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Morphogo: An Automatic Bone Marrow Cell Classification System on Digital Images Analyzed by Artificial Intelligence

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Keywords
Digital image · Bone marrow aspirate smear · Cell morphology · Automatic cell classification

Abstract
Introduction: The nucleated-cell differential count on the bone marrow aspirate smears is required for the clinical diagnosis of hematological malignancy. Manual bone marrow differential count is time consuming and lacks consistency. In this study, a novel artificial intelligence (AI)-based system was developed to perform cell automatic classification of bone marrow cells and determine its potential clinical applications. ***Materials and Methods:*** Bone marrow aspirate smears were collected from the Xinqiao Hospital of Army Medical University. First, an automated analysis system (*Morphogo*) scanned and generated whole digital images of bone marrow smears. Then, the nucleated marrow cells in the selected areas of the smears at a magnification of ×1,000 were analyzed by the software utilizing an AI-based platform. The cell classification results were further reviewed and confirmed independently by 2 experienced pathologists. The automatic cell classification performance of the system was evaluated using 3 categories: accuracy, sensitivity, and specificity. Correlation coefficients and linear regression equations between automatic cell classification by the AI-based system and concurrent manual differential count were calculated. ***Results:*** In 230 cases, the classification accuracy was above 85.7% for hematopoietic lineage cells. Averages of sensitivity and specificity of the system were found to be 69.4 and 97.2%, respectively. The differential cell percentage of the automated count based on 200–500 cell counts was correlated with differential cell percentage provided by the pathologists for granulocytes, erythrocytes, and lymphocytes ($r \geq 0.762$, $p < 0.001$). ***Discussion/Conclusion:*** This pilot study confirmed that the *Morphogo* system is a reliable tool for automatic bone marrow cell differential count analysis and has potential for clinical applications. Current ongoing large-scale multicenter validation studies will provide more information to further confirm the clinical utility of the system.

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Introduction

Bone marrow aspirate smear examination is a crucial part of the workup for diagnosing hematological diseases, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), multiple myeloma (MM), and lymphoma. The microscopic examination of bone marrow remains one of the key diagnostic procedures in hematology. In accordance with the newest guidelines related to the diagnosis of bone marrow and lymphatic system malignancies issued by the World Health Organization (WHO) [1], the importance of microscopic examinations of bone marrow aspirates, specifically the morphological criteria, has been further emphasized and defined to avoid ambiguity. However, manual bone marrow differential count is time consuming and tedious and requires well-trained, experienced technicians [2, 3]. Lack of diagnostic consistency also remains a problem. Currently, the manual microscope method is still considered the gold standard, despite the fact that well-known intraobserver variability among different pathologists may result in variable diagnostic opinions.

In recent years, there has been an increasing interest in developing computational methods to assist pathologists in histological analysis via digital images [4–6] and artificial intelligence (AI) systems [7]. Automated image processing systems have been developed to address the difficulties of cell classification in blood smear [4–6, 8, 9] and bone marrow aspirate smears [8, 10, 11]. Studies have shown that the CellaVision® DM96 [4, 6, 9] and DI-60 [12] digital systems are an efficient tool to perform leukocyte count and differential in clinical laboratories. Although critical improvements have been made during the last few years in hematology analyzers, no significant progress has been made in terms of automatic examination of bone marrow cells. Automated differential count of nucleated cells in bone marrow smears remains problematic and has not been sufficiently researched. The main difficulties lie in the following: (1) cells in the normal bone marrow are heterogeneous. Normal bone marrow contains mesenchymal cells, endothelial cells, and hematopoietic cells at different development stages with a spectrum of maturation, ranging from early-stage precursors to functionally mature cells. (2) In pathological conditions, specific cell types can proliferate to clonal leukemia cells or reduce rapidly as in conditions such as peripheral cytopenia. Most of the systems in the market are still challenged by relatively low specificity scores in the preclassification stage, resulting in the final result still being subject to an experienced pathologist's manual validation.

