

BRIEF REPORT

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Large Granular Lymphocytes and Large Granular Lymphocytic Leukemia: A Real-World Case-Control Study

Liu C. et al.: LGLs in LGLL: A Donor-Patient Study

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Abstract

Objective: This study aimed to compare differences in peripheral blood large granular lymphocytes (LGLs) between healthy donors and patients with large granular lymphocyte leukemia (LGLL), and explore methods to boost the sensitivity of peripheral blood smear examination for LGLL identification.

Materials and Methods: We retrospectively analyzed 391 healthy donors and 53 LGLL patients from 2023 to 2024.

Results: Results showed significant differences in LGL proportion, absolute count and its proportion in lymphocytes between the two groups (all $P < 0.001$). There was no significant difference between smear and flow cytometric results. ROC curve analysis determined 24% LGL proportion as the cutoff value.

Conclusion: Peripheral blood smear can be used for initial LGLL screening, and the thresholds of $0.5 \times 10^9/L$ LGL absolute count and 24% LGL proportion effectively screen LGLL patients.

Keywords: Large granular lymphocytes, Large granular lymphocytic leukemia, Peripheral blood smear, Morphology, Flow cytometry

Introduction

Large granular lymphocytic leukemia (LGLL) represents a clonal neoplastic proliferation of Large granular lymphocytes (LGLs), which is characterized by a notable elevation in the proportion of LGLs in peripheral blood. This study aimed to clarify the normal range and distribution pattern of LGLs in healthy individuals, thus facilitating the identification of LGLL[1].

Materials and Methods

Subjects

This study encompassed 391 normal donors and 53 patients diagnosed with LGLL, who were admitted to the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences (CAMS) during the period from 2023 to 2024. This study was approved by the Institutional Review Board of the Institute of Hematology & Blood Diseases Hospital (Approval No. QTJC2026004-EC-1, 21 January 2026), and informed consent was obtained from all participants.

All normal donors underwent a comprehensive screening for lympho - hematopoietic system diseases, and no relevant pathological abnormalities were detected.

Patients diagnosed with LGLL were identified in line with the diagnostic criteria specified in the 2022 World Health Organization classification for LGLL and the prevailing diagnostic criteria[2,3].

Morphological Assessment of Large Granular Lymphocytes

Donor and LGLL patient peripheral blood smears underwent Wright's staining. Lymphocytes with cytoplasmic azurophilic granules were defined as LGLs, irrespective of granule amount, cell or cytoplasm size. We manually counted 200 leukocytes via Olympus BX46 microscope; LGL absolute counts were calculated by multiplying same-day white blood cells (WBC) values by LGL percentages.

Statistical Analysis

Comparisons between groups were conducted using either the Mann - Whitney U test or the

Chi-squared test, as appropriate. Parameters exhibiting statistically significant differences were summarized through univariate and multivariate regression analyses. Receiver operating characteristic (ROC) analysis was employed to establish cut-off values for the variables. These analyses were carried out using SPSS 27.

Results

Donor Baseline Characteristics and Hematological Parameters

A total of 391 donors were recruited, including 293 males and 98 females, with a median age (and range) of 34 (8 - 62) years. The levels of WBC, red blood cells, hemoglobin, and platelets in the complete blood count all fell within the normal ranges. A line graph depicting the LGL-related parameters across different age groups is presented below (Figure 1).

In healthy donors, no statistically significant disparities were detected in LGL-associated parameters between males and females, as presented in Figure 2.

Basic Characteristics and Hematological Parameters of Patients with LGLL

A total of 53 patients were recruited, comprising 28 males and 25 females, with a median age of 56 years (age range: 23–75). A line graph depicting LGL - related parameters across diverse age groups is presented below (Figure 3). Simultaneous flow cytometry (FCM) analysis demonstrated that the median proportion of peripheral blood LGLs among lymphocytes was 74.45% (proportion range: 1.61–94.02%). No statistically significant disparity was detected between the results acquired by the two detection methods ($P = 0.692$).

In patients diagnosed with LGLL, no statistically significant disparities were detected in LGL-related parameters between male and female patients, as presented in Figure 4.

Analysis of Clinical Factors in Donors and Patients with LGLL

Statistical analyses were conducted on age, sex, and parameters related to LGLs, as presented in Table 1. In light of the preference for choosing younger male donors[4], the observed age disparity between the two groups was deemed to stem from selection bias. Consequently, age was not incorporated into the multivariate regression analysis. Logistic regression analysis indicated that the proportion of LGLs demonstrated a higher level of statistical significance (Table 2).

