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Leukemia segmentation and classification: A comprehensive survey

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ABSTRACT

Blood is made up of leukocytes (WBCs), erythrocytes (RBCs), and thrombocytes. The ratio of blood cancer diseases is increasing rapidly, among which leukemia is one of the famous cancer which may lead to death. Leukemia cancer is initiated by the unnecessary growth of immature WBCs present in the sponge tissues of bone marrow. It is generally analyzed by etiologists by perceiving slides of blood smear images under a microscope. The morphological features and blood cells count facilitated the etiologists to detect leukemia. Due to the late detection and expensive instruments used for leukemia analysis, the death rate has risen significantly. The fluorescence-based cell sorting technique and manual recounts using a hemocytometer are error-prone and imprecise. Leukemia detection methods consist of pre-processing, segmentation, features extraction, and classification. In this article, recent deep learning methodologies and challenges for leukemia detection are discussed. These methods are helpful to examine the microscopic blood smears images and for the detection of leukemia more accurately.

1. Introduction

Plasma in the blood fulfills an essential role to carry nutrients, hormones, proteins, and the reduction of waste from the human body. Blood is divided into 3 main types thrombocytes [1], erythrocytes [2], and leukocytes [3] because of its nature, shape, and cellular composition. Because blood cells are abundant, an excess or deficiency of any blood cell can result in a variety of health issues, including leukemia thalassemia [4], disease of sickle cell [5], anemia [6], marrow cancer, thyroid disorder, autoimmune disease, polycystic ovary, aplastic anemia, etc. To prevent and detect such types of diseases, it is essential to determine precise blood count. Manual methods to detect blood cancers are CBC, PBS, hemocytometer, and bone marrow test acquired by preparing blood film which successfully identifies abnormal cells, but recently many computer-aided methods are developed for automatic detection to improve performance and accuracy [7,8]. The automated blood cell analysis can be performed by applying image processing and deep learning technique [9]. Most automatic blood cells counting and analyzing systems consist of three main methods including feature extraction, classification, and segmentation of microscopic smear images. The goal of digital processing is to decrease the human errors, and cost [10–29].

The basic idea of detection is to derive knowledge of cells from various techniques to extract features, which is further used to segment images to diagnose WBC diseases mainly ALL, lymphocytopenia, AML, neutrophilic leukocytosis, and basophilia are some diseases caused by white blood cells.

1.1. Acute lymphoblastic leukemia

ALL occurs because of excessive production of undeveloped WBCs and prevents the production of healthy cells so it is necessary to analyze it at the primary stage. ALL arises mainly in children ranging between 2- and 10 years of age. Researchers have developed many mathematical-based methods to detect the nature and shape of blast or immature cells so they can perform accurate segmentation, an automatic leukocytes cell segmentation by using 4-moment statistical features and ANN and attained an accuracy of 97% is presented in Ref. [30]. Another deep

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Table 1
Types of leukemia disease [44].

Condition	Involved Cells	Causes	Morphology	Demographic
ALL	Immature B or T cells	Chromosomal irregularity affects B & T cells development	Small nuclei, limited cytoplasm, condensed chromatin	Children
CLL	Peripheral B or T cells	Chromosomal irregularity with hypermutation of naïve B cells	Condensed chromatin and scant cytoplasm	Adults, mostly men
AML	Immature myeloid-lineage cells	Mutation creates immature myeloid blast cells	Abnormal lissome, myeloblast, and monoblast	Adults
CML	Hematopoietic stem cells	Philadelphia translocation of chromosome	Elevate basophil and eosinophil with tyrosine kinase pathway	Rare in children, mostly cover 20–25 age

ALL classification method is recommended by using Naïve Bayesian, KNN, or SVM, and achieved the highest accuracy of 97.78% [31].

1.2. Acute myeloid leukemia

The myeloid line in blood cells causes tumors of AML, it is also categorized by the rapid progression of anomalous cells, but it is different from ALL according to Auer Rods seen under hemocytometer or microscope [32]. To detect this cancer at an early stage, a novel photo-diagnosis strategy is presented, based upon spectral features to classify AML from normal blood cells with an accuracy of 84%. Genomic classification and prognosis of AML are proposed in Ref. [33], which categories AML with TP53 mutation, IDH2R172 mutation, and chromosomal aneuploidies. The WHO approaches are summarized to extract specific features for disease classification including AML with CEBPA biallelic mutation and mutation with NPM1 and erythro-leukemia [34].

1.3. Lymphocytopenia

Lymphocytopenia occurs due to the production of low-level abnormal T-cell lymphocytes in blood cells, it is also referred to as lymphopenia [35]. T-cells and B-cells are the key factors of ICP treatment, the review of the quantitative and qualitative immune system with tumor environment is taken, they discovered more than 20% of patients were involved with lymphopenia, although $CD4^{+}$ lymphopenia is dangerous cancer that may lead to death [36]. Classification of lymphocytopenia is proposed which involved primary and secondary immune deficiencies, HIV infection, radiotherapy, zinc deprivation, abnormal lymphocyte trapping, idiopathic CD4 lymphocytopenia, and many others [37].

1.4. Neutrophilic leukocytosis

Neutrophilic leukocytosis occurs due to the high number of abnormalities in neutrophil types of WBCs, it is also known as Neutrophilia [38]. The utilization of neutrophils from bone marrow to tumor consists of three phases: expansion, maturation, and immature neutrophils [39]. Analysis of polycythemia of cancer patients based on their morphologic and medical features, which established obstinate and important neutrophilic leukocytosis for the time of their evolution to post-polycythemia myelofibrosis [40].

1.5. Basophilia

Basophilia cancer arises due to a huge amount of abnormalities in basophil cells but it is not a key feature that may lead a surgeon to diagnose the disease of lymphoid neoplasm. It is very rare because basophils are the least numerous myelogenous cells and cannot exceed $1 \times 10^{\wedge}9/L$ with 5% of PMF patients [41]. A diagnostic principle for the basophilic leukemia classification corresponds to basophils count greater than equal to 1000 per microliter and is also referred to as hyper-basophilia (HB) [42]. The bone marrow presented features of a myeloproliferative neoplasm with marked growth in maturation basophils. The basophils showed nuclear hyper-segmentation, abnormal granulation, and oddly low CD-38 expression as covered in Ref. [43].

The main four types of leukemia with their composition and effects are explained in Table 1.

As given in Fig. 1, according to Pakistan source Globocan 2020, in Pakistan 178,388 cases of cancer are predicted including all ages and both sexes. Among which 88,015 cases belong to male patients and 90,373 are female cases. The overall death cases are 117,149 occurred due to different cancer diseases while a 5% death rate is determined due to leukemia.

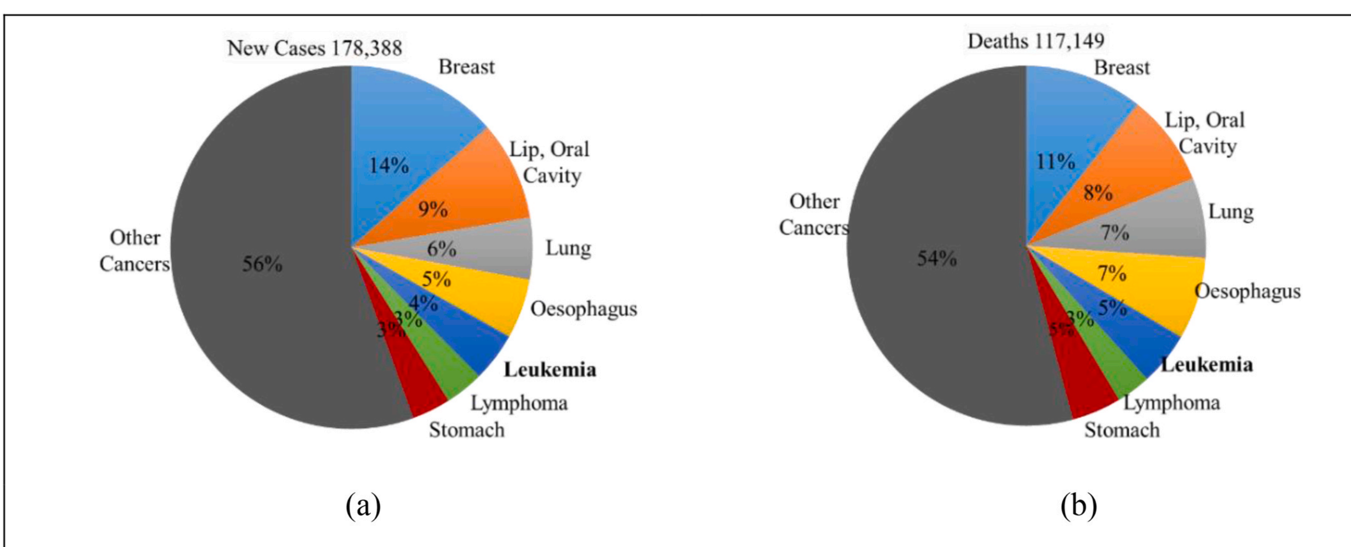

Fig. 1. WHO cancer statistics of Pakistan 2020 (a) New cases, (b) Deaths [45].

