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The Incidence and Clinicopathological Factors Associated with Bone Marrow Infiltration among Adult Lymphoma Patients in Malaysia

Shafini Mohamed Yusoff[1,2], Mohd Nazri Hassan[1,2*], Faezahtul Arbaeyah Hussain[2,3], Azlan Husin[2,4], Abu Dzarr Abdullah[2,4], Salfarina Iberahim[1,2], Zefarina Zulkafli[1,2], Marini Ramli[1,2], Noor Haslina Mohd Noor[1,2], Rosnah Bahar[1,2], Wan Suriana Wan Ab Rahman[2,5]

[1]Department of Haematology, School of Medical Sciences, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
[2]Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[3]Department of Pathology, School of Medical Sciences, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
[4]Department of Medicine, School of Medical Sciences, USM, 16150 Kubang Kerian, Kelantan, Malaysia.
[5]School of Dental Sciences, School of Medical Sciences, USM, 16150 Kubang Kerian, Kelantan, Malaysia.

*Corresponding author: nazrihas@usm.my

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Abstract
The bone marrow (BM) is the most common site of extra nodal involvement in lymphoid malignancies. BM assessment for lymphoma infiltration is crucial for lymphoma disease staging and can influence management and disease prognosis. This study aimed to determine the factors associated with bone marrow infiltration (BMI) among adult lymphoma patients in our centre. This was a cross-sectional study using retrospective clinical and laboratory data collected from 132 adult lymphoma patients investigated for BMI. BMI was determined by BM trephine biopsy with or without BM aspiration. Simple and multiple logistic regression were used for statistical analysis, and a p-value of less than 0.05 was considered significant. The mean age of patients was 48.6 years, with the majority being Malay (94.7%), male (61.4%) and B-NHL (63.6%). The overall incidence of BMI was 22.7% (30/132) and was higher in NHL than HL, at 28.2% (29/103) and 3.4% (1/29), respectively. Among NHL patients, the incidence of BMI by T-NHL was higher than by B-NHL, at 36.8% (7/19) and 26.2% (22/84), respectively. There was a significant association between BMI and platelet (Plt) level ($p = 0.015$), type of lymphoma ($p = 0.021$) and grade of lymphoma ($p = 0.026$). The only dependent factors for BMI were T-NHL, indolent lymphoma and haemoglobin (Hb) level, with the odds ratio of 23.167 ($p = 0.006$), 4.433 ($p = 0.009$) and 0.770 ($p = 0.022$), respectively. Patients with T-NHL, indolent lymphoma and lower haemoglobin level have significant risk for BMI. We recommended BM assessment for patient with NHL, indolent lymphoma and patient with low Plt and Hb level.

Keywords
Bone marrow; Bone marrow aspirate; Bone marrow trephine; Infiltration; Lymphoma

Introduction

Bone marrow infiltration (BMI) refers to the invasion of bone marrow by primary tumours, including haematological neoplasm such as lymphoma or non-haematological neoplasm; and it is essential for the staging of the disease because it can determine the management and prognosis of the patient [1, 2, 3]. The bone marrow (BM) is the most common site of extra nodal involvement in lymphoid malignancies, and the

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frequency of BM involvement varies according to the lymphoma subtypes [2]. The International Prognostic Index (IPI), which includes five variables; age, lactate dehydrogenase (LDH) level, performance status, tumour stage and extra nodal involvement, was developed to predict the prognosis of lymphoma patients.

BM involvement can influence both staging and extra nodal involvement as a patient initially staged as clinical stage 1 with only one positive IPI variable (low risk), will be reclassified as intermediate-high risk (IPI score 3) if BMI present, but would remain low-risk (IPI score 1) if there is no infiltration [2]. The current most useful method for the assessment of BMI is by pathological staging using bone marrow trephine biopsy (BMT) and/or bone marrow aspiration (BMA) because other methods of assessment, such as flow cytometry, magnetic resonance imaging and computed technology scan, are unable to precisely assess [2, 4].

The incidence of BMI among different types of lymphoma patients varies, ranging from <1%–10% in Hodgkin lymphoma (HL) and 40%–100% in non-Hodgkin lymphoma (NHL) [2, 5, 6]. Currently, there is a lack of data specifically focusing on the clinicopathological factors linked to BMI among adult lymphoma patients in Malaysia. Only a handful of global studies, primarily conducted before 2020, have addressed this topic. Our study aims to fill this gap by providing valuable, population-specific insights that can serve as a reference for understanding BMI patterns and related clinical factors among Malaysian lymphoma patients. In addition, there is a scarcity of studies globally that identify the factors influencing BMI among lymphoma patients. A previous study reported that among NHL patients, anaemia, neutropenia, thrombocytopenia and lymph nodes under the diaphragm were associated with BMI [6]. Meanwhile, among HL, BMI was common in lymphocyte-depleted subtypes and patients with cytopenia [5]. Thus, this study is aimed to determine the incidence and clinicopathological factors associated with BMI among lymphoma patients in our centre.

