Classification of acute lymphoblastic leukemia using deep learning

Amjad Rehman[1], Naveed Abbas[2], Tanzila Saba[3], Syed Ijaz ur Rahman[2], Zahid Mehmood[4], Hoshang Kolivand[5]

[1]College of Computer and Information Systems, Al Yamamah University, Riyadh, Saudi Arabia

[2]Department of Computer Science, Islamia College University Peshawar, Pakistan

[3]College of Computer and Information Sciences, Prince Sultan University, Riyadh, Saudi Arabia

[4]Department of Software Engineering, University of Engineering and Technology Taxila, Pakistan

[5]Department of Computer Science, Liverpool John Moores University, Liverpool, United Kingdom

Abstract

Acute Leukemia is a life-threatening disease common both in children and adults that can lead to death if left untreated. Acute Lymphoblastic Leukemia (ALL) spreads out in children's bodies rapidly and takes the life within a few weeks. To diagnose ALL, the hematologists perform blood and bone marrow examination. Manual blood testing techniques that have been used since long time are often slow and come out with the less accurate diagnosis. This work improves the diag- nosis of ALL with a computer-aided system, which yields accurate result by using image proces- sing and deep learning techniques. This research proposed a method for the classification of ALL into its subtypes and reactive bone marrow (normal) in stained bone marrow images. A robust segmentation and deep learning techniques with the convolutional neural network are used to train the model on the bone marrow images to achieve accurate classification results. Experimental results thus obtained and compared with the results of other classifiers Naïve Bayesian, KNN, and SVM. Experimental results reveal that the proposed method achieved 97.78% accuracy. The obtained results exhibit that the proposed approach could be used as a tool to diagnose Acute Lymphoblastic Leukemia and its sub-types that will definitely assist pathologists.

Keywords: Acute lymphoblastic leukemia, bone marrow, deep learning, segmentation and classification

1 | INTRODUCTION

Acute Lymphoblastic Leukemia or Acute Lymphocytic Leukemia (ALL) is a type of cancer caused by immature lymphocytes in bone marrow (Abbas et al., 2015, 2016). Leukemic cells spread in the blood quickly and spread out to different parts of the body like spleen, liver, lymph nodes, brain, and nervous system. However, ALL mainly affects the blood and bone marrow (Mughal, Muhammad, Sharif, Rehman, & Saba, 2018; Norouzi et al., 2014). It is also called acute childhood leukaemia because it is most common in children while chronic and myeloid leukaemia's are rare in children (http://www.hematology.org/Patients/Cancers/Leukemia.aspx). Different genetic approaches have been applied for malignancy of transforming cells and progeny to form leukemic cells clone. This increase of hematogenic cells is called leukaemia. Acute leukemia has more than 20% blasts in bone marrow. However, if it is not diagnosed and treated on time it can progress fast and takes life in a few months (Mughal, Muhammad, Sharif, Saba, & Rehman, 2017; Mughal, Sharif, & Muhammad, 2017; Mughal, Sharif, Muhammad, & Saba, 2017). According to FAB classification, ALL is classified into L1, L2, and L3 subtypes as shown in Figure 1, L1 type consists of a regular nuclear shape having homogenous chromatin, small nucleoli and scanty basophilic cytoplasm and small in size. However, irregular nuclear shape and clefting are found in large sizes of L2 blasts, large nucleoli, and variable chromatin are also often intensively basophilic (Mahopatara, Patra, & Satpathy, 2014). L3 are large in size or medium-large with prominent cytoplasmic vacuoles having two or three nucleoli's at least one and it has round to oval nucleus. For the detection of ALL and its subtypes, blood smears or bone marrow examination is held by hematologists in clinical laboratories under the microscope, which relies on the skills and experience of the

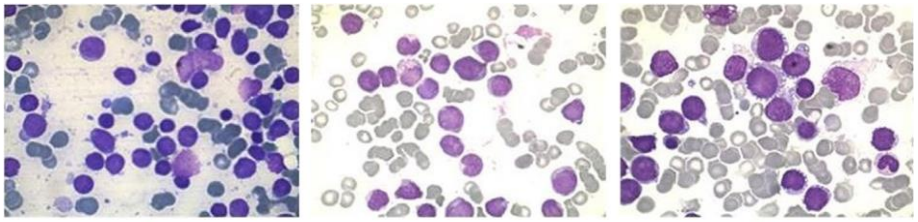

FIGURE 1 Subtypes of ALL [Color figure can be viewed at wileyonlinelibrary.com]

pathologists and the microscopy could be affected due to long time function (Rehman, Abbas, Saba, Mahmood, & Kolivand, 2018; Saba, 2012; Saba, Al-Zahrani, & Rehman, 2017; Waheed, Alkawaz, Rehman, Almazyad, & Saba, 2016; Jamal et al., 2017).

To overcome these limitations of manual screening the hematologists have to come up with an automated system, which could detect or classify the malignant lymphocytes. In literature, many researchers address the current problems of manual screening and aim for the automated detection, classification of ALL (Husham, Alkawaz, Saba, Rehman, & Alghamdi, 2016; Iqbal, Khan, Saba, & Rehman, 2017). Mahopatara et al., 2014 propose an ensemble of classifiers to detect ALL in blood microscopic images. Bhattacharjee and Saini (2015) employ watershed transformation and Gaussian mixture model (GMM) for the detection of ALL. Hayan et al. (2012) segment white blood cells nucleus and cytoplasm using GVF snake for the detection of leukaemia. Similarly, Kulkarni-Joshi and Bhosale (2014) propose a morphological analysis based technique for the identification of leukemic cells. Nee, Mashor, and Hassan (2012) employ watershed segmentation followed by morphological operations of white blood cells. Hayan et al. (2012) employ HSV color model and some morphological operations for the segmentation and localization of lymphoblast cells using peripheral blood images.

