SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL
DOI:http:/dx.doi.org/10.30733/std.2024.01749
Selcuk Med J 2024;40(3): 146-151

OPEN

DERLEME / REVIEW

Artificial Intelligence Studies and Data Analysis in Chronic Lymphocytic Leukemia: A Current Review

Kronik Lenfositik Lösemide Yapay Zeka Çalışmaları ve Veri Analizleri: Güncel Derleme

Can Ozlu[1], Aycan Acet[2], Berrin Korkut[3], Cumali Yalcin[4]

[1]Kütahya Health Science University, School of Medicine, Department of Internal Medicine, Clinic of Hematology, Kütahya, Türkiye
[2]Kütahya Health Science University, School of Medicine, Department of Internal Medicine, Kütahya, Türkiye
[3]Kütahya Health Science University, School of Medicine, Medicine Student, Kütahya, Türkiye
[4]Kütahya City Hospital, Clinic of Hematology, Kütahya, Türkiye

ÖZET

Yapay zeka, bilgiyi bir nesne olarak kabul eden, ondan bilgi çıkaran, bu bilginin ifade edilme yollarını araştırıp analiz eden ve daha sonra bu yöntemleri insanın entelektüel faaliyetini simüle etmek için uygulayan bir bilgi projesi olarak tanımlanabilir. Yapay zekanın, makine öğrenimi ve derin öğrenme dahil olmak üzere tıbbi uzmanlıklara çok benzeyen çeşitli alt alanları vardır. Derin öğrenme algoritmalarının veya çeşitli işlem katmanlarına sahip yapay sinir ağlarının, karmaşık doğrusal olmayan giriş-çıkış etkileşimlerini simüle etme ve düşük seviyeli veri temsillerinden desen tanımlama ve özellik çıkarımı gerçekleştirme kapasitesi, bu alandaki ilerlemeden büyük ölçüde sorumludur. Hematolojide yapay zeka son yıllarda dramatik ilerleme kaydetti. Ancak bu ilerlemenin büyük bir kısmı görünüşte dağınıktır ve bir hematoloğun takip etmesi zor olan tutarlı bir yapıdan yoksundur. Kronik lenfositik lösemi (KLL) ileri yaşlarda ortaya çıkan özel bir hematolojik kanser türüdür. Hastalığın patogenezinde monoklonal B hücrelerinin kanda, kemik iliğinde, dalakta ve lenf düğümlerinde kontrolsüz ve aşamalı olarak çoğalması sorumludur. KLL'li hastalar son derece değişken klinik seyirlere sahiptir ve genel sağkalım süreleri birkaç aydan on yıllara kadar değişebilir. Hastaların %30'unun hiçbir zaman tıbbi tedavi ihtiyacı olmamaktadır. KLL'nin aşırı heterojenliği göz önüne alındığında, yeni prognostik modellerin geliştirilmesi kaçınılmazdır. Şu anda, giderek artan sayıda araştırma, yapay zeka tabanlı modellerin KLL'yi ne kadar iyi teşhis edebildiğini ve prognozu tahmin edebildiğini göstermektedir. Bu makalede, kronik lenfoid lösemi tanısında yapay zekanın radyoloji, patoloji, genetik, tanısal ve terapötik uygulamalarına özel olarak odaklanarak hematolojide yapay zekanın güncel bir incelemesini sunacağız. Yapay zekanın kronik lenfositik lösemide mevcut en son teknoloji kullanımını ve gelecekteki potansiyel kullanımlarını gösteren seçilmiş makalelerden bir derlemeyi tartışacağız.

