



# Evaluation of the frequency of benign reactive lymphocytosis and lymphoproliferative disorders by flow cytometry in patients with persistent lymphocytosis in peripheral blood

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## Abstract

**Introduction:** Lymphocytosis is characterized by an elevation in the absolute lymphocyte count (ALC) to over 4000 lymphocytes per microliter among adults. In lymphocytosis, the important matter is whether lymphocytosis is a benign reactive condition or a neoplastic lymphoproliferative disorder (LPD), which can be determined by immunophenotyping methods by flow cytometry.

**Objectives:** Due to the need to use flow cytometry to confirm the diagnosis of patients with lymphocytosis, the purpose of this study was to compare the frequency of benign reactive lymphocytosis and LPDs in patients with persistent lymphocytosis using flow cytometry in the peripheral blood and report the results based on the patient's demographic characteristics.

**Materials and Methods:** This study was a cross-sectional study and the study population was all peripheral blood samples referred to Seyed Al-Shohada hospital in Isfahan to study the cause of absolute and persistent lymphocytosis by immunophenotyping analysis through flow cytometry between 2015 and 2020. Inclusion criteria were patients over 18 years of age with absolute lymphocytosis in complete blood count (CBC) or peripheral blood smear (PBS) who were examined by flow cytometry.

**Results:** This study involved 222 samples, 139 (62.6%) of the cases were male. The mean age was 60.41 (15.91) years. All samples had absolute lymphocytosis and were divided into two groups: benign, with 62 (27.9%), and malignant, with 160 (72.1%).

**Conclusion:** The relationship between gender and malignancy showed that the male gender was associated with an increased risk of malignancy. The mean age between the two groups of malignant and benign was determined by independent t test, and it was shown that the mean ( $\pm$ standard deviation) age of malignant cases is higher than the mean age of benign cases. It is recommended that cases of suspected lymphoproliferative cases and cases with cell counts below the lymphocytosis threshold be investigated in separate studies.

**Keywords:** Lymphocytosis, Flow cytometry, Benign reactive lymphocytosis, Lymphoproliferative disorders

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## Introduction

Lymphocytosis, a frequently encountered hematologic anomaly, is characterized by an absolute lymphocyte count (ALC) elevation to over 4000 lymphocytes per microliter among adults. The ALC is determined by multiplying the total white blood cell (WBC) count by the percentage of lymphocytes in peripheral blood. Depending on the underlying cause, various lymphocyte subsets [such as T, B, or natural killer cells (NK cells)] may increase in this. Lymphocytes typically constitute approximately 20% to 40% of the WBC count. Relative lymphocytosis is defined as a more than 40% increase in WBC in the presence of a

normal absolute white blood cell count (1).

Lymphocytosis reported by automated experimenters may include normal-looking lymphocytes (small lymphocytes, plasmacytoid lymphocytes or large granular lymphocytes [LGLs]), or lymphoid cells with abnormal morphology that may be indicator of blasts or lymphocyte variants. If cells with abnormal morphology (such as cerebriform cells and lymphoma cells or Downey cells) are present in the bloodstream, the term abnormal mononuclear cell pattern can be used regardless of the degree of lymphocytosis. If lymphocytosis is evident (In adults at least  $15 \times 10^9/L$ ), differentiation of neoplastic

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

This study evaluated lymphocytosis, characterized by an ALC in adults. It aimed to distinguish between benign reactive lymphocytosis and neoplastic LPDs using flow cytometry immunophenotyping. This study showed that male gender was associated with a higher risk of malignancy, and malignant cases tended to be older. The study suggests separate investigations for suspected lymphoproliferative cases and cases with lymphocyte counts below the threshold.

lymphocytosis (which is a lymphoproliferative disorder, LPD) from benign lymphocytosis will be simple. This difference is more difficult to diagnose when absolute lymphocytosis is less evident, unless other clinical and laboratory information is available and the Immunophenotype is determined by flow cytometry. If the lymphocytes are mature and there is no evidence of monoclonal T cell or aberrant phenotype, lymphocytosis is considered benign. In neoplastic lymphocytosis, the cell population can be composed mainly of small round lymphocytes, plasmacytoid lymphocytes, or LGLs. Disorders consisting of a mixture of small round lymphocytes, plasmacytoid lymphocytes, and a number of proliferative cells belong to the generalized chronic lymphocytic leukemia (CLL) disorders, and related disorders include lymphoplasmacytic lymphoma (LPL) (2).

