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Efficient assessment of peripheral blood lymphocytosis in adults: developing new thresholds for blood smear review by pathologists

Abstract

Background: Peripheral smear review is a critical, but labor intensive adjunct for evaluation of lymphocytosis. Standard practice based on consensus guidelines is to review cases with absolute lymphocyte count (ALC) >5×10^9/L. We hypothesize that identifying cases for review by applying appropriately adjusted ALC and age discriminators will decrease laboratory workload without compromising patient care.
Methods: 1170 complete blood counts with ALCs >5×10^9/L analyzed in the core laboratory during a 2-year period were included. Patients were categorized into diagnostic groups based on follow-up criteria. A total of 402 patients with new onset lymphocytosis who met criteria for reactive lymphocytosis (82%) or lymphoproliferative disorder (18%) were used to establish optimal ALC and age thresholds from receiver operating characteristic (ROC) curve analysis.
Results: ALC as a discriminator for neoplastic lymphocytosis had an ROC area under the curve (AUC) of 0.732. Selecting cases with ALC >10×10^9/L enriched the proportion of neoplastic cases in the review pool (90% specificity); however, many cases with ALC below this threshold were also neoplastic (52% sensitivity). For cases with ALC between 5 and 10×10^9/L, age as a discriminator had an ROC AUC of 0.886. Selecting patients >50 years old in this group for review captured the neoplastic cases while excluding the reactive cases (93% sensitivity, 62% specificity). When applied to a validation cohort, the predictive performance of the thresholds was maintained while reducing smears reviewed by 50%.
Conclusions: We show that modifying the standard 5×10^9/L ALC smear review threshold through retrospective analysis of institutional data can reduce laboratory workload without compromising quality.

Keywords: algorithm; decision limit; lymphocytosis; lymphoid leukemia; peripheral smear; screening.

DOI 10.1515/cclm-2014-0320
Received March 24, 2014; accepted May 28, 2014

Introduction

The speed and accuracy of automated hematology analyzers have revolutionized workflows in the clinical hematology laboratory. However, when abnormalities are detected, manual microscopic review of the peripheral smear is necessary to determine the next course of action. In the setting of lymphocytosis, the critical judgment is whether the lymphocytosis represents a benign reactive condition or a neoplastic lymphoproliferative disorder that requires additional flow cytometric evaluation. This decision frequently falls to the pathologist, who often has multiple competing responsibilities and whose involvement can significantly affect laboratory efficiency and productivity.

There are currently very few guidelines regarding how the clinical laboratory should deal with lymphocytosis. The International Consensus Group for Hematology Review recommends smear reviews for all first time lymphocytosis cases where absolute lymphocyte count (ALC) is >5×10^9/L in adults [1]. In a follow-up study, this criteria was implemented in approximately half of the laboratories surveyed with the other half implementing more conservative criteria that resulted in even greater numbers of smears requiring review [2]. To our knowledge, the only study presenting data driven criteria for smear review was published by Andrews et al. where 71 lymphocytosis cases that were referred for flow cytometry were analyzed and age-based ALC criteria were developed [3, 4].

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We hypothesized that establishing criteria for smear review based on retrospective analysis of lymphocytosis cases at our institution would decrease the number of smears requiring review without compromising patient care. By including all cases of lymphocytosis in a retrospective cohort design we hoped to avoid the selection bias of including only cases that were analyzed by flow cytometry, thereby increasing the applicability of the findings to the hematology laboratory. The analysis presented in the paper is intended to serve as a model for hematology laboratories seeking to increase efficiency by establishing workflows based on a rigorous data driven approach.

Materials and methods

Case selection and clinical information

This study was approved by the Health Sciences Institutional Review Board of the University of Wisconsin-Madison. The cases included in this study represent a cross section of patients who had complete blood counts (CBCs) performed at the core hematology laboratory of University of Wisconsin Hospital, a 566-bed teaching hospital with 83 intensive care beds, 113 outpatient clinics, and a National Cancer Institute designated comprehensive cancer center that treats approximately 20,000 cancer patients annually. During the time intervals included in this study, the core hematology laboratory operated two Sysmex XE-2100 automated hematology analyzers (Sysmex America Inc., Lincolnshire, IL, USA). Instrument flags prompting technician smear review and laboratory developed criteria prompting pathologist smear review are listed in Table 1.

