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Factors associated with bone marrow involvement in lymphoma staging bone marrow examination: A South African single-centre retrospective study

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Background: Accurate detection of bone marrow involvement (BMI) in lymphoma is important as it signifies stage 4 disease. Staging bone marrow examination (BME), therefore, influences treatment decisions and prognostication. The prevalence of BMI depends on multiple factors at presentation including lymphoma subtype, age, sex, human immunodeficiency virus (HIV) status and haematological parameters.

Aim: To determine risk factors for BMI in lymphoma staging.

Setting: The study was conducted in the department of haematological pathology, Tygerberg Hospital, Cape Town, South Africa.

Methods: Retrospective cross-sectional descriptive study in adult patients, reviewing BMI and associated parameters, during their initial lymphoma staging procedure between 2016 and 2019.

Results: Of a total of 387 lymphoma staging cases that were evaluated, 30.0% of them showed BMI. Diffuse large B-cell lymphoma, Hodgkin lymphoma and high-grade B-cell lymphoma were the most frequent subtypes diagnosed. The highest prevalence of BMI was in low-grade lymphomas. There was a statistically significant association between BMI and advanced age, pancytopenia and bicytopenia (anaemia with leucopenia, anaemia with thrombocytopenia or leucopenia with thrombocytopenia). Bicytopenia and pancytopenia showed high positive predictive values of BMI, respectively, 61.0% and 69.0%. Human immunodeficiency virus positivity (34.6%) was not predictive of BMI across all lymphoma subtypes. Normal blood counts had a high negative predictive value for BMI.

Conclusion: BME remains an important part of lymphoma staging with 30.0% of all lymphomas showing BMI.

Keywords: lymphoma staging; bone marrow involvement; HIV.

Introduction

Lymphoma is one of the most prevalent haematological malignancies rated 9th out of 36 cancers in 185 countries and represents the 11th major cause of cancer death worldwide.[1]

Annually, an estimated 544 000 cases of non-Hodgkin lymphoma (NHL) and about 83 000 cases of Hodgkin lymphoma (HL) are diagnosed globally.[1] The review of Pfreundschuh reported that advanced age is a significant negative prognostic factor in all lymphoma subtypes and is incorporated in the international prognostic index (IPI) for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma (MCL).[2] The 2020 global new case cumulative risk for HL (0.09) mirrors the figure for South Africa (0.09).[3] For NHL, the global new case cumulative risk is higher (0.62 vs 0.56).[3]

The 2019 United Nations Programme on human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) (UNAIDS) reported that 61% of the global new infections occurred in South Africa (SA).[4] In 2017, the Gauteng province (GP) had an average HIV prevalence of 17.6% compared to 12.6% in the Western Cape province (WC).[5] The burden of HIV-related lymphoma grew over the last decade in both the GP and WC province. Between the time periods of 2004–2006 and 2007–2009, the GP recorded a 17.7% increase (1897[44.3%] to 2225[62.0%]), whilst WC had an increase of 31% over the period 2002–2009.[6,7,8] HIV-related mortality declined from 231 000 in 2006 to 95 000 in 2014, a 74.0% reduction.[9] The antiretroviral therapy (ART) programme was introduced in SA, in 2004.[9]

Antiretroviral therapy and immune reconstitution increase the incidence of HL, whereas ART decreases the incidence of NHL.[10,11]

Bone marrow involvement (BMI) implies stage 4 disease which adversely affects the patient's prognosis and alters the management plan.[12] Worldwide, nearly 40% of lymphomas show BMI.[12] Bone marrow involvement is found in 25% – 40% of NHL and 5% – 14% of HL cases.[13,14,15,16] Bone marrow involvement is found in-between 25% and 40% of all HIV-associated NHL subtypes.[10] The HIV-positive patients with HL and various cytopenias have a 40% – 50% risk of BMI.[17] Bone marrow examination (BME) is a standard practice in many lymphoma staging protocols regardless of the likelihood of BMI.[18,19] International Working Group (IWG) guidelines favour less invasive imaging techniques such as positron emission tomography (PET)-CT, in fluorodeoxyglucose (FDG)-avid lymphomas.[20] The high sensitivity of PET-CT for BMI has recently called the continued use of BME into consideration.[20] If the PET-CT is performed, BME is no longer indicated for HL. For DLBCL, BME is only indicated if the PET-CT is negative and if identifying a discordant histology is important for patient management.[20] Bone marrow examination can be considered, if necessary.[18,19,20] In SA, BME remains an important staging tool, as access to imaging modalities is limited by resource constraints.

