



# Correlation of flow cytometry and bone marrow biopsy in marrow involvement of lymphoma patients

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## Abstract

**Introduction:** Non-Hodgkin's lymphomas (NHLs) are hematolymphoid malignancies. Bone marrow biopsy (BMB) is performed for staging. BMB findings are an important indicator of prognosis and treatment planning. In this study, we compared flow cytometry and BMB in marrow involvement of lymphoma patients.

**Objectives:** This study aimed to compare the frequency of involvement in bone marrow in flow cytometry and biopsy, compare the frequency of involvement in bone marrow in flow cytometry based on gender, compare frequency of bone marrow involvement in biopsy based on gender, compare mean age between two groups with bone marrow involvement and without bone marrow involvement in biopsy, compare mean age between two groups struggling with bone marrow involvement and without bone marrow involvement in flow cytometry, and compare mean ages between all genders struggling with bone marrow involvement and without bone marrow involvement in flow cytometry and biopsy

**Patients and Methods:** This study was cross-sectional, and the population included all patients affected by NHL, which bone marrow flow cytometry and biopsy performed for disease staging referred to Seyed Al-Shohada hospital affiliated with Isfahan University of medical sciences during 2016-2020. Four color flow cytometry devices (PARTEC CyFlow Space, Germany) with EXBIO antibody kits (Spain) were used.

**Results:** In this study, the number of samples was 107, of which 68 (63.6%) were male, and the mean (standard deviation) of the total age was 40.87 (18.98) years. All samples were diagnosed as lymphoma and were examined by bone marrow flow cytometry and biopsy. Flow cytometry frequency of bone marrow involvement was 14 (13.1%), and biopsy frequency of bone marrow involvement was 22 (20.6%). In 97 cases (90.6%), the diagnosis of both methods was the same. Nine patients (8.4%) had bone marrow involvement in biopsy only, and one case (1%) had bone marrow involvement in flow cytometry only. As a result, bone marrow involvement in patients with lymphoma who participated in this project is about 21.5%.

**Conclusion:** We concluded that evaluation of bone marrow involvement using combined methods is more efficient than biopsy or flow cytometry alone. We also recommended physicians use both methods at the same time.

**Keywords:** Bone marrow biopsy, Flow cytometry, Non-Hodgkin lymphoma

**Citation:** Nematollahi P, Mohammadi Jazi B, Forouzandeh N. Correlation of flow cytometry and bone marrow biopsy in marrow involvement of lymphoma patients. J Ren Endocrinol. 2023;9:e25087. doi: 10.34172/jre.2023.25087.

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## Introduction

Non-Hodgkin's lymphomas (NHLs) are hematolymphoid malignancies originating from normal B, T, and natural killer cells. All of them are differentiated from Hodgkin's lymphoma (HL) based on Reed-Sternberg (RS) cell diagnosis with specific immunophenotyping and have different biological and clinical features from HL. Although approximately 80-85% of HL patients are treated with chemotherapy and radiation therapy, the prognosis and course of the NHL disease seem to be unstable. The NHL is classified as NHL with B cell lineage, or T/NK-NHL, based on the neoplastic lymphocyte type. B, T, or NK cells, respectively. In any different group, there are lymphomas with rapidly growing, aggressive

behavior, like lymphomas that grow more slowly. HL) is a malignancy of adult B lymphocytes. It consists of about 10% of all lymphomas each year. Many cases of HL are classic HL (cHL); also, there is a second subtype of HL, nodular lymphocyte-predominant Hodgkin lymphoma. Although this diagnosis is morphologically similar to cHL, some evidence suggests it is biologically closer to slow B NHLs than cHL (1). In 2017, more than 72 000 novel NHL cases in the United States accounted for 4% of new cancers in men and women, making it the 8th and 9th most common cause of cancer-related death in all men and women, respectively. Its incidence is about ten times that of HL. Men are slightly superior to women, and white Americans are more prevalent than

Received: 6 May 2023, Accepted: 26 July 2023, ePublished: 14 August 2023

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### ■ Implication for health policy/practice/research/medical education

Bone marrow biopsy (BMB) is performed for staging non-Hodgkin's lymphomas (NHLs). BMB findings are an important indicator of prognosis and treatment planning. The use of flow cytometric analysis in the routine staging of NHL has been evaluated by several studies. Still, there needs to be more information and standard protocol to be found. Despite the use of flow cytometric methods and bone marrow aspiration in lymphoma staging, the pathological diagnosis of bilateral BMB is still the gold standard. In this study, we compared flow cytometry and BMB in marrow involvement of lymphoma patients.