One of the most prevalent abnormalities frequently encountered in the hematology laboratory is the presence of absolute lymphocytosis in peripheral blood. In lymphocytosis, the important matter is whether lymphocytosis is a benign reactive condition or a neoplastic LPD, which can be determined by methods of immunophenotyping by flow cytometry. When lymphocytosis is diagnosed as a new onset on complete blood count (CBC), it is necessary to make a peripheral smear and examine the slides. Peripheral blood smear (PBS) evaluation serves as a vital screening tool in reaching differential diagnoses that can briefly include two reactive groups or a malignant LPD (3,4).

Reactive lymphocytosis is usually restricted and normalizes after discontinuation of self-stimulatory antigen. The most prevalent and widely recognized reasons of reactions include viral infections (Epstein-Barr virus, hepatitis and cytomegalovirus) and drug-allergic reactions. A distinctive subtype of reactive lymphocytosis, known as transient stress lymphocytosis, remains somewhat less understood. This form of lymphocytosis typically resolves within a few hours, at most, within 1-2 days. It commonly occurs in patients experiencing various acute events like trauma, surgical procedures, exercise, cardiac events, and toxic exposures. Lymphocytosis can also be due to splenectomy, autoimmune diseases, other

chronic diseases or a neoplastic process (3–6).

In the past, leukemoid reactions were referred to as acute infectious lymphocytosis (ALL), often lasting 3 to 5 weeks and sometimes lasting longer. On the other hand, LPD is a clonal disorder with the potential to persist for months or even years. LPDs can be further categorized into various types based on their morphology, immunophenotyping, cytogenetics, molecular study results, and clinical symptoms. It is commonly acknowledged that malignant LPDs tend to be more common among the elderly, and various morphological patterns are linked to both reactive and malignant processes. Therefore, morphological assessment stands as a crucial screening tool for patients. Unfortunately, the precise predictive capability of morphological evaluation has not been extensively studied, and the optimal ACL to trigger the morphological assessment of peripheral smears has not been defined in the literature. LPDs encompass a heterogeneous assembly of disease characterized by monoclonal lymphocytosis, lymph node enlargement (lymphadenopathy), and the uncontrolled proliferation of lymphocytes infiltrating the bone marrow. These disorders frequently manifest in individuals with immunodeficiency. Within this context, there are two subsets of lymphocytes: T cell and B cell disorders. Various genetic mutations have been identified as potential contributors to LPD, which can either be iatrogenic (resulting from medical intervention) or acquired (7–9).

Lymphocytosis is more likely to indicate a neoplastic process as the patient ages and the most common cause is CLL. There are a number of less common B, T, and NK cell leukemia that may circulate in the peripheral blood and be diagnosed as lymphocytosis accidentally (10,11). According to the World Health Organization (WHO) classification published in 2008 and revision of the WHO classification of lymphoid neoplasms published in 2016, CLL, categorized as an LPD, consists of a population of monomorphic, round B lymphocytes that impact peripheral blood, bone marrow, and lymphatic tissues. CLL is an example of a clonal LPD, marked by peripheral B lymphocyte counts exceeding  $5 \times 10^5/L$  and a diagnosis characterized by reduced expression of specific markers including CD5, CD19, CD23, CD20, CD79b, and surface immunoglobulin genes. Among B-cell lymphocytic disorders are chronic B-cell lymphocytic leukemia, B-cell prolymphocytic leukemia, leukemic phases of non-Hodgkin's lymphoma (including mantle cell lymphoma), hairy cell leukemia, and splenic lymphoma with villous lymphocytes. Meanwhile, chronic T-cell LPDs encompass conditions like Sézary syndrome, T-cell prolymphocytic leukemia, adult T-cell leukemia, and large-granular lymphocytic leukemia (12–14).

