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*Research Article*

# A Decision Support System For Detecting Stage In Hodgkin Lymphoma Patients Using Artificial Neural Network and Optimization Algorithms

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## Abstract

Hodgkin-type lymphoma is a disease with unique histological, immunophenotypic, and clinical features. This disease occurs in nearly 30% of all lymphomas. Its treatable is high. However, the treatment plan is specified after the stage and risk status are determined. For this reason, it is an important process for doctors to decide on the stage of the disease correctly. Some of the data used for this decision are the patient's history, detailed physical examination, laboratory findings, imaging methods and bone marrow biopsy results. Hybrid FDG-PET is an important imaging method used in the medical world. This method is used in diagnosis, evaluation of response given to treatment, staging and restaging process. However, it is radiation-based. Therefore it has the possibility of producing undesirable results in the future. In this study, an artificial intelligence-based computer-assisted decision support system is done to reduce the number of used medical methods and radiation exposure. Data were obtained from the NCBI-GEO dataset. The evaluation of these data, which contains missing values, is handled in two ways. Firstly, samples with missing values in the initial evaluation are deleted from the dataset. Then, these data are trained with “trainlm” function in artificial neural network architecture. However, reducing the error value of the estimates is important. For this, the artificial neural network architecture is retrained with the artificial bee colony algorithm, particle swarm optimization algorithm and invasive weed algorithm, respectively. Secondly, the same operations are performed again on the dataset containing missing values. As a result of the training, the maximum performance was obtained for invasive weed and particle swarm optimization algorithms with 1,45547E+14 and 1,23103E+14 average error rates, respectively.

**Keywords:** staging in hodgkin lymphoma, artificial neural networks, particle swarm optimization algorithm, invasive weed optimization algorithm, constructing hybrid structure for decision support system

## 1. Introduction

Hodgkin-type lymphoma was described by Thomas Hodgkin in 1832. This disease occurs from the B cell lineage. It has unique histological, immunophenotypic and clinical features. It consists of nearly 30% of all lymphomas. Hodgkin lymphoma is classified into two groups according to the WHO (World Health Organization) guide. The first group is Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLP-HL), which constitutes 5% of Hodgkin lymphomas. The second group is Classical Hodgkin Lymphoma, which constitutes 95% of Hodgkin lymphomas. Classical Hodgkin Lymphoma group is also evaluated in 4 subclasses that are Nodular Sclerosis, Mixed Cellularity, Lymphocyte Rich and Lymphocyte Depleted. In this scale that constitutes 95% of Hodgkin lymphomas, the incidence rate of these subclasses is stated as 70%, 20%, 5% and 5%, respectively. The symptoms of Hodgkin lymphoma patients are manifested by painless enlargement of lymph nodes, spleen, and other immune tissues. Fever, night sweats, itchy skin, weight loss, loss of appetite and fatigue are other possible symptoms [1].

Hodgkin lymphoma is a treatable disease. The survival rate for 5 years is 81%. However, there is a possibility of the relapsing of the disease to different regions. This possibility is seen in nearly 30% of patients. Hodgkin lymphoma consists of 4 stages. Stage 1 is the involvement of a single lymph node

region or lymphoid structure. Stage 2 is the involvement of two or more lymph node regions for the same side of the diaphragm. Stage 3 is the involvement of lymph node regions or structures for both regions of the diaphragm. Stage 4 is the diffuse involvement of one or more extra lymphatic organs [1].

A treatment plan is made after determining the stage and risk group for HL patients. Characterizations for early-stage good risk, early-stage bad risk and advanced-stage are made. These characterizations are (Stage I-II, no adverse factor), (Stage I-II, any of the negative factors), (Stage III-IV disease) respectively [2].

The decision to be made for the stage of the disease by the doctors is important. Detailed physical examination, laboratory findings, imaging methods (chest x-ray, chest and CT scan), and bone marrow biopsy results are used for this decision. However, pathological examinations performed in NLP Hodgkin Lymphoma and Classical Hodgkin Lymphoma are monitored for different target cells and a sufficient sample is an important parameter in pathological examinations. On the other hand, biopsy evaluations containing insufficient malignant cells do not produce clear results. At the same time, it is stated that CT (Computed tomography), which is a radiological-based imaging method, is insufficient in demonstrating spleen involvement. In addition, nearly 15% of HL patients, which were described as an early stage in the staging process with CT, were shown to be advanced stage with PET-CT(Positron Emission Tomography-Computed Tomography). For this reason, the patient's history, detailed physical examination, laboratory tests, bone marrow biopsy and imaging approaches is a critical issues in order to decide on the correct diagnosis and stage [1][2].

Positron Emission Tomography is an approach that reaches the patient from vascular after the radioactive labelling of glucose sugar. The distribution of this substance in the body is examined using a scanner. Glucose is a substance used a lot, especially by lymphoma cells. Therefore, as a result of this process, the body's glucose metabolism changes and sick areas appear [2]. The PET-CT method is accepted in the medical world as a standard for the detection of tumour cells [2]. In the scope of this hybrid structure, while PET provides information on the distribution of glucose in the body, CT provides anatomical details of normal and pathological tissues in the body. Hybrid PET-CT is also used in diagnosis, evaluation of response given to treatment, staging and restaging [2][3]. FDG-PET/CT has a higher sensitivity than bone marrow biopsy [4]. Since 2014, the response given to treatment is evaluated according to CT and PET-CT [2]. Today, the most widely used PET radiopharmaceutical is fluorodeoxyglucose (FDG), a glucose analog labeled with Fluor-18 (F-18) [5]. After it is given to the body, it accumulates in the bladder. This results in an increase in the rate of radiation in the bladder and its membrane. On the other hand, the late effects of radiation are another important issue. Standard dose protocol or dose protocol varying according to weight is an important criterion to be considered in PET-CT procedures to be applied to the patient. However, it is stated that the rate of PET-CT facilities, where patient weight is taken into account, is 44% [3]. In addition, if there is a suspicion of pregnancy or if the breastfeeding process continues, it should be done under the control of a doctor within the scope of certain instructions [5]. Also, positron emission tomography is a medical method with high economic costs [4].