The proposed approach classifies ALL into L1, L2, L3, or normal types. Precise segmentation of blasts cells of the bone marrow images in HSV colour model and deep learning techniques for the classification of ALL are employed (Kulkarni-Joshi & Bhosale, 2014). Deep learning trains machines as such it comes to human vision naturally; its models are used for the classification of images, videos, text, and audios. The models are trained using a large number of label data and learn features from the data directly and no manual features are extracted and having more hidden layers to processed that features. Convolutional neural network (CNN) is one of the widely used types of deep learning in biological images data processing which excludes manual features extraction need and features are learnt directly from the image and then convolves it with input data for the classification to generate an accurate result (Iqbal, Ghani, Saba, & Rehman, 2018).

Further, this article is organized as such section 2 explores related work, sections 3 and 4 presents proposed material and methods, section 5 exhibits experimental results and discussion, finally, the conclusion and future work is presented in section 6.

2 | RELATED WORK

Mughal et al. (2018) propose a novel approach to remove the pectoral muscle in a mammogram using a discrete differentiation operator. The proposed technique is evaluated on standard MIAS dataset of 322 mammograms and a 20 contrasts enhanced digital mammographic images in order to achieve high accuracy in varying size of pectoral muscles.

Bibin, Nair, and Punitha (2017) develop a model for the detection of malaria parasites using Deep Beliefs Network. The main objective is to classify parasite and non-parasite. They train the model for the HSV color space conversion to segment the cells through region-based contours and finally used color and textures features for the classification of DBN. Jayoti et al. (2017) utilize histogram equalization and global threshold followed by morphological opening for the segmentation of nucleus of the blast cell and then subtract that from the preprocessed image to obtain cytoplasm. For classification, geometrical, chromatic, and statistical features are extracted to feed classifiers PCA-kNN, PCA-PNN, PCA-SVM, and PCA-SSVM. PCA-ANFIS in hierarchical way are applied and report maximum accuracy 97.6%. However, too many classifiers fusion take too much time to classify the images.

Vidhya, Kumar, Keerthika, Nagalakshmi, and Devi (2015) solve the problem of segmentation with k-mean clustering and used SVM for classification on the basis of Local Directional Pattern (LDP) features. Amin, Kermani, Talebi, and Oghli (2015) use k-mean clustering for the segmentation of lymphoblasts and extracts geometrical and statistical features for the classification of ALL and its subtypes and then classify it using multiclass support vector machine (SVM). However, the author's uses only nucleus features for the classification and claim 97% accuracy. Goutam and Sailaja (2015) present a framework to identify whether the cells are affected by acute myeloid leukaemia or normal by applying k-mean clustering on grayscale images for the segmentation of nuclei of the cell. LDP with textural features is used for the classification on SVM that produce 98% accuracy. Bhattacharjee and Saini (2015) propose a method for the detection of acute lymphoblastic leukemia, for segmentation they used watershed transforms followed by morphological operation. Morphological features are extracted and used GMM and Binary search tree for classification and the proposed method results with 95.56%.

Mahopatara et al. (2014) use k-means clustering in blood smear images to separate the region of interest. The technique extract RGB color features from entire images; finally, leukocytes shadowed C-means algorithm is used on $L^*a^*b^*$ (CIELAB) for segmentation. Then color space SCM clustering is used to segment nucleus, cyto- plasm and background from the sub-image (Mughal, Muhammad, Sha- rif, Saba, & Rehman, 2017). Morphological, textural, and color based features are extracted and features are normalized, selected. Multiple classifiers are used in classification process such as Naïve Bayesian,

K-nearest neighbor (KNN), Multilayer perceptron, Radial basis function neural networks, and SVM. Finally, 94.73% accuracy is reported for the classification of mature lymphocytes and lymphoblast. Kulkarni-Joshi and Bhosale (2014) suggest a technique based on thresholding for the detection of ALL blasts and segmenting nucleus. Otsu thresholding is applied and the background is removed to extract shape features for the blasts detection. Abbas and Mohamad (2014) present a method for the segmentation of lymphocyte nuclei to detect leukemia. Firstly, the image is convolved with 2*2/6 mask for repressing high values of RGB then Otsu method is applied to obtain nuclei, small areas are removed and nuclei is then dilated for the required results of segmenting nuclei and detecting leukemia resulting accuracy of 96.5%. Agaian, Madhukar, and Chronopoulos (2014) propose a screening system to detect myelogenous leukemia in blood; the image is converted to CIELAB and process L and components. Finally, k-mean clustering is used to segment the interested region. Color, shape, and texture having cell energy and Hausdorff dimension features are extracted for the classification of malicious blasts using SVM. The results exhibit 98% accuracy.

Jagadeesh, Nagabhooshanam, and Venkatachalam (2013) propose a technique for the detection of cancer cells in blood sample. The image is first converted into grayscale and binary format, morphological closing, erosion is applied for the smoothness and distortion elimination, map distance between black and white pixels. Watershed transform is applied for segmentation. Geometric, statistical, and texture features are used for the classification through SVM. Similarly, Joshi, Karode, & Suralkar, 2013use Otsu threshold method for segmentation and KNN for classification on the basis of textural and shape features.