Monoclonal B-cell lymphocytosis (MBL) is identified as an asymptomatic disease marked by the existence of fewer than 5000 B-monoclonal cells per microliter, and

the lack of any clinical signs or symptoms associated with a B-cell LPD. Persistent polyclonal B cell lymphocytosis is a benign proliferation of polyclonal B cells in which atypical dual-nucleated lymphocytes are present in the peripheral blood. However, the possibility of lymphoma should be considered. LGL leukemia is an uncommon, chronic lymphoproliferative disease distinguished by the clonal proliferation of LGLs. Lymphoma consists of two categories, non-Hodgkin's lymphoma and Hodgkin's lymphoma. Non-Hodgkin's lymphomas (NHLs) are adult T, B, and NK cells cancer. They are differentiated from Hodgkin's lymphoma (HL) based on the diagnosis of Reed-Steinberg (RS) cell, and have different biological and clinical characteristics compared to HL. The NHL can be classified as B-NHL, or adult T/NK-NHL based on whether the cancerous lymphocytes are B, T, or NK cells, respectively. B-cell NHLs include Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, marginal lymphoma, and LPL. T cell NHLs include fungal mycosis, peripheral T cell lymphoma, angioimmunoblastic T cell lymphoma, large anaplastic cell lymphoma, and other subtypes of adult PTCL, adult T cell lymphoma, and extra nodular NK/T cell lymphoma. HL is a malignancy that arises from mature B lymphocytes in adults. Types of Hodgkin's lymphoma include nodular lymphocyte-predominant Hodgkin lymphoma and classical HL (15–17).

Sun et al showed that LPDs exhibited a connection with advanced age and elevated lymphocyte counts, with an approximate threshold for morphology assessment set at around  $7 \times 10^9/L$  for lymphocyte count. Additionally, another study conducted by Victor Tseng et al in 2014 showed that if the absolute lymphocytosis standard is considered more than  $5 \times 10^9/L$ , the laboratory load will be reduced without compromising the result (3,4). Due to the gap in the literature in Iran, the need for this research was felt and our research team decided to do it.

### Objectives

- Comparison of frequency of benign reactive lymphocytosis and LPDs in patients with persistent lymphocytosis using flow cytometry in the peripheral blood.
- Comparison of frequency of benign reactive lymphocytosis in patients with persistent lymphocytosis based on gender.
- Comparison of frequency of LPDs in patients with persistent lymphocytosis based on gender.
- Comparison of the average age difference between two groups with benign reactive lymphocytosis and LPDs in patients with persistent lymphocytosis.
- Mean age between all genders with benign reactive lymphocytosis and LPDs.
- Comparison of the frequency distribution of types of malignancies in patients with LPDs.

## Materials and Methods

### Study design

This study is a cross-sectional investigation and the study population was all peripheral blood samples referred to Seyed Al-Shohada hospital in Isfahan to study the cause of absolute and persistent lymphocytosis by immunophenotyping analysis through flow cytometry (2015-2020). Sampling was conducted by census and finally 222 peripheral blood samples that were referred to Seyed Al-Shohada hospital in Isfahan to investigate the cause of absolute and persistent lymphocytosis (2015 and 2020). This condition was defined by increasing the number of ALC to more than 4000 lymphocytes per microliters in adult patients, analyzed, using immunophenotyped by flow cytometry.

The data collection tool in this study was a checklist and would include the following:

1. Demographic characteristics including age and gender
2. Immunophenotyping results including benign reactive lymphocytosis and LPDs (diagnosis of benign reactive lymphocytosis and LPDs was reported by flow cytometry).
3. The final result of the type of chronic LPD if possible (some LPDs are indistinguishable due to immunophenotyping in flow cytometry).

After collecting samples, the relative frequency and relevance of the results were compared. Stable lymphocytosis of the studied patients was obtained by flow cytometry from the files of the studied samples.

### Inclusion criteria

Patients over 18 years of age with absolute lymphocytosis in CBC or PBS who were examined by flow cytometry.

### Exclusion criteria

Exclusion criteria also included samples that were not suitable or optimal for immunophenotyping in terms of storage conditions before flow cytometry, cases of relative lymphocytosis, as well as deficiencies in demographic information of patients' records.

### Statistical analysis

Statistical analysis for this study was conducted using SPSS software version 16. In the descriptive statistics segment, data were summarized using counts, percentage frequencies, mean values, and standard deviations. In the analytical statistics section, the data were assessed by independent *t* tests and chi-square tests, with a significance level set at  $P < 0.05$ .

## Results

### Descriptive statistics

This study involved 222 samples, of which 139 (62.6%) were male. The mean age was 60.41 ( $\pm 15.91$ ) years. All

samples had absolute lymphocytosis and were divided into two groups; benign with 62 (27.9%) and malignant with 160 (72.1%). The three main types of malignancy were CLL with 134 cases (83.8% of malignancies), Mantle cell lymphoma with 10 cases (6.3% of malignancies) and B-chronic LPD with 10 cases (6.3% of malignancies), respectively. Together they accounted for 96.4% of the cases. Details of the types of malignancies are given in Table 1. The distribution of frequencies of benign and malignant cases based on gender and age is shown in Figures 1 and 2.