Anahtar Kelimeler: Kronik lenfositik lösemi, makine öğrenme, teşhis, yapay zeka

ABSTRACT

Artificial intelligence (AI) is characterized as a knowledge project that views knowledge as an object, draws conclusions from it, investigates and evaluates the forms that knowledge takes, and then uses these techniques to mimic human thought processes. Certain subfields of AI, such as machine learning and deep learning, bear a strong resemblance to medical specializations. The main driver of progress in this field is the ability of deep learning algorithms, or artificial neural networks with multiple processing layers, to simulate intricate nonlinear input-output interactions and to identify patterns and extract features from low-level data representations. AI in hematology has made dramatic progress in recent years. However, much of this progress is seemingly scattered and lacks a coherent structure that is difficult for a hematologist to follow. Chronic lymphocytic leukemia (CLL) is a special type of hematological cancer that occurs in older ages. Uncontrolled and gradual proliferation of monoclonal B cells in the blood, bone marrow, spleen and lymph nodes is responsible for the pathogenesis of the disease. Patients with CLL have extremely variable clinical courses, and overall survival times can range from several months to decades. Thirty percent of patients never need medical treatment. Given the extreme heterogeneity of CLL, the development of new prognostic models is inevitable. Presently, there is a growing body of research demonstrating the effectiveness of AI-based models in diagnosing and determining the prognosis of CLL. In this article, we will present an up-to-date review of AI in hematology, with a special focus on the radiology, pathology, genetics, diagnostic, therapeutic applications of AI from an AI perspective in the diagnosis of CLL, a specialized cancer of hematology that appears in advanced age. We will discuss a selection of selected papers demonstrating the current state-of-the-art use of AI in CLL and its potential future uses.

Keywords: Chronic lymphocytic leukemia, machine learning, diagnosis, artificial intelligence

Geliş Tarihi/Received: 17 May/Mayıs 2024 **Kabul Tarihi/Accepted:** 23 August/Ağustos 2024 **Yayın Tarihi/Published Online:** 27 September/Eylül 2024

Sorumlu Yazar/Corresponding Author: Can Ozlu, Kütahya Health Science University, School of Medicine, Department of Internal Medicine, Clinic of Hematology, Kütahya, Türkiye
e-mail: cozlu20@gmail.com

Atıf yapmak için/ Cite this article as: Ozlu C, Acet A, Korkut B, Yalcin C. Artificial Intelligence Studies and Data Analysis in Chronic Lymphocytic Leukemia: A Current Review. Selcuk Med J 2024;40(3): 146-151

Disclosure: *Author has not a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Artificial intelligence (AI) can be defined as a knowledge project that accepts information as an object, extracts knowledge from it, investigates and analyzes the ways in which it is expressed, and then applies these methods to simulate human intellectual activity (1). AI is the general term for the science of artificial intelligence. In addition to teaching computers to mimic human intelligence, it also employs computers to model human cognitive processes including learning, judgment, and decision-making. AI was initially just a collection of "if-then" rules. Over several decades, it has advanced to solve extremely complex and sophisticated algorithms. AI has several subfields, much like medical specializations, including machine learning (ML) and deep learning (DL).

AI can be applied to situational analysis. After then, the machine can "learn" this data and use the prediction tool in future instances that are similar. It can provide a dynamic shift to clinical decision-making to tailor patient care rather than adhering to a set methodology (2, 3). It has revolutionized labor productivity, reduced labor expenses, optimized the structure of human resources, and created new job demands. It plays an indispensable role in social development (4).

The capacity of deep learning algorithms, or artificial neural networks with several processing layers, to simulate intricate nonlinear input-output interactions and carry out pattern identification and feature extraction from low-level data representations, is largely responsible for this advancement. It has been demonstrated that certain deep learning models can perform on par with or better than current machine learning and quantitative structure-activity relationship (QSAR) approaches for drug development (5-7).

Monoclonal B cells proliferate uncontrollably and progressively in the blood, bone marrow, spleen, and lymph nodes in chronic lymphocytic leukemia (CLL), a mature B-cell neoplasm (8). It is recommended to use flow cytometry to verify the clonality of B cells in peripheral blood. Collectively, CD5, CD19, CD20, and CD23 are surface antigens on B cells expressed by CLL cells. Generally speaking, normal B cells express more of CD19, CD20, and CD79b than surface immunoglobulins (9).