Diagnostic Significance of the LGL Percentage for LGLL

A receiver operating characteristic (ROC) curve was established based on the LGL percentage of donors and patients with LGLL (Figure 5). The optimal cutoff value for the LGL percentage was ascertained to be 24% according to the maximum Youden index. Using 24% as the threshold, the sensitivity and specificity for analyzing LGLL were 0.792 and 0.995. Employing 24% as a threshold to distinguish healthy individuals from patients with LGLL was verified its discriminatory ability ($P < 0.001$) (Table 3). Based on the absolute LGL count levels and percentages derived from the data of 444 included cases, both donor and LGLL patients were classified into four groups:

1. Absolute LGL count $< 0.5 \times 10^9/L$ and LGL percentage $< 24\%$ (212 donors, 7 patients);
2. Absolute LGL count $\geq 0.5 \times 10^9/L$ and LGL percentage $< 24\%$ (177 donors, 4 patients);
3. Absolute LGL count $< 0.5 \times 10^9/L$ and LGL percentage $\geq 24\%$ (0 donors, 3 patients);
4. Absolute LGL count $\geq 0.5 \times 10^9/L$ and LGL percentage $\geq 24\%$ (2 donors, 41 patients).

Statistical analysis indicated a significant disparity in the distribution of cases among these four groups ($P < 0.001$). A detailed comparison of the case numbers is presented in Figure 6.

Discussion

This study analyzed LGL profiles in 391 healthy individuals and patients with LGLL. No significant age- or sex-related differences in LGL levels were observed among healthy participants. Both the proportion and absolute count of LGLs were markedly lower in healthy individuals than in LGLL patients. Currently, the diagnostic guidelines for LGLL clearly specify that the diagnostic criterion is an absolute LGL count $\geq 0.5 \times 10^9/L$ [1], but no precise cutoff value for the percentage of large granular lymphocytes has been established. Our data support $0.5 \times 10^9/L$ as a suitable diagnostic threshold for the LGL absolute count. The LGL percentage also differed significantly between the two groups. ROC analysis determined 24% to be the optimal diagnostic cut-off for LGL proportion. Combined use of an LGL absolute count of $0.5 \times 10^9/L$ and an LGL percentage above 24% provides effective and accurate screening for LGLL [3]. Morphological LGL assessment has observer bias. This study verified morphological detection correlates well with flow cytometry, supporting its reliability. Manual counting limits efficiency, while AI-assisted cell analysis offers promising, accurate and high-throughput optimization [5].

Clonal T cells of uncertain significance can exist in healthy people [6] and those with rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, aplastic anemia, immune thrombocytopenia [7,8,9,10,11], with a lower level than malignant T cells in T-cell LGLL and no inevitable disease progression. Reactive LGL expansion often occurs in viral infections and immunodeficiency states, and may potentially develop into LGLL [12,13,14]. Patients who have undergone solid organ transplantation or hematopoietic stem cell transplantation may experience LGL proliferation, which can present as clonal, oligoclonal, or polyclonal expansion; some patients may also exhibit cytopenias [15,16,17]. Patients with myelodysplastic syndromes also present varying degrees of LGL proliferation. Relevant abnormal proliferation may be controlled after targeted treatment. However, the specific impact of LGL proliferation on disease progression and prognosis remains unclear, and targeted depletion therapy shows limited clinical benefits [18,19,20].

Due to the limitations of the research institution and the retrospective nature of the study, data from patients with autoimmune diseases, infectious diseases, or other hematological disorders were not included in our study population. However, this aspect could be considered as a direction for future prospective investigations. Despite these shortcomings, our study demonstrates that an LGLs proportion $\geq 24\%$ and an LGLs absolute count $\geq 0.5 \times 10^9/L$ can serve as an initial screening method for LGLL, providing a more economical and rapid approach to identify patients who require further diagnostic workup to confirm LGLL.

Authorship Contributions: Surgical and Medical Practices: C.L., Y.Liu., Y.Li., S.C., W.C., Y.Z., Y.D., X.L.; Concept: C.L., Y.Liu., Y.Li., J.X., Q.S.; Design: C.L., Y.Liu., Y.Li., J.X., Q.S.; Data Collection of Processing: C.L., Y.Liu., Y.Li., S.C., W.C., Y.Z., Y.D., X.L., J.X., Q.S.; Analysis or Interpretation: C.L., Y.Liu., Y.Li.; Literature Search: C.L., Y.Liu., Y.Li., S.C., W.C., Y.Z., Y.D., X.L.; Writing: C.L., J.X., Q.S.

