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Detection of microcytic hypochromia using cbc and blood film features extracted from convolution neural network by different classifiers

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Abstract
Diagnosis of microcytic hypochromia is done by measuring certain characteristics changes in the count of blood cell and related indices. Complete blood count test (CBC) is the common process for measuring these characteristic changes. However, the CBC test cannot be completely relied upon since there are chances of false diagnosis as these characteristics are also related to other disorders. In order to rectify the same, other expensive and lengthy tests need to be done which leads to further delay in accurate diagnosis and which may prove detrimental. In an attempt to find the solution to this problem, this paper proposes a method that uses feature fusion for classification of microcytic hypochromia. Feature fusion means combining blood smear image features extracted by the deep convolutional neural network (CNN) and clinical features from CBC test. This fused data-set is further used to predict microcytic hypochromia. After obtaining fused data set we use linear discriminant analysis (LDA) and principal component analysis (PCA) to reduce data set dimensions which further results in less computational overhead. To differentiate between microcytic hypochromia patients and normal persons, k-nearest neighbors (k-NN), support vector machine (SVM), and neural network classification models are used. In order to check the performance of the above model, various evaluation metrics are used. Results achieved from the proposed method reflect that fused data set can effectively improve the identification ratio with a very limited number of patients diagnostic images and clinical data (10 for normal and 10 for β-thalassemia) and feed-forward back-propagation neural network on this data set achieved accuracy, sensitivity, and specificity of 99%, 1.00, and 0.98, respectively. The limited number of patients reduces the system complexity and researcher's time for getting data from different hospital to train the network.

Keywords Artificial neural network · Convolution neural network · K-nearest neighbors · Linear discriminant analysis · Principal component analysis · Support vector machine

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1 Introduction

Anemia is one of the most prevalent blood disorders and caused due to multiple reasons such as thalassemia, sickle cell anemia, vitamin B12 deficiency, and iron deficiency anemia [30]. About 800 million infants each year around the world are affected by anemia as per World Health Organization (WHO) report in 2004. Where as thalassemia affects about 3 lac infants born each year around the world, iron deficiency resulted in 273000 deaths [15, 27, 43]. According to National Family Health Survey (NFHS-3) conducted in 2005−2006, anemia was detected among 70% of children, 55% in females and 24% in males [4].

The root cause of anemia is abnormal size or number of red blood cells (RBCs) in the blood plasma of the human body. This, in turn, is due to lesser hemoglobin count or distorted hemoglobin presence in RBCs. This condition is medically termed as microcytic anemia.

Microcytic anemia is of three types namely hypochromic, normochromic and hyperchromic. Hypochromic anemia has lower than normal hemoglobin content in red blood cells resulting in paler color of RBCs. Normochromic anemia has normal amount of hemoglobin in red blood cells resulting in normal red blood cell color. Hyperchromic anemia has higher than normal hemoglobin content in RBCs resulting in red color darker than normal. Most microcytic anemias, however, are hypochromic only. Therefore the word 'microcytic anemin used in this paper generally refers to its hypochromic type only and all the further discussion is in the context of microcytic hypochromic anemia only. This is caused due to the following two reasons:

1. Iron Deficiency: Since hemoglobin is made up of iron, lower intake or absorption of iron by human body results in lower production of hemoglobin leading to lower number of RBCs.
2. Thalassemia: This happens due to the deletion or mutation of either of HBA1, HBA2 or HBB genes which encode α and β proteins present in the hemoglobin. In case of HBA1 or HBA2, it is termed as α Thalassemia and in the case of HBB, it is β Thalassemia. α and β Thalassemia are further classified into major and minor Thalassemia.

Microcytic anemia in today's medical science is diagnosed on the basis of complete blood count (CBC) results reported by automatic counters or analyzers. These counters measure or calculate values for important parameters such as RBC count, mean corpuscular volume (MCV), packed cell volume (PCV) and red cell distribution width (RDW) for RBCs. For hemoglobin, parameters like hemoglobin count, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are reported. Other approach is to examine stained peripheral blood smear under the microscope and to analyze any deviation in size, shape, and color of RBCs. Automatic Analyzers sample and count a large number of cells due to which values calculated are not affected by any local inter cellular variations and are very accurate. However, these analyzers like any other machine are programmed to do only specific tasks i.e. the calculation of the limited number of parameters. Any abnormal cell in the blood, therefore, cannot be identified by these analyzers which might have come into notice or observed during the manual inspection of peripheral blood smear image. In addition to this, analyzers do not directly detect any abnormalities in the shapes or colors of RBCs. Only inferential knowledge can be obtained about shape and color through the calculated parameters. Peripheral blood smear image analysis, therefore, becomes as important as automated analysis. This is exactly where deep learning in image processing comes into the picture as it takes into account all the morphological features of a red blood cell which can help hematologists become more productive, objective,

and consistent in diagnosis. It can be inferred from the above that both the peripheral blood smear image and results from automated analyzer contain vital information for accurate diagnosis.

This paper, therefore, proposes an approach which uses both blood smear image and calculated clinical features from the automated analyzer. This is done by extracting features from the stained blood smear images using layered architecture of deep convolutional neural network (CNN) and then combining these features with clinical features of CBC test. When we combine clinical and image features, length of features is too large and that creates complexity in the model. In the limited number of training examples, we can't work with a large number of features because it leads to overfitting. We use two major feature reduction methods such as LDA, PCA [17, 41]. PCA remove redundancy between features so that every features has different information about the disease and makes it more clear in terms of information about the classes. LDA chooses the features such that all features are separated in different classes. Many extensions of LDA and PCA have also been developed to enhance the performance and efficiency. For example, orthogonal LDA (OLDA), uncorrelated LDA (ULDA), and robust sparse linear discriminant analysis (RSLDA) for LDA [41] and 2−DPCA, PCAL1 norm, sparse PCA, robust PCA, and MPCA [17]. With the help of PCA and LDA, a compact representation of fused features is obtained, which reduces computational complexity and avoid overfitting thus improving the performance of microcytic anemia detection. This compact fused data set is further processed to develop a model for detection of microcytic anemia using KNN, SVM and neural network as classifiers.

2 Related work

In past, there have been attempts to classify and detect microcytic anemia or one of its sub types such as α-thalassemia, β-thalassemia and iron deficiency anemia. In all these cases, blood smear images were used or clinical features from CBC test were used to develop a model for automatic detection of microcytic anemia or its sub types. Related works relevant in this context are being described further.

C. Donato et al. [12] classifies red blood cell and white blood cell using k-nearest clustering method. Therefore, an automated and reproducible methodology could tackle the aforementioned obstacles more effectively.

