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Artificial Intelligence, Lymphoid Neoplasms, and Prediction of *MYC*, *BCL2*, and *BCL6* Gene Expression Using a Pan-Cancer Panel in Diffuse Large B-Cell Lymphoma

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Abstract: Background: Artificial intelligence in medicine is a field that is rapidly evolving. Machine learning and deep learning are used to improve disease identification and diagnosis, personalize disease treatment, analyze medical images, evaluate clinical trials, and speed drug development. **Methods:** First, relevant aspects of AI are revised in a comprehensive manner, including the classification of hematopoietic neoplasms, types of AI, applications in medicine and hematological neoplasia, generative pre-trained transformers (GPTs), and the architecture and interpretation of feedforward neural networks (multilayer perceptron). Second, a series of 233 diffuse large B-cell lymphoma (DLBCL) patients treated with rituximab-CHOP from the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) was analyzed. **Results:** Using conventional statistics, the high expression of *MYC* and *BCL2* was associated with poor survival, but high *BCL6* was associated with a favorable overall survival of the patients. Then, a neural network predicted *MYC*, *BCL2*, and *BCL6* with high accuracy using a pan-cancer panel of 758 genes of immuno-oncology and translational research that includes clinically relevant actionable genes and pathways. A comparable analysis was performed using gene set enrichment analysis (GSEA). **Conclusions:** The mathematical way in which neural networks reach conclusions has been considered a black box, but a careful understanding and evaluation of the architectural design allows us to interpret the results logically. In diffuse large B-cell lymphoma, neural networks are a plausible data analysis approach.



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Keywords: artificial intelligence; machine learning; artificial neural networks; lymphoma; hematological neoplasia; immuno-oncology; *MYC*; *BCL2*; *BCL6*; diffuse large B-cell lymphoma

1. Introduction

1.1. Classification of Hematopoietic Neoplasms

The current classification of hematopoietic neoplasms integrates data from several sources, including histological features, immunophenotype, molecular pathology, and clinical features [1]. Therefore, there is a consensus between pathologists, hematologists, oncologists, geneticists, and bioinformaticians [1–4]. The classification can be divided into myeloid neoplasms, lymphoid neoplasms, and other categories, such as mastocytosis and histiocytic/dendritic neoplasms [1,5].

Myeloid neoplasms derive from progenitor cells from the bone marrow and can differentiate into erythrocytes, granulocytes, monocytes, and megakaryocytes. They include myeloproliferative neoplasms, such as chronic myeloid leukemia, acute myeloid leukemia, and myelodysplastic syndromes [1,5].

Lymphoid neoplasms originate from B lymphocytes and T lymphocytes. They include precursor B- and T-cell lymphoid neoplasms (acute lymphoblastic leukemia/lymphoma), mature B-cell neoplasms, such as chronic lymphocytic leukemia, follicular lymphoma, diffuse large B-cell lymphoma, and multiple myeloma; mature T or natural killer (NK) cell neoplasms, such as peripheral T-cell lymphoma (PTCL); and Hodgkin lymphoma.

Hodgkin lymphoma is characterized by a mixed inflammatory cell background that includes a minority of neoplastic cells, known as Reed–Sternberg cells, and their variants, which are derived from germinal or post-germinal centers [1,5]. Figures 1 and 2 show a summarized version of the classification of hematopoietic neoplasms and characteristic histological images.

Myeloid neoplasms

Myeloproliferative neoplasms

- Chronic myeloid leukemia
- Classic BCR::ABL1-negative MPNs (Polycythemia vera (PV), Essential thrombocythemia (ET), Primary myelofibrosis (PMF))
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia (CEL)
- Myeloproliferative neoplasm, unclassifiable

Myelodysplastic neoplasms/syndromes (MDS)

Acute myeloid leukemia

Myeloid neoplasms with mutated *TP53*

Lymphoid neoplasms

Precursor lymphoid neoplasms

- B cell acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL)
- T cell acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL)

Mature B cell neoplasms

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Lymphoplasmacytic lymphoma (LPL)
- Monoclonal gammopathies
- Plasma cell neoplasms
- Hairy cell leukemia
- Marginal zone lymphoma (MZL)
- Follicular lymphoma
- Mantle cell lymphoma (MCL)
- Diffuse large B cell lymphoma (DLBCL)
- High-grade B cell lymphomas (Burkitt lymphoma (BL), Other high-grade B cell lymphomas)

Hodgkin lymphoma (HL)

- Classic HL (cHL) (Nodular sclerosis cHL, Mixed cellularity cHL, Lymphocyte-rich cHL, Lymphocyte-depleted cHL)
- Nodular lymphocyte-predominant HL (NLPHL)

Mature T cell or NK cell lineage

- Peripheral T cell lymphoma (PTCL) (Peripheral T cell lymphoma, NOS; Anaplastic large cell lymphoma (ALCL); Follicular helper T cell lymphoma; Extranodal NK/T cell lymphoma, nasal type; Subcutaneous panniculitis-like T cell lymphoma; Hepatosplenic T cell lymphoma; Primary intestinal T cell lymphomas)
- Primary cutaneous peripheral T cell lymphomas
- Adult T cell leukemia-lymphoma (ATL)
- T cell large granular lymphocyte (LGL) leukemia
- T cell prolymphocytic leukemia
- NK cell large granular lymphocyte (LGL) leukemia
- Aggressive NK cell leukemia

Other categories

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; Mastocytosis; Histiocytic/dendritic neoplasms; and others

Figure 1. Classification of hematopoietic neoplasms. This figure shows a simplified version of the classification with the most frequent and/or characteristic lymphoma subtypes.

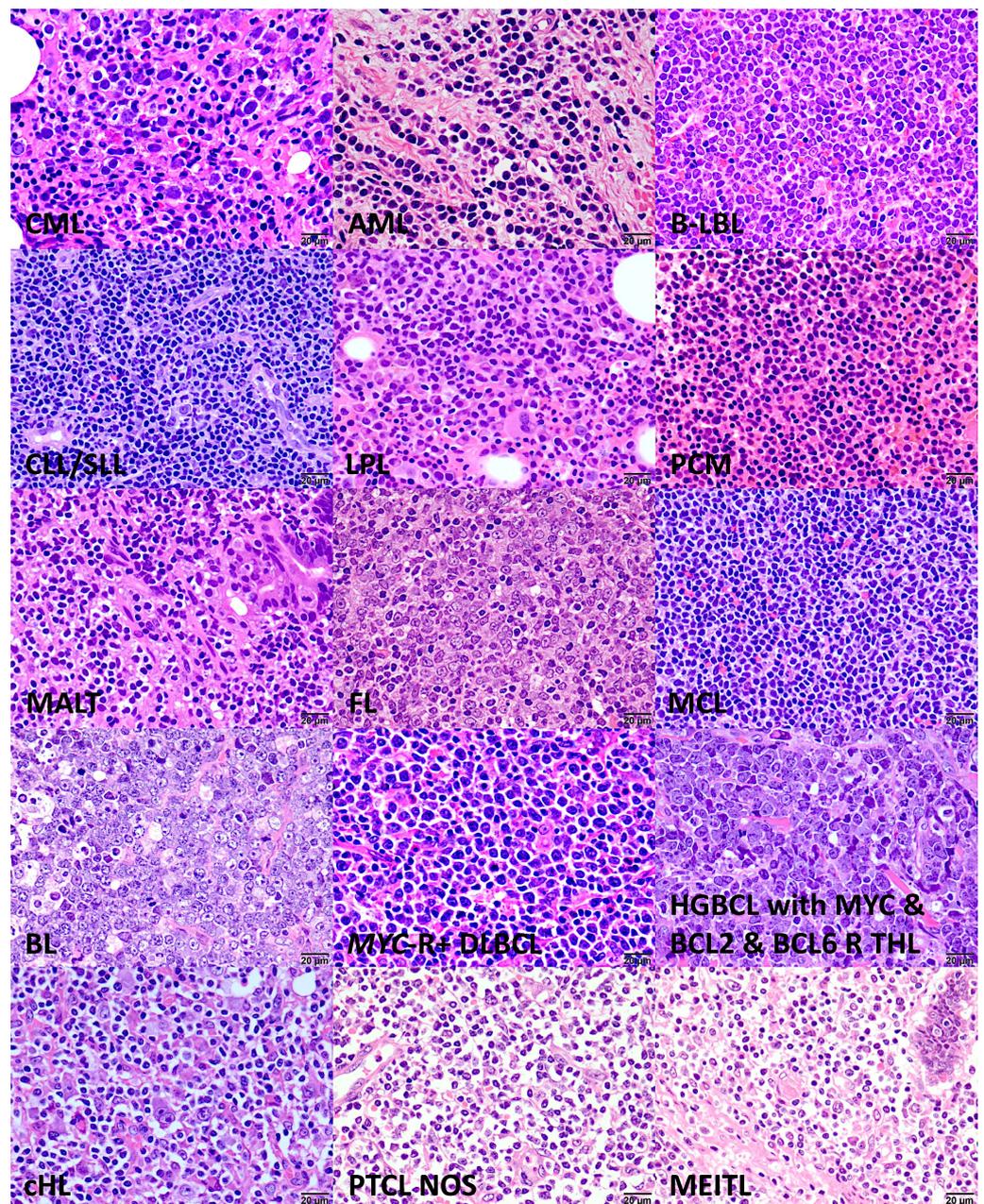


Figure 2. Histological images of lymphoma subtypes (Hematoxylin and Eosin staining; original magnification 400×). Chronic myeloid leukemia (CML), acute myeloid leukemia (AML), B lymphoblastic lymphoma (B-LBL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), lymphoplasmacytic lymphoma (LPL), plasma cell myeloma (PCM), mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL) with *MYC* rearrangement (*MYC*-R+), high-grade B-cell lymphoma with *MYC*, *BCL2*, and *BCL6* rearrangement (triple-hit lymphoma (THL)), classical Hodgkin lymphoma (cHL), peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).

1.2. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent non-Hodgkin lymphomas (NHLs) and mature B-cell neoplasms, accounting for around 20–25% of NHLs. DLBCL is a heterogeneous disease and has morphologic, genetic, and biologic characteristics [1,5].

The typical clinical presentation is a rapidly enlarging mass in the neck or abdomen. Extranodal involvement is common with high LDH levels, and “B” symptoms are present in 30% of the patients. Advanced stage III/IV is found in 60% of cases [1,5].

