and III). Diffuse infiltration was the dominant pattern in both NHL and HL cases.

Peripheral blood smear findings

PBS lymphocytosis was observed in 12 patients (9.6%), all of whom had NHL. No cases of peripheral blood lymphocytosis were identified among the patients with HL, including those with nodular lymphocyte-dominant Hodgkin lymphoma (NLPHL). The frequency of

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lymphocytosis was significantly higher in NHL than in HL (P = 0.001) (Tables I and III).

Logistic regression

Binary logistic regression analyses were performed to identify the factors associated with bone marrow involvement (Table IV). In the univariate analysis, the adult patients were found to have significantly higher odds of BMi than the pediatric patients (OR = 2.77, 95% CI: 1.05–7.35; P = 0.040). In addition, the patients with HL had significantly lower odds of BMi than those with NHL (OR = 0.34, 95% CI: 0.13-0.89; P = 0.029). Sex was not significantly associated with bone marrow involvement (OR = 0.50, 95% CI: 0.20-1.27; P = 0.144). The variables considered clinically relevant, including age group, sex, and lymphoma type, were subsequently entered into a multivariable logistic regression model. After adjustment for potential confounding, none of these variables remained independently associated with BMi. Adult age was associated with an adjusted OR of 1.57 (95% CI: 0.49-5.07; P = 0.452), male sex with an adjusted OR of 0.44 (95% CI: 0.17-1.18; P = 0.103), and HL with an adjusted OR of 0.39 (95% CI: 0.12-1.25; P = 0.112). The multivariable model demonstrated an acceptable goodness-of-fit according to the Hosmer-Lemeshow test (P = 0.721), indicating adequate calibration of the model. The overall model was statistically significant (Omnibus test, P = 0.035).

Table I: Demographic characteristics and bone marrow involvement in HL and NHL patients

Variable	Total (N = 125)	Non-Hodgkin lymphoma (N = 61)	Hodgkin lymphoma (N = 64)	P-value
Age group				
Adults (≥ 18 years)	96 (76.8%)	49 (80.3%)	47 (73.4%)	
Pediatric (< 18 years)	29 (23.2%)	12 (19.7%)	17 (26.6%)	
Adults (≥ 18 years)				
Male	67 (69.8%)	37 (75.5%)	30 (63.8%)	0.001
Female	29 (30.2%)	12 (24.5%)	17 (36.2%)	
Pediatric (< 18 years)				
Male	19 (65.5%)	7 (58.3%)	12 (70.6%)	
Female	10 (34.5%)	5 (41.7%)	5 (29.4%)	
Bone marrow involvement (Adults)				
Positive	18 (18.8%)	12 (24.5%)	6 (12.8%)	
Negative	78 (81.2%)	37 (75.5%)	41 (87.2%)	0.001
Bone marrow involvement (Pediatric)				
Positive	5 (17.2%)	4 (33.3%)	1 (5.9%)	
Negative	24 (82.8%)	8 (66.7%)	16 (94.1%)	
Bone marrow infiltration pattern				0.001
Diffuse	15 (65.2%)	10 (62.5%)	5 (71.4%)	

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Focal	5 (21.7%)	3 (18.8%)	2 (28.6%)	
Interstitial	3 (13%)	3 (18.8%)	0 (0.0%)	
Peripheral blood smear lymphocytosis				
Present	12 (9.6%)	12 (19.7%)	-	0.001
Absent	113 (90.4%)	49 (80.3%)	64 (100%)	

Note: The values are presented as mean ± standard deviation (SD) for the continuous variables and number (%) for the categorical variables. The statistical comparisons were performed using the independent samples t-test for the continuous variables and the Chi-square test for the categorical variables. A two-sided P-value of < 0.05 was considered statistically significant.