Table 1. Information of smears

Types	Cases	Types	Cases
AML	56	Abnormal blasts	7
ALL	28	Metastatic tumor cells	1
CLL	9	Hyperplastic bone marrow	55
CML	6	Hypoplasia of bone marrow	6
MDS	17	Reactive bone marrow	7
MM	16	No obvious abnormality	4
Abnormal granulocytes	1	Others	17

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma.

The *Morphogo* system integrates bone marrow cell differential count results with digital imaging to improve the efficiency and accuracy of the diagnosis of hematological diseases. A suggested use of this system is as an initial screening tool to filter out potential patients from healthy individuals. Any abnormal results that this system flags can then be sent out for subsequent ancillary tests, such as flow cytometry, molecular testing, or cytogenetic testing, which can then be used to finalize the diagnosis.

Materials and Methods

Bone marrow aspirate smears were randomly collected from the Xinqiao Hospital of Army Medical University. An analysis system (*Morphogo*) was applied to scan and generate whole digital images of bone marrow smears at a magnification of ×400; then, the nucleated marrow cells in the selected areas of the smears (×1,000) were analyzed by the software with AI-based platform. Automated cell classification results were reviewed and confirmed independently by 2 experienced pathologists. The cell classification performance of the system was evaluated using accuracy, sensitivity, and specificity. Correlation coefficients and linear regression equations between automatic cell differential counts by the system and manual count were also calculated.

Bone Marrow Aspirate Smears

Two hundred thirty cases of bone marrow direct aspirate smears from 76 males and 154 females (average age of 44.02 ± 21.22 years) were collected from historical archives and daily examinations in the Xinqiao Hospital of Army Medical University from November 26, 2018, to January 30, 2019. All smears were well stained by Wright-Giemsa protocol, and the smear and staining quality conformed to the requirements of the National Guide to Clinical Laboratory Procedures (NGCLP, fourth edition) or the recommendations of the International Council for Standardization in Haematology (ICSH). The smears were collected from patients with AML, acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL),

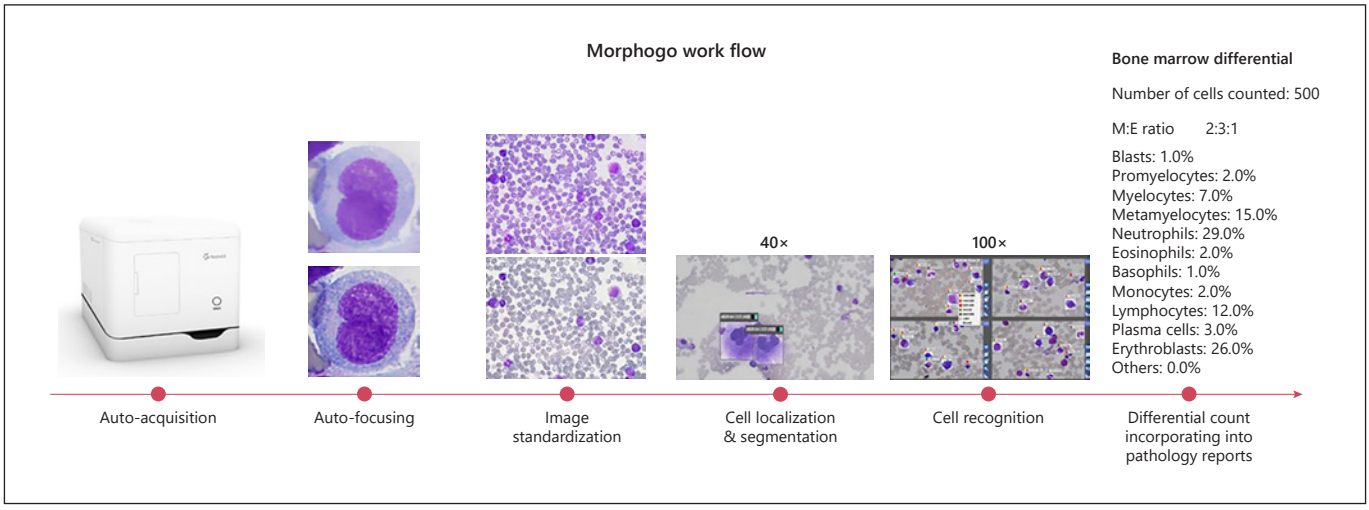

Fig. 1. The workflow of the *Morphogo* system.

chronic myeloid leukemia (CML), MDS, MM, infection, chronic anemia of unknown etiology, and so on (shown in Table 1). Another 111 cases of bone marrow direct aspirate smears from 64 males and 47 females, with an average age of 42.11 ± 21.21 years, were collected for correlation analysis.

