

ORIGINAL ARTICLE

Proposal of a Diagnostic Workflow for Peripheral Blood Smear Testing Based on Complete Blood Count Flag Analysis

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ABSTRACT

Background: Leukemia requires early detection, especially in acute forms, but standard tests such as bone marrow biopsy and molecular assays are often costly and unavailable in smaller hospitals. In these settings, complete blood count with peripheral blood smear examination provides a practical alternative. Analyzer-generated flags may suggest abnormal cells, yet false positives are common, and without a standardized protocol, smear review is often overlooked, leading to delayed diagnosis. This study aimed to develop and validate a stepwise peripheral blood smear protocol for small hospitals by analyzing blast-flagged complete blood count cases, correlating findings with diagnoses, and facilitating early leukemia detection and timely referral in resource-limited settings.

Methods: This retrospective study was conducted at a small hospital in South Korea. Three datasets were analyzed: 1) 60 patients diagnosed with leukemia (Jan 2020 - Dec 2024), 2) 633 CBC samples flagged with “Blast/Abn Lympho?” or “Left Shift” (Feb 2023 - Jan 2025), and 3) 43,450 CBC samples without any flagging or hematological abnormalities (control group). The flags were automated alerts indicating the presence of immature or abnormal white blood cells (WBCs), prompting PBS review. Descriptive statistics summarized demographic and hematological parameters, and group comparisons were performed using chi-squared and independent *t*-tests, with significance set at $p < 0.05$.

Results: Of the 633 flagged samples, 20 cases (3.2%) showed blast cells on PBS, 19 of which occurred in samples with elevated WBC counts. Several were confirmed as leukemia and referred early for treatment. Flagged cases showed significantly higher WBCs and lower hemoglobin levels than control cases ($p < 0.0001$), supporting the clinical relevance of analyzer flagging.

Conclusions: The proposed workflow facilitates the early detection of hematological malignancies using existing CBC flagging. Our study also underscores the pivotal role of clinical laboratory scientists in diagnostic decision-making, especially in resource-limited environments.

(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250936)

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KEYWORDS

blast cells, blood smear, diagnostic techniques, hematologic workflow, leukemia

INTRODUCTION

Leukemia is a hematological malignancy characterized by the uncontrolled proliferation of immature hematopoietic cells (blasts) in the bone marrow and peripheral blood. The accumulation of blasts disrupts normal he-

Manuscript accepted September 24, 2025

matopoiesis, resulting in cytopenia and diverse clinical symptoms [1-4].

Leukemia is classified by cell lineage (myeloid or lymphoid) and disease progression (acute or chronic). Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are aggressive and rapidly progressive, whereas chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) progress more slowly [4]. Myeloid leukemia is more common in adults, whereas lymphoid leukemia is predominant in children [5]. Early diagnosis is crucial, especially for acute forms, owing to rapid progression and poor prognosis.

Although bone marrow biopsy and molecular tests are the gold standard for diagnosing leukemia, they are often costly and inaccessible in many healthcare settings [6]. In contrast, peripheral blood smear (PBS) remains a vital, low-cost, and widely available method for detecting morphological abnormalities, making it especially valuable in small hospitals lacking advanced diagnostics [7-9].

Complete blood count (CBC) is a key test for detecting hematological disorders [7,10,11]. Automated analyzers generate flags, such as “blast” or “abnormal lymphocyte”, to indicate potential malignancy [11-14]. However, these flags may yield false positives, particularly in cases with low white blood cell (WBC) or minimal blast presence [11,15]. Abnormal WBC levels may also distort differential counts, such as absolute neutrophil count (ANC) [16]. Although scattergrams generated by analyzers such as the Sysmex XN series provide valuable visual cues [10,17,18], PBS remains essential for morphological confirmation. PBS remains an essential diagnostic tool for the early detection of hematological disorders, including leukemia [7,20,23,24]. Despite advances in automated hematology analyzers, identifying pathological cells such as blasts and atypical lymphocytes remains a challenge. This limitation is particularly critical in small- and medium-sized hospitals, where access to advanced diagnostics such as flow cytometry, immunophenotyping, and genetic testing is restricted. In such settings, PBS serves as a crucial confirmatory method [8,19].