Waranyu Wongseree and Nachol Chaiyaratana, classify thalassemia patients with the help of genetic programming (GP) and multi layer perceptron (MLP) [42]. In this decision trees based on GP and the neural network are applied as classifiers. 270 samples in this problem are taken from normal patients and different types of thalassemia patient and thalassemia trait. GP based classification trees and MLP with one hidden layer give the same performance as shown in [42]. In contrast, the MLP with two hidden layers do better than GP based classification trees.

Patcharaporn Paokanta et al. tried to provide a comparison between performances of different classification technique by altering the type of data to determine the appropriate data type for each technique [29] and use 127 β-thalassemia patients.

Principle component analysis (PCA) was used by S.R. Amendolia et al. in his research in which the features selected are Hb, Ht, MCV, and RBC. They did a comparative study of k-NN, SVM and MLP for the screening of thalassemia using 304 clinical records [3]. The results show in this study that when data available is limited, results of the MLP classifier are marginally better than those of SVM.

In knowledge discovery of β-thalassemia using PCA Research [29], This application gets the results of the blood test as their input and data is reduced before classification. Results show that the MLP is the best.

Anand Upadhyay tried to classify the β-thalassemia person using artificial neural network (ANN) based on their quantitative blood test [39]. In this study Hemoglobin A (HbA), hemoglobin A2 (HbA2), and fetal hemoglobin (HbF) are inputs of feed forward Neural network.

El-Sebakhy and Elshafei in [33] proposed an unconstrained functional networks classifier for thalassemia screening and compared its results with MLP and SVM. The results show that this unconstrained functional networks classifier are reliable, flexible, and perform better than the most common existing classifiers.

Hemochrome cytometric analysis generates some hematologic parameters and Amendolia et al. [2] use these parameters for the classification of thalassemia using ANNs. Different combinations of ANNs are applied, which classify thalassemia carriers and normal patients with 94% accuracy.

Eyad H. Elshami and Alaa M. Alhalees investigated the existence of thalassemia by using data mining classifiers for CBC test [16]. The experimental results of this investigation were bright with accuracy exceeding 90%.

Vishwas et al. [40] presented a method to detect sickle cell anemia and thalassemia which used thin blood smear microscopic images after applying a median filter for noise removal. He also enhances the image using morphological operations after separating overlapping RBCs using watershed segmentation method. A k-NN classifier was applied on these images to classify them further into dacrocytes (teardrop cells), sickle cells, ovalocytes, and normal Erythrocytes. This classification is accurate up to 80% and sensitive up to 88%.

Another method for detection of thalassemia blood cell was proposed by Nurhanis et al. [28] which used active contour. They identify deformed RBCs on the basis of their roundness and eccentricity. This active contour method identifies thalassemia blood cells with an accuracy of around 90%.

Setsirichok et al. in 2012 [34] differentiated thalassemia patients on the basis of abnormal hemoglobin, thalassemia trait using CBC and hemoglobin data. The data set contained eight attributes and 19 classes. During the study, NB and MLP were found to be most useful classifiers.

Masala et al. in 2013 [26] used the radial basis function (RBF) network, probabilistic neural network (PNN), and k-NN classifiers on the clinical data such as RBC count, HB, hematocrit (Ht), HbA2 and MCV from 304 cases to distinguish between normal patients and α-thalassemia carriers.

Barnhart-Magen et al. in 2013 [5] detected thalassemia minor patients using 1500 artificial neural networks for pattern recognition on the data set consisting of clinical features such as HB, MCV, MCH, RDW, RBC, and platelet count (PLT) of 526 patients. Two models were used, one with all six clinical features and the others using only MCV, RDW, and RBC as clinical features. Model with 3 features perform slightly better than the one with all six features.

Eshpala et al. in 2016 [20] used MLP model with 4 inputs, 100 neurons, and 1 hidden layer on the dataset consisting of CBC data for 395 patients to differentiate them into β-thalassemia (minor), iron-deficiency anemia, and healthy groups. Results were achieved with specificity, sensitivity, and accuracy of 92%, 94%, and 93.9% respectively.

In 2016, Hany A Elsalamony [14] used circular Hough transform on blood smear and classify with neural network into normal and different kinds of anemia like a sickle and microcytic.

Das et al. [10] in 2012 preprocessed peripheral blood smear images to remove the noise and uneven brightness with geometric mean filter. After this watershed segmentation

strategy and logistic regression classifier were applied to classify these images based on their morphological shape. Results were achieved with the accuracy of 86.87%, the sensitivity of 95.3%, and specificity of 94.13%.

Due to the ineffectiveness of above methods deep learning is now being used for feature extraction and classification. It automatically learned features from the cell data, instead of being guided especially.

A very deep CNN (more than 150 layers) was applied by Durant [38] for RBC classification. This method correctly detected 90.60%.

In addition, many big technology companies like Apple, Google, IBM, Facebook, and Microsoft have embraced and used deep learning in their research [18, 19, 25].

As can be seen from the above survey, most of the previous works applied classical machine learning classifiers. However, the size of the data used in these works was considerably large. On the contrary, this paper can effectively help in increasing the prediction power of the classifiers for identifying microcytic anemia patients with a relatively smaller data set.

Clinical parameter and blood smear are the important parameters to detect microcytic anemia as explained in the introduction above. Hence this paper focuses on the fusion of clinical features, and hierarchical features derived using CNN. Redundant fused features are removed with PCA and LDA and further pass-through different classiers like k-NN, SVM, and neural networks to identify data-set into normal patients and microcytic anemia patients.

Rest of the paper is divided into following section: Section 3 details on the data set, which is used in research methodology. Section 4 explains the methodology. Different evaluation methods discussed in Section 5, in Section 6 we present the experimental results, a comparative analysis, and a discussion, followed by the conclusion in Section 7.

3 Material and collection process

Samples were obtained from twenty patients, ten thalassemia patients and ten normal patients from the haematology department of All India Institute Of Medical Sciences (AIIMS), New Delhi. This was approved by AIIMS ethical committee. Venous blood is the choice for this test. 1.1 mm or 0.8 mm needle is suitable for most adults and 0.66 mm needle is selected for children. Blood is withdrawn from an antecubital vein and stored at 4°C until used. Frozen specimens should be thawed in a water bath or in a 37°C incubator, and then inverted several times to ensure homogeneity before being used for a test. The film in which blood spread must not be too thin and the tail of the film should be smooth. The microscope scans the stained blood film from the head to the tail and takes digital images of them and use classifiers to analyze the cells.

RBCs were imaged on a Nikon Eclipse E600 microscope under 100x oil objective lens using an Olympus DP 71 microscope digital camera at 1360×1024 image resolutions.

4 The proposed method

4.1 Feature extraction by convolution neural network

Deep learning directly examines the features from input data, and avoid hand drawn features [6]. CNN is a special deep learning technique [24], which is widely used in image classification and medical image analysis [7, 9, 31, 44].