Full blood counts are part of the initial diagnostic protocol for any suspected lymphoma. Because full blood counts are available routinely, establishing the significance of abnormal haematologic parameters would be valuable. There is limited data on the relationship between haematologic variables and BMI, particularly in SA. In the United States of America, Conlan et al. reviewed 317 patients with NHL and assessed the presence of haematologic abnormalities at initial staging. Anaemia was present in 42%, leucopenia in 6% and thrombocytopenia in 13% of that patient group. Bone marrow involvement was increased in cases with leucopenia and thrombocytopenia.[21] Lai et al. explored the frequency and clinical features of BMI in 94 NHL cases in Taiwan and found BMI in 30% of the cases at the time of diagnosis. Symptoms of anaemia, leucopenia or thrombocytopenia were found in 93% of the cases. Bone marrow involvement was improbable if the full blood count (FBC) was normal.[22] These two studies suggest that peripheral blood counts at the time of diagnostic staging of NHL may provide useful prognostic information. However, blood count parameters are influenced by other variables such as underlying disease process, comorbid conditions and therapeutic drugs.

This study was conducted to assess the factors associated with BMI of lymphomas in a WC setting.

Methods

We conducted a retrospective cross-sectional descriptive study of newly diagnosed lymphoma cases that had a staging BME in the period 2016–2019 at Tygerberg Hospital. Tygerberg Hospital is a 1384 bed tertiary institution located in the WC province of SA and is the main teaching hospital for Stellenbosch University Faculty of Medicine and Health Sciences. Naïve adults undergoing lymphoma treatment (> 18 years) who had adequate (≥ 15 mm) bone marrow trephine biopsies were included.[23] Patients with plasma cell neoplasms were excluded. Biopsies performed for follow-up or relapsed lymphoma, biopsies referred from other centres and discordant results between lymph node biopsy and BME, we excluded. Inadequate samples or cases where the bone marrow reports were incomplete were also excluded.

Lymphomas were classified using the World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues.[23] The following parameters were extracted from the National Health Laboratory Service (NHLS) TrackCare® Laboratory Information System (LIS) and captured on a Microsoft Excel® (Redmond, Washington, United States [US]) database: diagnostic lymph node histology, HIV status, leucocyte and platelet counts and haemoglobin. Patient age and sex, the adequacy of bone marrow biopsies and correlation with the lymph node histology were determined using BME reports.

Full blood counts were performed on the Siemens ADVIA®2120i Haematology System (Siemens Healthcare Diagnostics, Munich, Germany).The data were analysed using Microsoft Excel® and StataCorp 2019 statistical analysis software (StataCorp LP, College Station, Texas, US). Statistical inference was applied using 2-sample *t*-tests and Pearson's chi-square tests for age, sex, HIV status, lymphoma subtypes and peripheral blood cell counts. The frequency and percentage were calculated for non-numerical parameters, whilst the median, mean and interquartile range were used for numerical parameters. The median was used for most haematological parameters because of the skewed distribution of the data. The mean was used for haemoglobin because of its symmetric distribution. p-values ≤ 0.05 signified statistical significance.

Ethical considerations

Ethical approval was provided by the Health Research Ethics Committee at Stellenbosch University. Project ID: 14617. Ethics Reference No: S20/02/052.

A waiver of informed consent was obtained because of the retrospective nature of the study. Patient identity was permanently anonymised. The study was conducted in accordance with Helsinki Declaration as revised in 2013.