Methods

Patients

This cross-sectional study used retrospective clinical and laboratory data collected from 132 adult lymphoma patients (103 NHL and 29 HL) investigated for BMI from January 2010 to September 2017 in Hospital Universiti Sains Malaysia. The factors that might be associated with BMI include patient demographic (age, sex and race), disease characteristics (type of lymphoma, B symptoms, disease stages and grade, hepatosplenomegaly), and laboratory data (haemoglobin [Hb], platelet [Plt], white blood cell [WBC], LDH level) were retrieved from the medical record. Patient with inadequate information will be excluded from this study. The study was approved by Human Research Ethics Committee USM (USM/JEPeM/17120733) and carried out following the Declaration of Helsinki.

Lymphoma staging and grading

We applied the Lugano classification (Stages I, II, III, and IV) for lymphoma staging. The disease was categorized into early stage (Stages I and II) and advanced stage (Stages III and IV) [7]. Lymphoma grade is classified into 2 categories. Aggressive includes Burkitt lymphoma (BL), B and T lymphoblastic lymphoma (BLL, TLL), diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), natural killer cell lymphoma (NKCL), primary cutaneous anaplastic large cell lymphoma (PCALCL), anaplastic T-cell lymphoma (ATCL), T-cell granular lymphocytic leukaemia (TGLL), angioimmunoblastic T-cell lymphoma (AITCL), plasmablastic lymphoma (PL) and classical HL. The second group, indolent, includes follicular lymphoma (FL), primary mediastinal B-cell lymphoma (PMBL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LPL), mycosis fungoides (MF) and nodular lymphocytic predominant HL [8, 9].

Bone marrow infiltration assessment

BMI was determined by BMT using hematoxylin and eosin stain and immunohistochemical stain with or without BMA using May-Grunwald giemsa stain and flow cytometry. BMI was considered present if the lymphoma cell was identified in BMT and/or BMA. BMT is considered a gold standard for BMI assessment in lymphoma because it provides a more informative assessment of marrow fibrosis, cellularity, pattern of marrow involvement, topographical alterations of haematopoietic cells and extent of tumour infiltration [10]. However, inter-observer variability for bone marrow assessments was not assessed in this study due to the retrospective data review, which relied on pre-existing records.

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Statistical analysis
The data was analysed using Statistical Package for the Social Software (SPSS) version 24.0 (Armonk, NY: IBM Corp.). The descriptive results were expressed as frequency and percentage or mean and standard deviation (SD). Simple (SLR) and multiple logistic regression (MLR) were used for statistical analysis and a p-value of less than 0.05 was considered significant.

Results
Among 132 patients, the age ranged from 19 to 85 years with a mean of 48.6 years (SD ± 18.1), with the majority being Malay (94.7%) and male (61.4%). There are 29 (22.0%) HL and 103 (78.0%) NHL patients among the group. Most of the patients were B-NHL (63.6%) and suffering from an aggressive type (81.1%) and at advanced (III and IV) stage (75%). The details of the patient's characteristics are shown in Table 1.

Table 1: Demographic and clinical characteristic of study participants (n=132)

Characteristics	Frequency (%)	Mean (±SD)	Range
Age (year)		48.6 (18.1)	(19-85)
Age (year)			
18-59	90 (68.2)		
≥ 60	42 (31.8)		
Gender			
Male	81 (61.4)		
Female	51 (38.6)		
Race			
Malay	125 (94.7)		
Non-Malay	7 (5.3)		
Diagnosis			
Hodgkin lymphoma	29 (22.0)		
B non-Hodgkin lymphoma	84 (63.6)		
T non-Hodgkin lymphoma	19 (14.4)		
CT scan staging			
I	12 (9.1)		
II	21 (15.9)		
III	34 (25.8.)		
IV	65 (49.2)		
Lymphoma type			
Aggressive	107 (81.1)		
Indolent	25 (18.9)		
Hb (g/dL)		11.0 (2.3)	5.5-16.9
WBC ($x10^9$/L)		11.9 (26.0)	0.1-243.7
Plt ($x10^9$/L)		270.3 (150.2)	14-856
LDH (mmol/L)		433.0 (298.6)	149-2315