Table 1 Institutional pathologist smear review criteria and automated hematology analyzer instrument flags prompting technician smear review.

Pathologist smear review criteria	Instrument flags (Sysmex XE-2100)
– Blasts present[a]	– Blasts
– Lymphocytosis >5.0×10^9/L	– WBC abnormal scattergram
– Basophilia >0.5×10^9/L	– Left shift
– Cytopenias (ANC <1.0×10^9/L and PLT <75×10^9/L)	– Immature granulocytes
	– Atypical lymphocytes
– Abnormal granulocyte morphology	– Nucleated RBCs
	– RBC abnormal distribution
– Abnormal lymphocytes or mononuclear cells	– RBC lyse resistance
	– Reticulocyte abnormal scattergram
– Microorganisms present	
– RBC fragments >10/hpf	– Platelet clumps
	– Platelet abnormal distribution

[a]Excluded if blasts reported within the last 30 days. ANC, absolute neutrophil count; hpf, high power field; PLT, platelets; RBC, red blood cell.

For the primary cohort, the laboratory information system at the University of Wisconsin Hospital was queried for all CBCs performed between 1 January 2008 and 31 December 2009 with an automated differential showing an ALC >5×10^9/L. CBCs were sorted by discrete medical record numbers and each corresponding patient's electronic medical record was reviewed. Patients <18 years old were excluded. Pertinent clinical and laboratory data, such as age, clinical presentation prompting the CBC, any significant concurrent laboratory findings, previous diagnosis of a hematologic disorder, all other ALCs on record, any smear review comments, flow cytometry findings if performed, or any follow-up clinical information were recorded. Each patient with lymphocytosis was then classified into an outcome-based diagnostic group from criteria defined in Table 2.

A validation cohort of consecutive patients with ALC >5×10^9/L was subsequently assembled utilizing the same search and selection criteria at the same institution for the 6-month period between 1 July 2012 and 31 December 2012.

Data analysis

Optimal absolute lymphocyte count and age-based thresholds for smear review were established by analyzing receiver operator characteristic (ROC) curves and the resulting sensitivity, specificity, and Youden index (J) of cases categorized as benign or as a lymphoproliferative disorder with the statistical software package MedCalc version 12.4.0 (MedCalc Software, Ostend, Belgium). Standard descriptive statistics were calculated with Microsoft Excel 2013 (Microsoft, Redmond, WA, USA).

Results

Study populations

For the primary cohort, a total of 1170 complete blood counts with ALC >5×10^9/L were identified out of approximately 194,000 complete blood counts with differentials performed at the University of Wisconsin Hospital laboratory during the 2-year period between 1 January 2008 and 31 December 2009. Of these, 356 (30%) were serial blood counts performed on the same patient within 24-h intervals (Figure 1). These cases were identified by standard laboratory Δ check parameters and excluded from routine pathologist smear review. Another 180 cases (15%) had lymphocytosis with an attributed cause from a previous evaluation (Figure 1). None of these cases required any additional diagnostic or clinical intervention based on results of the pathologist review. The vast majority of these cases (63%) were chronic lymphocytic leukemia (CLL). In total 16% were non-Hodgkin lymphomas comprised of diffuse large B-cell lymphoma (5), follicular lymphoma (4), B-cell lymphoma not otherwise specified (4), marginal zone lymphoma (2), hairy cell leukemia (2), lymphoplasmacytic

Table 2 Classification criteria for lymphocytosis cases.