In small- and medium-sized hospitals, PBS testing is often skipped even after CBC, unless there is strong clinical suspicion [19], owing to limited staff and time constraints. In settings without on-site laboratory physicians, PBS interpretation and referral are often delayed, compromising timely diagnosis [13]. Although the diagnostic value of CBC flagging is well-established, the absence of a standardized follow-up protocol hampers early leukemia detection. Moreover, despite the fact that prior studies have discussed the importance of flagging [10,23], few have suggested practical workflows.

The aim of this study was to address this knowledge gap by proposing and validating a stepwise PBS protocol for resource-limited laboratories. By analyzing CBC-flagged cases and correlating them with PBS findings, we developed a stepwise algorithm to assist technologists in early leukemia detection and timely referral

in resource-limited settings. We hope to propose a stepwise PBS protocol for small- and medium-sized hospitals based on blast-flagged CBC cases and, by correlating PBS findings with diagnoses, demonstrate that early leukemia detection and timely referral are achievable even in resource-limited settings.

MATERIALS AND METHODS

Participants and Data Source

Three patient groups were evaluated in this retrospective study. Group 1 included 60 patients with confirmed leukemia diagnoses between January 2020 and December 2024, with available data on leukemia subtype, CBC parameters (WBC, hemoglobin [Hb], platelet count), age, and gender. The final diagnosis of leukemia was confirmed through review of clinical data, including bone marrow aspiration, flow cytometry, or hematopathologist reports, depending on availability. Group 2 comprised 633 CBC samples flagged with “Blast/Abn Lympho?” or “Left Shift” between February 2023 and January 2025; among these, cases with available PBS results were further analyzed for smear morphology and final leukemia diagnosis. The control group consisted of 43,450 CBC samples without any hematological abnormalities or flagging alerts. These served as a comparative baseline for evaluating CBC parameter profiles and determining the diagnostic specificity of automated flagging.

Inclusion and exclusion criteria: CBC tests were performed on patients who visited or were admitted to the hospital during the study period. For patients with multiple CBC tests, only one result per patient was included, selecting the sample with the highest WBC count to minimize duplication.

Instrumentation and analysis

CBC analysis was conducted using the Sysmex XN-2000 (Sysmex Corporation, Kobe, Japan). Two scattergram channels were used to assess abnormal cells [10]. The WDF (white blood cell differential) channel detects neutrophils, lymphocytes, monocytes, eosinophils, immature granulocytes (IGs), atypical lymphocytes, and blast flags [5], whereas the WNR (white cell nucleated) channel quantifies total WBCs, basophils, and nucleated red blood cells (NRBCs).

When a flag was triggered, a technologist prepared a PBS slide, stained it using Wright-Giemsa stain (YD Diagnostics Corp., Yongin, Korea), and examined it under $\times 1,000$ magnification. Blasts were identified by prominent nucleoli, immature chromatin, scant cytoplasm, or Auer rods [20]. Abnormal findings were reviewed by an on-site clinical pathologist or referred remotely if no specialist was available.

Statistical analysis

Statistical analyses were conducted using Microsoft Excel (2007) and Jamovi (v2.3.21; Jamovi, Sydney, Aus-

tralia). Descriptive statistics (mean, frequency, percentage) summarize gender, age, and CBC parameters (WBC, Hb, platelet count). Data were categorized into relevant groups (Tables 1 - 4), and intergroup differences were analyzed using chi-squared (χ^2) tests for categorical variables. For comparison between flagged samples (Group 2) and non-flagged controls, independent *t*-tests were performed to assess differences in CBC parameters and chi-squared tests were used for gender and age group distributions, with statistical significance set at $p < 0.05$.