SD: Standard deviation, CT: Computed tomography, Hb: Haemoglobin, WBC: White blood cell, Plt: Platelet, LDH: Lactate dehydrogenase,

DLBCL and FL are the main subtypes among B-NHL; PTCL and ATCL are the main subtypes among T-NHL. The overall incidence of BMI was 22.7% (30/132), whereby the incidence is higher in NHL compared to HL, with the incidence of 28.2% (29/103) and 3.4% (1/29), respectively. Meanwhile, among NHL patients, the incidence of BMI by T-NHL is higher than B-NHL, which was 36.8% (7/19) and 26.2% (22/84), respectively. Although the incidence of BMI by several subtypes of NHL was 25% or more, DLBCL showed

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a relatively low incidence of BMI (18.9%) and no documented BMI in a few NHL subtypes (PMBL, LPL, PCALCL, AITCL). The detail on the incidence of BMI according to lymphoma subtype is shown in Table 2.

Table 2: Incidence of bone marrow infiltration in overall patient and each lymphoma subtype (n=132)

	Total, n	BM infiltration, n (%)		p# value
		No	Yes	
Total	132	102 (77.3)	30 (22.7)	
Lymphoma subtype				0.012
Hodgkin lymphoma	**29**	**28 (96.6)**	**1 (3.4)**	
NS	12	11 (91.7)	1 (8.3)	
MC	12	12 (100.0)	0 (0)	
LD	1	1 (100.0)	0 (0)	
NLP*	4	4 (100.0)	0 (0)	
Non-Hodgkin lymphoma	**103**	**74 (71.8)**	**29 (28.2)**	
B non-Hodgkin lymphoma	**84**	**62 (73.8)**	**22 (26.2)**	
DLBCL	53	43 (81.1)	10 (18.9)	
FL*	12	7 (58.3)	5 (41.7)	
MCL*	4	3 (75.0)	1 (25.0)	
MZL*	4	2 (50.0)	2 (50.0)	
BL	3	2 (66.7)	1 (33.3)	
PMBL	2	2 (100.0)	0 (0)	
SLL*	2	1 (50.0)	1 (50.0)	
BLL	2	2 (100.0)	0 (0)	
LPL*	1	0 (0)	1 (100.0)	
PL	1	0 (0)	1 (100.0)	
T non-Hodgkin lymphoma	**19**	**12 (63.2)**	**7 (36.8)**	
PTCL	6	3 (50.0)	3 (50.0)	
ATCL	4	3 (75.0)	1 (25.0)	
NK/T	3	2 (66.7)	1 (33.3)	
PCALCL	3	3 (100.0)	0 (0)	
TLL	2	0 (0)	2 (100.0)	
AITCL	1	1 (100.0)	0 (0)	

*=indolent type of lymphoma, #=Pearson chi-square
AITCL: Angioimmunoblastic T-cell lymphoma, ATCL: Anaplastic T-cell lymphoma, BLL: B-lymphoblastic lymphoma, BL: Burkitt lymphoma, DLBCL: Diffuse large B-cell lymphoma, FL: Follicular lymphoma, LD: Lymphocyte depletion, LPL: Lymphoplasmacytic lymphoma, MC: Mixed cellularity, MCL: Mantle cell lymphoma, MZL: Marginal zone lymphoma, NK/T: Natural killer/T-cell lymphoma, NLP: Nodular lymphocyte predominant, NS: Nodular sclerosis, PL: Plasmablastic lymphoma, PMBL: Primary mediastinal B-cell lymphoma, PTCL: Peripheral T-cell lymphoma, PCALCL: Primary cutaneous anaplastic large cell lymphoma, SLL: Small lymphocytic lymphoma, TLL: T-lymphoblastic lymphoma

Clinicopathological factor associated with BMI

The effects of age, gender, race, haematological parameters (Hb, Plt, WBC count), LDH levels, B symptoms, lymphoma types, grade and stages on BMI were summarized in Table 3. In univariate analysis, we found that there was a significant association between BMI and the Plt level (crude OR=0.996, p=0.015), type of lymphoma (crude OR=10.973, p=0.021) and grade of lymphoma (crude OR=2.900, p=0.026). A higher Plt level is associated with a lower risk of BMI. Both T- and B-NHL is associated with higher risk of BMI compared to HL. Meanwhile, indolent type lymphoma was associated with a higher risk of BMI than aggressive type lymphoma. There were no significant differences between BMI with other factors analysed.