Classification	Criteria
Benign	
Resolved on follow-up	{ ALC $<5\times10^9$/L at or beyond 2 months of initial flag or ALC $<5\times10^9$/L on two or more consecutive samples within 2 months of initial flag and No ALC $\geq5\times10^9$/L at or beyond 2 months of initial flag
Clinically reactive	Positive heterophile antibodies indicating acute EBV infection Hematopoietic growth factors within 2 weeks
Negative by flow cytometry	No evidence of clonal lymphoid population by flow cytometry
Neoplastic	
Lymphoproliferative neoplasm	Flow cytometry demonstrates: New diagnosis of lymphoproliferative disorder or Relapse/leukemic transformation of previously known lymphoproliferative disorder
Non-lymphoproliferative neoplasm	Flow cytometry demonstrates a non-lymphoid hematologic malignancy
Unresolved	
Persistent	Any ALC $\geq5\times10^9$/L at or beyond 2 months in the absence of two or more consecutive ALC $<5\times10^9$/L (see 'Resolved' criteria) at any time
Lost to follow-up	Not enough data to classify lymphocytosis under 'Resolved' or 'Persisent' categories; e.g., No samples beyond 2 months of initial flag Only a single sample with ALC $<5\times10^9$/L within 2 months of initial flag

lymphoma (1), and large granular lymphocytic leukemia (1). Interestingly, 10% of the cases were patients undergoing treatment for acute leukemia, 14 acute myeloid leukemia and three acute lymphoblastic leukemia.

Excluding those CBCs identified by Δ check and those patients with a prior history of lymphocytosis, the primary cohort of 'new onset lymphocytosis' cases consisted of 634 cases from a 2-year interval. For the 6-month interval used to establish the validation cohort, a set of 175 cases of 'new onset lymphocytosis' was similarly assembled. The age distribution of both cohorts was similar, with bimodal peaks of patients between 18 and 23 and 45 and 64 years, and there was no significant difference of the mean age between the cohorts (p=0.13, t-test) (Figure 2A). The frequency distribution of cases sorted by ALC was also similar between the cohorts, with a decreasing frequency of high ALC cases (Figure 2B).

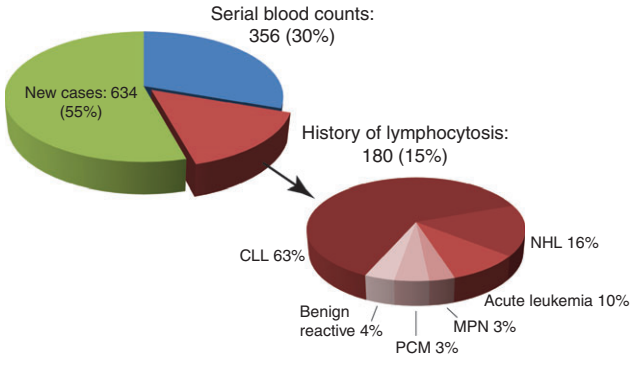


Figure 1 Characteristics of the primary cohort.
Pie chart (upper left) demonstrating the number and composition of cases with absolute lymphocyte count $>5\times10^9$/L for the period between 1 January 2008 and 31 December 2009 at University of Wisconsin Hospital core laboratory. Pie chart (lower right) showing the composition of 180 cases with a known prior history of lymphocytosis. CLL, chronic lymphocytic leukemia; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; PCM, plasma cell myeloma.

Diagnostic outcomes of new onset lymphocytosis cases

In the primary cohort, the prevalence of lymphoproliferative disorders remains between 5% and 15% until the ALC is $>9.5\times10^9$/L, where prevalence begins to increase to >35% (Figure 3).

Of the cases that were classified as benign, the greatest proportion were those that met the criteria for 'resolved' on a follow-up CBC (Figure 3). These cases had 1) either a follow-up ALC $<5\times10^9$/L at or beyond 2 months from the initial flag or at least two consecutive cell counts with ALC $<5\times10^9$/L within 2 months from the initial flag; and 2) no ALC $\geq5\times10^9$/L at or beyond 2 months from the initial flag (Table 2). A smaller fraction of the benign cases were classified as 'clinically reactive', defined as patients who

