Abyss. J. Eng. Comput. Vol. 1, No. 1, 2021, 1-10

Abyssinia Journal of Engineering & Computing

Automatic Early Detection and Classification of Leukemia from Microscopic Blood Image

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ABSTRACT

Leukemia is a form of blood cancer that affects white blood cells, and is one of the leading causes of death among humans. Currently, diagnosis of leukemia is done through visual inspection of microscopic images of blood cell, which is time consuming, tedious, and requires trained human experts. Therefore, the lack of an automatic, early, and effective leukemia detection system is a great challenge in Ethiopian hospitals. The main objective of this research is to develop an automatic early detection, and classification system to diagnose leukemia from blood image using machine learning and image processing algorithm. To do the research, 400 leukemic blood images and 50 normal blood images had acquired from Jimma University Specialized Hospital using digital microscope, and preprocessed with contrast enhancement. K-means image segmentation and feature extraction were applied by the system. Multi Class Support Vector Machine has used to provide detection and classification of leukemia disease based on the extracted features parameter. The leukemia disease detection and classification accuracy achieved by developed system is 94.62%. Moreover, 94.17% sensitivity and 100% specificity level has been gained by the system. It takes an average of one minute to provide the diagnosis result. The potential of digital image analysis for leukemia disease diagnosis using artificial intelligence; which is not tedious and time consuming is very beneficial when compared to the manual method. In the future, direct diagnosing system of leukemia without staining process is recommended.

Keywords: White Blood Cells; Segmentation; Feature Extraction; Support Vector Machine

INTRODUCTION

To understand the concept of leukemia in depth, it helps to know the normal blood cells form and its components. From all of the body's tissues, blood is unique due to its existence as the only fluid [1]. The blood smear under a microscope contains useful information for diagnosis of many diseases. There are three kinds of blood cells that are originated from a stem cell; red blood cells (RBCs), those cells carry oxygen all over the body, platelets that help to form blood clots to slow or stop bleeding, and white blood cells (WBCs) that help to fight infection and Platelets those help for blood clotting [2]-[4]. There are five types of WBC (shown in Figure 1) by percentage as: basophil (0–1%), eosinophil (1–5%), lymphocyte (20–45%), monocyte (2–10%) and neutrophil (50–70%). Whereas each WBC type has its own shape of a nucleus and cytoplasm, RBCs have no nuclei [5].

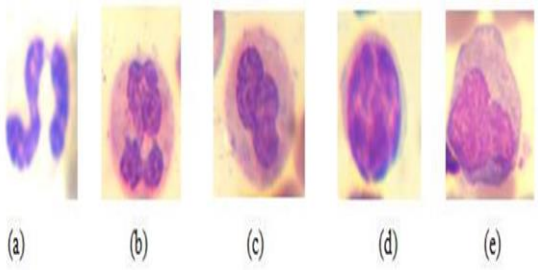

Fig 1. Different types of white blood cells (a) neutrophil, (b) basophil, (c) eosinophil, (d) lymphocyte, (e) monocyte

These cells are found naturally in the human body and work together to fight against infections. Being able to phenotypically differentiate these cells, serve as the basis for an image-processing based solution.

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Leukemia is therefore, a type of cancer pertaining to white blood cells (WBCs), in which abnormal and immature WBCs are produced by the bone marrow and enter the bloodstream [6], [7]. It generates the malignant white blood cells (WBCs) in the human body [8]. It is a type of hematopoietic disease that starts with the bone marrow and results in the development of blast cells. If it is detected late, it will result in death. Leukemia is one of the leading causes of deaths in the world, where an estimated 350,000 people is diagnosed with leukemia every year resulting in the death of 257,000 annually [9]. Unlike normal blood cells, these cells do not die when they become old or damaged; eventually building up and crowding out normal blood cells. The low level of normal blood cells can make it harder for the body to deliver oxygen to the tissues, control bleeding, or fight infections [10].