Multivariable analysis by MLR was applied for the factors that were found to be statistically significant, p<0.05 in univariate analysis (Plt level, type of lymphoma, grade of lymphoma) and not significant but clinically important, p<0.25 (age, race, Hb level, LDH, fever, disease stage). In multivariate analysis, NHL, T-NHL, indolent lymphoma and Hb level were found to be independent risks for BMI with the adjusted OR of 23.167 (p=0.006), 4.433 (p=0.009) and 0.770 (p=0.022) respectively. Plt level, which initially showed significant association in univariate analysis, was not significant in multivariate analysis.

Table 3 Clinicopathological factors associated with BMI among lymphoma patients using simple and multiple logistic regression (n=132)

Variables	Crude OR (95% CI)	p value[a]	Adjusted OR (95% CI)	p value[b]
Age (years)*	1.014 (0.991, 1.038)	0.221	0.991 (0.959, 1.024)	0.594
Gender (Male/Female)	1.633 (0.681, 3.917)	0.272	-	-
Race				
Non-Malay/Malay	2.722 (0.574-12.908)	0.207	5.900 (0.939, 37.075)	0.058
Hb (g/dl)*	0.875 (0.727, 1.055)	0.162	**0.770 (0.616, 0.963)**	**0.022**
WBC (x10⁹/L)*	1.006 (0.993, 1.020)	0.367	-	-
Plt (x10⁹/L)*	0.996 (0.992, 0.999)	**0.015**	0.997 (0.993, 1.000)	0.085
LDH (U/L)*	1.001 (1.000, 1.002)	0.067	1.001 (0.999, 1.002)	0.314
B Symptom				
Fever (Yes/No)	1.633 (0.720, 3.701)	0.240	1.492 (0.552, 4.033)	0.430
Night Sweat (Yes/No)	1.508 (0.365, 6.229)	0.570	-	-
Weight loss (No/Yes)	1.522 (0.315, 7.359)	0.602	-	-
Types of Lymphoma				
NHL/HL	10.973 (1.426, 84.418)	**0.021**	**23.167 (2.450-219.070)**	**0.006**
B-NHL/HL	9.935 (1.275, 77.418)	**0.028**	7.769 (0.965, 62.520)	0.069
T-NHL/HL	16.333 (1.807, 147.662)	**0.013**	**23.167 (2.450, 219.070)**	**0.006**
T-NHL/B-NHL	1.644 (0.574, 4.704)	0.354	-	-
Grade of lymphoma				
Indolent/Aggressive	2.900 (1.137, 7.396)	**0.026**	**4.433 (1.448, 13.570)**	**0.009**
Disease stage #				
Advance (III, IV)/Early (I, II)	1.892 (0.659, 5.428)	0.236	2.125 (0.604, 7.476)	0.240

*mean(SD), # by CT scan staging, [a] Simple logistic regression; [b] Multiple logistic regression using Backward LR method
CI: Confidence interval, Hb: Haemoglobin, HL: Hodgkin lymphoma, LDH: Lactate dehydrogenase, NHL: Non-Hodgkin lymphoma, OR: Odds ratio, Plt: Platelet, WBC: White blood cell

Discussion

We found that the overall incidence of BMI among lymphoma in our population was 22.7% (n=30) which predominantly involved NHL patients (n=29, 96.7%) and varied by the lymphoma subtype. This explains that BMI was more common in NHL than in HL. This result was comparable with the previous studies where the majority of BMI occurred in NHL (>90%) compared to HL (<10%) [11, 12, 13]. When comparing the lymphoma subtype, we found that BMI is more common among T-NHL (36.8%) compared to B-NHL (26.2%) and HL (3.4%) and the difference is statistically significant, p=0.012. These results are also comparable with the previous study where BMI was higher in T-NHL (15-17%) and B-NHL (11-19%) than in HL (4-12%) [11, 12]. Consequently, routine BM examination may not be warranted in HL patients especially for those young patient with low stage disease.

By multivariable analysis, we found that NHL and specifically T-NHL is a strong independent predictive factor for BMI, where the patient with NHL and T-NHL has increased odds of having BMI by 23.2 times than HL patients. Meanwhile, B-NHL was only significantly associated (p=0.028) with BMI in univariate analysis and was not in multivariable analysis. It indicates that B-NHL is only at high risk for BMI if that patient coexists with other risk factors such as abnormal cell count, including anaemia or thrombocytopenia. Another previous study reported that the subtype of lymphoma (B or T cell) was not a predictor of BMI. However, their study only involved NHL patients and did not compare with HL patients [6, 14]. Consequently, we recommended that BM examination is compulsory for all patients with NHL especially those with T-NHL.