CNN has numerous consecutive combinations of convolutional and sub-sampling (pooling) layers, followed by supervised classifier, where output of each layer is a set of two dimension feature map. These feature maps are used in the form of input of the next layer. There may be images, audio, and video signals as input. If color image is at the input, the output contains a set of the array where each feature map represents the features extracted at the locations of the corresponding input. Input is given to deep net which calculates it layer by layer to produce the final output. This output is then compared with the actual output. The error in the output is fed backward by back-propagation. In every step, for reducing the error, the backward model parameters are tuned. Generally, training is a recurrence process in which multiple passes of input data are included in the model conversion.

There are four main layers in CNN architecture: convolutional layer, activation layer, pooling layer, and classification layer. Complete CNN architecture is obtained by serially linking many of these layers as shown in Table 1. In convolutional layer, feature maps are obtained through convolution of the image with kernels. The kernels weights are tuned by back propagation. To reduce the parameters in the networks, all units of the same feature maps share the same kernels. This process increases efficiency and prevents over fitting. After convolutional layers, a nonlinear activation layer is applied to retrieve more complex properties of the input signal. It is also common to insert pooling (sub sampling) layer between two convolutional layers in order to reduce the spatial size of the representation. Max pooling function, which computes the maximum in an input patch by applying window function have shown better results [32]. CNN typically consist of several pairs of convolutional and pooling layers. After many such pairs, fully-connected layers further used to convert 2-D feature maps into a 1-D vector for final classification. Fully-connected layers are similar to NNs [23]. CNN trains the network in a similar way as ANNs, which use gradient descent methods and back propagation of the error for minimizing a loss function.

Table 1 CNN architecture

Layer	Kernel size	Stride	Pad
Input	N/A	N/A	N/A
Convolution	11	4	0
ReLU	1	1	0
Max-pooling	3	2	0
Convolution	5	1	2
ReLU	1	1	0
Max-pooling	3	2	0
Convolution	3	1	1
ReLU	1	1	0
Convolution	3	1	1
ReLU	1	1	0
Convolution	3	1	1
ReLU	1	1	0
Max-pooling	3	2	0
Fully-connected with 4096 neurons	1	1	0
Fully-connected with 4096 neurons	1	1	0
Fully-connected with 2 neurons	1	1	0

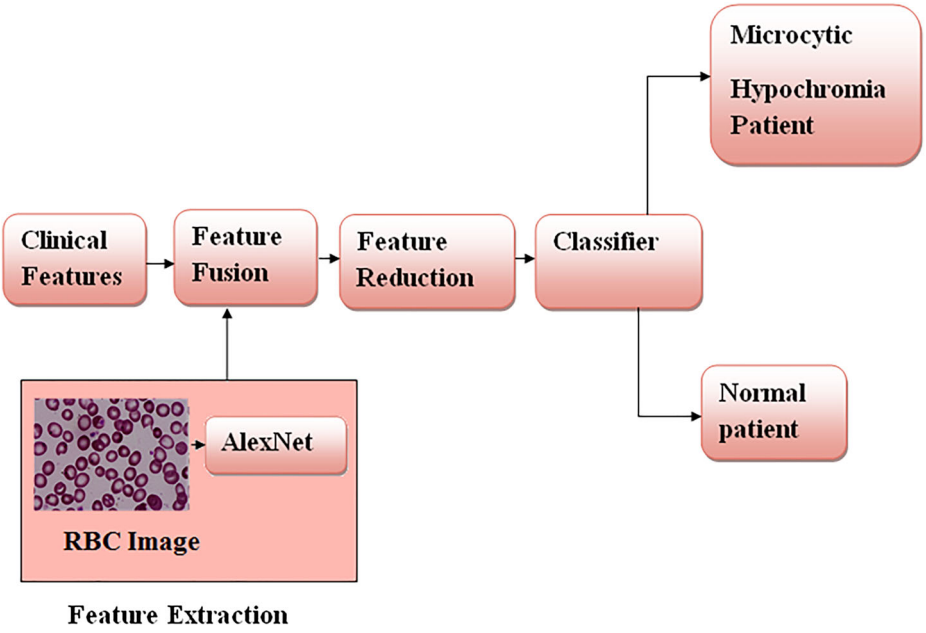


Fig. 1 Framework of proposed method

At present most popular CNNs are: AlexNet [23], Clarifai [45], VGG [36], and GoogLeNet [37]. This paper uses deep CNN for the extracting the features of microcytic anemia blood smear. These extracted features are not sufficient to detect microcytic anemia, therefore some clinical features are also used for classification of disease. KNN, SVM, and neural network are different classifiers that can be used for microcytic anemia screening. To the best of our knowledge, this is the first time fusion of clinical features and CNN features have been designed and trained for microcytic anemia classification. The structure of the proposed method is shown in Fig. 1.

In our method, we classify microcytic anemia from clinical and blood smear images data set. In this proposed work, we learn and extract the feature of blood smear images of anemia patients or normal patient at the fc8 layer of AlexNet. The AlexNet model was proposed by Alex Krizhevsky to accurately classify images from ImageNet Large-Scale Visual Recognition Challenge (ILSVRC) [23]. A subset of Imagenet data set with 1000 categories each having roughly 1000 images are used in ILSVRC. Neurons in fc layers are fully connected to the previous layer as in neural network. They produce a single vector output. The last fc layer uses softmax activation, and it used to classify the feature vector into number of classes. In our work, last fully-connected layers have 2 classes i.e. microcytic anemia and normal.

4.2 Feature fusion

In this study, the clinical data set for microcytic anemia diagnosis involves various characteristics of human blood. The major components of blood (1) RBC (2) WBC and (3) platelet. Table 2 summarizes the features extracted from these blood components. The objective of classification is to identify microcytic anemia gene carries and normal case groups correctly.

Table 2 Clinical features, derived from a blood cell analyzer, for the microcytic anemia classification

Feature	Description	Measurement unit	Normal Ranges
1	Red blood cell count (RBC)	million/mm3	male:4.5-5.5, female:3.8-4.8
2	Haemoglobin concentration (HB)	gram/decilitre	male:13-17, female:12-15
3	Haematocrit (HCT)	percent (%)	male:40-50, female:36-46
4	Mean corpuscular volume (MCV)	femtolitre	83-101
5	Mean corpuscular haemoglobin (MCH)	picogram	27-32
6	Mean corpuscular haemoglobin concentration (MCHC)	gram/decilitre	31.5-34.5
7	Red blood cell distribution width (RDW)	percent (%)	11.6-14
8	hemoglobin A1	percent (%)	95-98
9	hemoglobin A2	percent(%)	1.5-3.5
10	hemoglobin F	percent(%)	<2(age-dependent)
11	Mentzer index (MCV/RBC count ratio)	MCV/RBC Count	Thalassemia:<13, IDA:> 13

After feature extraction of AlexNet network above, these feature vectors are concatenated with clinical features to create high dimensional fusion features. Feature fusion helps to fully learn all the features. The details of their rich internal information thus help to improve the detection of microcytic anemia. The performance of the above method will be assessed on the bases of 20 sample groups. Out of these 20 sample groups, 10 are of anemic patients and 10 are of normal patients.