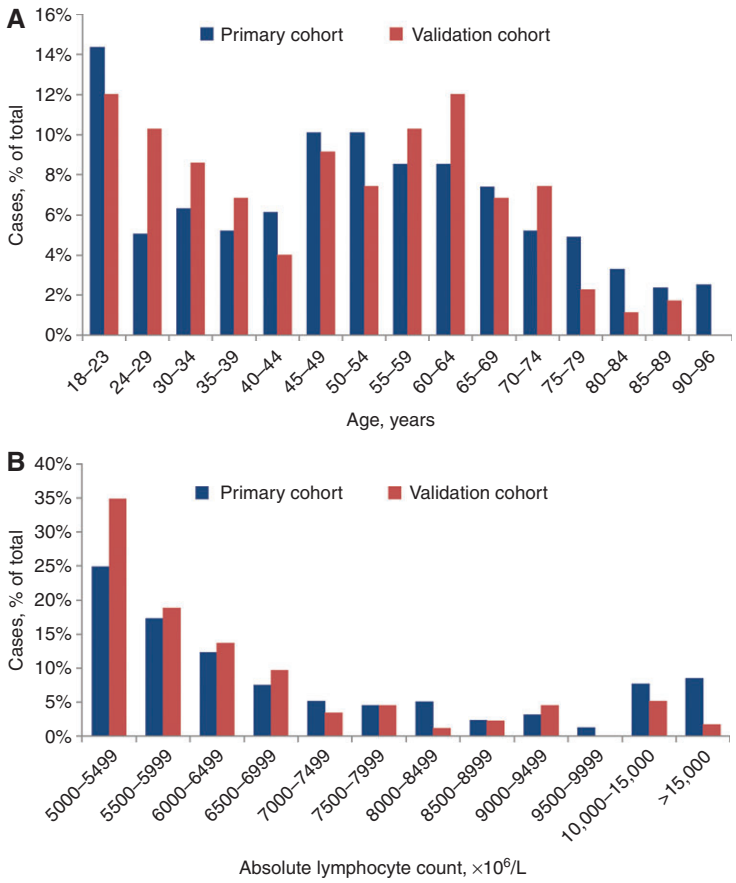
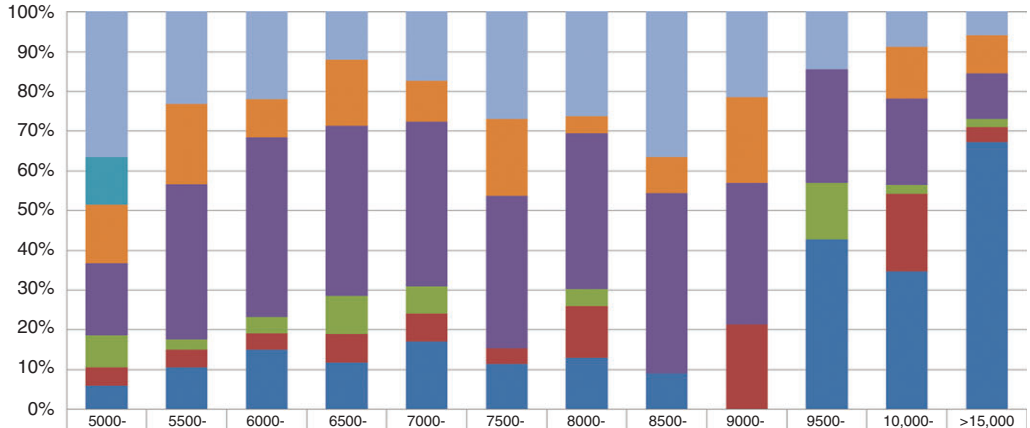


Figure 2 Distribution of new onset lymphocytosis cases by age and absolute lymphocyte count in the primary and validation cohorts.
(A) Case distribution by age. Note the intervals on the far right side and far left columns encompass wider ranges than those between them.
(B) Case distribution by absolute lymphocyte count. Note the two far right columns encompass wider ranges than those to their left.



	5000-5499	5500-5999	6000-6499	6500-6999	7000-7499	7500-7999	8000-8499	8500-8999	9000-9499	9500-9999	10,000-15,000	>15,000
Unresolved: Lost to follow up	72	26	16	5	5	7	6	4	3	1	4	3
Unresolved: persistent lymphocytosis	24	0	0	0	0	0	0	0	0	0	0	0
Benign: Clinically reactive	29	23	7	7	3	5	1	1	3	0	6	5
Benign: Resolved on follow up cell count	36	44	33	18	12	10	9	5	5	2	10	6
Benign: Negative by flow cytometry	16	3	3	4	2	0	1	0	0	1	1	1
Neoplastic: Non-lymphoma by flow cytometry	9	5	3	3	2	1	3	0	3	0	9	2
Neoplastic: Lymphoma by flow cytometry	12	12	11	5	5	3	3	1	0	3	16	35