Table II: Comparison of demographic and clinicopathological characteristics between pediatric and adult patients with lymphoma

Variable	Pediatric (< 18 years) (n = 29)	Adult (≥ 18 years) (n = 96)	P-value
Sex			
Male	19 (65.5%)	67 (69.8%)	**0.663**
Female	10 (34.5%)	29 (30.2%)	
Lymphoma type			
Hodgkin lymphoma	17 (58.6%)	47 (49.0%)	**0.362**
Non-Hodgkin lymphoma	12 (41.4%)	49 (51.0%)	
Bone marrow involvement			
Positive	5 (17.2%)	18 (18.8%)	**0.854**
Negative	24 (82.8%)	78 (81.2%)	
Bone marrow infiltration pattern			
Diffuse	3 (60%)	12 (66.7%)	0.09
Focal	1 (20%)	4 (22.2%)	
Interstitial	1 (20%)	2 (11.1%)	
Peripheral blood smear lymphocytosis			
Present	0 (0.0%)	12 (12.5%)	**0.022**
Absent	29 (100.0%)	80 (83.3%)	

Note: The values are presented as n (%). The continuous variables were compared using the independent-samples t-test, whereas the categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was used because an expected cell count was < 5. A two-sided P-value of < 0.05 was considered statistically significant.

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Table III. Frequency distribution of lymphoma subtypes, maturity, and bone marrow involvement

Subtype	Mature / Precursor	Patient count N (%)	Bone marrow involvement N (%)	Pattern of involvement
Hodgkin Lymphoma				
Classical Hodgkin Lymphoma	N/A	58 (90.6%)	7 (12.1%)	Diffuse: 5, Focal: 2
└ Nodular Sclerosis	N/A	28 (43.8%)	2 (7.1%)	Diffuse: 1, Focal: 1
└ Mixed Cellularity	N/A	19 (29.7%)	2 (10.5%)	Diffuse: 1, Focal: 1
└ Lymphocytic Depletion	N/A	3 (4.7%)	2 (66.7%)	Diffuse: 2
└ Lymphocyte Rich	N/A	8 (12.5%)	1 (12.5%)	Diffuse: 1
Nodular Lymphocytic Predominant HL (NLPHL)	N/A	6 (9.4%)	0 (0%)	–
Non-Hodgkin Lymphoma				
Diffuse Large B-Cell Lymphoma (DLBCL)	Mature	30 (49.2%)	7 (23.3%)	Diffuse: 5, Focal: 1, Interstitial:1
T-Cell Rich B-Cell Lymphoma	Mature	5 (8.2%)	1 (20.0%)	Diffuse: 1
Mantle Cell Lymphoma	Mature	4 (6.6%)	0 (0%)	–
Small Lymphocytic Lymphoma	Mature	3 (4.9%)	1 (33.3%)	Interstitial: 1
Burkitt Lymphoma	Mature	1 (1.6%)	0 (0%)	–
Marginal Zone Lymphoma	Mature	1 (1.6%)	0 (0%)	–
Primary Mediastinal Large B-Cell Lymphoma	Mature	1 (1.6%)	0 (0%)	–
Follicular Lymphoma	Mature	2 (3.3%)	1 (50.0%)	Diffuse: 1
B-Cell Lymphoma, NOS	Mature	2 (3.3%)	1 (50.0%)	Diffuse: 1
Anaplastic Large Cell Lymphoma	Mature (T-cell)	2 (3.3%)	0 (0%)	–
Angioimmunoblastic T-Cell Lymphoma	Mature (T-cell)	2 (3.3%)	2 (100%)	Diffuse: 1, Focal: 1
Peripheral T-Cell Lymphoma (NOS)	Mature (T-cell)	1 (1.6%)	0 (0%)	–
B-Cell Precursor Lymphoblastic Lymphoma	Precursor	6 (9.8%)	2 (33.3%)	Diffuse: 1, Interstitial:1
T-Cell Precursor Lymphoblastic Lymphoma	Precursor	1 (1.6%)	1 (100%)	Focal: 1

Note: The lymphoma subtypes were classified according to the World Health Organization (WHO) classification of hematolymphoid tumors. DLBCL = diffuse large B-cell lymphoma; NOS = not otherwise specified; NLPHL = nodular lymphocyte-predominant Hodgkin lymphoma. The BMi patterns were categorized as diffuse, focal, or interstitial infiltration. N/A = not applicable.

