



# 디지털 이미지 분석장비 UIMD PBIA를 이용한 백혈구감별계산 정확도 평가

## Evaluation of a Digital Image Analyzer UIMD PBIA for Determining White Blood Cell Differential Count

이종미 · 김명신 · 한경자 · 김용구

Jong-Mi Lee, M.D., Myungshin Kim, M.D., Kyungja Han, M.D., Yonggoo Kim, M.D.

가톨릭의과대학 진단검사의학교실

Department of Laboratory Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

**Background:** The UIMD PBIA (ANI CO., Suwon, Korea) is a newly developed automated digital image analyzer using innovative algorithms for the analysis of peripheral blood smears. We evaluated the accuracy and throughput of UIMD PBIA for the classification of white blood cells (WBCs).

**Methods:** A total of 29,605 cells in 242 clinical samples (192 samples with abnormal findings and 50 normal samples) were used to evaluate the classification accuracy and throughput of the UIMD PBIA. In addition, the total processing time for WBC classification by UIMD PBIA was measured to calculate the throughput.

**Results:** UIMD PBIA revealed outstanding performance for the identification of normal samples (99.0% accuracy) and five-part differentials (neutrophil, lymphocyte, monocyte, eosinophil, basophil, 99.2% accuracy). Misclassifications frequently occurred for immature granulocytes (83.6-93.9% accuracy), blasts (93.5% accuracy), and abnormal lymphocytes (81% accuracy). The pathogenic cells were likely to be misclassified into other classes of the same lineage. The average throughput was approximately 42 slides per hour. In cases with pancytopenia, the throughput was approximately 29 slides per hour.

**Conclusions:** The UIMD PBIA offers the most accurate results for WBC classification and the highest throughput, thereby reducing the technical workload, especially in cases with normal findings and pancytopenia. Accordingly, this study revealed the feasibility of using a digital switch in CBC analysis.

**Key Words:** Digital image analyzer, White blood cell differential count, UIMD PBIA, Throughput

## INTRODUCTION

Automated complete blood cell (CBC) analyzers have evolved to flag abnormal peripheral blood specimens. However, a manual

slide review for the validation of the CBC test results is inevitable. The Clinical and Laboratory Standards Institute (CLSI) guideline requires a manual differential count of 200 cells performed by two experienced diagnostic hematologists [1]. This job is laborious and quality control is difficult to apply. Automated digital image analyzers have been developed to address these difficulties [2]. Since the development of the first image analysis system in 1966, remarkable progress has been made regarding its processing speed and convenience [2, 3]. The automated image analyzer was produced by Cellavision (CellaVision AB, Lund, Sweden) in the early 2000s. This system is integrated into the DI-60 platform (Sysmex, Kobe, Japan), which is equipped with a hematology analyzer and slide-making devices. The performance of the Cellavision and DI-60 has been thoroughly evaluated in recent studies [3-10]. Prior studies revealed suboptimal accuracy in the identification of abnormal cells, especially blasts and immature granulo-

**Corresponding author:** Yonggoo Kim, M.D., Ph.D.

<https://orcid.org/0000-0003-2808-3795>

Department of Laboratory Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea

Tel: +82-2-2258-1642, Fax: +82-2-2258-1719, E-mail: yonggoo@catholic.ac.kr

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cytes. According to a recent paper by the International Council for Standardization in Haematology (ICSH), skilled morphologists must validate the automated results of classification using these devices. The paper also suggested that new instruments should possess improved accuracy for the classification of pathological cell types [9]. The UIMD PBIA (ANI CO., Suwon, Korea) is a novel automated digital image analyzer that uses innovative algorithms to review peripheral blood smears. This machine provides differential counts of white blood cells (WBCs) and morphological grading scores of red blood cells (RBCs) and platelets. Up to 12 stained slide glasses can be loaded into the input cassette, which is followed by continuous scanning of their barcodes and cells. This instrument provides high quality images and accurate differentials in a short time. In this study, we focused on the accuracy of the UIMD PBIA in the classification of WBC using heterogeneous clinical samples. In addition, we determined the throughput of the UIMD PBIA to establish its feasibility for clinical applications.