Instrument

In this study, an automated AI-based system utilizing convolutional neural networks was used to classify and analyze nucleated cells in bone marrow aspirate smears. This system, named *Morphogo* (Hangzhou Zhiwei Information and Technology Ltd.), utilizes 27 layers of neural networks. After training with over three thousand bone marrow samples, the system currently identifies more than 45 types of bone marrow cells. This system can scan the entire slide of a bone marrow smear using ×40 objective lens and subsequently acquire dozens of detailed cell images in a selected analysis area using ×100 objective lens. For every slide, the system can count and differentiate up to 500 nucleated cells.

Digital Workflow

The digital workflow of the system is as follows: first, the area for slide analysis was set up and the slides were put into the system in batches; clear cell images were obtained through autofocusing, and the color of the images with acid or base staining was standardized; then, nucleated cells of bone marrow on the digital images were located, segmented, and identified; finally, the count of cell classification was autocalculated and the results of the cell classification were generated into an analysis report (shown in Fig. 1).

Digitalized slides were obtained from routine examinations of bone marrow smears or archived samples within the last 5 years in the hospitals. Before scanning, an investigator manually selected an appropriate analysis area under the ×10 microscope for ×100 image capturing. Nucleated cells in the analysis area would be located and identified. Standards for selecting nucleated cell analysis areas included the following: (1) around the body-tail junction of the smear where nucleated cells found would be mostly independent but not too separated; (2) mature erythrocytes evenly distributed in a single layer; (3) staining of the smear was clearly red and blue. The system was operated by trained and qualified investigators, and the acquisition process strictly follows the instrument's standard operating procedure.

Cell Classification

In this study, nucleated cells in bone marrow were divided into 12 categories: myeloblasts, promyelocytes, myelocytes, metamyelocytes, neutrophils, eosinophils, basophils, monocytes, erythroblasts, lymphocytes, plasma cells, and others according to WHO classification. First, the preclassification of cells acquired from the selected analysis area was automatically processed and reported by the instrument. Then, the preclassification results were reviewed by investigators. The system was further validated by experienced hematopathologists in context of the diagnosis, and any cell types that the system labeled unidentifiable or incorrectly identified were corrected. Finally, results of cell classification would be subsequently released to the information system after investigators' review. The results of cell classification will be confirmed after manual proofreading. The consent among the reviewers was applied in order to avoid intraobserver variability. We tried to include some of the cytological dysplastic features such as nuclear-cytoplasmic dyssynchrony and hypogranularity as ancillary criteria to improve the accuracy of classification of the immature cells. A cell sample was classified as false positive (FP) or false negative (FN) if it was incorrectly identified by the system and reclassified by investigators. A confusion matrix of cell classification was generated based on these results. The sensitivity, specificity, consistency, false positive rate, and false negative rate were calculated based on the confusion matrix to evaluate the instrument's ability to preclassify nucleated cells in bone marrow aspirate smears.

Differential Counts and Cell Series Proportions

The selected up to 500 nucleated cells were acquired from each bone marrow aspirate specimen. To calculate cell series proportions, acquired nucleated cells were classified into 5 series: granulocytes, erythroid, lymphoid, monocytes, and plasma cells. For cell classification using the instrument, cell series proportions were calculated automatically after the machine completed its scanning