Patients with CLL have extremely varied clinical courses, and their overall survival times might range from several months to decades. Thirty percent of patients never need medical attention. The disease burden and treatment indications are determined using two distinct staging systems: Modified Rai and Binnet. The typical survival in early stage disease (Rai 0 or Binet A) is more than 10 years, while the average survival in advanced stage disease (Rai III-IV or Binet C) is about 2-3 years (10,11). The Chronic Lymphocytic Leukemia-International Prognostic Index (CLL-IPI) has been utilized in risk classification in recent years. It includes genetic data (age, clinical stage, beta-2 microglobulin, IGVH (immunoglobulin heavy chain variable) mutation, 17p deletion, and/or p53 mutation) as well (12).

Given the highly heterogeneous nature of CLL, the development of new prognostic models is inevitable. Presently, there is a growing body of research demonstrating the effectiveness of artificial intelligence-based models in diagnosing and determining the prognosis of CLL. In this article, we will present an up-to-date review of AI in hematology, with a special focus on the radiology, pathology, genetics, diagnostic, therapeutic applications of AI from an AI perspective in the diagnosis of chronic lymphoid leukemia, a specialized cancer of hematology that appears in advanced age.

Literature search strategy

In October 2023, the EMBASE and PubMed/MEDLINE databases were used to conduct a literature search of all papers using CLL machine learning applications. The search technique included terms associated with CLL (such as "chronic lymphatic leukemia," "chronic lymphocytic leukemia," and "CLL") as well as terms related to machine learning (such as "Artificial Intelligence," "machine learning," and "neural network").

Artificial Intelligence Applications in Chronic Lymphocytic Leukemia

Baseline peripheral blood samples were taken from 247 CLL patients who were not receiving treatment at The University of Texas MD Anderson Cancer Center and processed in accordance with the protocol in a prior study. Following established techniques, the somatic mutation status of IGHV genes and ZAP70 (zeta-associated protein 70) expression, as determined by flow cytometry or immunohistochemistry, were evaluated on blood or bone marrow samples. In the study, two experiments ("A" and "B") were subjected to k-medoid clustering using ten distance measurements in accordance with the Döhler hierarchy, with the assumption that this approach may identify prognostic groupings in CLL. Survival analysis employing the Cox analysis model, the log-rank test, and Kaplan-Meier curves was used to evaluate the prognostic efficacy. The results of the analysis showed statistically significant relationships between clusters and significant survival outcomes, which were represented as a "spectrum" of subgroups using multidimensional scaling. This approach identified known binary markers of prognosis and outcome with a high degree of accuracy (13).

A study including 737 treatment-naive CLL patients diagnosed at the Mayo Clinic used inverse probability of censoring weighting (IPCW) as a method for time-to-event data analysis. Along with the traditional logistic regression (LR) model, we used well-known machine learning approaches in our classification study, such as Support Vector Machines (SVM), Random Forests (RF), and Gradient Boosting Machines (GBM). While ML techniques did not yield appreciably better time to first treatment predictions, automated risk stratification via clustering outperformed models created with traditional survival analysis techniques in identifying patients at risk for treatment within a year. Finally, this study suggests a technique that clusters the finite probabilities of predictive ML models to automatically produce distinct risk strata. It has been demonstrated that conventional ML techniques can yield longitudinal prognostic information by adding a clustering

step (14).

