

## Review Article

# Machine Learning in Detection and Classification of Leukemia Using Smear Blood Images: A Systematic Review

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**Introduction.** The early detection and diagnosis of leukemia, i.e., the precise differentiation of malignant leukocytes with minimum costs in the early stages of the disease, is a major problem in the domain of disease diagnosis. Despite the high prevalence of leukemia, there is a shortage of flow cytometry equipment, and the methods available at laboratory diagnostic centers are time-consuming. Motivated by the capabilities of machine learning (machine learning (ML)) in disease diagnosis, the present systematic review was conducted to review the studies aiming to discover and classify leukemia by using machine learning. **Methods.** A systematic search in four databases (PubMed, Scopus, Web of Science, and ScienceDirect) and Google Scholar was performed via a search strategy using Machine Learning (ML), leukemia, peripheral blood smear (PBS) image, detection, diagnosis, and classification as the keywords. Initially, 116 articles were retrieved. After applying the inclusion and exclusion criteria, 16 articles remained as the population of the study. **Results.** This review study presents a comprehensive and systematic view of the status of all published ML-based leukemia detection and classification models that process PBS images. The average accuracy of the ML methods applied in PBS image analysis to detect leukemia was >97%, indicating that the use of ML could lead to extraordinary outcomes in leukemia detection from PBS images. Among all ML techniques, deep learning (DL) achieved higher precision and sensitivity in detecting different cases of leukemia, compared to its precedents. ML has many applications in analyzing different types of leukemia images, but the use of ML algorithms to detect acute lymphoblastic leukemia (ALL) has attracted the greatest attention in the fields of hematology and artificial intelligence. **Conclusion.** Using the ML method to process leukemia smear images can improve accuracy, reduce diagnosis time, and provide faster, cheaper, and safer diagnostic services. In addition to the current diagnostic methods, clinical and laboratory experts can also adopt ML methods in laboratory applications and tools.

## 1. Introduction

Among all types of blood cancers, leukemia is the most common form of malignancy in different age groups, especially in children. This abnormal phenomenon is caused by excessive proliferation and immature growth of blood

cells, which can damage red blood cells, bone marrow, and the defense system. In the United States, more than 3.5% of new cancer cases are leukemia, and in 2018 alone, this country reported more than 60,000 new cases of this cancer. Malignant white blood cells, or lymphoblast, in the blood reach other organs, such as the spleen, brain, liver, and

kidneys, and then metastasize to important tissues of the body [1–3]. There are different types of leukemia that hematologists in cell transplant laboratories can differentiate/diagnose based on microscopic images. If the slide is correctly stained, some types of leukemia can be more easily identified and distinguished than others, but more equipment is needed to determine underlying leukemia. Figure 1 shows the stained slides of the most common different types of leukemia.

An early diagnosis of leukemia has always been a challenge to researchers, doctors, and hematologists. Enlargement of lymph nodes, pallor, fever, and weight loss are the symptoms of leukemia, but they can also be associated with other diseases. Leukemia diagnosis is difficult in its early stages due to the mild nature of the symptoms. The most common leukemia diagnosis method is the microscopic evaluation of PBS, but the golden standard for leukemia diagnosis only involves taking and analyzing bone marrow samples [3–6].

In the last two decades, various studies have adopted machine learning (ML) and computer-aided diagnostic methods for laboratory image analysis, hoping to overcome the limitations of a late leukemia diagnosis and determine its subgroups. These studies have analyzed blood smears images for diagnosing, differentiating, and counting the cells in various types of leukemia [7, 8].

ML is a well-known branch of artificial intelligence, comprising algorithms and mathematical relations, which was quickly introduced to the domain of clinical research. ML enables computers to be programmed without explicit experience and learns from that experience. The outcome of using these methods in medical data processing has been extraordinary, and they have made remarkable success in disease diagnosis [9–11]. Research indicates that, in medical image processing, ML methods greatly aid complex medical decision-making processes by extracting and then analyzing the features of these images [12–14]. As the number of medical diagnosis tools increased and a large volume of high-quality data was produced, there was an urgent need for more advanced data analysis methods. Traditional methods could not analyze such a large volume of data or find data patterns.

## 2. Methodology

The present systematic review aimed to identify the studies on leukemia detection and diagnosis by using ML techniques for peripheral blood smear (PBS) image analysis. The systematic search strategy was developed based on previous studies and the criteria selected by the authors.

*2.1. Search Criteria.* This study mainly aimed to answer the following questions:

- (1) To what extent has ML been efficient in leukemia diagnosis and classification by using PBS images?

- (2) Which ML algorithm has achieved high efficiency in PBS analysis?
- (3) For the diagnosis and classification of what types of leukemia, has ML achieved better results?
- (4) How can healthcare systems benefit from using ML methods for leukemia detection and diagnosis?

By surveying electronic databases that provide scientific articles on two domains of medicine and computer sciences, the researcher concluded that PubMed, Web of Science, Scopus, and ScienceDirect contain the highest number of articles relevant to the title and objectives of this study. The search was performed by using leukemia, leukemia diagnosis, and detection and ML keywords, based on the inclusion and exclusion criteria, from 2015 to 10 November 2020, and relevant articles were extracted from the said databases. EMBASE and IEEE databases were removed from the domain of search due to the similarity in publications. Table 1 lists the inclusion and exclusion criteria.