Hayan et al. (2012) convert RGB images to HSV, H, and S bands are extracted and converted into binary. Fifteen disk shape structuring element is applied to erode S-band and open H band. Finally, images are reconstructed by morphological operator to find the centroid and axis length of the blasts cells to classify them on the basis of these features. This method also just segment the lymphoblast and localized them and shows the accuracy of 100% for localizing lymphoblast's. Nee et al. (2012) use S component of the HSV color model followed by erosion, dilation, and magnitude gradient used as edge detection and segmentation for the watershed transformation, the accuracy for this method is 94.5 but used for acute myeloid leukaemia and its subtypes. Pan, Park, Yang, and Yoo (2012) apply Extreme Learning Machine (ELM) for the segmentation of leukocytes, for sampling gradient threshold is used to choose peak gradient pixel. Then entropy for maximum is checked to segment multicolor object. The pixels on the edges is observed to classify on ELM, for leukocytes the image is converted to HIS and finally Otsu method is applied for the cytoplasm reveals good results but more complex architecture.

Abd Halim, Mashor, Nasir, Mokhtar, and Rosline (2011) propose a new method to solve the problem of segment nucleus in order to differentiate between ALL and AML for acute leukaemia. Global contrast stretching is applied to RGB images to enhance the region of interest for the classification. Latter, the images are converted to HSI color space. The nucleus is segmented through S component processing of the color space and nucleus is further segmented by applying fixed threshold for accurate segmentation. Region growing techniques are applied for the identification of blasts and nucleus.

Rezatofighi, Khaksari, and Soltanian-Zadeh (2011) design an automatic system for the recognition of five types of blood cells having three phases. In first phase, the nucleus is segmented using Gram-Schmidt algorithm following the classification to distinguish basophils on the basis of features co-occurrence matrix and LBP. While in second phase the images are preprocessed in grayscale and S component of the HIS color model, where the snake algorithm is applied for the segmentation of cytoplasm and finally, the other four types of WBC using morphological features are classified and resulted in the accuracy of 93.09%. Tabrizi, Rezatofighi, and Yazdanpanah (2010) utilized Learning Vector Quantization Neural Networks to classify white blood cells into its types by extracting morphological, textural, and color features from segmented nucleus, cytoplasm. The claimed classification accuracy is about 96%.

Sadeghian, Seman, Ramli, Kahar, and Saripan (2009) propose a segmentation technique to separate leucocytes from other components of blood to convert the images to gray level and sub-image the WBCs. Gradient vector flow model is used to find the nuclei. Hole filling is applied and nucleus is segmented following the zack thresholding for the segmentation of cytoplasm on subtracting nucleus from the grayscale image. The accuracy of the proposed method for segmenting nucleus is 92% while 78% is for cytoplasm. Adollah et al., 2008analyze process of the segmentation of blood cells for the purpose to diagnose different types of diseases, study, and treatment for the pathological disorders. Circular histogram based Otsu method is used to segment white blood cells, in another technique Entropy of a higher order as a feature for threshold over histogram of two dimensions is used on two color models RGB and HIS. Different methods are compared for the segmentation purpose like gray level threshold, morphological operations, different filtering techniques color match, and color threshold. In another method, firstly, the shape information is obtained by binarization following the generation of maximal intensity and the shape information is used. Finally, GVF is used for the detection of cells and seeded watershed for segmenting cells.

Theera-Umpon and Dhompongsa (2007) propose a method to classify WBC's on nucleus information, where pattern spectrum of every nucleus is calculated. Initially, two selected granulometric are taken as two features; area and high location of the spectrum. Bayes and neural network classifiers are used for classification.

Scotti (2005) present a system for the recognition of Lymphocyte whether blast cell or normal, Otsu's thresholding is applied for the segmentation of nucleus and the blasts are classified into their three subtypes L1, L2, L3, and later the cells on the basis of geometric features are classified by KNN classifier. However, the system is used for the classification of normal and blasts cells only.

3 | MATERIALS AND METHODS

3.1 | Data collection

The patient's data for this study is obtained from Amreek Clinical Laboratory Saidu Sharif Swat KP Pakistan. We only consider the slides of

the patients having ALL history, and some images of normal or reactive bone marrow having no history of leukemia are also taken, the slides are stained with Leishman stain and then examine on the microscope. The images are taken and classified into three subtypes of ALL that is L1, L2, L3, and normal with the help of hematologists forming a dataset.

3.2 | Image acquisition

Microscopic images of bone marrow with Leishman stain are witnessed optically and taken with Euromax digital camera microscope under normal lighting condition and oil immersion with the 100× lens at Amreek Clinical laboratory Swat KP Pakistan. Every snatch image is saved in the original form in three colors red, green and blue (RGB).

3.3 | Segmentation

Bone marrow images contain all the blood components but we are only interested in lymphoblast's that are actually immature lymphocytes for the classification of ALL. To segment the region of interest different methods are used by other researchers such as Rezatofighi et al., 2011apply Gram Schmid algorithm, k-means clustering technique is adopted by Goutam and Sailaja (2015), watershed transformation by Jagadeesh et al. (2013), and Otsu method followed by morphological operations by Abbas and Mohamad (2014). However, to obtain the region of interest in the current research, we propose a simple segmentation approach based on simple threshold method, which results in an efficient way. Figure 2 shows the whole classification framework. As preprocessing the image is first converted into HSV (Hue, Saturation, Values) color space, and then processed the S component of the specified color model to get the region of interest (Lymphoblast), as the information is more clear in this channel. Later, this simple threshold is applied that is the maximum threshold to find out in the S channel and then subtracted random values between 0 and that maximum threshold for getting the segmented blasts with accurate segmentation result from that maximum threshold. Finally, segmenting blasts hole filling is applied to cover the lost information and the image is then converted back to RGB, which results in the form of a segmented image having lymphoblast exhibited in Figure 3.

