Egypt. J. Chem. **Vol. 69**, No. 2 pp.505 - 511 (2026)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Optimizing MRD Identification in B-ALL Using CD123 as a Discriminator of Hematogones and B-Lymphoblasts

Mohamed S. Shouman [1], Hadia A. Heikal [1], Mohamed Tarif Mohamed[2], Fouad Mohamed Fouad [2], Mohamed F. Elshal [1],

[1] Molecular Biology Department, Genetic Engineering and Biotechnology Institute, University of Sadat City , Sadat City , Egypt

[2] Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Egypt

Abstract

Minimal Residual Disease (MRD) indicates the small quantity of cancer cells that may persist in the body following treatment, acting as a vital measure of relapse risk and influencing treatment strategies. The identification of MRD through flow cytometry can be difficult due to the similarities in physical and biological characteristics between normal B-cell precursors (hematogones) and malignant B-lymphoblasts, making differentiation challenging. This study explored whether the CD123 marker could enhance MRD detection and effectively separate hematogones from B-lymphoblasts in patients with B-acute lymphoblastic leukemia (B-ALL). We utilized a single-tube flow cytometry method with anti-human monoclonal antibodies targeting CD19, CD20, CD10, CD34, CD123, and CD45. Our results indicated that CD123 significantly improved the capability to differentiate hematogones from remaining B-lymphoblasts. CD123 was highly expressed on residual B-ALL cells, as evidenced by a considerable mean fluorescence intensity (MFI), while exhibiting moderate levels of expression on mature hematogones, and no expression on less mature hematogones or mature B cells. These findings clearly illustrate that evaluating CD123 expression enhances the precision of MRD detection in patients with B-ALL.

Keywords: Acute lymphoblastic leukemia, Minimal residual disease, MRD techniques, CD123, MRD, B-ALL, Flow cytometry.

1. Introduction

B-cell acute lymphoblastic leukemia (B-ALL) is a cancerous condition of the blood characterized by the unchecked growth of immature B-lymphoblasts. These abnormal cells spread throughout the bone marrow, bloodstream, and various other tissues, disrupting the normal production of blood cells and leading to a variety of symptoms. The treatment approach for B-ALL typically consists of several phases, including induction therapy, consolidation therapy, and maintenance therapy. These stages are aimed at achieving complete recovery, eliminating any lingering leukemia cells, and preventing the cancer from reoccurring [1,2]. Despite treatment progress, a condition known as minimal residual disease (MRD) can still be present in a large proportion of patients even after they achieve complete remission, indicating the presence of a small number of remaining leukemia cells. MRD serves two primary clinical purposes that impact patient management: first, it aids in assessing the effectiveness of initial treatment to categorize risk levels and modify therapy for patients deemed at higher risk of MRD [3,4]; and second, monitoring patients who are in full remission to detect any signs of MRD recurrence and allow for the initiation of a rescue therapy [5,6].

Multiparameter flow cytometry (MFC) immunophenotyping is a rapid technique that can detect minimal residual disease (MRD) at a 10^{-4} threshold, with results available in just a few hours [7,8]. The method relies on identifying immunophenotypic markers that differ from those present in normal hematopoietic cells, specifically associated with leukemic cells, known as the leukemia-associated immunophenotypic pattern (LAIP). Due to the immunophenotypic similarities between B-ALL blasts and hematogones (HG), which are normal B-cell precursors found in bone marrow, employing MFC to monitor MRD in B-ALL patients can be challenging. The markers most commonly used for leukemia lymphoblasts (LB) and HG tend to overlap [8]. Along with their shared phenotypes, LB and its noncancerous counterparts display similar Brugg morphological characteristics, which complicates their morphological differentiation in the bone marrow [9,10]. Elevated HG levels have been reported in several contexts, especially during the bone marrow regeneration phase, after bone marrow transplantation or chemotherapy [11], or in healthy newborns [12,13]. Under some circumstances, they make up 5 percent to over 50 percent of the cells [9]. As a result, recognizing atypical antigen expression in patients undergoing treatment for B-ALL is crucial for differentiating high-grade leukemia from remnants of or recurring leukemia.