DLBCL arises from B lymphocytes of the germinal center of follicles or the post-germinal zone [1,5]. The pathogenesis is multifactorial and includes aberrant *BCL6* expression, *TP53* downregulation, somatic hypermutation, *BCL2* and *MYC* overexpression, immune evasion by changes in the tumor immune microenvironment and immune checkpoint, and abnormal lymphocyte trafficking [5]. Based on the cell of origin classification and gene expression profiling, DLBCL can be divided into germinal center B-cell type (GCB), activated B-cell type (ABC), and unclassified (UNC) [5–12].

This diagnostic category includes other separate subtypes, such as T-cell/histiocyte-rich large B-cell lymphoma, primary DLBCL of the mediastinum, intravascular large B-cell lymphoma, Epstein–Barr virus-positive large B-cell lymphoma, primary DLBCL of the central nervous system, etc. [1]. Therefore, DLBCL is not a single disease but a collection of morphologically, genetically, and clinically different diseases [3].

The category high-grade B-cell lymphomas (HGBCLs) included the HGBCL, NOS, and HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements (DH or triple-hit [TH]) [1]. Further studies have supported the differentiation between HGBCL-DH-*BCL2*, GCB-DLBCL, NOS, and HGBCL-DH-*BCL6* [3]. HGBCL and NOS remain a diagnosis of exclusion of cases that are not HGBCL-DH and have intermediate-size cells, often with blastoid or Burkitt-like cytology, but they lack characteristics of DLBCL or Burkitt lymphoma [3]. Of note, more detailed descriptions are found in the publications of the currently updated lymphoma classification [3,4].

This histological variability of DLBCL is shown in Figure 3.

1.3. Types of Artificial Intelligence

Artificial intelligence (AI) is a discipline of data analysis that combines the information present in datasets with information technology and data processing methodology to solve problems. AI includes machine learning and deep learning methods that can make predictions (outputs) based on several predictors (inputs).

There are several definitions and subtypes of AI. The most commonly used AI is weak AI or narrow AI (ANI), which aims to solve specific and concrete problems, such as autonomous driving vehicles. Conversely, strong AI emulates the human mind. Within strong AI, two subtypes are defined. (1) Artificial general intelligence (AGI) equals the human mind, including awareness of oneself and the environment. AGI manages to identify problems, learn how to solve them, and make early plans to recognize and address emerging issues. (2) Artificial superintelligence (ASI) is more advanced than human intellect (Figure 4).

1.4. Applications of Artificial Intelligence in Medicine

Nowadays, there are many applications of AI, the most common being speech recognition that transforms human speech into text, virtual agents that are usually used in customer portals and replace frequently asked questions (FAQs), computer vision that acquires information and meaningful data from images and visual inputs and utilizes convolutional neural networks, recommendation engines that analyze previously data by algorithms and identify data trends, and automated trading in stocks.

AI has numerous applications in the medical field, and in recent years, there has been an exponential increase in the number of publications about AI in medicine. If properly designed and implemented, AI can be beneficial in the practice of medicine, including disease detection and diagnosis, personalized medicine, medical imaging, clinical trial effectiveness, and drug development (Table 1).

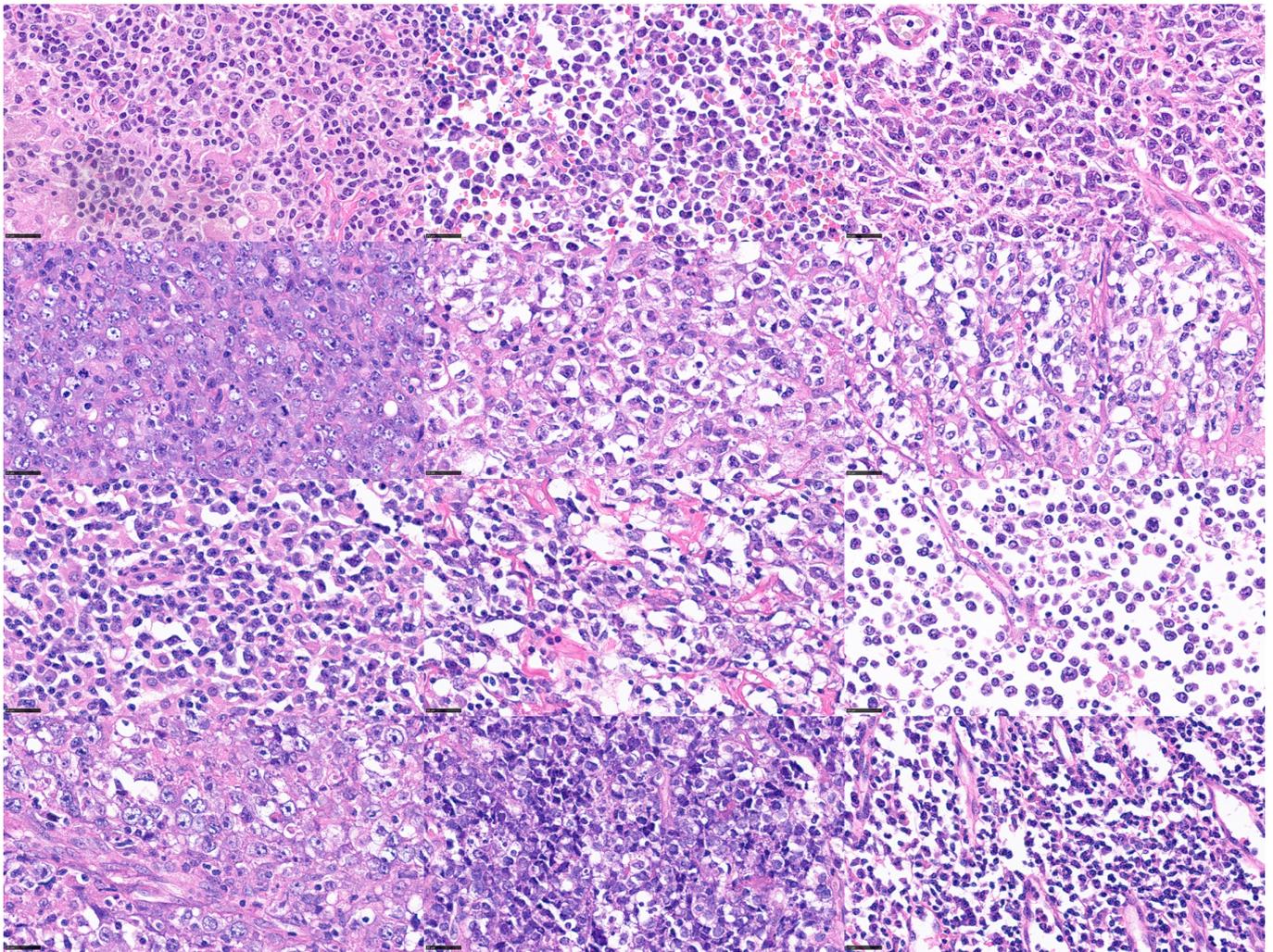


Figure 3. Histological variability of diffuse large B-cell lymphoma (DLBCL). DLBCL is one of the most frequent mature B-cell neoplasms. DLBCL is a heterogeneous disease with different morphologic, genetic, and biologic characteristics. scale bar = 25 μ m.

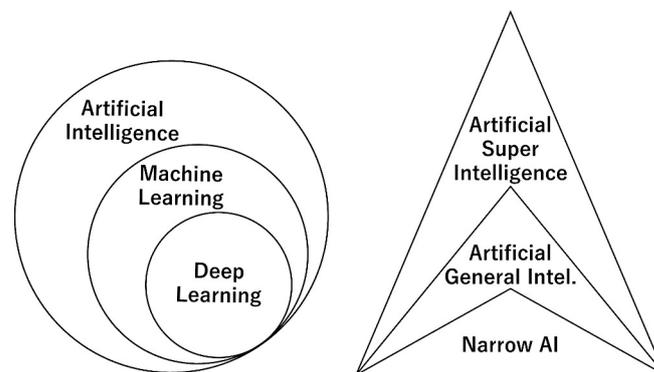


Figure 4. Types of artificial intelligence. Artificial intelligence (AI) is a broad term that includes several analytical techniques, such as machine learning and deep learning (artificial neural networks). AI can also be classified according to comparison with the human intellect, which is also based on an organic neural network, such as narrow AI, artificial general intelligence (AGI), and artificial superintelligence (ASI).

Table 1. Applications of artificial intelligence in the medical field.

1. Disease detection
1.1. Using DNA methylation analysis, a neural network was used for the early detection of hepatocellular carcinoma [13].
1.2. Several biochemical parameters from the cerebrospinal fluid were evaluated using Raman spectroscopy and convolutional neural networks for the early diagnosis of Alzheimer’s disease. The study achieved a good classification accuracy of around 90% and a good correlation with the clinical dementia rating score [14].
1.3. Several machine learning techniques and artificial neural networks were used to predict heart disease at an early stage using clinical, biochemical, and ECG data. In this study, the highest accuracy was achieved using random forests [15].
1.4. A machine learning algorithm was used to classify patients with coronary disease based on 31 features. The classification had an acceptable accuracy for the identification of severe disease [16].
2. Personalized medicine
2.1. A proof-of-concept analysis based on machine learning algorithms was used to classify patients with similar clinical and echocardiographic parameters to optimize the rate of responders to specific cardiac resynchronization therapies [17].
2.2. Several machine learning algorithms were used to identify patients with a higher probability of major depression and anxiety disorder and who would benefit from digital psychiatric interventions [18].
2.3. The Leukemia Artificial Intelligence Program (LEAP) used a machine learning method for the optimal treatment of tyrosine kinase inhibitors in patients with chronic myeloid leukemia [19].
3. Medical imaging
3.1. Mammogram images were evaluated by two radiologists using an AI-assisted method. The study showed that both methods provided comparable results [20].
3.2. Convolutional neural networks were used to detect lung nodules on chest computed tomography in patients with complex lung disease. The accuracy of the neural network was similar to that of experienced radiologists [21].
4. Clinical trials
4.1. A randomized, controlled clinical trial (NCT0438756) used an AI-based system to assist in the evaluation of mammography images. The study concluded that AI-supported screening was comparable to standard double reading [22].
4.2. The clinical trial NCT03954548 compared the evaluation of colonoscopy between a deep learning-assisted method and the standard method in patients undergoing colorectal cancer screening or surveillance. The study found that the AI method had a 2-fold lower misrate of colorectal cancer [23].
4.3. The clinical trial ChiCTR1800018403 used an AI-based system to evaluate endoscopic images for the early detection of gastric cancer. The study showed that the deep convolutional neural network and deep reinforcement learning method correctly predicted cancer lesions but with less performance than the human-based method [24]

1.5. Applications of Artificial Intelligence in Hematological Neoplasia

AI applications in the field of hematopathology have also been developed. An advanced PubMed search that focused on the title and abstracts with the keywords “artificial intelligence” and “lymphoma” resulted in 133 entries. Table 2 shows some of the most relevant studies (because of length restraints, not all valuable studies are shown). The types of AI-based analyses include the evaluation of clinicopathological features, gene expression, mutational landscapes using next-generation sequencing, histological characteristics, and

PE/TC images. The types of hematological neoplasia ranged from leukemia to Hodgkin's lymphoma and non-Hodgkin's lymphoma (Table 2).