FDG-PET, which is also included in the post-treatment evaluation process, may produce false positive results for some conditions. This situation causes the to be misdirected in the evaluation process due to post-treatment infections. As a result of misdirections; unnecessary radiation exposure, biopsies and patient anxieties occur [4].

In normal conditions, the prognosis of Hodgkin lymphoma is good. Especially if the disease is in its early stage and there are no undesirable factors, the healthy life expectancy for 5 years is nearly 90%. Even in the advanced stage of the disease, this rate is in the period of 70%-90%. For HL patients with a high probability of success, the main goals of future-oriented are to prevent the treatment's side effects and to make an early diagnosis. Depending on the late treatment, conditions such as breast cancer, thyroid cancer, GIS cancer, leukemia, soft tissue sarcoma, lung cancer and other different cancers, cardiovascular diseases, and organ failure may occur. Therefore, early diagnosis and early prediction of alternative treatment options are important in terms of preventing complications and unnecessary treatments [6].

In the literature, decision support systems using different methods have been constructed to evaluate the diagnosis, stage and response given to treatment of lymphoma disease. Because it is important to choose the correct diagnosis and staging for the treatment to be effective. In this context, in the [7] study a multiclass classification of non-hodgkin lymphomas was made. The best success rate achieved in this article, in which morphological and non-morphological descriptors were extracted from cell nuclei, was obtained as 0.956 with the linear regression approach. In the [8] study is provided to distinguish cancer lesions from other structures with FDG PET/CT. The maximum performance criterion reached with the SVM classifier was obtained as 0.91 for the AUC value. In the [9] study is aimed segmentation and classification of lymphoma histological images. Firstly, the segmentation process is carried out with evolutionary algorithms. Then, classification is provided with the Support Vector Machine method using the texture and color features extracted from the images. The best average accuracy rate is obtained with Differential Evolution technique as 99.38%. In the [10] study is classified centroblast and non-centroblast cells for microscopic images obtained through follicular lymphoma tissue biopsy with Support Vector Regression and Radial Basis Kernel Function. The average detection accuracy is obtained as 97.44%. The feature extraction method is developed in the [11] study to classify 3 lymphoma types (mantle cell lymphoma, follicular lymphoma and chronic lymphocytic leukemia). Features are extracted from lymphoma images using this developed method. Then these attributes are classified by decision tree (DT), support vector machines (SVM), random forests (RaF), naive bayes (NB), K-star (K*) classifiers. The best result achieved in a result of the classification process is obtained with the random forest. On the test dataset, this ratio is evaluated with the cross validation method and the AUC ratio is found as 0.963. In the [12] study used stained tissue images; benign lesion, carcinoma, and lymphoma data is classified with the weighted KNN model. The average success rate is improved with CLAHE and PCA methods. The maximum success rate achieved is obtained as 85.5%. In the [13] study, features are extracted from histological images using a convolutional neural network for the classification of malignant lymphatic images. Then these feature vectors are given as inputs to Convolutional Neural Networks, Support Vector Machines (SVM) and Random-Forests classifiers. The convolutional neural network model produced the best result with a classification success of 93.27%. In the [14] study, lymphoma images belonging to 3 classes is classified. In the classification process, Resnet 50, modified Resnet50 and 5-layer CNN structures are trained with different optimization algorithms. The achieved maximum accuracy is 0.9990 for the KIMIA Path 960 dataset and 0.9813 for the NIA Curated dataset.

Studies in the literature were carried out to create a computer-based decision support system. Because the treatment process can be difficult and laborious for both patients and doctors. The oncologists, especially for patients with HL uses critical parameters such as anamnesis, detailed physical examination, laboratory findings, imaging modalities (X-ray, CT scan, and PET-CT) and bone marrow biopsy results for early diagnosis, evaluation of response given to treatment, staging or restaging. [15][16][17][18][19][20] studies indicate that PET-CT imaging approach offers more successful outcomes in the process of deciding the stage of lymphoma disease compared to other approaches. All these approaches applied for the diagnosis and treatment of patients diagnosed with HL may cause anxiety on patients or radiation-based methods may produce undesirable results in the long term. For this reason, a decision support system was built to reduce the number of methods used in staging and the radiation exposure.

In this study, initially, diagnostic biopsy samples taken from Hodgkin lymphoma patients were obtained from the NCBI-GEO dataset. These data consist of IPS score, age, gender information, albumin level, hemoglobin level, lymphocyte ratio and white blood cell count features. However, some patient samples contain missing values. Therefore, 2 different evaluations were made regarding the data set. In the first evaluation, patient samples containing missing values from the dataset were deleted. The remaining 99 data were given as input to the artificial neural network. This model was trained with the trainlm function updating the bias and weight values according to the Levenberg-Marquardt approach. In this model consisting of 5 neurons and 1 hidden layer, the tansig and purelin transfer functions were used. The achieved error rate was found as 2.33185E+14. Then, the same processes were repeated for the dataset that contain missing values. The error rate reached for this evaluation was also found as 4.89165E+13.

However, in order to increase the power of the predictions and to give more successful decisions for the 4 stages, the same neural network was retrained with ABC, PSO and IWO algorithms. As a result of 1000 iterations, the most successful output for the test dataset that does not contain missing values was obtained as the artificial neural network trained with the PSO algorithm. The minimum error value reached on the test data set was found as 1.23103e+14. Then, the same operations performed with the optimization algorithms were performed again on 130 data that contain missing values. As a result of the training, the most successful output was obtained with the artificial neural network trained with the IWO algorithm. The minimum error rate reached for the second evaluation was found as 1.45547E+14. An improvement has been made on the test datasets for both evaluations and the achieved error rates are close values. This shows that the data of patients diagnosed with HL containing missing values can be tolerated with the hybrid use of artificial intelligence and optimization algorithms. At the same time, real-world data is likely to contain missing values. Consequently, it is planned that the created the computer-aided decision support system will give an idea to the doctors.

