UNIVERSITÀ DEL PIEMONTE ORIENTALE

School of Medicine

Department of Health Sciences

Master's Degree in Medical Biotechnologies

Graduation Thesis

Comparative analysis of the performance of automated digital cell morphology analyzers for leukocyte differentiation in hematologic malignancies: Mindray MC-80 versus West Medica Hema Vision

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SUMMARY

Rational of the study

Artificial intelligence systems are becoming increasingly widespread in the field of laboratory medicine, automating and therefore optimizing routine analyzes in hospital laboratories. Several hematology analyzers trained with artificial intelligence are currently available and widely in use, which are capable of pre-classifying cells in a highly performing way. Various research have been carried out aimed at comparing the activity of these instruments, but none of these studies have directly compared West Medica's Hema Vision and Mindray's MC-80, both of which are present in Clinical Biochemistry Laboratory. The aim of this study is to perform a comparative analysis of these two devices using peripheral blood samples from patients with abnormal complete blood count to evaluate their support for experienced operators in the evaluation of pathologic peripheral blood smears.

Planning of the study

This study was conducted from December 2022 to February 2024 at the Clinical Biochemistry Laboratory “Maggiore della Carità” University Hospital, Novara, Italy. 75 patients (M: F 53:47%; median (min-max) age 63 years old (1-90)), with hematological malignancies (ALL= 4, B-CLL=20, AML=20, CML=5, lymphoma= 20, infection=6) were analyzed. Their smears were compared using the MC-80, HV, and manual microscopy. According to REF, the agreement between microscopy (reference method, REF), HV, and MC-80, was expressed as the median (IQR) of a given cell population/feature, with REF-HV and REF-MC80 differences expressed as bias and 95% limits of agreement.

Results

Concordance was calculated for all complete blood count parameters, but only the following are reported: Neu% [REF: 23.5% (6.5-36.7); REF-HV: 0.09 (-0.35 to 0.54); REF-MC80: 0.21 (-1.16 to 1.57)]; Ly% [REF: 45% (12.5-77.8); REF-HV: -2.56 (-6.72 to 1.60); REF-MC80: 23.03 (16.99 to 29.08)]; Mo% [REF: 2.00% (0.50-4.9); REF-HV: -2.15 (-3.57 to -0.73); REF-MC80: -1.47 (-2.42 to -0.51)]; Eo% [REF: 1.0% (0.0-2.0); REF-HV: -0.44 (-0.77 to -0.11); REF-MC80: 0.08 (-0.25 to 0.40)]; Baso% [REF: 0.0% (0.0-0.5); REF-HV: -0.76 (-1.73 to 0.21); REF-MC80: -2.22 (-3.17 to -1.28)]; band cells [REF: 0.5% (0.0-1.5); REF-HV: -0.01 (-0.19 to 0.17); REF-MC80: -1.87 (-2.52 to -1.23)]; myelocytes [REF: 0.00% (0.00-0.5); REF-HV: 0.18 (-0.16 to 0.51); REF-MC80: -4.10 (-5.81 to -2.40)]; metamyelocytes [REF: 0.00% (0.00-0.4); REF-HV: 0.33 (0.04 to 0.63); REF-MC80: -0.56 (-0.98 to -0.14)]; blasts, all samples [REF: 0.0% (0.0-34.6); REF-HV: 10.07 (5.17 to 14.97), REF-MC80: -2.05 (-7.06 to 2.96)]; blasts, in acute leukemia [REF: 61.2% (31.5-91.5, 2.0-98.0); REF-HV: 32.55 (21.55 to 43.56), REF-MC80: 17.70 (10.18 to 25.23)]; smudge cells in CLL [REF: 64.8% (42.9-100.3); REF-HV: 0.67 (-2.03 to 3.36), REF-MC80: -48.43 (-70.86 to -26.00)].

Conclusions

Both technologies are optimal solutions. While Hema Vision's combination of manual and digitized techniques makes it more suitable for medium-sized laboratories, the MC-80 is the preferred solution for larger facilities that require complete automation and uncompromising image quality. Hema Vision and MC-80 provide valuable tools for the assessment of leukocyte populations, but their ability to accurately quantify abnormal cells, especially blasts, needs to be improved to reach the performance of expert operators.

1. INTRODUCTION

1.1 Artificial intelligence (AI), Machine Learning and Laboratory Medicine

Artificial intelligence (AI) is a computer technology that revolutionizes the way in which man interacts with machines, and machines with each other. We can define AI as the process through which machines and computer systems simulate human intelligence processes. Specific applications of AI include systems such as natural language processing, speech recognition, and computer vision. Artificial intelligence provides a robot with calculation qualities that allow it to carry out complex operations and "reasoning", which until recently were exclusive features of human reasoning, in a short time.

Thanks to artificial intelligence it is possible (at least this is the ultimate goal) to make machines capable of carrying out complex actions and "reasoning", learning from mistakes, and carrying out functions that were previously exclusive to human intelligence. Today in Italy and around the world, artificial intelligence is used in companies and beyond, to carry out tasks that would take a long time for humans.[1]

Artificial intelligence and machine learning have been introduced in the activity of laboratory medicine and will continue to influence it in the coming years in a substantial way, thanks to the enormous progress and rapid development of informatic subjects, and the enormous diffusion of health digital data. AI cumulates algorithms and technologies that allow computers to learn and solve intellectual tasks provided by humans; it speeds up processing and interpretation of data, and allows to efficiently perform the most comprehensive tasks, including medical image analysis.[2] AI systems are now capable of carrying out tasks in a highly performing way, so much so that they can partially, or even totally, replace the manual work of expert operators; many of the data generated in clinical laboratories are perfectly suited to fit into this context, being often structured, discrete, faithful and produced in large quantities.

To give a sort of definition, a machine learning model is a program that can find patterns or make decisions from a previously unseen dataset. This system, during the training phase, learns from examples (in a more or less supervised way). It is subsequently able to generalize and manage new data in the same application domain. In other words, it learns from examples to improve its performance for managing new data coming from the "same source".

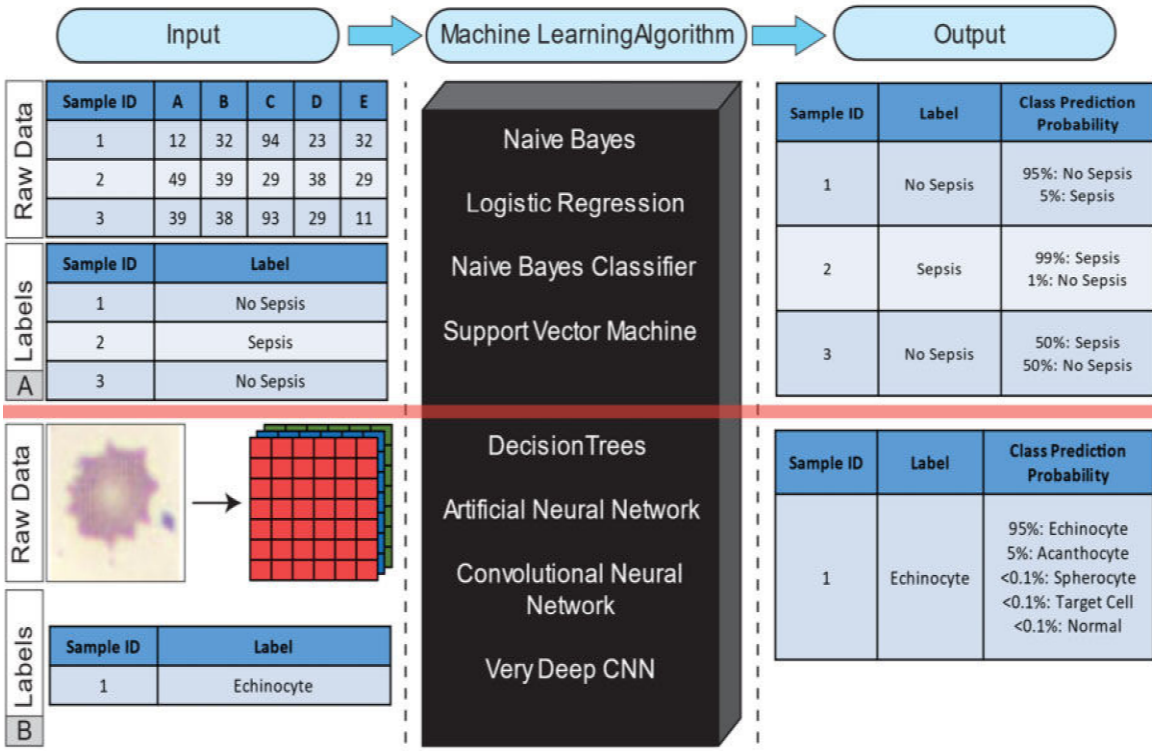

Figure 1. Supervised machine learning infographic using generalizable examples of structured and unstructured input data. (A) Structured data: prediction of a dichotomous variable (i.e. "sepsis" vs. "no sepsis"), using a collection of annotated analytes (analyte-A, analyte-B, . . . , analyte-E). Structured data can be analyzed by a machine learning algorithm, like the ones shown above the red line. The output of the machine learning algorithm can include a predicted probability for each possible class. The top-predicted class can then be compared to the original input label to evaluate the model's performance. B) Unstructured data: prediction of a categorical variable (i.e. erythrocyte morphology), using a 70 X 70 Images are unstructured arrays of numbers that typically range from 1 or 0 to 255. This data can be analyzed by a machine learning algorithm, such as those shown below the red line. The output of the machine learning algorithm includes a predicted probability for each class, which collectively equals 1. The top-predicted class can then be compared to the original input label to evaluate the model's performance.[3]

1.2 Artificial intelligence (AI), Machine Learning and Digital Morphology

In clinical chemistry and pathology, AI systems are adept at automating routine tasks. This includes the analysis of blood samples, the counting and classification of cells, and the detection of microorganisms in cultures. Automation of these processes not only speeds up laboratory operations but also reduces human error, ensuring consistent and reliable results. Moreover, AI-driven instruments can continuously learn and adapt from the data they process, enhancing their diagnostic capabilities over time.

In haematology, the examination of the morphological characteristics of leukocytes, red blood cells and platelets in peripheral blood smears plays a crucial role in the diagnosis of hematologic diseases. While conventional manual microscopy has long been considered the gold standard in cell analysis, it is associated with a number of challenges, such as the high workload, the need for continuous training and considerable inter-observer variability.[4] In addition, storage of conventional glass slides is associated with space issues and obtaining second opinions through manual microscopy is a problem. These challenges are particularly evident when dealing with abnormal cells, including malignant lymphoid cells and blast cells, where accurate identification and classification is critical.