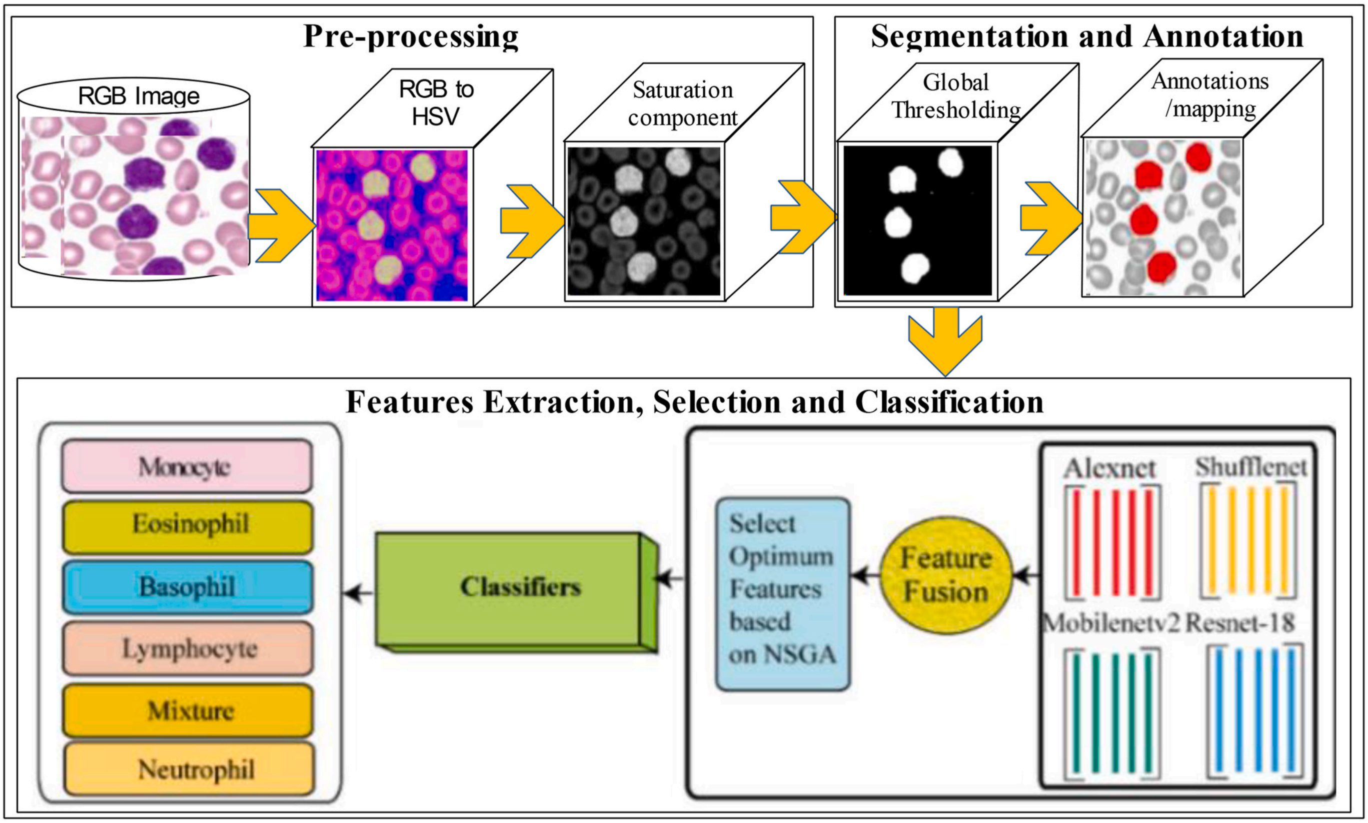

Fig. 2. Primary steps of the leukemia detection [18].

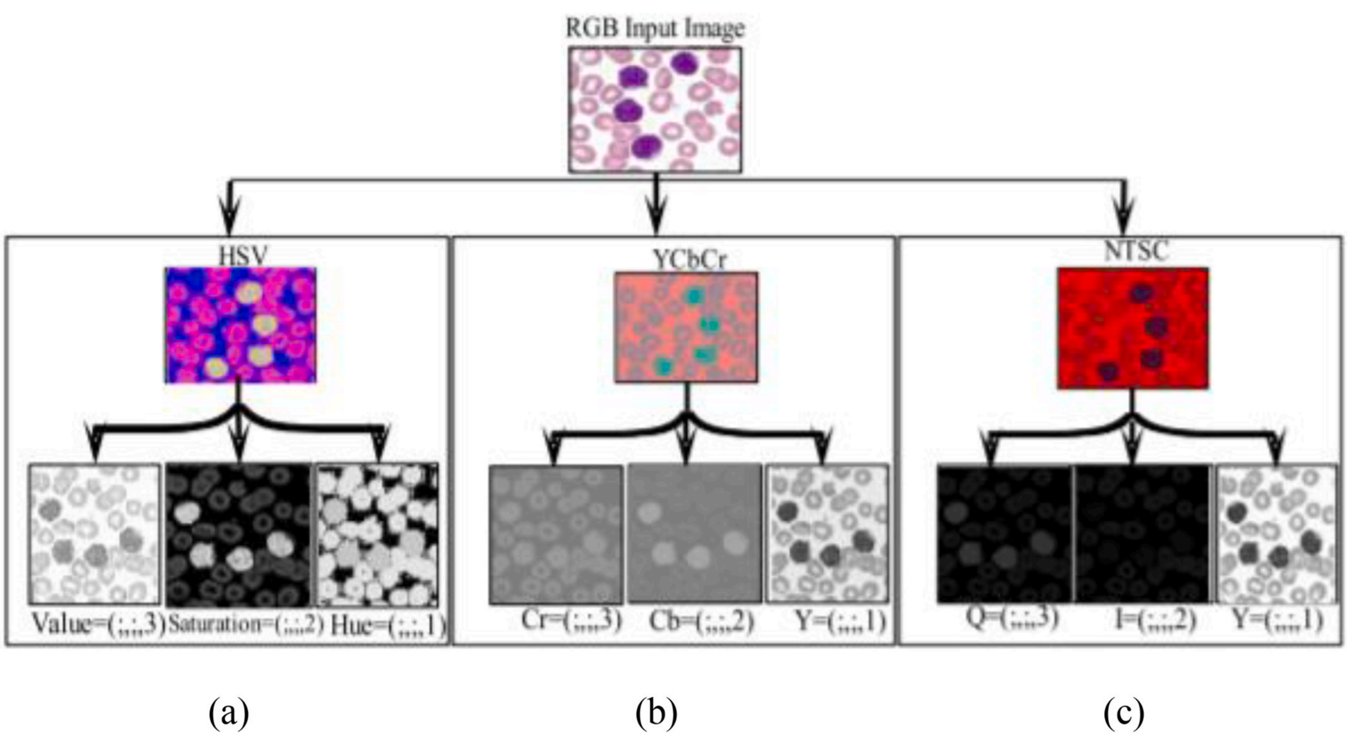

Fig. 3. Information of the nuclei based on different types of color spaces (a) HSV (b) YCbCr (c) NTSC (YIQ) [18].

1.6. Scope and objective

The purpose of this review is to analyze existing methods on the segmentation, classification of leukemia. Motivation, challenges, and recommendations are offered to scientists and students that provide help researchers to proposed a accurate method for the detection of blood abnormality. The major steps of leukemia detection are shown in Fig. 2.

This chapter concentrated on the challenges/problems of existing

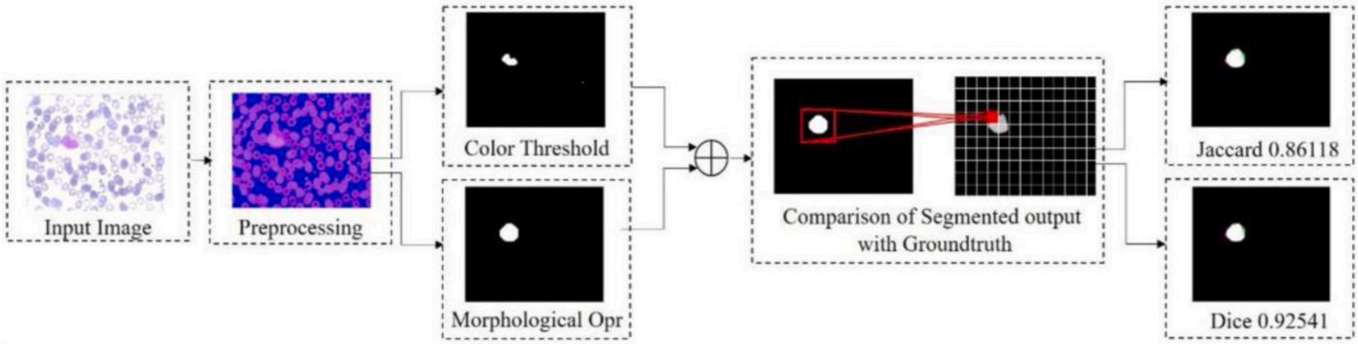

Fig. 4. WBCs segmentation [71].