## 2. Material and Method

This section presents an artificial intelligence-based study in order to correctly decide on the stage of patients diagnosed with lymphoma. In this study, firstly, an estimation process in which artificial neural networks are used in the training of the model takes place. Then, three different optimization algorithms named artificial bee colony, particle swarm and invasive weed are used to improve the obtained performance of predictions. The format of the dataset, classification method and optimization approaches are explained below.

### 2.1. Dataset

In this study, NCBI-GEO dataset is used. The used data has the id numbers in the GSM447610-GSM447739 range in the GSE17920 series and it is provided from the [21] site. The dataset consists of data containing values of diagnostic biopsy samples obtained from patients with Hodgkin lymphoma. In this study, estimation is done using IPS score, age, gender information, albumin level, hemoglobin level, lymphocyte ratio and white blood cell count values. However, there are missing values in the data obtained from 130 different individuals. For this reason, two separate evaluations are made. In the first evaluation, 130 different samples that all data is used. The second evaluation is carried out on 99 separate data that consists of not missing values. The IPS (International Prognostic Score) score, which is included in the features, is a feature that provides an evaluation of the prognosis on a certain scale. It is evaluated in the range of 0 to 7. An IPS value closer to 7 indicates increased risk [22]. 70% and %30 of the data used in this study are chosen randomly from all data as training and testing datasets. Then, these data are given as input to the artificial neural network architecture.

### 2.2. Used Neural Network Architecture and Optimization Algorithms

Artificial intelligence is a framework that enables the cognitive abilities of humans to be imitated by machines. It can be used in different fields such as mathematics, statistics, linguistics, computer science, neurobiology and psychology [23]. However, it also has a tendency to perform error-prone tasks that are studied using statistical methods and whose evaluation of human intelligence is impractical [24]. In particular, it provides an effective interpretation of the data created by people as a result of observation. It also has the power inferring for specific clinical diagnostic tasks from large and complex data stacks [24].

Artificial intelligence, which can be used as a decision support system in the medical field, performs the learning actions on the same type of data for a clinical diagnosis. Then it learns the interpretation function on the target data [24]. The interpretation task differs in the scope of the target problems, such as time series analysis, computer vision, or natural language processing [24].

Artificial intelligence is a discipline that contains machine learning, neural networks and deep learning [23]. The clinical data used in this study are analyzed with neural networks and then inferences are made.

Neural Networks are developed with inspiration from the biological nervous system. This structure consists of an input layer, an output layer and the hidden layer/layers. In the first stage of the structure, the properties of the data taken as input are automatically extracted. Then the weight values are adjusted and the activation function is applied. Weight values are updated to strengthen or weaken connections in the network to produce successful performance with mathematical functions defined by the system [23]. The activation function is used to teach the neural network nonlinear real-world problems that have a great impact on the performance of the network [25].

The neural network architecture used in this study is given in Figure 1.

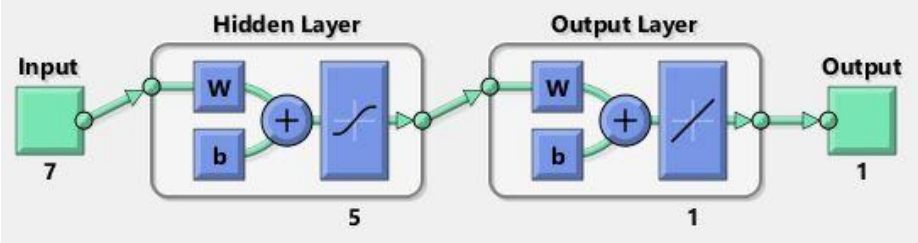


Figure 1 The neural network architecture used in this study

In this architecture adopting the feed-forward backpropagation approach, the inputs are transmitted along the next layers. The errors that occur in this process are fed back and a successful training model is obtained. The architecture used in the study consists of 1 hidden layer and it runs on 7 separate input features. The number of neurons in this hidden layer is defined as 5. The trainlm training function is selected for network's training. The trainlm function updating bias and weight values works according to Levenberg-Marquardt optimization [26]. Two different neural transfer functions are used to calculate the output from the input of each layer. These transfer functions defined as tansig and purelin are used in the hidden and output layers, respectively. These functions were selected as a result of fine-tuning. The graphical representation of the hyperbolic tangent sigmoid transfer function (tansig) and linear transfer function (purelin) is given in Figure 2 [26].

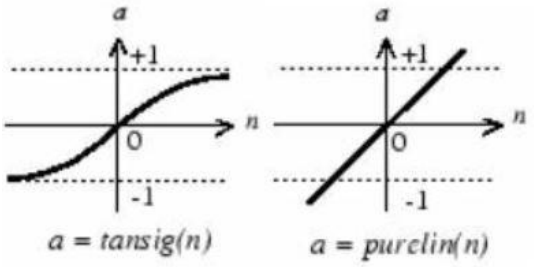


Figure 2 The transfer functions used in this study[26]

The one output is obtained about stage of disease after the classification. The maximum similarity between the real results and the results obtained from the training of the artificial neural network is achieved with the network structure expressed in Figure 1. However, it is important to increase the success of predictions. For this, optimization algorithms were used.

Optimization algorithms produce correct, stable and effective solutions for the available problems. Different optimization algorithms have been developed for real-life problems. Optimization algorithms are examined in two main frameworks as stochastic and deterministic optimization algorithms.

Stochastic optimization algorithms that contain randomness compared to deterministic optimization algorithms are evaluated in 2 parts heuristic and metaheuristic algorithms. In this study, metaheuristic algorithms are used. These algorithms are particle swarm optimization algorithm, artificial bee colony optimization algorithm and invasive weed optimization algorithm and it is based on colony intelligence [27].