When combined with other growth factors, IL-3 speeds up the progression of the cell cycle in early hematopoietic progenitor cells and promotes differentiation into different types of hematopoietic cells, including pre-B and pro-B cells [14]. The α chain of the human interleukin (IL)-3 receptor, known as CD123, is essential for the formation of the high-affinity heterodimeric IL-3 receptor [15]. Blood cancers are known for their high levels of IL-3R expression. The stimulation of cytokine receptors influences the survival, growth, and maturation of hematopoietic cells [16]. Our study aimed to enhance the impact of detection of minimal residual disease by multiparameter flow cytometry using CD123 to increase the sensitivity of detection of MRD and differentiate between mature b-cells, hematogones, and residual lymphoblastic cells. As far as we are

*Corresponding author e-mail: mohamedshoman.ms@gmail.com.; (Mohamed S. Shouman).

Received Date: 28 May 2025, Revised Date: 21 July 2025, Accepted Date: 03 August 2025

DOI: https://doi.org/10.21608/ejchem.2025.390059.11835

aware, this is the initial study utilizing CD123 MFI in a one-tube six-color flow cytometry panel aimed at distinguishing hematogones from leftover B-ALL cells residual in MRD detection.

2. Experimental (Materials and Methods)

I - Patients:

For recruitment of participants to our study, a sample size was established through a preliminary power analysis utilizing data from earlier research on minimal residual disease in B-ALL [3]. With an expected moderate effect size (Cohen's d = 0.5), a statistical power of 80% (β = 0.2), and a significance level of 0.05 (α = 5%), the minimum sample size necessary to detect a significant difference between the study groups was calculated to be 84 participants in the B-ALL group. To improve the statistical reliability and accommodate potential data variability or participant drop-out, we opted to include 100 B-ALL patients (after induction therapy or follow-up for MRD detection) and 50 control individuals (children with non-malignant hematological disease), surpassing the minimum requirement and enhancing the credibility of the study results. Age of ALL patients ranged from 1-72 years (Mean age 22.58 ± 17.98). They comprised 55 males (55%) and 45 females (45%). The control subjects were of different diagnoses; 35 ITP (70%), 5 reactive bone marrow (10%), 5 erythroid hyperplasia (10%), 5 eosinophilia (10%). All groups were recruited from Ain Shams University Hospital after taking approval from patients. An approval of the study was obtained from Ain Shams University academic and ethical committee with ethical approval number (FMASU MS 174/2023). Participants gave informed consent for the withdrawal and use of biological samples.

II - Sample Collection and Handling:

All participants subjected to complete medical history, physical examination, and laboratory investigations including complete blood count (by Medonic M-20- 20, Stockholm-Sweden), bone marrow examination, and immunophenotypic classification. One ml of bone marrow sample was collected from each selected case and control into a tube containing EDTA for immunophenotyping and flowcytometric analysis of MRD (minimal residual disease). Bone marrow samples were collected from B-ALL patients after induction therapy or follow-up for MRD detection.

III- Methods:

Flow cytometric analysis:

Reagents supplied:

Fluorochrome-conjugated antibodies to the following antigens were used to profile hematogones and B-ALL cells at indicated quantities per test: CD20 (FITC), CD34 (PE), CD19 (PerCP-Cy5.5), CD45 (APC), CD10 (APC-H7) and CD123 (BV605) were used at 10 µL per test (All monoclonal antibodies were purchased from Becton Dickinson, San Jose, CA). These antibodies were used in combination in one tube as a cocktail and were used for comparison or differentiation between residual lymphoblastic cells, Mature b-cells, and hematogones cells (Figure 1).

