Incorporating artificial intelligence into morphological diagnosis of acute leukemias: Current landscape, challenges and prospects (Review)

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Abstract. Acute leukemias (ALs) are a diverse group of hematological malignancies characterized by the abnormal proliferation of immature cells. Microscopic observation of cell morphology based on the French-American-British classification remains a fundamental diagnostic method for ALs. However, manual screening from bone marrow smear images is often inefficient, laborious and prone to subjective bias, leading to potential misdiagnosis or missed diagnosis. Artificial intelligence (AI), particularly machine learning (ML), has expanded human capabilities in analyzing complex datasets, leading to breakthroughs in multiple fields, including medical research and clinical practice. Increasingly, ML applications are being developed to diagnose hematological diseases by extracting and aggregating morphological characteristics from peripheral blood and bone marrow smears. However, applying ML methods to recognize cell morphology in hematological diseases presents unique challenges compared with other pathology subspecialties. The present review provided an overview of AI and ML applications in ALs diagnosis, focusing on cell segmentation and data mining methods from microscopy images, and highlights their advantages over manual microscopy.

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1. Introduction

Leukemia is a heterogeneous group of hematologic malignancies characterized by the clonal expansion and accumulation of neoplastic white blood cells. Most leukemias are classified into myeloid or lymphoid lineages based on the differentiation of leukemia stem cells and also may be further classified as either acute or chronic according to blast cells count (1). Acute leukemias (ALs), as a hematological malignancy with different morphological characteristics, include acute promyelocytic leukemia (APL), acute myeloid leukemia (AML, non-APL) and acute lymphocytic leukemia (ALL), account for ~42.7% of all leukemia cases and 54.8% leukemia-related mortality (1,2). These leukemias are characterized by a rapid increase of abnormally immature white blood cells, which inhibit normal blood cell production in the bone marrow (1). Despite the availability of advanced techniques available, including cytogenetics, immunophenotypes and increasing molecular genetics, the initial analysis of cell morphology continues to hold significance in numerous intramedullary and extramedullary pathological diagnoses (3). However, morphological analysis of ALs poses challenges due to its high subjectivity and shortage of skilled technicians specializing in hematopathology (4,5). Consequently, there is a critical demand for an automated and intelligent diagnostic assistance platform to enhance efficiency, alleviate examiner burden and advance medical research.

Artificial intelligence (AI), which emerged in the mid-20th century, focuses on developing computer algorithms capable of performing human-like tasks (6,7). AI is increasingly utilized across multiple domains within the medical field, offering potential benefits such as aiding radiologists in swiftly and precisely diagnosing tumors and assisting pathologists in improving the overall accuracy of cancer diagnosis (8,9). Key applications of AI are summarized in Fig. 1. Expertise in analyzing bone marrow cell morphology is vital for diagnosing and tracking the effectiveness of hematological disorders (10-12). Currently, numerous studies have attempted AI-assisted morphological examinations based on bone marrow smears and have acquired notable results (3,10,13-16). Early computer-assisted systems for hematological image analysis relied on rule-based algorithms and handcrafted feature extraction to classify blood cells, often constrained by limited computational power and dataset scale. With advancements in computational capabilities and the availability of large, annotated image datasets, these traditional approaches gradually evolved into data-driven machine learning (ML) methods, and subsequently into deep learning (DL) models capable of automatic feature learning and superior classification performance (17).

The present review first elaborated on the application of AI in image recognition, followed by a summary of previous and recent studies on bone marrow and/or peripheral blood cell morphology for the detection of various ALs, with particular emphasis on the latest progress and contributions in morphological image analysis performance for APL, AML (non-APL) and ALL. Finally, the current limitations and outline future directions for integrating AI into routine hematopathology practice are discussed.

2. AI for image recognition

In clinical practice, the diagnostic accuracy of cancer and/or numerous other diseases is largely dependent on the expertise of radiologists and pathologists, but notable inter-observer variability exists in reading and interpreting medical images (18). To address this, numerous computer-aided detection and diagnosis systems have been developed to help clinicians interpret medical images more effectively and support diagnostic decisions (3,19-22).

ML, a type of AI, refers to computer algorithms that use training data to acquire the ability to perform tasks. ML models can be classified into supervised, unsupervised and semi-supervised learning based on the intended output (23). During supervised learning, each trained image is labeled, and the model is optimized using these labels to predict categories for new images (24). Unsupervised learning examines unlabeled data to discover underlying patterns, while semi-supervised learning utilizes a small amount of labeled data along with unlabeled data to improve model performance (25). Regardless of the aforementioned learning methods described, they are all based on convolutional neural network (CNN) algorithms.

CNNs are widely used in computer vision to recognize and capture relevant details from visual data. Inspired by biological visual systems, CNNs process images through multiple layers, from detecting basic edges and textures in initial layers to identifying complex objects in deeper layers (26). They have been extensively applied in medical fields: In radiology for interpreting chest X-rays and classifying pulmonary nodules (27,28) and in pathology for classifying tumors, detecting lymph node metastases and predicting PD-L1 status directly from images (29-32). A notable milestone was reached in 2018, when the US Food and Drug Administration (US FDA) granted approval for a retinopathy detection system that relied on CNNs technology and fulfilled the necessary criteria for clinical application (33).

AI based on ML can utilize existing data more effectively than traditional analysis. As summarized by Rodellar *et al* (34), the AI for analyzing hematopathology data involves cell identification and segmentation, algorithm-based feature extraction, and subsequent classification based on these features (Fig. 2). ML models, particularly CNNs, have advanced to allow direct feature extraction and classification with minimal manual intervention. While CNNs have demonstrated high accuracy (>95%) in classifying numerous nucleated cell images, challenges remain in distinguishing morphologically similar lineages, such as lymphocytes and reactive lymphocytes (35,36). The present review subsequently explores how these AI methods are specifically applied to the morphological diagnosis of ALs.