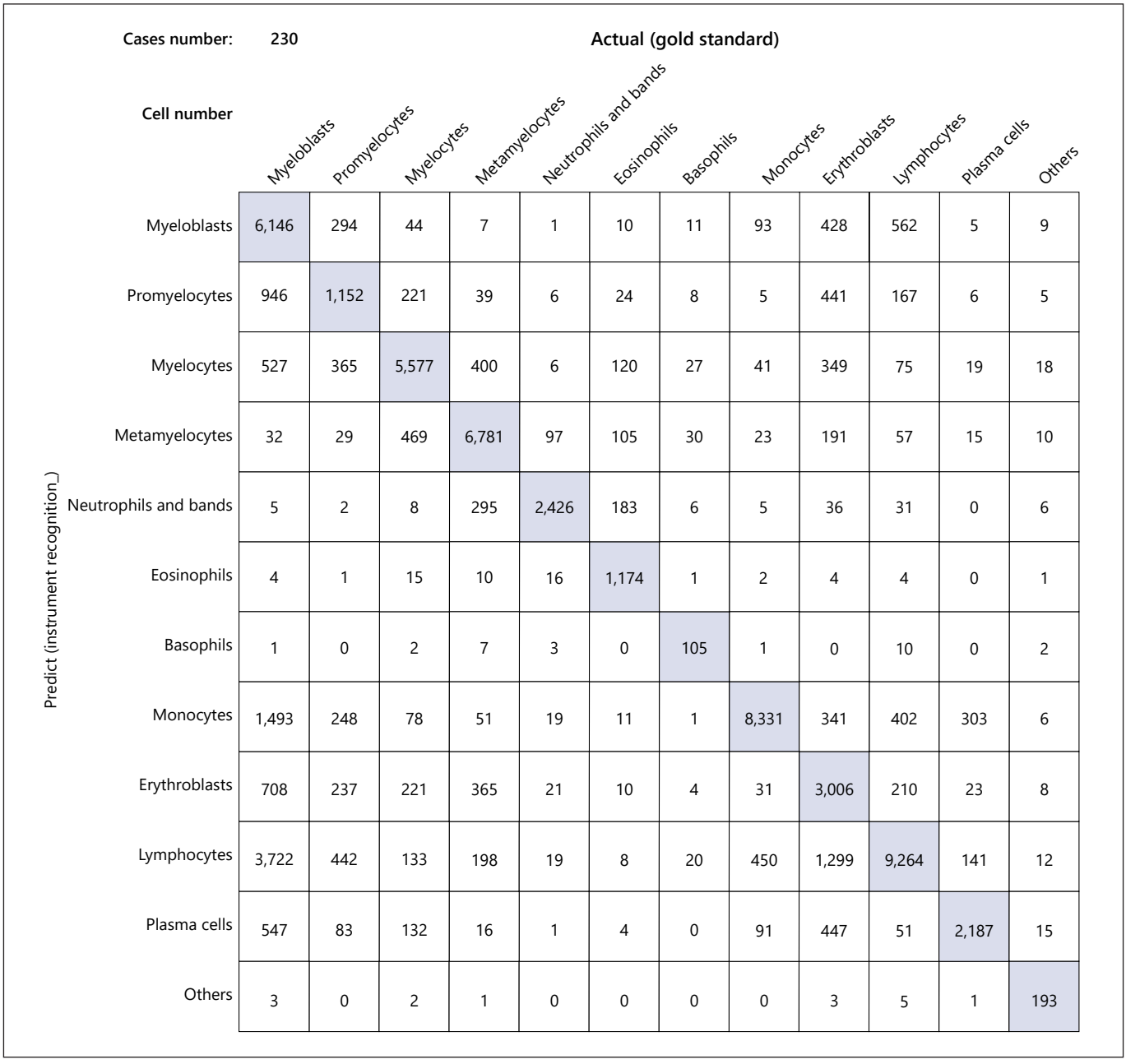

Fig. 2. The summary of data of predication and variance of cell classification obtained by automatic preclassification and manual proofreading of differential counts in the training set of 230 patients' bone marrow specimen.

and analysis of bone marrow aspirate smears. For manual bone marrow examinations, cell series proportions were first differentiated and calculated by laboratory technicians using standard microscopic techniques and then reviewed by an experienced pathologist.

A total of 111 pairs of sample data were obtained. Consistency analysis using linear regression was performed to evaluate the consistency between the automatic differential counts and the manual examination results.