The limitations of manual microscopy have driven the development and adoption of automated digital morphology (DM) systems in recent decades, such as the MC-80 analyzer (Mindray), CellaVision®DM9600 (CellaVision AB), Sysmex DI-60 (Sysmex Corp. Kobe, Japan/Based on the Cella Vision DM1200 platform), and Vision Hema (West Medica). Clinical laboratories have recently been enriched with these artificial intelligence-based tools for morphologic analysis of digital images of peripheral blood cells. The complete blood count (CBC) and the differentiated leukocyte count (DLC) are two highly requested tests;[5] indeed, they are essential to obtain information about the patient's condition, especially in the screening of hematologic diseases such as leukemias and lymphoproliferative disorders.[6] Nowadays, most medical laboratories use automated analyzers to routinely perform these examinations.[7] Hundreds of tests are performed every day, providing a huge

amount of data. These automated analyzers locate the cells in the blood smear and then use a camera to capture images of the individual white blood cells (WBCs) at high magnification. The digital images are the input for the computer system, which analyzes them using a neural network based on a large database of cells. What is really important for a machine learning algorithm to be well trained is precisely the vast availability of data, and clinical laboratories are a perfect source for this. For pre-classification, the system performs numerous calculations based on geometric, morphological features (shape, size and others), color and texture.[8] The individual cell images pre-classified by the software are displayed on a computer screen that provides an automatic differential count, and they can be confirmed or reclassified by the specialist. The reclassification is performed by experts (specialized biologists and/or clinicians) and is necessary at the end of the process to validate the results. Indeed, the machine may make some errors in the classification of the cells; experts can detect them and perform a manual reclassification using the software via a computer. These tools generally classify normal leukocytes with excellent accuracy and, with more variable accuracy, pathological cells (blasts, dysplastic cells, reactive lymphocytes, immature granulocytes, etc.).[9] Platelets (and aggregates) are also classified and can be visualized on the screen. The systems also recognize artifacts: they represent a morphological aspect that is not normally present in living cells and tissues (and is not due to real pathological changes).

These systems use state-of-the-art technology to analyze cell morphology in a more efficient, standardized and objective way. The most important aspects of digital morphology and its applications are efficiency and throughput, consistency and standardization, quality control, advanced imaging techniques and integration with information systems.[9] The benefits of these systems are many. Among the most important are their use for remote training and consultations, the ability to effectively archive images, and potentially better standardization within a laboratory and between different laboratories.

The Clinical Biochemistry laboratory where I completed my thesis internship has acquired two digitized morphology devices: the Mindray MC-80, the latest generation of an automated digital cell morphology analyzer developed by Mindray Medical International Ltd (Shenzhen, China), which has shown very good performance in screening hematologic diseases[7], and Vision Hema, a modern approach to automating blood smear analysis from West Medica.

There are still very few publications on MC-80 and Vision Hema technology. Zini et al.[10] analyzed the performance of the MC-80 and made a comparison with manual smear testing. Among the advantages of the MC-80 system, they appreciated the excellent morphologic reproducibility and similarity to microscope images of cells in normal and dysplastic specimens.

Yoon et al. evaluated the degree of agreement between the leukocyte formula obtained by an experienced hematologist by optical microscopy and the preclassification performed with Vision Hema, which showed reliable performance in differentiating leukocytes even in leukopenic and myelodysplastic samples.[11]

There is an increasing trend to compare the performance of different DM analyzers, such as Mindray MC-80 versus Sysmex DI-60 [12], Mindray MC-80 versus CellaVision DM9600 [7], but no work has yet compared Vision Hema (West Medica) with Mindray MC-80. The aim of the present study is to test the performance of leukocyte preclassification with Vision Hema (West Medica) in peripheral blood samples from patients with hematologic diseases and to compare the results with those obtained with the MC-80 analyzer (Mindray).

2. OBJECTIVE OF THE THESIS

The Clinical Biochemistry Laboratory at the “Maggiore della Carità” University Hospital (AOU) in Novara processes a large number of routine analyzes every day. The hospital's emergency services are in operation around the clock. Improving the efficiency, timeliness and traceability of data can be achieved through the management and IT tools available in the laboratory, including artificial intelligence and machine learning systems.

The development of numerous automated digital cell morphology analyzers has streamlined the standardization of differential counting of blood cells, overcoming the limitations of manual microscopic counting and thus increasing reliability and efficiency. In the field of hematological diseases, these tools are crucial for the analysis of peripheral blood and categorization of cells, which helps in the diagnosis of malignancies that can alert the physician even in the absence of specific symptoms. Although these automated digital cell morphology analyzers rely on artificial intelligence, each tool is characterized by its unique algorithms and working methods.

Several studies have aimed to compare automated digital cell morphology analyzers and evaluate their effectiveness using sample sets to highlight strengths and weaknesses. However, none of these studies have directly compared West Medica's Hema Vision and Mindray's MC-80, both of which are present in Clinical Biochemistry Laboratory. The aim of this study was to perform a comparative analysis of these two devices using peripheral blood samples from patients with abnormal complete blood count (CBC) requiring review of peripheral blood smears to evaluate their support for experienced operators in the evaluation of pathologic peripheral blood smears.

3. MATERIALS AND METHODS

3.1 Samples of the study

This study was conducted from December 2022 to February 2024 at the Clinical Biochemistry Laboratory "Maggiore della Carità" University Hospital, Novara, Italy. The study protocol was approved by the Ethics Committee of the University Hospital "Maggiore della Carità" (CE 200/2024) and was conducted in accordance with the current revision of Helsinki Declaration.

A total of 75 PB (Peripheral Blood) samples were collected from individuals who attended our hospital. These were patients (M 53%, F 47%, mean age = 57) with abnormal complete blood count (CBC) results and/or hematologic diseases in whom a revision of the PB smear was suggested. We selected the patient's first access to avoid artefacts due to treatments.

The integrated diagnoses of these 75 patients after performing complementary tests were: Acute Myeloid Leukaemia (AML) (n = 20), Chronic Lymphocytic Leukaemia (CLL) (n = 20), Acute Lymphoblastic Leukaemia (ALL) (n = 4), Chronic myeloid leukaemia (CML) (n = 5), Lymphoma (n = 20), viral infections (EBV) (n = 6).

Blood samples were collected in K2-EDTA tubes (BD Vacutainer™, Belliver Industrial Estate, Plymouth, UK) and analysed with the Mindray BC-6800Plus (version software 01.44.00.17983, Mindray Medical International Ltd., Shenzhen, China).

PB smears were prepared automatically using the slide maker and stainer SC-120 (Mindray, Shenzen, China) and stained with May Gruenwald-Giemsa (MGG).

3.2 WBC differentials by manual microscopy and digital morphology analyzers

3.2.1 WBC differentials by manual microscopy

White blood cells (WBCs) are a heterogeneous group of nucleated cells that are found in the bloodstream. Their normal concentration in the blood varies between 4000 and 10,000 per microliter. They play an important role in phagocytosis and immunity and thus in the defense against infections. Leukocytes can be analyzed using various techniques of varying complexity and sophistication. Both quantitative and qualitative properties can be assessed in the laboratory.[13]

The simplest test is the leukocyte count with differential diagnosis. The quality of the blood smear is important for an accurate manual cell count. This includes good slide preparation and a good staining procedure. Manual procedure of preparation of a blood smear is illustrated in Figure 2. The absolute number of each type of leukocyte, which is often more meaningful than its percentage, can be calculated if the differential count and the total number of leukocytes per unit volume are known.

Automated hematology analyzers are fast and effective screening tools for monitoring a patient's overall blood status. However, most of these automated systems are relatively ineffective at correctly detecting abnormal cells, causing the devices to issue "flag" messages when such cells are present in the blood. For this reason, manual differential counting of leukocytes by microscopy remains the current gold standard.

Manual differential counting of leukocytes has several limitations that are of critical importance to laboratory technicians, both from a diagnostic and an economic point of view. It is very labor intensive and time consuming, especially for highly leukopenic samples. Although it is recommended that at least 200 cells should be counted, it is often not possible to count more than 100 cells in highly leukopenic samples. This makes manual differentiation results less accurate in this type of patient. As the examination of slides from severely leukopenic samples is also extremely time-consuming, this increases the pressure on laboratories with many severely leukopenic samples. The number of such samples has increased significantly in hospital laboratories in recent years, mainly due to the

increasing number of patients receiving chemotherapy, radiotherapy and transplantation. In addition, the morphology of the leukocytes in these samples may be altered by the chemotherapy or radiotherapy, making manual differential counting even more difficult. For these reasons, manual WBC differentials have a higher variability in leukopenic samples.[14]

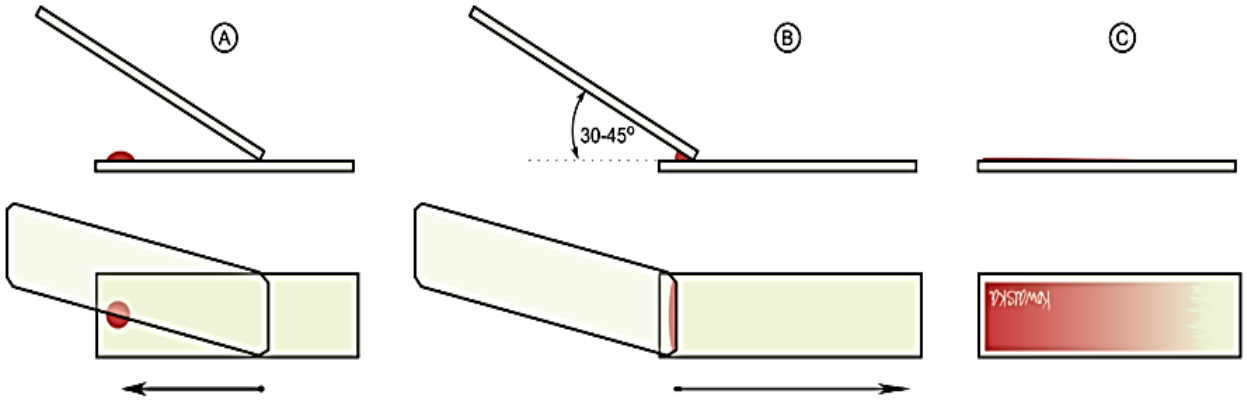

Figure 2. Preparation of a blood smear.[15]

3.2.2 West Medica Hema Vision

The Hema Vision System from West Medica enables the identification and pre-classification of leukocytes; in particular it identifies basophils, eosinophils, promyelocytes, myelocytes, metamyelocytes, blasts, band neutrophils, segmented neutrophils, lymphocytes, monocytes and reactive lymphocytes. It also enables the detailed analysis of platelets (normal, micro, macro) and erythrocytes (size, color, shape, inclusions) using 21 different parameters. Pathological and complex cells are displayed, such as cells with degenerative changes, immature forms of neutrophils, atypical forms of lymphocytes, blasts, erythroblasts, smudge cells and other non-WBC cells. By scanning the blood smear, we can make an additional assessment of atypical forms of leukocytes and platelet aggregations. The latest developments in artificial intelligence offer a solution to the tasks associated with automation in digital microscopy. West Medica's technologies speed up the diagnostic process,

shorten the analysis time and reduce the subjectivity of the results obtained. They improve the efficiency of the laboratory routine and bring microscopy analysis up to the state of the art. The surgical process can be resumed in various steps. First, the results from the hematology analyzer are transferred to Vision Manager, which automatically processes all data based on the blood smear microscopy decision-making rule set. The analysis of the blood smear is performed automatically by the software, as well as the processing of the data related to the blood smear microscopy results. Finally, the results are validated and the data stored.[16] A schematic representation of this workflow is shown in Figure 3.