African Americans. The prevalence increases with age, specifically after 40, but lymphomas are more prevalent malignancies during adolescence and young adulthood. With the diagnosis of about 8260 new cases in 2017 in the United States, the incidence of HL seems to stabilize. HL is more common in men and women, besides more customary in whites than blacks. In diagnosing this disease, a bimodal distribution with a peak incidence has been seen in patients in the twenties and in the eighties. A thorough clinical examination should carefully be done to look at the available peripheral lymph nodes, the size of the liver and spleen, the Waldeyer's ring, the attendance of pleural or pericardial effusion or ascites, the abdominal, testicular, or breast mass, and skin involvement because these manifestations may indicate the need for further evaluation and treatment interventions. Most patients with cHL introduce themselves with painless palpable lymphadenopathy. Many patients show these lymph nodes in their neck, supraclavicular region, and axilla. More than 50% of patients present with mediastinum during diagnosis of adenopathy; to a certain extent, these are the first manifestation that shows off the disease. Classic HL below the diaphragm is uncommon and usually happens with men who have aged more. One-third of patients present with "B" symptoms. HL may sometimes present as a fever of unknown origin. HL disease might appear with irregular manifestations, including severe, unexplained itching, skin abnormalities such as erythema nodosum, ichthyosis-like atrophy, paraneoplastic cerebellar degeneration, and other central nervous system disorders, nephrotic syndrome, immune hemolytic anemia, immune thrombocytopenia, hypercalcemia, and affliction in the lymph nodes after drinking alcohol. Bone marrow biopsy (BMB) is accomplished to stage diseases. The histology and clinical presentation of the lymphoma determine which imaging technique should be used. Ann Arbor staging system focuses on the number of mass sites (nodular and extra-nodular), location, and the existence of B symptoms. Positron emission tomography-computed tomography (PET-CT) scans are used to stage HL patients, and this is more accurate in assessing bone marrow than bone marrow biopsies because bone marrow involvement in cHL usually occurs in pieces and

may not be found on unilateral bone marrow biopsies. The initial evaluation of the HL or NHL patient is the same. Accurately determining the anatomical stage is an important part of the assessment of both diseases. Staging is done using the Ann Arbor system. Diagnosis of HL is possible by examining a sufficient biopsy specimen by an experienced hematopathologist. Staging is important to choose the right treatment intensity, but the prognosis for the right treatment is excellent for all stages. Most patients with HL are treated with chemotherapy alone or in an admixture of radiation therapy. Patients who suffer from advanced-stage disease do not have the advantage of adding radiation therapy to chemotherapy; as a result, they will be treated only by chemotherapy. Complete and accurate lymphoma staging is essential to determine the extent of disease involvement, as it affects the prognosis and appropriate treatment. However, the complexity of the bone marrow evaluation process has led to heterogeneity in the results obtained by different methods, and this is an obstacle to the clinical trial studies of lymphoma patients (2-10). Despite the continuous development of assistive devices used in the laboratory to assess the malignancy of lymphoma in the last decade, the study of bone marrow involvement in malignant lymphomas is still valuable and bilateral biopsy is the standard method. The usefulness of flow cytometric analysis in the routine staging of NHL has been evaluated by several studies. Still, there are deficiencies in information and standard protocol yet to be found. Despite the use of flow cytometric methods and bone marrow aspiration in lymphoma staging, the pathological diagnosis of bilateral BMB is still the gold standard (10-13). BMB findings are an important indicator of prognosis and treatment planning. Some groups are still in favor of using bone marrow aspiration collection. However, bone marrow aspiration may be the least sensitive of the diagnostic methods, as tissue intervention should be associated with successful aspiration and the absence of impurities in the blood. Previous investigations have shown that bone marrow involvement occurs in about 40% of all lymphomas in Western countries. Bone marrow involvement is diagnosed in most low-grade B-cell lymphomas, and most studies have reported bone marrow involvement in about 10 to 15 percent of large disseminated B-cell lymphomas (13-17). In 2015, a study was performed by Kim et al to learn the role of flow cytometry in the staging of non-Hodgkin lymphomas and concluded that flow cytometry is a useful method for assessing bone marrow in the staging of non-Hodgkin lymphomas. likewise, in 2004, a study was performed by Mazur et al to evaluate the role of simultaneous flow cytometry and BMB in the diagnosis of bone marrow lymphoid infiltration in NHL. They concluded that performing simultaneous BMB and flow cytometry to diagnose non-Hodgkin lymphoma infiltration was better than either alone (18-20).