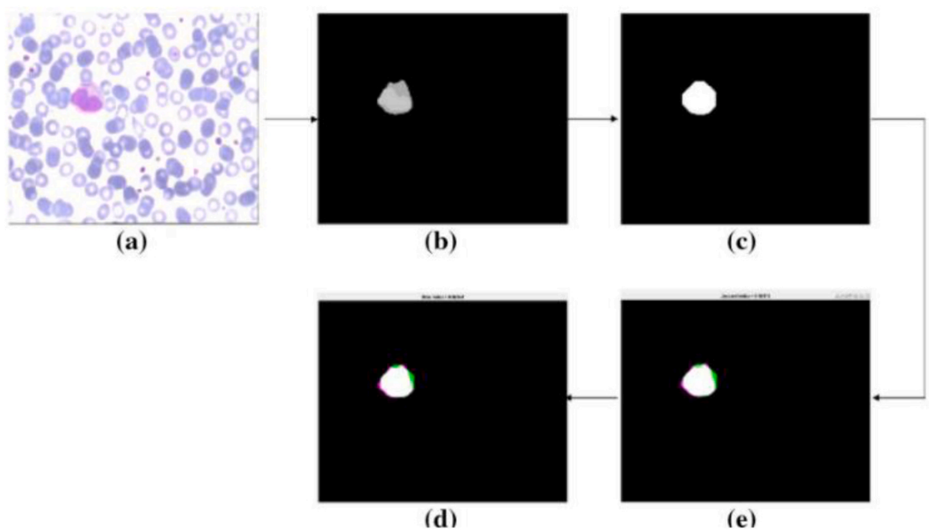

Fig. 5. Segmentation results (a) original image (b) ground truth (c) segmented region (d) jaccard index (e) dice index [71].

proposed methods. This review determines to deliver a literature review in the region of image processing. The organization of the document is arranged as below: Section I is an introduction that is already discussed above, and Section II describes preprocessing techniques. Section III focuses on image segmentation methods with challenges. Section IV and V focus on feature extraction and selection of optimal features. Section VI describes classification techniques. Section VII focuses in detail on different datasets that are freely available. Section VIII shows the performance evaluation matrices. Section IX and X cover the existing problems and conclusion.

2. Preprocessing

Preprocessing plays a significant role to improve the image quality. In the case of human blood smear detection, several algorithms are proposed to attain better results but still, more research work is required to enhance the results of preprocessing for detection, segmentation, and classification of disease. The preprocessing steps including image enhancement [46], denoising [47], and normalization [48]. Many authors proposed image processing techniques such as color space transformation [6], Otsu thresholding [49], fast discrete curvelet transform [50], localization [51], and smoothening filter (Gaussian, median, etc.) [52] and many others. The preprocessing algorithm proposed in Ref. [53] is used for the enhancement of blood smears and noise reduction to enhance edges by using curvelet transform-based wiener filter. The pre-processing techniques namely boundary box distortion, color distortion, and mirror flipping of images are presented in Ref. [54]. To increase the quality of the images, partial contrast stretching, and median filter are used [55].

2.1. Color space transformation

Color space conversion is the basic step of preprocessing to increase the divergence of the foreground from the background as shown in Fig. 3. To produce new picture components termed Cn, Mn, and Sn, the color components of HSV and CMYK are managed in Ref. [56]. A transformation process of color models with a logistic loss of weighted function is used to smooth the image quality [57] and achieved an accuracy of 97.92%. Another nucleus segmentation of leukemia blast cells is proposed with an accuracy of 85% that is achieved by the HSV and CMY model [6]. The mixture of morphological operations with thresholding for preprocessing that produced precise results of segmentation [58]. RGB to YCbCr conversion [59], modifying the contrast and smoothing to increase quality, then applying morphological operations [60] for segmentation of blood smears. Proposed WBCs semantic segmentation based on image enhancement steps is suggested in Ref. [61].

2.2. Image enhancement

It is the process to adjust digital pixels to make the proposed algorithm efficient. A method for the enhancement of the features by using histogram equalization is proposed in Ref. [62], the technique is utilized to improve texture details and structure of the input image. To enrich the contrast of microscopic images, morphological operations are

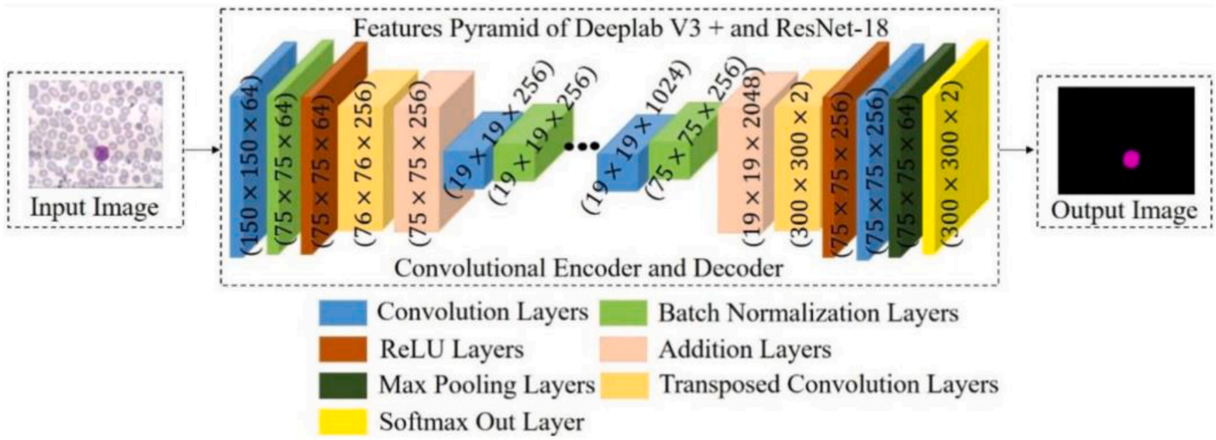

Fig. 6. Semantic segmentation model [71].

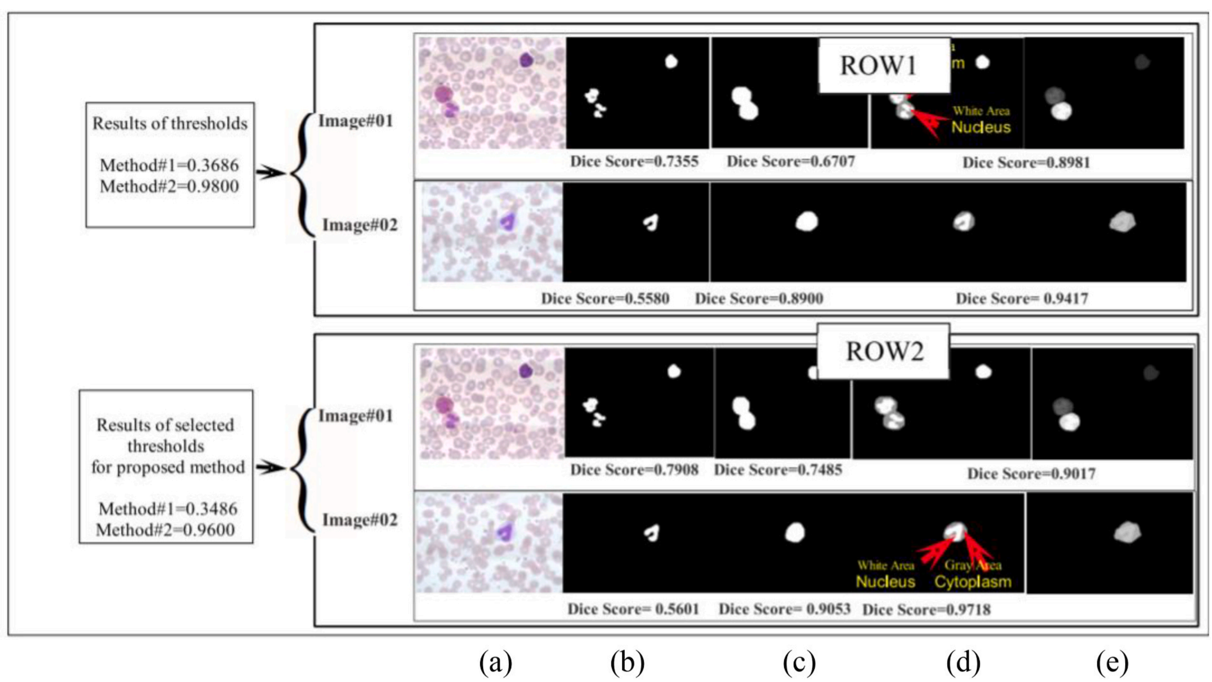

Fig. 7. Experiment for the selection of appropriate threshold value (a) input images (b) method#1 thresholding (c) method#2 thresholding (d) parallel fused results of both thresholding methods (e) ground annotated mask [18].

performed. Top-Hat transform is applied by choosing the mask and the result is obtained by the CIR measure [63]. A method based upon FDCT and USFFT for image contrast enhancement is also used [50]. Color thresholding-based morphological opening and closure procedures with area-based filters are applied to obtain the targeted WBC's region [64].

2.3. Noise removing

Noise removal is a process of filtering that makes the image smooth by leaving areas of contrast boundaries [57]. proposed an adhesive WBCs segmentation method but for preprocessing, apply a median filter to make dataset images noise-free. Smoothening is mostly required in algorithms but sometimes sharpening is performed where we have to prominent the information, therefore different filters like Sobel and canny filter to detect cell edges for WBCs segmentation are used in Ref. [65]. SRGAE-based salt-pepper noise reduction algorithm is an efficient algorithm that preserves the boundaries and edges [66]. A median filter with a 2×2 neighborhood and open area function is used to eliminate noise which helps to segment the cytoplasm from the cluster of leukemia, offered by Ref. [67]. This automatic method is further used for segmentation without any need to crop the image complexity.