4 | CLASSIFICATION PHASE

Discriminative features play an important role in the classification process (Iftikhar, Fatima, Rehman, Almazyad, & Saba, 2017; Rehman & Saba, 2014). Too many features confuse the classifier and too fewer features are not enough to classify accurately (Rahim, Rehman, Kurniawan, & Saba, 2017b). Sometimes a single feature plays a major role to classify the pattern (Fahad, Ghani Khan, Saba, Rehman, & Iqbal, 2018; Harouni, Rahim, Saba, Rehman, & Al-Dhelaan, 2014; Lung, Salam, Rehman, Rahim, & Saba, 2014; Meethongjan, Dzulkifli, Rehman, Altameem, & Saba, 2013; Rad, Rahim, Rehman, & Saba, 2016). For classification, different features and classifiers combinations are trained and tested. The classifier is configured according to the data for the efficient results, for this data is divided into training data set and test data set (Mahopatara et al., 2014). On training data set the model is trained, tested, and validated on test data. This paper proposes deep learning technique using Alexnet model with CNN for the classification of ALL into its subtypes and normal condition. The model is configured according to the data and the last three layers are fully connected, softmax, and classification layer is fine-tuned to the new layers of the classifier and is set according to the new data. This method is known as transfer learning. The data sets are also checked on other classifiers, that is, KNN, naïve Bayesin, and SVM for the performance evaluation.

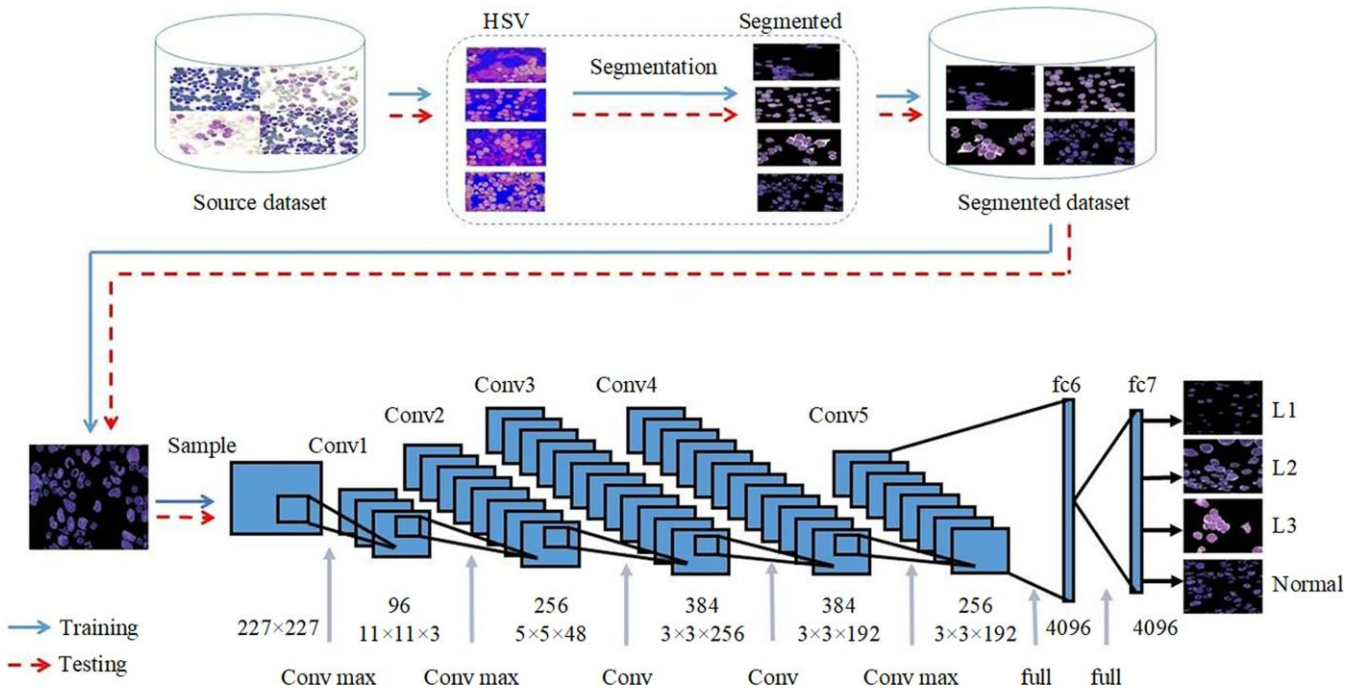

FIGURE 2 Proposed research framework [Color figure can be viewed at wileyonlinelibrary.com]

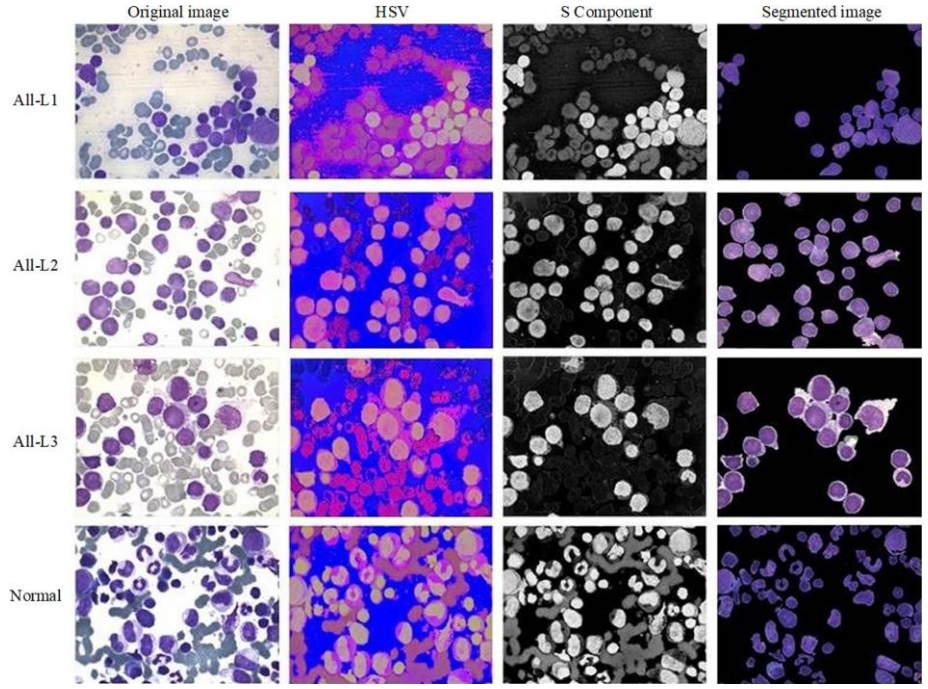

FIGURE 3 Segmentation results of the proposed approach [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Convolution neural networks (CNN)

