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Revolutionizing chronic lymphocytic leukemia diagnosis: A deep dive into the diverse applications of machine learning

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Abstract:
Chronic lymphocytic leukemia (CLL) is a B cell neoplasm characterized by the accumulation of aberrant monoclonal B lymphocytes. CLL is the predominant type of leukemia in Western countries, accounting for 25% of cases. Although many patients remain asymptomatic, a subset may exhibit typical lymphoma symptoms, ac- quired immunodeficiency disorders, or autoimmune complications. Diagnosis involves blood tests showing increased lymphocytes and further examination using peripheral blood smear and flow cytometry to confirm the disease. With the significant advancements in machine learning (ML) and artificial intelligence (AI) in recent years, numerous models and algorithms have been proposed to support the diagnosis and classification of CLL. In this review, we discuss the benefits and drawbacks of recent applications of ML algorithms in the diagnosis and evaluation of patients diagnosed with CLL.

1. Material and Methods:

1.1. Literature search strategy

A literature search of all studies pertaining to ML implementations in CLL was conducted using the PubMed/MEDLINE and EMBASE data- bases on the 11th of April 2023. Terms pertaining to CLL (e.g., “chronic lymphatic leukemia”, “chronic lymphocytic leukemia”, “CLL”) and machine learning (e.g., “AI”, “machine learning”, “neural network”) were used in the search strategy and combined using Boolean operators ‘AND’ or ‘OR’. After applying the search strategy, all of the identified studies were transferred to EndNote, where duplicates were eliminated.

The resulting studies were then transferred to Rayyan to conduct further screening and remove any additional duplicates. In addition, the refer- ences of the identified studies, review articles, systematic reviews, and meta-analyses were manually screened to identify additional studies.

The collected data included several aspects including the type of study, publication year, assessed outcome, model creation methods, used model(s), and evaluation metrics for the model(s) such as sensi- tivity (SEN), specificity (SPE), accuracy (ACC), and area under the receiver operating curve (AUROC). An online confusion matriX calcu- lator was used to obtain the evaluation metrics when these metrics were not explicitly reported in the reviewed articles’ manuscripts. In cases where multiple models were used in a study, the metrics for the best-performing model were extracted. The collected data also encom- passed the strengths and limitations of the studies.

1.2. Inclusion and exclusion criteria

The primary literature that discussed the use of ML algorithms in different CLL applications was considered for inclusion in this review. No date or language restrictions were considered. Research articles were included in the review if they met the following criteria: 1) The authors used a method that relies on the usage of ML to function, 2) The research reported conclusions regarding the reliability or accuracy of using such method, 3) The outcome of the research pertains to diagnosis and classification of CLL. Articles that were excluded from this review were non-English articles, animal studies, in vitro studies, abstracts, and re- view articles.

A total of 169 articles were identified through a search of PubMed and EMBASE databases. Duplicate articles were removed using Endnote® and Rayyan® software, resulting in 149 articles, which were further screened using Rayyan®. After screening, 14 studies met the inclusion criteria. Details of the screening process are provided in Fig. 1.

2. Role of ML in diagnosis and classification of CLL:

To diagnose CLL, two criteria must be met: 1) an absolute B lymphocyte count of 5000/μL in the peripheral blood with predomi- nantly mature small lymphocytes on smear examination, sustained for 3 months, and 2) evidence of immunoglobulin light chain restriction (kappa or lambda), low levels of surface membrane immunoglobulin (SmIg), and expression of B cell antigens (CD19, CD20, CD23) and CD5 on flow cytometric analysis of peripheral blood [5]. ML algorithms can aid this process by automating the interpretation of these tests and predicting the diagnosis, which can improve the efficiency of hematol- ogists and decrease the processing time for these tests. A summary of the advantages, disadvantages, and outcome addressed in each study is provided in Table 1. Additionally, Table 2 outlines the performance for the best ML models developed in the studies reviewed here.