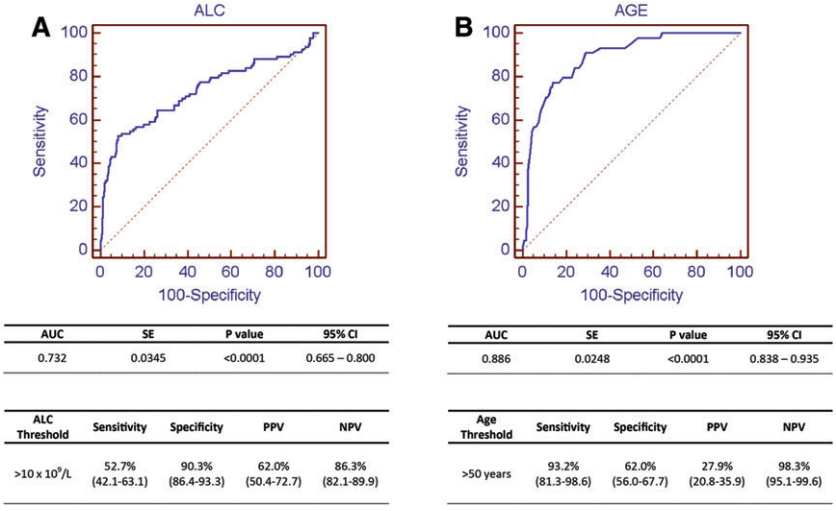
Figure 3 Diagnostic outcomes-based classification of cases sorted by absolute lymphocyte count in the primary cohort.
Each histogram bar represents a defined range of absolute lymphocyte counts (top row of table, $\times 10^6$/L) and is comprised of varying proportions of cases classified by diagnostic outcomes (y-axis percentages) with the absolute numbers of cases shown in the table.

had a clinically documented viral illness with or without serologic confirmation, and those patients who recently received hematopoietic growth factors. Finally, the smallest fraction of cases classified as benign were those found to be negative for lymphoproliferative disorder by flow cytometric immunophenotyping. Unresolved cases fell under two categories, 'lost to follow-up' and 'persistent'. Cases that were 'lost to follow-up' accounted for 6%–37% of cases in each ALC range (Figure 3) and were mostly instances where neither flow cytometry nor follow-up CBC were performed. 'Persistent' cases were those that had at least one follow-up CBC after an interval >2 months that never showed an ALC $<5\times10^9$/L and were never given a definitive diagnosis. Interestingly, 'persistent' cases were only identified in the cohort with ALC between 5.0 and 5.499×10^9/L and comprised 10% of this group.

The 'neoplastic non-lymphoproliferative disorder' cases (Figure 3) were those analyzed by flow cytometry and found to have a neoplastic diagnosis other than a lymphoproliferative disorder. These cases were predominantly newly diagnosed cases of acute myeloid leukemia (29), myeloproliferative neoplasms (9), acute lymphoblastic leukemia (1), and plasma cell leukemia (1). As these cases were additionally flagged for pathologist smear review by criteria other than lymphocytosis, including presence of blasts, immature myeloid cells, and atypical lymphocytes, they were excluded from further analysis.

Establishing a lymphocytosis threshold for smear review

After excluding the 232 cases that were classified as 'lost to follow-up', 'persistent', or 'neoplastic non-lymphoproliferative disorder' (Figure 3), 402 remaining new onset lymphocytosis cases that met criteria for reactive lymphocytosis (76.8%) or lymphoproliferative disorder (23.2%) were included in the ROC curve analysis of ALC as a discriminator of lymphoproliferative disorders. The ROC area under the curve (AUC) was 0.732, indicating ALC cannot completely separate the reactive and lymphoproliferative populations, but has potential as a screening discriminator (Figure 4A). At the optimal ALC cut-off of 10×10^9/L determined by the Youden index, the positive predictive value is 62.0% and the specificity is 90.3%. Accordingly, the pool of cases with ALC $>10\times10^9$/L is enriched with lymphoproliferative disorders and warrants pathologist review. The negative predictive value and sensitivity at this threshold are 86.1% and 52.1%, respectively, reflecting the AUC discussed earlier. As such, the pool of cases with ALC $<10\times10^9$/L also includes many lymphoproliferative