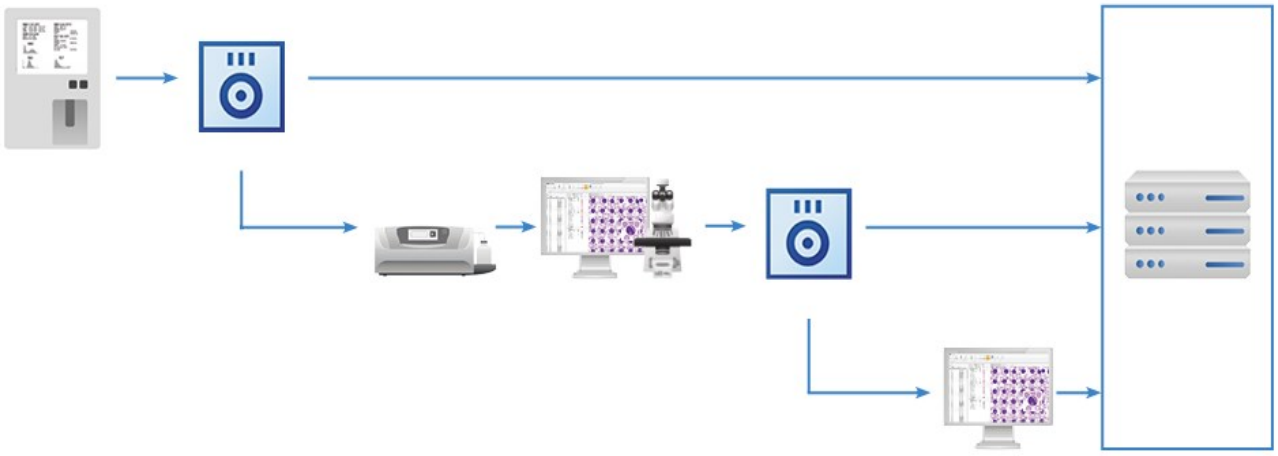

Figure 3. Illustration of the workflow of analyses in medium sized and large laboratories.[16]

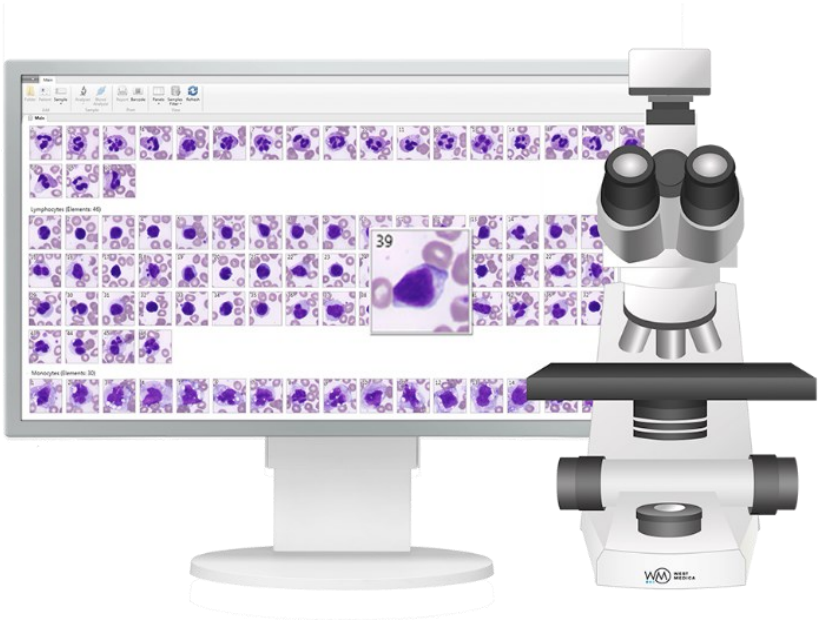

Figure 4. Hema Vision: flexible interface provides easy and convenient running.

3.2.3 Mindray MC-80

The new Mindray MC-80, showed in figure 5, is an automated digital cell morphology analyzer that automatically locates blood cells, takes photos and pre-classifies the blood cells in the film. The LabXpert software, as used in our laboratory, runs on computers with the Windows 10 operating system. The microscopic part has high-quality objectives, up to 100x magnification, automatic dripping of microscope oil and a sensor image camera with an advanced design.

Figure 5. Mindray MC-80 cell morphology analyzer.

The system captures the images in the film and then takes them to 20 different depths of field. A multi-layer fusion technology reconstructs and fuses the images captured at different depths to faithfully reproduce the cellular details and the methods used to visually focus the cells and their structures under the microscope. Based on this, the software pre-classifies the cells captured on the film and groups the cells of different classes based on the degree of maturity and any atypia. The MC-80 takes digital morphology analysis to the next level, providing clearer images that can capture anomalies in greater detail. With advanced algorithms, the analyzer enables better identification of

different cells with high throughput, resulting in higher productivity. The high-performance objective lens and advanced image sensor provide high-resolution images that reproduce the real sight under the microscope. Multilayer fusion technology simulates manual focus adjustment and accurately recreates the pathological features of cells, which is helpful for early detection of blood disorders and infectious diseases. Aerospace materials and a state-of-the-art high-frequency exposure algorithm are integrated to avoid blurred images. The MC-80 enables reliable pre-classification and pre-characterization of cells: white blood cells (especially abnormal cells), but also red blood cells (the pre-characterized morphology of erythrocytes can be changed with one click) and platelets (counting aid and accurate clumping). The process is continuous and the average speed corresponds to a preliminary analysis of 60 slides per hour (with an inevitable variability depending on the leukocyte count and the possible presence of artifacts). All these features result in a smart and fast process and less manual intervention.[17]

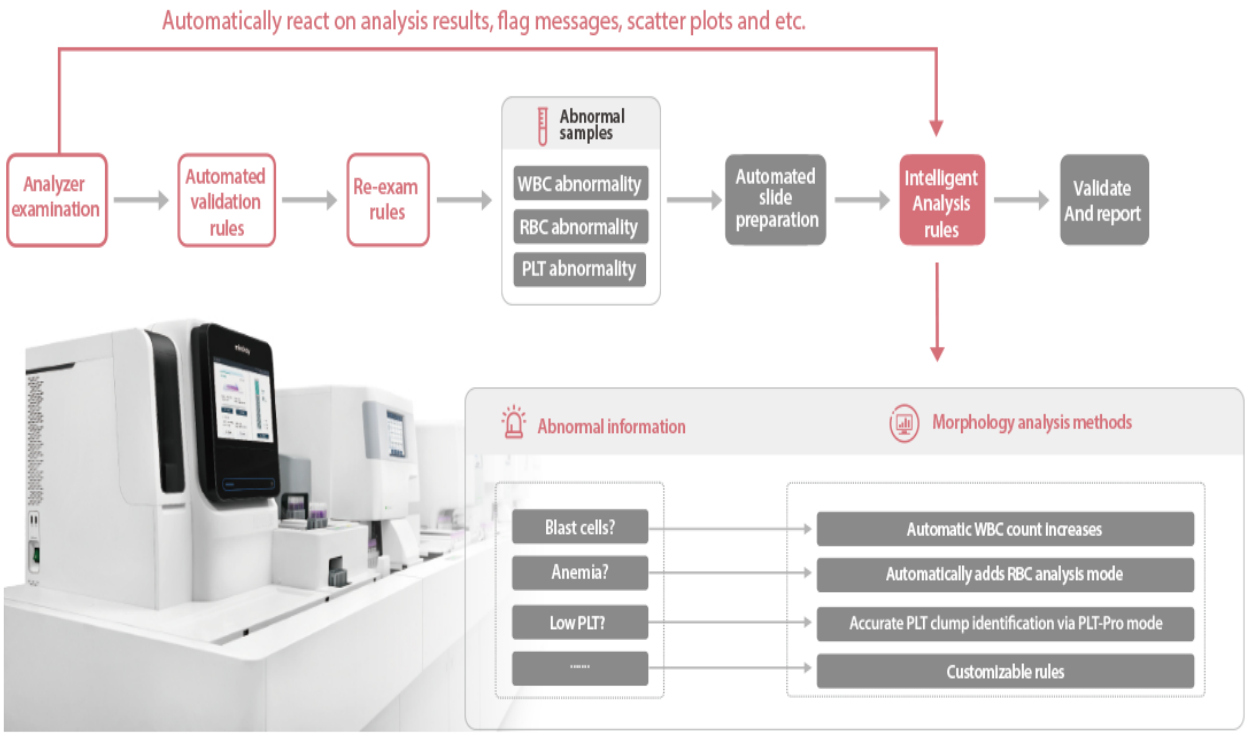

Figure 6. Schematic representation of the MC-80's workflow.

3.3 Statistical Analysis

Statistical analyses were performed by SPSS statistical software v.17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software v. 22.021 (MedCalc Software Ltd, Ostend, Belgium). Quantitative variables were expressed by the median and interquartile range (IQR), while qualitative variables as absolute and relative frequencies. Method comparison was performed considering microscopy as the reference method, using Bland-Altman analysis.

4. RESULTS

The study included 75 cases (M:F 53:47%; median (min-max) age 63 ys (1-90)), of which 4 (5.2%) ALL, 20 (26.7%) B-CLL, 20 (26.7%) AML, 5 (6.7%) CML, 20 (26.7%) lymphoma and 6 (8%) EBV. Demographical, clinical and CBC parameters of the cases investigated are reported in Table 1.