3. Conclusion and future considerations:

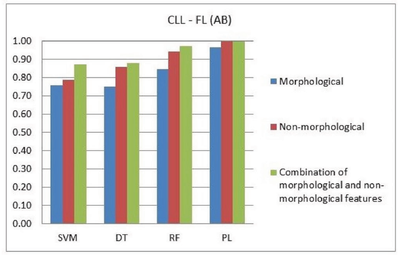
This review explored various approaches to enhance the diagnosis of CLL through the implementation of ML algorithms. A critical evaluation is conducted on multiple applications of ML models in CLL diagnosis using blood smears, flow cytometry, histopathological images, genetic data, and others. The current evidence suggests that AI can accurately predict CLL diagnosis, aid in CLL screening, identify potential bio- markers for diagnosis, and explore the underlying biochemical and molecular mechanisms in CLL. The majority of the ML models assessed in this review exhibit adequate performance in predicting CLL diagnosis. Specifically, the leading model in discriminating CLL from healthy cases demonstrated a sensitivity of 96.4% and specificity of 98.8%, along with an AUROC of 99.7%. Moreover, one model achieved 100% accuracy in distinguishing CLL from FL and MCL, while another model achieved the same level of performance in distinguishing CLL from CML, ALL, and AML. The application of AI and ML in the field of hematology offers a wide range of benefits. These technologies have the potential to enhance the efficiency and effectiveness of hematologists by automating various steps involved in patient workup, risk assessment, and treatment. Through the automation of these processes, hematologists can reallocate

potential integration of ML algorithms into clinical practice for the diagnosis and workup of patients with CLL.

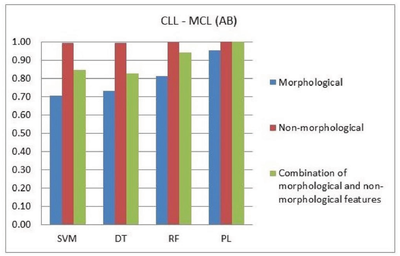
Despite the promising performance and potential advantages of employing ML models in CLL diagnosis, several important consider- ations need to be acknowledged [44,46–48]. Several reviewed models had limited sample sizes derived from a single center or laboratory, limiting their generalizability to other populations. Additionally, some studies only validated their models internally, thereby increasing the risk of overfitting and rendering their performance on unseen data un- known. To address this limitation, it is imperative to develop models with enhanced generalizability by employing large, homogeneous datasets obtained from multiple centers and laboratories.

In addition, most studies retrospectively evaluated the predictive abilities of ML models, with few prospective studies available. More- over, there is a lack of research evaluating the influence of these models on patient outcomes. Future investigations should focus on prospective assessment of the effect of ML models on CLL diagnosis, patient prog- nosis, and ultimately, patient outcomes.

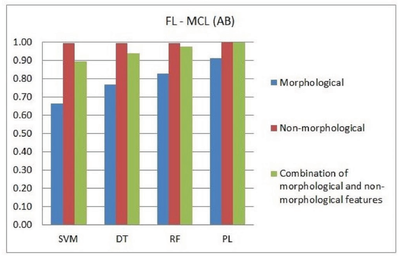
Finally, the integration of ML applications into direct patient care raises various ethical and medico-legal concerns. These issues encom- pass liability in case of medical errors, data privacy and security, the doctor-ML application interaction, comprehension of the capabilities and limitations of ML, as well as patient understanding of ML utilization in healthcare and its potential effects. To address these concerns, the development of an ethical framework specific to the clinical context of ML applications in healthcare is crucial. Furthermore, ML algorithms should be employed as aids to healthcare practitioners, complementing their role rather than replacing it. Doctors should undergo training and education on ML applications, including awareness of the variables considered and the sensitivity and specificity of the algorithms for spe- cific tasks. Through the effective resolution of these issues, the successful integration of ML algorithms into the care of CLL patients can be accomplished.