**Analytical statistics**

The relationship between gender and malignancy was performed by chi-square ( $\chi^2$ ) test and it was shown that male gender was associated with a higher risk of malignancy, which is statistically significant ( $P = 0.001$ ). The mean age between the two groups of malignant and benign was determined by independent  $t$  test and it was shown that the mean (standard deviation) age of malignant cases, which is 65.83 (12.76) years, is higher than the mean age of benign cases, which is 46.43 (14.75). This variance was statistically significant ( $P = 0.000$ ). It should be noted that prior to conducting the independent  $t$  test, the data's normality was checked by Shapiro-Wilk test.

**Discussion**

In the present study, we found that the mean age of malignant lymphocytosis is higher than that of benign

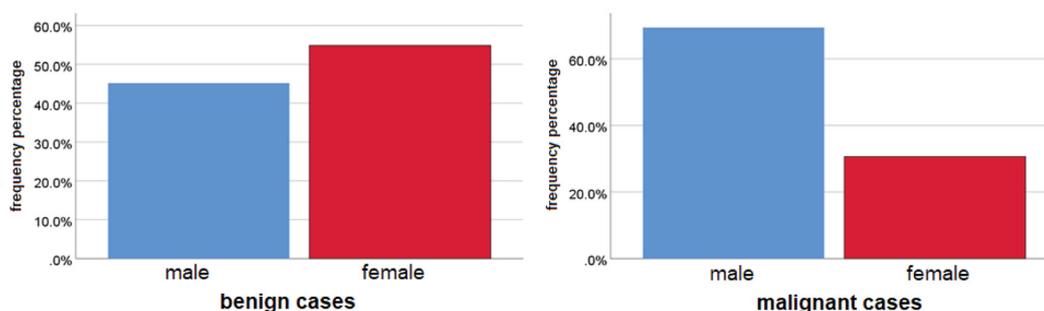
lymphocytosis. It was found that the ratio of malignant patients to total patients in men is higher than the ratio of malignant patients to total patients in women. The age distribution of lymphocytosis can vary depending on the type of lymphocytosis. CLL, for example, which is the most prevalent form of leukemia among adult patients in the United States typically presents with a median age of diagnosis at 70 years or in cases of Burkitt lymphoma is more common in children. But generally speaking, it can be said that the incidence of neoplastic cases in lymphocytosis increases with age. However, it should be noted that the number of lymphocytes increases physiologically with age. Therefore, different cut-offs have been considered for lymphocytosis at different ages, since Andrews et al conducted this procedure in their research too. Moreover, some cases of lymphocytosis, such as CLL, can show up with a normal lymphocyte count. Rawstron et al in their study of 910 patients with CLL found that up to 3.5% of cases could occur without an increase in lymphocyte count. Since 80% of malignancies in the present study are related to CLL and as mentioned above, the chance of lymphocytic malignancy increases with age, accordingly it can be said that the average age is higher in patients with malignant lymphocytosis compared to benign cases (10,18–20).

We found that, the ratio of malignant cases of lymphocytosis to benign cases is higher in men which were reported by previous studies too. Rawstron et al have previously found that men are more likely to develop CLL.

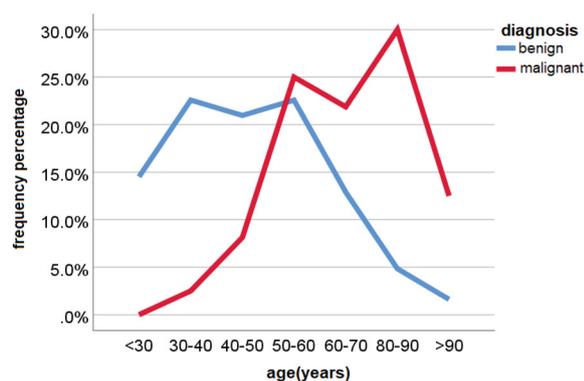
**Table 1.** The distribution of frequencies of types of malignancies

Types	Quantity	Frequency percentage	Cumulative percentage
CLL	134	83.8	83.8
Mantle cell lymphoma	10	6.3	90.1
B-chronic LPD	10	6.3	96.4
Monoclonal B-LPD	3	1.8	98.2
T-LPD	1	0.6	98.8
TLGL	1	0.6	99.4
AML	1	0.6	100.0
Total	160	100.0	

CLL, Chronic lymphocytic leukemia; T-LPD, T cell lymphoproliferative disorder; TLGL, T-cell large granular lymphocytic; AML, Acute myeloid leukemia.