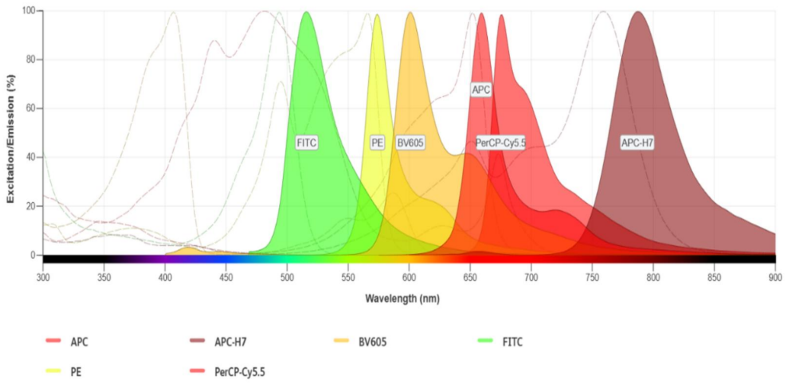

Figure 1: The spectrum of the panel used as outlined in the flow cytometer analysis protocol

Staining and Acquisition:

Staining was performed using the 6 color combinations of the conjugated antibodies listed in the preceding section by adding 10 µL of monoclonal antibody to BM sample and incubating tubes for 15 minutes in the dark at room temperature. Then, RBCs were lysed using BD FACSLysing solution (Becton Dickinson) for 10 minutes and centrifuged at 1,200 rpm for 5 minutes. The supernatant was aspirated and the pellet was resuspended and washed with 2.0 mL of phosphate-buffered saline (PBS) twice before being resuspended in 0.5 mL of PBS and examined. An isotype-matched negative control sample (BD Biosciences, San Jose, CA) was used in all cases to assess background fluorescence intensity. Stained cells were acquired

on a BD FACSCanto-10 flow cytometer (BD Biosciences) that was set up using validated quality assurance procedures. At least 1,000,000 events were acquired for cases.

Stained samples were analyzed using FACSDiva software (BD Biosciences) and analyzed in Kaluza software (Beckman Coulter, Brea, CA). The following gating strategies were used in the control group for analysis of hematogones and mature B lymphocytes (Figure 2). The control group was used to identify hematogones; besides, they were positive for CD10, CD20, CD34, and CD19; they were identified by their low side scatter and variable CD45 (dim to moderate) and divided into 2 groups. The first group comprised less mature hematogones that expressed CD34, CD19, CD20, CD10, and had dim CD45.

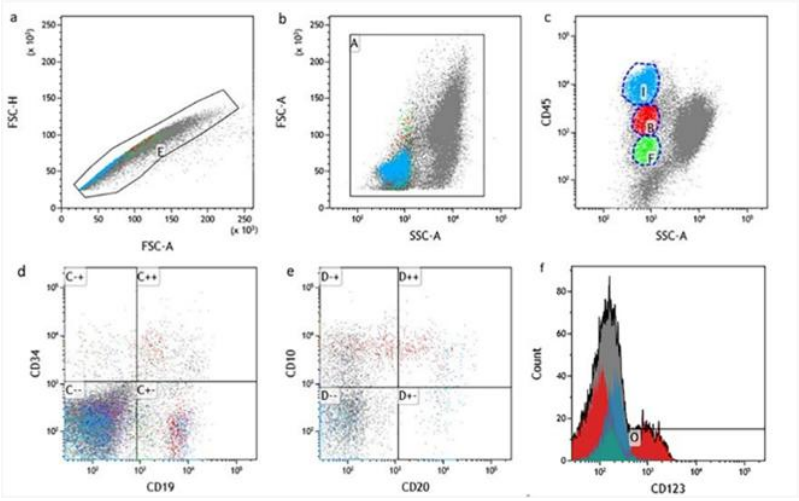

Figure 2: Flow cytometry histograms show CD123 expression on CD19+ B-cells either with CD20 or CD10. a: FSC-A vs FSC-H to exclude doublets. b: all single cells acquired. c: SSC-A log scale vs CD45 to differentiate white blood cells, and gates in this histogram are I: mature B-cells, B: more mature hematogones, and F: less mature hematogones. d, e, and f: expression of monoclonal on gating cells, which clearly shows that CD19+/CD10+/CD20- is expressed CD123 with low MFI (mean fluorescence intensity) (Figure 3).