(a)



(b)



(c)

Fig. 6. The AUC metric obtained with the AB method and the classifiers with the investigated lesions groups: (a) CLL-FL; (b) CLL-MCL and (c) FL-MCL “Reproduced with permission from do Nascimento et al., Computer Methods and Programs in Biomedicine; Published by Elsevier, 2018” [34].

their resources toward other critical aspects of clinical practice requiring human judgment, intuition, and empathy, such as patient care and research. In the realm of hematological malignancies, ML algorithms hold promise for improving patient care through activities such as screening, early diagnosis, risk stratification, treatment recommendations, and prognosis prediction [43–45]. Specifically, our review highlights the

REFERENCES :

[1] Strati P, Jain N, O’Brien S. Chronic lymphocytic Leukemia: diagnosis and treatment. Mayo Clin Proc 2018;93(5):651–64.
[2] Ghia P, Caligaris-Cappio F. Monoclonal B-cell lymphocytosis: right track or red herring? Blood 2012;119(19):4358–62.
[3] Siegel RL, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73(1):17–48.
[4] Yao Y, et al. The global burden and attributable risk factors of chronic lymphocytic leukemia in 204 countries and territories from 1990 to 2019: analysis based on the global burden of disease study 2019. Biomed Eng Online 2022;21(1):4.
[5] Hallek M, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131(25):2745–60.
[6] Shadman M. Diagnosis and treatment of chronic lymphocytic leukemia: a review. JAMA 2023;329(11):918–32.
[7] Rai KR, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):
219–34.
[8] Binet JL, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48(1):198–206.
[9] Shanafelt TD. Predicting clinical outcome in CLL: how and why. Hematology Am
Soc Hematol Educ Program 2009:421–9.
[10] Walter W, et al. Artificial intelligence in hematological diagnostics: game changer or gadget? Blood Rev 2023;58:101019.
[11] Elsabagh A, et al. Artificial intelligence in sickle disease. Blood Rev 2023:101102.
[12] Ferih K, et al. Applications of artificial intelligence in Thalassemia: a comprehensive review. Diagnostics (Basel) 2023;13(9).
[13] Elhadary M, et al. Applications of machine learning in chronic myeloid Leukemia. Diagnostics (Basel) 2023;13(7).
[14] Shouval R, et al. Machine learning and artificial intelligence in haematology. Br J Haematol 2021;192(2):239–50.
[15] Elsayed B, et al. Applications of artificial intelligence in Philadelphia-Negative myeloproliferative neoplasms. Diagnostics (Basel) 2023;13(6).
[16] Elshoeibi AM, et al. Applications of artificial intelligence in Thrombocytopenia. Diagnostics (Basel) 2023;13(6).
[17] Zhang H, et al. Differential diagnosis of hematologic and solid tumors using targeted transcriptome and Artificial Intelligence 2023;193(1):51–9.
[18] Zhu Y, et al. Identification of SiX Diagnostic Biomarkers for Chronic Lymphocytic Leukemia Based on Machine Learning Algorithms2022; 2022. p. 3652107.
[19] Xia D, et al. DNA methylation-based classification of small B-Cell Lymphomas: a proof-of-principle study 2021;23(12):1774–86.
[20] Iman M, Arabnia HR, Rasheed K. A review of deep transfer learning and recent advancements 2023;11(2):40.
[21] Abhishek A, et al. Automated detection and classification of leukemia on a subject- independent test dataset using deep transfer learning supported by Grad-CAM visualization83; 2023.
[22] Dese K, et al. Accurate machine-learning-based classification of leukemia from blood smear images. Clin Lymphoma Myeloma Leuk 2021;21(11):e903–14.
[23] Mohammed EA, et al. Toward leveraging big value from data: chronic lymphocytic leukemia cell classification 2017;6(1).
[24] Simonson PD, Lee AY, Wu D. Potential for process improvement of clinical flow cytometry by incorporating real-time automated screening of data to expedite
addition of antibody panels 2022;157(3):443–50.