*2.2. Data Extraction.* By examining the previous articles, details of their methods and results were extracted and recorded in specially designed forms [15]. Two researchers extracted the data, and the disagreements were resolved upon discussions. The extracted data elements included the title of the article, country, year of publication, the studied population, ML technique, evaluation method, and results.

*2.3. Quality Assessment.* The quality of the eligible studies was assessed by the criteria proposed by Qiao [15]. The assessment was performed based on five categories: unmet need (limits in current non-ML approach), reproducibility (feature engineering methods, platforms/packages, hyperparameters), robustness (valid methods to overcome overfit, the stability of results), generalizability (external data validation), and clinical significance (predictors' explanation and suggested clinical use). A quality assessment table was provided by listing "yes" or "no" for the corresponding items in each category.

## 3. Results

A total of 116 articles were extracted from the four credible databases based on the search strategy. After reading the articles' abstract and full text, applying the inclusion and exclusion criteria, and selecting articles relevant to the title of the present study, 17 full-text articles were finally deemed eligible and were and selected. This process was performed based on the PRISMA flowchart (Figure 2). As ML methods and their applications in blood smear image analysis have newly emerged, this systematic search was conducted over the past five years. A review of the articles showed that, over time, the use of ML methods in PBS image analysis has expanded; seven articles in 2020, five articles in 2019, and

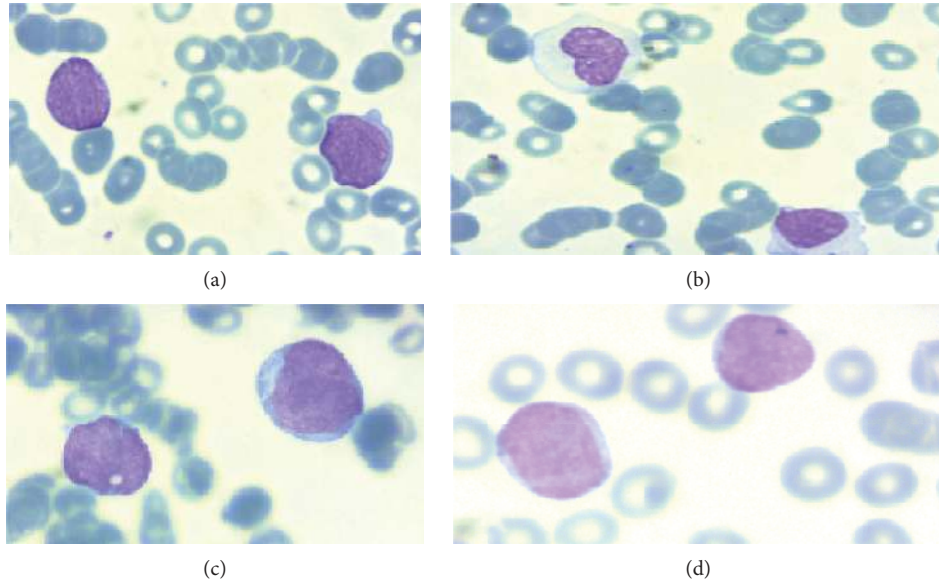


FIGURE 1: (a) AML (M1), (b) AML (M2), (c) B-ALL (pre-B), and (d) B-ALL (pro-B).

TABLE 1: Inclusion and exclusion criteria for review.

Inclusion criteria	Exclusion criteria
(i) Machine learning	(i) DNA
(ii) Deep learning	(ii) RNA
(iii) Leukemia	(iii) Microarray
(iv) Blood smear image	(iv) Other diseases
(v) Microscopic WBC image	(v) Non-English reference abstracts were excluded
(vi) Full-text article available	(vi) Histology and molecular images
(vii) Written in English	(vii) Models not based on ML algorithms
(viii) Published after 2015	(viii) Did not cover an original analysis (e.g., review, narrative)
(ix) Detection	(ix) Did not cover full details on methods
(x) Classification	

four articles in 2018 have focused on the diagnosis and classification of leukemia PBS images.

**3.1. Leukemia Image Datasets.** Diagnosis of leukemia in peripheral blood images is dependent on stained slide quality. Hence, a large number of quality standard datasets are not available. The majority of studies have employed published public datasets. To design and develop ML algorithms, hematologists have made some of these datasets (that include PBS images) available to researchers. ALL-IDB, one of the most well-known datasets published in two versions, has been utilized in many articles, most of which have diagnosed and classified acute lymphoblastic leukemia (ALL) via different ML techniques [16–21]. There is another published leukemia dataset called Benchmark for the development of ML algorithms, used by some studies. Most researchers have tested their proposed model only on homogeneous databases or private databases. However, a major challenge in a robust detection and classification model is the ability to diagnose the disease in databases with distinct characteristics [22]. Hence, to present a robust model and achieve reliable and valid results, some studies

have employed a combination of these datasets as a cross-dataset. Sharif has employed three datasets to achieve a system with high precision and efficiency in diagnosing various leukocytes [22]. Some researchers have also used local datasets in their studies. Among all types of leukemia diagnosed and classified by using ML, the most frequent type was ALL [23–26]. Figure 3 displays the diagnostic goals of various types of leukemia based on PBS image processing. In some articles, image analysis has been performed to count the leukocytes [19].