Results

Prevalence of bone marrow involvement by lymphoma

A total of 387 bone marrow biopsies were performed for lymphoma staging: 81 in 2016, 97 in 2017, 113 in 2018 and 96 in 2019. Thirty percent of patients had BMI (Table 1).

Lymphoma subtypes

The sample included 17 types of lymphoma (Figure 1). B-cell lymphomas cases of 366 (95%) were in majority, whereas T-cell lymphomas cases of 21 (5%) were in very low numbers. Of the B-cell lymphomas, 83% of them were NHL and 17% of them were HL.

Factors associated with bone marrow involvement

Subtype

Bone marrow involvement was mostly found in low-grade lymphomas: chronic lymphocytic leukaemia/small cell lymphoma (CLL/SLL) 93.7%, MCL 71.4%, FL 62.2% and marginal zone lymphoma (MZL) 60.0%. Lymphomas that predominantly showed no BMI included the more frequent lymphomas such as DLBCL, HL and high-grade B-cell lymphoma (HG-BCL), anaplastic large cell lymphoma (ALCL), mycosis fungoides (MF) and other lymphomas of large B-cells (OLLBC) such as primary effusion lymphoma, plasmablastic lymphoma and T-cell/histiocyte rich B-cell lymphoma. There were near equal numbers of involvement vs. non-involvement with regard to Burkitt lymphoma (BL) (53.3% vs 46.7%), nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) (60.0% vs 40.0%) and peripheral T-cell lymphoma (PTCL) (42.9% vs 57.1%) (Table 1).

TABLE 1: Table showing the prevalence and percentage of bone marrow involvement.

	Total		BM involvement		No BM involvement	
	n	%	*n*	%	*n*	%
Prevalence	387	100	117	30.0	270	70.0
B-cell Lymphoma						
Hodgkin lymphoma	63	17	13	20.6	50	79.4
Non-Hodgkin lymphoma Total	303	83	99	32.7	204	67.3
Chronic lymphocytic leukaemia/small cell lymphoma	16	-	15	93.7	1	6.3
Diffuse large B-cell lymphoma	126	-	15	11.9	111	88.1
Other lymphomas of large B cells	14	-	5	35.7	9	64.3
Marginal zone lymphoma	15	-	9	60.0	6	40.0
Follicular lymphoma	45	-	28	62.2	17	37.8
Burkitt lymphoma	15	-	8	53.3	7	46.7
Mantle cell lymphoma	7	-	5	71.4	2	28.2
Nodular lymphocyte predominant Hodgkin lymphoma	5	-	3	60.0	2	40.0
Lymphoplasmacytic lymphoma	1	-	0	0.0	1	100.0
High grade B-cell lymphoma	59	-	11	18.8	48	81.2
T-cell lymphoma						
Mycosis fungoides	5	-	0	0.0	5	100.0
Sezary syndrome	1	-	1	100.0	0	0.0
Peripheral T-cell lymphoma	7	-	3	42.9	4	57.1
Angioimmunoblastic T-cell lymphoma	1	-	0	0.0	1	100.0
Anaplastic large cell lymphoma	6	-	1	16.7	5	83.3
Natural Killer T-cell lymphoma	1	-	0	0.0	1	100.0

BM, bone marrow.

Age and gender

The median age was 54 years for those who showed BMI and 46 years for those without BMI (p = 0.001). Older patients (over 50 years of age) were more likely to have BMI. There were 192 (49.6%) females and 195 (50.4%) males in the cohort. Bone marrow involvement was found in approximately 29.0% of both sexes.

Human immunodeficiency virus status

Of the cohort, 134 (34.6%) were HIV positive and 34 (8.8%) had an unknown HIV status. Within the HIV-positive subgroup, 102 (76.1%) showed no BMI. Human immunodeficiency virus-positive cases with an associated lymphoma were predominantly seen in 14 (93.3%) BL cases and in 10 (71.4%) OLLBC cases. Human immunodeficiency virus positivity did not correlate with BMI in any specific lymphoma subtype ($p > 0.05$). Of note, only 8 (53.0%) of HIV-positive cases with BL had BMI were found. In the HIV-negative population, 70 (32%) cases showed BMI.