There are four most common types of leukemia divisions. These are:

This type of leukemia is most common and usually occurs in children aged 2-10 years and adults [11], [12]. ALL is distinguishable via inspection of the lymphocytes: i.e., small, blast cells are uniform, cytoplasm is scanty, round and usually contains single nucleoli inside nucleus [13] as shown in Figure 2.

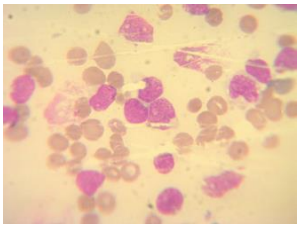


Fig 2. Acute Lymphocytic Leukemia

Acute Myeloid Leukemia (AML) – AML makes up 15–20% of childhood leukemia, roughly 60% of cases occur in people aged younger than 20 years [11]. AML is classified as having large cytoplasm than ALL and the cell is oval and usually contains Euler rod-shape in its cytoplasm. Figure 3 shows an AML image that was captured under digital microscope found in Jimma University Specialized Hospital (JUSH).

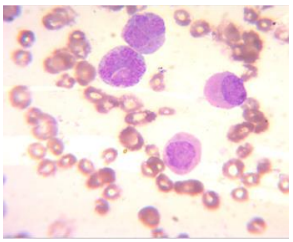


Fig 3. Acute Myeloid Leukemia

This type of leukemia often happens to older patients. This disease almost never affects children or teens. CLL is most notably classified by the presence of clefs as highlighted in Figure 4. Moreover, the appearance of vacuoles and the smear cells, which are abnormally large cells, enable us to differentiate this type of leukemia from the other types [14], [13].

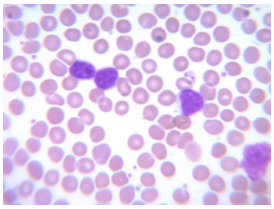


Fig 4. Chronic Lymphocytic Leukemia

Chronic myelogenous leukemia can be detected at any age patient, but in many cases, it is detected in the age between the ages of 35 to 45 years. CML cell is characterized by having a disproportionate number of myeloid cells, which are typically large (12-18 μm), exhibiting a sizeable nucleus with many nucleoli. Figure 5 depicts this fact [15][13].

Acute Lymphocytic Leukemia (ALL) –

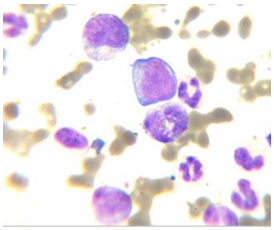


Fig 5. Chronic Myeloid Leukemia

Currently, in developing nations, suspicious and careful microscopic examination of the stained blood smear is the only way to diagnose leukemia [3]. After staining the blood, the hematologist would carefully examine and diagnose leukemia cell from the normal cell.

Using the current system, which is a laboratory test, if the hematologist is skilled enough, he/she could accurately diagnose the disease. However, it takes an average of 30 minutes to diagnose the disease of leukemia, which is time-consuming, and its accurate result would rely on the skill of the hematologist experience, i.e. prone to error. Moreover, early detection and diagnosis of leukemia is major challenging factor for lack of trained and experienced person examining the stained blood smear [16],[3]. Therefore, the lack of automatic, early and cheap leukemia detection system is a great challenge in today's health arena across the local hospitals.

The main objective of this research is to develop and design real time, automatic, efficient, and reliable system that helps to detect and classify blood cancer from microscopic blood image using image processing and Multi Class Support Vector Machine Learning algorithm.

Karthikeyan et.al, developed microscopic image segmentation using fuzzy-means for leukemia diagnosis [16]. Nineteen images were segmented using a c-means clustering algorithm and Histogram equalization and a median filter were used during the preprocessing step. Gabor texture extraction was applied to extract the features of WBC. Finally, SVM was used to detect ALL leukemia cells. In this case, using c-means clustering is time-consuming as compared to other algorithms; therefore, the system performs at slow speed, taking more than 2 minutes to function. Moreover, the system only focuses on ALL types of leukemia and the number of images used was not sufficient because in order to train the system in each sub-type of ALL images, more images are needed.

