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Explainable machine learning for leukaemia diagnosis: enhancing interpretability and trust

Hamza Abu Owida[1], Mohammad R. Hassan[2], Nidal Turab[3], Suhaila Abuowaida[4]
[1]Department of Medical Engineering, Faculty of Engineering, Al-Ahliyya Amman University, Amman, Jordan
[2]Department of Communications and Computer Engineering, Faculty of Engineering, Al-Ahliyya Amman University, Amman, Jordan
[3]Department of Networks and Cyber Security, Faculty of Information Technology, Al-Ahliyya Amman University, Amman, Jordan
[4]Department of Computer Science, Faculty of Information Technology, Al al-Bayt University, Mafraq, Jordan

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ABSTRACT

One of the major challenges in applying machine learning (ML) to leukaemia diagnosis is the limited interpretability of deep learning models such as artificial neural networks (ANNs) and convolutional neural networks (CNNs). While these models excel at detecting complex patterns in medical data, they often function as "black boxes," providing little transparency into their decision-making processes. This lack of explainability raises concerns in clinical practice, where understanding why a model predicts a specific leukaemia subtype is critical for guiding treatment decisions, including chemotherapy and bone marrow transplantation. To address these concerns, researchers are increasingly adopting explainable AI (XAI) techniques. Methods such as saliency maps, feature importance rankings, and attention mechanisms allow clinicians to visualize how specific factors such as genetic mutations, biomarkers, or cell morphology contribute to diagnostic outcomes. These interpretability tools not only enhance transparency but also foster trust among healthcare providers and patients. By bridging the gap between computational accuracy and clinical reliability, XAI ensures that ML models can be safely integrated into diagnostic workflows. Ultimately, explainable approaches strengthen confidence in AI-driven leukaemia diagnosis, supporting more informed medical decisions and improving patient care.

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Corresponding Author:

Nidal Turab
Department of Networks and Cyber Security, Faculty of Information Technology
Al-Ahliyya Amman University
Amman, Jordan
Email: N.turab@Ammanu.edu.jo

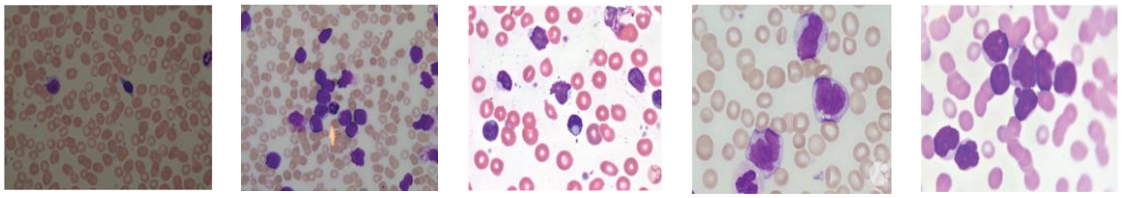
1. INTRODUCTION

Leukemia is a malignant cancer of the bone marrow and blood, characterized by the abnormal proliferation of blood cells, particularly white blood cells (WBCs). It is classified into four major subtypes: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [1]–[4]. Early and accurate diagnosis is critical, as each subtype requires a distinct therapeutic approach [5], [6]. Figure 1 illustrates specimens of normal leukocytes alongside representative images of the four leukemia subtypes, highlighting the morphological differences that underpin diagnostic evaluation. Figure 1(a) shows healthy leukocytes as a reference for normal cell morphology. Figure 1(b) shows ALL, while Figure 1(c) presents CLL. Figure 1(d) illustrates CML, and

Figure 1(e) shows AML. These images highlight the morphological differences between healthy leukocytes and the four major leukemia subtypes.