Table 2. Applications of artificial intelligence in hematological neoplasia.

1. Molecular pathology	
1.1.	More than 130 genetic markers, gene expression, and microenvironment data were used to classify the seven most frequent non-Hodgkin B-cell lymphomas (B-NHLs) [25].
1.2.	A supervised machine learning method used the expression of 6817 genes to predict the overall survival of patients with diffuse large B-cell lymphoma [8].
1.3.	A series of 123 cases of mantle cell lymphoma were analyzed using gene expression data and several machine learning and artificial neural networks. This research highlighted pathogenic genes and immune–oncology pathways [26].
1.4.	Based on the RNA expression of 1408 genes, next-generation profiling, and machine learning (geometric mean naïve Bayesian algorithm), several diagnostic entities, including carcinomas and lymphoma, were classified with good performance [27].
1.5.	The prognosis of diffuse large B-cell lymphoma was predicted using a feedforward neural network in a series of 414 cases and gene expression data, which correlated to other prognostic markers, including <i>MYC</i> and <i>BCL2</i> [28].
1.6.	Several mature B-cell neoplasms were analyzed using gene expression, immunohistochemical markers, machine learning, and neural networks. The study managed to classify the patients according to their lymphoma subtype and predict their survival. Pan-cancer analysis was also performed [29].
1.7.	Based on 730 immune–oncology genes, overall survival and cell-of-origin subtypes were predicted in a series of 106 cases of diffuse large B-cell lymphoma. The analysis included several machine learning and neural networks [30].
1.8.	Targeted RNA sequencing data obtained from a next-generation sequencing analysis platform were used to classify 418 cases of diffuse large B-cell lymphoma using AI and to predict the survival of the patients [31].
2. Medical imaging	
2.1.	A total of 31 variables were used by an artificial neural network to predict the 5-year recurrence after treatment of 114 patients with Hodgkin's lymphoma [32].
2.2.	A discrimination method that includes convolution and a neural network combined with the least absolute shrinkage and selection operator (LASSO) model was used to analyze the computed tomography data of 276 patients with enlarged cervical lymph nodes. The accuracy of this method was above 86% for lymphoma cases [33].
2.3.	The data of 5275 patients with lung and breast cancer and non-Hodgkin lymphoma were analyzed using an AI-based tool to create a predictive model of risk stratification and early disease detection [34].
2.4.	AI was used to analyze PET/CT images of 382 cases of diffuse large B-cell lymphoma (DLBCL) using only 2 maximum-intensity projection (MIP) images, and it correlated with the prognosis of the patients [35].
2.5.	The focal skeleton/bone marrow uptake (BMU) of FDG-PET/CT images was analyzed using an AI-based method in 201 patients with Hodgkin's lymphoma [36].
2.6.	Anterior segment optical coherence tomography (AS-OCT) images were used to classify between vitreoretinal lymphoma and uveitis in 28 patients using the xgboost python function with good performance (AUC 0.84–0.94) [37].

Table 2. Cont.

3. Histological and cytological images
3.1. Several artificial intelligence-based tools (Phyton SciPy package) were used to model several morphological biomarkers (nuclear size, cell density, and cell distance) to distinguish 125 tissue samples of chronic lymphocytic leukemia (CLL) progression to accelerated CLL (aCLL) or transformation to diffuse large B-cell lymphoma (Richter transformation; RT). The performance of the method was moderate, with an area under the curve (AUC) ranging from 0.66 to 0.94 [38].
3.2. A series of 287 samples from several hospitals were used to predict MYC rearrangement using histological slides of diffuse large B-cell lymphoma. The analysis had a good sensitivity of 0.93 but a low specificity of 0.52 [39].
3.3. Neural networks were used to differentiate between diffuse large B-cell lymphoma and Burkitt lymphoma in a series of 70 cases, including 10,818 images [40].
3.4. Hematoxylin and eosin (H&E) images of 388 cases were analyzed by AI to classify the samples into diffuse large B-cell lymphoma, follicular lymphoma, and reactive lymphoid tissue with high accuracy [41].
3.5. The images of 629 patients with non-Hodgkin lymphoma were analyzed using a convolutional neural network to stratify the patients according to different lymphoma subtypes. The algorithm had an accuracy of 96% [42].
3.6. Histological images of chronic lymphocytic leukemia were analyzed using AI in proliferation centers to identify the accelerated phase and Richter transformation based on nuclear characteristics [43].
3.7. Blood films from 591 samples were used to identify circulating abnormal cells (leukemic and dysplastic cells) [44].

1.6. Paradigm of Generative Pretrained Transformers

Generative pretrained transformers (GPTs) are a type of language model that belongs to the field of generative artificial intelligence [45]. These types of neural networks handle natural language processing analyses and were introduced by Google in 2017 [46]. A transformer is a deep learning architecture based on the multihead self-attention mechanism that learns context and understanding through sequential data analysis. It can translate text and speech in near real time [46]. The architecture is shown in Appendix A.

Transformers have several applications. For example, they can be used to analyze organic molecules for designing antiviral candidate analogs, so this type of analysis can accelerate drug discovery [47]. GPT technology has been applied in the medical field as well, but with a focus on language model capabilities, for example, in radiology reporting. A GPT-4 model processed 100 anonymized radiology reports. For each report, an AI-generated report was created. The AI-generated reports are reliable [45]. GPT-4 was used in data mining and labeling oncologic phenotypes from CT reports [48] and in writing operative notes made by ophthalmic teams following ocular or ophthalmic surgery [49]. Of note, ChatGPT is open access but not open source; it is closed source. Therefore, it is not possible to access or modify the model's source code and it cannot be subjected to peer review.

1.7. Function and Architecture of Multilayer Perceptron

Neural networks can be classified into feedforward neural networks, also known as multilayer perceptrons (MLPs), convolutional neural networks (CNNs), and recurrent neural networks (RNNs). MLPs are the primary focus of this article.

Physiological conditions and disease models can be described by numbers and relationships between numbers. The relationships between numbers are called functions ["f(x)", "x" being the input variable]. The goal of artificial intelligence is to write programs that can understand and predict these models or functions, or rather have the programs write themselves so that they can build their own functions [50].

Function approximation is the process of selecting a defined function among those that are well characterized and that approximates (i.e., matches) a target function (Figure 5A) [50–55]. In computer science, function approximation is used to make predictions and is also used when theoretical models are unavailable and are difficult to compute. Two types of situations can be found. First, a known target function can be approximated by other specific classes of functions that have more advantageous properties. Second, a target function may be unknown and only a series of points are known, and by several techniques, a more appropriate function is approximated [50–55].

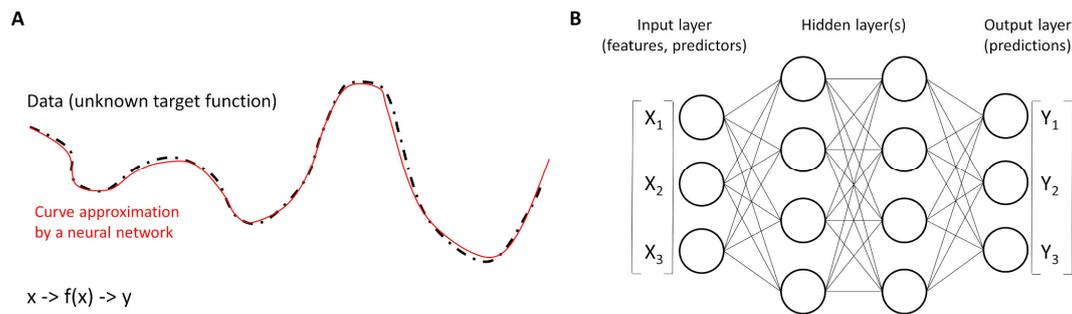


Figure 5. Functions and neural networks. (A) Neural networks work as universal function approximators to different curves of the dataset. In other words, a neural network is a function that approximates an unknown target function. (B) The basic units are called neurons and are organized into layers. The structure of a neural network is characterized by three parts: the input layer that contains the input fields (variables), one or more hidden layers, and an output layer (with a unit or units that represent the target fields). The units are connected by different connection strengths (weights).

Artificial neural networks have the ability of function approximation and build their own functions to approximate physiological conditions and disease models. Functions are “input-output machines”, in which an input set of numbers (i.e., predictors, “ x ”) is taken, and the output (create) is a corresponding set of numbers (“ y ”). The function $[f(x)]$ defines the relationship between these numbers $[(x \rightarrow f(x) \rightarrow y)]$ [56]. Neural networks are used when the definition of the functions that we are trying to approximate is unknown and only the dataset points of inputs and outputs are known. Curve fitting approximates a function that fits the data points, making it possible to accurately predict outputs given inputs that are not in the dataset [57–59]. Therefore, neural networks (NNs) work as a universal function approximator for different curves of datasets [60]. In other words, a network itself is a function that approximates an unknown target function $[f(x) \approx \text{NN}(x)]$.

A simple form of a neural network is the fully connected feedforward network (also known as multilayer perceptron) (Figure 5B). The inputs (X) are called features, and the outputs (Y) are predictions and take the form of vectors (arrays of numbers). The network comprises several simple functions called neurons (Figure 6A). The dimension of a neural network refers to the number of neurons in each layer.