3. Segmentation

Splitting the appearance of an image into several parts is referred to as segmentation. The most common sense of segmentation is to detect the ROI in the image as shown in Fig. 4. This is a dividing technique that divides a single image into small parts, these parts are referred to as segments. White blood cells are subdivided into five parts, according to the nucleus and cytoplasm each part is differentiating from the other as shown in Fig. 3 [68]. So WBC nucleus segmentation is a basic requirement that is mostly done by color space conversion and the k-means clustering algorithm [69]. A segmentation of leukocytes and its classification method [70] for the initial analysis of hematological infections give good performance with a 93% accuracy rate. Another WBCs segmentation method is proposed by Ref. [65] using sparsity and geometry

Table 2
Summary of the existing segmentation techniques.

Ref	Year	Dataset	Segmentation	Accuracy
[90]	2014	ASH	k-means	98.00%
[91]	2017	Private	k-mean + HRMF based segmentation	97.08%
[73]	2020	BCCD, ALL-IDB2, JTSC, CellaVision	K-mean clustering algorithm	99.42%, 98.61%, 97.57%, 98.86%
[92]	2018	Private	K-mean	99.67%
[93]	2012	Private	K-mean	95.00%
[94]	2018	ALL-IDB	K-mean	99.51%
[95]	2016	Private	Fuzzy C-Mean	98.85%
[96]	2010	Private	Fuzzy C-mean	95.00%
[97]	2021	BCCD	K-mean	99.70%
[98]	2021	ALL-IDB 1	Fuzzy C-mean	98.52%
[99]	2014	ALL-IDB	Zack algorithm	90.00%
[79]	2017	ALL-IDB	Otsu's thresholding	89.80%
[100]	2015	ALL-IDB	Otsu's thresholding	90.00%
[101]	2008	N/A	Thresholding	96.97%
[102]	2012	Private	Otsu's thresholding	88.69%
[103]	2016	ALL-IDB	Zack algorithm + watershed	90.00%
[80]	2017	BS images	Otsu's thresholding	94.20%
[31]	2018	Private	Thresholding	97.74%
[104]	2019	Private	Active contour thresholding	99.50%
[71]	2021	LISC	Morphological operations, color thresholding, Semantic neural network	99.70%
[105]	2018	ALL-IDB	Decision support system	98.10%
[106]	2019	ALL-IDB2	MI-based hybrid model	98.70%
[107]	2019	ALL-IDB	Deep learning	96.10%
[30]	2019	ALL-IDB	ANN and GA based on Deep segmentation	97.00%
[65]	2019	Rapid, Standard dataset	Sparsity and geometrical constraints	96.29%, 94.43%
[70]	2019	Private	SMACC and ISODATA algorithm	98.30%
[61]	2020	BS images	Semantic segmentation	97.40% RBCs, 93.30% WBCs, 85.10% Platelets
[108]	2011	CellaVision	Supervised Learning	72.50%
[109]	2004	N/A	Supervised Learning	95.30%
[110]	2021	CellaVision, JTSC, LISC	Semantic segmentation	96.10%
[111]	2018	Private	Region-based segmentation	98.70%
[112]	2016	Private	Region-based segmentation	95.80%
[113]	2019	Private	Region-based segmentation	90.00%
[114]	2017	Private	Watershed distance transform	94.28%
[115]	2018	Private	Watershed segmentation	90.30%
[116]	2012	Private	Markov Random based model	97.68%
[117]	2021	LISC	deeplabv3, Xception	99.00%
[118]	2022	ALL-IDB2	k-means clustering	97.35% DSC

constraints on rapid data containing 138 single WBC images and achieved an accuracy rate of 96.29% for WBC cells and 94.51% for WBC nucleus.

3.1. K-mean clustering

This technique is generally applied for segmentation and is also known as fuzzy C-mean clustering [72] or soft clustering, it divides the image into many clusters such that they should similar to each other as depicted in Fig. 5. K-mean clustering algorithm for WBC segmentation and then perform classification based upon this segmented image with an accuracy rate of 98.61 as discussed in Ref. [73]. A novel segmentation method by combining k-mean clustering segmentation, thresholding, and modified watershed algorithm, the obtained result was 94.03% for nucleus and 93.78% for cell segmentation is presented in Ref. [74]. LAB color space with unsupervised learning (fuzzy c-mean) is used to sub-divide the WBC's nuclei and an SVM classifier is applied to classify leukocytes based on color, textural and geometrical features. LISC dataset achieved 88.1% accuracy for segmentation and 92.8% for classification [75].

3.2. Semantic segmentation

Classifying each pixel of an image by directing it toward a specific label is referred to as semantic or deep segmentation as shown in Fig. 6. To solve challenges of segmentation, deep learning semantic segmentation with cutting edge technologies was proposed by Refs. [76–78], and [30]. Deeplab V3+ with AlexNet as semantic segmentation for leukocyte identification and localization is recommended in Ref. [51]. The proposed algorithm obtained 98.22% average accuracy, 84.22% mean IOU, and a mean precision of 98.42% for segmentation. Another semantic-based deep segmentation method is offered by built on ResNet-50 and DeeplabV3 +. The purposed method is evaluated by using three datasets. They achieved a 98.22% accuracy and 84.22% IOU with the LISC dataset.

3.3. Thresholding based segmentation

Based on intensity values or some threshold criteria, targeting a consistency of pixels in a specific region is referred to as thresholding-based segmentation, the threshold can be selected from the histogram of the input image as discussed in Refs. [79–82] and many others as shown in Fig. 7. In Ref. [56] the authors enclosed Otsu's thresholding to select the appropriate threshold for WBC nucleus extraction, the average accuracy obtained by this thresholding is 97.06% on the Cell division database. Extension of Otsu's equation is proposed using global and adaptive thresholding, this technique [83] is used for WBC segmentation and achieves 94.03% for adaptive and 99.39% for global thresholding. RGB is a standard color model and mostly conducted multilevel thresholding, while color thresholding is conducted for gray-level images based upon adaption and slight modification. Adaptive histogram thresholding is performed [84] by using a color threshold for leukocyte segmentation, this threshold distinguishes the complex background from the foreground. A novel approach based on Otsu and HSV threshold to detect and count WBCs, this technique is proposed to reduce false edges because of HSV values [85].

3.4. Region-based segmentation

Region or pixel-based segmentation directs specified criteria and neighbor pixel analysis to pick the region of interest from the microscopic images. Based on various parameters, the region growth approach gathered pixels or sub-regions in a picture into a bigger region. If the region does not fulfill some similarity requirement, the region splitting technique divides the ROI in a picture into separate regions [86]. In this study, several image segmentation approaches are focused on blood smear pictures that researchers have utilized to create automated detection applications or methods for recognizing and categorizing leukemia. A boundary representation is performed, and a segmentation map into regions was calculated. At each pair of pixels, the potentials of the Markov model with pairwise relations are computed using the edge probabilities present in an image, according to the author [87]. A kernel plotting of the data in an image by using a multi-region graph cut algorithm is presented in Ref. [88]. To accomplish the combined crop and maize tassel process of segmentation, a color modeling technique based on the region that comprises two steps is formed. That is color model prediction and region proposal creation [89]. Table 2 shows a research summary of Blood cell segmentation to the current state,

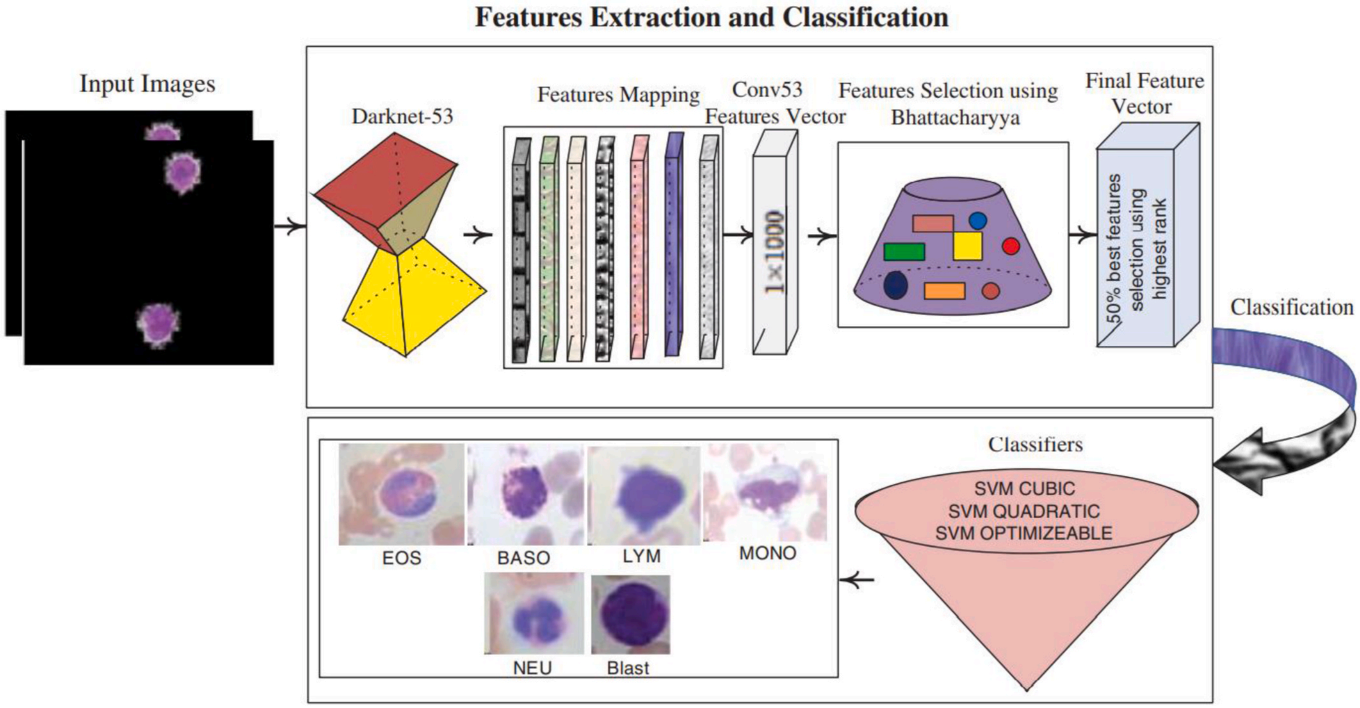

Fig. 8. Feature extraction process [120].

including the year, application area, the dataset used for testing or training devotions, features used, methods/techniques, classifier, and achieved accuracy (ACC) by the proposed algorithm.