Traditional diagnostic methods including peripheral blood smears, bone marrow biopsies, flow cytometry, cytogenetic analysis, and molecular testing remain the gold standard. However, these approaches are often labor-intensive, subjective, and prone to inter-observer variability [7]–[10]. In recent years, machine learning (ML), a subset of artificial intelligence (AI), has gained prominence for its ability to analyze complex datasets and uncover hidden patterns that may elude human experts. By leveraging diverse data sources such as medical records, blood tests, imaging, and genomics, ML models can automate diagnostic workflows, improve accuracy, and reduce turnaround times [11]–[13].

This review provides a comprehensive analysis of the current state of ML applications in leukemia diagnosis. It examines supervised, unsupervised, deep learning, and reinforcement learning techniques, outlining their respective strengths and limitations in clinical contexts. Furthermore, it discusses the challenges of integrating ML into medical practice particularly issues of interpretability and trust and proposes future directions to advance AI-driven leukemia diagnostics toward reliable, transparent, and patient-centered healthcare.



(a) (b) (c) (d) (e)

Figure 1. Image sample of; (a) healthy leukocytes, (b) Acute lymphoblastic leukemia (ALL), (c) Chronic lymphocytic leukemia (CLL), (d) Chronic myeloid leukemia (CML), and (e) Acute myeloid leukemia (AML)

2. BACKGROUND ON LEUKEMIA AND DIAGNOSIS

Leukemia is a heterogeneous disease with multiple subtypes, each requiring a specific diagnostic approach. Acute leukemia, including ALL and AML, is characterized by the rapid accumulation of immature WBCs (blasts) in the bone marrow, leading to an abrupt onset of symptoms such as fatigue, fever, and bleeding. Chronic leukemia, including CLL and CML, progresses more slowly and may be asymptomatic in its early stages [1], [13].

The diagnosis of leukemia involves a comprehensive, multi-step process aimed at accurately identifying the type and stage of the disease. One of the first and most critical diagnostic tools is a complete blood count (CBC), which measures the number and types of blood cells, including WBCs, red blood cells (RBCs), and platelets. Abnormal counts in these cells can provide an initial indication of leukemia. Elevated WBC counts or unusually low RBC and platelet levels are common in leukemia patients. Additionally, an increase in immature cells, such as blasts, often suggests the presence of leukemia, as these cells should not typically appear in the peripheral blood in large numbers [14], [15]. Following the CBC, a microscopic examination of a blood smear is performed to identify any abnormal cells, especially blasts, which are a hallmark of leukemia. This test provides visual confirmation of abnormal blood cell morphology and the presence of immature white cells, which supports the suspicion of leukemia [16], [17].

A more definitive test is a bone marrow biopsy, which is essential for confirming the diagnosis of leukemia. This procedure involves extracting a small sample of bone marrow, typically from the pelvis, to assess the percentage of present blasts. In healthy bone marrow, blasts make up less than 5% of cells, but in leukemia, this percentage can significantly increase. A high blast percentage not only confirms the diagnosis but also helps in determining the specific subtype of leukemia, which is critical for treatment planning [18], [19].

Flow cytometry is another crucial diagnostic technique used to analyze the expression of specific cell surface markers on leukemic cells. This method enables the classification of leukemia into subtypes, such as acute ALL or AML, by identifying distinct patterns of surface antigens on the abnormal cells [20]–[22]. Genetic testing also plays a key role in leukemia diagnosis. Chromosomal abnormalities, such as translocations (e.g., the Philadelphia chromosome in CML and mutations in AML, provide important diagnostic and prognostic information. These genetic changes can guide treatment decisions, as some mutations are associated with specific targeted therapies, influencing the overall management and prognosis of the disease [23]–[25].

Despite the availability of these diagnostic methods, challenges remain in ensuring the timely and accurate classification of leukemia subtypes. ML has the potential to address these challenges by automating diagnostic workflows, reducing inter-observer variability, and enhancing the interpretation of complex datasets [13].

3. MACHINE LEARNING FUNDAMENTALS

ML is a key subset of AI that empowers computers to learn from data, identify patterns, and make predictions or decisions without being explicitly programmed. By training ML models on large datasets, these systems can recognize complex relationships within the data and apply the knowledge gained to new, unseen instances. This capability makes ML highly valuable across various fields, including healthcare [26], [27]. Figure 2 explore the ML workflow.