4.3 Feature reduction

There are 1011 fused features in this proposed method, in which 11 features are clinical features and 1000 features are extracted from the fc8 layer of AlexNet. According to Hughes Phenomenon [35], adding More features on the same size of training set does not mean it will give more information and better classification performance as shown in Fig. 2.

There are limited training examples in the proposed method and number of features are large in numbers, they may have some irrelevant, and unnecessary features, in algorithm such as KNN and SVM, these irrelevant features introduce noise and the results are incorrect, and redundant features do not contribute additional information, they can cause a drop

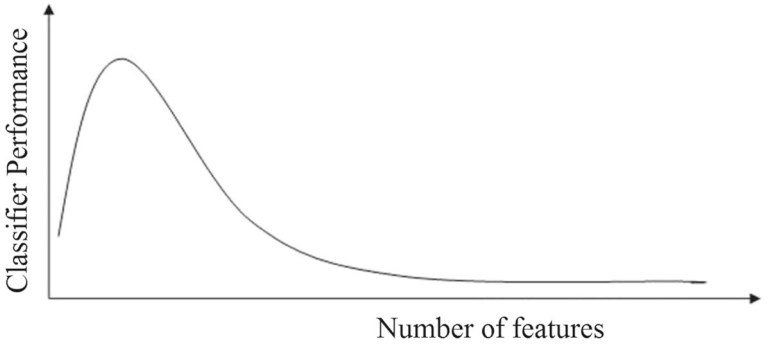


Fig. 2 Classifier performance based on number of features

in the performance of the learning algorithms. In the limited number of training examples, we can't work with a large number of features because it leads to over-fitting.

In proposed work, PCA, LDA use to find the small number of features which either improve classification accuracy or maintain the same accuracy and simplify the complexity of classifiers.

1. **Principal component analysis:** PCA projected a higher dimensional feature space into a lower one, such that new features are uncorrelated, cannot be reduced further and, have large variance or variation. These lower dimensional feature sets are used for better and faster classification.

   $A_1, A_2, ...A_P$ is P observations and each observation have N-dimensional features vector $\{A_{11}, A_{12}, A_{13}, ...A_{1N}\}$ and map it to a lower dimensional features space M $\{Z_1, Z_2, Z_3, ...Z_M\}$, where M<N.

   $$Z = W^T.A\,. \tag{1}$$

   One feature chooses in such a way that has the largest variance, and find that value of weights for which the projection select corresponds to the largest variance of Z_1. Other features choose in such a manner that they are uncorrelated and variance is maximum.

   $$max(var[Z_M])\,. \tag{2}$$

   PCA recover the original features from reduced features with minimum reconstruction error.

   PCA select M top principal components as a new axis that gives uncorrelated and large variance features which are called eigen vectors. That means PCA select M largest eigen vectors of co-variance matrix (Cov(A)), where A is training data points. Top eigen vector have maximum eigenvalues and in the direction of the largest variance.

   Select the number of new features, according to eigenvalues that contains the 90%, 95% or 99% of the information and this number is usually much smaller than the set of features you have before and eliminate those input features whose information is low in the eigen vectors.

   In this model, PCA select features that contain 95% of the information. PCA reduces the feature set with minimal loss of information but does not differentiate well among the classes.
2. **Linear discriminant analysis:** In Fig. 3 projections of two different class white and black points in two different directions is shown. PCA choose (a) direction in Fig. 3, because there is too much spread in (a) direction, it is not bothering that it is variance

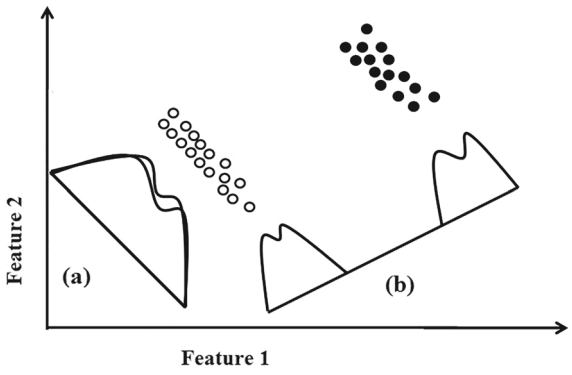


Fig. 3 PCA vs LDA

of class 1 or class 2, but LDA consider minimum overlap between different class and distance between mean of different classes are maximum and choose (b) direction for perfectly discriminant between two classes. In direction (a) all points mix to each other and very difficult to separate two class points, in the direction (b) all points are separated in two classes perfectly.

LDA reduces the feature set by minimizing loss of the class discrimination information.

LDA choose a projection that maximizes between class distances and minimizes within class distance. Maximization of between class distances means maximization of distance between means of different classes and minimization of within-class distance means scatter of class is as small as possible.

The objective function for 2 classes LDA is:

$$V(w) = \frac{(m_1 - m_2)^2}{s_1^2 + s_2^2}. \tag{3}$$

LDA tries to find such w that maximizes $V(w)$, LDA project feature space to the new feature space using w.

Feature fusion describes rich internal information of the image features. And after dimension reduction using PCA and LDA, a compact representation of fused features is obtained, which reduces computational complexity and improve the performance of microcytic anemia detection.

4.4 Classification

In this proposed model k-NN, SVM, and neural network are used for classification after applying PCA and LDA.

1. **k-nearest neighbors (k-NN)**: k-NN is a classification algorithm in which training examples do not process and learn a model, but it stores the training examples. It does not come up with the model apiary rather when it gets the test instances, it uses the stored instance in memory in order to find target value.

   Suppose I is a feature space and have different (X_I, Y_I) point in that space. For test instance, the nearest neighbor finds what is the closest instance in terms of X value and give Y value of X to new test instance target value. Instead of finding a single example which is closest to the test examples, k-NN finds k training examples which are nearest to test instance.