Neurons take many inputs (X) but only produce one output (Y). Each input is multiplied by its own weight (W), and in the equation, one extra weight known as bias is added (W_4) $[=W_1X_1 + W_2X_2 + W_3X_3 + W_4 \text{ (Bias)}]$ (Figure 6A). This weighted sum can be rewritten using linear algebra (Figure 6B). The inputs are included in a vector with an extra one for the bias. The weights are included in another vector. Figure 6(C1) shows an example of the dot product. After addition, the product is passed to an activation function to add nonlinearity to the neural network, such as ReLU. There are other types of activation functions, such as Leaky ReLU and sigmoid (Figure 6(C2)). In a neural network, the output vector is successively fed as inputs to the next layer until the final output. The point is that each neuron is responsible for learning a small piece or feature of the overall function, and a complicated function can be built by combining many neurons. Interestingly, with an infinite number of neurons, any function could be built. During the training of the

network, the values of the weights (parameters) are determined. The aim of the training is to minimize the network’s error (loss), which is a measurement of the difference between the predicted outputs and the real (true) outputs. With time, the loss decreases. The backpropagation algorithm is used to achieve this optimization. Gradient descent is an optimization algorithm that is commonly used to train machine learning models and neural networks. The network improves its predictions until one or more of the stopping criteria are met.

Appendix B describes activation functions in more detail.

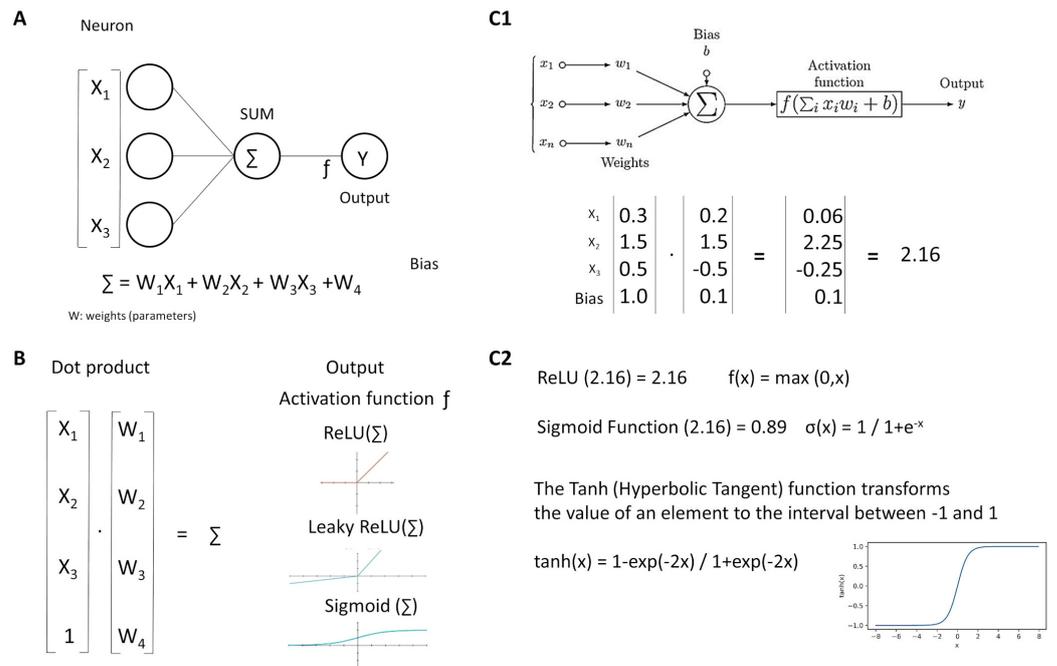


Figure 6. Neurons. Neural networks comprise several simple functions called neurons (A). Each input is multiplied by its weight, all values (including the bias) are added, and the product is transformed by the activation function (B). An example is shown (C1,C2).

1.8. Performance Parameters

The confusion matrix summarizes the predictions of the neural network against the true values of the dataset (Table 3). Accuracy is the percentage of cases correctly classified. Precision determines how accurately the neural network determines the positive outputs; high-precision neural networks are characterized by low false positive percentages. Recall measures the ability to detect positive predictions.

Table 3. Confusion matrix.

Confusion Matrix		True Class	
		Positive	Negative
Predicted class	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

Accuracy = (TP + TN)/(TP + TN + FP + FN).

Precision = TP/(TP + FP).

Recall/Sensitivity/True Positive Rate (TPR) = TP/(TP + FN).

False Positive Rate = FP/(FP + TN) = 1-Specificity.

Specificity = TN/(TN + FP).

F1 Score = TP/(TP + 0.5 (FP + FN)) = 2/(1/Precision) + (1/Recall).

The receiver operating characteristic (ROC) curves are used to compare the performance of the deep learning models. The ROC curve shows the relationship between the true positive rate (sensitivity) and the false positive rate (1-specificity). The area under the curve (AUC) ranges from 0 to 1, and larger AUC values indicate better performance. An AUC of 0.5 indicates no discriminative power (Figure 7).

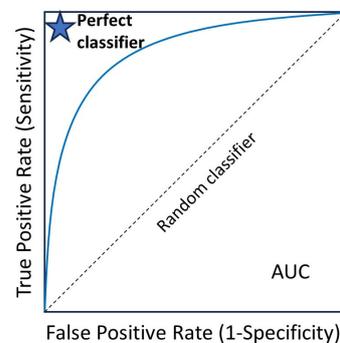


Figure 7. Receiver operating characteristic (ROC) curve. The area under the curve (AUC) ranges from 0 to 1, and larger AUC values indicate better performance. An AUC of 0.5 indicates no discriminative power. The “blue star” indicates the position of the AUC of 1.0.

2. Material and Methods

This section shows an example of a feedforward neural network analysis using a diffuse large B-cell lymphoma dataset.

The diffuse large B-cell lymphoma (DLBCL) dataset GSE10846 from the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) was downloaded from the National Center for Biotechnology Information (NCBI) webpage of the National Library of Medicine (<https://www.ncbi.nlm.nih.gov/>, last accessed on 25 December 2023).

This series is characterized by being very well annotated and reliable. It was last updated on 25 March 2019. This was a retrospective study that included 420 cases. For this study, 233 patients treated with rituximab-CHOP were selected, and 181 patients treated with CHOP were discarded.

RNA was extracted from frozen tissue samples and analyzed using the Affymetrix Human Genome U133 Plus 2.0 Array (HG-U133_Plus_2), which has 20,684 genes. It is a conventional series of DLBCL. All clinicopathological characteristics were described in our previous publication and the original LLMPP [61–63]. In summary, all cases were treated with R-CHOP, all were nodal biopsies, and the male/female ratio was 134/99. The mean age was 60.2 years (± 16.2 STD), with a range from 17 to 92 years, and the cases with more than 60 years were 120/233 (51.5%). According to the cell of origin classification, 107 of 233 (45.9%) cases were germinal center B-cell-like (GCB), 93/233 (85.8%) were activated B-cell-like (ABC), and 33/233 (14.2%) were unclassified. According to the International Prognostic Index (IPI), the score was 1 in 32/164 (19.5%), 2 in 69/164 (42.1%), 3 in 52/164 (31.7%), and 4 in 11/164 (6.7%).

Bioinformatics analysis used normalized and log₂-transformed data. It started by testing if the overall survival of the patients could be stratified using three relevant DLBCL pathogenic genes: *MYC*, *BCL2*, and *BCL6*. The survival of the patients was first tested using a Cox regression analysis. After searching for an adequate cutoff, the survival of the patients was tested using the Kaplan–Meier and log-rank tests.

A multilayer perceptron analysis was performed to predict the expression of *MYC*, *BCL2*, and *BCL6* as qualitative variables (low vs. high, using the same cutoff as that of the Kaplan–Meier analysis). The predictors were a pan-cancer panel of 758 genes for immuno-oncology and translational research that included clinically relevant actionable genes and pathways (Appendix C Figure A2). The neural network used the 758 genes as inputs, and the gene expression values were rescaled using the standardized formula. The dataset partition was the conventional 70% of the training set and 30% of the testing set. The best architecture was searched with a minimum of units in the hidden layer of 1 to a maximum of 1000. The type of training was batch, and the scaled conjugate gradient was an optimization algorithm. More details are provided in the Results section.

The algorithms of MLP are shown in [64].

3. Results

3.1. Neural Networks

This series of R-CHOP-treated DLBCL is a conventional series because the overall survival of the patients can be stratified according to the IPI and clinical stage. The gene expression of *MYC*, *BCL2*, and *BCL6* was correlated with overall survival.

The cutpoints of the gene expression values were searched, making equal percentiles on the scanned cases with two or three cutpoints and interval widths of 33% or 25%, and the survival analysis displayed three or four curves, respectively. Based on the plots, the most adequate cutpoint (i.e., cutoff) was defined as being the most statistically significant, but it also had a reasonable distribution of cases (Table 4).

Table 4. Cutpoints of *MYC*, *BCL2*, and *BCL6* genes.

Gene	Cutpoint	Distribution
<i>MYC</i>	≤12.0	176/233 (75.5%)
	12.01+	57/233 (24.5%)
<i>BCL2</i>	≤10.28	117/233 (50.2%)
	10.29+	116/233 (49.8%)
<i>BCL6</i>	≤12.37	67/233 (28.8%)
	12.38+	166/233 (71.2%)

High *MYC* expression was associated with unfavorable survival; Hazard Risk (HR) = 1.9 (95%CI 1.12–3.28); and $p = 0.019$ (Cox regression). High *BCL2* was also associated with poor prognosis; HR = 1.8 (95%CI 1.0–2.9); and $p = 0.036$. Conversely, high *BCL6* was associated with a favorable prognosis; HR = 0.4 (95%CI 0.2–0.6); and $p < 0.001$ (Figure 8).

A feedforward neural network was used to predict *MYC*, *BCL2*, and *BCL6* expression using a pan-cancer panel of 758 genes for immuno-oncology and translational research that includes clinically relevant actionable genes and pathways. The characteristics and parameters of the different neural networks are detailed in Table 5. The network performance was realistic and between 70% and 90% accuracy. The performance for the prediction of *BCL2* was moderate, with an area under the curve (AUC) of 0.783 and an accuracy of 73.4% for the training and 63.3% for the testing set. The performances of *MYC* and *BCL6* were higher, with AUCs of 0.925 and 0.939, respectively. The accuracies for *MYC* were 86.3% (training) and 88.9% (testing). The accuracies for *BCL6* were 88.2% (training) and 86.1% (testing). The first ten most relevant genes for the prediction of the marker, based on the sensitivity analysis, are also shown (Tables 5–8, Figures 9 and 10).