The first step is to define CNN architecture and its training that typically depends on the application and type of data. Layers of the architecture are input layer that defines the image size to the CNN and corresponds to width, height and number of channels of the given image, if the image is grayscale number of channel is 1, and if color then 3 (Iqbal et al., 2018). The second layer is convolution layer and it consists of the neurons that connect subregion of the image or layers output before it. The features localized by these regions after scanning the image is learned by convolutional layer.

Normalization layer is in between the Convolutional layer and ReLU layer to speed up the training process and reduce sensitivity. The activation is normalized by subtracting the mini-batch and divides the mini-batch standard deviation to optimize training and to increase the learning rate (Iqbal et al., 2018). The ReLU layer is a nonlinear activation function that is applied for convolution and batch normalization following threshold operation to each element having a value less than zero is set to zero.

$$F(x) = \begin{cases} x, & x \geq 0 \\ 0, & x < 0 \end{cases}$$

Convolutional layer followed by the max-pooling layer is used for downsampling to reduce the connections for fully connected layers. Through max-pooling rectangular region, values should be returned, if pool size is [3,3] it will return values of height 3 and width 3. Max-pooling also helps to reduce overfitting. Drop out layer sets the random values of input elements to zero with a given probability, without learning and works as max-pooling (Iqbal et al., 2018). To classify an image, all the features are combined in the last fully connected layer. For classification purpose softmax and classification layers follow final fully connected layer, it is also called output layer.

$$P(c_r|x,\Theta) = \frac{P(x,\Theta|c_r)P(c_r)}{\sum_{j=1}^{k} P(x,\Theta|c_j)P(c_j)} = \frac{\exp(a_r(x,\Theta))}{\sum_{j=1}^{k} \exp(a_j(x,\Theta))}.$$

Where $0 \leq P(c_r | x, \Theta) \leq 1$ and $\sum_{j=1}^{k} P(x,\Theta | c_j) = 1$. Moreover $a_r = \ln P(x, \Theta | c_r)P(c_r)$, $P(c_r | x, \Theta)$ is the conditional probability of the given class sample.

In the classification layer, the values of the softmax function assigns the input to one of the K exclusive classes using entropy function.

$$E(\theta) = -\sum_{i=1}^{n}\sum_{j=1}^{k} tij \ln yj(xi, \theta)$$

5 | EXPERIMENTAL RESULTS AND ANALYSIS

The data sets for this system consist of all the images of ALL subtypes, which include 100 images of L1, 100 images of L2, 30 images of L3 due to rare nature of L3, and 100 images of normal bone marrow. The data are divided into 80% as training set and 20% testing set to train the pre-train Alex net model using CNN. The CNN is configured for the data and the last three layers are fine tune through transfer learning. To evaluate the result the dataset is also checked on Naïve Bayesian, KNN (Mahopatara et al., 2014), and SVM with Histogram Oriented Gradient. The LBP features were extracted to train the classifiers using k-fold cross-validation technique where k = 10 shows in Table 1. While using this framework different experiments are performed; according to the given data the proposed method yields accuracy on 1.00e-04 learning Rate and 20 epochs to classify into four classes of the images. The system revealed 97.78% accuracy. To evaluate the desired results of the proposed system with recent existing systems for ALL diagnosis, comprehensive comparison is performed in Table 2 with different research works reported in state of art.

TABLE 1 Comparison of proposed system with other classifiers

Classifiers	Naïve Baysian	KNN	SVM	Proposed
Accuracy	78.34%	80.42%	90.91%	97.78%

The accuracy is plotted on the basis of iteration, as the time to process all the iteration is noted during the experiments. There is good accuracy rate for all experiments done on even low learning rate with a less number of epochs. Hence, it clearly shows that if the learning rate and epochs increased, the accuracy will be increased.

The proposed architecture is implemented in MATLAB 2017a with computer vision toolbox and Alexnet model on GPU. This takes hardly 163.63 s to train the model with 20 epochs. Figure 4 shows the classification accuracy with a number of 2500 iterations. The system trained for 10, 15, and then 20 epochs in each experiment with different learning rates. Figure 5 shows the loss during training period of the model.

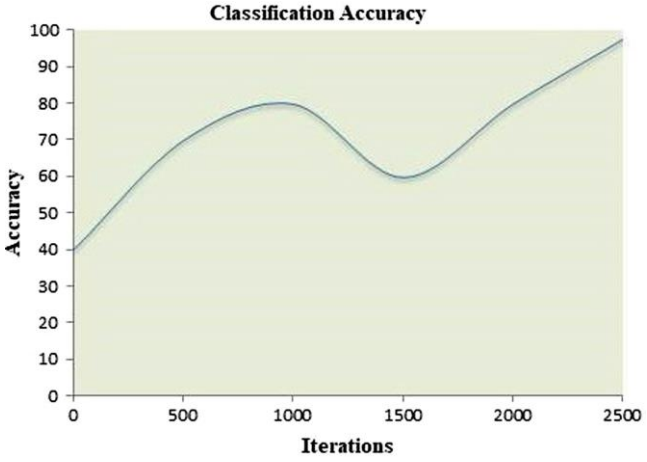

FIGURE 4 Classification accuracy of the proposed system [Color figure can be viewed at wileyonlinelibrary.com]