   Algorithm :

   (a) Save the training examples.
   (b) Get the test instance X_t.
   (c) Find the k training examples (X_1, Y_1), (X_2, Y_2),..... (X_k, Y_k) which are closest to X_t using distance function.
   (d) In classification problem, predict most frequent class from $Y_1, Y_2, ...Y_K$ as output Y_t

   The distance function between instances is measured in terms of the euclidean distance [13].
2. **Support vector machine (SVM):** In SVM technique, the optimal boundary is known as a hyper plane, this boundary use to separates the training data set into classes such

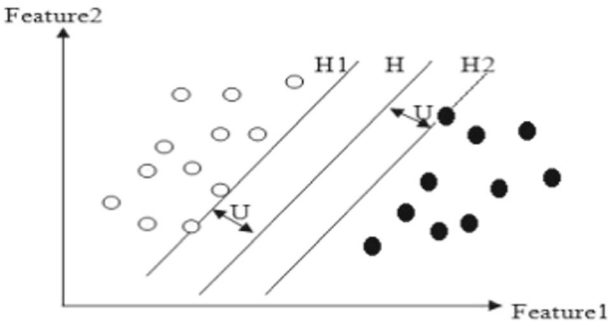


Fig. 4 Hyper plane diagram of SVM

that there is the maximum distance between the hyper plane and the closest points of the training set [22]. These points are called support vectors that show in Fig. 4.

In linear SVM's, the training data have to separate classifier by a hyper plane. SVM tries to maximize a distance between various classes [21]. After finding a proper hyper plane which maximizes the distance between the classes, we can efficiently provide a class to the unseen data. The distance between the closest points to the hyper plane is margin U, and choose such hyper plane that has the highest margin. The hyper plane H should be equidistant from the closest points of the two classes (white and black class in Fig. 4). These points are called support vectors. Suppose equation of hyper plane is:

$$w * x + b = 0 \tag{4}$$

The functional margin define as distance of set of training points $S = \{(x_1, y_1), (x_2, y_2), (x_3, y_3), ...(x_i, y_i)\}$ to hyper plane:

$$\gamma_i = y_i(w^T x_i + b)\,. \tag{5}$$

Among all the functional margin, smallest functional margin chooses that is margin U is shown in Fig. 4.

$$\gamma = \min_{j=1}^{j=i} \gamma_i\,. \tag{6}$$

According to geometric margin :

$$min \frac{1}{2} \left| |w^2| \right|.$$

with

$$y_i \left(w^T x_i + b \right) >= 1\,.$$

If α and β are lagrange multipliers, the solution of the wolf dual problem:

$$max \sum_{i}^{m} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{m} \alpha_i \alpha_j y_i y_j (x_i . x_j)\,, \tag{7}$$

and

$$\sum_{i=1}^{m} \alpha_i y_i = 0\,. \tag{8}$$

It is not always possible to separate the training data using a hyper plane that's why non-linear SVM is used [8].

If x is input features and use mapping original features space transform into new feature space $\phi(x)$, mapping data into a higher dimensional feature. In some cases, it is possible that training points are linearly separable in transformed space. If there are a big set of training examples lets M, so according to equation 4 M^2 computational need to perform in this case.

If x_i and x_j have dimensional d, computational time is $M^2 * d^2$.

In case of non-linear x input feature map to $\phi(x)$ a higher dimensional features space, in such case computational cost is much more than previous (linear).

By using kernel function, transformed new feature space achieve without any major implication on computational cost.

There are some commonly used kernel function:

(a) Linear kernel:

$$K\left(x_i, x_j\right) = x_i.x_j\,. \tag{9}$$

(b) Polynomial kernel:

$$K\left(x_i, x_j\right) = (1 + x_i.x_j)^p\,. \tag{10}$$

(c) Gaussian kernel (RBF):

$$K\left(x_i, x_j\right) = e^{-\frac{||x_i - x_j||^2}{2\sigma^2}}\,. \tag{11}$$

3. **Artificial neural network (ANN):** ANNs are machine learning algorithms that were originally inspired by the human brain. Tens of billions of neurons are in the human brain, which is highly interconnected and performs the very complex task.

Feed forward back propagation is most commonly used ANN neurons are spread over input layer, an output layer, and any other hidden layer between these two layers. Neurons in each layer are fully connected with the neurons of previous layer and neurons of the next layer using weighted connection [1]. The weights indicate the strength of the connection between neurons in different layers. In feed forward back propagation, neurons in the hidden layer process the data received by input layer and forward it to the output layer, and a feedback connected from the outputs to inputs. The output layer decides the class of the input [1]. The output of a link is the weighted sum of incoming data and adding bias according to (13):

$$y_j = \sum_{k=1}^{l} x_k.w_{kj} + \theta_j\,. \tag{12}$$

The number of input parameters determined the number of neurons in the input layer and the same process is followed for the output layer. Hidden layer, however, depends on the type of the problem.

Neural network is a three phase process:

First phase is training phase: In this, the data set gets process through the input layer, output layer and the hidden layers between input and output layers. In the output layer final decision is measured and compared with the actual class. Neural network transfer the result of output to neurons in the next layer through the transfer function.

The most commonly used transfer function is the sigmoid:

$$f(x) = \frac{1}{1 + e^{-x}}\,. \tag{13}$$

Neural network is supervised learning, so it learns the model with the help of training sets. In training process, parameters, weights, and biases are adjusted according to training algorithm in order to minimize error [11].

This weights and biases updating process is called back propagation.

$$Error(E) = \frac{1}{2}\sum_{k=1}^{m}\sum_{j=1}^{n}\left(y_{kj} - y'_{kj}\right)^2 . \tag{14}$$

In the back propagation, partial derivatives of the error function w.r.t. the various weights and biases are back propagated through the network, and weight update according to (16):

$$\delta w_{kj} = -\eta \frac{dE}{dw_{kj}} , \tag{15}$$

where η is called the learning rate.

The training process is performed until a minimum value of E from the act of differentiation is achieved, this finally gives the optimal neural network. This optimization can be done with stochastic gradient descent algorithm.

Second phase is verification phase, in which network is tested with data-set not used in the training phase.

Finally, in the testing phase, network predicts outputs for new input vectors.

5 Evaluation parameters

Next step is to asses effectiveness of the model based on metrics and data sets. Different performance metrics are used to measure the efficiency of different algorithms, also depending upon the data sets at hand.

The model cannot be tested using the training set, because the process of training the machine learning model has already tuned the estimated result of training data sets. Therefore, to assess the generalization error, the model needs to test the data sets that have not yet been seen. Therefore, for the purpose of testing the model, a labeled data set is required. This can be achieved by K-fold cross-validation by splitting the input data set into training and testing data set. K-fold refers to the division of data set into K number folds. Model is trained for each fold using out-of-fold data. Performance of model is assessed thereafter using in-fold data. Average of the testing error for all the folds are then calculated. This method requires multiple fits but gives a good predictive accuracy by efficient use of all the data. Due to multiple fits, it is good for small data sets. Various measurements are used to assess the performance of the different algorithm.