Haematological parameters

Out of the 387 lymphoma cases, 74.1% of cases showed anaemia, 13.7% showed leucopenia and 12.2% showed thrombocytopenia. Also, 4.1% of cases showed pancytopenia, 12.7% bicytopenia (anaemia with leucopenia, anaemia with thrombocytopenia or leucopenia with thrombocytopenia), 60.2% cases showed a single cytopenia and 23.0% cases showed no cytopenias. Of the 60.2% cases that had a single cytopenia, anaemia (median haemoglobin of 10.8 g/dL) was the most prevalent, with very small numbers showing isolated leucopenia and thrombocytopenia. There was no

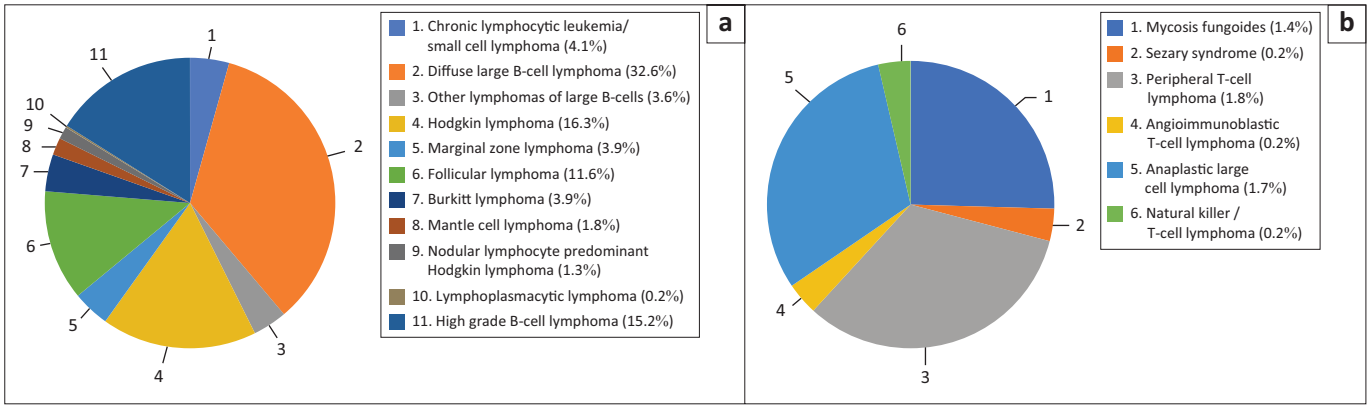


FIGURE 1: Pie chart showing the prevalence (percentage) of staging T- and B-cell lymphomas conducted between the years of 2016 and 2019 at Tygerberg Hospital. (a) B-cell lymphomas (95%); (b) T-cell lymphomas (5%).