For feature selection in genome-scale data sets, Morabito et al. present DeepSHAP Autocoder Filter for Gene Selection (DSAF-GS), a revolutionary deep learning and explainable AI-based method. Using a gene expression profiles database with over 20,000 genes, DSAF-GS was utilized to identify genes that were predictive of the prognosis of 217 cases of chronic lymphocytic leukemia. For additional examination, the top ten genes were chosen. The ten genes that were chosen had a predictive power on time to first treatment (TTFT) in CLL, according to univariate studies in a basic prognostic model that included IGHV mutation status, del(11q) and del(17p), NOTCH1 mutations, beta-2-microglobulin, Rai stage, and B-lymphocytosis. Only the genes IGF1R (hazard ratio [HR] 1.41, 95% CI 1.08-1.84, P=0.013), COL28A1 (HR 0.32, 95% CI 0.10-0.97, p=0.045), and QTRT1 (HR 7.73, 95% CI 2.48-24.04, p<0.001) showed a significant association with TTFT in multivariate analyses when combined with the prognostic factors of the basic model. Additionally, the model's goodness of fit increased, suggesting that it performed better than the baseline prognostic model (c^2 = 20.1, p = 0.002). DSAF-GS concluded by identifying the gene group critical to the prognosis of CLL and offering recommendations for future paths in biomolecular research (15).

Vergnolle et al. used data recording to classify 654 patients (446 peripheral blood samples, 193 bone marrow samples, and 15 pleural fluid samples) and generated clinical diagnoses. B-cell neoplasms with various diagnoses (CLL, lymphoplasmacytic lymphoma (LPL), marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL)) were designated based on this patient classification. Combining biological knowledge with mathematical techniques like regression tree (CART) models and classification algorithms produced a decision tree that correctly detects mature B-cell neoplasms. The CD5, CD200, FMC7, and CD43 were evaluated in this intricate decision tree. The Random Forest method was used to examine the outcomes. The primary finding regarding CLL is that users can diagnose and classify adult B-cell neoplasms with ease using the decision tree, which is also suggested for this purpose. Just three markers CD5, CD43, and CD200 integrated into AI research are sufficient to identify the majority of CLL cases. There's a chance that this research will boost productivity (16). Hoffman et al. examined the prediction power of explainable artificial intelligence (XAI) techniques to anticipate results by examining multiparameter flow cytometry (MPFC) data from peripheral blood samples belonging to 157 individuals with chronic CLL. Furthermore, results based on unique cell populations in MPFC dot plots were expected to be shown by XAI. Cell populations that were predicted to have poor outcomes (death, failure of first-line treatment) were identified using the ALPODS XAI algorithm. Through the use of receiver operating characteristic (ROC) curves, the diagnostic capacity of each XAI population was evaluated. ROC (AUC; 0.95 vs. 0.78) showed that 17 populations in the trial were better able to classify clinical outcomes than CLL-IPI. A population of CD4+ T cells with XAI (AUC; 0.78; 95% CI 0.70-0.86; p <0.0001) was the most effective single classifier. It was found that patients' prognosis was bad when their CD4+ T lymphocytes were low. The inclusion of CD4+ T cells increased the CLL-IPI's predictive power (AUC 0.83; 95% CI 0.77-0.90; p < 0.0001). Finally, the ALPODS XAI algorithm found highly predictive cell populations in CLL, indicating that it could aid in enhancing conventional prognostic scores like IPI (17).

Using digital microscopy to assess lymphocyte morphology, Marionneaux et al. conducted a retrospective analysis to examine the incidence of prognostic indicators in patients with atypical CLL (aCLL) and T-cell CLL (tCLL). The presence of trisomy 12, non-mutant IgVH, and CD38 expression-all linked to a poor prognosis-was found to be statistically significant as a prognostic marker in the aCLL group, but 13q14 deletions were less common than in the tCLL group (18).

Masic et al. used a decision tree approach to assess immunophenotype-based prognostic variables in 34 individuals with CLL. In this study, the C4.5 decision tree was simultaneously presented with 33 parameters (serum concentration of sCD23 and 32 distinct phenotypic characteristics). The most informative parameters were then identified, and a method was employed to categorize CLL patients based on the modified Rai staging system. As a result, it was demonstrated that the prognosis of CLL was influenced by the following two significant processes: 1. functionally compromised and imbalanced CD4 T-cell subpopulations in peripheral blood; 2. dysregulated function of the CD23 gene in B-cells and the appearance of sCD23 broken product in serum (19).