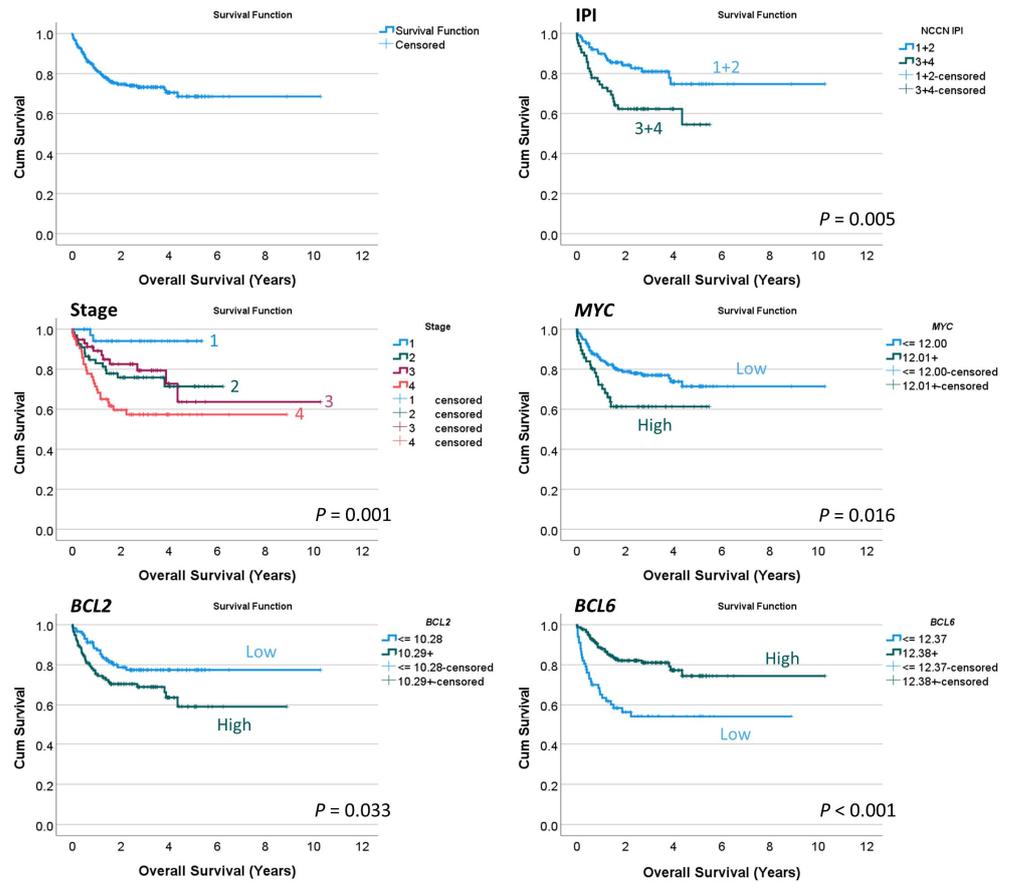


Figure 8. Overall survival analysis. This study used a conventional series of diffuse large B-cell lymphoma (DLBCL), as shown by the International Prognostic Index (IPI) and clinical stage that stratified patients according to survival. By gene expression, high MYC and BCL2 levels were associated with poor overall survival. Conversely, high BCL6 levels were associated with a favorable outcome.

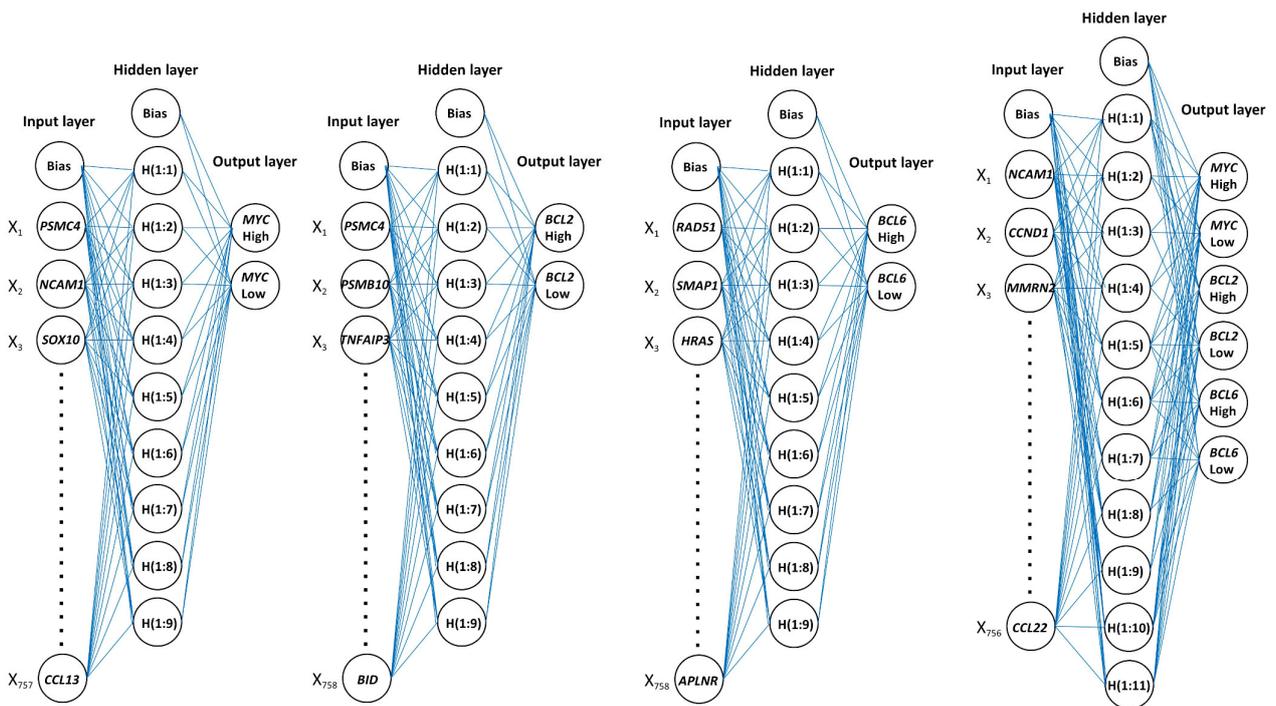


Figure 9. Architecture of neural networks.

Table 5. Neural network characteristics.

	<i>MYC</i>	<i>BCL2</i>	<i>BCL6</i>	<i>MYC, BCL2, and BCL6</i>
Training set	161/233 (69.1%)	173/233 (74.2%)	161/233 (69.1%)	159/233 (68.2%)
Testing set	72/233 (30.9%)	60/233 (35.8%)	72/233 (30.9%)	74/233 (31.8%)
Input layer				
Units	757	757	758	756
Rescaling	Standardized	Standardized	Standardized	Standardized
Hidden layer				
Number	1	1	1	1
Units	9	9	10	11
Activation function	Hyperbolic tangent	Hyperbolic tangent	Hyperbolic tangent	Hyperbolic tangent
Output layer				
Predicted variables	1	1	1	3
Units	2	2	2	6
Activation function	Softmax	Softmax	Softmax	Softmax
Error function	Cross-entropy	Cross-entropy	Cross-entropy	Cross-entropy
Classification percentage correct				
Training set	86.3%	82.2%	88.2%	76.7%, 81.1%, and 83.6%
Testing set	88.9%	63.3%	86.1%	83.8%, 67.6%, and 77.0%
Area under the curve (AUC)	0.925	0.783	0.939	0.81, 0.86, and 0.86
First and most relevant predictors	<i>PSMC4, NCAM1, SOX10, PTPRC, PSMB10, C5AR1, IL6, CBLC, FCGR3B, and MTOR</i>	<i>PSMC4, CNTFR, PSMB10, TNFAIP3, MLH1, CXCR2, FADD, CD7, AREG, and TBXAS1</i>	<i>RAD51, SMAP1, HRAS, SFRP1, LAG3, BTLA, TICAM1, BCL2L1, G6PD, and ICAM2</i>	<i>NCAM1, CCND1, MMRN2, RAD51, TIGIT, THY1, BTLA, ITGA2, HCK, and SFRP1</i>

Table 6. Confusion matrix for *MYC* prediction.

Training Observed	Predicted		Testing Observed	Predicted	
	Low	High		Low	High
Low	115	7	Low	50	4
High	15	24	High	4	14

Accuracy: 86.3% (training), 88.9% (testing).

Table 7. Confusion matrix for *BCL2* prediction.

Training Observed	Predicted		Testing Observed	Predicted	
	Low	High		Low	High
Low	74	16	Low	20	7
High	30	53	High	15	18

Accuracy: 73.4% (training), 63.3% (testing).

Table 8. Confusion matrix for *BCL6* prediction.

Training Observed	Predicted		Testing Observed	Predicted	
	Low	High		Low	High
Low	31	15	Low	17	4
High	4	111	High	6	45

Accuracy: 88.2% (training), 86.1% (testing).

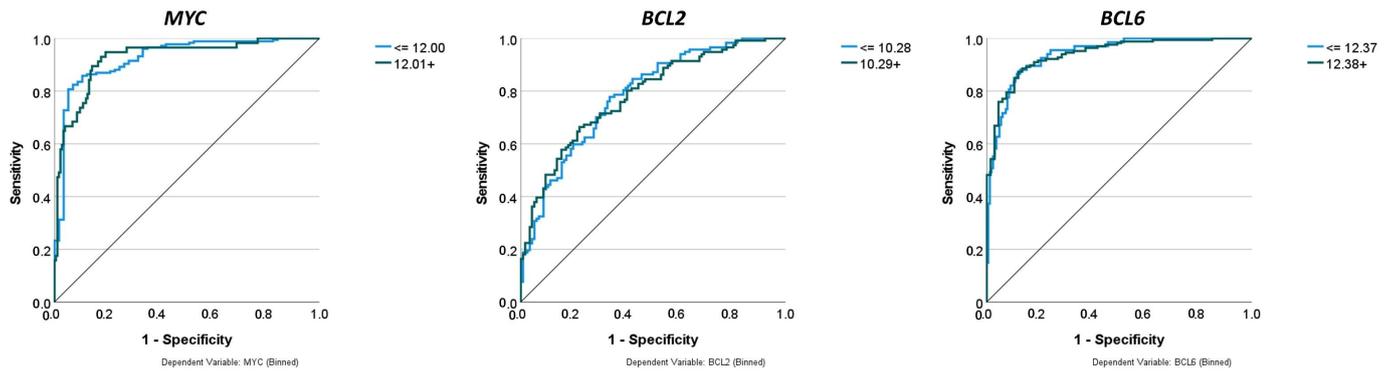


Figure 10. Comparison of performance using receiver operating characteristic (ROC) curves. The neural networks predicted the gene expression of *MYC*, *BCL2*, and *BCL6* as binary variables (high vs. low). The predictors were 758 genes of a pan-cancer panel of immuno-oncology and translational research that includes clinically relevant actionable genes and pathways. The areas under the ROC curves were 0.925, 0.783, and 0.939, respectively.