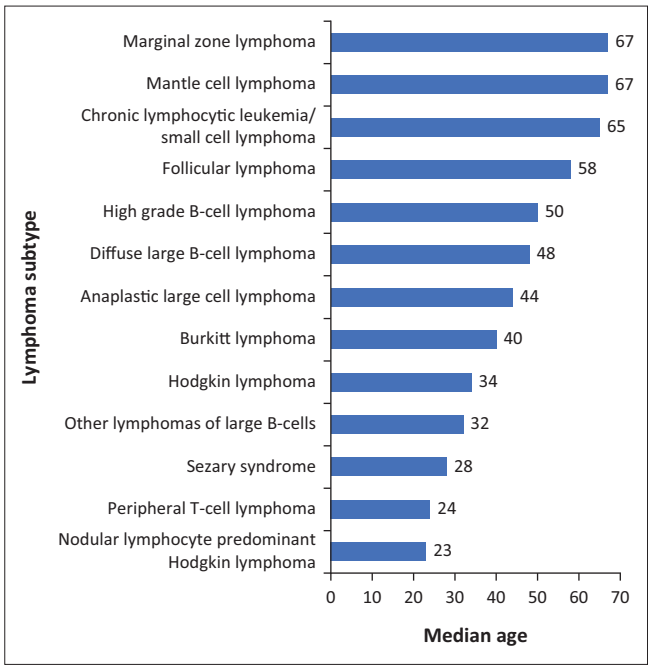
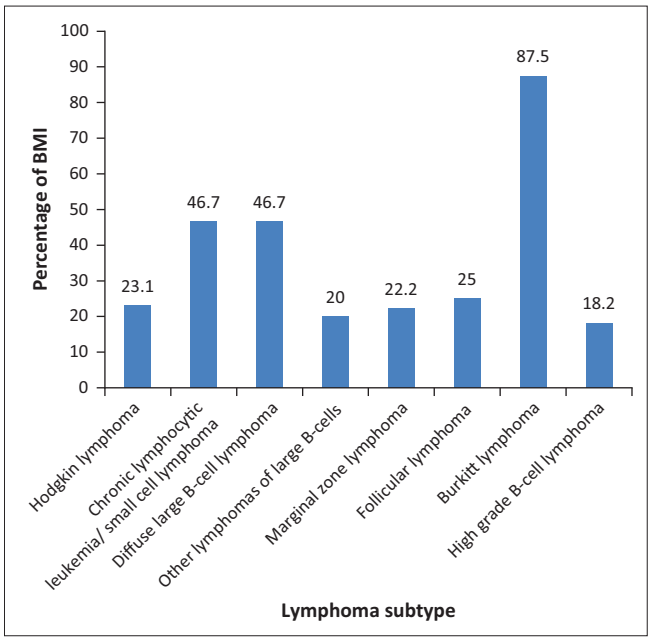


FIGURE 2: Bar chart showing the median age of bone marrow involvement in different lymphoma subtypes.



BMI, bone marrow involvement.

FIGURE 3: Bar chart showing the percentage of bone marrow involvement in different lymphoma subtypes presenting with thrombocytopenia.

statistically significant association between anaemia and any lymphoma subtype. Thrombocytopenia was predominantly seen in CLL/SLL and BL (Table 2a).

In relation to BMI, 87 (74.4%) of patients had anaemia, 24 (21.0%) had leucopenia and 37 (31.2%) had thrombocytopenia. Leucopenia was seen in DLBCL and HG-BCL. Leucocytosis with CLL/SLL, MZL, MCL and PTCL was observed. Bone marrow involvement in BL had the highest correlation with thrombocytopenia (87.5%) (Figure 3 and Table 2a). Bone marrow involvement in combination with either pancytopenia or bicytopenia showed statistical significance ($p = 0.0001$) and high positive predictive values (69% and 61%, respectively). Normal FBC parameters (no cytopenia) had a high negative predictive value (NPV) for the absence of BMI in 76.0% cases (Table 2b).

Discussion

Prevalence

The number of staging bone marrow biopsies performed shows an increasing trend over the study period. This increase may be attributed to population growth and increase in HIV infections. Between 2016 and 2019, the WC population increased by 9%, from 6 279 730 to 6 844 272.[24,25] The prevalence of HIV infection increased from 6.6% in 2016 to 10.9% in 2019.[26,27] Previous studies at our institution showed an increase in all types of lymphoma, from 6.0% to 37.0% (2002–2009), although the increase was in both HIV-positive and HIV-negative patients for the period 2005–2016.[8,28]

Sung et al. reported that globally, 87% of new lymphoma cases were NHL and 13% were HL. Our findings were similar for NHL but not for HL.[1] Other factors such as HIV and its treatment may explain the differences.