RESULTS

Distribution of leukemia subtypes by gender and age

From January 2020 to December 2024, 60 consecutive patients (27 men and 33 women) diagnosed with leukemia were included in the study without further selection. Among these, AML was the most common subtype in both genders, whereas no cases of ALL were observed. Subtype distribution did not differ significantly by gender ($p = 0.680$) or age ($p = 0.890$). AML predominated over CML and CLL across all age groups (Table 1).

Distribution of leukemia subtypes according to CBC results

WBC count

When grouped by WBC count, most patients (88%) showed leukocytosis ($> 10 \times 10^3/\mu\text{L}$), and over one-third (37%) had extreme leukocytosis ($\geq 100 \times 10^3/\mu\text{L}$). AML cases were distributed across all WBC ranges, including three patients with leukopenia ($< 4 \times 10^3/\mu\text{L}$) and 14 with extreme leukocytosis. CML cases were observed only in patients with elevated WBC counts ($> 10 \times 10^3/\mu\text{L}$), and CLL was less common overall. Despite these distribution patterns, no statistically significant differences in WBC count ranges were observed among subtypes ($\chi^2 = 5.17$, $p = 0.522$) (Table 2). The WBC cutoff values used in this study ($> 10 \times 10^3/\mu\text{L}$, $< 4 \times 10^3/\mu\text{L}$, and $\geq 100 \times 10^3/\mu\text{L}$) were derived from internationally recognized hematology reference ranges and thresholds commonly applied in previous leukemia research [7,10,23].

Hb level

The mean hemoglobin level was 8.2 g/dL. For descriptive analysis, Hb levels were categorized as < 7 g/dL, 7 - 10 g/dL, and > 10 g/dL. Approximately 30% of patients were in the < 7 g/dL category, in which AML predominated (17/18 cases). This avoids attributing these study-specific bins to WHO severity criteria, which vary by age, gender, and physiological group. CLL occurred more frequently in the higher Hb range (> 10 g/dL). Although the difference in anemia severity among leukemia subtypes did not reach statistical significance ($\chi^2 = 9.00$, $p = 0.061$), the trend suggests a possible association (Table 3).

Platelet count

When patients were categorized by platelet count, AML predominated among patients with thrombocytopenia, whereas higher platelet counts correlated with more CML and CLL cases. A significant association was observed between platelet count and leukemia subtype ($p = 0.037$), representing an observed trend consistent with previous reports that platelet count patterns differ among leukemia subtypes (Table 4) [2]. The platelet count categories ($< 140 \times 10^3/\mu\text{L}$, $140 - 400 \times 10^3/\mu\text{L}$, $> 400 \times 10^3/\mu\text{L}$) were based on standard clinical reference ranges and cutoffs used in prior hematological studies [2,7,24].

Common note on absence of ALL cases

No acute lymphoblastic leukemia (ALL) cases were identified in our study. This absence likely reflects our institution's characteristics (a single small regional hospital with limited pediatric hematology-oncology services) combined with the retrospective, single-center study design and patient referral patterns; suspected ALL cases are typically transferred to tertiary centers before CBC/PBS testing is performed on site.

WBC flagging analysis

This study classified 633 flagged CBC samples (Feb 2023 - Jan 2025) by WBC range and showed blast cells in 20 cases (3.2%), 19 of which occurred in samples with elevated WBC counts. All nine cases with WBC $> 100 \times 10^3/\mu\text{L}$ were blast-positive, confirming that leukocytosis correlates with malignancy. One blast-positive case occurred in a sample with a normal WBC count, whereas the low-WBC case showed NRBC features, highlighting the limitations of automated detection and emphasizing the need for manual smear reviews in all flagged cases (Figure S1) [3].