An AI model was developed using raw multiparameter flow cytometry data from 20,622 routine diagnostic samples, both diseased and healthy. It was able to distinguish between seven subtypes of mature B-cell neoplasms and distinguish between diseased and healthy samples. Seventy percent of instances could be classified by the AI model at a 95% CI or higher. It was suggested that more samples would be used to train AI to produce better outcomes, particularly for uncommon subtypes (20).

Salama et al. assessed whether an AI model might enhance diagnostic process in a clinical laboratory setting and how well it performed in identifying minimal residual disease (MRD) in 202 post-treatment CLL patients. Using ten color MRD panels of CLL patients who had received treatment, deep neural networks (DNNs) were trained. The MRD's "true" classification was confirmed by expert study. The results showed that DNN and expert analysis had a strong association (r > 0.999; Passing-Bablok slope = 0.997 (95% CI: 0.988-0.999) and intercept = 0.001 (95% CI: 0.000-0.001)). MRD was dramatically lowered with DNN, going from 15 minutes per case in manual processing to 12 seconds per case (21).

AI models were created utilizing 682 whole blood count data (88 verified CLL patients and 594 control groups) in a prior study by Padmanabhan et al. It has been proven that whole blood count-oriented AI models can improve patient outcomes and provide timely medical care while using less resources and at a lower cost (22).

4149 CLL patients' records from the Danish National CLL registry between 2004 and 2017 were examined by Agius et al. One of the main issues for CLL patients is infections. Nevertheless, there aren't many infection prediction models. The CLL therapy-Infection Model (CLL-TIM), which was validated in both internal and external cohorts, was created in that study. It identifies individuals at risk of infection or CLL therapy within two years of diagnosis. Using information from 4,149 CLL patients, 28 ML algorithms make up CLL-TIM. With 72% precision and 75% recall, the model can handle various types of data, including the high percentage of missing data that is typical in real-world scenarios. In order eliminate worries over the application of complicated ML algorithms in clinical settings, CLL-TIM offers explainable predictions for every CLL patient using uncertainty estimates and customized risk variables (23).

El Hussein et al. performed nuclear segmentation using stain-normalization from digitized whole slide images of lymph node biopsies (125 patients; 44 CLL, 34 accelerated CLL, 47 richter transformation of diffuse large B-cell lymphoma (RT-DLBCL)) from 2009 to 2021 to differentiate CLL, accelerated CLL, RT. They then used nuclear filtering to exclude overlapping nuclei with software. Cell nuclear size histogram by measuring nuclear size was the next application. Next, examined samples based on nuclear density and nuclear color components were further investigated by cellular density analysis and distance proximity analysis of cells to obtain their final markers. Finally, the synergistic effects of sequentially adding these biomarkers were evaluated to enhance diagnostic accuracy. El Hussein et al. suggest that the model of cell identification by nuclear size, nuclear density, cellular density and nearest neighbor distance can be used as artificial intelligence parameters to help in the differentiation and diagnostic evaluation of CLL, accelerated CLL, RT (24).

The difference between richter transformation and accelerated CLL transformation in the natural course of the disease is not easily understood by physicians. Physicians need to perform lymph node biopsy to ensure this awareness, which can be challenging in terms of diagnosis. Current guidelines are limited for differentiating CLL from its progressive forms, these differentiations are subject to the experience of the morphologist, and often the evaluation of limited biopsy specimens is not entirely useful.