The second group was composed of more mature hematogones lacking CD34 but with moderate CD45 expression. CD123 was examined in relation to CD34, CD19, CD10, and CD20 in both groups of hematogones. Indeed, hematogones had to be identified to be distinguished from blast cells, as it morphologically similar to blast cells. So, after treatment, any cells with a different pattern of hematogones were considered as blast cells (MRD) (Figure 3).

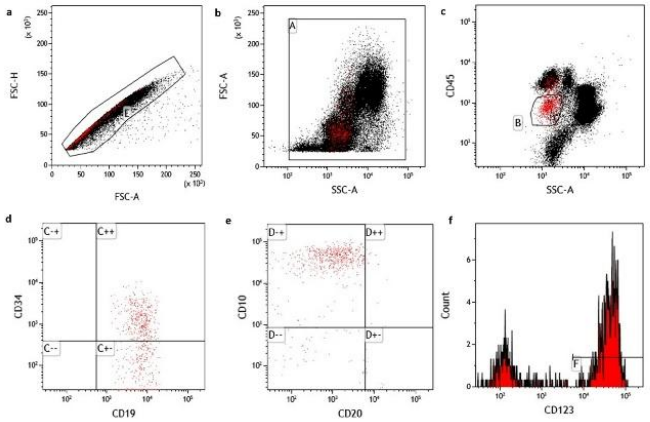

Figure 3: Flow cytometry histograms show CD19+ B-cells are CD10 and negative for CD20 and express CD123 with high MFI for clearly a marker for residual lymphoblast leukemic cells. a: FSC-A vs FSC-H to exclude doublets. b: all single cells acquired. c: SSC-A log scale vs CD45 to differentiate white blood cells with dim CD45 expression in a region of blast cells. d, e, and f: expression of monoclonal on gating cells, which clearly shows that CD19+/CD10+/ CD34+/CD20- is expressing CD123 with high MFI (mean fluorescence intensity).

Molecular testing

For the molecular detection of the BCR/ABL p210 fusion transcript, total RNA was isolated from bone marrow aspirates utilizing the RNeasy Mini Kit (Qiagen, Germany), followed by reverse transcription using a high-capacity cDNA synthesis kit. Quantitative real-time PCR (qRT-PCR) was subsequently performed employing primers specific to the major BCR-ABL1 breakpoint cluster region. The forward primer targeting either the BCR exon 13 or 14 region was: 5′-TCCGCTGACCATCAATAAGGA-3′, and the reverse primer targeting ABL exon 2 was: 5′-TGAGCGGCTTCACTCAGACC-3′. These primers facilitated the amplification of both b2a2 (e13a2) and b3a2 (e14a2) fusion

transcripts, resulting in amplicons of approximately 310 bp and 385 bp, respectively. An ABL control gene was amplified using internal primers (Forward: 5′-GATGTAGTTGCTTGGGACCC-3′, Reverse: 5′-GAGCGGCTTCACCTGAGTGA-3′) to verify RNA integrity and the efficiency of amplification. qPCR reactions were conducted on a StepOnePlus. Standard curves and Ct thresholds were utilized for the detection of fusion genes. For consistent clinical reproducibility, results were cross-validated using the QIAGEN BCR-ABL p210 RT-PCR Kit following the manufacturer's guidelines.

IV- statistical analysis*:*

Data were collected and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard error, and ranges when parametric and median, inter-quartile range (IQR) when data were found non-parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between two paired groups with quantitative data and non-parametric distribution was done by using the Willcoxon test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. *The p-value was considered significant as P > 0.05.*

2. Results

A cohort of 100 patients with acute lymphoblastic leukemia (ALL) was followed at the Hematology Clinic, Ain Shams University Hospital. The study included 55 males (55%) and 45 females (45%), with a median age of 18.5 years (range: 1-72). A comprehensive MRD panel was utilized, and CD123 was found to be a highly significant marker in distinguishing ALL patients from healthy controls. This finding suggests that CD123 could be a valuable biomarker for monitoring disease progression and treatment response in ALL patients. Here, we describe the application of noteworthy significance levels for the Wilcoxon Rank test, t-test, Pearson correlation, and ROC analysis.