Agreement for different cell populations between microscopy (reference method, REF), Hema Vision (HV) and Mindray MC-80 (MC-80), considering the whole sample (n=75), was reported in Table 2. With the exception of monocytes and eosinophils, bias and the interval including 95% of the differences (95% limits of agreement) were wider for the comparison microscopy-MC80 than for the comparison microscopy-Hema Vision. For Hema Vision, a significant bias was observed only for monocytes, eosinophils and metamyelocytes, while for MC-80 a significant bias resulted for lymphocytes, monocytes, basophils, band cells, myelocytes and metamyelocytes (Table 2).

Hema Vision and MC-80 were also compared with microscopy for pathological cell populations within specific subgroups (Table 3). The agreement between microscopy and MC-80 was better than Hema Vision for blasts (both in the whole sample and in the acute leukemia subgroup) but worse for smudge cells, even after the removal of 1 outlier (Table 3). For Hema Vision, a significant bias was observed for blasts (both in the whole sample and in the leukemia subgroup), while for MC-80 a significant bias resulted for blasts only in the acute leukemia subgroup and for smudge cells in the CLL subgroup (Table 3).

Characteristic	Statistics (n, % or median, IQR, min-max)
Sex, M:F	53:47%
N	75
Diagnosis, n (%) **-ALL** **-B-CLL** **-AML** **-CML** **-Lymphoma** **-EBV infection**	 4 (5.2%) 20 (26.7%) 20 (26.7%) 5 (6.7%) 20 (26.7%) 6 (8%)
WBC, 10^6/L	20.02 (9.94-97.91; 1.32-619.50)
Neutrophils, 10^6/L	4.15 (2.39-6.32; 0.18-216.39)
Lymphocytes, 10^6/L	7.06 (3.11-23.79; 0.55-536.49)
Monocytes, 10^6/L	0.52 (0.27-1.66; 0.00-51.42)
Eosinophils, 10^6/L	0.13 (0.04-0.32; 0.00-4.87)
Basophils, 10^6/L	0.02 (0.00-0.06; 0.00-3.96)

Table 1. Demographical, clinical and CBC parameters of the 75 cases investigated.

Cell population (%)	Microscopy, median (IQR, min-max)	Microscopy – Hema Vision	Microscopy - Mindray MC80
Neutrophils	23.5% (6.5-36.7, 0.0-52.0)	Bias: 0.09 (-0.35 to 0.54) 95% LoA: -3.69 to 3.88	Bias: 0.21 (-1.16 to 1.57) 95% LoA: -11.45 to 11.86
Lymphocytes	45.0% (12.5-77.8, 0.0-99.2)	Bias: -2.56 (-6.72 to 1.60) 95% LoA: -38.04 to 32.92	Bias: 23.03 (16.99 to 29.08)* 95% LoA: -28.50 to 74.57
Monocytes	2.0% (0.5-4.9, 0.0-23.9)	Bias: -2.15 (-3.57 to -0.73)* 95% LoA: -14.25 to 9.95	Bias: -1.47 (-2.42 to -0.51)* 95% LoA: -9.63 to 6.70
Eosinophils	1.0% (0.0-2.0, 0.0-9.5)	Bias: -0.44 (-0.77 to -0.11)* 95% LoA: -3.26 to 2.38	Bias: 0.08 (-0.25 to 0.40) 95% LoA: -2.70 to 2.85
Basophils	0.0% (0.0-0.5, 0.0-8.1)	Bias: -0.76 (-1.73 to 0.21) 95% LoA: -9.03 to 7.50	Bias: -2.22 (-3.17 to -1.28)* 95% LoA: -10.27 to 5.81
Band cells	0.5% (0.0-1.5, 0.0-19.9)	Bias: -0.01 (-0.19 to 0.17) 95% LoA: -1.54 to 1.52	Bias: -1.87 (-2.52 to -1.23)* 95% LoA: -7.37 to 3.62
Myelocytes	0.0% (0.0-0.5, 0.0-26.1)	Bias: 0.18 (-0.16 to 0.51) 95% LoA: -2.65 to 3.00	Bias: -4.10 (-5.81 to -2.40)* 95% LoA: -18.64 to 10.43
Metamyelocytes	0.0% (0.0-0.4, 0.0-15.2)	Bias: 0.33 (0.04 to 0.63)* 95% LoA: -2.20 to 2.86	Bias: -0.56 (-0.98 to -0.14)* 95% LoA: -4.15 to 3.04

Table 2. Agreement between microscopy, Hema Vision and Mindray MC-80 in the whole sample (n=75). In the second column, median % (IQR, min-max) of different cell populations resulting from microscopy are indicated. Differences are reported (third and fourth columns) as absolute differences between cell populations, considering microscopy as the reference method, specifically microscopy(%) – Hema Vision(%) and microscopy(%) – Mindray MC80(%). Each cell includes bias (95% CI) and 95% limits of agreement (95% LoA) as calculated by Bland-Altman analysis. *: Statistically significant bias.

Cell population (%) Subgroup	Microscopy, median (IQR, min-max)	Microscopy – Hema Vision	Microscopy - Mindray MC80
Blasts All samples, n=75	0.0% (0.0-34.6, 0.0-98.0)	Bias: 10.07 (5.17 to 14.97)* 95% LoA: -31.70 to 51.84	Bias: -2.05 (-7.06 to 2.96) 95% LoA: -44.72 to 40.62
Blasts ALL+AML, n=24	61.2% (31.5-91.5, 2.0-98.0)	Bias: 32.55 (21.55 to 43.56)* 95% LoA: -18.52 to 83.63	Bias: 17.70 (10.18 to 25.23)* 95% LoA: -17.23 to 52.64
Smudge cells CLL, n=20	64.8% (42.9-100.3, 7.9-206.3)	Bias: 0.67 (-2.03 to 3.36) 95% LoA: -10.64 to 11.97	Bias: -48.43 (-70.86 to -26.00)* 95% LoA: -139.64 to 42.77

Table 3. Agreement between microscopy, Hema Vision and Mindray MC-80 in different subgroups. In the second column, median % (IQR, min-max) of different cell populations resulting from microscopy are indicated. Differences are reported (third and fourth columns) as absolute differences between cell populations, considering microscopy as the reference method, specifically microscopy(%) – Hema Vision(%) and microscopy(%) – Mindray MC80(%). Each cell includes bias (95%CI) and 95% limits of agreement (95% LoA) as calculated by Bland-Altman analysis. *: Statistically significant bias.

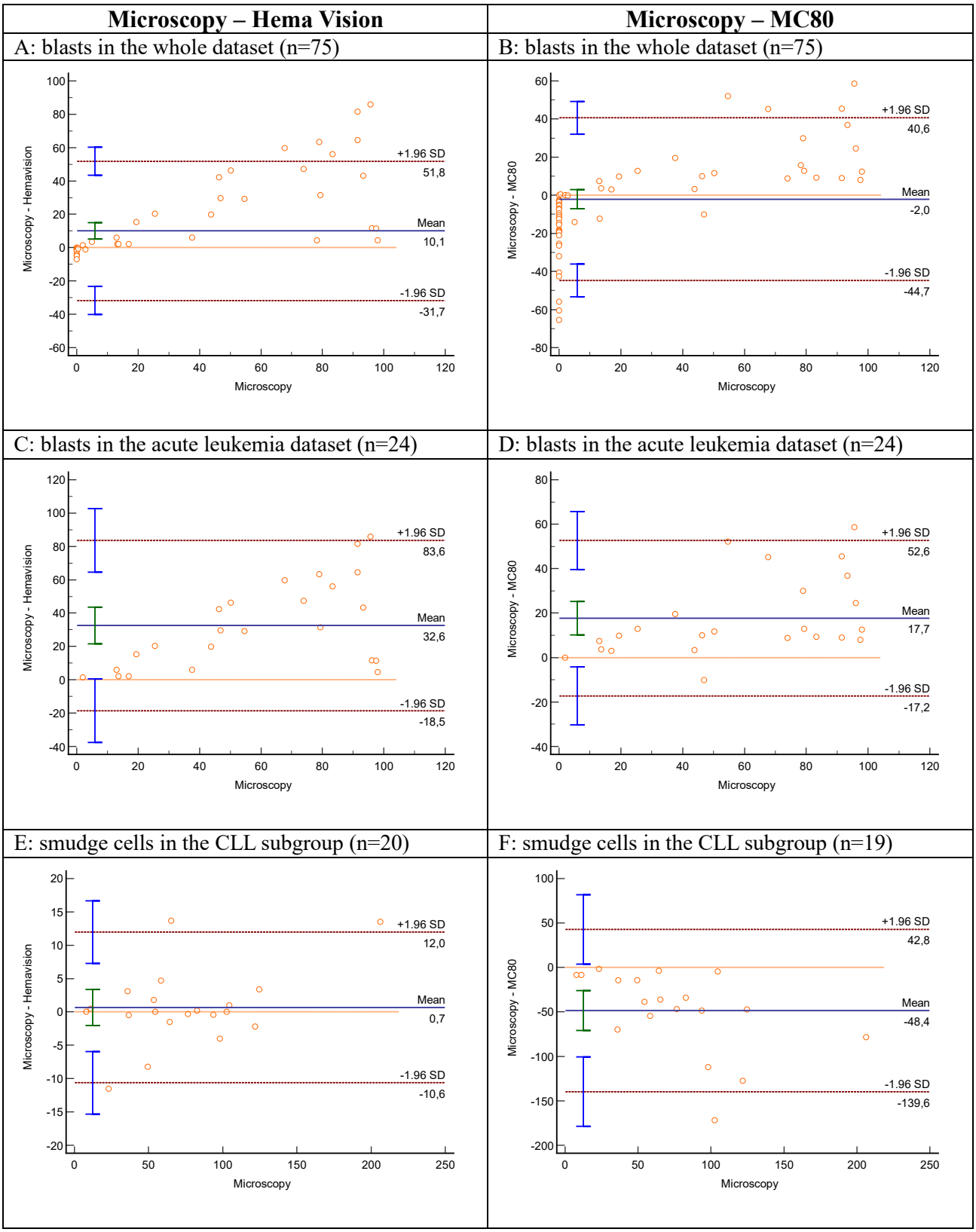

Figure 7. Bland-Altman analysis for the comparison between microscopy-Hema Vision (A, C, E) and microscopy-MC80 (B, D, F) for blasts in the whole dataset (A, B), blasts in the acute leukemia subgroup (C, D) and for smudge cells in the CLL subgroup (E, F). In F, 1 outlier was removed (see text).