1. True negatives (TN): When the model correctly classifies a negative class person to negative class.
2. True positives (TP): When a person is actually of positive class and the model classify his case as the positive class comes under true positive.
3. False positives (FP): When a person is a negative class and the model incorrectly classify his case as the positive class comes under false positives.
4. False negatives (FN): When a person is a positive class and the model incorrectly classify his case as the negative class comes under false negatives.

5. Accuracy: The ratio of the number of correct predictions to the total number of predictions.

$$Accuracy = \frac{TN + TP}{TN + TP + FN + FP}. \tag{16}$$

6. Specificity: Specificity is also known as true negative rate, the ratio of negative data points that are classified as negative, with respect to all negative data points.

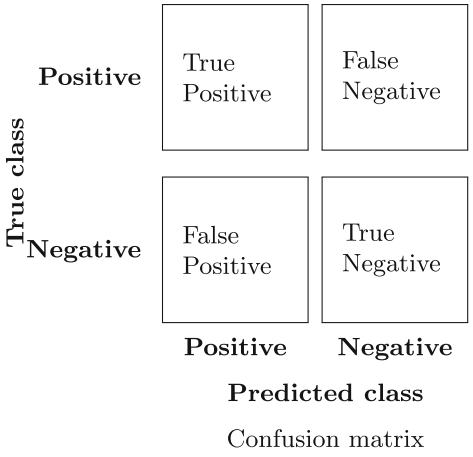
$$Specificity = \frac{TN}{TN + FP}. \tag{17}$$

7. Sensitivity (True positive rate): When positive class correctly classify as positive class with respect to all positive class.

$$Sensitivity = \frac{TP}{TP + FN}. \tag{18}$$

8. Error rate (ERR): It is define as number of all incorrect predictions divided by the total number of predictions.

$$ERR = \frac{FN + FP}{FP + TN + TP + FN}. \tag{19}$$



Confusion matrix

9. Receiver operating characteristics (ROC) and area under curve (AUC): The ROC is a useful graphical technique for visualizing classifiers performance and plot with false positive rate and true positive rate on X and Y axis respectively. High AUC tells that model better classify patients in disease or non disease person.

5.1 Performance criteria on medical domain

All the evaluation parameters as explained above shows the performance level of different model on medical domain.

1. Suppose a test has 90% sensitivity that means it will correctly classify disease result for 90% of people who have the disease but will return a normal class for 10% of the people who have the disease. The best sensitivity is 1.0, whereas the worst is 0.0. High

sensitivity (1) is desirable in medical domain. If any diseased person wrongly classifies then he or she may not get the treatment, thus the life of that person can be in danger.
2. Suppose a test has 90% specificity that means it will correctly classify normal class for 90% of people who do not have the disease but will classify a disease class for 10% of the people who are normal person. The best specificity is 1.0, whereas the worst is 0.0. If any normal person wrongly classifies as a diseased person, then he or she is given further treatment. This results in wast of time and money but does not harm any one's life.
3. AUC and ROC are commonly used in medical decision making. AUC value ranges from 0 to 1. AUC value is 0 for the model whose prediction is 100% incorrect and 1 for model whose prediction is 100% correct. When AUC is 0.7, it means there is 70% chance that model will be able to distinguish between positive class and negative class.
4. Minimizing false positive: In this paper, 10 out of 20 people have microcytic anemia. The positive class refers to a normal person and negative class refers to microcytic anemia patients. False positive therefore need to be minimized as this will diagnose the anemic patient as the normal one and therefore presenting a greater risk by not initiating the treatment when required.

6 Results and discussion

Three classification algorithms and two feature reduction methods are applied to predict microcytic anemia using data sets of 20 patients each data set containing 11 clinical features and 1000 RBC image features extracted from CNN using MATLAB R2017b with zero cost. Because of 1011 fused features (11 clinical and 1000 extracted features from CNN) and the limited number of training examples, it leads to over-fitting that's why we use feature reduction methods. In this case, PCA and LDA are applied to reduce the dimension of the feature vector. With the help of LDA as a feature reduction method, only 100 features were selected for the satisfactory performance of classification and with PCA, the proposed model took 95% explained variance and that gives 23 feature set for classification. After LDA and PCA, KNN, SVM, and neural network classification algorithms are used to classify normal and diseased patients. All these classification algorithms were also used in many papers over clinical data of many patients as shown in related works, because it is very easy to use and implement. The performance of all the above techniques is higher when a data set obtained by fusion of clinical features and image features is used rather than independent data sets of clinical and image features. This is evident from the parameter values shown in Table 3.

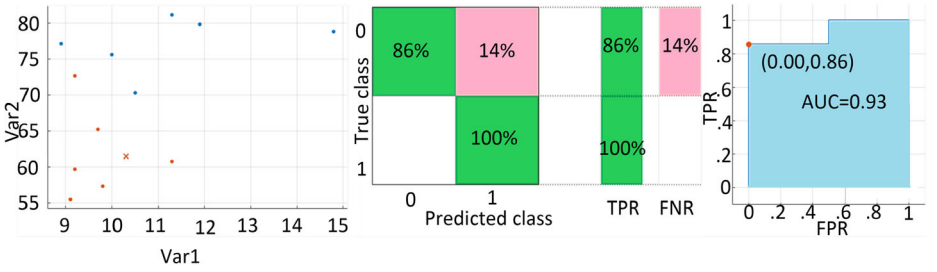
1. **Use of clinical features:** In clinical model Fig. 5, 11 clinical features of microcytic anemia are used to classify with the help of classifiers and get maximum 0.93 AUC in ROC curve. Confusion matrix of KNN, and NN in Fig. 5 shows maximum 91 $\pm$ 2% accuracy and 0.86 sensitivity. Results obtain from SVM are similar to KNN hence not shown separately. For clinical features, the network shown in Fig. 5b is created with 11 inputs, 2 hidden layer one having 10, and the other having 5 hidden neurons, and linear output neuron.
2. **Use of image features:** In image model, Fig. 6, 1000 image features of microcytic anemia are used to classify with the help of classifiers and get maximum 0.88 AUC in ROC curve. Confusion matrix of KNN, SVM, and NN in Fig. 6 shows maximum 78 $\pm$ 2% accuracy and 0.67 sensitivity. For image features, the network shown in Fig. 6c is created with 1000 inputs, 2 hidden layer one having 10, and the other having 5 hidden neurons, and linear output neuron.