**3.2. Overview of Machine Vision Techniques in PBS Image Analysis.** Examining the methods adopted by the reviewed studies indicated that two categories of machine vision techniques have been used in PBS image analysis; machine learning and its important subclass, deep learning, are two categories of learning algorithms. The first strategy relies on selective image feature extraction. These methods are common in the extraction of a volume of image features via mathematical and ML algorithms. In this view, the goal of feature extraction is to obtain a set of image descriptors. By finding the relationship between these descriptors, the

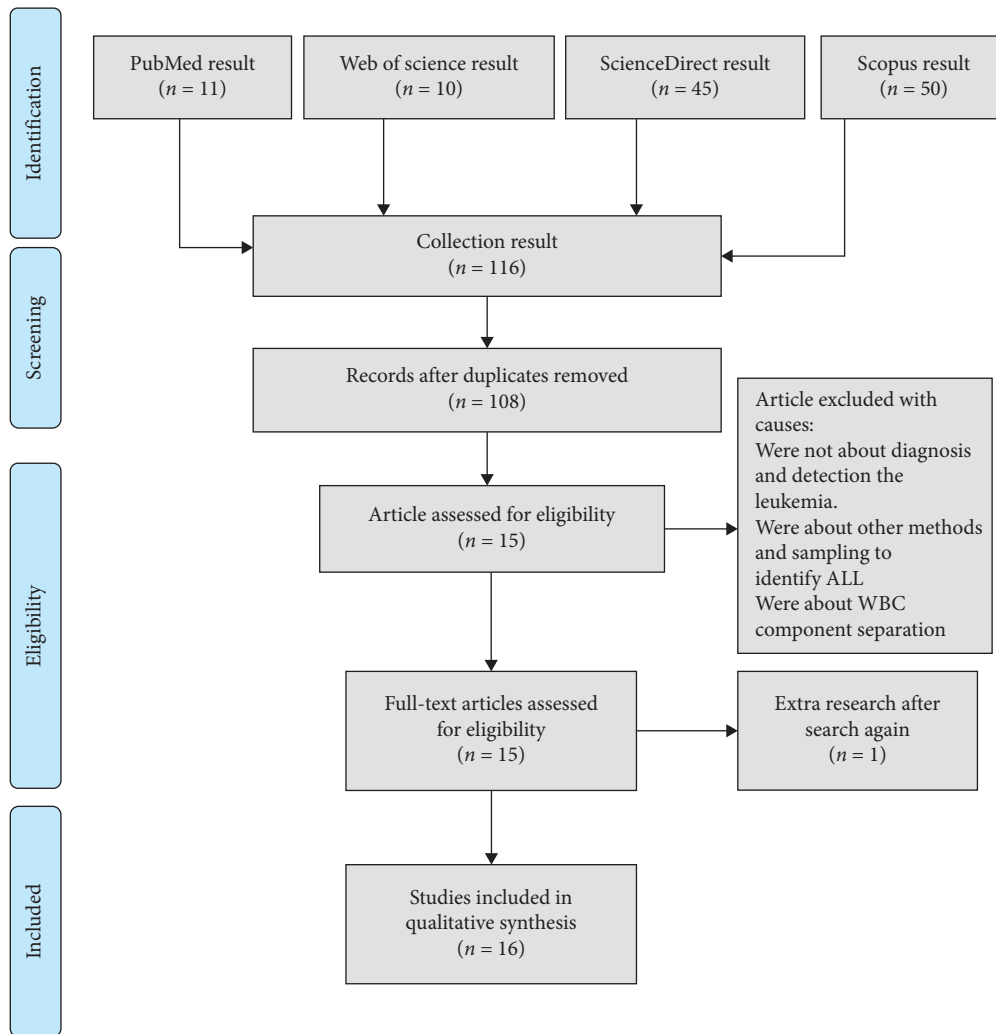


FIGURE 2: PRISMA flow diagram of the review process and exclusion of papers.

patterns determining the images can be discovered [17, 19]. Several classes of features have been considered by researchers and analyzed via ML algorithms to select the most valuable and most effective classification performance. The features extracted from the cytomorphological structure can include cell form, nucleus structure, chromatin, etc. Many articles consider other features as well. Table 2 summarizes the most common features in the field of blast analysis.

Al-jaboriy et al. used the nuclear-to-cytoplasmic ratio, nucleus compactness, nucleus form factors, nucleus eccentricity, nucleus elongation, and nucleus rigidity [17, 23, 24, 27]. Among seven studies, which used traditional ML algorithm, four used the SVM method alone and with other algorithms [18–20, 24] and three utilized ANN and other algorithms [17]. Note that these algorithms are among the most popular algorithms in medical image processing.