Patel, et al., presented a system called automated leukemia detection using the microscopic image. The system used Median and Wiener filters in the preprocessing step. A K-means segmentation approach was used for white blood cell extraction. They used SVM method for classification of leukemia [17]. Features like statistical, shape, color and texture were extracted in order to help in detecting leukemia. Here, only one type of leukemia was classified, i.e., the ALL type of leukemia. Furthermore, the overlapping cells were not properly analyzed by this system. Even if the data set used was not stated, over all detection accuracy of 93.5% was achieved by the system.

Rawat J., et.al., proposed a computer-aided diagnostic system for detection of leukemia using microscopic images [1]. An auto SVM binary classifier was used for better detection accuracy. They were used a dataset of 130 ALL infected images, 65 images were used for training and the subsequent half were employed for testing of the proposed system. However, the overall accuracy of the system is 92%. Nevertheless, the system only identified normal patients and diagnosed only the ALL type of leukemia.

Classification of acute leukemia using medical-knowledge-based morphology and CD marker has been done by [18]. Based on current medical knowledge, the coarse-to-fine concept and some important cell features are applied in the proposed method. The coarse step consists of pre-processing and classification processes that output ALL, AML, and healthy blood-cell groups. The classified ALL and AML groups are consequently processed in the fine step by pre-processing, feature-extraction, and classification to categorize in to L1, L2, L3, M1, M2, M3, M4, M5, M6, or M7 sub-types. These subtype classification results are finally processed in the decision-making process by comparison with CD markers in order to confirm the blood-cell sub-types.

Rawat.J. et.al. proposed a computer assisted classification framework for prediction of acute lymphoblastic and acute myeloblastic leukemia. The proposed technique improves the AML and ALL diagnostic accuracy by analyzing color, morphological and textural features from the blood image using image processing and to assist in the development of a computer-aided screening of AML and ALL. The paper endeavors at proposing a quantitative microscopic approach toward the discrimination of malignant from normal in stained blood smear. The proposed technique firstly segments the nucleus from the leukocyte cell background and then computes features for each segmented nucleus [19].

N.H.A. Halim et al. explore an Automatic Blasts Counting for Acute Leukemia based on blood samples [20]. They proposed an image processing technique for automatic counting the number of blasts present in the slide of leukemia. Segmentation based on HSV (Hue, Saturation and Value) color space will be used in order to eliminate the white blood cells (WBC) from the background. The experimental results show that the proposed system has provided the highest average accuracy of 97.8% for counting both ALL and AML cases.

Even if a lot of research had been done to improve leukemia disease detection using image processing algorithm, almost all of them were done for the ALL type of leukemia with limited data sets. The following Table summarizes the above works and their gap for easiness of understanding.

Table 1: Summary of some recent comparative study of different leukemia detection and classification system

MATERIALS AND METHODS

The main task in developing the system was image acquisition. Since the microscopic images have different artifacts, the images need to be preprocessed using appropriate pre-processing methods. Therefore, this section begins by explicating the details of image acquisition and image-processing techniques for WBC segmentation. Finally feature extraction and classification method used in this work has been briefly discussed. Figure 6 shows the overall block diagram used for developing the system.

From Figure 6, once the system read blood image it will preprocess it in order to help for correct segmentation of WBCs. This will help for accurate feature extraction of the image, which intern helps for classification of leukemia in its respective type.

Table 2. Comparison of the proposed method with the previous studies

Authors	Method	Preprocessing	Segmentation
[16]	Microscopic image segmentation using fuzzy C-means for leukemia diagnosis	Histogram equalization, Median filter	Fuzzy C-means clustering algorithm
[17]	Automated leukemia detection using the microscopic image	Median and Wiener filters	K-means segmentation
[1]	Computer-aided diagnostic system for detection of leukemia using microscopic images	Contrast enhancement	Not stated
[18]	Classification of acute leukemia using medical-knowledge-based morphology and CD marker	low-pass filter	Cluster of differentiation (CD)marker K-means
[19]	Computer assisted classification framework for prediction of acute lymphoblastic and acute myeloblastic leukemia.	Histogram equalization, Order statistic filter.	Global thresholding