3. Morphology diagnosis of ALs by AI

The diagnosis and classification of ALs are conventionally achieved through microscopic observation of cell morphology from bone marrow smear by hematologists according to 5th World Health Organization classification criteria (37). This process is heavily reliant on the examiner's expertise, underscoring the need for automated systems to enhance diagnostic consistency and efficiency. AI offers transformative potential in this field by enabling high-throughput image analysis and facilitating classifications that may elude human observers. Conventional image-based AI systems typically follow a three-stage pipeline: Object segmentation, feature extraction and disease classification (38). Boldú *et al* (39) proposed a ML model for AL lineage diagnosis using peripheral blood smears, which demonstrated high diagnostic performance by achieving 100% sensitivity, 92.3% specificity and 93.7% precision for myeloid leukemia, and 89% sensitivity with 100% specificity and precision for lymphocytic leukemia, suggesting a potential screening role in in routine hematology. Alcazer *et al* (40) developed an AI-based prediction model, termed AI-PAL, for diagnosing APL, AML (non-APL) and ALL. The model was stratified into confidence and overall variants based on prediction probability scores. In internal and external validation, the confidence model achieved accuracies of 99.7, 98.8 and 99.5% for APL, AML (non-APL) and ALL, while the overall model yielded corresponding accuracies of 87.9, 86.3 and 96.1%, respectively. However, real-world performance was more moderate, with area under the receiver operating characteristic curve (AUROC) values of 0.67 for ALL and 0.71 for AML (41).

Recent advances in CNNs have led to models with near-perfect metrics, such as 98.37% accuracy using an Orthogonal SoftMax Layer-based model (42), 99.37% accuracy with the BSNEU-net framework (43) and 96.15% accuracy with LeuFeatx, a VGG16-adapted feature extractor (44).

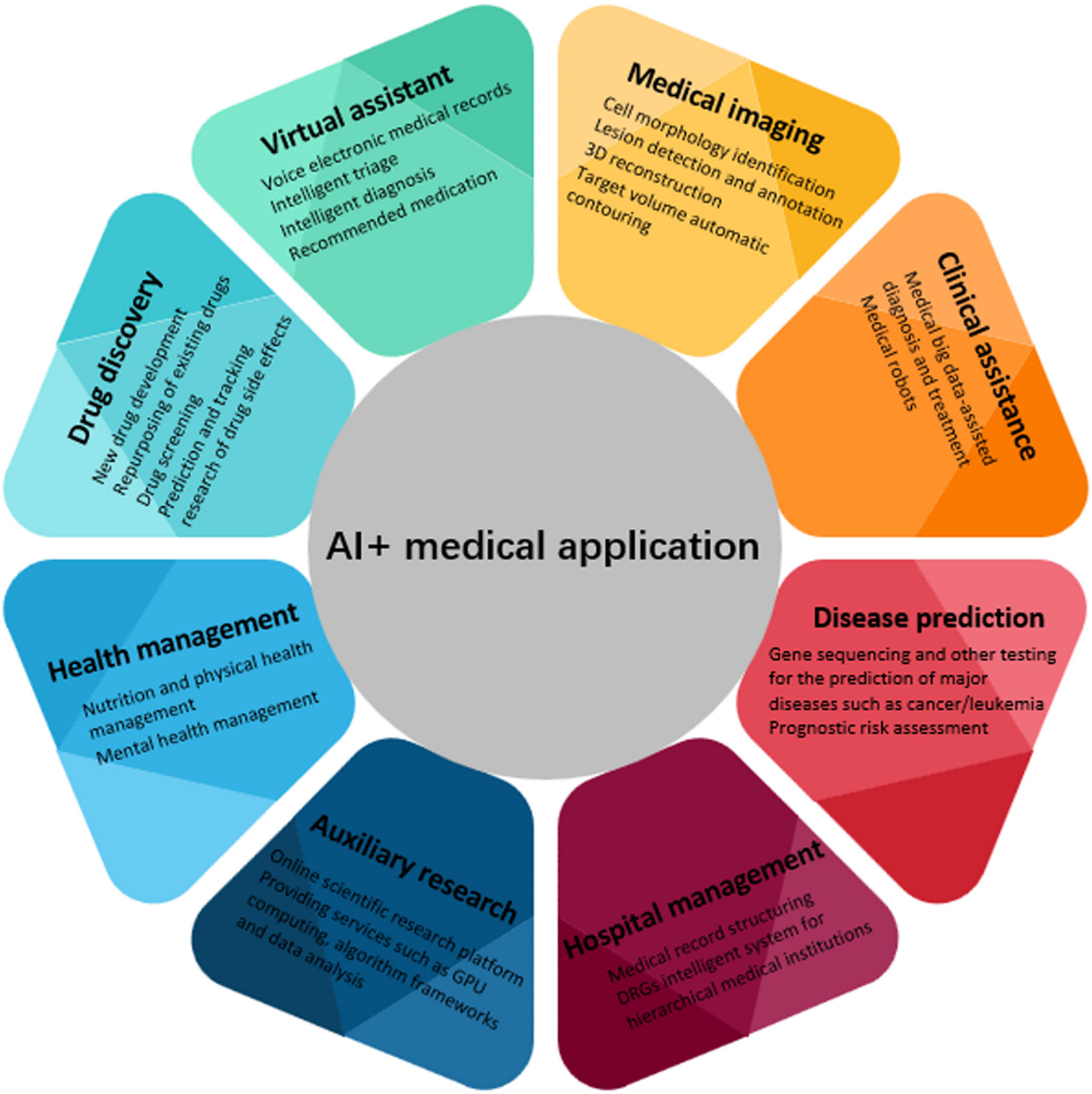

Figure 1. Application scenarios of AI in the medical field. AI, artificial intelligence.