4.1 Case 1: Acute Lymphocytic Leukemia

The case of a male patient, 46 years old, who comes from the hematology department is presented. The complete blood count shows neutrophilic leukocytosis and thrombocytopenia. Light microscopic examination revealed the presence of immature monomorphic elements, which accounted for 79.5% of the total leukocytes. The diagnosis, which was confirmed by flow cytometric analysis, suggests a phenotype consistent with acute lymphoblastic leukemia (B-ALL). In particular, the analysis revealed the presence of a number of blasts with B-lymphoid orientation equal to 78% of the total leukocytes, whose immunophenotypic characteristics are listed below.

Positive: CD34++ CD33+/- (21%) CD123+/- (22%) HLA-DR++ CD38++ (72%) CD45RA+ (59%) CD19++ CD10++ CD13+/- (20%) cyCD22+ (46%) sCD22++ (92%) CD79a++ TdT++.

Negative: CD117- CD11b- CD66b- CD64- CD14- CD56- CD3- CD45RO- CD2- CD5- CD4- CD8- CD7- TCR alfa beta- TCR gamma delta- CD138- CD20- cyCD3- MPO-.

CD34+ cells = 0.5% of total leukocytes CD117++ CD33+ (54%) CD123-.

The granulocyte population presents expression of markers indicative of elements at different maturation levels.

Hema Vision preclassified 31 blasts (15,6%), while MC-80 preclassified 98 blasts (49%).

The images of blasts taken by Hema Vision (Figure 8-A) and MC-80 (Figure 8-B) are shown below.

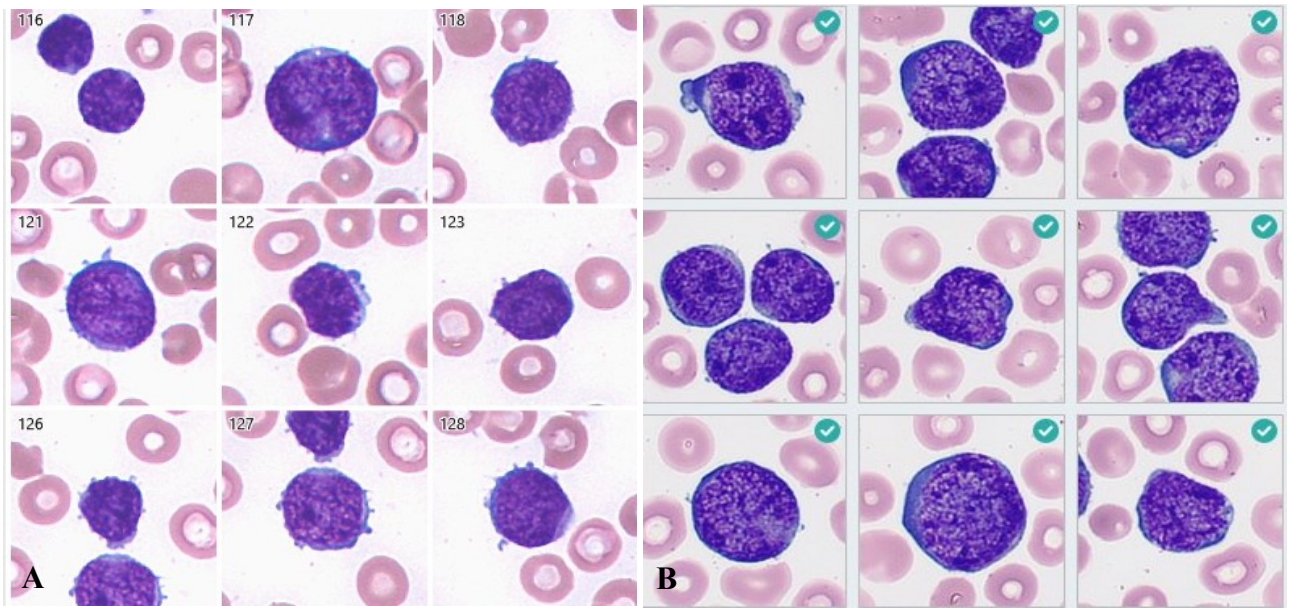

Figure 8. Blasts captured by Hema Vision (A) and MC-80 (B).

4.2 Case 2: Chronic Lymphocytic Leukemia

The second clinical case presented is a male patient, 58 years old, who was admitted to the hematology clinic. The complete blood count showed a marked lymphocytosis. Light microscopic examination revealed the presence of an atypical lymphocyte population and some smudge cells. The diagnosis, confirmed by flow cytometric analysis, indicates a phenotype consistent with chronic lymphocytic leukemia (B-CLL). In particular, the analysis highlighted the presence of clonal expansion of B lymphocytes equal to 73% of lymphocytes and 42% of total leukocytes, with the following immunophenotypic characteristics: Kappa++ low/med CD19++ CD20++ low/med CD5++(88%) CD23++(80%) CD38+(47%) CD43++ CD22++ CD79b+(63%) CD200++. Lambda- CD10- CD11c- CD25- CD103- FMC7-.

Hema Vision preclassified 102 lymphocytes (51%) and 74 smudge cells (37%); MC-80 preclassified 65 lymphocytes (32.5%) and 102 smudge cells (51%).

Below are images of atypical lymphocytes and smudge cells captured with Hema Vision (Figure 9) and MC-80 (Figure 10).

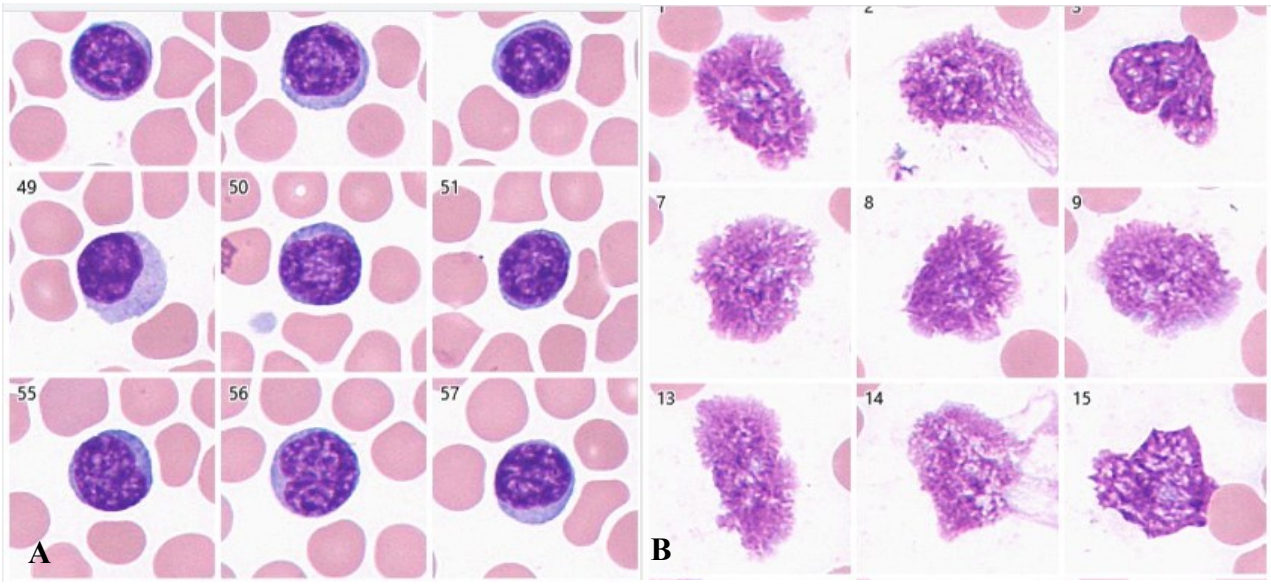

Figure 9. Atypical lymphocytes (A) and smudge cells (B) of B-CLL captured by Hema Vision.

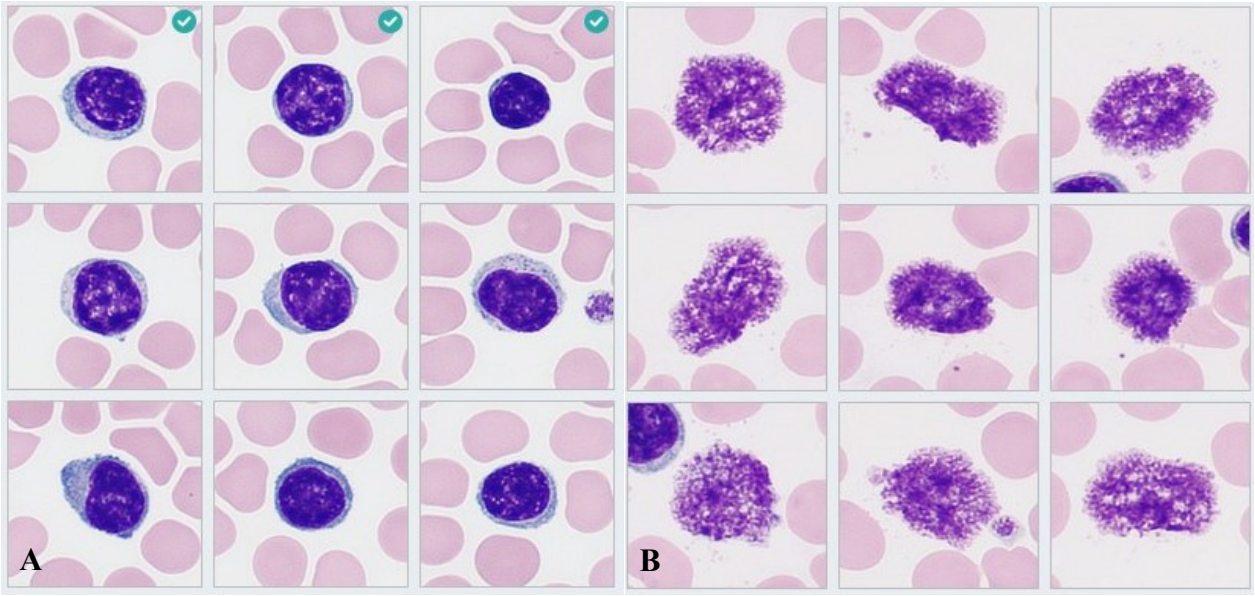

Figure 10. Atypical lymphocytes (A) and smudge cells (B) of B-CLL captured by MC-80.