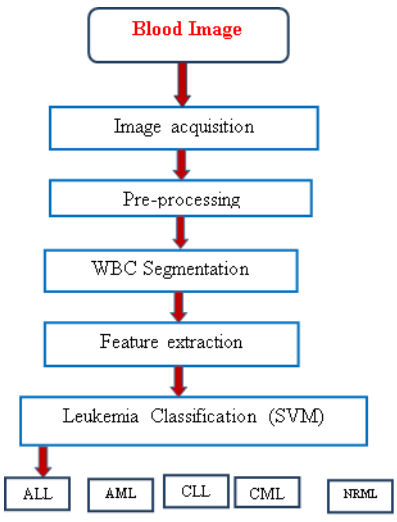


Fig 6. The overall development block diagram of the system

Image acquisition

One of the core tasks in medical image processing using computer vision is collecting intended images from the available sources. Three hematologists were participated to prepare new blood smear and to collect the already prepared blood smear from the laboratory store.

In this research, a total of 450 images have been used for developing the system. Among them, 100 images were used for each type of leukemia and 50 images have been obtained from normal blood. Among these 70 images of ALL type of leukemia and all normal blood, images have been taken from ALL_DB online dataset [21]. The remaining 30 images of ALL have been acquired from Jimma University Specialized Hospital (JUSH) laboratory. For AML, CLL and CML types of leukemia, 30 images were taken from the stained blood smear brought from Nottingham University Hospital found in United Kingdom and 70 images were from JUSH hematology laboratory setup. The digital microscope that has been used in this research was model AE-S104 that has an overall of up to 1000x (with 100x objective and 10x eyepiece) magnification. Figure 7 below shows image acquisition procedure.

(a)

(b)

(c)

Fig 7. (a) Over all setup (the digital microscope) (b) Different leukemic case sample slides used for image acquisition (c) During microscopic image acquisition and labeling

Image pre-processing

The purpose of image pre-processing was to remove unwanted objects and noise from the blood image so that it becomes ready for the subsequent image segmentation process [22], [15]. Under pre-processing step, the following methodology has been applied.

1. Resize an image: to decrease the computational time, the original RGB image (2592 by 1944 pixels) has reduced to 300 by 300 pixels.

2. Image enhancement: This helps to create a uniform illumination field over the image. In this work, the image intensity adjustment function was used to change intensity from 0.1 default value to 0.9. After that, the Gaussian filter was implemented to diminish the effects of camera noise and spurious pixel values.

3. De-blurring the image: Wiener filter has been applied to the image as it is a powerful tool to remove these noises and to de-blur the image [23],[1],[24].

Image segmentation

Image segmentation is the process of extracting the region of interest from the image especially WBCs since leukemia affects WBC. In this research K-means segmentation and Marker controlled watershed segmentation algorithms were applied to successfully segment the region of interest.

The k-means clustering algorithm has segmented the region of interest (i.e., white blood cells) and separates it from the other blood cells like RBC and platelets. K-means is selected because it is faster than one of the well-known threshold methods, Otsu method and fuzzy C-means method [15]. Since some leukemia cells that will appear at the edge of the image result in decrease in accuracy of the system it has removed by border cleaning algorithm. Moreover, in order to separate the overlapped cells of blood, Marker-Controlled Watershed Segmentation was applied and finally it is labeled in order to help in geometric feature extraction. When the picture has been taken from digital microscope, some of the leukocytes and monocytes were on the edge of the image, leaving a portion of the cellular bodies along the edge of the image [24]. These partial leucocytes and monocytes posed errors in the study and only lymphocytes and myelocytes have been considered, and thus it becomes necessary to determine whether they are blast cells or not.

Thus, in the image cleaning process, all the objects, which were not leucocytes and monocytes, and all objects, which were on the edge of the image, have been removed as objects that are connected to the image border are partially obscured and usually not suitable for subsequent analysis. Solidity is used to find out the density of the components. Solidity value can be obtained by dividing the area to the convex hull of each component. If the solidity value is one then it can be said that it is a solid object. If the solidity value is, less than one then we can say it is a component having irregular boundaries [9]. The threshold value which was used for identifying the abnormal components has been obtained from the image, which contained leucocytes and monocytes only; experimentally validated as 0.91 to be the threshold value for solidity. The components that were having solidity value less than the threshold have been removed.