3.5. Challenges in the segmentation of WBCs

- As compared to the classification process, the labels of ground-truth images used for segmentation. It is very difficult to highlight the target part and to detect the edge of an object in microscopic images with low resolution. ALL-IDB, LISC, and BloodSeg are open-source databases but it is still not enough to accommodate the needs.
- In many image segmentation applications, training is essential. The training phases of deep network designs, on the other hand, take a long time.
- The overfitting problem mostly occurs when targeted domain images are small in size. Vanishing gradient is also one of the major problems in deep semantic segmentation [119].

4. Features extraction

Feature extraction is a method to identify features after the segmentation process based on machine learning techniques [120] as presented in Fig. 8. In this process, all novel features are converted into new features of reducing space without eliminating and substituting original features with reduced representative sets.

4.1. Hand-crafted features

Hand Crafted features denote to properties of various algorithms using the data present in the image itself. There are many handcrafted features some of which are explained below:

4.1.1. HOG features

A histogram of Gradient is the most common method to extract HOG features. Leukemia detection based upon a combination of HOG features with Logistic regression is performed in Ref. [121] and achieved 96% accuracy. Another approach of HOG features extraction from a k-mean clustering-based segmented image is used for WBC's classification [122]. By using this approach categorization of WBC is proposed based upon its shape of nuclei with an accuracy rate of 95%. Different feature extraction techniques to extract features of RBCs and WBCs from public or private blood smear datasets are the HOG descriptor to extract hand-crafted features and Gabor wavelet transforms to extract Gabor features [123]. A robust method as K-medoids algorithm [124] to extract WBCs features, LBP, and hue saturation extract shape and spectral features from a textual measurement of leukocytes.

4.1.2. Shape and color features

For WBC classification shape features are extracted from nuclei information such as area, circularity, solidity, perimeter, and NC ratio in blood smear images. ALL recognition model [125] proposed by using texture, color, and shape features, as contribution vectors for SVM to classify ALL-IDB datasets as blast and normal cells. To improve the performance of segmentation and representation of features, an angle convex cone algorithm is proposed with a self-organizing technique for leukocyte segmentation [70]. These proposed techniques combined spectral features and texture features with shapes to categorize different types of leukocytes. For WBC classification color features are dug out from both cytoplasm and nuclei information in blood smear image, the cytoplasm is in different colors, therefore, a color histogram is commonly used to calculate mean and variance value [64]. evaluated the deep learning model over traditional techniques based upon segmentation and handcrafted feature extraction and achieved 99.8% accuracy by using CNN. Texture feature-based classification method is proposed for disease detection with a 99.66% accuracy rate [10].

4.1.3. Gabor features

Gabor filter is a simple and linear filter mainly used for image smoothing [126]. An auto-robust analyzer for WBC classification is proposed which extracts most general features like geometric features, GLSM, and Gabor features [127] that are passed to LSDA and achieved a 96% accuracy rate. Texture and Gabor feature-based cancer detection methods are proposed by using an SVM classifier and achieved the highest accuracy of 84.5% [128]. Another GFM is proposed for

Table 3
Brief overview of the feature extraction methods.

Ref#	Year	Features	Classifier	Dataset	Accuracy
[140]	2014	Morphological + textural + color	ensemble of classifiers (EOC)	PBS images	99.00% ACC
[141]	2015	Histogram, based texture features	MLP	PBS images	87.80% ACC
[142]	2016	Morphological shape features + color histogram features	SVM	BS images	95.28% precision
[143]	2017	GLCM + PPCA	RF	ALL-IDB1	99.04% ACC
[144]	2018	GLRLM	SVM	ALL-IDB1	96.97% ACC
[145]	2018	Eigen color + HOG + ULBP	ANN, SVM	Experimental dataset	87.20% ACC
[106]	2019	LDP + color histogram	Deep CNN	ALL-IDB2	98.70% ACC
[64]	2019	Shape + color + texture	CNN	PBS images	99.60% ACC
[146]	2019	ResNet with FPN based features	N/A	JTSC, CellaVision, BCISC, LISC	99.54%, 94.32%, 98.94%, 98.44% Precision
[147]	2019	LBP energy & LBP entropy-based features	KNN, Logistic Regression, Random Forest & Decision Tree	LISC	97.30% ACC
[10]	2019	DOST, PCA and LDA	RF + ADBRF	ALL-IDB1	98.67%, 99.66% ACC
[148]	2019	SURF and shape features	KNN, SVM, RF	OASIS	92.70% ACC
[149]	2019	LBP and GWF features	SVM, KNN, DT and Naïve Bayes	BRATS	97.00% SE
[150]	2020	Deep features using VGGNet	SVM, MLP, KNN, Adaboost, Naive Bayes, and Decision Trees	ALL-IDB1, ALL-IDB2	80–90% ACC
[151]	2020	Deep features using CNN	SVM	WBCs dataset master	98.92% ACC
[152]	2020	AlexNet, Google Net, ResNet_50 based features	(QDA)	WBC dataset	97.95% ACC
[73]	2020	Deep features using CNN	CNN	BCCD, ALL-IDB2, JTSC, CellaVision	98.61% ACC
[153]	2020	Handcrafted features with Fast YOLO + UNet	N/A	BS images	94.00% Mean Score
[154]	2020	LBP and deep features	ANN	RIDER and BRATS	99.00% ACC
[155]	2020	DarkNet-19 based YOlOV2 features	O-NB and O-DA	ALL-IDB1, ALL-IDB2	97.20% ACC, 100.00% ACC
[156]	2020	Geometry + texture features	SVM	ALL images	75.42% ACC
[157]	2021	Salient features	Naïve Bayes, SVM, Decision Tree and KNN	ALL-IDB	99.39% ACC
[158]	2021	Grid-based, statistical, and texture	Taylor–MBO-based SVM	ALL images	94.57% ACC
[157]	2021	MobilenetV2 and ResNet18	Softmax	ALLIDB1	99.39% ACC
[159]	2022	VGG16	Softmax	ALL IDB1	98.40% ACC
[160]	2022	VGG16 and UNET	Softmax	ALL images	95.00% Recall rate

conducting SCIs objective evaluation because the Gabor filter is reliable with the reaction of the human graphic system [129]. The extraction of global facial features from the Gabor wavelet filter by using NN and KNN classifier is done by Ref. [130], they also performed Caltech, Yale B, ORL, and Yale to validate the recognition rate.

4.1.4. SIFT and SURF features

SIFT, SURF, BRIEF, BRISK, and SAFTA have also featured descriptors and depend upon image processing techniques to transform local pixels into a compact vector. A cell classification system is proposed, based upon handcrafted features like SIFT, SURF, DAISY, and ORB features [131] which are signified by visual words model and then passed to SVM and MLP classifier. The proposed method achieved a 97.22% accuracy rate for SIFT and SURF features using the ALL-IDB dataset. A simple approach for WBC recognition based on three key point detectors SIFT, CenSure and FAST performed dense regular sampling strategies with 80% mean accuracies proposed in Ref. [132]. SURF function is an inscription utilized to extract color characteristics from an image, the genetic algorithm with SURF technique is embedded in Ref. [133] improving performance metrics and achieving 92% accuracy for extraction of functions. FAST [134], and CenSurE [135] detectors are discussed while SIFT, BRISK, SURF, FREAK, and BRIEF feature descriptors are discussed to obtain interesting key points for feature extraction within the e-ROI from blood smear images. A feature fusion approach may also be performed by merging handmade features to get superior performance metrics [136]. SFTA, GWF, and LBP features are fused to make a new feature vector space for tumor segmentation are presented by Ref. [137], 100% sensitivity is achieved on BRATS datasets. Another feature fusion-based technique is also recommended, which includes SFTA, LBP, and HOG features. The fusion vector is passed to different classifiers and the highest achieved accuracy is 99.0% DSC for tumor estimation [136].

4.2. Deep features

Traditional segmentation approaches, quantitative and qualitative characteristics extracting and feature matching have been effectively achieved but certain restrictions remain because of inadequate resilience [120]. A convolutional neural network prepares effective categorization based on the automated extraction of features. The layered structure as the fundamental aspect of deep learning in 2006 is suggested by Ref. [138]. Deep learning may be accomplished using a variety of algorithms. Deep learning is used to calculate hierarchical and higher-level characteristics that are difficult to extract using standard machine learning approaches. To begin the classification process, different CNN architectures are utilized to access fully connected layers for features extraction. WBCs features extraction filtered by SESSA using a powerful CNN construction as VGGNet, this method achieved an accuracy of 83.2% [139]. Overview of the existing features extraction methods are mentioned in Table 3.