Table 1: shows that the analysis of MRD levels with and without CD123 showed a statistically significant difference (p = 0.001, Wilcoxon Rank test). While the medians for both groups remained at 0, the presence of CD123 led to a slightly decreased mean MRD value (4.96% compared to 5.82%) and less variability, evident from the narrower range and lower SEM. These results indicate that the inclusion of CD123 improves the precision and reliability of MRD detection.

Table 1: Comparison between MRD with/without CD123 percentages

MRD	**Without CD123 %**	**With CD123 %**	**Test value‡**	**P-value**	**Sig.**
	No. = 100	**No. = 100**			
Mean ± SEM	5.82 ± 1.83	4.96 ± 1.59	-3.355	0.001	HS
Median(IQR)	0 (0 – 0.03)	0 (0 – 0.04)			
Range	0 – 89.1	0 – 80.5			

P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS). ‡: Wilcoxon Rank test

Using Pearson correlation analysis, strong positive correlations were observed between MRD positivity and the expression of CD34, CD20, CD10, CD123, and CD19, suggesting their potential role in the persistence of minimal residual disease in ALL patients. In contrast, age expression showed no significant correlation with MRD. These findings highlight the importance of including these specific CD markers in MRD monitoring strategies for ALL patients (Table 2).

Table 2: Correlation of MRD with CD123 % with CD markers tested in the panel

	MRD with CD123 %	
	r	**P-value**
Age	-0.055	0.589
CD34 %	**0.716****	**0.000**
CD20 %	**-0.729****	**0.000**
CD10 %	**0.645****	**0.000**
CD123 %	**0.833****	**0.000**
CD19	**0.418****	**0.000**

Table 3 presents a comparative analysis of the mean fluorescence intensity (MFI) of CD19+/CD123+ cells between hematogones and residual B-lymphoblasts. A significant difference was observed in CD123 MFI between hematogones and residual B-lymphoblasts ($p < 0.001$), with minimal range overlap and low standard error, confirming the strong discriminatory power of CD123 expression in distinguishing these two populations.

Table 3: Correlation of MFI (CD19+/CD123+) between Hematogones and Residual lymphoblast B-cells

Cell Population	Hematogones	Residual B-Lymphoblasts
MFI (CD19+/CD123+)	1118.16 ± 30.90	48206.24 ± 2938.43
Range	661 – 1683	10404 – 92614

The receiver operating characteristic (ROC) curve presented in Figure 4 illustrates the diagnostic performance of MFI (CD19+/CD123+) in differentiating between hematogones and residual B-lymphoblasts. The x-axis represents specificity (false positive rate), and the y-axis represents sensitivity (true positive rate). The ROC curve appears to have a high AUC, indicating excellent diagnostic performance and suggesting that the MFI of CD19+/CD123+ can effectively discriminate between the two cell populations

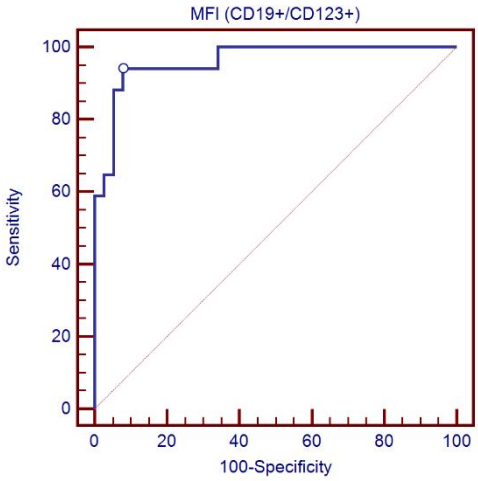

Figure 4: The receiver operating characteristic (ROC) curve

Table 4: Receiver operating characteristics (ROC) curve to assess MFI (CD 19+/CD 123+) to differentiate between Hematogones and Residual lymphoblast B-cell cases.