The basic logic of the algorithm is the gathering of entities with limited capabilities in order to achieve the targeted purpose. It is inspired by communities that can easily find answers to difficult problems [27][28]. This indicates the spreading behaviour of bird colonies organized for foraging purposes, honey bees in which foraging behaviour is simulated, and weeds invading the field for the particle swarm optimization algorithm, artificial bee colony algorithm and invasive weed algorithm, respectively [27].

Optimization algorithms are methods that optimally solve the relevant problem under certain conditions for complex and difficult targets. It plays an important role in improving performance [27]. For this reason, 3 different optimization algorithms were used in the training of artificial neural networks and the evaluations were made again.

## 3. The Research Findings and Discussion

The hyperparameters of the artificial neural network model adopting the feedforward backpropagation approach are fine-tuned. Then, the artificial neural network model is trained. The outputs of classification produced by the trained model on the training and testing dataset that do not contain missing values are presented in Figure 3.

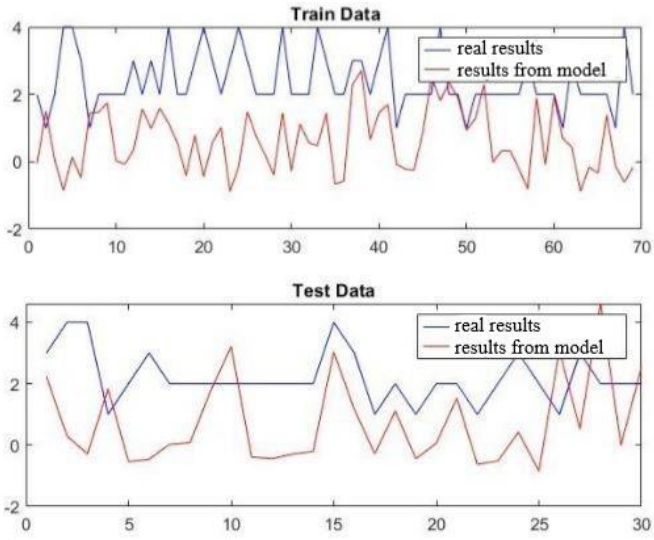


Figure 3 The outputs produced by the artificial neural network architecture trained with the trainlm function for the dataset that does not contain missing values

When Figure 3 is examined, the predictive power of the outputs obtained even after the fine-tuning process is not found enough. For this reason, the training of artificial neural networks was carried out with optimization algorithms instead of trainlm function. Thus, the predictive power of artificial neural networks were increased with the 3 different optimization algorithms(artificial bee colony optimization algorithm, particle swarm optimization algorithm and invasive weed optimization algorithm). Then a comparison was made via alternative solutions in the staging and restaging of patients diagnosed with lymphoma on 99 data that do not contain missing values. The outputs of classification produced in the training and test datasets for the 4 stages of patients diagnosed with HL are given in Figures 4, 5 and 6, respectively.

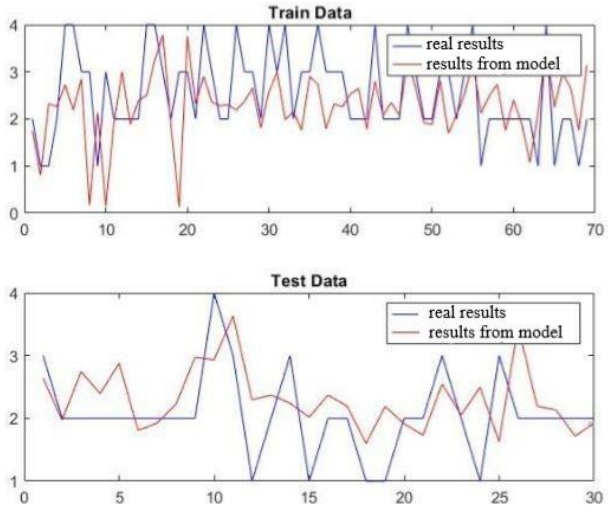


Figure 4 The outputs produced by the artificial neural network architecture trained with the ABC optimization algorithm for the dataset that does not contain missing values

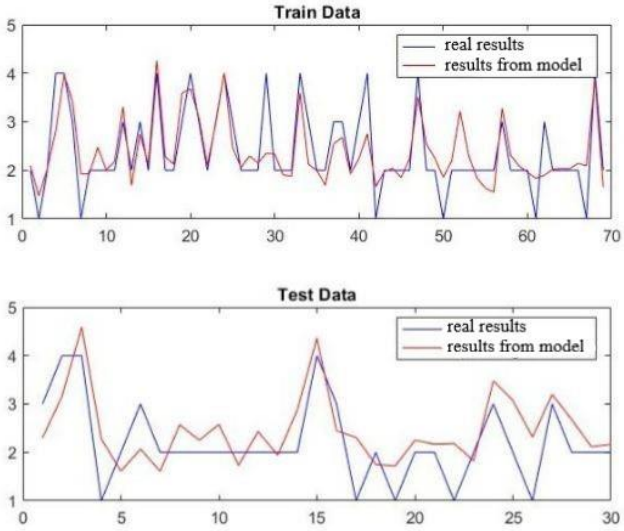


Figure 5 The outputs produced by the artificial neural network architecture trained with the PSO optimization algorithm for the dataset that does not contain missing values

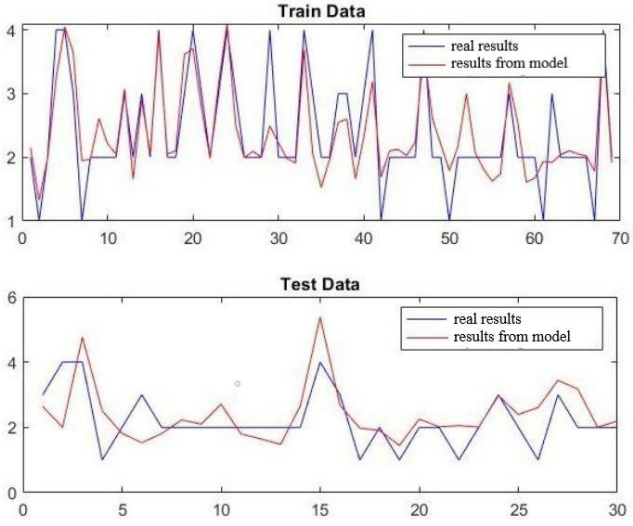


Figure 6 The outputs produced by the artificial neural network architecture trained with the IWO optimization algorithm for the dataset that does not contain missing values

The same evaluation is repeated for 130 different samples, among which there were missing data. The results of classification obtained using 3 different optimization algorithms are given in Figures 7.8 and 9, respectively.