## MATERIALS AND METHODS

### 1. The automated digital image analyzing system, UIMD PBIA

The automated digital image analyzer, UIMD PBIA, is equipped with a slide cassette, a slide barcode scanner, a microscope with two objectives (OPYMPUS UPLXAPO 10x and PLXN 100x), a camera (SONY XCL-SG510C, 2,464×2,056 pixel), and a computer system for acquisition and classification software (UPBA-12A, version1.0). The slide cassette can load up to 12 slides at a time. The graphical user interface is equipped with an operating system setting, real-time analysis monitoring, data storage, classification results, and reports. The captured WBC images are pre-classified into 13 types of cells: neutrophils, metamyelocytes, myelocytes, promyelocytes, lymphocytes, abnormal lymphocytes, monocytes, eosinophils, basophils, blasts, plasma cells, nucleated RBCs, and reactive lymphocytes. A manual reclassification is available using the “drag and drop” function on the screen. Both absolute count and percentages are presented in the final report. The nucleated RBC and artifacts (smudge cells) are counted separately (Supplementary Fig. 1).

### 2. Sample evaluation

A total of 242 clinical samples submitted for routine CBC analy-

sis at the Seoul St Mary’s hospital were selected and sorted based on the result of conventional differential count. The classification accuracy was determined by analyzing 192 samples of 11 sample types, including nucleated erythrocytes (N=60), leukopenia (N=20), neoplastic dysgranulopoiesis (N=10), non-neoplastic dysgranulopoiesis (N=10), neutrophil precursors  $\geq 10\%$  (N=10), neutrophil precursors  $\geq 10\%$  (N=10), and abnormal cells such as myeloblasts and monoblasts (N=20) lymphoblasts (N=15), mature B cell neoplasm (N=15), mature T cell neoplasm (N=7), and plasma cell and/or reactive lymphocytes (N=15). Fifty samples without abnormal findings were also analyzed to evaluate the negative predictive power. The blood samples collected in anticoagulant tubes (BD vacutainer spray-coated K2EDTA tubes, Becton Dickinson, USA) were processed according to a standardized protocol. Blood films were prepared using slide maker and stainer (SP-10, Sysmex, Kobe, Japan) in an automated hematology slide preparation unit.

This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul St. Mary’s Hospital (KC16DISI0316). The IRB waived the requirement of informed consent from patients as de-identified PB slides were used for the routine analysis.

### 3. Study design

The clinical evaluation was performed to assess the performance and reliability of the UIMD PBIA in normal and abnormal cases. Accordingly, at least 100 WBCs in each slide, captured and pre-classified by UIMD PBIA, were subsequently reviewed and corrected independently by two morphologists with over 30 years of experience in blood morphology examination. Discordant classifications between the two morphologists were discussed to obtain the final results. Manual curation was achieved with reference to the results of manual microscopic observation. Manual differential counts (200 cells) using light microscopy based on CLSI H20-A2 [1] were independently obtained by the two morphologists. To determine the accuracy of WBC classification, the average values of the two post-classifications by the two morphologists were compared with the pre-classification results. The accuracy of the classification was determined using 12 sample types (normal and abnormal samples) and 13 cell types. The throughput was determined by measuring the total processing time for WBC classification by UIMD PBIA.

## RESULTS

### 1. WBC classification accuracy

The WBC pre-classification using the UIMD PBIA was compared with the post-classification levels to determine the classification accuracy. Overall, 97.1% of the pre-classification by UIMD PBIA for 29,065 cells was consistent with the reclassification. The UIMD PBIA had the highest accuracy for normal samples (99.0%), followed by samples with pancytopenia (97.7%), lymphoblasts (97.6%), mature T cell neoplasm (97.4%), neutrophil precursor more than 10% (97.3%), mature B cell neoplasm (97.3%), neoplastic dysgranulopoiesis (97.2%), neutrophil precursor less than 10% (97.0%), nucleated RBC (96.3%), non-neoplastic dysgranulopoiesis (96.3%), myeloblasts and/or monoblasts (95.9%), and plasma cells and/or reactive lymphocytes (95.6%) (Table 1).