Despite these promising results, barriers to clinical deployment remain, due to high computational demands, sensitivity to hyperparameters and variability in image quality. The present review synthesized the performance and limitations of representative AI models in diagnosing APL, AML (non-APL) and ALL (Fig. 3), with emphasis on their clinical feasibility and intended roles.

APL. APL is a medical emergency associated with an early mortality rate of up to 30%, necessitating rapid and accurate diagnosis (45). Morphologically, APL is characterized by abnormal promyelocytes with heavy granulation and Auer rods (46). While cytomorphology remains the fastest diagnostic modality, definitive confirmation often requires cytogenetic and molecular testing (47-49).

AI models, particularly CNNs, have been developed to assist in rapid morphological screening. For instance, Qiao *et al* (50) proposed a compact CNN that distinguished promyelocytes from normal nucleated cells with accuracies of 96.53 and 99.20% on two public datasets (APL-Cytomorphology-LMU and -JHH; The Cancer Imaging Archive). Eckardt *et al* (14) developed a multi-stage DL platform for automated bone marrow smear analysis, reporting an average precision and recall of 0.97 for cell segmentation and an AUROC of 0.8575 and 0.9585 for distinguishing APL from non-APL AML and healthy donors, respectively, enabling timely diagnosis of APL and early intervention for patients. Manescu *et al* (51) introduced a multi-instance learning (MILLIE) method, which detected APL with an area under curve (AUC) of 0.94±0.04 in peripheral blood

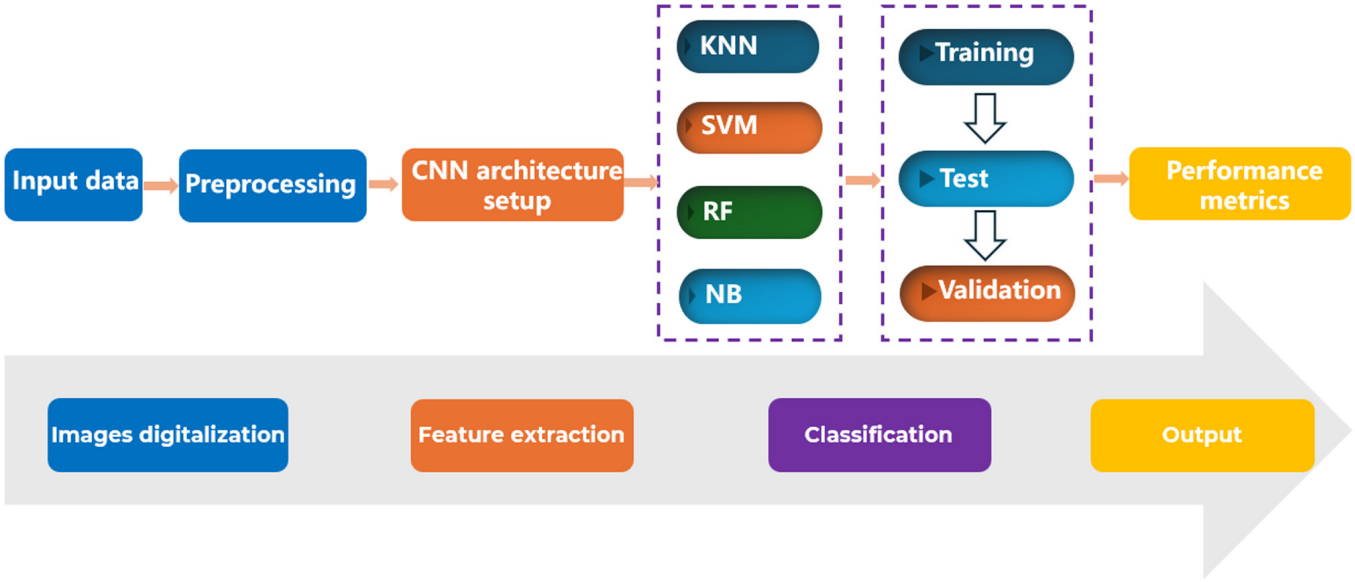

Figure 2. Overall workflow and application of artificial intelligence system for microscopic diagnosis. CNN, convolutional neural network; KNN, K-nearest neighbor; SVM, support vector machine; RF, random forest; NB, naive bayes.

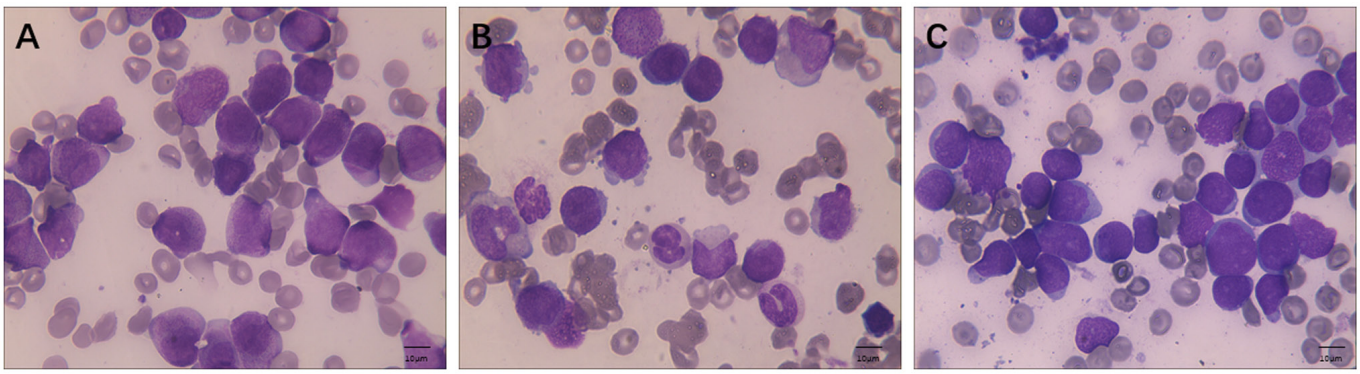

Figure 3. Representative images cell morphology of acute leukemias (A) acute promyelocytic leukemia, (B) acute myeloid leukemia and (C) acute lymphoblastic leukemia. Scale bar, 10 μm. Images were captured at the Department of Hematology, Changhai Hospital, Naval Medical University (Shanghai, China).