The parameter estimates of the neural network are shown in [65].

The independent variable importance analysis performs a sensitivity analysis, which calculates the relevance of each predictor in determining the neural network. The analysis is based on the combined training and testing samples, or only on the training sample if there is no testing sample. As a result, it creates a table and a chart displaying the importance and normalized importance of each predictor. The table has been uploaded to Zenodo repositories; please refer to the data availability statement.

3.2. Gene Set Enrichment Analysis (GSEA)

This study used a 758 gene pan-cancer panel of immuno-oncology and translational research, which included clinically relevant actionable genes and pathways as input variables to predict *MYC*, *BCL2*, and *BCL6* expression. The prognostic relevance of this panel was also tested using other conventional bioinformatics techniques, such as GSEA [66–68]. The GSEA was performed on the following biological states (i.e., phenotypes): overall survival (dead vs. alive), *MYC* expression (high vs. low), *BCL2* (high vs. low), and *BCL6* (high vs. low) using the same cutoffs of the neural networks analyses. The primary result of the GSEA is the enrichment score (ES), which reflects the degree to which a gene set is overrepresented at the top or bottom of a ranked list of genes [68]. The leading-edge subset of a gene set is the subset of members that contribute most to the ES. For a positive ES, the leading-edge subset is the set of members that appear in the ranked list prior to the peak score. A negative ES is the set of members that appear subsequent to the peak score [68]. Figure 11 shows the results of the GSEA, with the genes of the leading edges. Additionally, due to the relevance of *MYC*, the GSEA of *MYC* included several gene sets in the molecular signatures database (MSigDB), including hallmark (H), positional (C1), and curated (C2) gene sets. Several associations were found. For example, high *MYC* expression correlated with a high expression of genes associated with protein response, *MYC* targets, DNA repair, oxidative phosphorylation pathways, and chromosome 3p25 locus-associated genes (Figure 12).

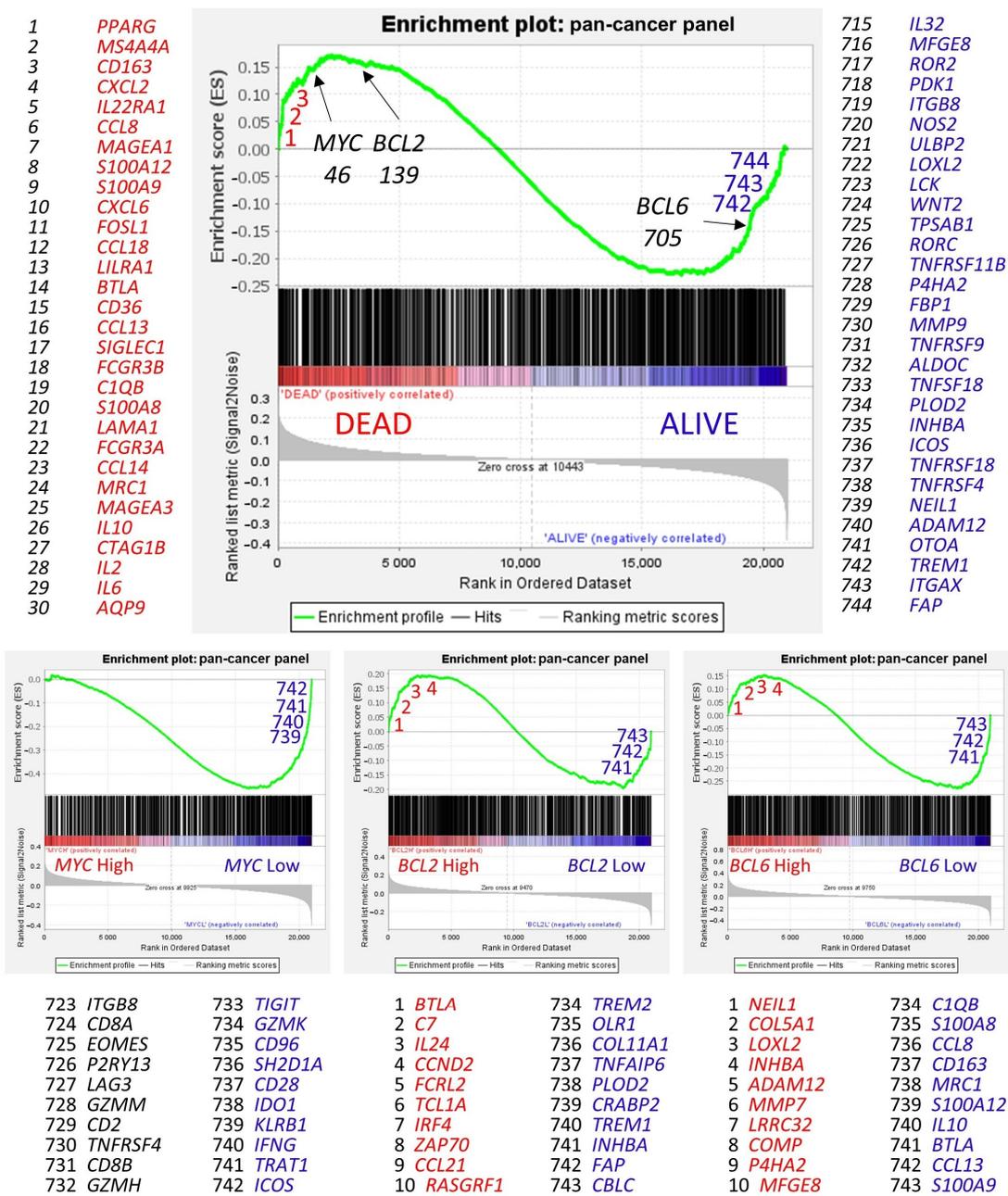


Figure 11. Gene set enrichment analysis (GSEA). Gene set enrichment analysis (GSEA) is a computational method that determines whether an a priori defined set of genes shows statistically significant, concordant differences between two biological states (e.g., phenotypes) [66–68]. GSEA was performed using (i.e., the priori-defined set of genes) the 758 genes of the pan-cancer panel of immuno-oncology and translational research as predictors, which includes clinically relevant actionable genes and pathways. The predicted variables (i.e., phenotypes) were the overall survival outcome, such as dead vs. alive, and the MYC, BCL2, and BCL6 expression (high vs. low groups, the same as the neural networks). In the GSEA, the genes are ranked based on their rank metric score and running enrichment score (ES). The ES reflects the degree to which a gene set is overrepresented at the top or bottom of a ranked list of genes [66–68], for example, the gene expression profile of patients who died.

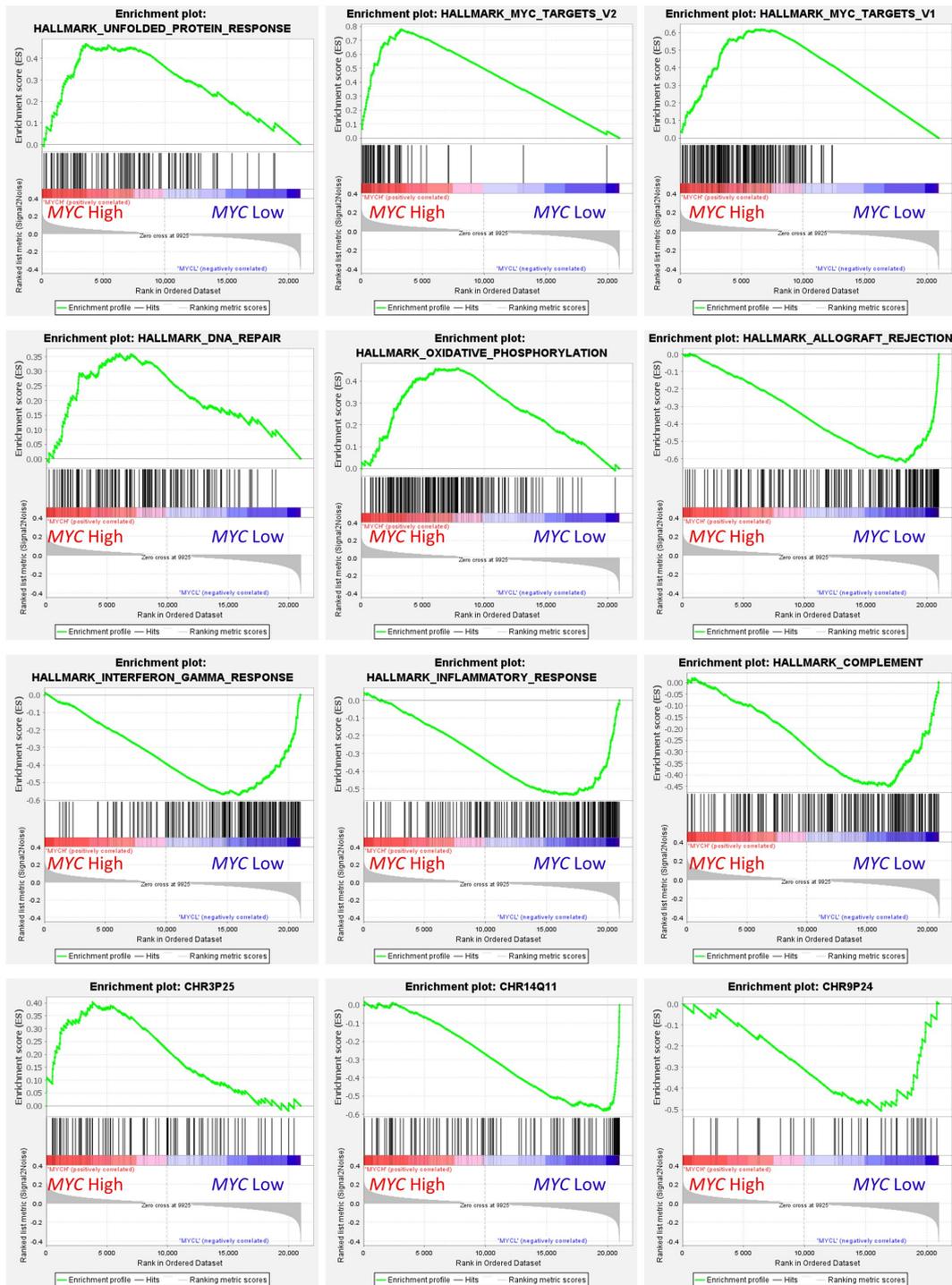


Figure 12. Gene set enrichment analysis (GSEA) on MYC expression groups. GSEA analysis was performed using as predictors several gene sets of the Molecular signatures database (MSigDB), including hallmark (H), positional (C1), and curated (C2) gene sets. The predicted variable (phenotype) was the MYC expression (high vs. low groups), the same as the neural networks. This figure shows some of the most relevant GSEA plots. High MYC expression correlated with high expression of genes associated with protein response, MYC targets, DNA repair, oxidative phosphorylation pathways, and chromosome 3p25 locus-associated genes. Low MYC expression correlated with allograft rejection, interferon gamma response, inflammatory response, complement, and chromosome 1q11 and 8p24.