CBC parameter comparison between flagged and control groups

CBC parameters were compared between the flagged and control groups to assess the diagnostic significance of automated flagging. The flagged group exhibited significantly higher WBC counts ($23.76 \pm 17.44 \times 10^3/\mu\text{L}$) than the control group ($6.43 \pm 1.69 \times 10^3/\mu\text{L}$; $p < 0.0001$). Hb levels were significantly lower in the flagged group (11.55 ± 2.68 g/dL) than in the control group (13.40 ± 2.02 g/dL; $p < 0.0001$). Platelet counts did not differ significantly between groups ($p = 0.110$) (Table 5). To assess the adequacy of sample size and detectability of group differences, effect sizes and statistical power were calculated for each CBC parameter. WBC and Hb showed large effect sizes (Cohen's $d = 6.47$ and -0.91 , respectively), with statistical power reaching 1.00. Although the platelet count difference yielded a small effect size ($d = 0.13$), the large sample size still provided a power of 0.92, indicating sufficient sensitivity to detect a true difference.

Table 1. Distribution of leukemia subtypes by patients' gender and age (n = 60).

Leukemia subtype	AML	ALL	CML	CLL	Total	χ ² (p-value)
No. of patients	44 (73.3%)	0 (0%)	12 (20%)	4 (6.7%)	60	
Gender						
Male	20	0	6	1	27	0.771 (0.680)
Female	24	0	6	3	33	
Age (years)						
< 50	9	0	4	1	14	1.130 (0.890)
50 - 70	15	0	4	1	20	
> 70	20	0	4	2	26	

Table 2. Distribution of leukemia subtypes by WBC count category (n = 60).

WBC count ($\times 10^3/\mu\text{L}$)	AML	ALL	CML	CLL	Total	χ^2 (p-value)
0 - 4	3	0	0	0	3	5.17 (0.522)
4 - 10	4	0	0	0	4	
10 - 100	23	0	5	3	31	
> 100	14	0	7	1	22	
Total	44	0	12	4	60	

Normal WBC range: $4.0 - 10.0 \times 10^3/\mu\text{L}$.

Table 3. Distribution of leukemia subtypes by hemoglobin level (n = 60).

Hemoglobin (g/dL)	AML	ALL	CML	CLL	Total	χ^2 (p-value)
< 7	17	0	1	0	18	9.00 (0.061)
7 - 10	17	0	7	1	25	
> 10	10	0	4	3	17	
Total	44	0	12	4	60	

Normal hemoglobin range: 13 - 17 g/dL for males, 12 - 16 g/dL for females.

Table 4. Distribution of leukemia subtypes by platelet count category (n = 60).

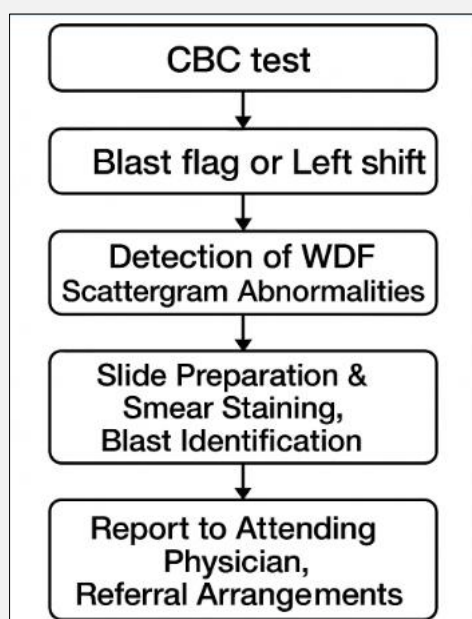
PLT count ($\times 10^3/\mu\text{L}$)	AML	ALL	CML	CLL	Total	χ^2 (p-value)
< 140	35	0	4	2	41	10.24 (0.037 *)
140 - 400	6	0	5	1	12	
> 400	3	0	3	1	7	
Total	44	0	12	4	60	

Normal platelet count range: $140 - 400 \times 10^3/\mu\text{L}$. * - $p < 0.05$.

Table 5. CBC parameters between flagged and control groups.