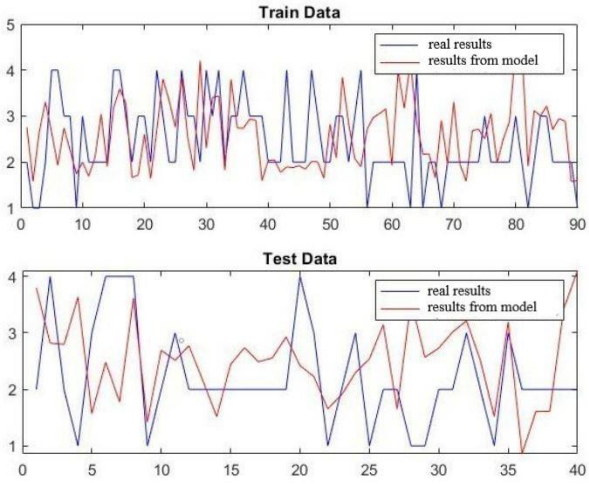


Figure 7 The outputs produced by the artificial neural network architecture trained with the ABC optimization algorithm for the dataset that contains missing values

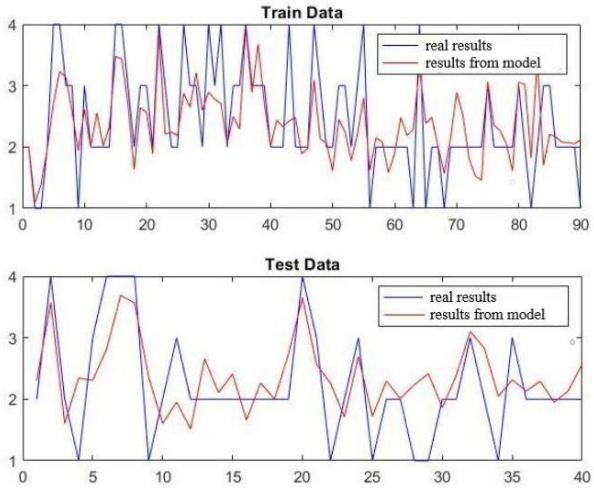


Figure 8 The outputs produced by the artificial neural network architecture trained with the PSO optimization algorithm for the dataset that contains missing values

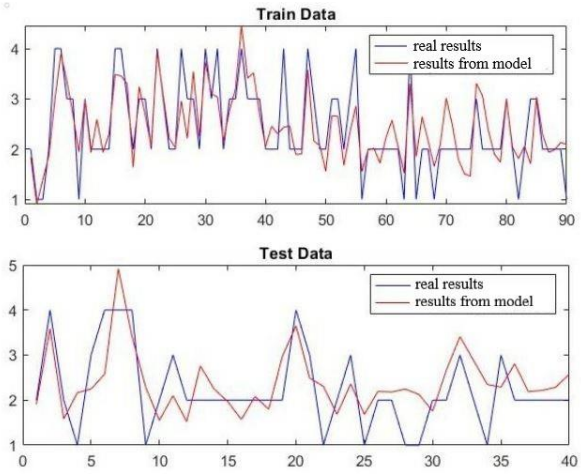


Figure 9 The outputs produced by the artificial neural network architecture trained with the IWO optimization algorithm for the dataset that contains missing values

The outputs produced in the dataset with and without missing data are fuzzy values. These results are produced to give an idea to doctors. The output will be interpreted according to the evaluation process of the doctors. However, a statistical evaluation process is also carried out in this study. In this evaluation process, the target fuzzy value will be characterized according to the phase to which it is closest mathematically. The outputs obtained statistically in the dataset with and without missing data are given in Table 1 and Table 2.

Table 1 Evaluation criteria reached for the dataset with missing data

| FOR MISS. DATA | Stage 1 | | | Stage 2 | | | Stage 3 | | | Stage 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Criteria | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. |
| YSA | 0.14 | 0.60 | 0.23 | 0.5 | 0.13 | 0.21 | 0 | 0 | 0 | 0 | 0 | 0 |
| YSA ABC | 0 | 0 | 0 | 0.59 | 0.76 | 0.66 | 0.14 | 0.2 | 0.16 | 0 | 0 | 0 |
| YSA PSO | 0 | 0 | 0 | 0.6 | 0.705 | 0.64 | 0.25 | 0.4 | 0.307 | 1 | 0.66 | 0.79 |
| YSA IWO | 0.50 | 0.2 | 0.285 | 0.76 | 0.76 | 0.76 | 0.44 | 0.80 | 0.57 | 1 | 0.66 | 0.79 |

Table 2 Evaluation criteria reached for the dataset without missing data

| FOR FULL DATA | Stage 1 | | | Stage 2 | | | Stage 3 | | | Stage 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Criteria | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. | Prec. | Sens. | F scr. |
| YSA | 0 | 0 | 0 | 0.64 | 1 | 0.78 | 0.20 | 0.16 | 0 | 0 | 0 | 0 |
| YSA ABC | 0.50 | 0.14 | 0.22 | 0.50 | 0.36 | 0.42 | 0.18 | 0.50 | 0.27 | 0.16 | 0.20 | 0.18 |
| YSA PSO | 0 | 0 | 0 | 0.64 | 0.81 | 0.71 | 0.37 | 0.50 | 0.42 | 1 | 0.80 | 0.88 |
| YSA IWO | 0 | 0 | 0 | 0.57 | 0.72 | 0.63 | 0.11 | 0.16 | 0.13 | 1 | 0.60 | 0.75 |

The sensitivity criterion given in Table 1 and Table 2 gives the rate at which the target data is estimated correctly among all the predictions belonging to the same category. The Precision criterion gives the rate at which the target data is predicted correctly in all categories. The F criterion is the harmonic mean of the sensitivity and precision criteria. This criterion provides that outliers are taken into account [29].