[25] Ng DP, Zuromski LM. Augmented human intelligence and automated diagnosis in flow cytometry for hematologic malignancies 2021;155(4):597–605.
[26] Zhao M, et al. Hematologist-level classification of mature B-cell neoplasm using
deep learning on multiparameter flow cytometry data 2020;97(10):1073–80.
[27] Silva M, et al. Lymphocyte volume and conductivity indices of the haematology
analyser Coulter® GEN.STM in lymphoproliferative disorders and viral diseases 2006;28(1):1–8.
[28] Park SH, et al. Sepsis affects most routine and cell population data (CPD) obtained using the Sysmex XN-2000 blood cell analyzer: neutrophil-related CPD NE-SFL and
NE-WY provide useful information for detecting sepsis. Int J Lab Hematol 2015;37 (2):190–8.
[29] Jung YJ, et al. Evaluation of cell population data on the UniCel DXH 800 coulter
cellular analysis system as a screening for viral infection in children. Int J Lab Hematol 2012;34(3):283–9.
[30] Furundarena JR, et al. The utility of the Sysmex XE-2100 analyzer’s NEUT-X and
NEUT-Y parameters for detecting neutrophil dysplasia in myelodysplastic
syndromes. Int J Lab Hematol 2010;32(3):360–6.
[31] Haschke-Becher E, et al. A new high-throughput screening method for the detection of chronic lymphatic leukemia and myelodysplastic syndrome. Clin
Chem Lab Med 2008;46(1):85–8.
[32] Haider RZ, et al. Beyond the in-practice CBC: the research CBC parameters-driven machine learning predictive modeling for early differentiation among leukemias 2022;12(1).
[33] Steinbuss G, et al. Deep learning for the classification of non-Hodgkin Lymphoma on histopathological images 2021;13(10).
[34] Do Nascimento MZ, et al. Lymphoma images analysis using morphological and non-morphological descriptors for classification163; 2018. p. 65–77.
[35] Akkus Z, et al. Deep learning for brain MRI segmentation: state of the art and future
directions. J Digit Imaging 2017;30(4):449–59.
[36] Ehteshami Bejnordi B, et al. Using deep convolutional neural networks to identify and classify tumor-associated stroma in diagnostic breast biopsies. Mod Pathol
2018;31(10):1502–12.
[37] Wang X, et al. Searching for prostate cancer by fully automated magnetic resonance imaging classification: deep learning versus non-deep learning. Sci Rep 2017;7(1):15415.
[38] Shin HC, et al. Deep convolutional neural networks for computer-aided detection:
CNN architectures, dataset characteristics and transfer learning. IEEE Trans Med Imaging 2016;35(5):1285–98.
[39] Janowczyk A, Madabhushi A. Deep learning for digital pathology image analysis: a comprehensive tutorial with selected use cases. J Pathol Inform 2016;7:29.
[40] Zhang J, et al. Classification of digital pathological images of non-Hodgkin’s
lymphoma subtypes based on the fusion of transfer learning and principal component analysis 2020;47(9):4241–53.
[41] Fˇer´e M, et al. Implementation of a classification strategy of Raman data collected in
different clinical conditions: application to the diagnosis of chronic lymphocytic leukemia 2020;412(4):949–62.
[42] Filzmoser P, Liebmann B, Varmuza K. Repeated double cross validation 2009;23 (4):160–71.
[43] Obstfeld AE. Hematology and machine learning. J Appl Lab Med 2023;8(1):
129–44.
[44] Muhsen IN, et al. Machine learning applications in the diagnosis of benign and
malignant hematological diseases. Clin Hematol Int 2021;3(1):13–20.
[45] Radakovich N, Nagy M, Nazha A. Artificial intelligence in hematology: current challenges and opportunities. Curr Hematol Malig Rep 2020;15(3):203–10.
[46] Ngiam KY, Khor IW. Big data and machine learning algorithms for health-care delivery. Lancet Oncol 2019;20(5):e262–73.
[47] Hedderich DM, et al. Artificial intelligence tools in clinical neuroradiology:
essential medico-legal aspects. Neuroradiology 2023;65(7):1091–9.
[48] Eckardt J-N, et al. Application of machine learning in the management of acute myeloid leukemia: current practice and future prospects. Blood Adv 2020;4(23): 6077–85.