Locally, Phillips and Opie reported the findings at Groote Schuur Hospital (GSH) which is also in the WC province.[29] During their study period, 2005–2010, they reported that 915 (82%) of the staging bone marrows were for NHL and 63 (18%) of them were for HL. This is consistent with our findings and the global studies.[3]

We found a reduction in the proportion of BME performed for HL from 26% in 2016 to 15%, 13% and 16%, respectively, for the period 2017–2019. The local policy of performing staging BME for all newly diagnosed lymphomas was followed during that period because of the uncertainty about the impact of high HIV and TB burden in FDG-avid lymphomas on PET-CT results. The absolute number of BME performed as part of staging for HL was not independently determined, the relative number being derived from the bone marrow biopsy register. There was a high frequency of DLBCL (32.6%) and HG-BCL (15.2%) which is consistent with the findings of Phillips and Opie.[29] The relative increase in DLBCL and HG-BCL may, therefore, explain the reduction in the percentage of HL and increase in NHL.

Associated factors and their relationship to bone marrow involvement

Lymphoma subtypes

In studies conducted in the WC province, Phillips and Opie reported BMI of 25.2% for HL and 37.6% for NHL, Naidoo et al. reported 23.7% for HL and Swart et al. reported 37.0% for HL.[28,29,30] However, our findings showed comparatively lower BMI in both HL (20.6%) and NHL (32.7%).

Lymphomas that showed the most BMI were CLL/SLL (93.7%), MCL (71.4%), FL (62.2%) and MZL (60.0%). These low-grade lymphomas are frequently diagnosed incidentally

TABLE 2a: Table showing the peripheral blood count parameters and bone marrow involvement in different lymphoma subtypes.

Lymphoma subtypes	Total BMI	Leucocytosis		Leucopenia		Anaemia		Thrombocytopenia	
		n	%	*n*	%	*n*	%	*n*	%
B-cell Lymphoma									
Hodgkin lymphoma	13	2	15.4	3	23.1	13	100.0	3	23.1
Non-Hodgkin lymphoma Total	99	40	-	21	-	74	-	34	-
Chronic lymphocytic leukaemia/small cell lymphoma	15	12	80.0	1	6.7	12	80.0	7	46.7
Diffuse large B-cell lymphoma	15	4	26.7	6	40.0	12	80.0	7	46.7
Other lymphomas of large B cells	5	0	-	1	20.0	5	100.0	1	20.0
Marginal zone lymphoma	9	5	55.6	2	22.2	5	55.6	2	22.2
Follicular lymphoma	28	7	25.0	6	21.4	16	57.1	7	25.0
Burkitt lymphoma	8	3	38.0	1	13.0	7	88.0	7	87.5
Mantle cell lymphoma	5	3	60.0	0	-	2	40.0	0	-
Nodular lymphocyte predominant Hodgkin lymphoma	3	0	-	0	-	3	100.0	0	-
Lymphoplasmacytic lymphoma	0	0	-	0	-	0	-	0	-
High grade lymphoma	11	2	18.2	4	36.4	8	72.7	2	18.2
T-cell lymphoma									
Mycosis fungoides	0	0	-	0	-	0	-	0	-
Sezary syndrome	1	1	100.0	0	-	1	100.0	0	-
Peripheral T-cell lymphoma	3	3	100.0	0	-	2	66.0	1	33.3
Angioimmunoblastic T-cell lymphoma	0	0	-	0	-	0	-	0	-
Anaplastic large cell lymphoma	1	0	-	0	-	1	100.0	0	-
Natural Killer T-cell lymphoma	0	0	-	0	-	0	-	0	-

TABLE 2b: Table showing cytopenias with frequency, percentage and predictive value for bone marrow involvement.

Lymphoma subtypes	Total	BM involvement		No BM involvement		Positive predictive value (%)	Negative predictive value (%)
		n	%	*n*	%		
Pancytopenia	16	11	2.8	5	1.3	69	31
Bicytopenia	49	30	7.8	19	4.9	61	39
Single cytopenia	233	55	14.2	178	46.0	24	76
No cytopenia	89	21	5.4	68	17.6	24	76
Total	387	117	30.2	270	69.8	30	70

BM, bone marrow.

and are found to have more BMI by virtue of going undetected for prolonged asymptomatic periods.

The low number of DLBCL with BMI (11.9%) is comparable with the 11.0% – 33.0% BMI rate reported in some international studies.[31,32]

In our cohort, rare lymphoma subtypes staged included lymphoplasmacytic lymphoma, Sézary syndrome (SS), angioimmunoblastic lymphoma and natural killer (NK) T-cell lymphoma. Because of the limited number of cases, statistical interpretation was not possible.