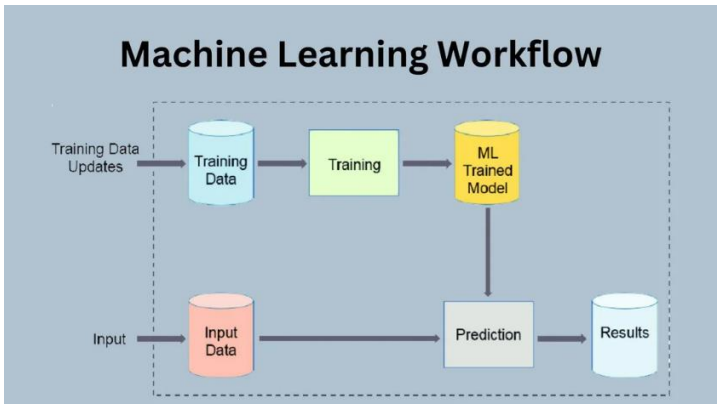


Figure 2. The ML workflow

There are several types of ML algorithms, each suited to different tasks and data types. Supervised learning is the most used approach, where the model is trained on labeled data, meaning that each input is associated with a known output [28]. For example, in medical diagnosis, input data such as patient characteristics and imaging results are paired with the correct diagnosis. The model learns to map inputs to outputs so it can predict diagnoses for new patients. This is particularly useful in applications like disease detection and classification [29].

Unsupervised learning differs in that the model is trained on data without labeled outcomes. Instead of predicting a known result, the model seeks to uncover hidden patterns and structures within the data. This approach is useful in discovering new subtypes of diseases or clustering patients into groups based on their symptoms or genetic data, potentially leading to better personalized treatments [30].

Semi-supervised learning is a hybrid of supervised and unsupervised learning. It is particularly useful when labeled data is scarce but large amounts of unlabeled data are available. This allows the model to leverage information from both data types to improve its performance [31]. Lastly, reinforcement learning involves training a model to make decisions by interacting with an environment and receiving feedback in the form of rewards or penalties. Though less common in medical diagnosis, reinforcement learning holds potential for optimizing treatment strategies, especially in personalized medicine, by simulating different treatment paths and predicting the outcomes [32].

The success of ML models depends on the quality of the data they are trained on. In the context of leukemia, relevant data types include clinical records, blood test results, imaging data, genetic profiles, and proteomics. Proper data preprocessing, feature extraction, and selection are crucial steps to ensure that the model can learn meaningful patterns from the data [33].

4. ML APPLICATIONS IN LEUKEMIA DIAGNOSIS

One of the most widely researched applications of ML in leukemia diagnosis is the automated analysis of blood smear images. Blood smears are commonly used in the diagnostic process to identify abnormal cells, including leukemic blasts. Traditionally, pathologists visually examine smears under a microscope, which is a time-consuming and subjective process.

According to Sasaki *et al.* [34], improving treatment outcomes and increasing survival rates for CML patients are dependent on using suitable and effective ML classifiers. Although AI for CML is still in its early phases, preliminary studies have shown promising results in important areas such as diagnosis, prognosis, and personalized treatment. Using blood and bone marrow samples, AI methods have shown remarkable accuracy in diagnosing leukaemia subtypes like CML. Convolutional neural networks (CNNs) achieved above 95% accuracy in differentiating CML cells from microscopic images, according to a study by Huang *et al.* [35]. AI has the ability to greatly improve diagnostic accuracy and efficiency, as demonstrated by this exceptionally high level of accuracy. Furthermore, a plethora of AI models have been developed that outperform conventional prognostic ratings in predicting the progression of diseases and the efficacy of treatments.