**Figure 1.** The distribution of frequencies of benign and malignant cases based on gender.



**Figure 2.** The distribution of frequencies of benign and malignant cases based on age.

It should be mentioned that in healthy people, the number of lymphocytes in men is higher. This was confirmed by Abdullah et al by examining and counting the blood cells of people who did not have lymphocytosis. It should be noted that in some studies, the role of gender, although present, was not statistically significant (21,22).

The results of our study showed that the most common malignancy is CLL, which was predictable because according to the American Cancer Society, CLL is the most common malignant lymphocytosis in the United States. The epidemiological features of CLL are that it is more common in men at a ratio of 1.2: 1 to 1.7: 1 than in women. It is considered a disease in the elderly whose average age at diagnosis is approximately 70 years. The national cancer organization estimates that the disease's prevalence among individuals in the United States is about 200 000 (6 per 1000) and accounts for 1.1 percent of all cancers (23–27).

The results of our study showed that the second malignancy in lymphocytosis is Mantle cell lymphoma with an incidence of about 1 case per 100 000 people; this malignancy can be considered the second most common disease in malignant lymphocytosis. Although Mantle cell lymphoma is generally rare, it is common in lymphocytosis and according to Hamad and Mangla's research, NHL is the most common in proliferative lymphocytosis. Hamad and Mangla stated that LGL leukemia has a low prevalence among malignant lymphocytosis, and this was consistent with our study (1,28–30).

Our study has several limitations. One of the limitations is that although flow cytometry is a suitable method there may be a small percentage of error in determining the type of malignant lymphocytosis and it will be difficult to differentiate CLL from other types of malignancy. Additionally, as described above, there may be cases of malignancy that are present in normal cell lymphocyte counts and therefore have not been investigated in this study. It can be said that to diagnose lymphocytosis, the threshold number of lymphocytes can be determined differently according to the age of the patients because the

number of lymphocytes at different ages is physiologically different.

Finally, it is recommended that cases of suspected lymphoproliferative cases and cases with cell counts below the lymphocytosis threshold be investigated in separate studies.

## Conclusion

Our study showed that, the relationship between gender and malignancy showed that the male gender was associated with an increased risk of malignancy. The mean age between the two groups of malignant and benign was determined by independent *t* test, and it was shown that the mean ( $\pm$ standard deviation) age of malignant cases is higher than the mean age of benign cases. It is recommended that cases of suspected lymphoproliferative cases and cases with cell counts below the lymphocytosis threshold be investigated in separate studies.

## Limitations of the study

1. One of the limitations is that although flow cytometry is a suitable method, there may be a small percentage of error in determining the type of malignant lymphocytosis and it will be difficult to differentiate CLL from other types of malignancy.
2. Likewise, there may be cases of malignancy that are present in normal cell lymphocyte counts and therefore have not been investigated in this study.
3. It can also be said that to diagnose lymphocytosis, the threshold number of lymphocytes can be determined differently according to the age of the patients because the number of lymphocytes at different ages is physiologically different.

## Authors' contribution

**Conceptualization:** Behnoosh Mohammadi Jazi.

**Data curation:** Noushin Maktoobian.

**Formal analysis:** Noushin Maktoobian.

**Funding acquisition:** Behnoosh Mohammadi Jazi.

**Investigation:** Noushin Maktoobian.

**Methodology:** Behnoosh Mohammadi Jazi.

**Project administration:** Behnoosh Mohammadi Jazi.

**Resources:** Noushin Maktoobian.

**Validation:** Behnoosh Mohammadi Jazi.

**Visualization:** Pardis Nematollahy.

**Supervision:** Behnoosh Mohammadi Jazi.

**Writing—original draft:** Noushin Maktoobian.

**Writing—review and editing:** Behnoosh Mohammadi Jazi, Pardis Nematollahy.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethical code #IR.MUI.MED.REC.1400.386). Accordingly, written informed consent was taken from all participants before any intervention.

This study was extracted from M.D/MSc thesis of Noushin Maktoobian at this university (Thesis #3400338). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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