In the study of El Hussein et al., artificial intelligence examined pale nodules consisting mostly of small lymphocytes and paraimmunoblasts known as proliferation centers. These nodules were evaluated with heat value histograms in 3 different disease areas with richter transformation, accelerated CLL and typical CLL. After this assessment, according to the heat value histogram score, the values above 0.288 indicate richter transformation, values below 0.228 indicate CLL, and values between 0.228 and 0.288 indicate accelerated CLL. These definitions have been studied in excisional biopsy specimens. This study illustrates that by combining the automation of PC mapping with the study of cell nuclear size and mean nuclear density, it is possible to develop an architecture-based method for objectively determining the extent of proliferation centers in CLL cases with suspected clinical disease progression (25). The lymphocyte identification in the study had an F1 score of 0.97 and a recall value of 0.96. Three distinct morphological categories of lymphocytes that somewhat correspond to distinct stages of the development of the disease were found by cluster analysis. From the same patient, they retrieved cellular morphological data at various time intervals in order to examine the lymphocyte's long-term evolution. The findings indicated some of the same patterns seen in the previously reported cluster analysis. Correlation analysis provided additional evidence for the prognostic value of factors based on cell morphology. In conclusion, this work offered insightful information about the dynamics of lymphocytes in CLL as well as future directions for further investigation. It was found that morphologic changes can be used as a useful tool to assist determine when to intervene most effectively in CLL patients (26).

Zhu et al. examined the genetic traits of CLL patients. Six datasets, including control samples and CLL, were obtained from the Gene Expression Omnibus database for their investigation. R software was utilized to find possible diagnostic biomarkers by least absolute shrinkage and selection operator (LASSO) regression, weighted gene coexpression network analysis (WGCNA), and differential gene expression analysis. Using differential gene expression analysis and WGCNA, a total of 47 differentially expressed genes (DEGs) and 25 potential hub genes were identified. Six hub genes were found to be possible CLL indicators by using LASSO regression analysis based on 14 genes that overlapped between DEGs and putative hub genes: ABCA6, CCDC88A, PMEPA1, EBF1, FILIP1L, and TEAD2. Patients with CLL have aberrant immunological statuses, according to functional analysis (27).

However, the majority of ML prognostic models for CLL overlook a number of factors and non-linear interactions between them. This reduces the accuracy of the models and makes it difficult to predict how the disease will progress (28). DL models, while their great capacity, are typically not readily interpretable, making it challenging to determine the exact cause and effect relationship between the inputs and outcomes. This is an even more serious issue in the field of bioinformatics, where it is essential to comprehend how a gene's expression can impact a patient's course with cancer, for instance, in the context of genomics (29). Recent studies on AI in CLL have some limitations. Some of these include sample size, generalizability, and lack of prospective analysis. In addition, most studies evaluated the predicted data of ML models retrospectively, Future studies should focus on prospectively evaluating the impact of ML models on CLL diagnosis, prognosis, and patient outcomes.

We asked chat GPT about Challenges in Artificial Intelligence Applications in Chronic Lymphocytic Leukemia Treatment*:

Data Access and Quality: AI models require large amounts of high-quality data. However, it can be difficult to find large and reliable data sources due to the rarity of chronic lymphocytic leukemia.

Heterogeneity: CLL demonstrates considerable heterogeneity among patients. Having patients with different genetic profiles, personalities and treatment responses may enable the applicability of a general AI model.

Complex Genetic Factors: The genetic basis of CLL is extremely complex. AI models may be limited in their ability to improve and unravel these genetic interactions.

Treatment Management and Monitoring: CLL treatment often requires personalized therapy. AI may be limited in monitoring, evaluating and recommending treatment responses and side effects.

Ethical Issues: The use of AI may raise ethical issues due to the sensitive production and involvement of genetic information. Personal privacy, information security and genetic counseling should be considered with caution.

Clinical Decision Making Uncertainties: CLL treatment processes are often complemented by performances. AI's ability to cope with performance may be limited in perspective, and full integration into clinical decision-making can be challenging.

Regulation and Standards: Standardization regarding the use of AI in medical practice is not yet fully in place. This may mean a lack of standards or uncertainty of AI calculations in the treatment of CLL.Despite these challenges, AI could be a potential tool to work on CLL and other types of cancer. However, the ethical, legal and scientific data on this technology need to be increased.