The second view comprises methods in which feature extraction is performed automatically, and the researcher plays no role in feature selection. In these methods, building blocks of convolution neural network, including convolution and pooling layers, process the values corresponding to the pixels; in this way, features are extracted automatically

[28, 29]. Then, the features are classified by feeding the features to a layer containing one or more classifiers. These methods extract important features and neglect less important ones. A review of the studies revealed that, to extract and process the features of PBS images for leukemia detection, many studies have employed the CNN algorithm and its state-of-the-art models [30–33]. The features of leukocytes by Vogado [22] simultaneously achieved using CaffeNet, AlexNet, and Vgg-f architectures, which, at that time, were among the most efficient CNN [22]. Figure 4 illustrates the frequency of use of both methods, ML and DL. The frequency of using ML for medical data analysis is daily increasing.

**3.3. Segmentation in PBS Images.** Segmentation is a common task in natural and medical image analysis. The researchers to achieve better classification rates use different types of segmentation. Segmentation is a method for image pre-processing applied for feature extraction and selection and could be considered as the first stage of feature extraction. Segmentation with the goal of extracting a cell from context

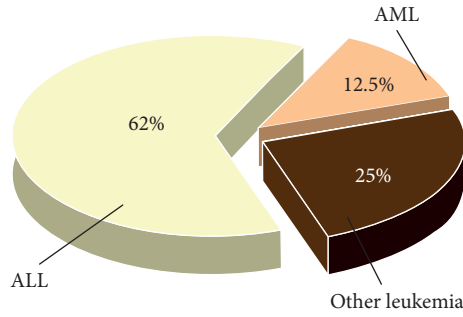


FIGURE 3: The aim of studies in processing different types of leukemia PBS using ML.

TABLE 2: The most common features used in blast analysis using ML.

Class of features	Parameters
Color features	(i) Mean color intensity for red component
	(ii) Mean color intensity for green component
	(iii) Mean color intensity for blue component
	(iv) Mean color intensity for hue component
	(v) Mean color intensity for saturation component
	(vi) Mean color intensity for value component
Texture features	(i) Homogeneity
	(ii) Contrast
	(iii) Correlation
	(iv) Energy
Statistical features	(i) Mean
	(ii) Variance
	(iii) Skewness
Wavelet features	(i) Mean of HARR A coefficient
	(ii) Mean of HARR H coefficient
	(iii) Mean of HARR V coefficient
	(iv) Variance of HARR A coefficient
	(v) Variance of HARR H coefficient
	(vi) Variance of HARR V coefficient
Morphological features	(i) Area, perimeter, roundness, elongation, form factor, length-to-diameter ratio, compactness, discrete Fourier transform

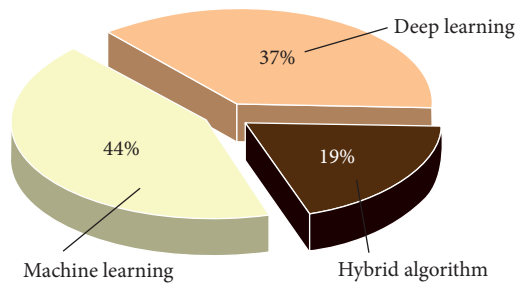


FIGURE 4: Different machine learning views in PBS image analysis.

or its nuclei from the cytoplasm provides an accurate view of the structure and features of the blast, and the ML technique by analysis the origin of the blast can identify leukemia or its

subtypes. Several studies have diagnosed leukemia by segmenting and then extracting the features of some of these segments; other studies, however, have diagnosed leukemia without segmentation and merely by extracting the features from the entire image [12, 34–37].

**3.3.1. Overview of Segmentation Techniques.** Several studies trying to detect and differentiate leukocytes used ML techniques to segment and extract this cell and its nuclei from other blood cells. The main types of segmentation techniques include thresholding methods, boundary-based segmentation, region-based segmentation, and hybrid technology combining boundary and region standards, and most of the techniques combine boundary and region criteria [38–40]. Two techniques of blood smear image segmentation are more prominent and have received more attention from researchers. In the first view, which is based on the concept of thresholding and change color channels in the scope of cell sets, only the extraction of blasts without considering blasts feature is considered in research, and then the model is trained on these blasts [41]. In this method, the rest of the blood components like RBC are removed from the context of the images and, therefore, from the machine learning input. Al-jaboriy et al. using this type of segmentation removed all other blood components such as RBC cells and other erythrocyte lines and extracted only WBC cells, which include lymphocytes and lymphoblast. Figure 5 shows a view of this type of segmentation.

Another class of segmentation is object detection, in which segmentation is not performed from the edge of the cell, and the crop is done around the ROI surrounding the cell frame, accommodating other cellular components. In this type of segmentation, this entire box is fed to the model to learn its usage. This segmentation model has been used in many studies due to its high similarity between blood cells and their sensitivity to differentiation. This segmentation has been referred to as localization in some studies. In this type of segmentation, the noise components in the learning process are minimized. Figure 6 shows this type of segmentation. Other ML methods of segmentation are clustering [42], Gram–Schmidt orthogonalization method [43], edge detection, region growing [44], and optimization-based method [45]. In blood cell segmentation, more traditional ML algorithms have been used.