smears and 0.99±0.01 in bone marrow smears without requiring cell-level annotations. Integrating MILLIE into clinical workflows may markedly improve detection throughput and reduce cognitive human errors. Recently, our previous study exhibited a CELLSEE model for APL screening, which demonstrated a joint diagnostic performance achieving 93.00% accuracy and 100% recall at magnifications of x10 and x100 in batch samples, thereby ensuring no APL cases were missed (52). The aforementioned models for rapid diagnosis of APL demonstrated satisfactory morphological recognition performance (Table I).

AML (non-APL). AML represents the most common type of AL, with an incidence rate of ~33.5% among all leukemias (2). The morphological characteristics of AML blasts are as follows: i) The cell size is moderate; ii) the nucleus is generally round or ovoid, and may exhibit indentation and folding; iii) the nuclear chromatin is finely granular and lacy with distinct nucleoli; iv) the amount of cytoplasm varies, is basophilic, and frequently contains variable numbers of azurophilic granules; and v) a small proportion of blasts may show Auer rods (37).

Diagnosis is primarily based on blast cell counts in bone marrow or peripheral blood (53), with subclassification into M0-M7 according to French-American-British classification criteria (54). However, cellular morphological examination is an efficient but highly demanding task, relying on well-trained and experienced medical professionals. Therefore, there is a need for an automated AML classification system that overcomes these issues.

Initial applications of ML in this domain relied on traditional algorithms. For instance, techniques such as K-means and fuzzy C-means clustering were primarily employed for the segmentation of nuclei and cells in bone marrow smears, serving as foundational tools for the screening and identification of AML (55,56). The advent of DL has markedly improved diagnostic performance. Huang *et al* (57) combined preprocessing algorithms with a CNN to achieve 99% accuracy in AML classification, demonstrating the viability of transfer learning in this context. Building on these preprocessing techniques, several integrated DL frameworks have been developed for comprehensive AML recognition and classification. Wang *et al* (58) constructed an ImageNet-pretrained

Table I. Studies utilizing AI for APL morphological diagnosis.

First author, year	Purpose	AI model	Validation strategy/dataset	Performance results	Highlight	(Refs.)
Qiao *et al*, 2021	Timely APL diagnosis	End-to-end pipeline based on CNN model	Public database	Precision, 0.9920; AUC, 0.9977	Distinguishing promyelocytes from normal leukocytes	(50)
Eckardt *et al*, 2022	APL prediction and diagnosis	Deep learning based on CNN	Clinical dataset	Precision and recall 0.97; ROC, 0.8575 (APL vs. AML); ROC, 0.9585 (APL vs. HD)	Earlier diagnosis vs. genetics/molecular biology	(14)
Manescu *et al*, 2023	Improving APL diagnostic efficiency and reducing human error	Multiple instance learning for leukocyte identification	Public database	AUC, 0.94 (blood films); AUC, 0.99 (bone marrow)	Augmented throughput for blood film assessment	(51)
Xiao *et al*, 2024	Rapid APL screening	CELLSEE model based on CNN	Clinical dataset	Accuracy, 0.93; precision, 0.85; recall, 1.00	Rapid, batch-sample screening	(52)

APL, acute promyelocytic leukemia, CNN, convolutional neural network, HD, healthy donors, AUC, area under curve, ROC, receiver operating characteristic, AML, acute myeloid leukemia.

CNN for recognizing aplastic anemia (AA), myelodysplastic syndromes (MDS) and AML, achieving an AUC of 0.968, accuracy of 0.929 and sensitivity of 0.857 for AML recognition in the testing set, providing a convenient tool for clinical doctors to distinguish AA, MDS and AML. More advanced DL pipelines have since been developed to address increasingly complex diagnostic tasks. Eckardt *et al* (59) extended DL applications to predict nucleophosmin 1 mutation status directly from morphological images, attaining an AUROC of 0.92. Yu *et al* (60) developed AMLnet, a DL pipeline capable of AML subtype discrimination with image- and patient-level AUCs of 0.885 and 0.921, respectively, offering a rapid prescreening and decision support tool for morphological pathologists. Other notable models include a hybrid deep convolutional autoencoder-CNN model by Elhassan *et al* (61), which reported 97% accuracy, 97% sensitivity and 98% precision for classifying atypical AML cells. In the realm of image segmentation, Zhang *et al* (62) employed an AML conditional generative adversarial network (AMLcGAN) for blast segmentation, achieving a precision of 0.8496 and a recall of 0.8831. The application of DL has also extended to peripheral blood smear analysis. For instance, an auxiliary classification GAN evaluated by Zhang *et al* (63) achieved 97.1% accuracy for AML screening. More recently, Aby *et al* (64) conducted a comparative study of activation functions within deep neural networks, specifically InceptionV3, ResNet50v2 and VGG16, for AML subtype classification. The findings indicated that the Gaussian Error Linear Unit function yielded the highest accuracy of 94.02% when implemented in InceptionV3. Cheng *et al* (65) developed an AI model using 65,039 myeloblast images from 205 patients with AML to identify *RUNX1::RUNX1T1* fusion gene abnormalities via cell morphology, which achieved a maximum sensitivity of 95.65% and specificity of 92.68% under different thresholds, enabling effective recognition of this genetic alteration. Collectively, these studies underscore the strong capability of DL-based systems in enhancing the accuracy and efficiency of AML diagnosis and classification (Table II).