In their article titled "Phase classification of CML using CNNs," Khosla and Ramesh [36] used TensorFlow to train a CNN model to categorise CML histology images. Using state-of-the-art CNN architecture, researchers have mapped out the steps involved in CML development. The best course of treatment for CML depends on accurately identifying the patient's current stage of the disease. The results showed that the CNN has a 99.6 % success rate in predicting different stages of CML.

In order to conduct their study, Dese *et al.* [37] obtained 250 peripheral blood smears from the haematology department at Jimma University medical centre in Ethiopia. Eosin, methylene blue (wright stain), and Sudan black B were used to stain the smears in order to make it easier to identify the subtypes of leukaemia. The diagnosis of leukaemia was reached after two experienced haematologists examined the smears under the microscope separately. The digital images were processed using K-means clustering to separate white blood cells, RBCs, and platelets. The computer-assisted technique was able to diagnose and classify leukaemia subtypes with a sensitivity of 97.86% and a specificity of 100%. An autonomous ML leukaemia classification and diagnostic model was created and tested by Sakthiraj [38]. The leukaemia dataset was used to train a hybrid CNN that could classify samples with the help of a SoftMax-CNN layer and extract features. The classification accuracy was further enhanced by incorporating an HCNN-IAS.

To identify subtypes of leukaemia from microscopic images using CNNs, Ahmed *et al.* [39] utilised the publicly available ALL-IDB and ASH image bank datasets. Data was enhanced using seven different picture processing algorithms. In addition, a CNN architecture was designed to detect all varieties of leukaemia. Traditional ML methods including decision tree, naive bayes, support vector machine, and k-nearest neighbor were also explored with CNN modelling. In order to assess performance, a 5-fold cross-validation approach was used. Results showed that CNN model achieved 88.25% accuracy for leukaemia vs healthy classification and 81.74% accuracy for multiclass categorization of all subgroups.

Baig *et al.* [40] used CNN architecture to classify different forms of leukaemia in images of blood smears. CNN model based on deep learning principles to classify samples as ALL, AML, or MM using microscopic smear images. The CNN model consisted of two distinct CNN blocks, CNN-1 and CNN-2. The capability to identify cancerous leukaemia cells through microscopic examination was proven by the suggested framework. When compared to the other classification algorithms, the bagging ensemble method performed the best, with a calculated accuracy rate of more than 97.04%

One successful application of ML in this area is the use of decision trees and random forests to classify leukemia subtypes based on surface marker expression patterns. These models can handle the high-dimensional nature of flow cytometry data and provide interpretable results, making them useful for clinical decision-making [12].

5. CHALLENGES AND LIMITATIONS

Despite the promising potential ML models in leukemia diagnosis, several challenges remain. These include ensuring model interpretability, overcoming data quality issues, and addressing the limited availability of large, annotated datasets. Additionally, models must be robust and generalized across diverse patient populations to build trust among clinicians for reliable integration into routine medical practice [41].

ML models trained on specific datasets may not generalize well to new, diverse patient populations. The lack of generalization reduces the trust clinicians can place in these models, as predictions may not be reliable across different demographics or clinical settings. Additionally, many ML models have not undergone rigorous clinical validation, which is crucial to ensure their safety and effectiveness in real-world applications [42].

The performance of ML models is highly dependent on the quality and quantity of data used for training. In leukemia diagnosis, obtaining large, well-annotated datasets from diverse populations can be challenging. Furthermore, incomplete, or noisy data may introduce biases or inaccuracies in the model's predictions, further complicating the model's interpretability and limiting its clinical utility [43].

The use of ML models in healthcare, particularly for diagnosing critical conditions like leukemia, raises ethical and legal concerns. For instance, in cases where the model provides a diagnosis that contradicts a human expert's judgment, determining accountability can be challenging. If an ML-driven diagnosis leads to incorrect treatment or patient harm, the question of liability becomes complex. The opaque nature of many ML models exacerbates these concerns, as it can be difficult to trace errors back to specific factors or decisions [44].