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>1683	0.961	94.12	92.11	84.2	97.2

Table 5 shows that r = 0.252 with a P-value = 0.011. This indicates a weak but statistically significant positive correlation between CD123 expression and the presence of the BCR/ABL fusion gene. This indicates that BCR/ABL-positive cases may have some degree of association with CD123 expression in the context of MRD.

Table 5: correlation of MRD with CD123% and BCR/ABL gene by PCR

	MRD with CD123 %	
	r	**P-value**
MRD without CD123 %	**0.807****	**0.000**
BCR/ABL fusion gene by PCR	**0.252***	**0.011**

4. Discussion

The identification of minimal residual disease (MRD) in B-cell acute lymphoblastic leukemia (B-ALL) is increasingly acknowledged as a crucial element in patient management, impacting treatment choices and prognostic results. Our study assessed a simplified MRD test that includes CD19, CD10, CD34, and CD123 markers, supporting previous research findings that underscore the importance of MRD monitoring.

Several studies have confirmed that MRD status is a strong independent predictor of relapse risk and long-term survival in both pediatric and adult B-ALL populations. [17,18]. Notably, research by Saygin et al. highlights that MRD detection is the

most powerful predictor of relapse and survival, utilizing reliable methods such as multi-color flow cytometry, quantitative polymerase chain reaction (qPCR), and next-generation sequencing (NGS) [19]. Additionally, the presence of MRD post-induction therapy is strongly associated with negative outcomes, leading to intensified treatment for high-risk patients. Efficient MRD detection allows clinicians to categorize patients based on relapse likelihood, facilitating personalized therapeutic approaches [18].

Our results emphasize the effectiveness of CD123 as a highly sensitive marker for distinguishing normal hematogones from residual leukemic cells. Prior studies have similarly noted consistent expression of CD123 in leukemic cells and its absence in normal hematopoietic populations, enhancing MRD detection specificity. The integration of this marker into our proposed test enhances accuracy, aligning with other studies that advocate for using multiple markers to improve sensitivity. For instance, a study found that high-throughput sequencing of immunoglobulin gene rearrangements detected MRD in cases positive by flow cytometry without false negatives, demonstrating the efficacy of an advanced technique [20].

Accurate MRD detection carries significant clinical implications, enabling healthcare providers to categorize patients into different risk groups. Evidence suggests that patients with detectable MRD may require intensified treatment or alternative therapies like targeted agents or stem cell transplantation [21]. Clinical trials have shown that adapting therapy based on MRD status improves patient outcomes. Furthermore, regular assessments enable dynamic disease monitoring, allowing for prompt therapeutic adjustments upon detection of persistent MRD to potentially prevent relapse [22-24].

While our proposed test shows promise, incorporating analysis of CD123 in MRD test panel could enhance diagnostic capabilities further. A more comprehensive assessment of MRD status, overcoming limitations linked to traditional methods, is still required. Despite the promising outcomes of our study, we acknowledge limitations like a small sample size and potential biases in patient selection. Future research should prioritize multicenter studies with larger cohorts to validate our findings across diverse populations. Longitudinal studies tracking MRD dynamics during treatment could offer valuable insights into optimal monitoring intervals and therapeutic adjustments.

5. Conclusion

In conclusion, our study validates the usefulness of adding CD123 to the conventional MRD detection panel markers, which include CD19, CD10, and CD34, for detecting MRD in B-ALL patients. The expression of CD123 on residual B-ALL lymphoblasts helps accurately distinguish small populations of residual B-ALL lymphoblasts from hematogones and mature B cells. The MRD assay used in this study is a simplified, one-tube, six-color method for detecting MRD in B-lineage ALL. However, CD123 alone cannot differentiate cell types without additional markers in the panel. The high sensitivity of CD123 enhances detection accuracy and supports previous research emphasizing the importance of reliable MRD assessment for guiding clinical decisions. Further research is necessary to confirm these findings and determine their practical application in real-world settings. Improving MRD detection methods will enable clinicians to make better-informed treatment choices that improve patient outcomes in B-ALL.

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