ALL. ALL accounts for roughly 9.2% of all leukemia cases and primarily affects children, featuring excessive proliferation of lymphocytes in the bone marrow. Despite a favorable cure rate in the pediatric population, ALL still accounts for 6.7% of cancer-related deaths among all age groups (2,66). Diagnosis relies on cytomorphology, immunology and genetics, but resource limitations often restrict access to advanced assays, making morphological assessment indispensable. The morphological features of ALL blasts are as follows: i) The cell size is moderately small to small; ii) the nuclei are mostly round with coarse granular or blocky nuclear chromatin, which is coarser than that of AML blasts; iii) nucleoli are generally small and distinct, though inconspicuous in some cases; iv) the cytoplasm is extremely scanty and basophilic, occasionally containing a few azurophilic granules; and v) basket cells and mitotic figures are commonly observed (37). With the continuous development of AI, there have been numerous studies on morphological computer-aided diagnosis for ALL (Table III).

Early applications of DL demonstrated excellent performance in the diagnosis of ALL. Shafique *et al* used a DL CNN for ALL diagnosis, achieving 100% sensitivity, 98.11% specificity and 99.50% accuracy, enabling high performance without the need for microscopic image segmentation (67). Rehman *et al* (68) also employed a CNN-based model for ALL-training, with a reported accuracy of 97.78% for the

Table II. Studies utilizing AI for AML morphological diagnosis.

First author, year	Purpose	AI model	Validation strategy/dataset	Performance results	Highlight	(Refs.)
Huang *et al*, 2020	Establishing an objective, rapid and accurate leukemia classification method	The perfect reflection algorithm and a self-adaptive filter algorithm based on CNN	Clinical dataset	Accuracy, 0.90	Faster, more accurate and more objective compared with traditional manual microscopes.	(57)
Wang *et al*, 2022	Automatically distinguishing AA, MDS, and AML	CNN model	ASH image bank	AUC, 0.968; accuracy, 0.929; sensitivity, 0.857	Distinguishing AA, MDS, AML with high accuracy	(58)
Liu *et al*, 2022	Automatically classifying AML-M1 and M2 subtypes	Random forest method and broad learning system	TCIA open database	Accuracy 0.998; AUC, 0.998; F1-score, 0.998; recall, 0.996	Enabling classification of AML-M1 and M2 subtypes	(13)
Eckardt *et al*, 2022	Detecting AML and predicting NPM1 mutation status	Multi-step DL	Clinical dataset	AUROC, 0.9699 (AML vs. HD); AUROC, 0.92 (prediction for NPM1 mutation)	Predicting NPM1 mutation status from myeloblast morphology	(59)
Yu *et al*, 2023	Diagnosing and classifying AML	AMLnet, a deep-learning pipeline based on bone marrow images	Clinical dataset	AUC, 0.885 (image level); AUC, 0.921 (patient level)	Rapid prescreening and decision-making aid	(60)
Elhassan *et al*, 2023	Building an AML classification model	GT-DCAE WBC augmentation model	AML-Cytomorphology-LMU	Accuracy, 0.97, sensitivity, 0.97; precision, 0.98	Introducing a hybrid data augmentation model	(61)
Zhang *et al*, 2024	Accurately differentiating myeloblasts	AMLcGAN	Clinical dataset	Precision, 0.8496; recall, 0.8831	Aiding pathologists in accurate AML diagnosis	(62)
Zhang *et al*, 2024	Assessing ACGAN applicability	ACGAN model	TCIA dataset	Precision, 0.975; recall, 0.973; F1 scores, 0.974	High performance compared with other advanced methods	(63)
Aby *et al*, 2025	Exploring the effectiveness of various CNN architectures for AML subtyping	VGG16, InceptionV3 and ResNet50v2	ASH image bank	Accuracy, 0.9283 (VGG16); accuracy, 0.9402; (InceptionV3) accuracy, 0.9253 (ResNet50v2)	Demonstrating potential of CNN for automated AML subtyping and identifying GELU as the optimal activation function	(64)

AA, aplastic anemia; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; NPM1, nucleophosmin 1; CNN, convolutional neural network; HD, healthy donors; DL, deep learning; AUC, area under curve; AUROC, area under receiver operating characteristic; AMLcGAN, AML conditional generative adversarial network; GT, geometric transformation; DCAE, deep convolutional autoencoder; WBC, white blood cell; ACGAN, auxiliary classification generative adversarial network; GELU, gaussian error linear unit; TCIA, The Cancer Imaging Archive.

diagnosis of ALL and subtype classification. These foundational studies catalyzed rapid growth in AI-based ALL diagnosis using cell image recognition.

Subsequent studies in 2021 explored diverse architectural approaches. Rezayi *et al* (69) compared ResNet-50, VGG-16 and a proposed convolutional network, achieving accuracies

Table III. Included studies utilizing AI for ALL morphological diagnosis.