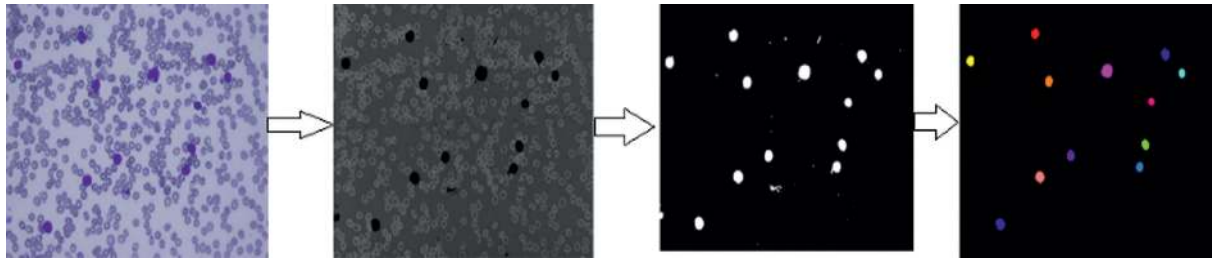


FIGURE 5: Localization, preprocessing, and thresholding segmentation [23].

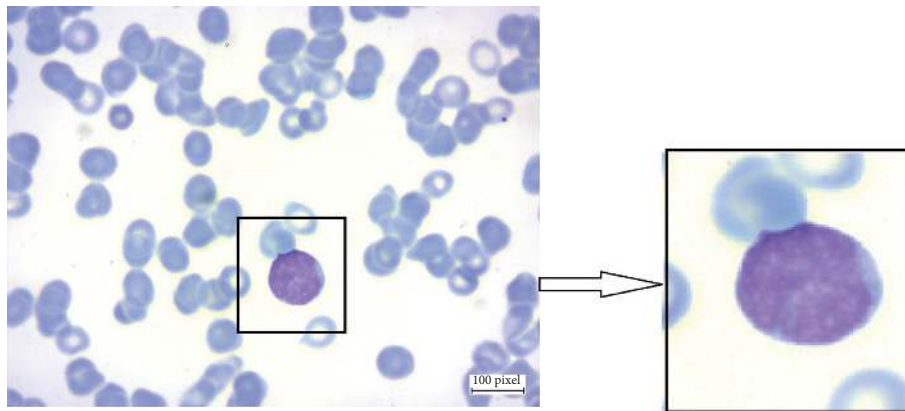


FIGURE 6: Blast segmentation-based object detection.

**3.3.2. Overview of the ML Algorithm in Blood Cell Segmentation.** Machine learning plays an important role in blood image segmentation, and segmentation is one of the first steps in identifying leukemia in blood smear images. Different machine learning algorithms have been used in most segmentation techniques. The purpose of cell segmentation is to identify the boundary between the nucleus and the cytoplasm for further characterization, such as the characterization of the nuclear properties, the properties of the cytoplasm, and the nuclear-to-cytoplasmic ratio, which is useful for explosive identification [39, 46, 47]. Many segmentation algorithms have been presented in the literature and the traditional ML algorithms based on selected features were the main and popular algorithms. Machine learning algorithms are used in the computational core of two categories of segmentation types. They are pixel-based image segmentation and region-based segmentation. Some other studies used shaped-based segmentation (threshold-based, edge-based, and region-based techniques) instead of region-based segmentation. Among the different types of machine algorithms, clustering class algorithms had the most acceptance and efficiency. Kim et al. used clustering algorithms in the threshold, edge detection, pixel clustering, and region growing segmentation [48]. Kekre et al. used k-mean and fuzzy c-mean algorithm vector quantization on the color pixel to segment the blood cells [44], and also Viswanathan used morphological contours (edge detection, erosion, and dilation) as features in the fuzzy c-mean algorithm to achieve a high-performance model in

leukemia segmentation [46]. The other popular ML algorithm is watershed algorithm, which separating component-based morphological or other features presented in Table 2 treats pixels values as a local topography. The application of watershed segmentation to a distance map increases efficiency. Watershed segmentation is based on the idea of a catchment basin of a contour map. In other words, the water droplets follow the image gradient flow along the path to reach a local minimum. Many studies have used the watershed algorithm for segmentation. Using this algorithm has been easier and more acceptable than other algorithms [49–51]. Other ML algorithms such as SVM, ANN, and decision tree have been used frequently to segment blast in blood smear images. Table 3 lists the studies that have performed segmentation using the ML algorithm to extract blasts or their features for specific purposes, not just for leukemia detection or classification. Several of this research uses segmentation to extract nuclei of blast or other WBC cells.

Segmentation for leukemia detection or diagnosis is particularly much crucial. The accurate feature extraction and leukemia classification are proportionately dependent on the correct segmentation of the maximized and cropped lymphocytes. Table 4 presents the studies which have analyzed PBS images to diagnose (detect) or classify different kinds of leukemia based on the indicators considered in the present study. Some studies have merely diagnosed leukemia and aimed for its primary detection based on cell morphological changes [19, 21, 22, 25, 26, 75, 76].