4.3 Case 3: Acute Promyelocytic Leukemia

Female patient, 69 years old, admitted from the hematology department. Complete blood count shows leukocytosis, anemia and thrombocytopenia. Light microscopic examination revealed the presence of an immature monomorphic population accounting for 50% of the total leukocytes, as well as Auer bodies. The diagnosis, confirmed by flow cytometric analysis, suggests a phenotype consistent with acute myeloid leukemia, probably of the AML-M3 subtype. The analysis revealed the presence of a quote of myeloid-oriented blasts equal to 76% of the total leukocytes, whose immunophenotypic characteristics are listed below.

Positive: CD117+(65%) CD123+/-(26%) CD33++ CD13++ CD64++ CD11b+(34%) CD45RA++ CD38++ MPO++(72%).

Negative: CD34- CD66b- HLA-DR- CD16- CD56- CD14- CD45RO- CD3- CD5- CD7- CD4- CD8- TCR alfa beta- TCR gamma delta- CD20- CD19- CD10- CD138- TdT- cyCD22- cyCD3- cyCD79a-

.

There is also a small cluster of CD34+ cells equal to 0.6% of total leukocytes, myeloid, CD117++ CD33++ (78%) CD123-.

Hema Vision preclassified 51 blasts (25.4%) and 0 promyelocytes; MC-80 preclassified 5 blasts (2.5%) and 41 atypical promyelocytes (20.5%).

Below are images of atypical promyelocytes captured with Hema Vision (Figure 11-A) and MC-80 (Figure 11-B).

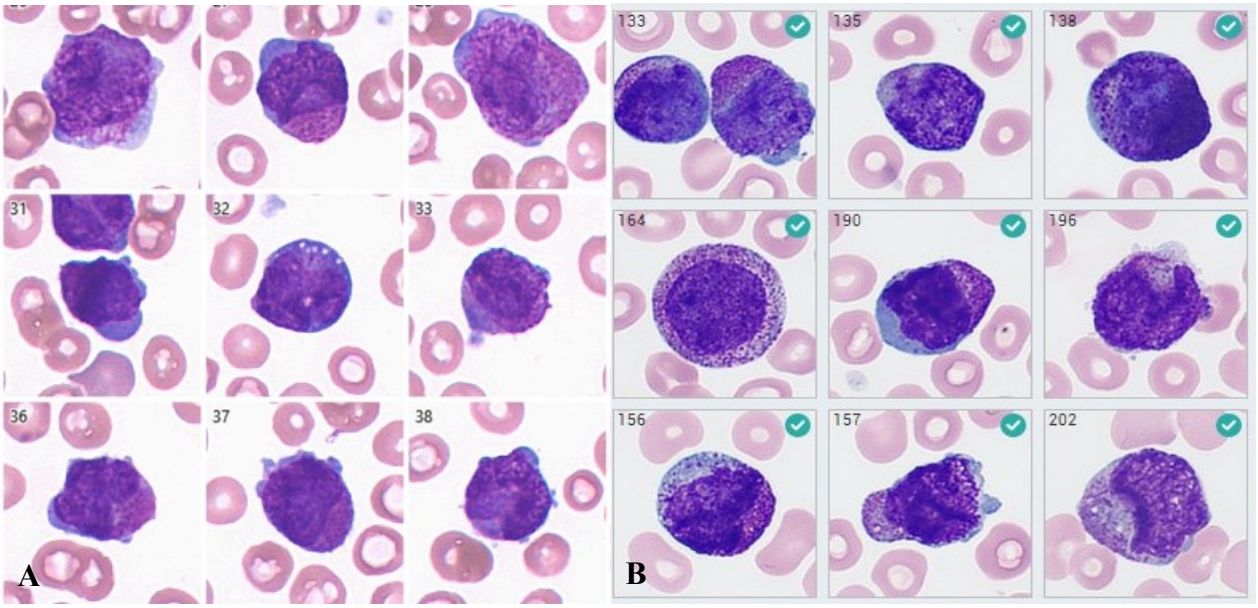

Figure 11. Atypical promyelocytes captured with Hema Vision (A) and MC-80 (B).

4.4 Case 4: Hairy Cell Leukemia

Female patient, 44 years old, admitted to the hematology clinic. The complete blood count shows pancytopenia. Light microscopic examination revealed the presence of atypical villous lymphocytes ("hairy cells") justifying a hematologic examination. The diagnosis, confirmed by flow cytometric analysis, suggests a phenotype consistent with a B-clonal lymphoproliferative disorder: evaluation of the global expression of markers indicates a possible form of Hairy Cell Leukemia (HCL), which needs to be complemented by histologic evaluation. CD19+ B lymphocytes are equal to 27% of lymphocytes and 17% of total leukocytes: a portion of them, equal to 5% of lymphocytes and 3% of total leukocytes, is clonally restricted for the lambda chain. The immunophenotype of the patient is the following: lambda++ bright CD19++ CD20++ med/bright CD200++ CD23+ (44%) CD38+ (62%) CD22++ bright CD79b++bright CD25++ CD11c++ CD103++ FMC7++ CD43+ (68%). Kappa-CD5-CD10-.

Both Hema Vision and MC-80 recognized and pre-preclassified hairy cells: images from both devices are shown in Figure 12.

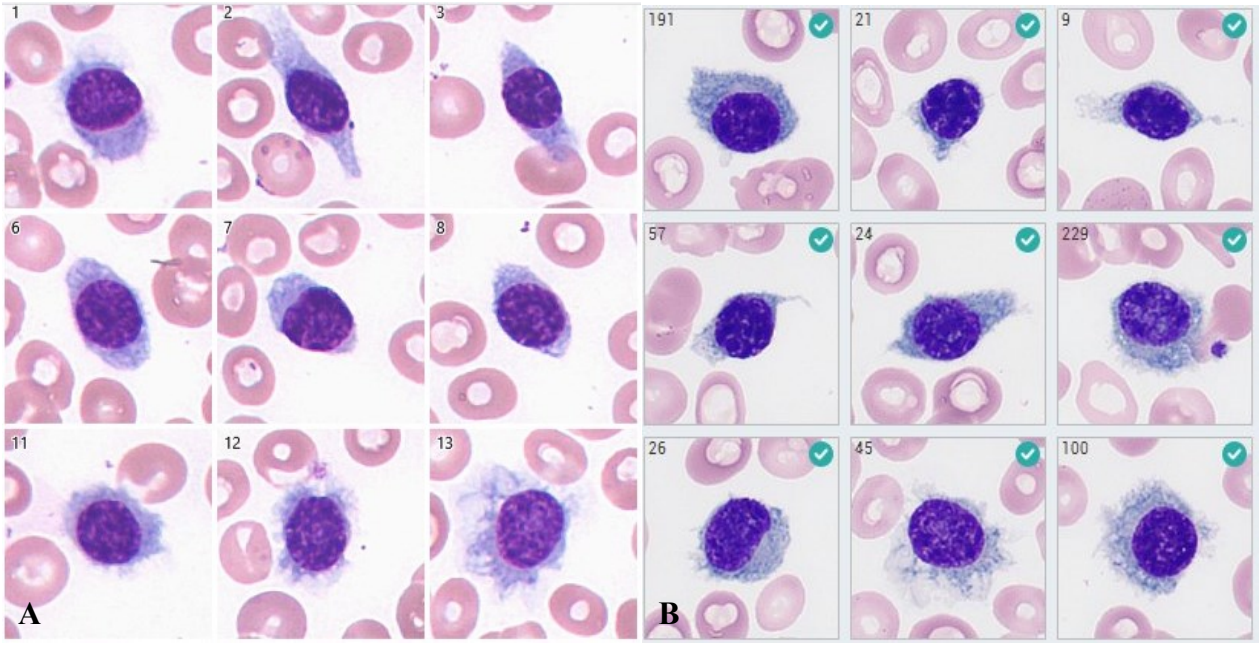

Figure 12. Villous lymphocytes ("hairy cells") captured with Hema Vision (A) and MC-80 (B).

4.5 Case 5: Follicular Lymphoma

Male patient, 56 years old, admitted to the hematology clinic. The complete blood count shows leukocytosis with a marked basophilia. Light microscopic examination revealed the presence of atypical lymphocytes. The diagnosis, confirmed by flow cytometric analysis, suggests a phenotype consistent with B-clonal lymphoproliferative disorder, which needs to be integrated by histologic evaluation. A partially reduced positivity for the CD19 marker, controlled and confirmed by the use of different fluorochromes, is signaled. Flow cytometric exam highlighted the presence of clonal expansion of B lymphocytes equal to 60% of lymphocytes and 34% of total leukocytes, with the following immunophenotypic features: lambda++ bright CD19+ (50%) CD20++ bright FMC7++ CD79b++ CD22++. Kappa- CD10- CD200- CD5- CD38- CD123- CD11c- CD25- CD103- CD23- CD43-.

Hema Vision preclassified 183 lymphocytes (87,9%), while MC-80 preclassified 49 lymphocytes (24,5%).

Below are images of atypical lymphocytes captured with Hema Vision (Figure 13-A) and MC-80 (Figure 13-B).

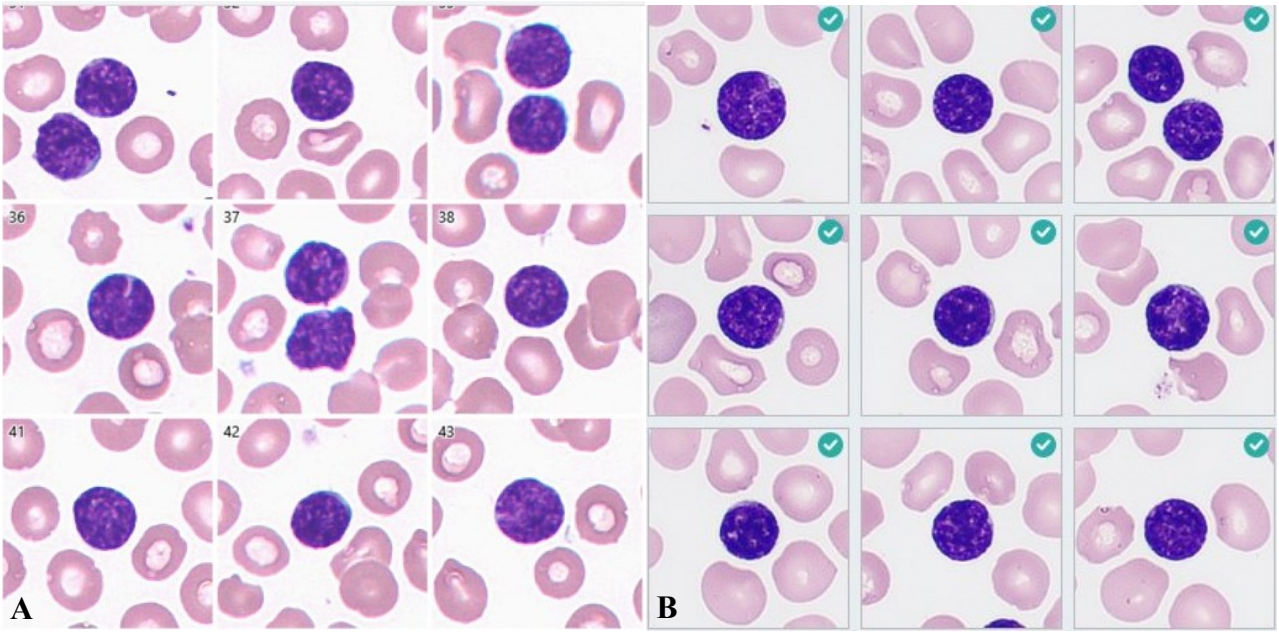

Figure 13. Atypical lymphocytes captured with Hema Vision (A) and MC-80 (B).