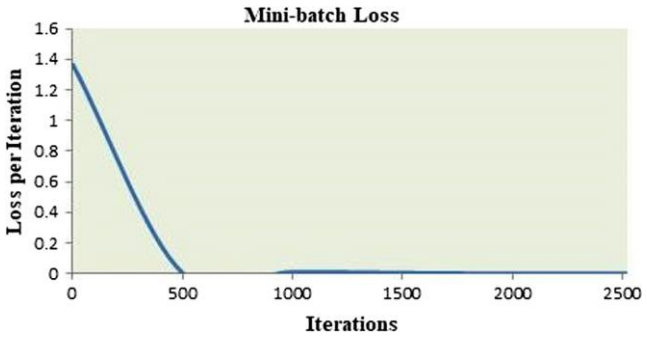

FIGURE 5 Loss during training the proposed model [Color figure can be viewed at wileyonlinelibrary.com]

6 | CONCLUSION AND FUTURE WORK

This research work has presented a complete architecture based on deep learning techniques for the classification of ALL and achieved 97.78% accuracy with efficient processing time. The system consists of convolution layers, max-pooling layers to train the model and fully connected layer, softmax and classification layer to classify the image. The proposed approach has acceptable performance, takes the bone marrow image as input, perform segmentation, and classify as normal if the marrow is not affected or into subtype L1, L2, and L3. The novel contribution of this study is the segmentation technique which is not applied before. The researchers did not use the automted methods earlier to segment whole cell nucleus as well as cytoplasm (as Amin et al., 2015 segmented only nucleus and extracted features for classification). While according to the morphology of L2 and L3 blasts the segmenation is very important for the accurate classification, and deep learning techniques used for the classification of ALL are considered the novelty of this research. In this study, the Convolutional neural net is used for understanding deep features and the ability to classify the images taking advantage to gain an increase in classification accuracy. Findings of the proposed system exhibit the superiority of the train model. The proposed approach is an assistance for the laboratory experts and pathologists which has a great clinical impact for Leukemia patients. As future work, the approach still needs improved

TABLE 2 Results analysis and comparison on ALL-IDB

References	Features employed	Classifier(s)	Test set	Accuracy (%)
Rawat, Singh, Bhadauria, Virmani, and Devgun (2017)	Morphological features	PCA-kNN, PCA-PNN, PCA-SVM, PCA-SSVM, and PCA-ANFIS	260	97.6
Singh, Bathla, and Kaur (2016)	Shape and texture features	Neural network	108	97.2
Singhal and Singh (2016)	Texture features	SVM	260	93.8
Viswanathan (2015)	Shape, color, and texture features	Fuzzy system	108	98.0
Amin et al. (2015)	Shape and texture features	SVM	21	97.0
Neoh et al. (2015)	Shape, texture, and color features	Dempster-Shafer	180	96.7
Bhattacharjee and Saini (2015)	Shape features	ANN	120	95.2
Singhal and Singh (2015)	Shape and texture features	SVM	260	92.3
Rawat et al. (2017)	Shape and texture features	SVM	196	89.8
Putzu, Caocci, and Di Ruberto (2014)	Shape, color, and texture features	SVM	267	92.0
Putzu and Di Ruberto (2013)	Shape and texture features	SVM	245	92.0
Proposed approach	CNN features	CNN	330	97.78

accuracy to segment overlapped cells. Additionally, future work might be fruitful by application of different deep learning models to improve the classification accuracy.

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REFERENCES

Abbas, N., & Mohamad, D. (2014). Automatic color nuclei segmentation of leukocytes for acute leukemia. *Research Journal of Applied Sciences, Engineering and Technology*, *7*(14), 2987–2993.

Abbas, N., Mohamad, D., Abdullah, A. H., Saba, T., Al-Rodhaan, M., & Al-Dhelaan, A. (2015). Nuclei segmentation of leukocytes in blood smear digital images. *Pakistan Journal of Pharmaceutical Sciences*, *28*(5), 1801–1806.

Abbas, N., Saba, T., Mohamad, D., Rehman, A., Almazyad, A. S., & Al-Ghamdi, J. S. (2016). Machine aided malaria parasitemia detection in Giemsa-stained thin blood smears. *Neural Computing and Applications*, *29*(3), 1–16. https://doi.org/10.1007/s00521-016-2474-6

Abd Halim, N. H., Mashor, M. Y., Nasir, A. S. A., Mokhtar, N. R., & Rosline, H. (2011). *Nucleus Segmentation Technique for Acute Leukemia.* IEEE 7th International Colloquium on Signal Processing and its Applications, Penang, Malaysia.

Adollah, R., Mashor, M. Y., Nasir, N. F. M., Rosline, H., Mahsin, H., & Adilah, H. (2008). *Blood cell image segmentation: A review*. In N. A. Abu Osman, F. Ibrahim, W. A. B. Wan Abas, H. S. Abdul Rahman & H. N. Ting (Eds.), 4th Kuala Lumpur International Conference on Biomedical Engineering 2008. Springer, Berlin, Heidelberg: *IFMBE Proceedings, 21*, 141–144.

Agaian, S., Madhukar, M., & Chronopoulos, A. T. (2014). Automated screening system for acute myelogenous leukemia detection in blood microscopic images. *IEEE Systems Journal*, *8*(3), 995–1004.

Amin, M. M., Kermani, S., Talebi, A., & Oghli, M. G. (2015). Recognition of acute lymphoblastic leukemia cells in microscopic images using K-means clustering and support vector machine classifier. *Journal of Medical Signals and Sensors*, *5*(1), 49–58.