TABLE 3: Studies that used ML algorithms for blast segmentation.

Author	Type of feature extracted	ML segmentation technique	No. of data and details	Performance (accuracy %)
Begum and Razak [52]	Morphological operations erosion, dilation, opening, and closing of nuclei	SVM	Not mentioned	83%
Jothi et al. [53]	Morphological, wavelet, color, texture, and statistical features, and other features	Naive Bayes, linear discriminant analysis, K-nearest neighbor, support vector machine, decision tree, and ensemble random under sampling boost	300	(60%–100%)
Gajul and Shelke [54]	Not mentioned	K-mean clustering and morphological operations	40	—
Vogado et al. [22]	Not identified	Automatic feature extraction	Three datasets	99%
Agaian et al. [55]	Color, texture, shape, and Hausdorff dimension feature	Using k-means clustering	80	98%
Negm et al. [51]	Geometric, color, texture, and size feature of blast	Using k-means clustering	75	99.5%
Su et al. [39]	Color and morphology features	k-means cluster and constructing a cell image by hidden Markov random field	61	96%
Goutam and Sailaja [56]	LDP feature	Using k-means clustering	90	98%
Shankar et al. [57]	Color, shape, and texture	Threshold by using the Zack algorithm	33	96%
Viswanathan [46]	Morphological contour (edge detection, erosion, and dilation)	Fuzzy c-means	—	98%
Patel and Mishra [58]	Geometric, color, texture, and size feature of cell	K-mean clustering and the Zack algorithm	7	93%
Zhao et al. [12]	Morphological operation and granularity feature are selected automatically	CNN and SVM	9	94%
Karthekeyan and Poornima [59]	Geometrical, texture, and color	Fuzzy c-means	19	90%
MoradiAmin et al. [37]	Geometrical and statistical feature	Fuzzy c-means	21	98%
Rawat et al. [60]	Morphological operation	Global thresholding and morphological opining	260	(79%–95.4%)
Mishra et al. [61]	Texture and color	Marker-controlled watershed segmentation	190	96%
Bhattacharjee and Saini [36]	Morphological operation	Morphological operations erosion, dilation, opening, and closing	120	96%
Khobragade et al. [62]	Geometrical and statistical	Otsus’s thresholding and Sobel operator	Not mentioned	90%
Patil and Raskar [41]	Color, shape, and texture	Thresholding by using Otsu’s method	Not mentioned	Not mentioned
Rawat et al. [34]	Shape features	Global thresholding and morphological opining	420	96.75%
Neelam et al.	Texture features	K-mean clustering followed by expectation maximization algorithm	Not mentioned	80%
Singh et al. [63]	Shape and texture features	ANN	ALL-IDB (no: 108)	97.2%
Singhal and Singh [64]	Texture features	SVM	ALL-IDB (no: 260)	93.8%
Zhang et al. [65]	Shape features	Fuzzy system	Local (not mentioned)	Not mentioned
Neoh et al. [66]	Shape, texture, and color features	Dempster–Shafer	ALL-IDB (no: 180)	96.7%
Amin et al. [67]	Shape and texture features	SVM	Local (no: 21)	97%
Viswanathan [46]	Shape, color, and texture features	Fuzzy c-means classifier	ALL-IDB (no: 108)	98.0%

TABLE 3: Continued.

Author	Type of feature extracted	ML segmentation technique	No. of data and details	Performance (accuracy %)
Bhattacharjee and Saini [36]	Shape features	ANN	ALL-IDB (no: 120)	95.2%
ElDahshan et al. [68]	Not mentioned	Field	ALL-IDB (no: 300)	Not mentioned
Rawat et al. [60]	Shape and texture features	SVM	ALL-IDB (no: 196)	89.8%
Putzu et al. [35]	Shape, color, and texture features	SVM	ALL-IDB (no: 267)	92.0%
Mohapatra et al. [70]	Shape and texture features	Ensemble classifier	Local dataset (no: 104)	94.7%
Nasir et al. [71]	Shape and color features	MLP_BR	Local dataset (no: 230)	95.7%
Mohapatra et al. [72]	Shape and texture features	ANN	Local dataset (no: 100)	Not mentioned
Madhloom et al. [73]	Shape and texture features	kNN clustering	Local dataset (no: 260)	92.5%
Pedreira et al. [74]	Multiple clinical and laboratorial features	ANN	Local dataset (no: 189)	98.2%

TABLE 4: Characteristics of studies that used machine learning algorithms in the detection and classification of blood smears.