AUC	SE	P value	95% CI
0.732	0.0345	<0.0001	0.665 – 0.800

ALC Threshold	Sensitivity	Specificity	PPV	NPV
>10 x 10^9/L	52.7% (42.1-63.1)	90.3% (86.4-93.3)	62.0% (50.4-72.7)	86.3% (82.1-89.9)

AUC	SE	P value	95% CI
0.886	0.0248	<0.0001	0.838 – 0.935

Age Threshold	Sensitivity	Specificity	PPV	NPV
>50 years	93.2% (81.3-98.6)	62.0% (56.0-67.7)	27.9% (20.8-35.9)	98.3% (95.1-99.6)

Figure 4 Receiver operating characteristic (ROC) curves for absolute lymphocyte count (ALC) and age as discriminators for lymphoproliferative disorders.
(A) A total of 402 patient's ALCs and diagnoses (benign vs. lymphoproliferative disorder) were assessed to determine the sensitivity and specificity of various ALC thresholds. The area under the curve (AUC) represents the overall ability of ALC to predict for lymphoproliferative disorders in this population where disease prevalence was 23.1%. Values in brackets represent 95% confidence interval. (B) The ages of 322 patients with ALC $<10\times10^9$/L were used to generate the ROC curve assessing that ability of age to predict for lymphoproliferative disorders in this population where disease prevalence was 13.4%. CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SE, standard error.

disorders and further stratification is necessary to determine which of these cases warrant pathologist smear review.

Establishing an age threshold for smear review in cases with ALC between 5 and 10×10^9/L

Of the 402 cases included in the ALC ROC curve analysis, 323 had an ALC $<10\times10^9$/L. These cases were included in the ROC curve analysis of age as a discriminator of lymphoproliferative disorders. Disease prevalence in this population was 13.6% and the ROC area under the curve was 0.886 (Figure 4B). At an age cut-off of 50 years, the sensitivity and negative predictive value were 93.2% and 98.3%, respectively. Accordingly, the pool of cases comprised of patients <50 years old with ALC between 5 and 10×10^9/L are unlikely to harbor lymphoproliferative disorders.

Validation of ALC and age thresholds

The ALC and age thresholds established from the primary cohort were validated on 111 cases with definitive outcomes (cases 'lost to follow-up', 'persistent', or 'neoplastic non-lymphoproliferative disorder' were excluded) from the validation cohort of 175 'new onset lymphocytosis' cases. The predictive values generated when the 10×10^9/L ALC threshold was applied to the validation cohort were superior to those used to establish the threshold, with a specificity of 97.9% for the validation cohort compared to 90.3% in the primary cohort (Table 3). Likewise, application of the 50-year-old age threshold to the remaining cases with ALC between 5 and 10×10^9/L showed 100% sensitivity and negative predictive value in the validation cohort compared to 93.2% sensitivity and 98.3% negative predictive value in the primary cohort.

Table 4 Truth table for pathologist smear review.

	Final classification		
	Lymphoproliferative disorder	Benign reactive lymphocytosis	Total
Pathologist interpretation			
Suspicious, recommend flow cytometry	106 (TP)	31 (FP)	137
Benign reactive lymphocytosis	4 (FN)	51 (TN)	55
Total	110	82	192

Performance of pathologist smear review in discriminating between benign lymphocytosis and lymphoproliferative disorders

Of the 402 cases of new onset lymphocytosis with a defined outcome, 192 had an associated pathologist comment in the electronic record that committed to either a benign reactive lymphocytosis or was suspicious for a lymphoproliferative disorder with a recommendation to perform flow cytometry (Table 4). All unresolved cases were excluded from this analysis. Benign reactive cases were either confirmed by flow cytometry, met 'resolved' criteria on follow-up, or were documented to be 'clinically reactive'. Lymphoproliferative disorders were identified by flow cytometric immunophenotyping characteristics and the disease prevalence in this population was 57.3%. Of 137 cases deemed suspicious for neoplasia by a pathologist, 106 (77.4%) were found to be lymphoproliferative disorders by flow cytometry. Of 55 cases favored to be reactive by a pathologist, 46 were followed clinically and met 'resolved' criteria on follow-up, while nine were assessed by flow cytometry despite their favored benign disposition. Interestingly, flow cytometry revealed four of the nine to be lymphoproliferative disorders (Table 4). It could not be determined if, for these particular cases, there were other factors that prompted flow

Table 3 Performance of established thresholds on 111 new onset lymphocytosis cases with definitive outcomes in the validation cohort.