Age and gender

The median age for cases with BMI was 54 years versus 46 years for cases with no involvement. This difference was statistically significant ($p = 0.001$) and showed that patients over 50 years of age are more likely to have BMI. According to Pfreundschuh, age is one of the strongest factors for survival in all patients diagnosed with lymphoma.[2] Elderly patients with lymphoma have more adverse outcomes and BMI further worsens the prognosis.[2]

In our study, gender had no bearing on the lymphoma subtype or BMI.

Follicular lymphoma, CLL/SLL, MCL and MZL occurred more frequently in the elderly within our cohort. According to Federico et al., these low-grade, mostly indolent B-cell lymphomas account for more than 50% of all malignant lymphomas.[33] Morra et al. found that the incidence of histological BMI in low-grade NHL was significantly higher than in other lymphoma groups, indicating that the majority behave as systemic diseases from their onset.[34] Biological factors influencing the higher rates of BMI may include their mature B-cell phenotype, expression of antiapoptotic proteins, altered expression of surface receptors to evade the immune system and expression of different cytokines and chemokines to name a few.[35,36,37,38,39,40]

Follicular lymphoma often involves bone marrow (40% – 70%) and is widely regarded as a systemic disease.[35] Despite widespread disease, patients are usually asymptomatic.[23] The unique overexpression of the antiapoptotic protein B-cell lymphomas (BCL2) and tumour microenvironment, along with its slow growing (Ki-67 < 20%) nature makes presentation in the elderly common.[23]

In contrast to FL, CLL/SLL usually presents with disseminated stage 4 disease (80% – 90%). Involvement of extranodal sites is common, with the bone marrow (72%)

being the most common site.[36] The interaction between chemokines and chemokine receptors (α4β1 with CXC chemokine receptor 4 [CXCR4]) induces adhesion to bone marrow stromal cells, and interaction of integrin α4β1 with fibronectin inhibits apoptosis by inducing elevated BCL-2 levels.[37]

Mantle cell lymphoma also presents with advanced systemic disease with BMI.[23] There is constitutive dysregulation of the cell cycle, deoxyribonucleic acid (DNA) damage response alterations and activation of cell survival pathways that are integrated to drive pathogenesis. High levels of CXCR4/5 and very late antigen-4 (VLA-4) play a role in migration to the bone marrow. The indolent non-nodal subgroup has low expression of SRY-related HMG-box (SOX11) related to mobility and is involved with downregulation of the DNA damage pathway and cell adhesion genes.[38]

Marginal zone lymphoma includes nodal and extranodal MZL, mucosa-associated lymphoid tissue (MALT) lymphoma and splenic marginal zone lymphoma (SMZL). Presentation is predominantly in the elderly (> 50 years) who show frequent bone marrow and peripheral blood involvement. There are no characteristic cytogenetic abnormalities and oncogenes that define these subgroups, and all of them show molecular heterogeneity.[39,40] Possible contributing factors to BMI include the fusion of the apoptosis inhibitor-2 gene in MALT lymphoma, NOTCH2 (10% – 25%) and Krüppel-like factor 2 (KLF2) (10% – 40%) which occur in SMZL, physiologically driving proliferation and commitment of mature B-cells to the marginal zone.[23]

Human immunodeficiency virus

Approximately, one third of patients (34%) in our study were HIV-positive, with the predominant lymphoma subtypes in this group being BL (93.3%) and OLLBC (71.4%). This high frequency of HIV-associated BL mirrors that seen previously in other studies at our centre and at other academic sites in the WC province.[1,3,29] Given the high prevalence of HIV in SA, it is expected that BL would be one of the most common subtypes.