Table 3 Classification parameters of clinical, image, and fused method

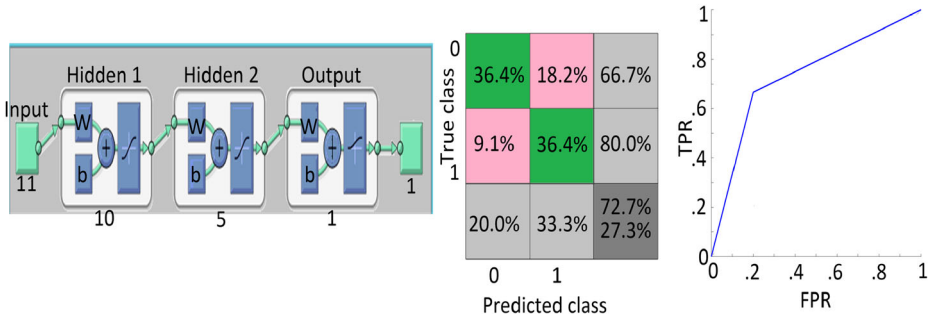
Model	Technique	Accuracy(%)	Sensitivity	Specificity
Clinical model	K-NN	93	0.86	1.00
Clinical model	SVM	93	0.86	1.00
Clinical model	NN	72.8	0.67	0.80
Image model	K-NN	67.4	0.67	0.84
Image model	SVM	78	0.71	0.85
Image model	NN	79.8	0.65	0.91
Fused model	K-NN, PCA	96±2	0.93	1.00
Fused model	K-NN, LDA	99±1	1.00	1.00
Fused model	SVM, PCA	98±2	1.00	0.98
Fused model	SVM, LDA	99±1	1.00	1.00
Fused model	NN	99±1	1.00	0.98

3. **Use of fused features:** In proposed model, PCA and k-NN gives 95.5 ±1%, 0.93, and 0.1 accuracy, sensitivity, and specificity respectively in Fig. 7a and provide 1.00 AUC in ROC curve. LDA and k-NN gives 99 ± 1%, 1, and 1 accuracy, sensitivity, and specificity respectively in Fig. 7b and AUC is 1.

   Proposed model with PCA and LDA are used in Fig. 8 for classification with SVM, and gives a maximum of 98±2%, 99±1% accuracy respectively.



(a)



(b)

Fig. 5 Clinical model **a** KNN, **b** NN

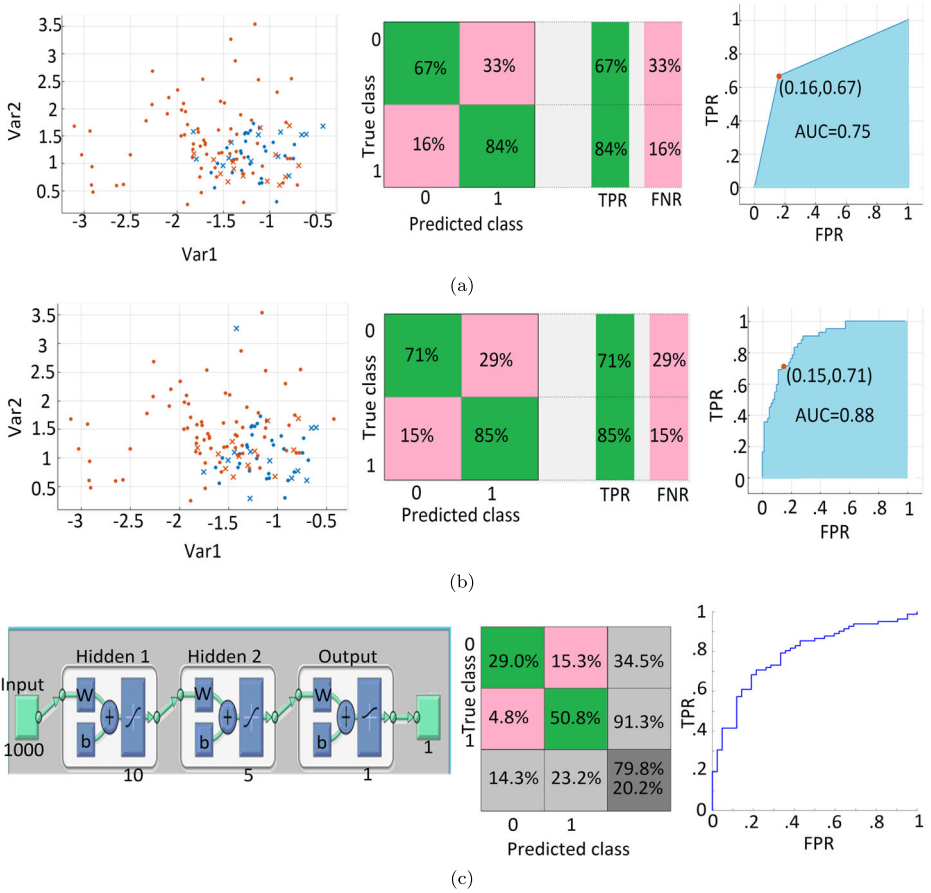


Fig. 6 Image model with **a** K-NN, **b** SVM, and **c** NN

For fused features, 1011 inputs are used as shown in Fig. 9. Proposed model NN provide 1 sensitivity and 99% accuracy. Sensitivity in proposed method is 1 which is no doubt better than using clinical and image features independently.

It is clearly shown in prediction model diagram from Figs. 5 and 6 that with help of all the clinical and image features alone, red and blue dots do not classify properly. It is clearly shown from prediction model of Figs. 7 and 8 that LDA chooses features which classify themselves correctly. We have already made clear in Section 5.1 (performance criteria on medical domain) that sensitivity must be high as much as possible for the life benefit of patients. By using our fused method k-NN, SVM, and NN gives high sensitivity than clinical and image model independently. The main objective of this work is to show how efficiently fused model work to identify microcytic anemia with minimum number of patients. Table 4 presents a comparison of selected studies including proposed model in the classification of different blood disorders diseases like iron-deficiency, thalassemia, sickle cell anemia based on the number of clinical records and performance. Table 4 shows that proposed model achieve high performance with very limited number of patients. Other approaches in Table 4 have also achieved reasonable accuracy levels but with the data set of large