Threshold	Sensitivity	Specificity	PPV	NPV
ALC $>10\times10^9$/L	50.0% (23.0–77.0)	97.9% (92.7–99.7)	77.8% (40.0–97.2)	93.1% (86.3–97.2)
Age >50 years (where ALC $\leq10\times10^9$/L)	100% (59.0–100)	60.0% (49.4–69.9)	15.6% (6.5–29.5)	100% (93.7–100)

NPV, negative predictive value; PPV, positive predictive value. Values in brackets represent 95% confidence interval.

cytometric evaluation that would in turn also increase the probability of a neoplastic diagnosis. From the truth table (Table 4), the sensitivity and specificity of pathologist smear review in detecting lymphoproliferative disorders was 96.3% and 62.1%, respectively. These findings are likely subject to verification bias though, as only nine of the 55 cases favored to be reactive by a pathologist underwent flow cytometric analysis.

Discussion

Whether a patient with absolute lymphocytosis requires further laboratory evaluation or not is frequently determined by a pathologist's review of the peripheral smear. In a vast majority of cases, lymphocytosis is secondary to benign reactive conditions and recommending a follow-up CBC for resolution is the best course of action [5]. Pathologist review of smears with a high probability of being benign reactive lymphocytosis is an inefficient use of resources. Accordingly, optimizing thresholds for smear review can shrink the pool of cases requiring review by reducing the number of reactive cases in the pool and facilitate re-allocation of resources.

Proposed screening algorithm for adults with new onset lymphocytosis

We propose a screening algorithm depicted in Figure 5A for adults with new onset lymphocytosis. Pathologist smear review is recommended for all cases where ALC is $>10\times10^9$/L. These recommendations stem from ROC analysis of ALC as a primary discriminator for lymphoproliferative disorders. The threshold ALC of 10×10^9/L has a 90.3% specificity for lymphoproliferative disorders (Figure 4A), however, the group of cases with ALC $<10\times10^9$/L also harbors a large number of lymphoproliferative disorders. To address this, age is utilized as a secondary discriminator to screen for lymphoproliferative disorders where ALCs are between 5 and 10×10^9/L. We show that age is an effective discriminator of disease in this population with an ROC curve AUC of 0.886 (Figure 4B). The age threshold of 50 years has a negative predictive value of 98.3% and sensitivity of 93.2%. When applied to the validation cohort, the threshold ALC of 10×10^9/L has 97.9% specificity for lymphoproliferative disorders and the age threshold of 50 years has a negative predictive value and sensitivity of 100% (Table 3).

Applying the algorithm proposed in Figure 5A to the primary cohort would have excluded 196 of 634 new lymphocytosis cases (30.9%) from pathologist review. Among the excluded cases would have been three cases of lymphoproliferative disorders, two patients with large granular lymphocytic leukemia and one patient with hairy cell leukemia (Figure 5B). All three patients are still being followed expectantly and none have required treatment to date. Applying this algorithm to the validation cohort of 175 new lymphocytosis cases would have excluded 87 cases from pathologist review, decreasing the proportion of new lymphocytosis cases requiring pathologist review by 49.7% with no lymphoproliferative disorder