Statistical Analysis

Numerical variables were described as mean and SD ($x \pm s$). Correlation coefficient was determined by the *Pearson correlation test*. All analyses were performed using SPSS 18 (IBM, Chicago, IL, USA), Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA), and Python 3.6.5 (Python Software Foundation) with libraries of Pycm 2.1 [13]. All the tests were performed by the 2-tailed test, with $p < 0.05$ considered statistically significant.

Table 2. Performance of the instrument to classify nucleated cells in bone marrow aspirates

Class	Accuracy, %	Sensitivity, %	Specificity, %	FPR, %	FNR, %
Myeloblasts	85.7	43.5	97.2	2.8	85.7
Promyelocytes	94.6	40.4	97.0	3.0	94.6
Myelocytes	95.0	80.8	96.7	3.3	95.0
Metamyelocytes	96.3	83.0	98.2	1.8	96.3
Neutrophils	98.8	92.8	99.1	0.9	98.8
Eosinophils	99.2	71.2	99.9	0.1	99.2
Basophils	99.8	49.3	100.0	0.0	99.8
Monocytes	94.4	91.8	94.8	5.2	94.4
Erythroblasts	91.9	45.9	96.9	3.1	91.9
Lymphocytes	87.8	85.5	88.3	11.7	87.8
Plasmocytes	97.1	80.7	97.8	2.2	97.1
Others	99.8	67.7	100.0	0.0	99.8
Macroaverage	95.0	69.4	97.2	2.8	95.0

FPR, false positive rate or fall out; FNR, false negative rate or miss rate.

Results

Performance of Cell Classification

In this study, a total of 65,986 nucleated cells were obtained from 230 bone marrow smears using digital scanning by the system. The confusion matrix of cell classification obtained by automatic preclassification and manual proofreading is shown in Figure 2. The rows correspond to the true classification, and the columns correspond to the AI-predicted result. Diagonal and off-diagonal cells correspond to correctly and incorrectly classified observations, respectively. The results of accuracy, sensitivity, specificity, consistency, false positive rate, and false negative rate of bone marrow nucleated cell preclassification by the instrument were calculated by using morphological classification results of nucleated cells reviewed and audited by researchers as the final results of standard.

The accuracy of morphological preclassification of nucleated cells in bone marrow aspirate smears by the instrument was above 85.7% for every class of granulocytes, including myeloblasts, promyelocytes, myelocytes. metamyelocytes, neutrophils, eosinophils, and basophils. The classification accuracies of erythrocytes, lymphocytes, monocytes, and plasma cells were 91.9, 87.9, 97.1, and 99.8%, respectively. Sensitivity varied greatly with cell types, ranging from 40.4% for promyelocytes to 92.8% for neutrophils, with an average value of 69.4%. The specificities were above 88.3% for all classes of nucleated cells, with an average value of 97.2% and a range of 88.3–99.9%. The false positive rate was <5%, ranging from 0.02 to 3.3%, with exception for monocytes and lymphocytes, with the false positive rate of 5.2 and 8.9%. The false negative rate varied greatly with cell types and ranges from 7.2% for neutrophils to 59.6% for promyelocytes (shown in Table 2).

Agreement of Differential Proportions

The consistency of classification results of the instrument and manual differential with microscope of nucleated cells in bone marrow aspirates was assessed by correlation analysis. Results show that there are high correlations between the 2 methods for granulocytes, erythrocytes, and lymphocytes ($r \geq 0.762$, $p < 0.001$, shown in Fig. 3a–c). Linear regression equations are as follows: granulocytes $Y = 0.845\ X + 0.076$, erythrocytes $Y = 0.863\ X$, and lymphocytes $Y = 0.795\ X + 0.040$. However, there are only low correlations between the 2 differential methods for monocytes and plasma cells ($r < 0.459$, $p < 0.001$, shown in Fig. 3d, e), and there is no correlation for myeloblasts ($p = 0.110$, shown in Fig. 3f). The scatterplots of differential proportions of 2 methods are shown in Figure 3.

