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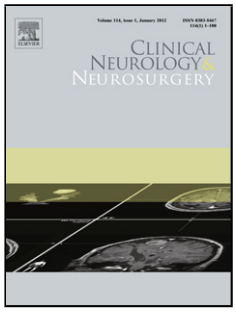

Prediction value of preoperative findings on meningioma grading using artificial neural network

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Prediction Value of Preoperative Findings on Meningioma Grading Using Artificial Neural Network

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Highlights

- Blood biomarkers are associated with meningioma grade with different correlations.
- High monocyte count and high LMR are associated with high grade meningioma.
- Artificial neural network can acceptably be used to specify meningioma grading.
- Artificial neural network can evaluate data and obtain a functional response.

Objectives: Meningioma is the most common brain tumor in adults. Grade 1 meningiomas have excellent prognoses, but grades 2 and 3 usually have worse outcomes, higher recurrence rates, and higher mortality rates. Preoperative determination of tumor grade may be helpful in deciding the

type of surgery and the rate of resection. Blood markers have been used to predict the rate of malignancy and prognosis of tumors in different regions, including the brain. The current study investigated the use of blood markers on predicting meningioma grade.

Patients and Methods: Patients with newly diagnosed meningiomas were retrospectively reviewed. Data on the patients' demographics, tumor locations, blood markers, and tumor pathology grades was extracted. The relationship between preoperative findings and tumor grade was statistically analyzed, and using the same findings and an artificial neural network, the accuracy of tumor grade prediction was evaluated.

Results: This study included 95 patients, 69 cases (72.4%) of grade 1, 23 cases of grade 2 (24.4%) and 3 cases of grade 3 (3.2%) meningiomas. Monocyte and neutrophil counts as well as lymphocyte-to-monocyte ratio (LMR) were significantly different between low grade and high grade meningiomas, with higher monocyte and neutrophil counts and higher LMR associated with high grade meningiomas ($p<0.05$). Evaluation of the data with an artificial neural network using RBF with 5 variables (age, monocyte count, LMR, platelet-to-lymphocyte ratio (PLR), and neutrophil count) indicated that tumor grade can be determined with 83% accuracy using an artificial neural network.

Conclusion: A preoperative high monocyte count and high LMR are associated with high grade meningioma. An artificial neural network using preoperative data can acceptably be used to characterize meningioma tumor grades.

Keywords: brain tumor, blood marker, meningioma, monocytes, artificial neural network, lymphocyte-to-monocyte ratio (LMR)

Introduction

Meningioma is the most common primary brain tumor in adults (1, 2), and its incidence is 8.3 of every 100,000 individuals (3). According to the 2016 WHO Classification of Tumors of the Central Nervous System, meningiomas are divided into three grades. Grades 2 and 3 meningiomas have a

higher probability of recurrence (4). In terms of prevalence, 81.1% are grade 1, 16.9% are grade 2, and 1.7% are grade 3 tumors (5). Grades 2 and 3 meningiomas are more aggressive, and the chance of recurrence in five years is about 50% and 90%, respectively (5). The mortality rates at ten years are about 53% and 100% for grade 2 and grade 3 meningiomas, respectively (5). Age and gender are effective variables in meningioma incidence, and some genetic diseases such as NF2 and a history of radiation therapy are recognized as risk factors (2).

Hematologic markers have been implicated as a risk factor for malignancy in some tumors and have been shown to be contributory to the rate of post-operative tumor recurrence (6-8). Moreover, they may be predictors of response to treatment in advanced gastric metastases (7). Higher neutrophil-to-lymphocyte ratio (NLR) levels are associated with a poor prognosis and less survival in brain metastases (9). Some studies have shown that higher NLR, platelet-to-lymphocyte ratio (PLR), and lower lymphocyte-to-monocyte ratio (LMR) values are accompanied by a poor prognosis in glioma (9-11). In meningiomas, higher levels of leukocytes and lower LMRs have been suggested as factors in predicting higher grades of tumors (12).

This study investigated the relationship of demographic characteristics, tumor location, and blood markers with meningioma tumor grades. In addition to statistical analysis tools, artificial neural networks were used as an auxiliary factor in predicting tumor grade.