Morphological operations like opening, erosion, dilation and hole filling have been used for successful application of markers of controlled watershed segmentation. Erosion operation causes the nucleus to shrink in size. Dilation increases pixels to the boundaries of the nucleus (i.e., changes them from off to on) [24]. Area opening was used to remove connected components between the nuclei of cells without affecting the size, a deleterious side effect of erosion. To fill the hole; hole filling operation has been applied on the system. This will increase the accuracy of system to detect leukemia.

Feature extraction

An image feature is a distinguishing primitive characteristic or attribute of an image [24]. In this step, different features for each type of leukemia image were extracted by using different parameters. These parameters will help further for classification of leukemia in its respective types using machine learning algorithms [1].

1. Geometric features: Area, Perimeter, Aspect ratio, Compactness, Equivalent diameter, Solidity, Eccentricity, Roundness, Elongation, Major and Minor Axes.

2. Texture features and Statistical features: Contrast, Correlation, Homogeneity, Mean, Variance, RMS (Root Mean Square, Standard deviation, Skewness, Kurtosis, Energy, Entropy, Inverse difference moment (smoothness).

3. Color features: In this research, the RGB color spaces were transformed into HSV color spaces. Their mean color values have been obtained [13], [25].

Classification

Once all necessary features have been extracted from the image, and these extracted features yield the calculated data base on the mentioned parameters; the next task was training and testing of the extracted data. The task of assigning the unknown test vector to a known class is defined as classification [26]. Due to its effectiveness in this research, Support Vector Machine has been used by comparing with other machine learning algorithms like Artificial Neural Network and K-nearest neighbor.

Support Vector Machine

The SVM is a supervised classifier and an optimal hyper plane used to categorize the given inputs. The hyper plane focuses on the training cases that are placed at the edge of the class descriptors. These training cases are called support vectors [27], [28]. The hyper plane then tries to split the positive samples from the negative samples. The machine was originally designed and developed for binary classification. However, researchers have increasingly become interested in multi-class SVM [8]. Instead of binary classification, multi-class support vector machines have been used in this paper for the classification of affected or healthy patients via image analysis as well as the further classification of the respective types of leukemia. The support vectors can be either linearly separable or non-linearly separable. Hard-margin SVMs can address linearly separable problems. Figure 8 shows how support vector machine is working in order to classify positive sample from negative one.

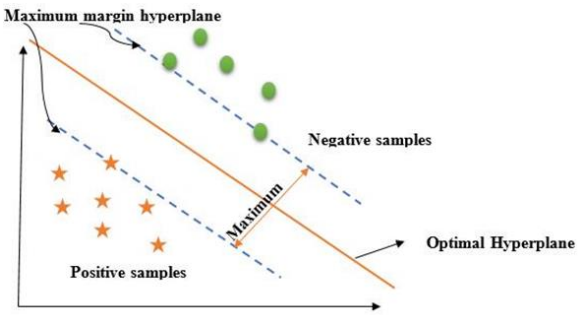


Fig 8. SVM classifier

Throughout training phase, Multiclass SVM takes the extracted features of each type of leukemia cells. In this research work, 70% of images (320 images) were used for training purposes, and 30 % of the images (130 images) were used for testing purposes. Therefore, features will be automatically extracted for those 70% of images (320 images) for each leukemia type. These features, which were extracted based on different parameters, were trained using Multiclass SVM.

The final graphical user interfaced (GUI) system has seen on Figure 9 below which has been developed using [29]. It helps the users to acquire blood image, to label it and see the type of cancer result without any difficulty. Moreover, the user can also save the segmented image if he/she wants for further analysis. The overall system has developed on MATLAB 2017a Software. At the glans, the user loads the acquired blood image from the digital microscope. Then the user uses push segmented and labeled button to segment the white blood cell part of blood image (since leukemia affects only WBC), which was done by k-means segmentation and labeled by marker-controlled water segmentation method. Finally, the user selects the cancer result push button to diagnose the cancer type.