Discussion/Conclusion

In the study, we analyzed the cells in the bone marrow smears using digital slides and automated cell analysis techniques. Morphological analysis of blood smears [10] and bone marrow smears [1] is still an essential element of hematological diagnostics. In peripheral blood, automated blood cell analysis techniques are well established and widely used. The successful detection and classification of mature peripheral blood cells demonstrate high

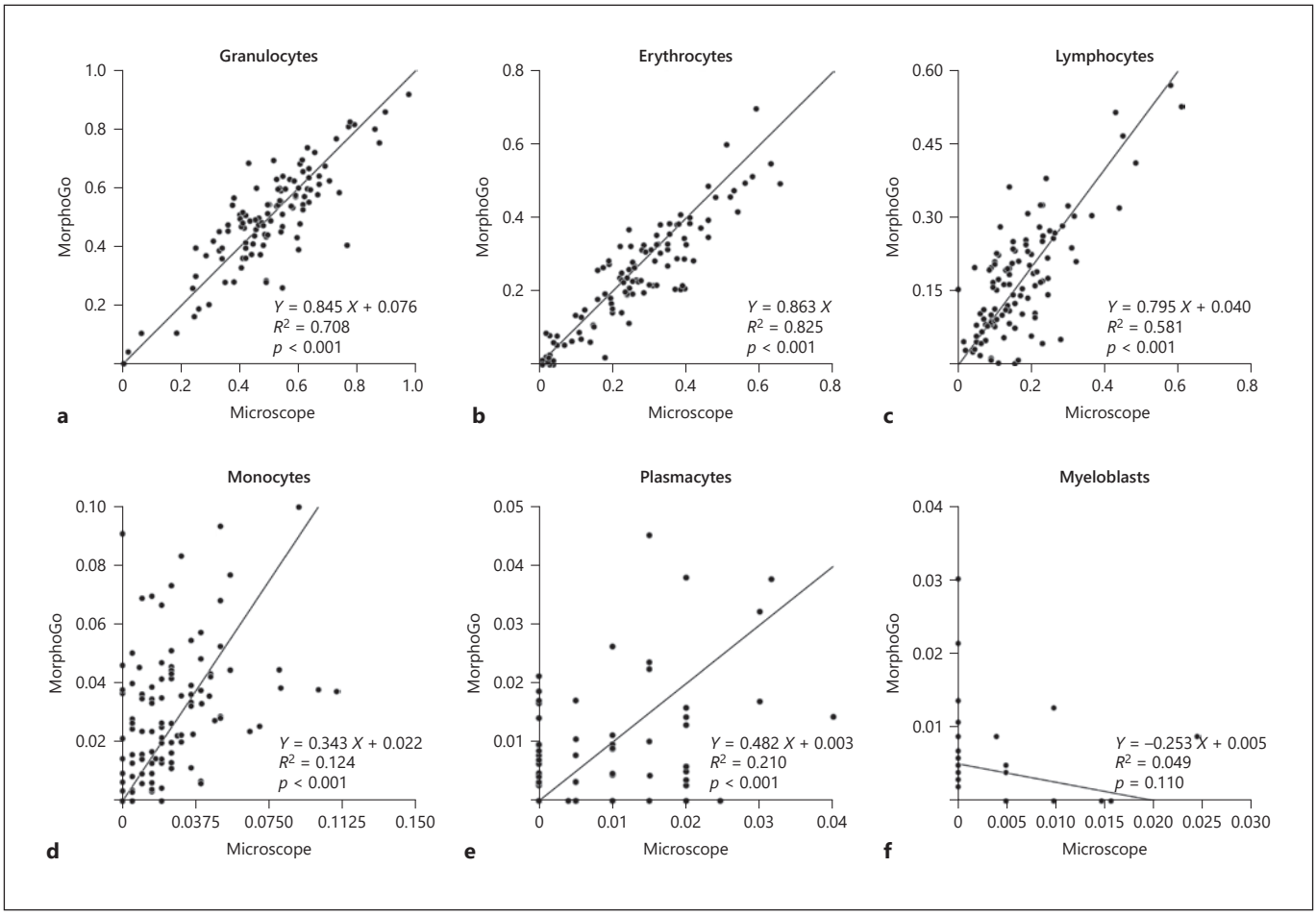

Fig. 3. The correlation of the computer differential cell counts with manual differentials by an experienced pathologist is provided. Scatterplots with lines of linear regression generated following paired counts of 111 patients' marrow smears are shown for each data set. The relative proportions of granulocytes (**a**), erythrocytes (**b**), lymphocytes (**c**), monocytes (**d**), plasma cells (**e**), and myeloblasts (**f**) are measured.