First author, year	Purpose	AI model	Validation strategy/dataset	Performance results, %	Highlight	(Refs.)
Shafique *et al*, 2018	Automating ALL detection and classification	AlexNet, a deep convolutional neural network	ALL-IDB	Accuracy, 99.50; specificity, 98.11; sensitivity, 100.00	Providing directions for diagnosing other leukemias	(67)
Rehman *et al*, 2018	Improving ALL diagnosis	Computer vision toolbox and Alexnet model on GaPU based on CNN	Amreek Clinical Laboratory	Accuracy, 97.78	Novel image segmentation technique	(68)
Rezayi *et al*, 2021	Facilitating rapid ALL identification and classification	A convolutional network with ten convolutional layers and 2x2 max-pooling layers-with strides 2	ALL-IDB and ASH image bank	Test accuracy, 85.79; validation accuracy, 82.10	Improved accuracy with increased image volume	(69)
Pałczyński *et al*, 2021	Autonomously classifying ALL	Hybrid artificial intelligence systems	ALL-IDB Database	Accuracy, 97.50	Demonstrating advantages of transfer learning	(70)
Jiang *et al*, 2021	Timely and accurate ALL diagnosis	ViT-CNN ensemble model	VGG-16	Accuracy, 99.03	Combining vision transformer and CNN architectures	(71)
Mirmohammadi *et al*, 2021	Classifying ALL, normal, reactive and atypical cells	RF classifier	Images data from the author's own laboratory samples	Accuracy, 98.00	Superior performance vs. other common classifiers	(72)
Musleh *et al*, 2022	Realizing early and rapid ALL diagnosis	ALL Detector, a deep learning-based network to distinguish patients with ALL	ALL-IDB2 database	Accuracy, 98.00	Best performance in distinguishing ALL from healthy groups	(73)
Jawahar *et al*, 2022	Realizing early ALL diagnosis	ALNett, a deep neural network	ResNet50, VGG-16, AlexNet, GoogleNet	Training accuracy 99.73; test accuracy, 91.13; F1-score, 0.96	Improved tool to aid clinical decision-making	(74)
Almadhor *et al*, 2022	Establishing automated ALL prediction techniques	KNN, SVM, RF, NB	C-NMC leukemia dataset	Accuracy, 90 (SVM vs. other algorithms)	Practical method for determining ALL diagnosis	(75)
Atteia *et al*, 2022	Autonomously identifying ALL in blood images	Bayesian-based optimized CNN	ALL-IDB1, ALL-IDB2	Test accuracy, 100.00; test specificity, 100.00; test sensitivity, 100.00	Bayesian-optimized CNN outperforming other models	(76)
Chen *et al*, 2022	Rapidly and accurately detecting ALL	Resnet101-9 ensemble model	C-NMC leukemia dataset	Accuracy, 85.11; F1-score, 88.94	Ensemble model outperforming individual ResNet-101	(77)
Abunadi *et al*, 2022	Developing diagnostic systems for early ALL detection	ANN, FFNN, SVM, AlexNet, GoogleNet and ResNet-18 consist of hybrid systems	ALL-IDB1, ALL-IDB2	Accuracy, 100.00	Improved accuracy via hybrid model combinations	(78)

Table III. Continued.

First author, year	Purpose	AI model	Validation strategy/dataset	Performance results, %	Highlight	(Refs.)
Albeeshi *et al*, 2023	Finding an effective and fast method for ALL diagnosis	VGG16 pre-trained, and using SVM and MLP classification algorithms	VGG16, SVM	Best training accuracy, 92.27; best validation accuracy, 85.62	Enhanced performance via learning rate adjustment	(79)
Ahmed *et al*, 2023	Assisting in early ALL detection	DenseNet121, ResNet50, and MobileNet consist of hybrid systems	C-NMC 2019 and ALL-IDB2	Accuracy, 100.00; precision, 100.00; specificity, 100.00; sensitivity, 100.00	Significantly improved detection via hybrid systems	(80)
Kaur *et al*, 2023	Early and accurate ALL detection	Deep Skip Connections-Based Dense Network	Kaggle dataset	Accuracy, 97.89; sensitivity, 99.13; specificity, 96.76	Efficiently handling challenges in existing diagnosis models.	(81)
Huang *et al*, 2024	Timely ALL diagnosis	Ensemble-ALL model	C-NMC leukemia dataset	Accuracy, 96.26; precision, 96.26; specificity, 96.26	Valuable contributions to ALL diagnosis	(82)
Jawahar *et al*, 2024	Detecting ALL	Deep Dilated Residual Convolutional Neural Network	Kaggle dataset	Training accuracy, 99.86; test accuracy, 91.98	Leveraging optimized algorithms and parallel processing for high workloads	(83)
MoradiAmin *et al*, 2024	Developing an accurate and efficient system for identifying ALL cells	A novel CNN	Images data from the author's own laboratory samples	Accuracy, 97.00	Eliminating manual feature extraction in classification	(84)
Elrefaie *et al*, 2024	Improving criterion for classifying ALL microscopic images	Neural network classifier based on Bayesian regularization method	ALL-IDB2 dataset	Accuracy, 98.70; sensitivity, 99.30; specificity, 98.10	Combining Bayesian regularization with neural networks	(85)
Alsaykhan *et al*, 2024	Exploring the automated detection of ALL	Hybrid SVM-PSO model	ALL-IDB1 and ALL-IDB2 dataset	Accuracy, 97.40	Novel hybrid algorithm improving detection performance	(86)
Mei *et al*, 2025	Achieving early ALL diagnosis	Progressive shrinking convolutional neural network model	Images data from the author's own laboratory samples	Accuracy, 92.51	Enhancing diagnostic efficiency and accuracy for experts	(87)
Mei *et al*, 2025	Enabling rapid whole slide analysis of ALL	SGLNet framework	Images data from the author's own laboratory samples	Average precision, 95.90	Facilitating large-scale clinical diagnosis	(88)
Anand *et al*, 2025	Early diagnosis and detection of ALL.	Deep optimized CNN	Images data from the author's own laboratory samples	Accuracy, 96.00; precision, 95.00	Achieving superior performance by adjusting hyperparameters	(89)

ALL, acute lymphoblastic leukemia; KNN, K-nearest neighbor; SVM, support vector machine; RF, random forest; NB, naive bayes; IBD, image database; CNN, convolutional neural network; ANN, artificial neural network; FFNN, feed forward neural network; IDB, Image DataBase; SGL, spatially guided learning.

ranging from 81.63 to 84.62%. The proposed network is simpler than the two pretrained networks and can be employed by pathologists to recognize ALL. Furthermore, an optimized IoT-friendly neural network achieved 97.5% accuracy for ALL classification (70), while a ViT-CNN ensemble model reached 99.03% accuracy in distinguishing blasts from normal cell images to support diagnosis (71). Additionally, a Random Forest classifier integrated with image enhancement yielded 98% accuracy for recognition of ALL (72).