Bhattacharjee, R., & Saini, L. M. (2015). Detection of Acute Lymphoblastic Leukemia using Watershed Transformation Technique. International Conference on Signal Processing, Computing and Control (2015 ISPCC). IEEE Conference, India.

Bibin, D., Nair, M. S., & Punitha, P. (2017). Malaria parasite detection from peripheral blood smear images using deep belief networks. *IEEE Access*, *5*, 9099–9108.

Fahad, H. M., Ghani Khan, M. U., Saba, T., Rehman, A., & Iqbal, S. (2018). Microscopic abnormality classification of cardiac murmurs using ANFIS and HMM. *Microscopy Research and Technique*, *81*(5), 449–457. https://doi.org/10.1002/jemt.22998

Goutam, D., & Sailaja, S. (2015). Classification of acute myelogenous leukemia in blood microscopic images using supervised classifier. *International Journal of Engineering Research & Technology (IJERT)*, *4*(1), 569–574.

Harouni, M., Rahim, M. S. M., Al-Rodhaan, M., Saba, T., Rehman, A., & Al-Dhelaan, A. (2014). Online Persian/Arabic script classification without contextual information. *The Imaging Science Journal*, *62*(8), 437–448. https://doi.org/10.1179/1743131X14Y.0000000083

Hayan et al. (2012). An Image Processing Application for the Localization and Segmentation of Lymphoblast Cell Using Peripheral Blood Images. *Journal of Medical Systems*, *36*(4), 2149–2158.

Husham, A., Alkawaz, M. H., Saba, T., Rehman, A., & Alghamdi, J. S. (2016). Automated nuclei segmentation of malignant using level sets. *Microscopy Research and Technique*, *79*(10), 993–997. https://doi.org/10.1002/jemt.22733

Iftikhar, S., Fatima, K., Rehman, A., Almazyad, A. S., & Saba, T. (2017). An evolution based hybrid approach for heart diseases classification and associated risk factors identification. *Biomedical Research*, *28*(8), 3451–3455.

Iqbal, S., Ghani, M. U., Saba, T., & Rehman, A. (2018). Brain tumor segmentation in multi-spectral MRI using convolutional neural networks (CNN). *Microscopy Research and Technique*, *81*(4), 419–427. https://doi.org/10.1002/jemt.22994

Iqbal, S., Khan, M. U. G., Saba, T., & Rehman, A. (2017). Computer assisted brain tumor type discrimination using magnetic resonance imaging features. *Biomedical Engineering Letters*, *8*(1), 5–28. https://doi.org/10.1007/s13534-017-0050-3

Jagadeesh, S., Nagabhooshanam, E., & Venkatachalam, S. (2013). Image processing based approach to cancer cell prediction in blood samples. *International Journal of Technology and Engineering Sciences*, *1*(1), 1–10.

Jamal, A., Hazim Alkawaz, M., Rehman, A., & Saba, T. (2017). Retinal imaging analysis based on vessel detection. *Microscopy Research and Technique*, *80*(7), 799–811.

Joshi, M. M. D., Karode, A. H., & Suralkar, S. R. (2013). White blood cells segmentation and classification to detect acute leukemia. *International Journal of Emerging Trends & Technology in Computer Science (IJETTCS)*, *2*(3), 147–151.

Jayoti et al. (2017). Classification of acute lymphoblastic leukaemia using hybrid hierarchical classifiers. *Multimedia Tools and Applications*, *76*(18), 19057–19085.

Kulkarni-Joshi, T. A., & Bhosale, D. S. (2014). A fast segmentation scheme for acute lymphoblastic leukemia detection. *International Journal of Advanced Research in Electrical, Electronics and Instrumentation Engineering*, *4*(1), 2278–8875.

Lung, J. W. J., Salam, M. S. H., Rehman, A., Rahim, M. S. M., & Saba, T. (2014). Fuzzy phoneme classification using multi-speaker vocal tract length normalization. *IETE Technical Review*, *31*(2), 128–136. https://doi.org/10.1080/02564602.2014.892669

Mahopatara, S., Patra, D., & Satpathy, S. (2014). An ensemble classifier system for early diagnosis of acute lymphoblastic leukemia in blood smear images. *Neural Computing & Applications*, *24*, 1887–1904

Meethongjan, K., Dzulkifli, M., Rehman, A., Altameem, A., & Saba, T. (2013). An intelligent fused approach for face recognition. *Journal of Intelligent Systems*, *22*(2), 197–212.

Mughal, B., Muhammad, N., Sharif, M., Rehman, A., & Saba, T. (2018). Removal of pectoral muscle based on topographic map and shape-shifting silhouette. *BMC Cancer*, *18*, 778.

Mughal, B., Muhammad, N., Sharif, M., Saba, T., & Rehman, A. (2017). Extraction of breast border and removal of pectoral muscle in wavelet. *Biomedical Research*, *28*(11), 5041–5043.

Mughal, B., Sharif, M., & Muhammad, N. (2017). Bi-model processing for early detection of breast tumor in CAD system. *The European Physical Journal Plus*, *132*, 266.

Mughal, B., Sharif, M., Muhammad, N., & Saba, T. (2017). A novel classification scheme to decline the mortality rate among women due to breast tumor. *Microscopy Research and Technique*, *81*(2), 171–180.

Nee, L. H., Mashor, M. Y., & Hassan, R. (2012). White blood cell segmentation for acute leukemia bone marrow images. *Journal of Medical Imaging and Health Informatics*, *2*, 278–284.

Neoh, S. C., Srisukkham, W., Zhang, L., Todryk, S., Greystoke, B., Lim, C. P., … Aslam, N. (2015). An intelligent decision support system for leukaemia diagnosis using microscopic blood images. *Scientific Reports*, *5*, 14938.