## Objectives

- Comparison of the frequency of involvement in bone marrow in flow cytometry and biopsy
- Comparison of the frequency of involvement in bone marrow in flow cytometry based on gender
- Comparison of frequency of bone marrow involvement in biopsy based on gender
- Comparison of mean age between two groups with bone marrow involvement and without bone marrow involvement in biopsy
- Comparison of mean age between two groups struggling with bone marrow involvement and without bone marrow involvement in flow cytometry
- Mean ages between all genders struggling with bone marrow involvement and without bone marrow involvement in flow cytometry and biopsy

## Patients and Methods

### Study design

This method was a cross-sectional study, and the population of the study included all patients affected by NHL which bone marrow flow cytometry and biopsy performed for disease staging referred to Seyed Al-Shohada hospital affiliated to Isfahan University of Medical Science for staging the disease during 2016-2020. We utilized Four-color flow cytometry devices (PARTEC CyFlow Space, Germany) with EXBIO antibody kits (Spain).

### Inclusion criteria

All patients with NHL had undergone a biopsy for staging and had a BMB sample and bone marrow aspiration for flow cytometry.

### Exclusion criteria

If the flow cytometry sample was dilute and the specimen was unsatisfactory for evaluation by histopathology.

### Sampling

The census conducted a sampling process and examined all BMB specimens of patients diagnosed with lymphoma. The estimated sample size by Seyed Al-Shohada hospital was 120, out of which 107 samples were obtained.

The data collection in this study was done based on the information in the file and data collection form. All patients diagnosed with lymphoma who suffered from flow cytometry and BMB were studied, regardless of flow cytometry and biopsy results. An experienced pathologist evaluated aspiration samples and biopsy specimen involvement. Then the frequency of bone marrow involvement based on flow cytometry was analogized with the frequency of bone marrow involvement based on biopsy.

### Statistical analysis

Statistical analysis of this study was performed by

SPSS software version 16. The descriptive statistics section described the data based on number, frequency percentage, mean, and standard deviation. The analytical statistics section analyzed them by independent t-test and chi-square tests, and the *P* value was considered <0.05.

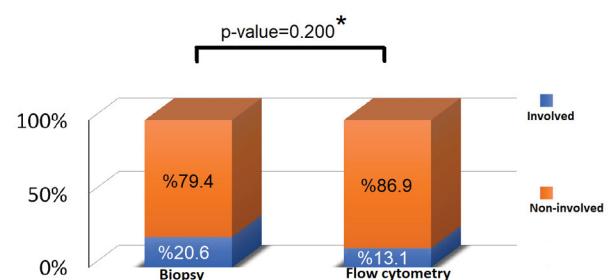
## Results

### Descriptive statistics

In this study, the number of samples was 107, of which 68 (63.6%) were male, and the mean (standard deviation) of the total age was 40.87 (18.98) years. All samples were diagnosed as lymphoma and were examined by bone marrow flow cytometry and biopsy. They were divided into two groups with or without bone marrow involvement in both methods. The flow cytometry frequency of bone marrow involvement was 14 (13.1%), and the biopsy frequency was 22 patients (20.6%). In 97 cases (90.6%), the diagnosis of both methods was the same. Nine subjects (8.4%) had bone marrow involvement in biopsy only, and 1 case (1%) had bone marrow involvement in flow cytometry only. As a result, bone marrow involvement in patients with lymphoma who participated in this project is about 21.5%. The frequency of involvement in bone marrow was compared between the two methods, and it was found that there was no significant difference between the two methods. You can see the results of this comparison in [Figure 1](#).

The frequency of bone marrow involvement was analyzed by the chi-square test for both flow cytometry and biopsy, stratified by sex. The results revealed no statistically significant difference in bone marrow involvement between the two sexes in either the flow cytometry or biopsy assessments (see [Figures 2 and 3](#)).

Then the frequency of involvement in bone marrow in flow cytometry and biopsy methods was compared based on the mean age. First, the normality of the variables was confirmed by Kolmogorov-Smirnov test and then the mean of the two groups was evaluated by independent t-test. The mean age between the two groups with bone marrow involvement and without bone marrow involvement in biopsy was statistically significant, yet all this comparison was not statistically indication in flow cytometry. The consequences of statistical analysis of the



**Figure 1.** Comparison of the frequency of involvement in bone marrow during flow cytometry and biopsy.  $\chi^2 (1) = 2.137, P = 0.200$ .