Parameter	Flagged group (n = 633)	Control group (n = 43,450)	p-value
WBC count ($\times 10^3/\mu\text{L}$)	23.76 $\pm$ 17.44	6.43 $\pm$ 1.69	< 0.0001 ***
Hemoglobin (g/dL)	11.55 $\pm$ 2.68	13.40 $\pm$ 2.02	< 0.0001 ***
PLT count ($\times 10^3/\mu\text{L}$)	250.32 $\pm$ 152.90	240.43 $\pm$ 71.51	0.110

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, WBC: white blood cell, Hb: hemoglobin, PLT: platelet count. *** - $p < 0.001$.

**Figure 1. Protocol for peripheral blood smear examination in a small hospital laboratory.**

Source: Created by the authors from original concept and data generated in this study.

Comparison of demographics between flagged and control groups

Comparison of the flag group (n = 633) and the control group (n = 43,450) in the CBC analysis revealed no significant difference in gender distribution ($\chi^2 = 1.43$, $p = 0.232$).

In contrast, age distribution differed significantly between the groups ($\chi^2 = 163.66$, $p < 0.0001$). The flag group demonstrated a higher proportion of patients aged ≥ 70 years (46.0% vs. 23.9%) and a lower proportion aged < 50 years (29.9% vs. 38.5%) compared with the control group (Table S1).

WDF scattergram

Figures S2 - S4 show representative WDF scattergrams from this study, including a normal case, an acute myeloid leukemia (AML) case, and a chronic myeloid leukemia (CML) case, illustrating distinct distribution patterns in each condition [5,18].

DISCUSSION

This study evaluated CBC cases with blast-related flags in a small hospital to assess the diagnostic value of PBS. WBC count remains a key marker for detecting hematological malignancies. The Sysmex XN-2000 generates flags for atypical patterns that trigger smear

review [16,19,21]. Automated flagging was helpful, particularly in samples with high WBC counts, but unreliable in blast-dominant or leukopenic cases, requiring manual confirmation [12,15,16]. Blasts also appeared in samples with normal WBC counts, showing the limitations of automation alone.

Among the 60 leukemia cases, platelet count category was significantly associated with leukemia subtype, and thrombocytopenia was most frequently observed in AML [2]. Higher WBC and lower Hb levels in flagged groups compared with controls reflected earlier findings that these abnormalities are common in malignancies [15,17,24]. These results support the use of CBC-derived parameters as triggers for PBS review, consistent with international guidelines [23].

Despite the utility of CBC flagging, PBS is often omitted in small hospitals due to staff shortages, lack of protocols, and absence of specialists, which risks delayed diagnosis [11,19]. Our stepwise protocol addresses these gaps by providing practical criteria that enable laboratory scientists to initiate PBS when necessary. The WDF scattergram displays leukocyte distribution as a dot plot, supporting early detection of hematological abnormalities [10,17,22]. Normal samples show distinct clusters of leukocytes, whereas blasts create new or diffuse patterns [18]. In our study, abnormal scattergram findings reliably indicated malignant cells, consistent with reports that scattergram features differ by leukemia subtype [18]. These visual cues also aid differentiation of leukemia, infection, and inflammation [17] and, when integrated into automated systems, may enhance flagging algorithms and standardize PBS referral criteria [4].

Based on these results, we propose a practical four-step PBS protocol tailored to small hospital environments: [Step 1] Trigger for PBS Review: initiate PBS when any of the following appear in CBC results, consistent with international guidelines [23]:

- “Blast/Abn Lympho?” or “Left Shift” flags
- WBC > 10,000/ μ L or < 4,000/ μ L (low counts may still include blasts but yield false flags, requiring confirmation) [12]
- IG $\geq$ 2.0% [22,25]
- Unexplained leukocytosis or leukopenia

[Step 2] Abnormal WDF Scattergram Review: check for atypical patterns suggesting blasts or abnormal lymphocytes.

[Step 3] PBS Examination [7]: Prepare and stain slides with Wright-Giemsa, evaluate under $\times$ 1,000 for blasts or Auer rods. Findings are reviewed by a hematopathologist, or reported directly to physicians if none is available. Smear review prevents misinterpretation of inaccurate ANC values [15,16].

[Step 4] Reporting and clinical referral: urgently report suspected blasts as “possible leukemia” and assess the need for referral to a tertiary center or hematology-oncology specialist.