The UIMD PBIA displayed the maximum accuracy for the pre-classification of neutrophils (99.9%), followed by eosinophils (99.8%), lymphocytes (99.1%), nucleated RBCs (97.0%), monocytes (96.6%), plasma cells (96.3%), myelocytes (93.9%), promyelocytes (93.9%), reactive lymphocytes (93.6%), blasts (93.5%), basophils (91.6%), metamyelocytes (83.6%), and abnormal lymphocytes (81%) (Table 2).

Table 3 presents details of the pre-classification results and corrected results by experts in the other categories. The most frequent misclassifications occurred for abnormal lymphocytes and metamyelocytes. Approximately 13.9% (11/79) of abnormal lymphocytes were reclassified into blasts and approximately 13.4% (112/836) of metamyelocytes were reclassified into neutrophils.

Conversely, approximately 13.6% (12/88) of abnormal lymphocytes were misclassified into blasts, and lymphoblasts were frequently misclassified into lymphocytes (0.7%, 17/2,381), reactive lymphocytes (0.7%, 17/2,381), and abnormal lymphocytes (0.5%, 11/2,381) by UIMD PBIA. The median WBC counts per slide captured by UIMD PBIA was 121 (95% CI: 119–123). The classification accuracies were not associated with the cell counts (correlation coefficient  $r = -0.019$ ,  $P = 0.768$ ).

### 2. Throughput

The throughput of UIMD PBIA were measured for samples with normal findings (N=50), nucleated RBCs (N=60), and other find-

**Table 2.** WBC pre-classification accuracy of the UIMD PBIA based on cell type

Cell type	Total	Correct	Incorrect	Accuracy
Neutrophil	9,516	9,511	5	99.9%
Metamyelocyte	836	699	137	83.6%
Myelocyte	624	586	38	93.9%
Promyelocyte	148	139	9	93.9%
Lymphocyte	7,747	7,676	71	99.1%
Abnormal lymphocyte	79	64	15	81.0%
Monocyte	1,845	1,782	63	96.6%
Eosinophil	435	434	1	99.8%
Basophil	214	196	18	91.6%
Blast	2,486	2,324	162	93.5%
Plasma cell	271	261	10	96.3%
Nucleated RBC	813	789	24	97.0%
Reactive lymphocyte	4,591	4,296	295	93.6%
Total	29,605	28,757	848	97.1%

**Table 1.** WBC pre-classification accuracy of the UIMD PBIA based on sample type

Sample type	Sample characteristics	Number of samples	Cell counts	Accuracy	Appendix*
Total samples	-	242	29,605	97.1%	
Samples with NRBC	Nucleated RBC $\geq 5\%$	60	7,568	96.3%	1-1
Samples with pancytopenia	WBC $< 1 \times 10^9/L$	20	2,481	97.7%	1-2
Samples with dysgranulopoiesis	Neoplastic dysgranulopoiesis (MDS, MPN/MDS)	10	1,276	97.2%	1-3
	Non-neoplastic dysgranulopoiesis (post-chemotherapy)	10	1,230	96.3%	1-4
Samples containing neutrophil precursors	Neutrophil precursors $< 10\%$	10	1,187	97.0%	1-5
	Neutrophil precursors $\geq 10\%$	10	1,148	97.3%	1-6
Samples containing abnormal cells	Myeloblasts and/or monoblasts	20	2,552	95.9%	1-7
	Lymphoblasts	15	1,871	97.6%	1-8
	Mature B cell neoplasm	15	1,764	97.3%	1-9
	Mature T cell neoplasm	7	1,109	97.4%	1-10
	Plasma cell and/or reactive lymphocytes	15	1,783	95.6%	1-11
Normal samples	-	50	5,532	99.0%	1-12

\*The appendix with details of the results is presented in the supplementary Table 1.