Warren McClatch and Walterspitz designed the first artificial networks in the early 1940s (13). Heb designed the first law of learning in 1949 (14). Roosevelt and several other researchers presented a large family of neural networks called positrons (15). The use of neural networks diminished, but after some time artificial neural networks regained their popularity, and until the late 1980s, the use of artificial neural networks expanded (15).

How Neural Networks Work

Neural networks are simple operating elements that work in parallel. These elements are inspired by the biological nervous system. In nature, the performance of neural networks is determined by how the components are connected. ANN (Artificial Neural Network) is an artificial model of a

natural neural network in which the connections between components are set by adjusting the amount of each connection as its weight. Adjusting the weight of each connection between the elements of an artificial neural network is called training. In Figure 1, the network is adapted based on matching the input with the relevant output. In general, a large number of input and output pairs are required to properly adjust the weights (with the same neural network training).

Neural networks are used in many fields, such as implementing complex functions, cancer diagnosis, MRI image processing, classification of disease grading, and EEG and ECG analysis (16-18). Neural networks have different types and, depending on the type of data, one or more neural networks can be used. The most common neural networks are positron, Hopfield, multi-layer perceptron (MLP), radial basis function (RBF), and self-organizing feature map (SOFM). Every neural network has a special characteristic that determines the power of that network.

To illustrate the function of a neural network and how to learn, a simple example is presented in Figure 2. Consider a neural network like Fig. 2, where the aim is to identify a specific type of cancer, and there are two blood markers and one answer for each patient. As shown in Figure 2, the blood markers are M1 and M2 and the final answer is Ans.

To begin, the weights were randomly set. Then, the first patient's blood markers were assigned to the network, and it produced an output in the Answer field. This output was compared to the patient's actual response value and, based on this comparison, the weights were changed. This was done multiple times for all patients so that the network output for each patient had the least difference with the real value. In other words, the network was trained.

Material and Methods

This study retrospectively reviewed a database of newly diagnosed meningioma patients admitted to Imam Hossein Hospital in Tehran between October 2016 and October 2018. The research protocol was approved by the hospital's Institutional Ethics Committee (IEC). Patients older than 18 years of age with meningioma tumors newly diagnosed according to the 2007 World Health

Organization classification of tumors of the central nervous system were included in the study. Excluded from the study were patients with (1) a history of malignancy or chemotherapy; (2) any history of previous brain injury such as stroke, brain tumor, moderate or severe brain injury; (3) a history of previous neurologic deficit unrelated to meningioma; (4) infection or inflammatory disease at the time of diagnosis and blood sampling; (5) consumption of drugs that change the proportion of blood cells such as corticosteroids; (5) a lack of access to blood marker results or pathology reports; (6) a white blood cell (WBC) count >10000.

Demographic data, side of tumor, blood cell counts, and the ratio of cells were determined, and statistical analysis was performed using SPSS (version19.0, IBM, USA). The student's t-test was used to compare variables, and the univariate logistic regression test was used to determine which variables correlated with tumor grade. After statistical analysis, ANN was used to evaluate the accuracy of preoperative markers in predicting tumor grading.

MATLAB (2019a) software was used to evaluate the data in the neural network used, i.e. radial basis function (RBF). As shown in Figure 3, RBF is a network that uses radial basis functions as an activity function, and the output of this network is a linear combination of radial functions and is widely used in classification and prediction. RBF was used, because the data obtained in this study was distributed over a complex nested and islanded feature space.

RBFs have three layers and are characterized by a set of input layers, an output layer, and a layer of processing units called the hidden units layer. Each hidden unit implements a radial basis function.

The weight change algorithm plays an important role in neural networks, and the weights of the output layer of the RBF network are updated using the back propagation algorithm:

$$\Delta W = \eta(y - O)\big(O(1 - O)\big)\varphi(x)$$

where η is the learning rate of the output layer of the RBF neural network by which the weight can be manipulated, and $\varphi(x)$ is the hidden layer outputs of the RBF classifier and is produced using the following Gaussian function:

$$d(x_i, c_j) = \|x_i, c_j\| = \left(\sum_{u=1}^{p} |x_{iu} - c_{ju}|^2\right)^{1/2}$$

$$\varphi(x) = e^{\left(-\frac{d(x_i, c_j)^2}{2\sigma_j{}^2}\right)}, j = 1,2,3, \ldots, k\,; i = 1,2,3, \ldots., Q$$

in which x_i is the i^{th} input vector, Q is the input dimension, c_j is the center of the j^{th} neuron in the hidden layer which are obtained using the K-means clustering method, and σ_j is the Euclidean distance between the center of the j^{th} neuron in the hidden layer and the nearest of its neighborhood, which is later multiplied by a constant β. The optimal value for β is larger than one and is determined during experiments.