However, there is a disadvantage to this evaluation process. For an example where the real stage is 1, the model can produce a fuzzy value of 1.51. In this case, the stage predicted by the computer-aided system will be 2. For this reason, the performance produced by the same fuzzy outputs will change with different evaluation approaches to be produced by computer aided systems. For this, it is aimed that the evaluation process is interpreted by the doctors and evaluated as a new parameter. For this reason, the improvement of the methods applied in this study on the outputs is explained with the mean error value.

The classification outputs produced by the artificial neural network model trained with 3 different optimization algorithms during 1000 iterations on the training and testing dataset are examined. The average error rates obtained according to the optimization algorithms are given in Table 3.

Table 3 Average error values trained according to models

| **Structures trained on the training and test dataset** | **Average error for 130 data** | **Average error for 99 data** |
|---|---|---|
| YSA (TRAIN DATASET) | 4,81727E+13 | 2,40011E+14 |
| YSA (TEST DATASET) | 4,89165E+13 | 2,33185E+14 |
| ABC_YSA (TRAIN DATASET) | 4,47807E+13 | 1,53627E+14 |
| ABC_YSA (TEST DATASET) | 6,21566E+13 | 1,27148E+14 |
| PSO_YSA (TRAIN DATASET) | 1,67974E+13 | **1,25067E+14** |
| PSO_YSA (TEST DATASET) | 2,4747E+13 | **1,23103E+14** |
| IWO_YSA (TRAIN DATASET) | **1,29518E+14** | 1,29518E+14 |
| IWO_YSA (TEST DATASET) | **1,45547E+14** | 1,45547E+14 |

Table 3 shows the average error data produced by the artificial neural networks trained with the trainlm training function, ABC, PSO and IWO algorithms on the dataset with and without missing values, respectively. Results obtained from Table 3 show that the artificial neural network architecture is not successful enough in deciding the stage of patients diagnosed with HL. Therefore, the same artificial neural network is retrained with ABC, PSO and IWO algorithms to improve the error rate and general performance. The most successful training on the test dataset that contains missing values that they did not see during the training is the artificial neural network trained with the IW optimization algorithm. However, the most successful training on the test dataset that does not contain missing values is the artificial neural network trained with the PSO optimization algorithm. At the same time, the results produced on the dataset that contains missing values are close to the results produced on the dataset that does not contain missing values. It has been experimentally proven that artificial neural network architecture can tolerate this situation in datasets that contain missing values in patients diagnosed with HL. Because real-world data is likely to contain missing values. This hybrid structure produces a result that can increase the final performance even on missing data.

Additionally trained these architectures are not good enough to predict samples that are stage 1. The reason for this situation is the scarcity of data belonging to stage 1. The model cannot produce successful predictions because it cannot learn the patterns related to the first stage sufficiently. To compensate for such a situation, the number of samples belonging to the first stage should be increased. Also, the addition of different clinical data on the diagnosis of HL is an advantage for increasing successful predictions.

Different methods are used for lymphoma disease in the literature. Table 4 shows some studies in the literature.

Table 4 includes some of the studies done in the scope of lymphoma disease from the past to the present. These studies usually involve an estimation process that is used image processing, classification algorithms or statistical methods. On the other hand, this study decides on the staging or restaging process of individuals diagnosed with HL on 7 different clinical data. A different and hybrid structure is used in the study. It has been experimentally proven that this approach can also be used to decide the stage of data with missing values. It is thought that this study including a different approach compared to the studies in the literature will contribute to the literature.

Table 4 Studies related to patients diagnosed with HL

| References | Aims & Methods | Evaluation Results |
|---|---|---|
| [30] | This study makes a classification based on histological grades of Follicular lymphoma images with MBIR approach. | Classification accuracy in identifing for histological grades of grade 1,2 and 3 is obtained as %74.9, %84.6 and %95.0. |
| [31] | This study provides a prediction for the subtypes of main malignant lymphoma with SVM and RF classifiers. | The sensitivity and precision rate is obtained as %97.0 and %94.1 respectively. |
| [32] | This study realizes a prognastic information for HL and NHL patients with CTTA using Kaplan-Meier and Cox regression methods. | This pilot study shows that complementary prognostic information for interim FDG-PET is provided. |
| [33] | This study presents a classification for histological images of non-Hodgkin lymphoma with SWT and ANOVA approaches. | Best result is obtained with ANOVA approach as %100 accuracy. |
| [34] | This study applied a method to classify for three types of lymphoid cells with Fuzzy C-Means clustering algorithm. | Maximum classification performance has at HCL cells. Rate of HCL cells taking place in group 3 is %98. |
| [35] | Detection of centroblast cells on H&E stained Follicular lymphoma tissue samples with the computer-aided system that has 2 steps for specifying staging. | It has %80.7 detection accuracy. |
| [36] | Classification of 3 types of malignant lymphoma is provided with two-stage approach. | The best signal was obtained as %98-%99 for unseen images. |