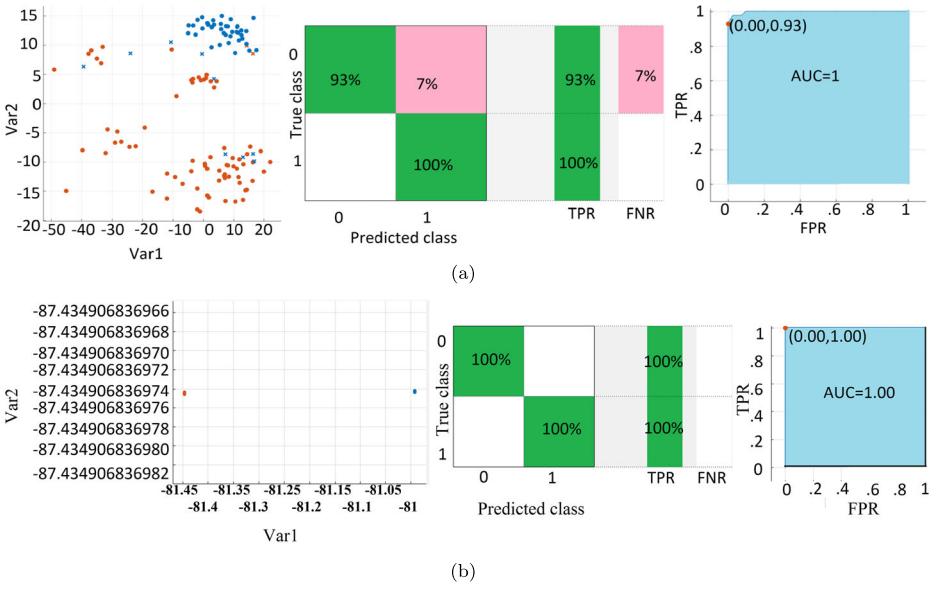


Fig. 7 proposed model with K-NN **a** PCA, **b** LDA

number of patients. It is often not possible to obtain such large data set from recognized and trusted organization. Reasons often vary from confidentiality or statutory clauses of patients diagnosis to the limitation of logistical resources of an organization to maintain such large data sets over a period of time. Problem of collecting data gets even more Severe in case of a rare disease.

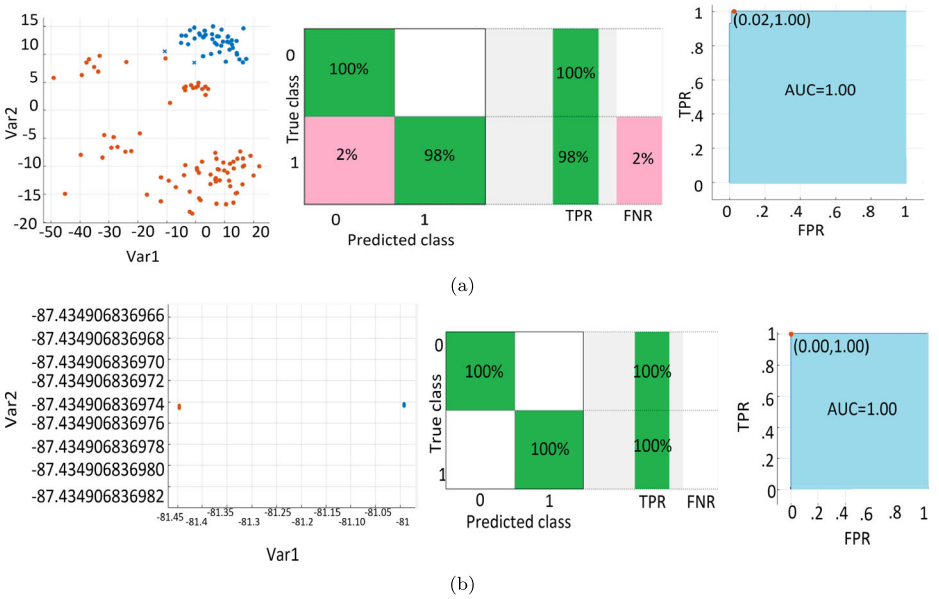
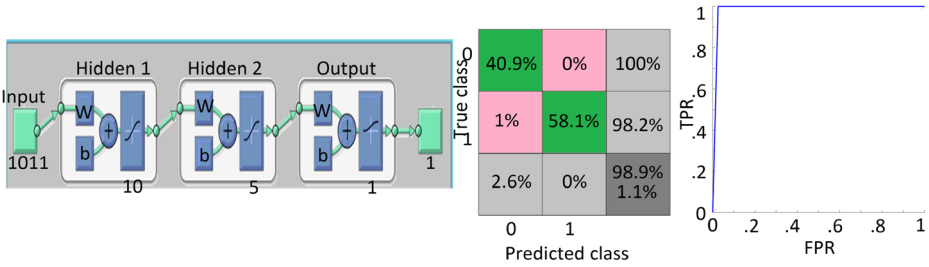


Fig. 8 proposed model with SVM **a** PCA, **b** LDA



(a)

Fig. 9 Neural network with fused data microcytic anemia classification

As discussed with most of the Doctors, they do not believe only on the clinical features for confirmation of microcytic hypochromia they also see the smear image of RBC. Thus same concept is used in this paper and good results are obtained by fusing the image and clinical features.

6.1 Limitation

As explained in the result section both clinical and blood image smear features are important and therefore fusion of both is used along with deep learning for accurate detection of microcytic hypochromia. However, this depends on quality of biopsy procedure with the most important being blood smear specimen. In order to ensure that the deep learning classification approach gives correct results, the resolution of computer scanned images from the blood smear is high enough to provide sufficient information for classification. At times image capture is not of proper resolution due to procedural mistakes leading to classification error.

Table 4 A comparison of different studies in microcytic anemia classification based on number of patients and performance

Author (Year)	Method	Number of patients	Performance
S.R. Amendolia et al. [3]	MLP, SVM	304	Accuracy: 94%, specificity: 95%, sensitivity: (SVM-83%, MLP- 92%)
Eyad [16]	Decision Tree, Naïve Bayes, and Neural Network	46920	Accuracy: 93.64%, 93.7%, and 95.71%
Setsirichok et al. [34]	decision tree, naïve Bayes classifier, MLP	1402 and 8054	Accuracy: 89.88%, 92.77%, 92.34%
Masala et al. [26]	RBF, PNN, KNN	304	specificity: 91%, sensitivity: 92%
Barnhart-Magen et al. [5]	ANN	526	specificity: 96.8%, sensitivity: 90%
Eshpala et al. (2016)	MLP	395	Accuracy: 92%, specificity: 94%, sensitivity: 93.9%
Proposed model	K-NN, SVM, NN	20	Accuracy: 99±1% specificity: 99% sensitivity: 98%

7 Conclusion

In this paper, we propose an application of deep convolutional neural network for microcytic hypochromia detection with the limited number of patients data. There are many existing convolutional neural network architectures, In our case, the fc8 layer of AlexNet CNN model is used for features extraction from microcytic hypochromia patients blood smear. Clinical features and extracted features form CNN networks are fused together for disease detection with k-NN, SVM, neural network classifiers and different feature selection methods like PCA and LDA. On analysis of different classifiers and feature reduction methods, we came to an outcome that fused features give better performance (accuracy, sensitivity, and specificity) than clinical features and image features alone with the limited number of patients, this is also summarized in Table 3. Table 4 compares the various previous studies done in literature with the proposed novel model which shows that the proposed model is better as compared to all the applied methods in previous studies. Experimental results demonstrated that when a model trained with the data of limited patients, then fused features can categorize patients more accurately.

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