$$\sigma_j = \beta * min\|c_j - c_n\|, n, j = 1,2,3, \ldots \ldots, k \; and \; n \neq j$$

$$O_{ik} = \sum_{j=0}^{k} [\varphi_j(x_i) w_{kj}], k = 1,2,3, \ldots \ldots, m$$

The RBF network input used in this study consisted of age, monocyte count, neutrophil count, PLR, and LMR. The output also contained low or high grade tumor. In the method used in this study, feature vectors were given as inputs to the RBF artificial neural network. The network generated two outputs for each input sample of training data. The artificial neural network produced two outputs with different values, and the higher value output was considered as the network response to the data. At every step, the three criteria of accuracy, recall, and precision were calculated, and their averages are reported.

The evaluation data was used to determine the stopping point of the training process, and the test data was used to calculate accuracy.

The three stages of training, validation, and testing were performed for patients at a ratio of 2:1:1, and the structure of neurons was assumed to be constant. This ratio was chosen because it is a common selection and based on the dataset and number of network weights and parameters.

In addition to the 2:1:1 ratio, this study applied another training method to a separate neural network. In this method, in the training phase five mentioned markers were designed as input and dichotomized tumor grades were considered as the network output. After being designed, the network was activated; 70% of the data was used for the network training step and 30% for testing, and the accuracy rate was determined. This process was repeated many times to achieve the best results.

In both methods, the selection of cases between benign and malignant cases for training, evaluation, and testing was done randomly. Comparing the two methods, the results of the 2:1:1 method were slightly better in this study; therefore, to avoid ambiguity, the 2:1:1 ratio was used to express the results.

Results

This study recruited 118 patients with meningiomas. Twenty-three cases were excluded because of multiple surgeries (6), a history of cancer or inflammatory disease (5), a WBC greater than 10,000 (10), or insufficient data (2). A total of 95 patients were included in this study, of which 69 cases (72.4%) had grade 1, 23 cases (24.4%) had grade 2, and 3 cases (3.2%) had grade 3 meningiomas. Among the participants, 37 (39%) were male and 58 (61%) were female. All participants were between 18 and 78 years of age. The patients' demographic characteristics and blood markers and their proportions are summarized in Table 1. Forty cases (58%) of benign tumor were located at the base of the skull, and 19 (73%) cases were diagnosed as high grade meningioma. The means of all blood markers except monocytes were higher in the high grade group.

No significant difference in age was observed between the two groups. More tumors were seen in females than males, but significantly more high grade tumors were seen in males (p<0.003). There was a significant number of right-sided high grade tumors, but due to the small number of cases, this result must be interpreted cautiously. No significant relationship was found between tumor location and grade of malignancy. Among blood markers, monocyte count, neutrophil count, and LMR were significantly different between the two groups; higher monocyte and neutrophil counts and higher LMR were associated with a higher grade of tumor. Univariate logistic regression analysis indicated that LMR, monocyte counts, and neutrophil counts were significantly associated with tumor grade. In multivariate logistic analysis no independent variable was significantly associated with tumor grade.

The distribution of the values of the variables is shown in Charts 3 and 4. In the box plots, values equal to 50% of the data distribution of each variable are specified as black boxes. The difference in height between every specific variable in the lower or upper grade indicates the greater value of that variable in predicting the tumor grade. Chart 1 shows that the absolute values of monocytes and PMN differ from the other cells, so they are noteworthy variables. Chart 2 shows that LMR and then PLR can be considered as valuable variables.

In this study, elementary and abstract structures according to the data were prepared using the feature selection techniques. Chart 3 shows the order of the features one-dimensionally and reveals that the most important features are LMR, PMN, and monocyte count.

Chart 3 shows that the LMR index is more capable of detecting the tumor grade than the others, and data such as gender or tumor location cannot be contributory. It is important to note that detection based on a combination of the parameters can produce additional values. In this study, various combinations of the variables in Chart 3 were assigned to the RBF artificial neural network. Those networks that were trained with age, PLR, LMR, neutrophil count, and monocyte count had a higher performance and illustrated lower MSE (mean squared error) than any others.