4.6 Case 6: Virosis (EBV)

Female patient, 15 years old, admitted from the pediatrics department. The complete blood count shows leukocytosis with a marked lymphocytosis. Light microscopic examination revealed the presence of reactive lymphocytes compatible with a virosis; haematological investigation is recommended. Serological testing confirmed EBV (Epstein-Barr Virus) infection: EBV VCA IgM > 160 UI/ml, EBV VCA IgG 15,5 UI/ml.

Hema Vision preclassified 16 plasmacytes (8%) and 11 reactive lymphocytes (5,5%); MC-80 preclassified 0 plasmacytes and 33 reactive lymphocytes (16,5%).

Below are images of reactive lymphocytes captured with Hema Vision (Figure 14-A) and MC-80 (Figure 14-B).

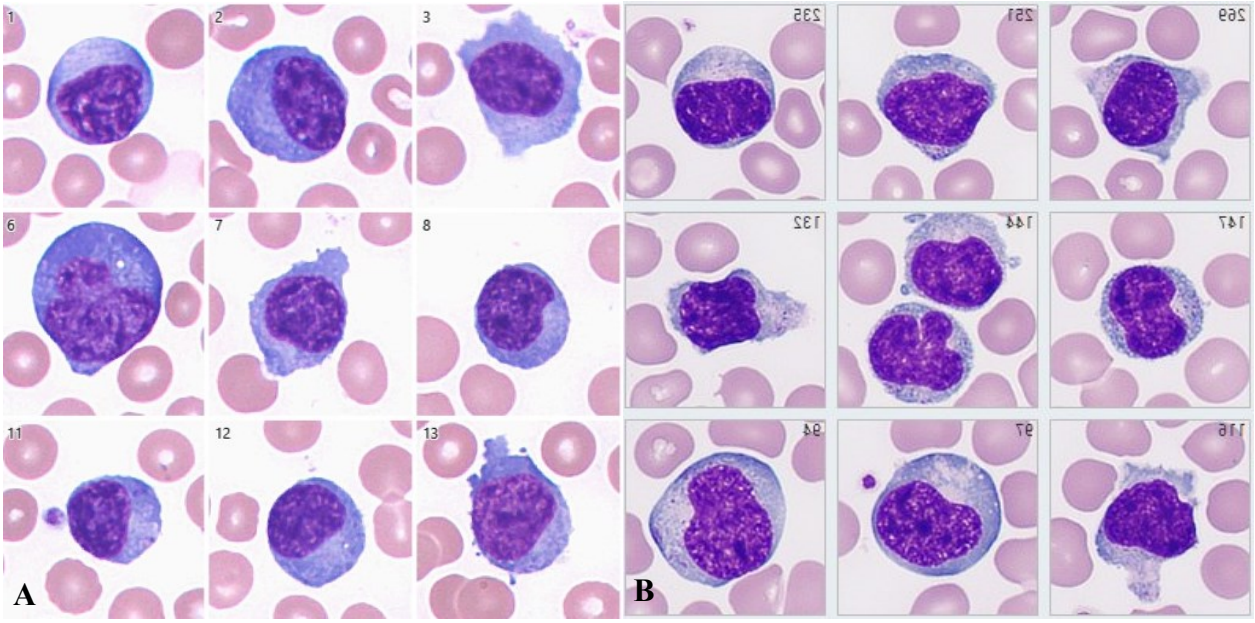

Figure 14. Reactive lymphocytes captured with Hema Vision (A) and MC-80 (B).

5. DISCUSSION

The development of automated digital cell morphology analyzers has facilitated the standardization of differential counting of blood cells and overcome the disadvantages of manual microscopic counting, which has increased reliability and efficiency.[18] These analyzers use advanced imaging techniques such as high-resolution microscopy and digital imaging to capture detailed cell images.

Many digital morphology systems are designed to integrate seamlessly with laboratory information systems (LIS) and other digital health platforms. This integration streamlines workflows, facilitates data management, and improves the overall connectivity of diagnostic processes.[19]

Recently, more and more morphology analyzers have started incorporating artificial intelligence (AI) algorithms to support leukocyte classification and continuously improve their analytical capabilities. These systems can learn, adapt, and evolve from large data sets to recognize better and classify various cellular abnormalities. In addition, these analyzers support important functions in laboratory hematology, including digital image storage, educational purposes, and training opportunities.[20]

In the study described, the performance of two automated hematology analyzers, the Mindray MC-80 (Mindray) and the Vision Hema (West Medica), was compared to manual microscopic counting, which is considered the gold standard. Peripheral blood smears from patients with different hematologic diseases were analyzed to ensure a high variability of cell morphologies.

The study showed that the Vision Hema analyzer showed better agreement with manual microscopy than the MC-80. This assessment is based on a direct comparison between automated pre-classifications and manual counts performed on peripheral blood smears from patients with hematologic disorders. However, the bias found in Vision Hema concerning monocytes, eosinophils, and metamyelocytes would not change the diagnostic-therapeutic processes: for these leukocyte subpopulations, the information provided by Vision Hema was in any case sufficiently accurate for daily clinical use. Moderate to high agreement between Vision Hema and manual microscopy, except basophils, was also observed in the study by Yoon et al.[21]

In contrast, pre-classification of MC-80 showed significant bias compared to manual light microscopy reading for lymphocytes, monocytes, basophils, band cells, myelocytes, and metamyelocytes. However, only the bias in lymphocytes and basophils would have a significant clinical relevance that would influence the diagnostic and therapeutic process.

In particular, the MC-80 misidentified smudge cells as basophils, leading to misclassification, and some abnormal lymphocytes were misidentified as blast cells in lymphoid diseases, leading to an underestimation of lymphocyte presence compared to manual microscopy (Table 3 and Figure 7).

Low performance in the identification of immature granulocytes (band cells, myelocytes and metamyelocytes) was also reported in a previous study by Khongjaroensakun et al.[22]

A critical aspect of our study was the underestimation of the percentage of blasts in peripheral blood by both digitized morphology technologies compared to the expected values observed by the experienced hematologist. This discrepancy is particularly significant and varies between the two platforms studied.

Hema Vision detects blasts with an average percentage of 32.55%, which is lower than that determined by the expert's manual observation. On the other hand, MC-80 performed better, but not without limitations. MC-80 underestimated the percentage of blasts by 17.50% compared to the expected blasts. Our results are consistent with several previous studies.[23,7,11]

This underestimation of blast percentage by both platforms could have important clinical implications. Blasts are critical for diagnosing and monitoring various hematologic disorders, including leukemic diseases. Accurate identification and quantification of blasts are critical for establishing the correct treatment plan and monitoring response to therapy. The margin of error shown in our analysis therefore suggests that the results obtained with these technologies need to be manually verified, especially in critical clinical cases. It may be useful to develop more sophisticated and specific machine-learning algorithms for blast detection. In addition, the implementation of continuous calibration processes that rely on feedback from experienced hematologists could improve the accuracy of the platforms.

However, the MC-80 is the first digital morphology analyzer to provide pre-classification for abnormal promyelocytes and abnormal lymphocytes, a feature that is clinically important for screening acute promyelocytic leukemia (APL) and lymphoma.

Among the AML patients enrolled in the study, we found 2 cases of APL. In both samples, abnormal promyelocytes were automatically identified by the device (Figure 5), confirming the ability of the MC-80 to detect these abnormal cells.

Early detection of promyelocytes in the blood smear and then early diagnosis of APL through the detection of promyelocytes is crucial as this form of leukemia progresses rapidly and aggressively and requires rapid and accurate diagnosis to initiate treatment quickly and avoid severe and potentially fatal complications such as disseminated intravascular coagulation (DIC).[24]

Furthermore, in this study we found that the MC-80 can detect abnormal lymphocytes, as these were automatically identified in some smears from patients with nodal or splenic marginal zone lymphoma (MZL), mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL); an ability that was also demonstrated in the study by Merino et al.[7]

Further studies are needed to investigate the system's ability to identify promyelocytes and abnormal lymphoid cells.

One of the main limitations of our study is the small size of the sample analyzed. This is because we decided to consider only the blood counts of patients on their first admission to the emergency department. This particular selection allowed us to focus on a “clean” group of clinical cases, without ongoing drug and/or chemotherapeutic treatments, but it also limited the number of cases analyzed.

In addition, our study focused exclusively on the assessment of the morphology of the leukocyte populations by the Hema Vision and MC-80 platforms. Although this analysis provided valuable information on the capabilities of both technologies in correctly identifying and classifying different white blood cell populations, we did not examine the morphology of the erythrocyte and platelet populations.[25,26]

This is an important aspect that would merit further investigation. The morphology of erythrocytes and platelets can provide crucial insights for the diagnosis and monitoring of various hematologic disorders. However, the inclusion of a dedicated case history for the analysis of erythrocytes and platelets requires a different methodological approach and a specific sample, which was not the subject of our current study.

In conclusion, while recognizing the strengths of our work, which is the first to compare the performance of Hema Vision and MC-80 in the assessment of leukocyte morphology, we must nevertheless point out that further studies that consider larger samples and a more complete spectrum of blood cell populations are required for a full evaluation of the diagnostic capabilities of these technologies.