5. Features selection

A subset of original features which are selected or reduced is referred to as selected features, it removes or cuts out those features that are weak, noisy, and unpredictable by selecting relevant features without

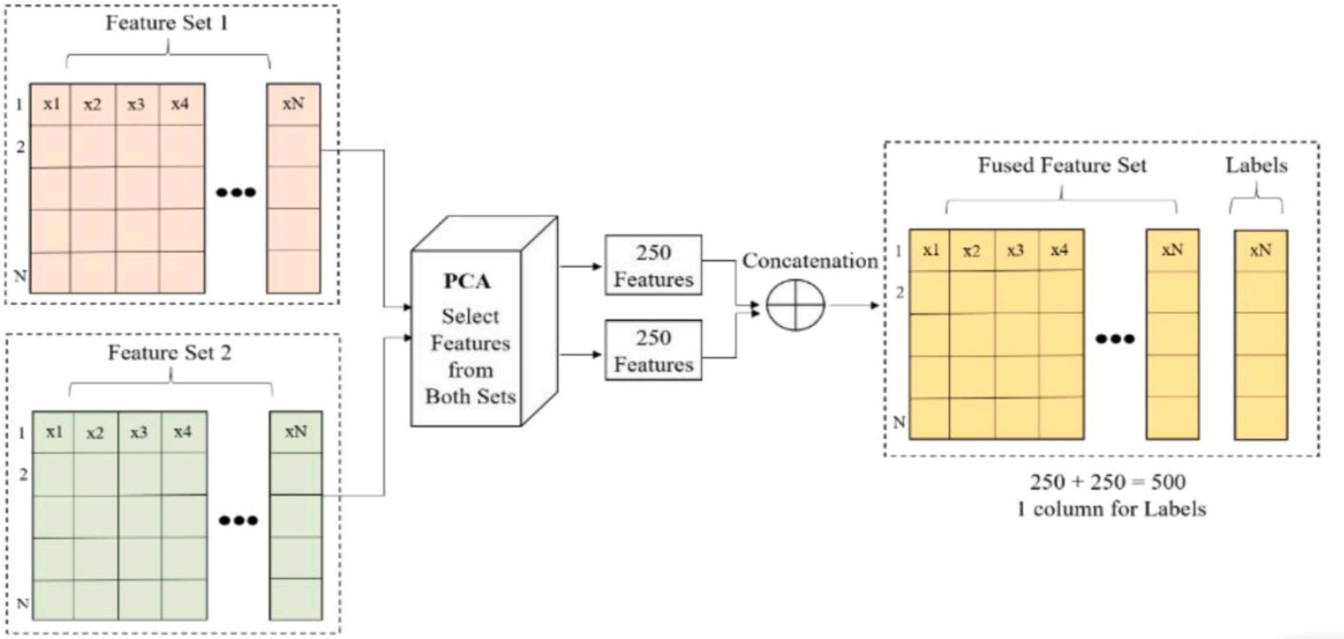

Fig. 9. Feature extraction, selection, and fusion process [71].

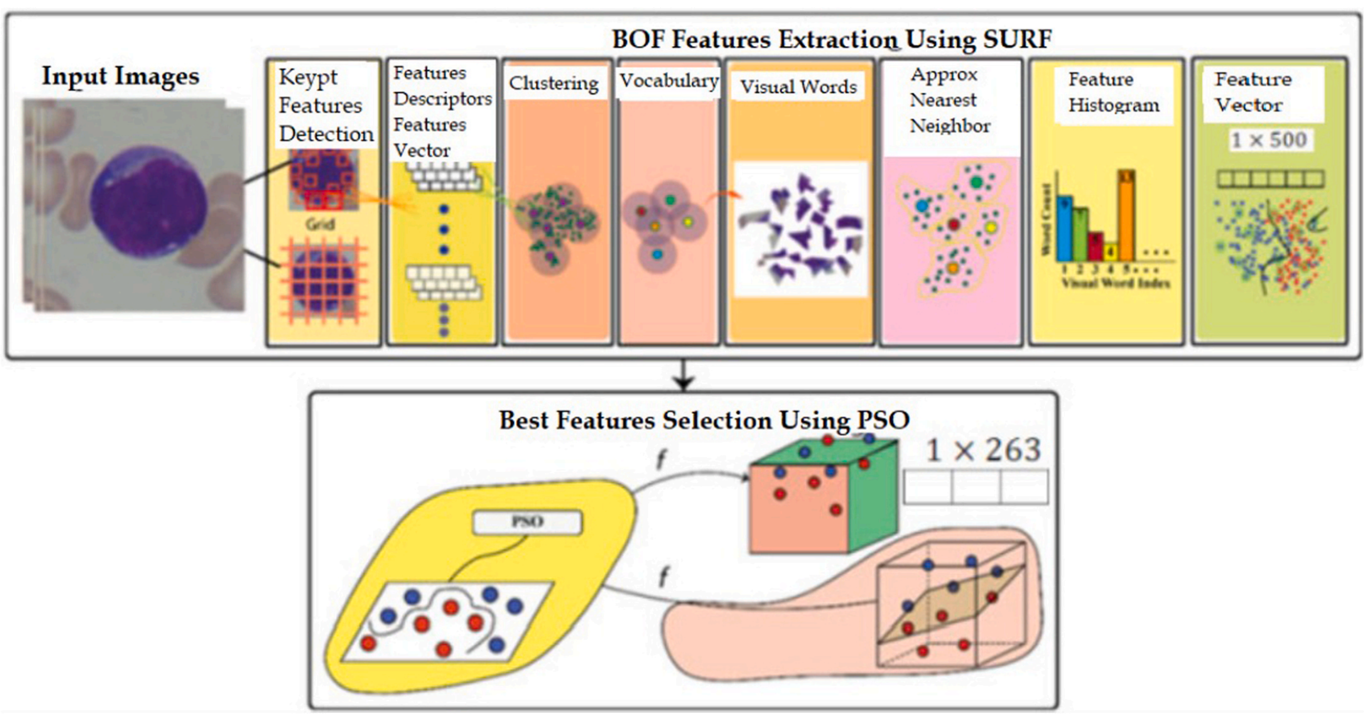

Fig. 10. Features extraction and selection process [155].

affecting the performance and accuracy of the algorithm as illustrated in Fig. 9. Therefore different efficient Neural Network algorithms are used to optimize the best features [161].

In Fig. 9, the general feature selection techniques are mentioned. It is a well-defined and famous topic of machine learning and especially in medical data mining to solve problems of the curse of dimensionality [162].

5.1. *Principal component analysis*

A unique methodology for transmuting interrelated values into innovative separate variables or values that are unrelated to one another is referred to as PCA. An effectual model for WBC nuclei recognition using PCA fusion is presented in Ref. [56], the developing algorithm was tested on three diverse datasets and achieved an accurateness rate of 97.06%. An acute leukemia classification method [163] contains subsections using a PCA-based neural network developed with 94.2% accuracy respectively. PCA and Relief-based hybrid features selection model is offered by Ref. [164] which reduces 50% of irrelevant and redundant features from the dataset. Another multi-class classification of leukemia is proposed for selecting optimal features from PCA and the selected features are then categorized by using a fuzzy-SVM classifier

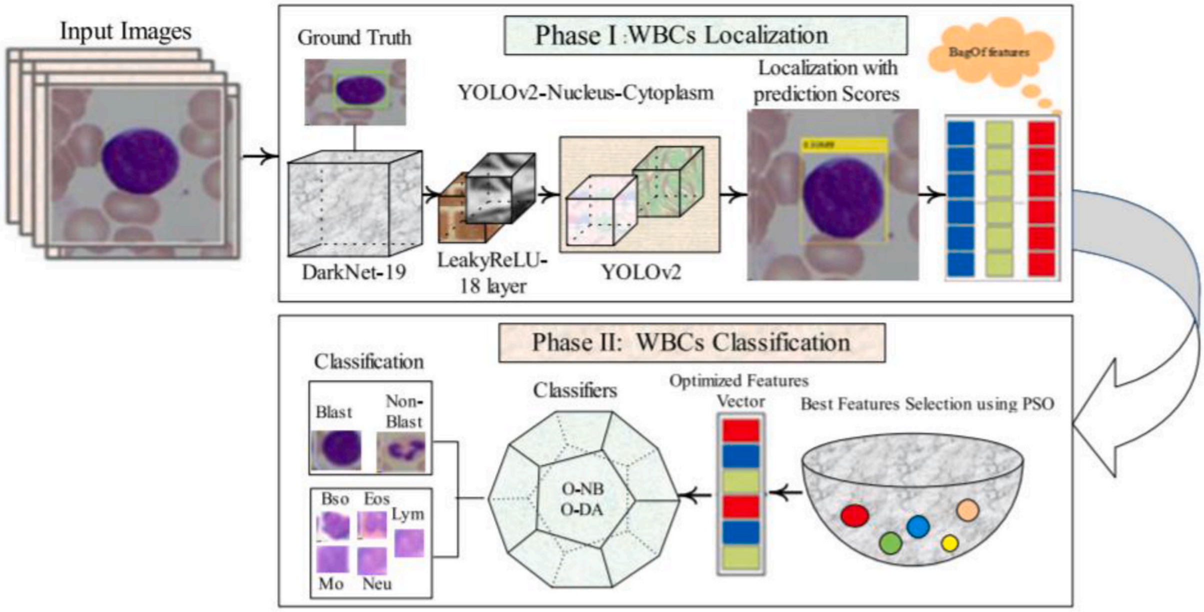

Fig. 11. Features extraction and classification process [155].

Table 4
Summary of overall proposed classification techniques.