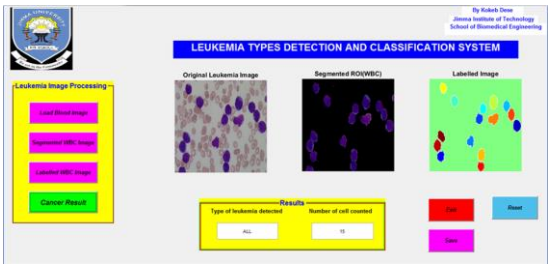
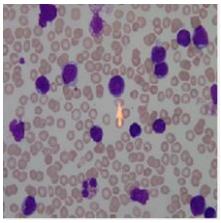


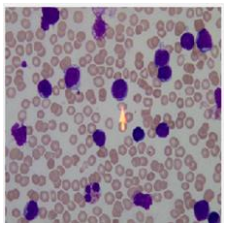
Fig 9. Graphical user interface development of the system

RESULTS AND DISCUSSIONS

Using the developed system, the results obtained are shown below. In Figure 10, the input image and the preprocessed image, adjusted by image adjustment to enhance the contrast of the image and filtered by a Gaussian filter and Wiener filter. This means Figure 10(a) shows the original captured image from digital microscope. As shown from this image, it is the contrast of the image which is not uniform and blurred type of image. Therefore in order to have uniform contrast all over the image, contrast enhancement image processing method was applied, and to remove the stepper and pepper noise as well as blurredness happened during image capturing process, Gaussian and Wiener filter was applied on the image. The resulting image of this preprocessed image is shown on Figure 10 (b).



(a)



(b)

Fig 10. Original and Filtered image (a) Original image (b) Resized, contrast adjusted, Gaussian and wiener filtered image

Figure 11 below explicated the K-means clustering segmented blood image. As it is depicted in the figure, k-means segmented image, it contains the region of interest parts, which is WBC since leukemia affects only this type of cell. Therefore, this segmented part has been selected for further analysis in the system.

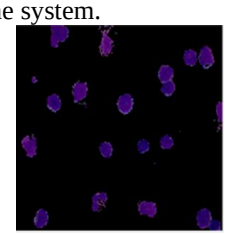
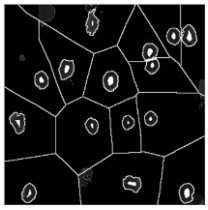
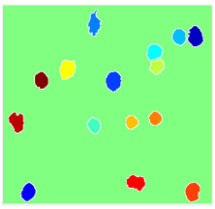


Fig 11.: The k-means segmented image

Figure 12 below demonstrates the marker-controlled watershed segmented image. This means Figure 12 (a) shows how the Marker Control Watershed line draws lines on segmented image to disconnect the overlapped cells. In this image, the connected nucleus of WBCs is disconnected and labeled accurately. This means in order to calculate the geometric parameters of each cell, the overlapped cells need to be disconnected and labeled accurately. In order to disconnect the overlapped cell of nucleus, the marker controlled image processing segmentation method was applied and provided good result, which is shown in Figure 12 (b).



(a)



(b)

Fig 12. Marker controlled segmentation process (a) Marker controlled line superimposed on final segmented image (b) Marker controlled watershed transformed image

For testing of data, 30% of images from the total number of images collected for each type of leukemia was employed corresponding to 130 images which have been used for testing purposes. Figure 13 below shows the confusion matrix of the automatic classification results using multi-class Support Vector Machine classification algorithm.