Norouzi, A., R., Altameem, M. S. M., Saba, A., Rada, T., Rehman A., A. E., & Uddin, M. (2014). Medical image segmentation methods, algorithms, and applications. *IETE Technical Review*, *31*(3), 199–213. https://doi.org/10.1080/02564602.2014.906861

Pan, C., Park, D. S., Yang, Y., & Yoo, H. M. (2012). Leukocyte image segmentation by visual attention and extreme learning machine. *Neural Computing and Applications*, *21*, 1217–1227.

Putzu, L., Caocci, G., & Di Ruberto, C. (2014). Leucocyte classification for leukaemia detection using image processing techniques. *Artificial Intelligence in Medicine*, *62*(3), 179–191.

Putzu, L., & Di Ruberto, C. (2013). White blood cells identification and classification from leukemic blood image. Proceedings of the International Conference on Bioinformatics and Biomedical Engineering, March 18–20, 2013, Copicentro Editorial, Granada, Spain, p. 99–106.

Rad, A. E., Rahim, M. S. M., Rehman, A., & Saba, T. (2016). Digital dental X-ray database for caries screening. *3D Research*, *7*(2), 1–5. https://doi.org/10.1007/s13319-016-0096-5

Rahim, M. S. M., Norouzi, A., Rehman, A., & Saba, T. (2017). 3D bones segmentation based on CT images visualization. *Biomedical Research*, *28*(8), 3641–3644.

Rahim, M. S. M., Rehman, A., Kurniawan, F., & Saba, T. (2017). Ear biometrics for human classification based on region features mining. *Biomedical Research*, *28*(10), 4660–4664.

Rawat, J., Singh, A., Bhadauria, H. S., Virmani, J.,. &., & Devgun, J. S. (2017). Classification of acute lymphoblastic leukaemia using hybrid hierarchical classifiers. *Multimedia Tools and Applications*, *76*(18), 19057–19085.

Rehman, A., Abbas, N., Saba, T., Mahmood, T., & Kolivand, H. (2018). Rouleaux red Blood Cells splitting in microscopic thin Blood smear images via local maxima, circles drawing, and mapping with original RBCs. *Microscopic Research and Technique*, *81*(7), 737–744. doi. org/https://doi.org/10.1002/jemt.23030

Rehman, A., & Saba, T. (2014). Neural networks for document image preprocessing: State of the art. *Artificial Intelligence Review 4*(2), 253–273. doi. org/https://doi.org/10.1007/s10462-012-9337-z

Rezatofighi, S. H., Khaksari, K., & Soltanian-Zadeh, H. (2011). Automatic recognition of five types of white blood cells in peripheral blood. *Computerized Medical Imaging and Graphics*, *35*(4), 333–343.

Saba, T. (2017). Halal food identification with neural assisted enhanced RFID antenna. *Biomedical Research*, *28*(18), 7760–7762.

Saba, T., Al-Zahrani, S., & Rehman, A. (2012). Expert system for offline clinical guidelines and treatment. *Life Science Journal*, *9*(4), 2639–2658.

Sadeghian, F., Seman, Z., Ramli, A. R., Kahar, B. H. A., & Saripan, M. I. (2009). A framework for white blood cell segmentation in microscopic blood images using digital image processing. *Biological Procedures*, *11*(1), 196–206.

Scotti, F. (2005). Automatic morphological analysis for acute leukemia identification in peripheral blood microscope images. CIMSA 2005 – IEEE International Conference on Computational Intelligence for Measurement Systems and Applications Giardini Naxos, July 20–22, 2005, Italy.

Singh, G., Bathla, G., & Kaur, S. (2016). Design of new Architecture to detect leukemia cancer from medical images. *International Journal of Applied Engineering Research*, *11*(10), 7087–7094.

Singhal, V., & Singh, P. (2015). Correlation based feature selection for diagnosis of acute lymphoblastic leukemia. Proceeding of International Symposium on Women in Computing and Informatics. ACM, New York.

Singhal, V., & Singh, P. (2016). Texture features for the detection of acute lymphoblastic leukemia. Proceeding of International Conference on ICT for Sustainable Development. Springer, Singapore. pp. 535–543.

Tabrizi, P. R., Rezatofighi, S. H., & Yazdanpanah, M. J. (2010). Using PCA and LVQ Neural Network for Automatic Recognition of Five Types of White Blood Cells. 32nd Annual International Conference of the IEEE EMBS Buenos Aires, August 31–September 4, 2010, Argentina.

Theera-Umpon, N., & Dhompongsa, S. (2007). Morphological Granulometric features of nucleus in automatic bone marrow white blood cell classification. *IEEE Transaction on Information Techonology in Biomedicine*, *11*(3), 353–359.

Trupti et al. (2014). A fast segmentation scheme for acute lymphoblastic leukemia detection. *Int J Adv Res Electr Electron Instrum Eng*, *3*(2), 7252–7258.

Vidhya, C., Kumar, P. S., Keerthika, K., Nagalakshmi, C., & Devi, B. M. (2015). *Classification of acute lymphoblastic leukemia in blood microscopic images using SVM*. In: International Conference on Engineering Trends and Science & Humanities (ICETSH), p. 185–189.

Viswanathan, P. (2015). Fuzzy C means detection of leukemia based on morphological contour segmentation. *Procedia Computer Science* 58, 84–90.

Waheed, S. R., Alkawaz, M. H., Rehman, A., Almazyad, A. S., & Saba, T. (2016). Multifocus watermarking approach based on discrete cosine transform. *Microscopy Research and Technique*, *79*(5), 431–437. https://doi.org/10.1002/jemt.22646