Table IV. Univariate and multivariable logistic regression analysis of the factors associated with bone marrow involvement

Variable	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (≥ 18 vs. < 18 years)	**2.77 (1.05–7.35)**	**0.040**	**1.57 (0.49–5.07)**	0.452
Gender (Male vs. Female)	0.50 (0.20–1.27)	0.144	0.44 (0.17–1.18)	0.103
Lymphoma (Hodgkin lymphoma vs. non-Hodgkin lymphoma)	0.34 (0.13–0.89)	**0.029**	0.39 (0.12–1.25)	0.112

Note: Binary logistic regression was performed with bone marrow involvement (BMi; positive vs. negative) as the dependent variable. For age group, the pediatric patients (< 18 years) were the reference category. For sex, the female patients were the reference category. For lymphoma type, non-Hodgkin lymphoma (NHL) was the reference category. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are presented. The multivariable model included age group, sex, and lymphoma type. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test (P = 0.721).

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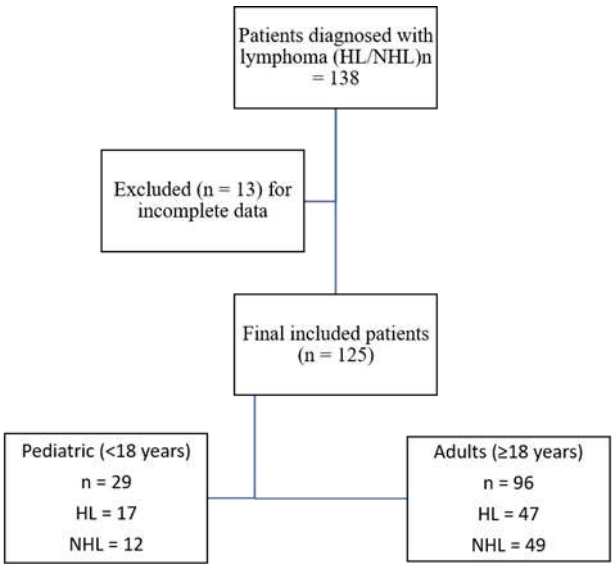