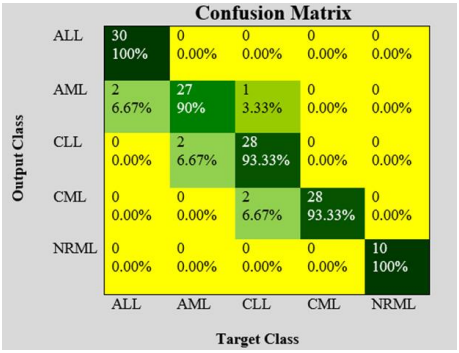


Fig 13. Classification Confusion matrix

Generally, in the above result, it is shown that, using image adjustment function in combination with Gaussian filter and wiener filter will provide good preprocessed image. Moreover, the k-means clustering method shows appropriate segmentation of white blood cells. Since leukemia affects white blood cells, segmenting WBC will help the system to recognize leukemia. MATLAB 2017a was used to develop the system. Figure 13 depicts the average classification accuracy of ALL, AML,CLL,CML and normal blood cells achieved using MCSVM, which is 100%, 90%, 93.33%, 93.33% and 100% respectively. Furthermore, to measure the overall performance of the detection and classification system using multiclass support vector machine, the average accuracy, sensitivity and specificity of the system has been calculated below [30].

Sensitivity= TP/((TP+FN))

Specificity= TN/((TN+FP))

Accuracy= ((TN+TP))/((TN+TP+FN+FP))

Table 2. Comparison of the proposed method with the previous studies

Authors	Preprocessing	Segmentation
Our method	Image adjustment Gaussian filter Wiener filter	k-means clustering Marker controlled watershed segmentation Morphological operation
[16]	Histogram equalization, Median filter	Fuzzy C-means clustering algorithm
[17]	Median filter Weiner filter	k-means Zack algorithm Histogram equalization
[1]	Median filter	Not stated
[18]	low-pass filter	Cluster of differentiation (CD)marker K-means
[19]	Histogram equalization, Order statistic filter.	Global thresholding

From the total number of parameter calculated and formula given above, average sensitivity of 94.17%, specificity of 100% and average accuracy of 94.62% has achieved by the system

Now, in the following table, the proposed system of this research that shows higher accuracy using Multi Class Support Vector Machine, which was averaged over twenty times stimulation as compared to some of previous studies. The methodology used by previous work is stated on related work part of this document. Almost all studies were focused on only one type of leukemia detection and classification, i.e. ALL. However, in this work, four types of leukemia were detected and classified with good accuracy results, especially using Multi-Class Support Vector Machine.

CONCLUSIONS

Blood cancer is a major problem, which affects the production and function of the blood cells. It is important to detect in early stages. In this research, the researchers have used images of blood cells acquired from Jimma University Specialized Hospital, Nottingham University Hospital and ALL_DB online database. Three hematologist experts have served as clinical collaborators of this research in labeling the images acquired from laboratory setup.

To develop the algorithm, the image acquired from stained blood image was preprocessed to decrease noises that imposed during acquisition time. The next core step of the algorithm development was segmentation of the preprocessed image by using k-means segmentation and marker-controlled segmentation. Well-segmented leukemic blood images are also improving the sensitivity and specificity of the blood cancer detection and species classification.

This elucidates the potential of digital image analysis applied for leukemia disease diagnosis; which is not tedious, not time consuming, less error-prone and requires minimal expertise when compared to the manual method of leukemia diagnosis. This will be beneficial for today's rapidly improving healthcare environment as early detection and classification of leukemia will yield better patient outcomes. For the future, it will be better to innovate a method that avoids the staining process and directly queries the disease from a raw blood sample.

Conflict of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper

ACKNOWLEDGEMENTS

We would like to acknowledge Mr. Lealem Gedefaw, Mr. Zewudineh Sehalemariamand Dr. Diriba Fufa, who helped us during data acquisition and labeling of this research on behalf of Jimma University Specialized Hospital. Moreover, we want to thank Dr. Kindey Anley, Mr. Mohammed Aliy and Mr. Zelalem Adbar for their constructive advice and guidance throughout the research. At the last, but not the least, our deepest gratitude goes to Engineer Wasihun Alemayehu on behalf of Jimma Institute of Technology, School of Biomedical Engineering for his hellacious help. Above all, we thank our God who gave us the knowledge and wisdom when we were doing this research.

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