In 2022, several innovations were introduced. The ALL Detector achieved 98% accuracy in distinguishing patients with ALL from healthy individuals, serving as a screening tool (73), and a deep neural network-based model that employs depth-wise convolution with different dilation rates to classify nucleated cell images and yielded a classification accuracy of 91.13%, which is useful for ALL categorization (74). Among traditional ML algorithms, such as K-nearest neighbor, support vector machine (SVM), random forest and naive bayes, SVM performed best with 90.0% accuracy for predicting ALL (75). A Bayesian-optimized CNN achieved 100% across all evaluation metrics, showing superiority over existing DL systems developed for ALL diagnosis (76). A ResNet101-9 ensemble model attained 85.11% accuracy, which performed well in classifying ALL (77), and a hybrid artificial neural network-feedforward neural network-SVM model achieved 100% accuracy for diagnosis of ALL (78).

In 2023, model development continued with varied architectures. A VGG16 model combined with SVM and multilayer perceptron (MLP) classifiers yielded a training accuracy of 92.27% and a validation accuracy of 85.62%, achieving fast and accurate diagnosis (79). The hybrid CNN-RF and CNN-XGBoost systems exhibited 100% AUC, accuracy and sensitivity, thereby supporting effective early diagnosis of ALL (80). Furthermore, a Deep Skip Connections-Based Dense Network tailored for ALL diagnosis obtained 99.37% accuracy, 99.71% sensitivity, 99.03% specificity and an AUC of 99.37%, demonstrating the potential of an effective tool for early and accurate diagnosis of ALL (81).

In 2024, the focus shifted toward model refinement and clinical applicability. An ensemble-ALL model achieved notable performance, with accuracy, precision, recall, F1-score and kappa scores of 96.26, 96.26, 96.26, 96.25 and 91.36%, respectively; this model has made valuable contributions to medical image recognition, particularly for the diagnosis of ALL (82). A Deep Dilated Residual CNN demonstrated minimal computational complexity and improved the discrimination of crucial features for accurate multi-class blood cell image recognition, with an accuracy rate of 91.98% (83). Another deep neural network-based model has a classification accuracy of ~97% for ALL and lymphocyte subtypes (84). A method leveraging Hilbert Huang supervision achieved 98.7% accuracy, 99.3% sensitivity, and 98.1% specificity for classifying normal and blast ALL cell images, which could assist in the screening of ALL (85). Additionally, a hybrid detection model combining SVM with particle swarm optimization reported an accuracy of 93%, which is superior to stand-alone algorithms and exhibiting increased overall performance, an improved confusion matrix and a higher detection rate of ALL (86).

In 2025, Mei *et al* (87) carried out two related studies on lymphoblastic leukemia detection: in one study, they proposed a lightweight model focusing on throughput (111 slides per second) with a maintained accuracy of 92.51%, reflecting the trend of developing clinically applicable efficient models. Furthermore, Mei *et al* (88) built a high-quality dataset containing 1,794 microscopic images and developed the spatially-guided learning framework, which solved key challenges in whole-slide leukemia detection and achieved a mean average precision of 95.9% for ALL. In addition, Anand *et al* (89) proposed a deep optimized CNN model for early ALL diagnosis, which, optimized with the Adam optimizer among other methods, attained an accuracy of 0.96 and a precision of 0.95 after fine-tuning the corresponding hyperparameters.

Despite these advances, to the best of our knowledge, no model has undergone rigorous external validation in real-world cohorts, and challenges related to model interpretability, data heterogeneity and computational efficiency still persist.

A comparison of AI methodologies reveals distinct trade-offs among data requirements, interpretability, computational efficiency and clinical roles (Table IV). Traditional ML models offer high interpretability and low computational cost but require manual feature engineering and plateau in performance. Classic deep CNNs achieve state-of-the-art accuracy through automated feature learning but suffer from low inherent interpretability and high computational demands. Lightweight architectures balance efficiency and accuracy, making them suitable for point-of-care applications. Hybrid models combine the strengths of DL and ML, offering moderate interpretability and robust performance on smaller datasets. Ensemble methods, while often achieving top benchmark performance, entail high complexity and risk of overfitting. Generative models are valuable for data augmentation and unsupervised segmentation but may produce artifacts. Clinically, lightweight CNNs are preferable for rapid screening in resource-limited settings, whereas hybrid or ensemble models may serve as high-precision diagnostic aids in well-equipped laboratories.

4. Conclusions and perspectives

ALs are life-threatening diseases that can lead to death if left untreated. Currently, microscopic bone marrow examination remains the primary diagnostic procedure. However, given the dynamic nature of hematological diseases and the frequent presence of atypical cell morphology, there is a growing need for an automated, efficient and highly accurate diagnostic system, which would help eliminate intra- and inter-observer variability and improve diagnostic consistency. Previous studies have demonstrated that AI significantly outperformed manual microscopy in diagnosing and subtyping AML based on bone marrow cell morphology, as well as in predicting the *RUNX1:RUNX1T1* AML subtype. This advantage is particularly evident in metrics such as sensitivity and positive predictive value (60,65).