Another limitation lies in the steep learning curve for healthcare professionals to understand and effectively use ML tools. Even with interpretable models, there is a gap in the technical knowledge needed by clinicians to understand the underlying principles and functionality of ML algorithms. Without adequate training, clinicians may resist adopting these technologies or may misinterpret the model's outputs, further reducing trust in ML-driven decisions [45]–[48].

Addressing these challenges requires ongoing research and development in both ML and clinical informatics. Improving model interpretability, enhancing transparency, and ensuring robust clinical validation will be crucial for building trust in ML applications for leukemia diagnosis, ultimately leading to better integration into clinical practice and improved patient outcomes.

6. CONCLUSION

The integration of ML into leukemia diagnosis represents a transformative advancement in medical practice, offering the potential to improve early detection, diagnostic accuracy, and efficiency in clinical decision-making. By leveraging large-scale datasets including gene expression profiles, biomarkers, and imaging data ML models can uncover complex patterns that may be difficult for clinicians to detect, thereby enabling earlier intervention and improved patient outcomes. However, the widespread adoption of ML in oncology is hindered by challenges of interpretability and trust. Deep learning models, while powerful, often operate as “black boxes,” obscuring the rationale behind their predictions. This lack of transparency raises concerns about reliability, accountability, and ethical implications, particularly in high-stakes scenarios such as leukemia diagnosis, where misclassification can have life-threatening consequences. To address these challenges, the development of explainable AI (XAI) methods is essential. Techniques such as SHAP (shapley additive explanations) and local interpretable model-agnostic explanations (LIME) provide insights into the contribution of features such as genetic mutations, blood cell counts, or protein markers to diagnostic outcomes. These tools bridge the gap between computational predictions and clinical expertise, enabling physicians to validate AI-driven recommendations with confidence. Ultimately, the successful integration of ML into leukemia diagnosis requires prioritizing interpretability alongside performance. By fostering transparency and trust through XAI, ML can evolve from research applications into reliable, patient-centered tools in real-world oncology, paving the way for safer and more effective AI-assisted healthcare.

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BIOGRAPHIES OF AUTHORS



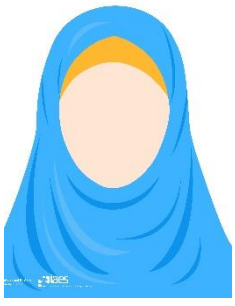
Hamza Abu Owida Ph.D. in Biomedical Engineering, assistant professor at the Medical Engineering Department, Al-Ahliyya Amman University, Jordan. Research interests focused on biomedical sensors, nanotechnology, and tissue engineering. He can be contacted at email: h.abuowida@ammanu.edu.jo.



Mohammad R. Hassan has completed his Ph.D. from Baku State University, Azerbaijan. He is an associate professor in the Computer Engineering Department at the Faculty of Engineering at Al-Ahliyya Amman University. Hassan is a member of the Jordanian Engineering Association. He has published numerous research papers in various journals and conferences, covering topics such as machine learning, computer networks, intelligent transportation systems, and mobile learning adaptation models. He can be contacted at email: mhassan@ammanu.edu.jo.



Nidal Turab Ph.D. in computer science professor at the Networks and Cyber Security Department, Al-Ahliyya Amman University, Jordan. His research interests include WLAN security, computer networks security and cloud computing security, eLearning, and IoT. He can be contacted at email: N.turab@ammanu.edu.jo.



Suhaila Abuowaida received the B.Sc. degrees in Computer Information System, M.Sc. degrees in Computer Science from AL alBayt University, Jordan, in 2012 and 2015, respectively, and the Ph.D. degree in Computer Science from Universiti Sains Malaysia, Malaysia, in 2023. Dr. Abuowaida is currently working as an assistant professor with the Computer Science Department, Zarqa University, Jordan. Her research interests include deep learning, depth estimation, point cloud, and computer vision. She can be contacted at email: suhilaowida@gmail.com.