Figure 1. STROBE flowchart of patient selection

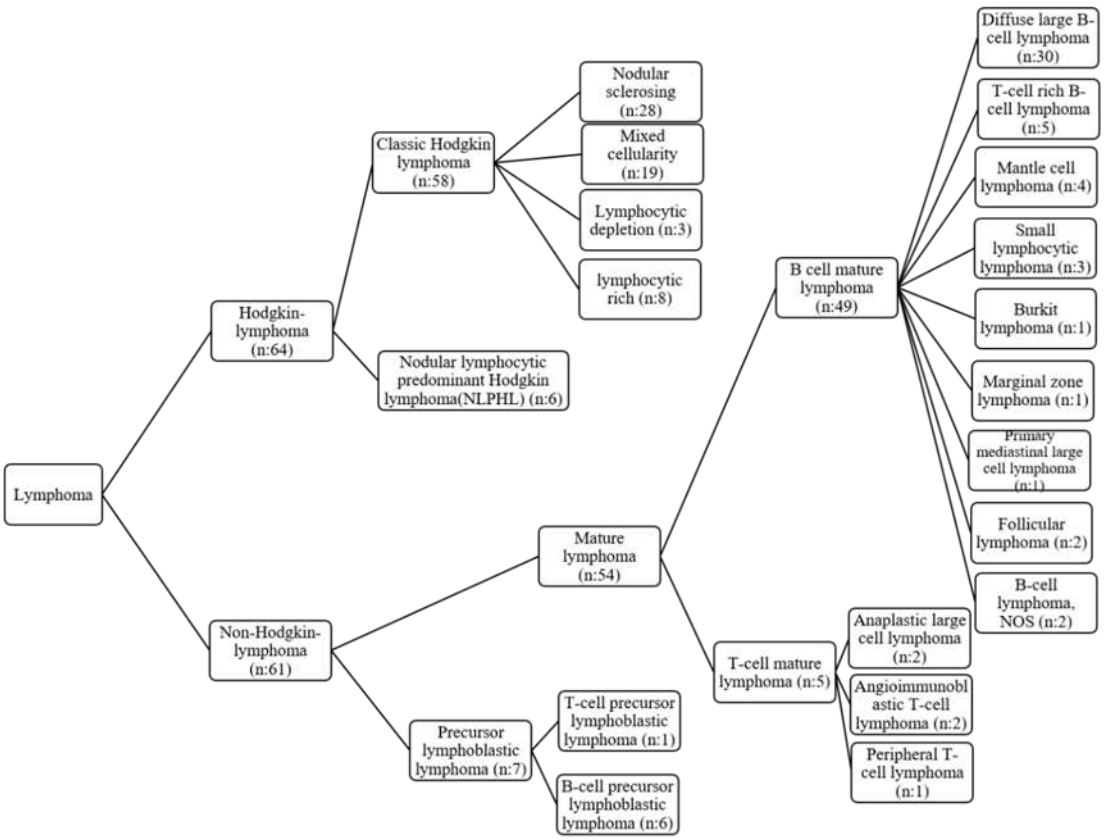

Figure 2. Lymphoma subtype distribution

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Discussion

This study evaluated the BMi and PBS findings in pediatric and adult patients with HL and NHL. The principal findings were that BMi was significantly more frequent in NHL than in HL, diffuse infiltration represented the dominant marrow involvement pattern following histopathological re-evaluation, and peripheral blood lymphocytosis was observed exclusively in patients with NHL. In addition, the comparison of the pediatric and adult patients revealed no significant differences in the frequency of BMi, despite the well-recognized epidemiological differences between lymphoma types across the age groups.

In this cohort, lymphomas were of overall dominance in the males. This finding is broadly consistent with previous epidemiological studies reporting differences in the age distribution and incidence patterns of HL and NHL (8, 9, 19, 20). Although the pediatric and adult patients differed in age by definition, no significant difference was observed in the BMi frequency between the two age groups. In the univariate analysis, adult age was associated with higher odds of BMi; however, this association did not remain statistically significant after adjustments for sex and lymphoma type. Given the small number of the pediatric patients and BMi events in this cohort, the findings should be interpreted cautiously and not be considered as evidence of an independent effect of age on BMi (21-23).

Moreover, CHL, particularly the nodular sclerosis subtype, represented the majority of HL cases, whereas diffuse large B-cell lymphoma (DLBCL) was the dominant NHL subtype. This distribution is in agreement with previous epidemiological reports describing nodular sclerosis as the most common HL subtype and DLBCL as the most prevalent mature B-cell lymphoma worldwide. The minor differences among the published studies could potentially be related to geographic variation, referral patterns, environmental exposures, or differences in Epstein-Barr virus prevalence. However, these factors were not directly assessed in the present study and, therefore, cannot be established as explanations for the observed differences (16).

BMi was significantly more frequent in NHL than in HL. This is consistent with the previous studies demonstrating that marrow infiltration is more common in biologically aggressive lymphoma subtypes (22, 24).

Peripheral blood lymphocytosis was identified exclusively in the patients with NHL, whereas no cases were observed among the patients with HL, including NLPHL. This finding is consistent with the previous reports indicating that lymphopenia, rather than lymphocytosis, is the characteristic peripheral blood abnormality in classical HL, particularly in an advanced-stage disease. Accordingly, PBS findings should be interpreted as complementary to, rather than a substitute for, bone marrow examination. However, given the small number of the patients with lymphocytosis in this cohort and the lack of formal diagnostic performance assessment, the peripheral blood findings alone should not be considered sufficient to establish a lymphoma subtype or predict BMi (17).