In recent years, AI has begun integrating into clinical hematology. By June 2025, the US FDA had already approved 20 AI/ML-based devices to assist hematologists or medical laboratory technicians in extracting information

Table IV. Comparison of AI techniques in medical image analysis.

Technique	Representative architectures	Data and annotation requirements	Interpretability	Strengths	Weaknesses	Typical clinical role	(Refs.)
Traditional ML (feature-based)	RF, SVM, k-means, fuzzy C-means	Small to medium datasets; handcrafted features; annotation for seg. and labels	High (features human-defined)	Fast training; transparent decisions; works with limited data; easy to deploy	Performance saturates; poor generalization; manual feature engineering is labor-intensive	Screening tools, educational aids, legacy systems	(13,55,56, 72,84,85)
Classic deep CNNs	VGG16, ResNet50, InceptionV3	Large datasets (thousands/class); pixel/image-level labels	Low (black box); post-hoc explanations (Grad-CAM)	SOTA accuracy; automatic feature learning; transfer learning mitigates data scarcity	Computationally expensive; overfitting risk; sensitive to hyperparameters; low inherent interpretability	High-performance classifiers, research prototypes	(2,10,39, 42,44,51, 52,57,58, 59,68,69, 73,79,89)
Lightweight or efficient CNNs	MobileNet, EfficientNet, compact CNN	Moderate datasets; benefits from pretraining	Low to moderate	Real-time inference; point-of-care feasible; low power	Slightly lower accuracy than large models; still lacks built-in interpretability	Bedside decision support, large-scale screening	(43,50,60, 65,87,88)
Hybrid models	CNN + RF, CNN + SVM, CNN + XGBoost	Moderate datasets; leverages pretrained CNN features	Moderate (CNN features visualizable)	Balances accuracy and interpretability; often outperforms pure DL on small data	Two-stage pipeline; not fully end-to-end optimized	Generalizable tools when training data limited	(9,15,40, 70,74,76, 78,80,81, 83,86)
Ensemble models	Voting/averaging of multiple CNNs, CNN + ViT	Large datasets; multiple models required	Very low	Robustness; often top benchmark scores	High computational cost; complex deployment; risk of over-ensembling	Competition solutions, seldom deployed clinically	(14,71, 77,82)
Generative models	AMLcGAN, ACGANs	Unlabeled/paired data for synthesis/segmentation	Low	Data augmentation; segmentation without extensive labels	Training instability; mode collapse; synthetic images may miss diagnostic details	Enhancing training sets, unsupervised segmentation	(62,63)
Vision transformers	ViT, Swin Transformer	Very large datasets (>1M) or strong pretraining	Very low	Captures global context; can outperform CNNs on massive data	Extreme data hunger; extensive regularization needed; limited validation in cytology	Cutting-edge research, potential future tools	(61,67, 75)

ML, machine learning; CNN, convolutional neural network; SVM, support vector machine; RF, random forest; DL, deep learning; SOTA, state-of-the-art; CAM, class activation mapping; ACGAN, auxiliary classification generative adversarial networks.

from specimens (https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices). To date, none of the specific AI models in this review have received FDA approval for standalone diagnosis of ALs. However, several AI-based digital pathology and hematology systems have been cleared for broader clinical use in supporting cell counting, segmentation or pre-classification tasks. This trend not only underscores the growing recognition of the potential of AI-augmented diagnostic workflows but also expands the broad application of AI in leukemia, encompassing minimal residual disease monitoring, prediction of genetic abnormalities, prognostic stratification and treatment management.

AI adoption in this field faces several significant challenges, and it cannot yet fully replace human expertise. First, in data quality and standardization: Variations in staining protocols, smear preparation, imaging parameters and scanner types introduce technical artifacts. Future efforts must prioritize standardized protocols or AI-based normalization techniques to minimize these inconsistencies. Second, model generalization and real-world performance: While several models achieve high accuracy (>95%) on internal or curated datasets, their performance often declines in external, real-world validation. Prospective, multi-center clinical trials using consecutive patient samples are essential to assess true generalizability. Third, interpretability and trust: The 'black-box' nature of numerous DL models hinders clinical trust. Integrating explainability tools, such as attention maps or saliency maps that highlight decision-relevant cellular regions, is crucial for transparency. Fourth, integration into clinical workflows: Successful adoption depends on seamlessly embedding AI into existing diagnostic pathways. Finally, ethics and application: Data privacy, algorithm transparency and clinician acceptance present critical hurdles that must be addressed to ensure ethical, trustworthy and effective deployment. Key considerations include defining its role, as a triage tool, a diagnostic assistant or an independent system, each requiring different levels of sensitivity, specificity and regulatory approval. Additionally, regulatory and legal frameworks for AI-aided diagnoses must be established alongside technological development.

Future studies should not only focus on improving model performance but also emphasize practical clinical application. Based on the findings of the aforementioned studies, key directions for improvement include: i) Reducing the impact of staining and imaging variations; ii) enriching and diversifying databases; iii) establishing standardization; iv) preventing systemic errors and biases; v) validating models through clinical trials and regulatory processes; and vi) integrating multimodal data. Notably, education on AI-assisted diagnostics should also be incorporated into medical curricula to prepare future practitioners.

In summary, addressing these challenges requires a concerted interdisciplinary effort combining hematology, pathology, computer science and biomedical engineering. Through collaborative innovation and rigorous validation, AI could evolve into a reliable adjunct in the morphological diagnosis of ALs.

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Competing interests

The authors declare that they have no competing interests.

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