6. CONCLUSION

Currently, morphologic examination is the primary method for rapid and accurate diagnosis of patients with hematologic malignancies. The identification of abnormal cells, especially blast cells and abnormal lymphoid cells, is a challenge. According to the World Health Organization (WHO), the diagnosis of acute leukemia (AL) requires a combination of medical history, morphological examination, molecular genetic analysis, and immunophenotyping.[27] Cytomorphology is an indispensable starting point for the diagnosis of hematologic diseases and remains crucial in hematologic diagnostics as it enables rapid assessment of samples and facilitates efficient and cost-effective diagnostic procedures. Trained hematologists can easily recognize abnormalities in cell morphology and distinguish between normal and abnormal (possibly leukemic) cells.[28]

In laboratory medicine, however, we are observing an increasing deficit of dedicated, trained, and experienced hematology experts and an increase in hematological diseases. Digitized morphology can be a great support in a time of staff shortage.

In our study, we investigated two digitized morphology technologies to understand how well they can support the experienced operator in the assessment of pathological peripheral blood smears. Each of the platforms studied had unique characteristics that influenced their effectiveness and adaptability to different laboratory environments.

Our data showed that Hema Vision has lower discordance in identifying different leukocyte populations and higher accuracy in classifying atypical lymphocytes and smudge cells in chronic lymphocytic leukemias compared to MC-80. However, the Hema Vision showed limitations in the accurate detection of blasts and atypical lymphocytes associated with different types of lymphomas. On the other hand, the MC-80 was particularly effective in detecting blasts and atypical lymphocytes and provided better image quality than the Hema Vision. The MC-80's high-performance lens and advanced image sensor provide high-resolution images that reproduce the real image under the microscope, making it easier for the operator to accurately distinguish between different pathological cells.

In addition, the MC-80 integrates seamlessly with Mindray's CAL 8000 hematology line. This makes it the ideal choice for large laboratory routines where test volume management is critical and full automation is crucial for efficient workflow management. Its ability to fully integrate automation and deliver high image quality makes it indispensable for those areas where speed and accuracy are essential for processing large volumes of samples daily.

In contrast, Hema Vision cannot be directly integrated into an automation line for hematology. This may seem like a limitation, but Hema Vision represents an ideal balance between manual light microscopy and automation. It allows the operator to examine the digitized slide as if under a light microscope and provides a flexibility that is well suited for situations where the workload is not so high that full automation is required, but operational efficiency is still desired.

To summarize, both technologies are optimal solutions. While Hema Vision's combination of manual and digitized techniques makes it more suitable for medium-sized laboratories, the MC-80 is the preferred solution for larger facilities that require complete automation and uncompromising image quality. Hema Vision and MC-80 provide valuable tools for the assessment of leukocyte populations, but their ability to accurately quantify abnormal cells, especially blasts, needs to be improved to match the reliability of manual observation by experts. Continuous training of algorithms based on users' experience in daily routine could be the solution to optimize pre-classification.

To date, however, the cell reclassification and morphological review should be performed by trained and experienced hematology experts as described in the ICSH review and recommendations.[9]

7. BIBLIOGRAPHY

1. https://www.agendadigitale.eu/tag/intelligenza-artificiale/
2. https://wm-vision.com/en/product/hema
3. Herman DS, Rhoads DD, Schulz WL, Durant TJS. Artificial Intelligence and Mapping a New Direction in Laboratory Medicine: A Review. Clin Chem. 2021 Nov 1;67(11):1466-1482. doi: 10.1093/clinchem/hvab165. PMID: 34557917.
4. Brereton M, De La Salle B, Ardern J, Hyde K, Burthem J. Do We Know Why We Make Errors in Morphological Diagnosis? An Analysis of Approach and Decision-Making in Haematological Morphology. EBioMedicine. 2015 Jul 18;2(9):1224-34. doi: 10.1016/j.ebiom.2015.07.020. PMID: 26501122; PMCID: PMC4588379.
5. Tefferi A, Hanson CA, Inwards DJ. How to interpret and pursue an abnormal complete blood cell count in adults. Mayo Clin Proc. 2005 Jul;80(7):923-36. doi: 10.4065/80.7.923. PMID: 16007898; PMCID: PMC7127472.
6. Gulati G, Song J, Florea AD, Gong J. Purpose and criteria for blood smear scan, blood smear examination, and blood smear review. Ann Lab Med. 2013 Jan;33(1):1-7. doi: 10.3343/alm.2013.33.1.1. Epub 2012 Dec 17. PMID: 23301216; PMCID: PMC3535191.
7. Merino A, Laguna J, Rodríguez-García M, Julian J, Casanova A, Molina A. Performance of the new MC-80 automated digital cell morphology analyser in detection of normal and abnormal blood cells: Comparison with the CellaVision DM9600. Int J Lab Hematol. 2024 Feb;46(1):72-82. doi: 10.1111/ijlh.14178. Epub 2023 Sep 25. PMID: 37746889.
8. Merino A, Puigví L, Boldú L, Alférez S, Rodellar J. Optimizing morphology through blood cell image analysis. Int J Lab Hematol. 2018 May;40 Suppl 1:54-61. doi: 10.1111/ijlh.12832. PMID: 29741256.
9. Kratz A, Lee SH, Zini G, Riedl JA, Hur M, Machin S; International Council for Standardization in Haematology. Digital morphology analyzers in hematology: ICSH review and recommendations. Int J Lab Hematol. 2019 Aug;41(4):437-447. doi: 10.1111/ijlh.13042. Epub 2019 May 2. PMID: 31046197.
10. Zini G, Mancini F, Rossi E, Landucci S, d'Onofrio G. Artificial intelligence and the blood film: Performance of the MC-80 digital morphology analyzer in samples with neoplastic and reactive cell types. Int J Lab Hematol. 2023 Dec;45(6):881-889. doi: 10.1111/ijlh.14160. Epub 2023 Aug 28. PMID: 37641457.
11. Yoon S, Hur M, Park M, Kim H, Kim SW, Lee TH, Nam M, Moon HW, Yun YM. Performance of digital morphology analyzer Vision Pro on white blood cell differentials. Clin Chem Lab Med. 2021 Jan 20;59(6):1099-1106. doi: 10.1515/cclm-2020-1701. PMID: 33470955.

12. Ye X, Fang L, Chen Y, Tong J, Ning X, Feng L, Xu Y, Yang D. Performance comparison of two automated digital morphology analyzers for leukocyte differential in patients with malignant hematological diseases: Mindray MC-80 and Sysmex DI-60. Int J Lab Hematol. 2024 Jun;46(3):457-465. doi: 10.1111/ijlh.14227. Epub 2024 Jan 11. PMID: 38212663.
13. Blumenreich MS. The White Blood Cell and Differential Count. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston: Butterworths; 1990. Chapter 153. PMID: 21250104.
14. Kim AH, Lee W, Kim M, Kim Y, Han K. White blood cell differential counts in severely leukopenic samples: a comparative analysis of different solutions available in modern laboratory hematology. Blood Res. 2014 Jun;49(2):120-6. doi: 10.5045/br.2014.49.2.120. Epub 2014 Jun 25. PMID: 25025014; PMCID: PMC4090333.
15. https://boule.com/knowledge-center/manual-microscopy-procedure/
16. https://wm-vision.com/en/product/hema
17. https://www.mindray.com/en/products/laboratory-diagnostics/hematology/cellular-analysis-line/mc-80
18. Kratz A, Lee SH, Zini G, Riedl JA, Hur M, Machin S; International Council for Standardization in Haematology. Digital morphology analyzers in hematology: ICSH review and recommendations. Int J Lab Hematol. 2019 Aug;41(4):437-447. doi: 10.1111/ijlh.13042. Epub 2019 May 2. PMID: 31046197.
19. Xing Y, Liu X, Dai J, Ge X, Wang Q, Hu Z, Wu Z, Zeng X, Xu D, Qu C. Artificial intelligence of digital morphology analyzers improves the efficiency of manual leukocyte differentiation of peripheral blood. BMC Med Inform Decis Mak. 2023 Mar 29;23(1):50. doi: 10.1186/s12911-023-02153-z. PMID: 36991420; PMCID: PMC10061886.
20. Lin E, Fuda F, Luu HS, Cox AM, Fang F, Feng J, Chen M. Digital pathology and artificial intelligence as the next chapter in diagnostic hematopathology. Semin Diagn Pathol. 2023 Mar;40(2):88-94. doi: 10.1053/j.semdp.2023.02.001. Epub 2023 Feb 15. PMID: 36801182.
21. Yoon S, Hur M, Park M, Kim H, Kim SW, Lee TH, Nam M, Moon HW, Yun YM. Performance of digital morphology analyzer Vision Pro on white blood cell differentials. Clin Chem Lab Med. 2021 Jan 20;59(6):1099-1106. doi: 10.1515/cclm-2020-1701. PMID: 33470955.
22. Khongjaroensakun N, Chaothai N, Chamchomdao L, Suriyachand K, Paisooksantivatana K. White blood cell differentials performance of a new automated digital cell morphology analyzer: Mindray MC-80. Int J Lab Hematol. 2023 Oct;45(5):691-699. doi: 10.1111/ijlh.14119. Epub 2023 Jun 20. PMID: 37338111.

23. Ye X, Fang L, Chen Y, Tong J, Ning X, Feng L, Xu Y, Yang D. Performance comparison of two automated digital morphology analyzers for leukocyte differential in patients with malignant hematological diseases: Mindray MC-80 and Sysmex DI-60. Int J Lab Hematol. 2024 Jun;46(3):457-465. doi: 10.1111/ijlh.14227. Epub 2024 Jan 11. PMID: 38212663.
24. Cingam SR, Koshy NV. Acute Promyelocytic Leukemia. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29083825.
25. Kim HN, Hur M, Kim H, Kim SW, Moon HW, Yun YM. Performance of automated digital cell imaging analyzer Sysmex DI-60. Clin Chem Lab Med. 2017 Nov 27;56(1):94-102. doi: 10.1515/cclm-2017-0132. PMID: 28672770.
26. Yu H, Ok CY, Hesse A, Nordell P, Connor D, Sjostedt E, Pechet L, Snyder LM. Evaluation of an automated digital imaging system, Nextslide Digital Review Network, for examination of peripheral blood smears. Arch Pathol Lab Med. 2012 Jun;136(6):660-7. doi: 10.5858/arpa.2011-0285-OA. PMID: 22646275.
27. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. doi: 10.1182/blood-2016-03-643544. Epub 2016 Apr 11. PMID: 27069254.
28. Haferlach T, Schmidts I. The power and potential of integrated diagnostics in acute myeloid leukaemia. Br J Haematol. 2020 Jan;188(1):36-48. doi: 10.1111/bjh.16360. Epub 2019 Dec 6. PMID: 31808952; PMCID: PMC6973013.