Abbreviations: NRBC, nucleated RBC; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

Table 3. Details of the pre- and post-classification results

		User classification (Post-classification)													
		NE	ME	MY	PR	LY	LV	MO	EO	BA	BL	PC	NR	AR	Total
UIMD-PBUA (Pre-classification)	NE	9,511	0	0	0	1	0	1	0	0	0	0	0	3	9,516
	ME	112	699	0	0	2	0	16	3	0	1	0	0	3	836
	MY	0	1	586	0	6	0	18	2	0	5	1	2	3	624
	PR	0	0	0	139	0	0	5	0	0	0	0	0	4	148
	LY	7	1	1	0	7,676	5	1	1	0	17	7	5	26	7,747
	LV	0	0	0	0	2	64	1	0	0	11	0	0	1	79
	MO	20	10	11	0	11	6	1,782	0	0	3	2	0	0	1,845
	EO	1	0	0	0	0	0	0	434	0	0	0	0	0	435
	BA	5	0	0	2	0	0	1	0	196	1	0	0	9	214
	BL	5	1	0	1	78	12	29	1	1	2,324	6	1	27	2,486
	PC	0	0	0	0	0	0	1	0	0	2	261	5	2	271
	NR	5	5	0	0	3	0	0	1	0	0	1	789	9	813
	AR	187	7	4	0	53	1	9	1	5	17	2	9	4,296	4,591
	Total	9,853	724	602	142	7,832	88	1,864	443	202	2,381	280	811	4,383	29,605

Abbreviations: NE, neutrophil; ME, metamyelocyte; MY, myelocyte; PR, promyelocyte; LY, lymphocyte; LV, abnormal lymphocyte; MO, monocyte; EO, eosinophil; BA, basophil; BL, blast; PC, plasma cell; NR, nucleated RBC; AR, reactive lymphocyte.

Table 4. Throughput of the UIMD PBIA

Sample types	Total Time*	Number of slides	Second/Slide	Slides/Hour	Number of cells	Second/Cell
Total	05:43:30	242	85.16	42.27	29,605	0.69
Normal samples	01:07:05	50	80.50	44.72	5,532	0.72
Abnormal samples	04:36:25	192	86.38	41.67	24,073	0.68
Samples with nRBC	01:31:02	60	91.03	39.55	7,568	0.72
Pancytopenia samples	00:41:20	20	124.04	29.02	2,755	0.90

\*Total time is presented as hour:minute:second.

ings (N=192). The total processing time was measured and divided by the number of slides and cells. Approximately 5 hours and 43 minutes were required to process 242 slides, suggesting a run time of 85 seconds per slide. The average throughput was approximately 42 slides per hour. Based on sample type, samples with normal findings had the best throughput (44.72 slides/hour), followed by other findings (41.67 slides/hour), nucleated RBCs (39.55 slides/hour), and pancytopenia (29.02 slides/hour) (Table 4).

Table 5. Comparative accuracy of digital image analyzers

Sample types	Octavia [5]	DM96 [5]	DM96 [6]	DM96 [4]	DI-60 [7]	DI-60 [8]	UIMD PBIA
Segmented neutrophils	94.4%	98.6%	99.5%	92.5%	98.9%	96.6%	99.9%
Band neutrophils	10.5%	22.9%		57.1%	14.1%	63.0%	
Eosinophils	95.4%	93.5%	79.9%	63.2%	67.8%	39.6%	99.8%
Basophils	58.4%	84.7%	54.1%	80.0%	41.1%	87.0%	91.6%
Lymphocytes	94.3%	95.2%	94.9%	96.4%	86.6%	88.9%	99.1%
Atypical lymphocytes						70.7%	93.6%
Abnormal lymphocytes							81.0%
Plasma cells							96.3%
Monocytes	65.0%	94.0%	87.6%	81.4%	88.7%	66.3%	96.6%
Blast cells	84.4%	78.5%	76.6%	65.1%	93.1%	56.0%	93.5%
Metamyelocytes			32.6%	53.2%	23.6%	33.0%	83.6%
Myelocytes			37.7%		30.6%	75.0%	93.9%
Promyelocytes			77.6%		30.6%	88.5%	93.9%
Nucleated RBCs			89.6%	86.7%	30.6%	94.4%	97.0%
Five differentials			87.2%	87.9%	88.4%	87.9%	99.2%
All	87.0%	92.0%	89.2%	82.0%	87.6%	86.0%	97.1%