sensitivity scores [6, 14, 15]. Although some progress has been made in the study of automated analysis of bone marrow cells [8, 10, 11], it is still dependent on the traditional method of manual microscope evaluation, which has limitations [2]. The *Morphogo* system, which enables digital image acquisition and the automatic cell image analysis of bone marrow smears and isolated display of immature cells, dysplastic cells, and blasts, will help improve these problems.

Concurrently, the instrument can also provide a new workflow and utility for any hematology lab. The digital workflow will help improve the efficiency of bone marrow smears and standardize the examination process, and the generated high-quality digital images can also be easily stored, reviewed, and used as teaching material. The system's software first locates, preclassifies, and displays bone marrow nucleated cells, and afterward, the cytologists can review and reclassify the cells, which helps to improve the efficiency of normal cell classification and screen for abnormal cells. Current digital image techniques have been partially successful in peripheral blood analysis as a screening tool for blood cells and some blood diseases [16], although these digital image processing systems are relatively slow and have limited automation [2].

Myeloblasts and promyelocytes are important in diagnosing hematological diseases [1]. In this study, the accuracy and the specificity of the instrument for classifying nucleated cells in bone marrow smears were both high, while the sensitivity varied depending on cell types with limitation in distinguishing the cells with subtle morphological differences such as promonocytes, pro-

myelocytes, and blasts. This indicates that the AI system needs more extensive training in large scale of not only diversified but also well-representative cell types. The recognition of very early erythroblasts is still challenging due to the overlapping features with myeloblasts and hematopoietic stem cells; however, distinguishing between them is important for diagnosing specific hematological disease with marrow regeneration after chemotherapy and/or engrafted hematopoietic stem cell transplantation. Once the system has been trained enough to reach high sensitivity to different cells, it would make digital imaging a good fit as a screening tool for cell quantification, for example, and could be of great help during follow-up of patients with MDS and AML during treatment.

The instrument still has some limitations when extracting sufficient morphological details from erythroblasts due to the instrument's inability to focus on small erythroblasts. Erythroblasts are usually on a different depth of *z* axis from other larger cells and it is only visible on a tiny portion of the camera viewing area. Since erythroblasts are in a similar size category as mature lymphocytes and no detailed features of erythroblasts can be extracted, the instrument is unable to distinguish erythroblasts from mature lymphocytes in some cases. Therefore, to counter this discrepancy, a much larger sample size of erythroblasts needs to be collected in follow-up studies for continued training of the AI system. Our laboratory has been using these specific features to train the computer system with satisfying results.

Another challenge that needs to be addressed for diagnostic purposes is the identification and differentiation of blasts in morphological perspective because for certain pathological conditions it is necessary to clearly distinguish subtle morphological differences among myeloblasts, promyelocytes, pronormoblasts, monoblasts, and lymphoblasts. Combining this with state-of-the art immunophenotyping by flow cytometry and molecular studies will help solve this issue.

As the result showed, the false positive rate of classifying nucleated cells in bone marrow was generally low (<5%) except for monocytes and lymphocytes. The false negative rate of the system was relatively high (>5%) because morphological changes often occur within the same type of cell in the clinical practice. Especially in certain pathological conditions, a higher frequency of irregular forms of cells is found. While they can all be artificially categorized as a specific type of cell, it is possible for the cells to appear slightly variable due to the spectrum of maturation. Since not all forms of cells were accumulated in the AI training set, slight morphological changes in the same type of cells were unrecognizable by the instrument and labeled as "other." To solve this problem, a large range of various forms of the same cell type must be collected, and the training set can be further divided into subtypes according to morphological changes.