Ethics

Ethics Committee Approval

The study was approved by the Institutional Review Board of the Institute of Hematology & Blood Diseases Hospital, *** Academy of Medical Sciences & **** Medical College (study approval number:

QTJC2026004-EC-1, date: 21.01.2026).

Informed Consent

Informed consent was obtained from all individual participants included in this study.

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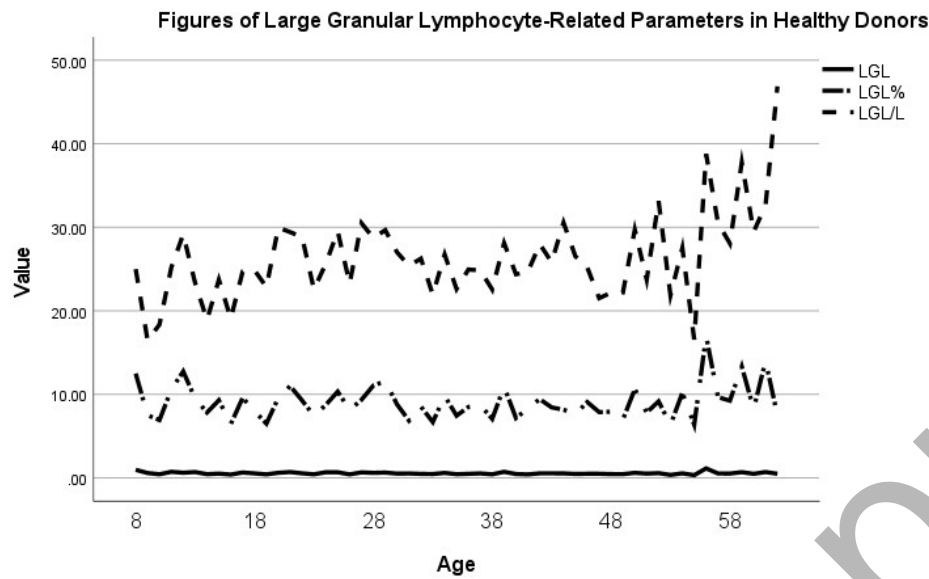
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LGL: Absolute Count of Large Granular Lymphocytes; LGL%: Proportion of Large Granular Lymphocytes in Leukocytes; LGL/L: Proportion of Large Granular Lymphocytes in Lymphocytes

Figure 1. LGL-related parameters across different age groups in healthy donors. LGL: Absolute count of large granular lymphocytes, which was calculated by multiplying the WBC count by the percentage of LGLs. The median (range) absolute LGL count was $0.4635 (0.07 - 1.9) \times 10^9/L$; LGL%: Proportion of large granular lymphocytes in leukocytes. The median (range) proportion of LGLs was 8% (1 - 26.5%); LGL/L: Proportion of large granular lymphocytes in lymphocytes. The median (range) percentage of LGLs among lymphocytes was 25% (3.53 - 61.73%).