The findings of this study should be interpreted within the context of current lymphoma staging strategies, in which FDG positron emission tomography/computed tomography (FDG-PET/CT) plays a central role in the initial evaluation and staging of lymphoma, particularly in HL and selected aggressive NHL subtypes. FDG-PET/CT allows for the comprehensive assessment of metabolically active diseases and the detection of BMi with high sensitivity in FDG-avid lymphomas, thereby limiting the need for routine BMB in many patients with HL. Nevertheless, BMB may retain its clinical and diagnostic value in certain circumstances, such as discordant or indeterminate imaging findings, suspected low-FDG-avid lymphoma subtypes, unexplained cytopenias, or clinically warranted histopathological confirmation of bone marrow involvement. Accordingly, BMB should not be regarded as a universally required component of lymphoma staging, but rather as a complementary diagnostic procedure whose utility depends on the clinical context,

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lymphoma subtype, and findings from contemporary imaging and laboratory evaluation. Overall, our findings support the continued relevance of bone marrow examination in selected patients while emphasizing an integrated approach that incorporates clinical, laboratory, histopathological, and modern imaging data, particularly FDG-PET/CT, into contemporary lymphoma staging (25).

Study limitations and future directions

This study has several limitations that should be considered when interpreting the findings. First, the retrospective design and the single-center setting may limit the generalizability of the results to other populations. Second, the relatively small sample size, particularly the limited number of the pediatric patients and those with BMi, may have reduced the statistical power to detect independent associations in multivariable logistic regression analyses. In particular, only 23 patients had BMi, resulting in a low number of outcome events for the multivariable model. Consequently, the regression estimates may be less precise and potentially unstable, and the adjusted associations should, therefore, be interpreted cautiously and considered hypothesis-generating rather than definitive. Third, only the patients with complete BMB, BMA, and PBS records were included, which may have introduced a selection bias. In addition, detailed clinical information, including disease stage, treatment history, PET/CT findings, molecular characteristics, and long-term follow-up data, was unavailable for many patients, precluding the assessment of the prognostic significance of BMi and its association with survival outcomes. Finally, several lymphoma subtypes were represented by only a few cases, preventing reliable subtype-specific analyses and limiting the interpretation of the findings for these rare entities.

Despite these limitations, the study provides valuable data on BMi in both pediatric and adult patients with Hodgkin and non-Hodgkin lymphoma from a Middle Eastern referral center. Future prospective multicenter studies with larger patient populations should incorporate comprehensive clinical, radiological, molecular, and outcome data to validate these findings, identify the factors independently associated with BMi, and better define its prognostic significance across different lymphoma subtypes and age groups.

Conclusion

In this retrospective single-center cohort, BMi was more frequent in NHL than in HL, with diffuse infiltration representing the dominant histopathological pattern. No significant difference in BMi frequency was demonstrated between the pediatric and adult patients. Although adult age and lymphoma type were associated with BMi in univariate analyses, neither remained independently associated with BMi after multivariable adjustments. Peripheral blood lymphocytosis was observed exclusively in the patients with NHL; however, given its low frequency and the lack of diagnostic performance assessments, this finding should be considered descriptive rather than a specific diagnostic or predictive marker. The relatively small number of BMi events, limited pediatric subgroup, retrospective design, and single-center setting restrict the precision and generalizability of the findings. Therefore, the results should be considered hypothesis-generating and validated in larger, prospective, multicenter studies.

Availability of Data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare no conflict of interests regarding this research.

Funding

This study was conducted without any external funding or financial support.

Ethical Considerations

The study was performed according to the Declaration of Helsinki, and its design was approved by the ethics committee of Shahid Sadoughi University (IR.SSU.MEDICINE.REC.1400.403).
Informed consent was obtained from the individual patients or their relatives to use their data for educational or research purposes. No personal information was used at the time of data extraction.

Authors' Contributions

- M.V. contributed to study conception and design, pathology review, data interpretation, supervision of the study, and manuscript editing.
- S.E. contributed to data interpretation, pathology review, manuscript editing, and final approval of the manuscript
- A.M. contributed to data collection, data analysis, literature review, and manuscript drafting.

All the authors approved the final version of the manuscript and agreed to be accountable for every aspects of the work.

Artificial Intelligence Use Disclosure Statement

ChatGPT (OpenAI; GPT-4, 2025) was used solely for language editing, grammar correction, and improvement of the linguistic clarity of the manuscript. It was not used for data collection, data analysis, statistical analysis, interpretation of results, or generation of the original scientific content. All the scientific contents, analyses, interpretations, and conclusions were developed and verified by the authors.

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