When potential morphologic or numeric abnormalities are encountered in a specific case, the automatic capture of digital images will speed up and streamline laboratory workflow. As samples of different forms of cells are added to the instrument's database, the instrument can then identify future samples more accurately. To reduce the false negative rate, the threshold for the system to recognize a certain type of cell should also be adjusted. Furthermore, more attention should be paid to cell types with high false negative rates, and manual examination under a microscope for these types of cells should be carried out when necessary to confirm cell classification.

Correlations between automatic cell classification by the instrument and manual examination under a microscope were analyzed for a preliminary study purpose. The results confirmed the high level of correlations between the automatic classification and manual examinations for granulocytes and erythrocytes. The correlations for different stages of lymphocytes and monocytes are still not optimal. In the literature, both lymphocytes and monocytes have been reported to obtain a good correlation in peripheral blood by other automatic systems [4, 15, 17]. One possible explanation is due to the relatively lower percentage of such cells in the whole nucleated cells in the bone marrow smear. In addition, the selection bias of the scanning location on digital images by instrument's automatic cell classification may not be identical to the manual examinations. Therefore, the final classification of a spectrum of immature myeloid progenitor cells with subtle variability may need additional manual adjustment and supervision to ensure proper results. In peripheral blood, our automated system also shows a good correlation when compared with manual differentiation as well as systems [14]. Therefore, for bone marrow, further extensive training by machine learning and the mathematical algorithm will improve the accuracy of our system. The high sensitivity of our system makes digital imaging extremely suitable as a screening tool for the presence of blast or other malignant cells in marrow aspirates. The potential utility of our system in the diagnosis of MDS, AML, MPN, or MM patients are still under investigation. In addition, the capacity of analyzing a much larger number of cells (more than 500 cells) will significantly improve the accuracy of the percentage of blast count in

most of the common clinical scenarios such as MDS or AML follow-up marrow examination after treatment with chemotherapy or bone marrow transplant.

In summary, this study introduced the technology of automatic classification of nucleated cells by digital images of bone marrow aspirate smears and validated the feasibility of automatic classification system. The implementation of the system into clinical hematology labs will lead to a higher sensitivity and specificity in the detection and classification of hematological diseases. With the application of digital image processing and AI technology in hematology lab automation tracks, the future workflow of hematology labs will be significantly simplified. The technology will provide standardized workflows and automated image-based processes to drive efficiency and quality across the lab. The results obtained in this study show that the AI-based bone marrow morphological analysis system can be a tool for bone marrow smear differential analysis. In the future, large-scale multicenter validation studies are warranted to further validate the clinical utility of this system. The integration of automatic digital image-generated differential count with clinical medical record, immunophenotyping by flow cytometry, cytogenetics, fluorescence in situ hybridization, and next-generation sequencing technology all together will be the future of diagnostic hematology.

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Statement of Ethics

The study protocol STU-2019-0762 (International Multicenter Testing and Validation Computer-Aided System by Artificial Intelligence in the Differential Cell Count on Digital Images of Bone Marrow Aspirates) was reviewed and approved by UTSW Institute's IRB committee on research. The marrow slides were assigned with unique numbers, and all patients' personal information was decoded and not identifiable. The study has been granted an exemption from requiring ethics approval of IRB.

Conflict of Interest Statement

Xinyan Fu, Qiang Li, and Ju Lu are employees of Hangzhou Zhiwei Information & Technology, Ltd. Dr. Mingyi Chen was on the advisory board and received research grant support from ALABS of Zhiwei Information & Technology, Ltd. All the other authors declare that they have no other conflicts of interest.

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Author Contributions

This study was based on multicenter collaborations. Mingyi Chen, Fengqi Fang, and Ju Lu designed and supervised the study. Xiangui Peng led the team of cytologists who carried out cell classification of bone marrow smears. Xiangui Peng and Qiang Li collected raw data of the study. Xinyan Fu, May Fu, and Mingyi Chen carried out data analysis, graphing, illustration, writing, and revision of the manuscript. All the authors contributed to the editing and proofreading of the final manuscript for submission.

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