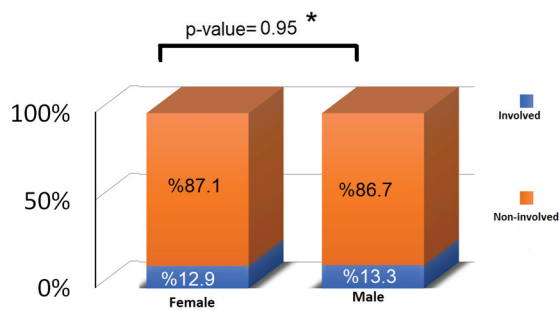


Figure 2. Comparison of the frequency of involvement in bone marrow in flow cytometry based on gender.  $\chi^2 (1) = 0.004$ , \* $P = 0.95$ .

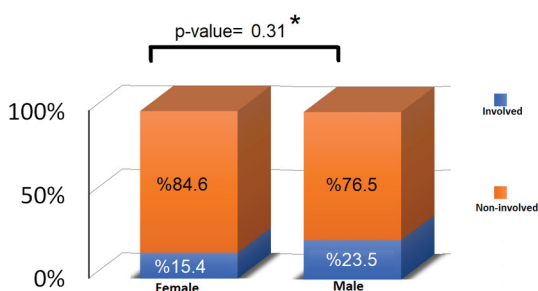
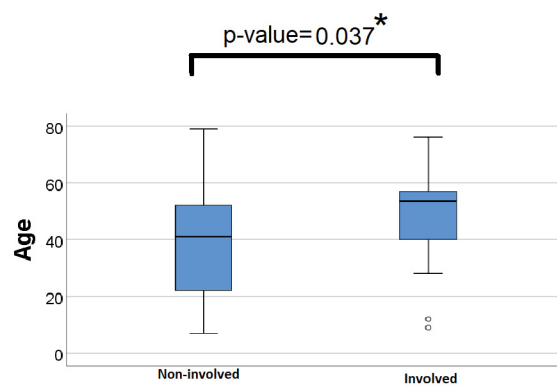


Figure 3. Comparison of the frequency of involvement in bone marrow in biopsy based on gender.  $\chi^2 (1) = 1.007$ , \* $P = 0.31$ .

above cases can be seen in Figures 4 and 5 and the Table 1.

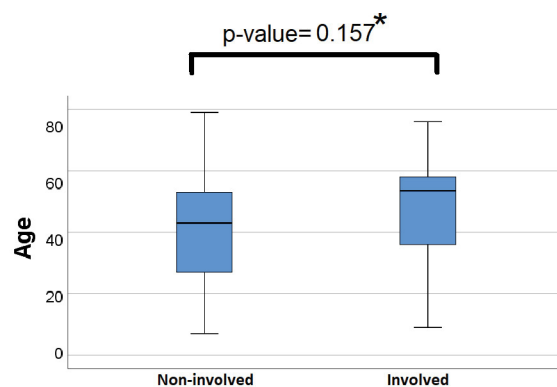
**Discussion**

We found that the mean age was higher between groups of people with involvement in bone marrow, but this was only statistically confirmed by biopsy. There was no difference between men and women in either method. Our study again found that the biopsy method showed a higher percentage of involvement in bone marrow in patients with lymphoma than the flow cytometry method. However, it should be noted that the two ways were not statistically different. According to this finding, statistically, both methods have the same accuracy in diagnosing bone involvement in bone marrow in patients with lymphoma. As mentioned in the results section, about 8.4% of cases had only participation in bone marrow in the biopsy method, and 1% had only involvement in bone marrow in the flow cytometry method. The prevalence of bone marrow involvement in patients with lymphoma who participated in this project was about 21.5%, and the



**Biopsy**

Figure 4. Comparison of mean age between two groups with involvement in bone marrow and without involvement in bone marrow in biopsy.  $t(105) = -2.11$ , \* $P = 0.037$ .



**Flow cytometry**

Figure 5. Comparison of mean age between two groups with involvement in bone marrow and without involvement in bone marrow in flow cytometry.  $t(105) = -1.42$ , \* $P = 0.157$

overlap of these two methods was about 91%. It can be said with great confidence that it should be a biopsy if we have to choose between flow cytometry and biopsy. In most overlap studies, the results of the two methods are close to 90%, and the prevalence of bone marrow involvement is similar to the results of our studies. These studies show that the percentage of bone marrow involvement discovered by biopsy is higher than flow cytometry alone.