Ref	Year	Classes	Methods	Dataset	Images	Accuracy
[188]	2018	2	Transfer learning with SVM classifier	Private	891	99.00% with WBCs
[189]	2018	10	L-moment invariant features with SVM and DT	CellaVision and ALL-IDB	460 Total	97.23% with WBCs
[76]	2018	3	Data augmentation, Semantic segmentation with VGG-16	Private	42	94.93% with WBCs
[190]	2018	2	Morphological operations, Color-based segmentation, Circle Hough Transform	ALL-IDB	30	96.92% with WBCs
[191]	2018	4	Data Augmentation, Gaussian noise filter, PECNN	Private	410	99.37% with WBCs
[107]	2019	5	WBCsNet, Fine-tuning approach of Alex Net, Overfeat Net, Lenet_50	ALL-IDB, Dataset 2, and Dataset 3	2551 Total	96.10% with WBCs
[147]	2019	5	OBBA, RF-KNN, DT and Logistic regression	LISC	237	97.91% with WBCs
[30]	2019	2	Statistical features Extraction, GA-based features selection, and ANN segmentation	ALL-IDB1	108	97.00% with WBCs
[192]	2019	5	LeNet with a fusion of VGGNet, Inceptionv3, Xception	BCCD	352	96.00% (binary WBCs) 87.00% (multi-class)
[193]	2019	3	CBC based on Naïve Bayes, C4.5 and Random Forest	CBC test data	200	96.09% with Blood Cells
[194]	2019	N/A	Median filter, binary mask creation, watershed segmentation	Private	30	98.99% with WBCs
[195]	2020	2	Data augmentation, Features extraction using ReLU layer, CNN based detection	ALL-IDB1 and ALL-IDB2	108, 360	99.50% with WBCs
[196]	2020	2	Shape, texture feature extraction, Gini index based Fuzzy Naïve Bayes	ALL-IDB1	108	95.91% with WBCs
[78]	2020	2	Median filter, Multiclass weighted loss-based segmentation	ALL-IDB1	108	97.92% with WBCs
[197]	2020	5	R-CNN Architecture, Alex net, Google Net, VGG-16, Resnet_50, Softmax classifier	BCCD, LISC	410, 242	97.52% with WBCs
[61]	2020	3	Semantic segmentation with DCED and VGG 16	ALL-IDB1	103	97.45% with RBCs 93.34% with WBCs
[198]	2020	5	Deep learning with Capsule network, classification	LISC	263	96.86% with WBCs
[73]	2020	4	Color space conversion, K- mean segmentation, CNN	BCCD, ALL-IDB 2	367, 260	98.61% with WBCs
[174]	2020	15	ROI based Segmentation with a deep CNN AlexNet model	Hospital dataset	9000	95.92% with RBCs
[199]	2020	3	CSF and ESF coefficient-based Chan-Vese segmentation	Hospital dataset	45	97.00% (normal), 95.00% (elongated) BCs
[200]	2020	5	Edge strength Cue with Gabor cut model for segmentation	ALL-IDB1,Cella vision, and LISC	300-500, 60, 51	99.73% with WBCs
[197]	2020	5	R-CNN with selective search, SSD, YOLOV3 deep detection models	BCCD, LISC	410, 242	99.00% with WBCs
[201]	2020	2	Fuzzy mathematical morphology of intuitionistic fuzzy sets, Atanassov's algorithm	CellaVision	100	99.41% with WBCs
[10]	2020	5	Otsu, Deep feature extractor, PCA feature selector, and KNN classifier	LISC	65	95.46% with WBCs
[202]	2021	2	CNN, Leuknet and AlexNet	ASH	168	94.12% with WBCs
[203]	2021	6	WBC profiler, ResNet-152, WBCaps and Deep Vote with Tsne	Leukocyte images	976	89.00% specificity with WBCs

Table 5
Summary of publicly available datasets.

Ref#	Dataset	Resolution Size	Samples	Images	Channels	Classes
[207, 210]	ALL-IDB1	2592 × 1944	510	109	24 bits	2
[207, 211]	ALL-IDB2	2592 × 1944	130	260	24 bits	2
[197]	BCCD	640 × 480	4888	364	24 bits	3
[212]	LISC	720 × 576	400	100	24 bits	5
[56, 213]	BloodSeg	640 × 480	365	367	24 bits	4

and provided accuracy of 96.92% [165].

5.2. Genetic algorithm and entropy

The fundamental optimization tool of the feature selection method is GA [166] (Genetic Algorithm). In Ref. [167], four different algorithms (RGA, RGA-T, FRGA, and FRGA-T) are proposed to enhance the performance of GA and overcome the problems of feature selection, the proposed algorithm was tested with 23 benchmarks datasets. RGA-T was superior against other competitors after the evaluation of results because it gives optimal performance and also offers feature reduction with a 95.86% accuracy rate. A hybrid filter method based on the grouping of GA and PSO referred to as smart HGP-FS, is recommended to achieve an optimal solution and reduce complications that occurred in feature selection. The entropy-based selection selects those features which provide the highest gain in information. An efficient leukocytes segmentation entropy-based function with mathematical morphology and boundary detection method is developed by Ref. [53]. The accuracy rate of the segmented image is 95.78% which is further fed into a neural network to classify leukocytes into five subclasses. A novel Bat-inspired algorithm is developed by Ref. [168] for feature selection, this algorithm is based upon a bird's eye view to calculate entropy and select the best 11 features from 35 features for differential WBC count and classification with a 97.66% accuracy rate.

5.3. Linear discriminant analysis

LDA is a general tool for feature reduction. The process of feature reduction is excluding abundant variables and choosing the dominant features to increase the performance of learning algorithms [169]. A lymphoblast classification scheme referred to as DOST for features extraction is recommended by Ref. [10]. This technique is based upon a hybrid grouping of LDA and PCA to acquire the most appropriate features with a 99.66% accuracy rate for ALL classification. A novel LDA based upon bispectral invariant features to generalize extracted features obtained from HEp-2 specimen segmented cell shape. Accuracy is achieved by using SVM which is 91.25%, 86.02%, and 89.14% with different datasets respectively [170]. The features extraction and selection process is presented in Fig. 10.

Different hand-crafted and deep networks are used to extract feature maps. To remove redundant features, and to improve the accuracy rate prominent features ate selected by different features selectors.

6. Classification

Deep learning techniques for image or object classification and recognition are reviewed in past years [171]. To achieve high accuracy of automatic classification we use deep models such as autoencoders, constrained, Boltzmann machines, and CNN [172]. Datasets without labels are abundant to apply image processing algorithms, CNN is one of the famous, efficient, and easy methods to adopt which classify unlabeled data. Feature selection using CNN is used to predict which class an item belongs to Ref. [173]. Features extraction and classification process are mentioned in Fig. 11.

6.1. Support vector machine

Based on geometrical and statistical extracted features [174] AlexNet model, are used. These classifiers are used to test sickle cell and to predict abnormalities in SCA (sickle cell anemia) patients while AlexNet achieved the highest accuracy of 95.92% respectively. Convolutional Neural Network is mostly used for blood cell classification [175], embedded this CNN algorithm with ECOC [176] (error-correcting output codes) and SVM to classify RBCs into further 3 types and to improve performance and reached a 92.06% accuracy rate while CNN with ADCN (Attentive Dense Circular Net) and SVM are embedded to classify RBCs according to malarial disease and achieved accuracy rate at 94.61% [177]. used three deviations of SVM to compare precision on features set. The proposed method is utilized to categorize cancerous and normal MRI of the brain and show its validation with three benchmark datasets and achieved an accuracy of 97.1%.

6.2. K-Nearest neighbor classifier

KNN is a pretentious procedure that stocks all existing variables and classifies new variables built on relationship terms or measures. An algorithm referred to as OBBA based on four different classifiers as KNN, Logistic regression, and Decision tree for classifying WBCs, OBBA compared the performance of these classifiers and accomplished an accuracy of 97.30% by Ref. [146]. WBCs classify into five subtypes: Neutrophil, Basophil, Eosinophil, Monocyte, and Lymphocyte. The classification method [178] is executed by consuming a clustering procedure with the PNN classifier which gives results from 98 to 99%.

6.2.1. Deep algorithm classifier

Different deep algorithms [179] are used with Logistic regression (0.72) with Random forest (0.80) [180], Bagging classifier (0.81) [181], Voting classifier (0.81) [182], Support vector classifier (0.82) [183], AdaBoost classifier (0.82) [184] and Xception model [185]achieved highest F1 score of 0.90 [186]. The pre-trained models are effective and reliable for image detection and classification purpose. CNN [16,17], ResNet-50, ResNet-18 with random forest, and regression head classifier are proposed in the IoHT (Internet of health things) framework. These proposed frameworks achieved a classification rate of 97.89% in Ref. [187] for the detection and classification of a blood cell. Table 4 shows a research summary of Blood cell detection, segmentation, and classification from 2018 up to and around the current state, including the categories/classes, methods/techniques, dataset, number of blood smears used for testing and training purposes and achieved accuracy by the proposed algorithm.

6.3. Challenges in the classification of WBCs

- Transfer learning is a well-known method for deep learning classifier training. Transfer learning improves the transferability of deep learning, reduces the size of public datasets, and allows academics to tackle a variety of issues with ease. As a result, cell classification problems resolve by transfer learning are sure to be effective.
- The difficult aspect of deep learning methods is that it needs a big amount of labeled datasets for training. Many datasets are readily available, but their ground truth labels are not. However, in the field of digital processing, there is currently a dearth of open source accessible datasets [204]. A large dataset increases the likelihood of the classifier discovering duplicate patterns, which are incorrect.
- Irrelevant features cause an increase in rule-based size, due to which the performance of classifiers will be decreased. Unrelated and redundant genes in the blood can cause overfitting for ML, Naïve Bayes, and KNN [205].