## Conclusion

This study was done to decide on the staging or restaging process of patients diagnosed with hodgkin lymphoma. For this reason, firstly, data containing the values of diagnostic biopsy samples were obtained from the NCBI-GEO dataset. However, the dataset contains missing values. For this reason, the data were evauated as 2 separate datasets with and without missing values. In the first stage, the data was trained with the trainlm function of the artificial neural network approach. Then, the same artificial neural network architecture was retrained with ABC, PSO and IWO algorithms in order to reduce the error prediction rate and produce more successful predictions. Optimization algorithms achieved an improvement in the error rates produced as a result of the training. The most successful training on the test dataset with missing values was realized with the IW optimization algorithm and the most successful training on the test dataset without missing values was with the PSO optimization algorithm. For these optimization algorithms in which artificial neural networks are trained, the average error rates achieved for both complete and incomplete datasets are close. Therefore, this hybrid approach has proven its usability on real-world data that may contain missing values for patients diagnosed with HL. This situation will cause a decrease in the use of PET-CT, which is costly. On the other hand, the final performance tends to increase with this hybrid structure having a different target. For this reason, it is expected that the performance of the study will increase with the addition of new clinical data to the dataset in the future. Also, it can be preferred for diseases that are difficult to diagnose. Consequently, it is thought that the present study will contribute to the literature. Finally, since our approach can tolerate the lack of data, it is thought to be a contribution, especially for studies where data collection is difficult and costly.

## References

[1] A. W. MD, A. Q. MD, A. Dasgupta 'Hodgkin lymphoma - Chapter 14', H*ematology and Coagulation (Second Edition)*, pp. 217–225, 2020.

[2] Z. Abbasov, 'Hodgkin Hastalığı Tanılı Hastaların Klinik, Laboratuar Bulguları ve Tedavi Sonuçlarının Değerlendirilmesi', *Uzmanlık Tezi, İstanbul Üniversitesi,* 2017.

[3] T. Şahmaran and M. Bayburt, 'Pozitron Emisyon Tomografi-Bilgisayar Tomografi (PET-BT) Uygulamalarında Hastanın Aldığı Radyasyon Dozunun Belirlenmesi', *Kafkas Univ. Inst. Nat. Appl. Sci. J.*, vol. 13, no. 1, pp. 58–63, 2020.

[4] S. Y. Aksoy and M. Halac, 'Pediatrik Hodgkin lenfomalarda FDG PET/BT', *Turk Onkol. Derg.*, vol. 30, no. 4, pp. 240–251, 2015, doi: 10.5505/tjoncol.2015.1218.

[5] Ç. Soydal *et al.*, 'F-18 FDG PET/CT Practice Guideline in Oncology', *Nucl. Med. Semin.*, vol. 6, pp. 339–357, 2020, doi: 10.4274/nts.galenos.2020.0028.

[6] P. Ö. Kara, 'Pediatrik Lenfomalarda PET_BT Görüntüleme', *Turkiye Klin. J Nucl Med-Special Top.*, vol. 3, no. 1, pp. 93–99, 2017.

[7] T. P. De Faria, M. Z. Do Nascimento, and L. G. A. Martins, 'Understanding the multiclass classification of lymphomas from simple descriptors', *Proc. - 2021 Int. Conf. Comput. Sci. Comput. Intell. CSCI 2021*, pp. 1202–1208, 2021, doi: 10.1109/CSCI54926.2021.00250.

[8] C. Lartizien, M. Rogez, E. Niaf, and F. Ricard, 'Computer-aided staging of lymphoma patients with FDG PET/CT imaging based on textural information', *IEEE J. Biomed. Heal. Informatics*, vol. 18, no. 3, pp. 946–955, 2014, doi: 10.1109/JBHI.2013.2283658.

[9] T. A. A. Tosta, M. Z. Do Nascimento, P. R. De Faria, and L. A. Neves, 'Application of Evolutionary Algorithms on Unsupervised Segmentation of Lymphoma Histological Images', *Proc. - IEEE Symp. Comput. Med. Syst.*, pp. 89–94, 2017, doi: 10.1109/CBMS.2017.69.

[10] E. Michail, K. Dimitropoulos, T. Koletsa, I. Kostopoulos, and N. Grammalidis, 'Morphological and textural analysis of centroblasts in low-thickness sliced tissue biopsies of follicular lymphoma', *2014 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBC 2014*, pp. 3374–3377, 2014, doi: 10.1109/EMBC.2014.6944346.

[11] M. Goncalves Ribeiro, L. Alves Neves, G. Freire Roberto, T. A. A. Tosta, A. S. Martins, and M. Z. Do Nascimento, 'Analysis of the Influence of Color Normalization in the Classification of Non-Hodgkin Lymphoma Images', *2018 31st SIBGRAPI Conference on Graphics, Patterns and Images (SIBGRAPI)*, pp. 369–376, 2018, doi: 10.1109/SIBGRAPI.2018.00054.

[12] A. E. Nugroho, W. D. Lukito, I. Anshori, W. Adiprawita, H. A. Usman, and O. Husain, 'CLAHE Performance on Histogram-Based Features for Lymphoma Classification using KNN Algorithm', *Proceeding 15th Int. Conf. Telecommun. Syst. Serv. Appl. TSSA 2021*, 2021, doi: 10.1109/TSSA52866.2021.9768221.

[13] N. Hatipoglu and G. Bilgin, 'Classification of Malignant Lymphoma Types Using Convolutional Neural Network', *2020 Med. Technol. Congr.*, 2020.

[14] A. Ganguly, R. Das, and S. K. Setua, 'Histopathological Image and Lymphoma Image Classification using customized Deep Learning models and different optimization algorithms', *2020 11th Int. Conf. Comput. Commun. Netw. Technol. ICCCNT 2020*, 2020, doi: 10.1109/ICCCNT49239.2020.9225616.

[15] A. I. Kamel, T. F. Taha Ali, and M. A. Tawab, 'Potential impact of PET/CT on the initial staging of lymphoma', *Egypt. J. Radiol. Nucl. Med.*, vol. 44, no. 2, pp. 331–338, 2013, doi: 10.1016/j.ejrnm.2012.12.008.