CONCLUSION

This review analyzes the use of AI as a prognostic factor in CLL survival, to predict time to first treatment initiation, to identify gene profiles and biomarkers affecting prognostic models, to confirm disease diagnosis and improve treatment efficiency, to assist in the development of the IPI score, to distinguish between atypical CLL and typical CLL on digital microscopic examination. It summarizes the diagnosis, classification, prognosis, infection management and treatment of patients with CLL, emphasizing new prognostic and predictive factors and new treatment strategies in flowcytometric molecule determination, minimal residual disease determination, increasing clinical efficiency. All these reasons show the potential of artificial intelligence applications in all aspects of chronic lymphocytic leukemia, from diagnosis to treatment. We suggest that artificial intelligence should be studied much more in CLL, which is a heterogeneous disease, and it will shed light on new developments.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

Address correspondence to: *Can Ozlu, Kütahya Health Science University, School of Medicine, Department of Internal Medicine, Clinic of Hematology, Kütahya, Türkiye*
e-mail: *cozlu20@gmail.com*

REFERENCES

1. Duan L, Xu L. Business Intelligence for Enterprise Systems: A Survey. IEEE Transactions on Industrial Informatics. 2012;8(3):679–87. Doi: 10.1109/TII.2012.2188804
2. Kaul V, Enslin S, Gross SA. History of artificial intelligence in medicine. Gastrointest Endosc. 2020;92(4):807-12. doi: 10.1016/j.gie.2020.06.040
3. Li D Xu, Yang Lu, Ling Li. Embedding Blockchain Technology into IoT for Security: a Survey, IEEE Internet of Things Journal. 2021;8(13):10452-73. Doi:10.1109/JIOT.2021.3060508
4. Duan N, Liu LZ, Yu XJ, et al. Classification of multichannel surface-electromyography signals based on convolutional neural networks, J. Industr. Integr. Manag. 2019;15:201-6. Doi: 10.1016/j.jii.2018.09.001
5. Lenselink EB, Ten Dijke N, Bongers B, et al. Beyond the hype: Deep neural networks outperform established methods using a ChEMBL bioactivity benchmark set. J Cheminform. 2017;9(1):45. Doi: 10.1186/s13321-017-0232-0.
6. Goh GB, Siegel C, Vishnu A, et al. Chemception: A deep neural network with minimal chemistry knowledge matches the performance of expert-developed QSAR/QSPR models. ArXiv. 2017;abs/1706.06689. Doi: 10.48550/arXiv.1706.06689
7. Unterthiner T, Mayar A, Klambauer G, et al. Deep learning as an opportunity in virtual screening. In: Proceedings of the deep learning workshop at NIPS. Cambridge, MA, United States: MIT Press. 2014;27:1-9.
8. Fidan K. Chronic lymphocytic leukemia. J Curr Hematol Oncol Res. 2023;1(3):59-67. Doi:10.51271/JCHOR-0014.
9. Ozbalak M, Erdogan Ozunal I, Berk S, et al. Killer Immunoglobuline Like Receptor gene analysis in Chronic Lymphocytic Leukemia and its relation with autoimmunity. J Ist Faculty Med 2021;84(2):227-36. Doi:10.26650/IUITFD.2020.0037
10. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.
11. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48(1):198-206. Doi: 10.1002/1097-0142(19810701)48:1<198::aid-cncr2820480131>3.0.co;2-v.
12. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17:779-790. Doi: 10.1016/S1470-2045(16)30029-8
13. Coombes CE, Abrams ZB, Li S, et al. Unsupervised machine learning and prognostic factors of survival in chronic lymphocytic leukemia. J Am Med Inform Assoc. 2020;27(7):1019-27. Doi: 10.1093/jamia/ocaa060
14. Chen D, Goyal G, Go RS, et al. Improved Interpretability of Machine Learning Model Using Unsupervised Clustering: Predicting Time to First Treatment in Chronic Lymphocytic Leukemia. JCO Clin Cancer Inform. 2019;3:1-11. Doi: 10.1200/CCI.18.00137
15. Morabito F, Adornetto C, Monti P, et al. Genes selection using deep learning and explainable artificial intelligence for chronic lymphocytic leukemia predicting the need and time to therapy. Front Oncol. 2023;13:1198992. Doi: 10.3389/fonc.2023.1198992
16. Vergnolle I, Ceccomarini T, Canali A, et al. Use of a hybrid intelligence decision tree to identify mature B-cell neoplasms. Cytometry B Clin Cytom. 2023 Aug 4. doi: 10.1002/cyto.b.22136
17. Hoffmann J, Eminovic S, Wilhelm C, et al. Prediction of Clinical Outcomes with Explainable Artificial Intelligence in Patients with Chronic Lymphocytic Leukemia. Curr Oncol. 2023;30(2):1903-15.