This protocol has notable clinical implications (Figure 1).

This protocol offers a cost-effective model for early detection of hematological malignancies in small- to medium-sized hospitals without advanced diagnostics. It strengthens the role of laboratory scientists as decision-makers and, by standardizing PBS interpretation and reporting, reduces unnecessary testing and delays. Early identification of acute leukemia is particularly critical for improving survival.

This study has some limitations. First, it was conducted in a single regional hospital, limiting generalizability, as analyzer models, staffing, and workflows differ across institutions. Multicenter validation is therefore needed. Second, analyzer flagging performance varies by manufacturer and setting; thus, observed patterns may not be universally applicable [21]. Third, inter-observer variability in PBS interpretation was not assessed, underscoring the need for standardized criteria to improve consistency.

Future research may expand in several directions. Multicenter studies should validate CBC flagging and PBS review criteria in diverse clinical settings to ensure external validity and support guideline development. Advances in AI-based PBS image analysis show promise in improving blast detection and even classifying acute leukemia subtypes, enhancing diagnostic accuracy and workflow efficiency [4,9,26]. Standardization of peripheral PBS review through national guidelines and institutional standard operating procedures (SOPs) should be strengthened via education and policy support. This study proposes a practical SOP (Appendix 1) for clinical adoption.

The four-step protocol was successfully incorporated into our laboratory workflow, resulting in standardized PBS reviews, internal training resources, improved technologist proficiency, earlier recognition of hematological malignancies, and faster clinical communication. These outcomes demonstrate its feasibility in similar hospitals and its potential to enhance early detection and patient outcomes.

CONCLUSION

This study demonstrated that implementing PBS testing in response to blast or abnormal leukocyte flags in CBC results facilitates the early detection of hematological malignancies in small- to medium-sized hospitals. Among 633 flagged cases, 20 cases (3.2%) revealed blast cells, some leading to confirmed leukemia diagnoses and timely clinical referral, facilitating early intervention. CBC profiles of flagged samples showed significantly higher WBC and lower Hb levels than control samples, reinforcing the diagnostic value of automated flagging as a trigger for PBS.

The proposed four-step protocol - comprising CBC flag review, scattergram analysis, PBS interpretation, and clinical referral - offers a practical, cost-effective, and diagnostic workflow for small hospitals. It eliminates reliance on advanced technologies while empowering

laboratory scientists to serve as frontline diagnostic agents. With multicenter validation, the protocol may serve as a foundation for standardized early detection guidelines for hematological malignancies.

This protocol addresses the limitations of automated hematology analyzers by facilitating blast detection even in cases with normal or low WBC counts. Furthermore, statistical analysis showed that platelet count was significantly associated with leukemia subtype, whereas WBC count and hemoglobin level were not; WBC count and hemoglobin level differed significantly between the flagged and control groups. These findings support the use of multiple CBC-derived parameters to guide PBS prioritization and highlight the value of incorporating morphological assessment into routine diagnostics for early leukemia detection.

Future research should aim to validate the proposed protocol across diverse institutions to confirm its generalizability. Overall, the protocol not only supports early leukemia detection but also offers a foundation for SOPs in hematological diagnostics, particularly in resource-limited settings.

Declaration of Generative AI in Scientific Writing:

The authors acknowledge the use of ChatGPT (OpenAI, 2025) for English translation and language refinement. All manuscript content was checked and approved by the authors.

Data Availability:

The datasets analyzed in this study, including CBC results and PB smear interpretations, contain sensitive clinical information and are not publicly available. However, de-identified data may be available from the corresponding author upon reasonable request and institutional approval.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval:

The study protocol was approved by the Institutional Review Board of Dankook University (IRB file No. DKU 2025-02-003-001, approval date: April 3, 2025)

Patient Consent:

This study was a retrospective data-only study; therefore, the need to obtain informed consent from the patients was waived by the Dankook University IRB.

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Declaration of Interest:

The authors declare no conflicts of interest.

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