4. Discussion

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent non-Hodgkin lymphomas and mature B-cell hematological neoplasms. DLBCL is not a single disease but a group of different diseases that differ in terms of morphological, genetic, and clinical characteristics [1,3]. There are several morphological subtypes, such as centroblastic, immunoblastic, and anaplastic, but their identification by histopathologists suffers from reproducibility. There are other phenotypic variants, such as the CD5 positive, MYC positive, and BCL2 positive, which tend to be associated with a poor prognosis [1–3,69–72].

The classification using cell-of-origin markers that include germinal center B-cell-like, activated B-cell-like, and unspecified is clinically relevant. Cell-of-origin classification requires the use of gene expression data, which are not always available. However, cell-of-origin classification can also be achieved using immunohistochemistry combining the assessment of CD10, BCL6, and MUM-1 (IRF4) [1]. Recently, the lymphoma classification has been updated with the incorporation of additional molecular features [2–4,69–76].

The 2016 WHO classification included the category of high-grade B-cell lymphoma (HGBCL) with *MYC*, *BCL2*, and/or *BCL6* rearrangements, which confer double-hit or triple-hit status and poor prognosis [1]. In this study, the gene expression of a large series of R-CHOP-treated DLBCL was analyzed, focusing on the expression of *MYC*, *BCL2*, and *BCL6*. The results showed that a high expression of *MYC* and *BCL2* was associated with poor prognosis, and *BCL6* with a favorable outcome. Importantly, the neural network was able to predict these genes using a pan-cancer panel of 758 genes for immuno-oncology and translational research that included clinically relevant actionable genes and pathways. For each marker, the most relevant cancer genes are different. For example, *MTOR* is associated with *MYC*, and *CCND1* with *BCL6*. Of note, the accuracy for *BCL2* prediction was moderate to low. Therefore, the results of *BCL2* must be taken with more caution.

The neural network analysis was complemented with a gene set enrichment analysis (GSEA). The genes highlighted in the leading edges are the ones more relevant for the gene expression of *MYC*, *BCL2*, and *BCL6* phenotypes (high vs. low). In a clinical setting, the simplest approach would be to look into *MYC*, *BCL2*, and *BCL6* gene expression or protein levels, including the rearrangement by FISH. Additionally, as shown in Figure 8, relevant markers would be *CD163*, *CD16*, *IL10*, and *IRF4*, among others.

Neural networks are a subtype of machine learning and include deep learning algorithms. The architecture of the neural network comprises node layers, including an input layer, one or more hidden layers, and an output layer. When the output value of an individual node is above a specified threshold, the node is activated and sends data to the next layer. When the value is below the threshold, no data are passed. The principal focus of this study was feedforward networks, but there are other types of neural networks. For example, recurrent neural networks are used in natural language processing and speech recognition. Conversely, convolutional neural networks are often used in computer vision analysis. Convolutional neural networks have three main types of layers: a convolutional layer, a pooling layer, and a fully connected layer. There are many architectures, such as AlexNet, VGGNet, GoogleNET, ResNet, etc. This study focused on multilayer perceptron, which is a type of feedforward network, to analyze gene expression data, but the analysis of histological images could be performed in the future as well, focusing on lymphoma and other hematological diseases, such as leukemia, myeloma, and myelodysplastic syndromes.

The birth of artificial intelligence (AI) was denoted by Alan Turing's seminal work "Computing Machinery and Intelligence", which described AI as systems that act like humans. AI combines computer science and robust datasets to make predictions and classifications based on input data [77]. Our group has worked in predictive analytics and AI in recent years in the field of lymphoma [78] and other diseases, such as celiac disease [79] and ulcerative colitis [80]. In the lymphoma field, we identified several markers of relevance, such as *ENO3* [28], *TNFAIP8* [81], *PD-L1* [81], *CASP8* [82], *CSF1R* [61], immune response [83], *RGS1* [26], *FOXP3*, *PD-1*, *IL10*, and *CD163* [29,30,84], as well as *BCL6* in DLBCL [85,86] and FL [87]. Therefore, we have proven that this technology is useful.

A turning point in AI has been the release of OpenAI's ChatGPT, which is a trained conversational model. However, it is important to point out that thinking and making our own decisions is what makes us human. Letting machines think for us makes us less free and less conscious. Therefore, no machine should be made in the likeness of the human mind [77].

5. Conclusions

Artificial intelligence in medicine uses machine learning and neural network models to improve disease identification and diagnosis, personalize disease treatment, analyze medical images, evaluate clinical trials, and speed up drug development.

The mathematical way in which neural networks reach conclusions has been considered a black box, but a careful understanding and evaluation of the architectural design allows us to interpret the results logically. In diffuse large B-cell lymphoma, neural networks are a plausible data analysis approach.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tokai University, School of Medicine (IRB20-156).

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are available upon request to Joaquim Carreras (joaquim.carreras@tokai.ac.jp). The algorithms of MLP are shown in Carreras, J. (2024). Multi-layer perceptron (Version 1). Zenodo. <https://doi.org/10.5281/zenodo.10727457>. The parameter estimates of the MLPs are shown in Joaquim, C. (2024). MLP parameter estimates (Version 1) [Data set]. Zenodo. <https://doi.org/10.5281/zenodo.10804249>. The independent variable importance is in Joaquim, C. (2024). Independent variable importance (Version 1) [Data set]. Zenodo. <https://doi.org/10.5281/zenodo.10805431>, accessed on 29 December 2023.

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Conflicts of Interest: The author declares no conflicts of interest.

Appendix A

Figure A1: Model architecture of the transformer.

This figure depicts the general architecture of the transformer. It uses stacked self-attention and point-wise, fully connected layers for both the encoder (left) and the transformer (right) [46].

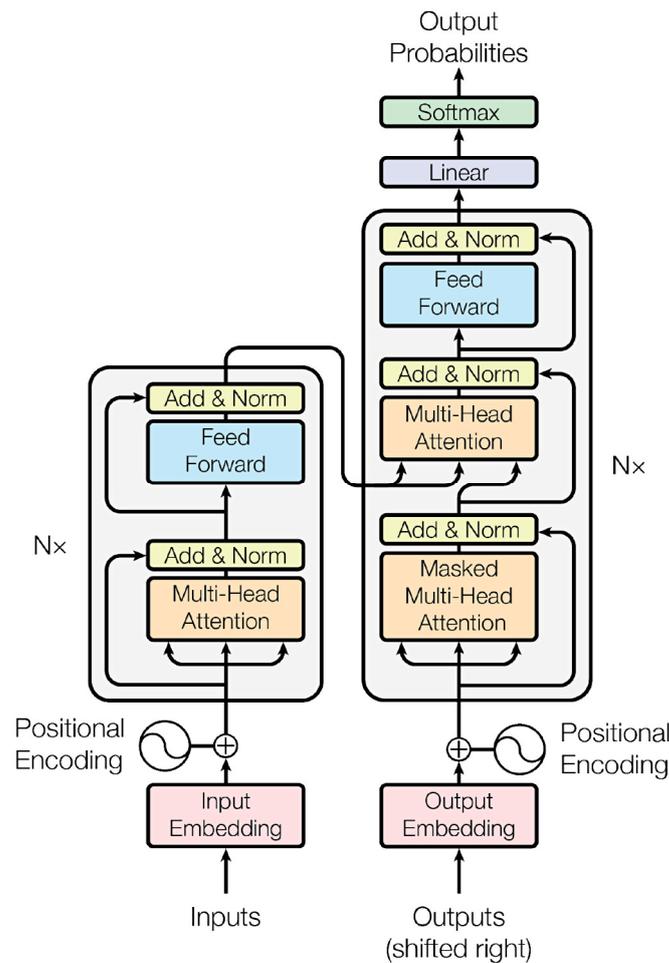


Figure A1. Usually, the guideline is to use ReLU first and later test the others.

Appendix B

Activation functions

Neural networks use activation functions to add nonlinearity. There are three types of neural network activation functions: binary step function, linear activation function, and nonlinear activation function. Regarding nonlinear, the most frequent are the sigmoid/logistic activation function, Tanh function (hyperbolic tangent), ReLU function, leaky ReLU, parametric ReLU, ELU, softmax function, swish, GELU, and SELU [88–91].

Usually, the guideline is to use ReLU first and later test the others.

Additional guidelines are as follows. The ReLU activation function is used in hidden layers but the sigmoid/logistic and Tanh functions are not. The Swish function is used when the neural network depth is greater than 40 layers.

For the output layer, the type of activation function depends on the type of problem that the neural network is handling. Regression uses a linear activation function, binary classification of the sigmoid/logistic, and multiclass classification of the softmax. Multilabel classification is for the sigmoid [88–91].

In the hidden layer, the type of activation function also changes. Convolutional neural networks (CNNs) use ReLU and recurrent neural networks use Tanh and/or sigmoid.