Doi: 10.3390/curroncol30020148.
18. Marionneaux S, Maslak P, Keohane EM. Morphologic identification of atypical chronic lymphocytic leukemia by digital microscopy. Int J Lab Hematol. 2014;36(4):459-64. Doi: 10.1111/ijlh.12167
19. Masić N, Gagro A, Rabatić S, et al. Decision-tree approach to the immunophenotype-based prognosis of the B-cell chronic lymphocytic leukemia. Am J Hematol. 1998;59(2):143-8. Doi: 10.1002/(sici)1096-8652(199810)59:2<143::aid-ajh7>3.0.co;2-y
20. Zhao M, Mallesh N, Höllein A, et al. Hematologist-Level Classification of Mature B-Cell Neoplasm Using Deep Learning on Multiparameter Flow Cytometry Data. Cytometry A. 2020;97(10):1073-80. Doi: 10.1002/cyto.a.24159
21. Salama ME, Otteson GE, Camp JJ, et al. Artificial Intelligence Enhances Diagnostic Flow Cytometry Workflow in the Detection of Minimal Residual Disease of Chronic Lymphocytic Leukemia. Cancers (Basel). 2022;14(10):2537. Doi: 10.3390/cancers14102537
22. Padmanabhan R, El Alaoui Y, Elomri A, et al. Machine Learning for Diagnosis and Screening of Chronic Lymphocytic Leukemia Using Routine Complete Blood Count (CBC) Results. Stud Health Technol Inform. 2023;305:279-82. Doi: 10.3233/SHTI230483
23. Agius R, Brieghel C, Andersen MA, et al. Machine learning can identify newly diagnosed patients with CLL at high risk of infection. Nat Commun. 2020;17;11(1):363. Doi: 10.1038/s41467-019-14225-8
24. El Hussein S, Chen P, Medeiros LJ, et al. Artificial intelligence strategy integrating morphologic and architectural biomarkers provides robust diagnostic accuracy for disease progression in chronic lymphocytic leukemia. J Pathol. 2022;256(1):4-14. Doi: 10.1002/path.5795
25. El Hussein S, Chen P, Medeiros LJ, et al. Artificial intelligence-assisted mapping of proliferation centers allows the distinction of accelerated phase from large cell transformation in chronic lymphocytic leukemia. Mod Pathol. 2022;35(8):1121-5. Doi: 10.1038/s41379-022-01015-9
26. Wang Y, Liu H, Wang H, et al. Enhancing morphological analysis of peripheral blood cells in chronic lymphocytic leukemia with an artificial intelligence-based tool. Leuk Res. 2023 Jul;130:107310. Doi: 10.1016/j.leukres.2023.107310
27. Zhu Y, Gan X, Qin R et al. Identification of Six Diagnostic Biomarkers for Chronic Lymphocytic Leukemia Based on Machine Learning Algorithms. J Oncol. 2022 Nov 24;2022:3652107. Doi: 10.1155/2022/3652107
28. Agius R, Parviz M, Niemann CU. Artificial intelligence models in chronic lymphocytic leukemia–recommendations toward state-of-the-art. Leuk Lymphoma. 2022);63:265–78. Doi: 10.1080/10428194.2021.1973672
29. Graham G, Csicsery N, Stasiowski E, et al. Genome-scale transcriptional dynamics and environmental biosensing. Proc Natl Acad Sci. 2020;117(6):3301–6. Doi: 10.1073/pnas.1913003117