This very high OR of 23.2 for BMI in T-NHL compared to HL could be due to the aggressive biological nature of T-NHL, which has a higher propensity for systemic spread, including to the BM. However, this OR might be overestimated due to factors like small sample size, insufficient adjustment for confounders, and potential patient selection biases, such as referral bias from tertiary centres or selective inclusion of more severe cases. Additionally, diagnostic biases, like more frequent or thorough workup in T-NHL patients, may lead to higher detection rates of BMI in this group, further contributing to the elevated OR.

We found that indolent lymphoma (37%, 10/27) such as FL, MCL, MZL, SLL and LPL (NHL), and NLP (HL) involves BM much more commonly than aggressive lymphoma (19%, 20/105) such as DLBCL, BL, PMBL, BLL, T-NHL and HL except NLP. This study showed that indolent lymphoma is an independent factor for BMI, in which they have increased odds of having BMI by 4.4 times than aggressive lymphoma. This result was consistent with a previous study which reported that indolent B-NHL involves BMI more frequently than aggressive B-NHL [4, 6]. Thus, we recommended all patient with indolent type of NHL required BM assessment for proper disease staging.

In contrast to indolent NHL, DLBCL which account for the majority of aggressive types in our cases, have a relatively lower incidence of BMI (<20%) compared to other types of aggressive lymphoma and this finding was consistent with another study [2, 15]. DLBCL with BMI confers a very poor clinical outcome [15]. BM assessment in DLBCL may be warranted in advance-stage patients with unexplained cytopenia (anaemia or thrombocytopenia). Meanwhile, BL and PL has relatively higher rate of BMI compare to DLBCL.

This recent study also found that Hb level is an independent factor for BMI in lymphoma patients, where an increase in 1 g/dL of Hb level has decreased the odds of having BMI by 23%. A previous study also reported that Hb level was a predictor of BMI. They reported that patients with Hb level of >11 g/dL was a negative predictor for BM involvement among NHL patients [6]. Meanwhile, other studies reported that besides Hb level, other abnormalities of blood count include thrombocytopenia, lymphopenia and neutropenia also as a predictor of BMI among NHL and HL patients [6, 13, 16]. However, we did not find Plt and WBC count as an independent predictive factor for BMI, although there was an association of Plt level with BMI at univariate analysis. This indicates that patients with thrombocytopenia are at high risk for BMI only if other risk factors were coexisting in a particular patient and not on their own. When multiple risk factors coexist, the likelihood of having a BMI is increased [5].

We also could not find the association of other selected clinicopathological factors, including LDH level, B symptoms, and disease stages, with BMI in our patients. B symptoms (fever, weight loss and night sweat) were reported to be a more common and significant risk of having BM involvement in HL patients but not associated with BMI in NHL patients [5, 6, 16]. Meanwhile, LDH was reported to be significantly raised in patients with BMI compared to those without infiltration, and it was significantly associated with risk of BMI but was not an independent predictor of BMI in NHL patients [6, 17]. The disease stage was previously reported as a significant risk factor for BMI in HL patients; however, this association was not observed in the present study [16]. Due to inconsistent findings in the previous report, there was disagreement on the suggestion of the BM assessment in HL patients. Howell et al 2002 proposed that BM assessment in HL should be restricted to patients with advanced stage (IIB or III disease) [13]. However, Sudalaimuthu et al, 2017 suggest that BM assessment in HL patients should not be restricted to high risk cases alone but to perform on all adult patients [5].

Based on our study findings, we recommend incorporating the following parameters; all cases of NHL, particularly T-cell NHL and indolent lymphoma subtypes, as well as patients presenting with low Plt and Hb levels in screening strategies to identify candidates for BM assessment for infiltration in our population. However, it is important to note that this screening strategy may not applicable to other population and should be validated accordingly.

There a few limitations of this study. First, it was conducted at a single centre, which may restrict the generalizability of the findings to the broader Malaysian population. The participant pool is predominantly Malay, which may limit the relevance of the findings to other ethnic groups. Additionally, the study's retrospective design may weaken its ability to establish cause-and-effect relationships, whereas a prospective approach could provide stronger evidence by directly tracking BMI changes over time. We were also unable to account for inter-observer variability and other potential confounding factors, such as the patient's comorbid conditions or prior treatments, in the statistical analysis. These factors could have influenced the findings.

Conclusions

In conclusion, patients with T-NHL, indolent lymphoma and low Hb level were an independent risk for having BMI. BM assessment is recommended in patient with NHL, all T-NHL, indolent lymphoma and patient with low Plt and Hb level. However, since the analysis involved a combination of both NHL and HL patients, different results might occur if the analysis was done in a separate patient group. It can have explained why some or our results were inconsistent with previous studies that only focused on one patient group.

Conflict of Interests

All the authors declare there was no conflict of interest. All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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