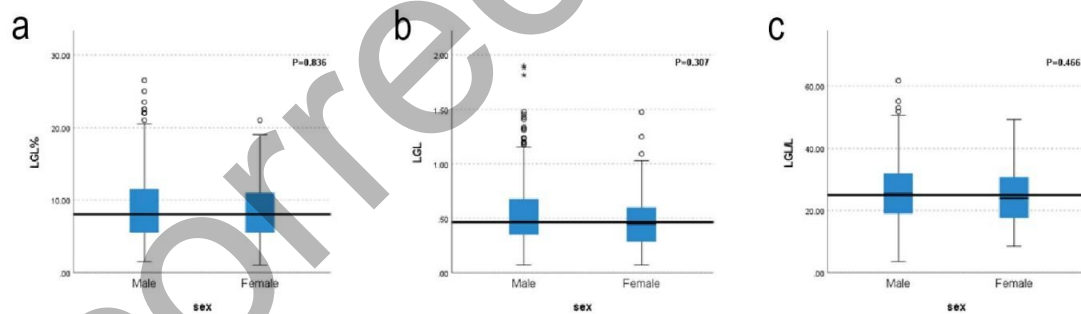
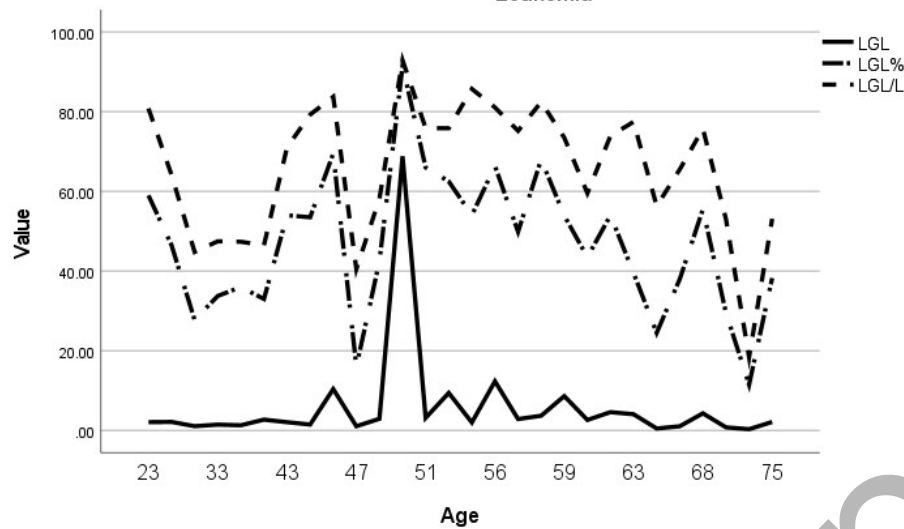


Figure 2. Comparison of LGL percentage (a), absolute count (b), and proportion among lymphocytes (c) between males and females in healthy donors.

Figures of Large Granular Lymphocyte-Related Parameters in Patients with Large Granular Lymphocytic Leukemia



LGL: Absolute Count of Large Granular Lymphocytes; LGL%: Proportion of Large Granular Lymphocytes in Leukocytes; LGL/L: Proportion of Large Granular Lymphocytes in Lymphocytes

Figure 3. LGL-related parameters across different age groups in LGLL patients. LGL: Absolute count of large granular lymphocytes. The median (range) absolute count of LGLs was $2.2964(0.24-68.84 \times 10^9/L) \times 10^9/L$; LGL%: Proportion of large granular lymphocytes in leukocytes. The median (range) proportion of LGLs was 53.5% (6-94%); LGL/L: proportion of large granular lymphocytes in lymphocytes. The median (range) proportion of LGLs among lymphocytes was 74.45% (1.61-94.02%).

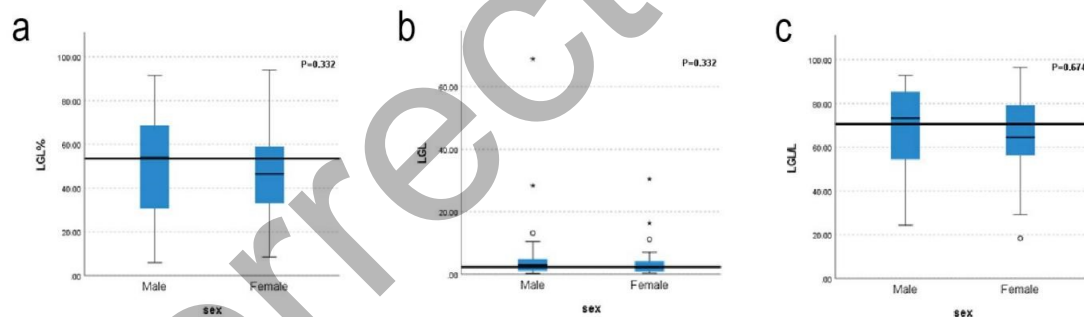


Figure 4. Comparison of LGL percentage (a), absolute count (b), and proportion among lymphocytes (c) between males and females in LGLL patients.