Chart 4 shows that after 50 training sessions the efficiency of the network was about 83% at the highest level. Chart 5 shows that the MSE index reached the lowest level in the 50 training courses. The artificial neural network used in this study had a hidden layer, an input layer, and an output layer. The input layer consisted of five nodes (monocyte, LMR, neutrophil, age and PLR), and the output layer consisted of two nodes that represented each of the two specific grades of meningioma (low and high). If both output points are enabled or if none of the outputs are enabled, the network is unable to categorize correctly for this particular entry or, in other words, for these specific patients.

Based on the results of information processing with the artificial neural network in this study and using different combinations of data, it was shown that simultaneous inputs can be effective in predicting preoperative tumor grade, and it is more valuable than statistical analysis alone. RBF with this data can predict tumor grade with an accuracy of 83%.

Table 2 shows the parameters related to the performance of the artificial neural network. As shown in this table, ANN had an acceptable AUC (0.694). Comparing the F_Measure + and F_Measure- revealed that ANN had a better estimation of low grade meningioma, because the number of the low grade meningiomas was much higher. The Matthews correlation coefficient (MCC) is another parameter used in this study to evaluate ANN, and the results indicated that the relationship between the observed value, the predicted value, and the MCC value in this study was 0.4719.

Discussion

In this survey, the preoperative predictive values of blood markers, tumor location, and demographic characteristics of cases with pathologic grades of newly diagnosed meningiomas were studied. Both statistical analysis and an artificial neural network were used to evaluate their values in specifying the grade of the meningiomas.

Systemic inflammation can be a predictor in the prognosis of some tumors. The association between worse survival and some inflammatory factors such as leucocytosis, thrombocytosis, and high NLR or PLR has been demonstrated (6, 8, 19-21). In the treatment of gastric cancer, higher levels of NLR are a negative prognostic factor in response to metastatic tumor management (7). High levels of neutrophils due to increased growth factors, angiogenesis, and increased paraneoplastic signals can simultaneously increase tumor growth and the lymphocytes involved in apoptosis and cell reduction (1). The production of thrombopoietic cytokines can lead to paraneoplastic thrombocytosis (22). Blood markers seem to be more valuable compared with age and gender in diagnosing brain tumors (23). NLR has been reported as an independent factor in poor prognosis of glioma or RDW as a gender-independent factor in brain tumors (24-26).

The comparison of healthy cases and patients with brain tumor revealed that blood markers such as hemoglobin, monocyte count, and MLR were decreased and platelet and neutrophil levels were increased in patients; these changes were also observed in low grade meningioma and gliomas (19). Mononuclear cells that are primarily T cells and macrophages infiltrate and react to tumor cells (27). Higher leukocyte counts and lower LMR levels were associated with higher grade meningioma in examining changes in blood cells and inflammatory factors in meningioma (12).

In the current study, higher monocyte and LMR levels were associated with higher grade probability, which is consistent with similar reports that absolute monocyte can be an independent factor correlated with higher grade; this may be related to the role of monocytes in the destruction of tumor cells (12, 19, 28). In this study, the relationship between LMR and tumor grade was positive, and high grade meningioma tumors have a higher LMR. Ruo-Fei Liang et al., however, evaluated a series of 944 meningiomas and reported that high grade tumors have a lower LMR grade. This incompatibility of results cannot be justified (12). Because of the low prevalence of malignant variants, the number of high grade cases in this study was low, and this can limit the results of the analysis. Due to this impediment, it is recommended that future studies with larger sample sizes be conducted.

The strength of this study is the use of a neural network in the simultaneous evaluation of all blood factors plus age, gender, and location of the tumor in predicting tumor grade. Due to its structure, the neural network uses different variables with different weights based on their diagnostic value and can provide a more accurate answer for probable evaluation in determining tumor grade. The diagnostic value of the artificial neural network used in this study is low (AUC=0.694) and it seems that by using more data, the network can achieve higher accuracy and be appropriate for clinical use. The weights of the inputs were important in determining the structure, training, and type and number of neural network inputs. Although some of these indices did not have statistically appropriate parameters, they did contain hidden knowledge in the study set. The results regarding the performance of the artificial neural network are consistent with the statistical results, so it can be consider as a valuable factor in predicting meningioma grade before surgery.