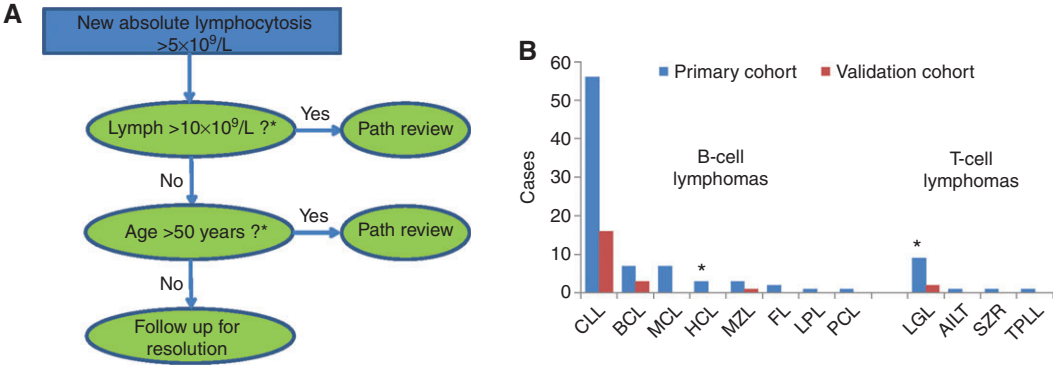


Figure 5 Proposed screening algorithm for new onset lymphocytosis cases.
(A) Flow chart depiction of proposed screening algorithm. * Values are based on institutional data and may not be broadly applicable. (B) Column graph showing the case distribution of 92 lymphoproliferative disorders in the set of 402 cases with definitive diagnoses in the primary cohort (blue) and 22 lymphoproliferative disorders in the set of 111 cases with definitive diagnoses in the validation cohort (red). * Asterisk denotes columns containing cases that would have escaped pathology smear review under the proposed screening criteria and include one case of hairy cell leukemia and two cases of large granular lymphocytic leukemia, all from the primary cohort. AITL, angioimmunoblastic T-cell lymphoma; BCL, B-cell lymphoma unspecified; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; HCL, hairy cell leukemia; LGL, large granular lymphocytic leukemia; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PCL, plasma cell leukemia; SZR, Sezary syndrome; TPL, T-cell prolymphocytic leukemia.

cases excluded (Figure 5B). The higher efficiency gain in the validation cohort is largely due to a smaller proportion of patients with ALC $>10\times10^9$/L and a slightly greater proportion of younger patients in the validation cohort (Figure 2A and B).

We also assessed how effective pathologist smear review was in triaging cases for additional testing by flow cytometry. Our findings suggest that while pathologist smear review appears to have a high sensitivity (96.3%) for identifying lymphoproliferative disorders, this number may be inflated by verification bias as most cases deemed benign on smear review were not assessed by flow cytometry. The positive predictive value of smear review by a pathologist was 77.4%, supportive of the notion that non-neoplastic transient lymphocytosis, such as stress lymphocytosis, can morphologically mimic lymphoproliferative disorders [6, 7].

Limitations

This study can be used as a model to improve laboratory efficiency. As a single institution investigation, generalized application of the presented ALC and age thresholds is not recommended. These values are dependent upon disease prevalence, which may vary considerably between laboratories that serve different patient populations, e.g., cancer patients. It is also important to emphasize that of all patient populations, the pediatric population typically has the highest proportion of benign reactive lymphocytosis cases. Accordingly, we felt this population should be assessed independently and patients <18 years of age were excluded from this study. In contrast to previous studies that solely assessed cases evaluated by flow cytometry [3], a design that is subject to selection bias, this is a retrospective cohort study that captures a cross section of all lymphocytosis cases. However, in contrast to selection bias, this design is subject to verification bias. The majority of the cases that received the gold standard diagnostic test of flow cytometry were those that were deemed suspicious by a pathologist (Table 4). While some benign reactive lymphocytosis cases underwent flow cytometric assessment, the vast majority were classified as benign based on follow-up CBC criteria. This could lead to overestimation of the sensitivity of pathologist smear review and in turn, overestimate the sensitivity of the ALC and age thresholds that are presented.

Conclusions

To our knowledge, this is the first retrospective cohort study evaluating predictors of lymphoproliferative disorders in patients presenting with lymphocytosis. Our findings suggest pathologist smear review is relatively sensitive in detecting lymphoproliferative disorders, but because of the time, effort, and cost of a pathologist smear review, it is a practical necessity to minimize the number of cases requiring review without compromising patient safety. We show that this can be achieved by establishing data driven ALC and age thresholds for smear review. We present this as a rational laboratory approach to safely and efficiently address the issue of peripheral blood lymphocytosis in adults.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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