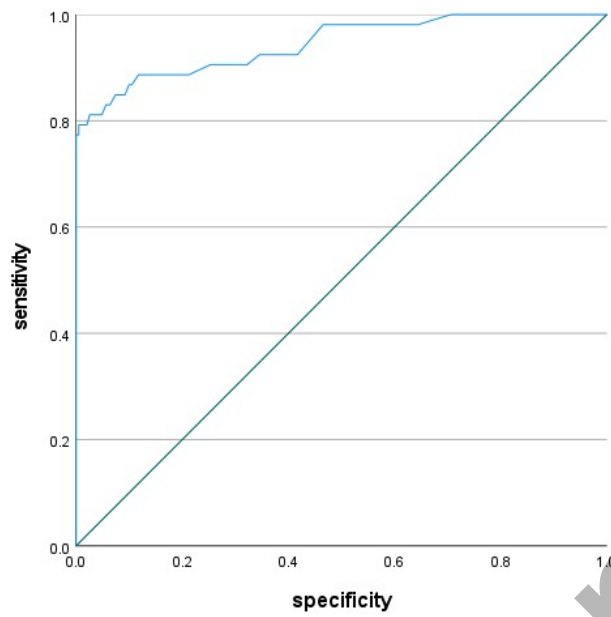


Figure 5. ROC curve for distinguishing healthy donors from LGLL patients based on LGL percentage. The area under the curve (AUC) was 0.945.

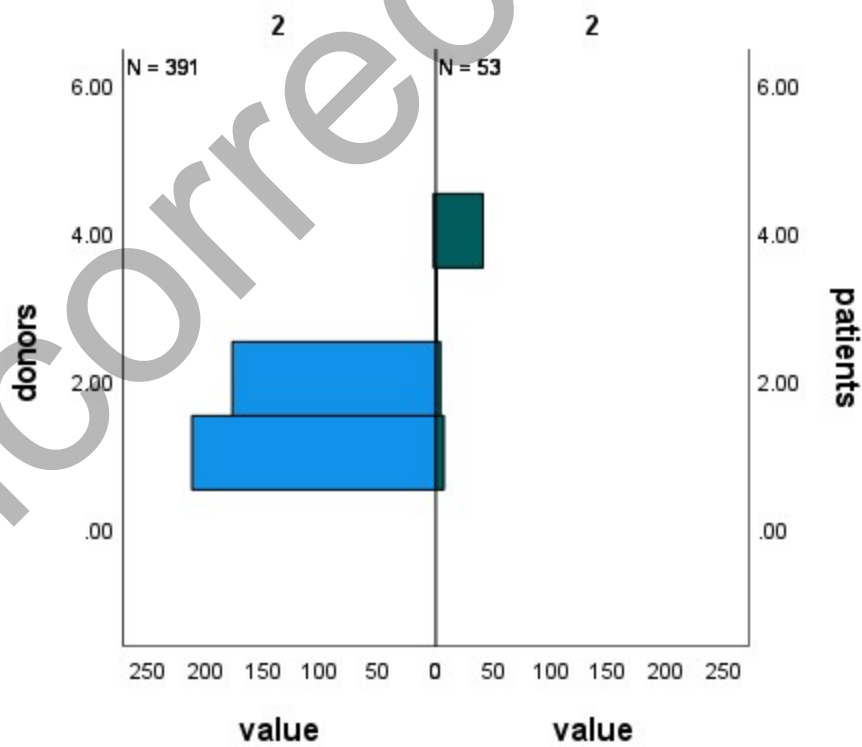


Figure 6. Distribution of healthy donors and LGLL patients based on absolute LGL count and percentage thresholds.

Table 1. Comparison of baseline characteristics and LGL-related parameters between healthy donors

	Donor (n=391)	Patients (n=53)	P-value
Age(y.o.), median(range)	34(8-62)	56(23-75)	<0.001
Sex, male/female	293/98	28/25	<0.001
LGL(%), median(range)	8(1-26.5)	53.5(6-94)	<0.001
LGL counts($\times 10^9/L$), median(range)	0.4635(0.07-1.9)	2.2964(0.24-68.84)	<0.001
LGL/L(%), median (range)	25(3.53-61.73)	70.66(18.4-96.41)	<0.001

and LGLL patients.

Table 2. Results of logistic regression analysis for distinguishing healthy donors from LGLL patients.

	B value	Wald value	Exp(B)	Exp(B) 95%CI		P-value
				Lower bound	Upper bound	
LGL%	0.174	9.376	1.190	1.064	1.330	0.002
LGL	-0.153	3.325	0.858	0.728	1.012	0.068
LGL/L	0.048	1.631	1.049	0.975	1.129	0.202

Table 3. Distribution of donors and LGLL patients using 24% as the cutoff value for LGL percentage.

	LGL%		P-value
	$\geq 24\%$	$< 24\%$	
Donors	2	389	<0.001
Patients	42	11	