Other researchers show similar results to our study. Here are some examples of this research. In 2015, a

Table 1. Mean ages between men and women with involvement in bone marrow and without involvement in bone marrow in flow cytometry and biopsy

	No. of samples	Mean age (y)	No. of involved biopsies	Mean age (y)	No. of non-involved biopsies	Mean age (y)	No. of involved flow cytometry	Mean age (y)	No. of non-involved flow cytometry	Mean age (y)
Female	39	42.64	6	57	33	40.03	5	59.4	34	40.18
Male	68	39.85	16	45.13	52	38.23	9	41	59	39.68
Total	107	40.87	22	48.36	85	38.93	14	47.57	93	39.86

cross-sectional study was done by Cabezas-Quintario et al, after studying patients referred to a medical center in Madrid, Spain, for ten years, the researchers were finally able to obtain a sample size of 356. Both flow cytometry and biopsy examined all of these individuals, and after the examinations, it was observed that the overlap rate of these two methods was about 86%. The team found that the relative frequency of involvement in the bone marrow along “positive flow cytometry-negative biopsy” was about 5%.

In comparison, the percentage of cases with “negative flow cytometry-positive biopsy” was 9 percent. Although these researchers did not compare the two methods, the results of this study indicate that the biopsy method is more accurate than the flow cytometry. However, this issue needs to be statistically confirmed. One of the differences between our study and Cabezas-Quintario et al study is that these researchers needed to calculate the prevalence of involvement in bone marrow in patients with lymphoma due to their research design. Another difference was that the researchers in the study presented the study’s results by type of lymphoma. In contrast, in our study, only the involvement or non-involvement of patients’ bone marrow was discussed, not its kind (21).

In the study of Song et al, the researchers examined patients with NHL using flow cytometry and biopsy for bone marrow involvement. The results of their study on participation in the bone marrow, which was done by the above two methods, showed that 25.7% of all patients have involvement in the bone marrow. The overlap of the results of the two methods in this study was 88.3%. In this study, two methods were evaluated separately based on lymphoma type. They found that in patients with T-cell lymphoblastic lymphoma and B-cell NHL, the relative frequency of bone marrow involvement with “positive flow cytometry-negative biopsy” is more common. In patients with T and NK cell NHL, “negative flow cytometry-positive biopsy” is more common. The most significant difficulty in comparing our results is that this study results have been published in China, and it is not possible to access the full text of the article. Another limitation of this comparison, as in the previous one, was that the researchers presented the results based on lymphoma type. Like the previous study, this study could have performed more analytical statistics between the two methods. Gender and mean age classification were not performed (22).

Evaluation of the diagnostic valence of various marrow in bone assessment methods in patients with lymphoplasmacytic lymphoma was the subject of a study conducted by Garcia-Reyero et al. The study, published in 2020, showed that in 24 patients, biopsy was more accurate than flow cytometry, and unlike the previous two studies, the difference was statistically significant. Molecular methods performed diagnosis confirmation, and it was confirmed that biopsy is a more sensitive method.

Although this study, unlike the previous two studies, this study performed statistical analysis and comparison to our study was possible, we faced some limitations. One of the limitations was that Garcia-Reyero et al. They only examined Lymphoplasmacytic lymphoma. Another limitation was that the researchers needed to calculate the prevalence of involvement in bone marrow in patients with lymphoma due to the design of their study. Gender and mean age classification were not performed in this study (23).

In 2021, Okamoto et al published research that was broadly similar to our study. The researchers studied 221 Japanese patients struggling with large B-cell lymphoma and found that the prevalence of bone marrow involvement is about 7.7% using biopsy and 12.2% using flow cytometry. They found that the overlap of the two methods was 86.4%. There are several limitations to compare to our study. One of the limitations was that they only examined diffuse large B-cell lymphoma. They did not perform analytical statistics between the two methods, and they did not compare the two methods based on gender and mean age (24).

### Conclusion

We concluded that evaluation of bone marrow involvement using combined methods is more efficient than biopsy or flow cytometry alone, and we recommended physicians use both forms simultaneously.

### Limitations of the study

Our limitations include the need for more classification based on lymphoma type and the lack of definitive confirmation of involvement with molecular methods.

Additional investigations should involve bone marrow evaluation, with a particular focus on differentiation based on the specific lymphoma type. By considering the distinct characteristics of each lymphoma subtype, these studies can offer valuable insights into bone marrow involvement, leading to improved diagnoses and more tailored treatment strategies.

### Authors’ contribution

Conceptualization: PN.  
Data curation: NF.  
Formal analysis: NF.  
Funding acquisition: PN  
Investigation: NF.  
Methodology: PN.  
Project Administration: PN.  
Resources: NF.  
Supervision: PN.  
Validation: PN.  
Visualization: BMJ.  
Writing—original draft: NF.  
Writing—review and editing: PN, BMJ.

### Conflicts of interest

The authors declare that they have no competing interests.

**Ethical issues**

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (Ethical code #IR.MUI.MED.REC.1400.136). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D thesis of Negin Forouzandeh at this university (Thesis #340073).

**Funding/Support**

Nil.

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