## DISCUSSION

Remarkably, the UIMD PBIA classified WBCs with an accuracy of 97%. Of note, the overall accuracy of the market leaders, Sysmex DI-60 and CellaVision DM96, ranges from 82% to 89% [4-8]. The UIMD PBIA displayed outstanding performance in the analysis of normal samples (99.0% accuracy) and five-part differentials (99.2%). According to the results, UIMD PBIA can replace the manual slide review process in the clinical laboratory with a low incidence of abnormal samples (Table 5).

Misclassifications were relatively high for immature granulocytes (83.6–93.9%), blasts (93.5%), and abnormal lymphocytes (81%). Nevertheless, UIMD PBIA had the lowest frequency of misclassification compared with other instruments (Table 5). UIMD PBIA has improved classification accuracy as it utilizes self-learning artificial intelligence. More than 300,000 PB slides from the real world were used to develop the classification algorithm. However, pathogenic cells were still likely to be misclassified into another class in the same lineage. Notably, this is a common phenomenon of image analyzers; thus, a careful review of blasts and abnormal lymphocytes is warranted [7, 8].

The UIMD PBIA distinguishes abnormal lymphocytes from atypical lymphocytes, consistent with reactive lymphocytes as suggested by the ICSH guideline [11]. To the best of our knowledge, this study included the largest number of samples with abnormal lymphoid cells (mature B cell neoplasm, N=15, mature T cell neoplasm, N=7) and plasma cells (N=15), and is the first report of classification accuracies involving abnormal lymphoid cells and plasma cells using a digital image analyzer without additional image processing [12-14]. The classification accuracy of plasma cells was acceptable (96.3%); however, as described previously, the abnormal lymphocytes were still insufficient (81%).

The UIMD PBIA yielded a significantly higher throughput than its competition and processed 42 slides per hour [7, 9, 15]. In the case of pancytopenia, UIMD PBIA processed 29 slides per hour. The cell tracking system minimizes the time required to search cells on the slide using an efficient path-finding algorithm.

Despite the commercial availability of high-performing automated digital image analyzers, these devices are supportive rather than an alternative to the microscopic slide review system and are associated with limited accuracy and throughput.

This study comprehensively investigated the newly developed

digital image analyzer, UIMD PBIA, which offers the most accurate WBC classification results with the highest throughput. This improvement reduces the workload of the morphologist, especially in cases involving normal findings and pancytopenia [16]. Overall, this study demonstrates the feasibility of using the digital image analyzer, UIMD PBIA, as a digital switch for CBC testing.

## 요 약

**배경:** UIMD PBIA (ANI CO., 한국)는 새롭게 개발된 말초혈액 혈구 이미지의 자동화 분석장비이다. 본 연구에서는 UIMD PBIA의 백혈구 분류의 정확도와 처리속도를 평가하였다.

**방법:** 이상소견이 있는 환자 검체 192건과 이상소견이 없는 정상인 검체 50건을 포함한 총 242건의 말초혈액 도말로부터 얻어진 29,605개의 백혈구 세포 이미지를 이용하여 장비의 정확도와 처리속도를 분석하였다.

**결과:** UIMD PBIA는 정상인 검체에서 99%의 정확도를 보였고, 다섯 종류의 백혈구감별계산에서 99.2%의 정확도를 보였다. 오분류는 미성숙과립구, 모세포, 비정상 림프구에서 빈번하게 발생하여 이들에 대한 분석의 정확도는 81-93.9% 수준이었다. 비정상 혈구들은 같은 계열의 다른 세포로 분류되는 경향을 보였다. 장비의 처리속도는 시간당 42개 슬라이드였으며, 혈구감소증이 있는 경우는 시간당 29개 슬라이드였다.

**결론:** UIMD PBIA는 빠르고 정확한 백혈구 분류 결과를 제공하며, 특히 정상소견이나 혈구감소증이 있는 경우 유용하게 이용될 수 있을 것으로 생각된다.

## Conflicts of Interest

None declared.

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