Appendix C

A2M	BRCA2	CD276	CLEC5A	DKK1	FGF18	FGF18	HES1	IKBKB	ITGB3	MAP3K7	NKG7	PMS2	RPTOR	STAT3	TNFRSF17	WNT4
ABC1	BRD3	CD28	CLEC7A	DLL1	FGF9	FGF9	HEY1	IKBKG	ITGB8	MAP3K8	NLRCS	PNOC	RRM2	STAT4	TNFRSF18	WNT5A
ACVR1C	BRD4	CD300A	CLEC1L	DLL4	FGFR1	FGFR1	HIF1A	IL10	ITPK1	MAPK10	NLRP3	POLD1	RSAD2	STC1	TNFRSF18	WNT5B
ADAM12	BRP1	CD36	CMKLR1	DNAJC14	FLNB	FLNB	HK1	IL10RA	JAG1	MARCO	NOD2	POLR2A	RLN3	STING1	TNFRSF18	WNT7B
ADGRE1	BTLA	CD38	CNTRF	DNMT1	FLT1	FLT1	HK2	IL11	JAG2	MELK	NOS2	PPARG	S100A12	STK11P	TNFRSF25	ZAP70
ADM	C1QA	CD3D	COL11A1	DPP4	FOSL1	FOSL1	HLA_A	IL11RA	JAK1	MET	NOTCH1	PPARGC1B	S100A8	SYK	TNFRSF4	ZC3H12A
ADORA2A	C1QB	CD3E	COL11A2	DTX3L	FOXP3	FOXP3	HLA_B	IL12RB2	JAK2	MFGES	NOTCH2	PRF1	S100A9	TAF3	TNFRSF8	ZEB1
AKT1	C2	CD3G	COL17A1	DTX4	FPR1	FPR1	HLA_DMA	IL15	JAK3	MFNG	NRAS	PRKAA2	SAMD9	TAP1	TNFRSF9	ZEB2
ALDOA	C5	CD4	COL4A5	DUSP1	FPR3	FPR3	HLA_DMB	IL16	KAT2B	MGMT	NRDE2	PRKACB	SAMSN1	TAP2	TNFRSF10	
ALDOC	CSAR1	CD40	COL5A1	DUSP2	FSTL3	FSTL3	HLA_DOA	IL17A	KDR	MICA	NTSE	PRKCA	SBNO2	TAPBP	TNFRSF13B	
ANGPT1	C7	CD40LG	COL6A3	DUSP5	FUT4	FUT4	HLA_DOB	IL18	KIF2C	MICB	OAS1	PRKX	SDHA	TAPBP	TNFRSF13B	
ANGPT2	CASP1	CD44	COMP	E2F3	FYN	FYN	HLA_DPA1	IL18R1	KIR3DL1	MIC67	OAS2	PLRL	SELE	TBC1D10B	TNFRSF18	
ANGPTL4	CASP3	CD47	CPA3	EDN1	FZD8	FZD8	HLA_DPB1	IL1A	KIR3DL2	MLANA	OAS3	PROM1	SELL	TBP	TNFSF4	
ANLN	CASP8	CD48	CRABP2	EGF	FZD9	FZD9	HLA_DOA1	IL1B	KIT	MLH1	OASL	FRS5	SELP	TBX21	TNFSF8	
APC	CASP9	CD5	CSF1	EGFR	G6PD	G6PD	HLA_DQB1	IL1R2	KLRB1	MMP1	OAZ1	PSMB10	SERPINA1	TBXAS1	TNFSF9	
APHIB	CBLC	CD58	CSF1R	EGR1	GAS1	GAS1	HLA_DR1	IL1RN	KLRD1	MMP7	OLFML2B	PSMB5	SERPINB5	TCF3	TNKS	
AP5	CCL1	CD6	CSF2	E1F2AK2	GBP1	GBP1	HLA_DRB1	IL2	KLRK1	MMP9	OLR1	PSMB8	SERPINH1	TCL1A	TFSS3	
APLN	CCL13	CD69	CSF2RB	E1F2B4	GBP2	GBP2	HLA_E	IL21R	KRAS	MMRN2	OTOA	PSMB9	SFSA1	TDO2	TFPI	
APOE	CCL14	CD7	CSF3	E1F4EBP1	GBP4	GBP4	HLA_F	IL22RA1	LAG3	MRC1	P2RY13	PSMC4	SFRP1	TFR3	TFPI1	
APOL6	CCL18	CD70	CSF3R	ELOB	GHR	GHR	HMGAI1	IL24	LAI1	MRE11	P4HA1	PTCD2	SFRP4	TGFB1	TFPI2	
AQP9	CCL19	CD74	CS2	ENO1	GIMAP4	GIMAP4	HMG1B1	IL2RA	LAMA1	MRPL19	P4HA2	PTEN	SFXN1	TGFB2	TRAF1	
AREG	CCL2	CD79A	CTAG1B	ENTPD1	GIMAP6	GIMAP6	HNF1A	IL2RB	LAMB3	MS4A1	PALMD	PTGER4	SGK1	TGFB3	TRAF1	
ARG1	CCL20	CD79B	CTLA4	EOMES	GLI1	GLI1	HRA5	IL2RG	LAMC2	MS4A2	PARP12	PTGS2	SH2D1A	TGFB3	TREM1	
ARG2	CCL21	CD80	CTNNA1	EPCAM	GLS	GLS	HSD11B1	IL32	LCK	MS4A4A	PARP4	PTFN1	SHC2	TGFB2	TREM2	
ARND1A	CCL22	CD84	CTS5	EPN2AIP1	GLUD1	GLUD1	ICAM1	IL33	LDHA	MS4A4A	PARP9	PTPRC	SIGLEC1	THBD	TRIM21	
ARNT2	CCL3	CD86	CTSW	ERBB2	GLUL	GLUL	ICAM2	IL34	LDHB	MSH2	PC	PUM1	SIGLEC5	THBS1	TSLP	
ATF3	CCL4	CD8A	CX3CL1	ERCC3	GMIP	GMIP	ICAM3	IL4	LGALS9	MSH6	PCK2	PVR	SIGLEC8	THY1	TTCA3	
ATM	CCL5	CD8B	CX3CR1	EROL1	GNG4	GNG4	ICAM5	IL6	LIF	MTOR	PDCC1	RAD50	SIRPA	TTCA1	TTCA1	
AXIN1	CCL7	CD96	CXCL1	ESR1	GNLY	GNLY	ICOS	IL6R	LILRA1	MX1	PDCC1L2	RAD51	SIRPB2	TIE1	TTST1	
AXL	CCL8	CD220	CXCL10	EXO1	GOT1	GOT1	ICOSLG	IL7R	LILRB2	MX1	PDGFA	RAD51C	SLAMF7	TIGIT	TTST2	
B2M	CCNA1	CD25C	CXCL11	EZH2	GOT2	GOT2	ID4	INHBA	LILRA5	MYC	PDGFB	RASAL1	SLC11A1	TLK2	TNIP1	
BAD	CCNB1	CDH1	CXCL12	F2RL1	GPC4	GPC4	IDO1	IRF1	LILRB2	MYC1	PDGFRB	RASGRF1	SLC16A1	TLR1	TNIP2	
BAMBI	CCND1	CDH11	CXCL13	FADD	GPR160	GPR160	IER3	IRF2	LILRB4	MYD88	PDK1	RB1	SLC1A5	TLR2	UBA7	
BATF3	CCND2	CDH2	CXCL14	FAM124B	GFSM3	GFSM3	IFI16	IRF3	LOXL2	NBN	PDZK1P1	RB2	SLC2A1	TLR3	UBB	
BAX	CCND3	CDH5	CXCL16	FAM30A	GUSB	GUSB	IFI27	IRF4	LRR3C2	NCAM1	PECAM1	RELA	SLC7A5	TLR4	UBE2C	
BCB3	CCNE1	CD82	CXCL2	FANCA	GZMA	GZMA	IFI35	IRF5	LTB	NGR1	PF4	RELB	SMAD5	TLR5	UBE2T	
BES1	CCNG0	CDK6	CXCL3	FAP	GZMB	GZMB	IFI6	IRF7	LTBP1	NDUFA4L2	PFKFB3	RELN	SMAP1	TLR7	UBEP2	
BCAT1	CCR2	CDK1V1A	CXCL5	FAS	GZMH	GZMH	IFIH1	IRF8	LY9	NECTIN1	PFKAM	REN	SNAI1	TLR8	VCAM1	
BC12	CCR4	CDK1V1C	CXCL6	FASLG	GZMK	GZMK	IFIT1	IRF9	LY96	NECTIN2	PGPEP1	RICTOR	SNCA	TLR9	VCAN	
BCL2L1	CCR5	CDKN2A	CXCL8	FBP1	GZMM	GZMM	IFIT2	ISG15	LYZ	NEIL1	PIA5A	RIFK1	SOCS1	TMEM140	VEGFA	
BCL6B	CD14	CDKN2B	CXCL9	FCAR	H2AX	H2AX	IFIT3	ITGA1	MAGEA1	NF1	PIK3CA	RIFK2	SOX10	TMLUB2	VEGFB	
BID	CD163	CEACAM3	CXCR2	FCGR1A	HAVCR2	HAVCR2	IFITM1	ITGA2	MAGEA12	NFAM1	PIK3CD	RIFK3	SOX11	TNF	VEGFC	
BIRC3	CD19	CEBBP	CXCR3	FCGR2A	HCK	HCK	IFITM2	ITGA4	MAGEA3	NFATC2	PIK3CG	RNLS	SOX2	TNFAIP3	VHL	
BIRC5	CD1C	CENPF	CXCR4	FCGR2B	HDAC11	HDAC11	IFNA1	ITGA6	MAGEA4	NFIL3	PIK3R1	ROBO4	SPB	TNFAIP6	YSIR	
BLK	CD2	CEP55	CXCR6	FCGR3A	HDAC3	HDAC3	IFNA1	ITGA6	MAGEB2	NFKB1	PIK3R2	ROCK1	SP1	TNFRSF10B	VTCN1	
BLM	CD209	CE53	CYBB	FCGR3B	HDAC4	HDAC4	IFNG	ITGAL	MAGEC1	NFKB2	PIK3R5	ROR2	SPRY4	TNFRSF10C	WDR76	
BMP2	CD244	CGAS	DAB2	FCGR2T	HDAC5	HDAC5	IFNGR1	ITGAM	MAGEC2	NFKB1A	PKM	RORC	SREBF1	TNFRSF10D	WNT10A	
BNIP3	CD247	CHUK	DDR2	FCN1	HDC	HDC	IFNGR2	ITGAV	MAML2	NFKBIE	PLA1A	RPL23	SRP54	TNFRSF11A	WNT11	
BNIP3L	CD27	CLEC14A	DEPTOR	FCRL2	HELLS	HELLS	IGFBP2	ITGAX	MAP3K12	NGFR	PLA2G2A	RPL7A	STAT1	TNFRSF11B	WNT2	
BRCA1	CD274	CLEC4E	DIPK2B	FGF13	HERC6	HERC6	IHH	ITGB2	MAP3K5	NID2	FLOD2	RFS6KB1	STAT2	TNFRSF14	WNT2B	

Figure A2. Gene panel.

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