First author, year of publication, and country	Aim of the study	Data	ML method	Validation results	More information
Al-jaboriy et al., 2019, Malaysia [17]	ALL segmentation	Blood smear images (ALL-IDB)	ANN	Accuracy = 97%	The proposed model detected 625 cells out of 540 WBC
Al-Tahhan et al., 2020, Egypt [19]	Automatic detection ALL	Blood smear images (ALL-IDB2)	KNN SVM ANN	Accuracy of testing = 100% F1-score = 100%	Quadratic SVM has the best performance in detecting ALL among ALL-IDB2 dataset
Bodzas et al., 2020, Czech [24]	Automated detection of ALL	Blood smear images (local)	SVM ANN	Sensitivity = 100% Specificity = 95.31%	Artificial neural network has the best performance in detecting ALL
Boldú et al., 2019, Spain [23]	Automatic recognition of different types of blast	Peripheral blood images (local)	LDA	Six groups of cell accuracy = 85% and for some class, accuracy was 97%	Classification accuracy for the six groups of cell types was 85.8
Dasariraju et al., 2020, USA [27]	Detection and classification of immature leukocytes for diagnosis of AML	Single-cell morphological dataset of leukocytes from AML patients and nonmalignant (public)	RF	Accuracy of detection of immature = 92.99% Accuracy for classification of immature leukocytes for types = 93.45%	Segmentation, feature extraction, detection and classification, and calculation modules were applied
Fathi et al., 2018, Egypt [16]	Classification of ALL from normal cases	Blood smear dataset (ALL-IDB)	SVM with a Gaussian radial basis kernel	Accuracy = 96.2% Sensitivity = 97.3% Specificity = 95.3%	Goal of this research was to design a framework for classification of cancer based on medical images



TABLE 4: Continued.

First author, year of publication, and country	Aim of the study	Data	ML method	Validation results	More information
Fan et al., 2019, China [77]	Localization and segmentation	Four commonly used blood smear dataset (BCISC, LISC, and 2 other released datasets)	DNN	Dataset 1: precision = 0.995% Dataset 2: precision = 0.994% Dataset 3: precision = 0.989% Dataset 4: precision = 0.984%	Proposed Leukocyte Mask architecture to gain best precision result with all datasets
Khilji et al., 2020, Bangladesh [75]	Detection of ALL	ALL dataset (C_NMC)	CNN-based different models (encrypted)	Accuracy = 77.934%	Proposed model compared with other state-of-the-art model and gain better accuracy
Nagiub Abdelsalam et al., 2018, Egypt [26]	Detection of all types of leukemia	Leukemia microscopic	CNN	Accuracy = 99.98%	Different types of pretrained (CNN) models were applied and Inception-v3 model had the highest accuracy
Nagiub Abdelsalam et al., 2019, Egypt [25]	AML detection	AML microscopic images (local)	CNN (ResNet-101)	Accuracy = 100% Sensitivity = 100%	Even deep neural networks: AlexNet, GoogLeNet, VGG16, VGG19, Inception-v3, ResNet50, and ResNet10
Praveena and Singh, 2020, India [78]	Segmentation and classification of ALL	ALL-IDB2	Sparse-FCM and deep convolutional neural network	Accuracy = 93.5% Sensitivity = 95.28% Specificity = 93.89%	Grey Wolf-based Jaya optimization algorithm was applied for training CNN
Sharif et al., 2020, Pakistan and Qatar [76]	Recognition of different types of leukocytes	LISC, ALL-IDB1, and ALL-IDB2 malignant (public)	Localization using YOLOv2. Classification using PSO	Accuracy for ALL-IDB1 = 97.2% Accuracy for ALL-IDB2 = 100% Accuracy for LISC > 99%	Naïve Bayes and discriminant analysis and particle swarm optimization was used
Vogado et al., 2018, Brazil [22]	Diagnosis of ALL	ALL-IDB1 ALL-IDB2 Leukocytes CellaVision	CNN (AlexNet + CaffeNet + Vgg-f) and SVM	Accuracy = 100% Precision = 100%	Goal of this research was to design a framework for classification of cancer based on medical images (3 architectures were used in feature extraction, SVM for classification)
Shafique and Tehsin, 2020 Pakistan [79]	Detection and classification of ALL	ALL-IDB1 and ALL-IDB2	CNN (AlexNet)	ALL detection accuracy = 99.50%, ALL subtype classification = 96.06%, dataset precision = 0.984%	After detection, ALL subtype was classified based FAB classification system. Datasets
Hegde et al., 2018, India [18]	Detection of nuclei and classification of WBC	Leishman	SVM	Accuracy of detection of lymphocyte = 100%	After segmentation, the nucleus of WBC cells different kinds of them was classified

TABLE 4: Continued.

First author, year of publication, and country	Aim of the study	Data	ML method	Validation results	More information
Jha and Dutta, 2019, India [21]	Detection of ALL	ALL-IDB2	Proposed hybrid segmentation + Chrono-SCA-ACNN	Accuracy = 99% Sensitivity = 100%	Nucleus and cytoplasm segmentation using Chrono-SCA-ACNN (chronological sine cosine algorithm-based actor-critic neural network)

#### 4. Discussion

Microscopic evaluation of PBS images is the most common primary method of leukemia diagnosis in its early stages. Still, a manual examination of these smears can cause errors in determining the type of the disease and lead to non-standard reports. Moreover, the examination of these smears is tiresome and time-consuming, thus influencing the diagnostic precision. Accordingly, there is a need for an automatic method to provide a precise diagnosis, without being affected by the technicians' experience or the operator's fatigue and job pressures [49, 80].