Table 6
Summary of the future gap and limitations of the existing methods.

Ref#	Year	Methods	Dataset	Results	Research Gaps/Challenges/Advantages/Limitations
[106]	2019	Fuzzy C means, active contour, statistical, and color features, Cosine Chronological Sine classifier	ALL-IDB2	98.70% accuracy	- Ensemble optimization methods are beneficial to increasing classification accuracy.
[67]	2019	Random forest, KNN, decision tree, and naive Bayes classifiers	ALL-L1, ALL-L2, ALL-L3,	98.60% accuracy	- Border cells extraction and classification methods can be used for the detection of acute leukemia lymphoblastic.
[214]	2020	HSI to L*a*b color spaces conversion, k-means clustering, CNN model with Adam optimizer	BCCD, ALL-IDB2, JTSC, CellaVision	98.61% accuracy	- Analysis of adaptive noise using pre-processing techniques. - Reducing confusion rate of eosinophil and neutrophil. - Establish a CNN model to classify 40 WBC types which are vital for leukemia recognition.
[179]	2020	Regional Convolutional Neural Networks (AlexNet, GoogLeNet, VGG16, ResNet50),	BCCD, LISC	Accuracy of 94.00% on Alexnet, 95.00% on VGG-16, 95.00% on GoogleNet, 96.00% on ResNet-50	- Proposed a network based on four pertained deep models. - The architecture will be applied to real-time images. - Manual combination of LISC and BCCD dataset to increase images.
[215]	2020	Edge Boxes method	ALL-IDB	97.00% Accuracy	- Lesion detection using a simple region proposal approach. - The recall value is slightly lower than other approaches due to the used constraints. - A deep supervised learning model needs to be proposed for the classification of subtypes.
[216]	2020	Capsule networks	LISC	Accuracy of [Basophil- 94.87%, Eosinophil 97.37%, Lymphocyte 100.0%, Monocyte 94.87%, Neutrophil 97.37%]	- WBC capsule Net Reach high success with limited data - Will be evaluated with different datasets - Images should be of the same size to avoid overfitting
[217]	2020	Edge-based geometric active contours	ALL-IDB	92.09% F-index	- The proposed work doesn't consider multiple cells in a single image. - Will improve performance to overcome the problem of overlapped and cytoplasm segmented cells.
[218]	2022	Pre-trained VGG16 model	ALL_IDB2	96.15% Accuracy	- Large-scale imaging data is required for better training and testing to improve the results. - Explainable models are required for the justification of classification results.
[219]	2022	ODLHBD-ALLD, fuzzy c-means, competitive swarm optimization, EfficientNetB0, ABiLSTM	ALL-IDB1	96.00% Accuracy	- Instance-based deep segmentation models are helpful to improve the performance of lesion segmentation. - The Ensemble DL method can be used to enhance the performance of the classification.
[221]	2021	Adaptive unsharpening, shallow CNNs	ALL-IDB2	96.84% Accuracy	- Another DL model can be tested to increase the detection accuracy.
[202]	2021	AlexNet and LeukNet	ASH	94.12% accuracy	- To overcome the overfitting problem, large-scale datasets are required to improve classification accuracy.
[223]	2021	AlexNet and LeNet-5	Local dataset	98.58% accuracy 96.25% accuracy	- The pre-trained model will be tested for the detection of leukemia cells such as ALL.
[224]	2021	Data augmentation, LeukNet with VGG-16	ALL-IDB1 and ALL-IDB2	Average 98.61% accuracy	- The imbalance data problems might be handled by applying a generative adversarial model.
[225]	2021	Wiener filter, Statistical, texture, color, and geometric features, SVM	Local dataset	97.69% accuracy	- The unstained images should be pre-processed to improve the quality. - The optimized feature extraction and selection methods are required for accurate classification.
[226]	2021	Data augmentations, rebalancing, Ensemble neural network	C-NMC-2019 ALL	86.2 0% accuracy	- To solve the data imbalance problem adversarial network is applied to create the synthetic images – - The features optimization and fusion methods are required for accurate classification.
[227]	2021	Resizing, data augmentation, YOLOv4	ALL-IDB1 & C-NMC-2019	Precision of [96.06%, 98.7 0%]	- Detection scores will be improved by adopting a tiny-YOLOv4 model
[228]	2021	Chi-squared (Chi2) for features selection, logistic vector tree LVTrees classifier, SVM	Local dataset	100.0% accuracy	- To avoid the overfitting problem, different datasets are combined for model training
[229, 230]	2021 2022	Data augmentation, YOLO v2 VGG Annotator tool, FRCNN	Local dataset	96.00% precision rate 1.85 AUC	- Pre-processing methods are helpful for the improvement of detection accuracy
[157]	2021	MobilenetV2, ResNet18	ALL-IDB1 ALL-IDB2	Accuracy [99.39%,97.18%]	- Informative features extraction/selection and fusion methods are required to enhance the classification accuracy
[231]	2021	Efficient Channel Attention (ECA), VGG16	C-NMC 2019	91.10% accuracy	- The false-positive rate is reduced by employing pre-processing, features extraction, and selection methods.
[232]	2021	Inception v3, XGBoost	C-NMC 2019	98.60% F1 score	- The classification accuracy is decreased due to the data imbalance and the small number of images. Therefore, GANs model is required to resolve the imbalance problem.
[233]	2021	LebTLBO, Otsu, Kapur, multi-thresholding	ALL-IDB	Dice scores of [0.565731 to 0.60281]	- GAN with transfer learning models and optimum features selection methods are required for accurate leukemia classification.
[234]	2021	CLAHE, EfficientNetB0, ResNet50, SVM, ACO	BCCD	98.44% accuracy	- Features fusion methods are helpful to enhance the classification accuracy of the different types of leukemia.
[235]	2020	GoogleNet, AlexNet, Vgg16	ALL-IDB	99.13% accuracy	- The proper selection of features extraction and selection methods are helpful for accurate classification.

7. Datasets

Numbers of datasets are publicly available that are used by researchers for the validation of proposed methods. Many authors had tested their proposed algorithms by using their private clinical data from different hospitals. These datasets have few samples of images to train machine learning algorithms, but these are not publicly available [206]. ALL-IDB [207] is a famous and most challenging standard dataset published and updated in different years for the recognition of leukemia. Iran Medical Science University provides a public dataset that is available at IUMS-IDB2 including 100 microscopic images having 732 × 572 sizes discussed in Ref. [206]. IEEE's 2012 SMC conference [208] also presented a dataset available at SMC-IDB 3, the dataset that has peripheral blood images of 367 with 640 × 480 sizes, assimilated from stained slides with the same method as ALL-IDB working. A blood cell detection dataset is another open dataset using 100 marked images with labels as 2237 RBCs and 103 WBCs that are updated 7 months ago. WBC image dataset offered in 2019 is obtained from JTSC by using an N800-D microscope, this dataset images have 120 × 120 pixels size. LISC is composed and collected from HO and BMT research centers and contains hematological images acquired from healthy blood subjects and was firstly used in 2011. LISC has a 720 × 576 pixels size image and have 5 subclasses commonly used for classification. BCCD has 364 images of size 640 × 480, it is a small-scale publicly available dataset published in 2018. BloodSeg holds 367 images of blood cells with 640 × 480 pixels' size attained by an ophthalmic microscope with a CCD colored camera [209].

Table 5 shows the commonly available public dataset which is used for leukemia detection and classification, a dataset with their properties is explained below:

8. Discussion and future direction

In this manuscript, recent literature regarding the detection, segmentation, and classification of WBCs is reviewed, and it is indicated that there are still spaces for improvements [220,222]. The future gap and limitations of the existing methods are mentioned in Table 6.

After the comprehensive literature, we observed that the unavailability of a large-scale balance imaging dataset leads to the overfitting problem [218]. Pre-processing methods are required to improve the quality of the input images that are helpful for the accurate detection of leukemia cells [229,230]. GAN models are utilized to avoid the imbalanced data problem. Another option is for different datasets to be combined to create a single large-scale dataset to avoid the overfitting problem [232,233]. Investigation of the optimal features extraction, selection, and fusion approaches are required to increase the detection accuracy [234]. Segmentation of the leukemia cells is also a challenging task such as variable size, shape, color, irregular boundaries, and similarity among the cytoplasm/nucleus. To overcome the existing challenges novel pre-processing and instance-based semantic segmentation methods are required for precise lesions segmentation [219]. The explainable deep learning models should be used to justify the results of the classification [218]. The sub-classification of leukemia lymphoblastic is a challenging task [67], this problem might be handled by applying tiny detectors such as the YOLOv4 model which is computationally less expensive and provide accurate detection [227].

9. Conclusion

In this research, pre-processing, classification, feature extraction or selection, and segmentation approaches for leukocytes/leukemia detection are discussed. Blood cell classification problems resolve by transfer learning that are more effective to learn the complex patterns. The difficult aspect of deep learning methods is that it needs a big number of labeled datasets for training. Many datasets are readily available, but their ground truth labels are not. Irrelevant features cause an increase in rule-based size, due to which the performance of classifiers is decreased. Unrelated and redundant genes in the blood can cause overfitting for ML, Naïve Bayes, and KNN.

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