[16] N. H. E. D. Behairy, T. A. Rafaat, A. S. E. D. El Nayal, and M. I. Bassiouny, 'PET/CT in initial staging and therapy response assessment of early mediastinal lymphoma', *Egypt. J. Radiol. Nucl.*

*Med.*, vol. 45, no. 1, pp. 61–67, 2014, doi: 10.1016/j.ejrnm.2013.11.009.

[17] A. Elsammak, 'Clinical usefulness of PET-CT in staging, evaluation of treatment response and restaging of thoracic lymphoma', *Egypt. J. Radiol. Nucl. Med.*, vol. 48, no. 4, pp. 1073–1081, 2017, doi: 10.1016/j.ejrnm.2017.04.005.

[18] R. A. Elshafey, N. Daabes, and S. Galal, 'FDG-PET/CT in re-staging of patients with non Hodgkin lymphoma and monitory response to therapy in Egypt', *Egypt. J. Radiol. Nucl. Med.*, vol. 49, no. 4, pp. 1076–1082, 2018, doi: 10.1016/j.ejrnm.2018.06.003.

[19] M. Panebianco *et al.*, 'Comparison of 18F FDG PET-CT AND CECT in pretreatment staging of adults with Hodgkin's lymphoma', *Leuk. Res.*, vol. 76, pp. 48–52, 2019, doi: 10.1016/j.leukres.2018.11.018.

[20] D. Albano *et al.*, 'Diagnostic and Clinical Impact of Staging 18F-FDG PET/CT in Mantle-Cell Lymphoma: A Two-Center Experience', *Clin. Lymphoma, Myeloma Leuk.*, vol. 19, no. 8, pp. e457–e464, 2019, doi: 10.1016/j.clml.2019.04.016.

[21] 'NCBI Gene Expression Omnibus'. https://www.ncbi.nlm.nih.gov/geo.

[22] M. D. Christian Steidl, et al., 'Tumor-Associated Macrophages and Survival in Classic Hodgkin's Lymphoma', *N. Engl. J. Med.*, vol. 362, no. 10, pp. 875–885, 2010.

[23] D. A. Hashimoto, T. M. Ward, and O. R. Meireles, 'The Role of Artificial Intelligence in Surgery', *Adv. Surg.*, vol. 54, pp. 89–101, 2020, doi: 10.1016/j.yasu.2020.05.010.

[24] R. Dias and A. Torkamani, 'Artificial intelligence in clinical and genomic diagnostics', *Genome Med.*, vol. 11, pp. 1–12, 2019, doi: 10.1186/s13073-019-0689-8.

[25] S. Hayou, A. Doucet, and J. Rousseau, 'On the impact of the activation function on deep neural networks training', *Arxiv*, 2019.

[26] 'MathWorks-Help Center'. https://www.mathworks.com/help/.

[27] C. Doğan, 'Balina Optimizasyon Algoritması ve Gri Kurt Optimizasyonu Algoritmaları Kullanılarak Yeni Hibrit Optimizasyon Algoritmalarının Geliştirilmesi', 2019.

[28] E. G. Dada, S. B. Joseph, D. O. Oyewola, A. A. Fadele, H. Chiroma, and S. M. Abdulhamid, 'Application of Grey Wolf Optimization Algorithm: Recent Trends, Issues, and Possible Horizons', *Gazi Univ. J. Sci.*, vol. 35, no. 2, pp. 485–504, 2022, doi: 10.35378/gujs.820885.

[29] F. Akalın and N. Yumuşak, 'DNA genom dizilimi üzerinde dijital sinyal işleme teknikleri kullanılarak elde edilen ekson ve intron bölgelerinin EfficientNetB7 mimarisi ile sınıflandırılması', *Gazi Üniversitesi Mühendislik-Mimarlık Fakültesi Derg.*, vol. 37, no. 3, pp. 1355–1371, 2022, doi: 10.17341/gazimmfd.900987.

[30] O. Sertel, J. Kong, U. V. Catalyurek, G. Lozanski, J. H. Saltz, and M. N. Gurcan, 'Histopathological image analysis using model-based intermediate representations and color texture: Follicular lymphoma grading', *J. Signal Process. Syst.*, vol. 55, pp. 169–183, 2009, doi: 10.1007/s11265-008-0201-y.

[31] M. Lippi *et al.*, 'Texture analysis and multiple-instance learning for the classification of malignant lymphomas', *Comput. Methods Programs Biomed.*, vol. 185, 2020, doi: 10.1016/j.cmpb.2019.105153.

[32] B. Ganeshan *et al.*, 'CT-based texture analysis potentially provides prognostic information complementary to interim fdg-pet for patients with hodgkin's and aggressive non-hodgkin's lymphomas', *Eur. Radiol.*, vol. 27, pp. 1012–1020, 2017, doi: 10.1007/s00330-016-4470-8.

[33] M. Z. Nascimento, L. Neves, S. C. Duarte, Y. A. S. Duarte, and V. R. Batista, 'Classification of histological images based on the stationary wavelet transform', *J. Phys. Conf. Ser.*, vol. 574, 2015, doi: 10.1088/1742-6596/574/1/012133.

[34] E. S. Alférez, A. Merino, L. E. Mújica, M. Ruiz, L. Bigorra, and J. Rodellar, 'Digital Blood

Image Processing and Fuzzy Clustering for Detection and Classification of Atypical Lymphoid B cells', *Jornades Recer. Euetib 2013*, pp. 1–12, 2013.

[35] O. Sertel, G. Lozanski, A. Shanáah, and M. N. Gurcan, 'Computer-aided detection of centroblasts for follicular lymphoma grading using adaptive likelihood-based cell segmentation', *IEEE Trans. Biomed. Eng.*, vol. 57, no. 10, pp. 2613–2616, 2010, doi: 10.1109/TBME.2010.2055058.

[36] N. V. Orlov *et al.*, 'Automatic classification of lymphoma images with transform-based global features', *IEEE Trans. Inf. Technol. Biomed.*, vol. 14, no. 4, pp. 1003–1013, 2010, doi: 10.1109/TITB.2010.2050695.