Upon a search in scientific databases, it was found that no comprehensive systematic review had been conducted on PBS image analysis via ML methods. Therefore, the authors conducted a review study on the applications of ML in the diagnosis and classification of different types of leukemia based on PBS images. By comparing the previous studies, the present research answered the questions posed by the researcher at the outset.

In terms of smear preparation, several factors (e.g., illumination condition, staining time, blood film thickness, and a defect in the film) lead to undesirable visual artifacts or different color distributions in the laboratory images. These issues complicate the precise detection and monitoring of blood smears. As processing these smear images by ML is problematic, preprocessing is necessary [81]. As for leukemia detection using ML algorithms, data preprocessing (e.g., preparation, normalization, and segmentation) can promote the precision of leukemia detection. For precise leukemia detection with minimum error via ML methods, it is suggested that a set of preprocessing techniques be adopted for dataset preparation.

The selection of effective features is the bedrock of preliminary processing of blood smears via ML methods. In cases where the researcher could control the selection and analysis of blood cell features, the main problem was selecting these features to determine leukemia. Some studies have used color and shape, while others have utilized texture and different texture metrics as the features of blast cells. The manual selection of the most important features is always associated with some degree of error, and this process is always viewed as a major challenge. Medical texts have not mentioned any of these features selected by manual methods

as a definitive method for leukemia differential diagnosis [1, 24, 82]. Thus, the selection of several important features from among a large number of features is a completely algorithmic process, and promoting the efficiency of feature selection depends on the algorithm's method. The studies demonstrated that methods extracting fewer cell features have attained a lower precision in leukemia diagnosis. It seems that, to achieve better results in leukemia detection and diagnosis, one can adopt feature extraction methods based on hybrid algorithms or swarm intelligence and pay attention to further coverage of the feature space. It is also recommended that a set of various features, including geometrical, statistical, and morphological ones, be used for leukemia detection. ML methods require manual feature extraction and selection; if the number of images is acceptable for DL, instead of ML, it is better to use the DL method owing to its mechanism.

A major problem associated with leukemia diagnosis via ML algorithms in different studies is the lack of comprehensive datasets of leukemia smear images, an issue which causes problems for the ML methods, e.g., overfitting. Based on the studies, and with respect to the data-driven nature of these methods, one can show that diagnostic errors are higher in the case of smaller datasets. This is why the results of many studies cannot be confirmed because small/local datasets have been used. Thus, to have a robust ML method for leukemia diagnosis/classification, a comprehensive dataset with sufficient data is required, yet the datasets existing in the reviewed studies did not satisfy this basic need. Of course, there are techniques for increasing the data, which, by processing the main images, create new images that maintain the features of the main images. To overcome this problem in DL, numerous studies have reported that augmentation techniques can lead to better results in terms of pattern recognition [47–49]. It seems that image augmentation can lead to better coverage of data space and markedly improve the results of leukemia detection by using these methods. Based on the review of previous studies and the results of smear processing, it can be concluded that ML methods and techniques have received more attention for the diagnosis and classification of acute leukemia, whether AML or ALL, compared to other types. No comprehensive study has examined the performance of traditional and visual leukemia diagnosis by using smear images. However,

studies that have diagnosed leukemia via ML techniques have achieved extraordinary results, with a disease detection mean accuracy of >96%. Although the applications of machine learning in disease diagnosis and blood cell imaging are still evolving, the use of these algorithms in cell counting and blood cell type differentiation is expanding in the healthcare industry. Nowadays, the use of cell counter devices to determine and count blood components based on ML is becoming more common. It is thought that, in the near future, bone marrow transplant laboratories could replace traditional devices with applications and software based on ML, especially DL, to offer a timely method and assist a diagnosis with high certainty and low detection error in the early stages.

## 5. Conclusion

Blood smear image analysis is a vital role in the diagnosis of many blood-related diseases. The diagnosis of leukemia in its early stages and the first smears can lead to immediate diagnosis and the quick initiation of the treatment. Blood smear image analysis by ML methods can aid the diagnosis of early-onset leukemia and the determination of subtypes with a minimum error at the shortest time, so that the process of treatment can be immediately started. A promising future direction for research can be the application of novel ML algorithms, in particular, DL, in computer-aided detection (CAD) systems, whole-slide imaging (WSI), and even apps and software at hematology laboratories, to help the pathologists and oncologists in better detecting leukemia. In the 2018 meeting of the American Society of Hematology, Höllein et al. investigated 43 roles of AI in MFC for B cell lymphoma and leukemia diagnosis. By using the data of 38416 patients and control groups, a model was developed by using neural networks. This system achieved 97% precision in determining normal and abnormal cells. Still, the precision of B cell lymphoma and leukemia classification was 74%. Thus, it is recommended that, in the near future, the use of ML algorithms for the analysis of blood smear images progresses from the phase of modeling to the phase of implementation.

## Data Availability

No data were used to support the findings of this study.

## Ethical Approval

This study was approved by Iran National Committee for Ethics in Biomedical Research with Approval ID IR.SBMU.RETECH.REC.1399.735.

## Disclosure

This study was part of a PhD project conducted at Shahid Beheshti University of Medical Sciences, Tehran, Iran.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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