Human immunodeficiency virus-associated lymphomas (134), across all subtypes showed BMI of 20.1% in B-cell NHL and 3% in HL. There was no statistically significant difference in BMI between the HIV-positive 32 (23.9%) and negative 70 (32.0%) lymphoma subgroups ($p = 0.926$). This shows that HIV status on its own is a poor predictor of BMI. Human immunodeficiency virus associated BL showed eight cases (53.3%) of BMI within our study. This percentage of BMI (53.3%) closely mirrors that seen at GSH in HIV associated BL, the second largest hospital in WC, after our institution.[29] Bone marrow is one of the most common extranodal sites of BL other than the gastrointestinal tract, and may lead to cytopenias.[41] One third (32.0%) of our HIV-negative cases showed BMI, with the highest frequency associated with low-grade lymphomas.

Haematological parameters

We found 60.2% of the lymphoma cases presented with a single cytopenia, of which anaemia was the most prevalent and just under a quarter of cases had normal FBC parameters.

A United States study of 317 patients with NHL (54 low grade, 180 intermediate grade, 76 high grade and seven unclassified) evaluated for the presence of haematologic abnormalities at diagnostic staging BME. In the study, anaemia was present in 42% of patients, leucopenia in 6% and thrombocytopenia in 13%. However, the association between BMI and anaemia was not statistically significant ($p = 0.12$). Patients with BMI were more likely to have leucopenia ($p = 0.006$) and thrombocytopenia ($p = 0.011$).[21] These data suggest that haematologic evaluation at the time of diagnostic staging of NHL provides useful prognostic information.

In comparison to the above studies, the most frequent haematologic abnormality at diagnosis in our cohort was anaemia (median haemoglobin [Hb] of 10.8 g/dL), of which 87 patients (74.4%) had BMI. Despite anaemia being a common finding, there was no statistically significant association between its presence and any lymphoma subtype. Our findings are in keeping with the study by Colan et al. who found anaemia to be an independent predictor of BMI.[21]

There was a low percentage of BMI amongst DLBCL and HG-BCL cases within our cohort presenting with leucopenia. This finding was not in keeping with the findings of Colan et al., however, our study subcategorised lymphoma subtypes that were not specifically mentioned, and this may be a caveat in this interpretation.[21] Thrombocytopenia was predominantly seen in BL (53.3%) followed closely with CLL/SLL (43.8%). Burkitt lymphoma showed the highest correlation between thrombocytopenia and BMI (87.5%).

We found a statistically significant association between pancytopenia or bicytopenia and BMI ($p = 0.0001$) with a PPV (positive predictive value) of 69% for pancytopenia and 61% for bicytopenia. Normal blood counts had a NPV of 70%, for the absence of BMI. These findings correlate with Lai et al. and Howell et al. who showed that a normal blood count made BMI highly unlikely.[22,42]

Limitations

Paediatric cases, follow-up, relapse and cases with subsequent involvement were excluded. Bone marrow involvement within our study may have been present in inadequate trephine biopsies of < 15 mm which were not included. The patients' comorbid conditions, drug history, CD4 count, viral load and treatments status were not considered but may be important. Further analysis of the individual combinations of bicytopenia was not made. High-grade B-cell lymphoma was used as a broad lymphoma category and did not individually categorise each into either HG-BCL or high grade B-cell lymphoma, not otherwise specified.

Conclusion

This study highlights the importance of BME in lymphoma staging. Advanced age, pancytopenia and bicytopenia are independent risk factors for BMI, whereas normal peripheral blood counts showed a high NPV for BMI. Lymphoma subtype, sex, HIV status, anaemia and leucopenia at presentation are not predictive risk factors for BMI. The above findings may guide future studies on lymphoma staging and expand our data for predictive risk factors for BMI.

In both HL and DLBCL, BME is no longer required if a staging PET-CT scan is available.[20,23,43] The following subtypes of lymphoma should not be staged with PET/CT unless it is required for assessment of possible transformation of disease: CLL/SLL, lymphoplasmacytic lymphoma, MZL and MF.[20,43] Bone marrow examination still remains a highly relevant staging investigation in all other lymphomas with or without haematological abnormalities.[23,44,45,46,47]

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

R.K.L. and Z.C.C. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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