This study had some limitations. It is a retrospective study with a limited sample size. In this study, the results cannot be generalized due to the low number of high grade meningiomas. Secondary infection, smoking and underlying diseases such as diabetes and lung, kidney and liver disorders can affect the statistical results and performance of the artificial neural network. To generalize the results and clinical use, a higher sample size study can be helpful. However, more neural network training with a larger sample size and the use of more variables such as tumor volume, lesion characteristics, and preoperative clinical symptoms can provide more accurate screening and more effective results.

Credit Author Statement

Hamid Reza Khayat Kashani: conceptualization, methodology, project administration. **Shirzad Azhari:** writing- reviewing and editing. **Hossein Nayebaghayee:** data curation. **Sohrab Salimi:** visualization, Investigation. **Hasan Reza Mohammadi:** software and formal analysis. All authors discussed the results and contributed to the final manuscript and revision.

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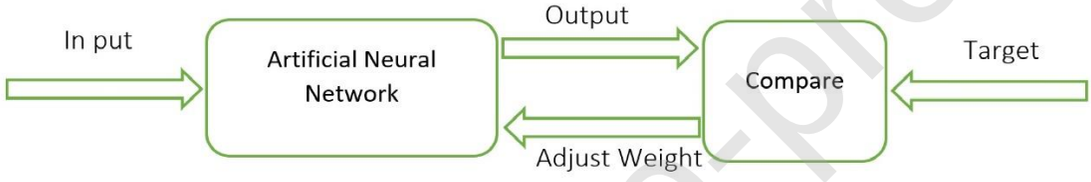


Figure 1. Simple expression of how neural network works

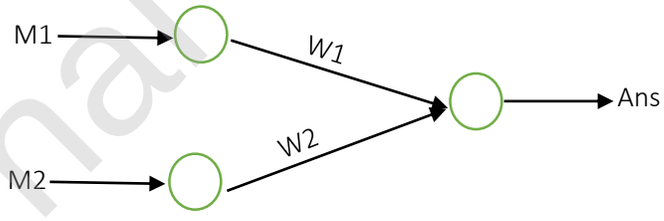
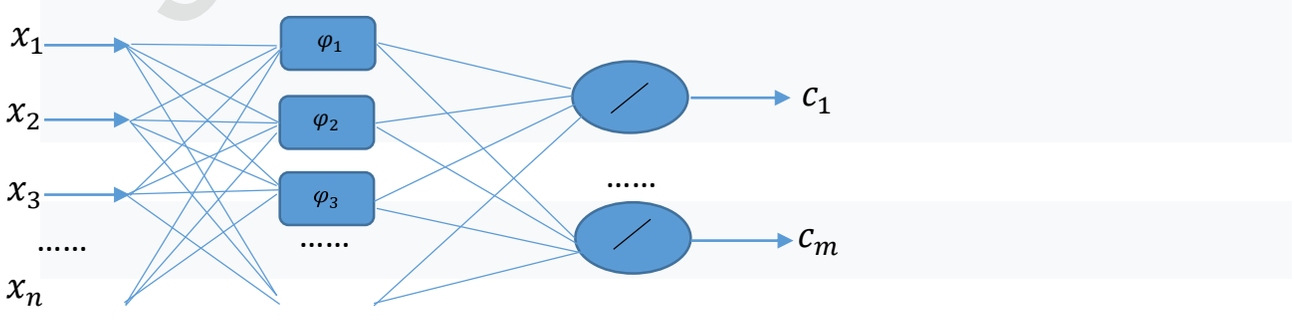


Figure 2. Schematic view of input and weighting data and neural network response



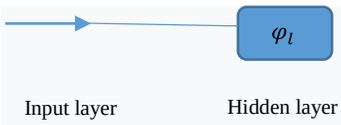


Figure 3. This figure shows a schematic view of the three layers of artificial neural network

Table 1. Distribution of demographic data, tumour location and blood markers in patients with meningioma.

	LOW GRADE	HIGH GRADE	P VALUE
AGE	**52(23-78)**	**52(18-72)**	**0.951**
SEX			
MALE	**24**	**13**	**0.003**
FEMALE	**45**	**13**	
SIDE			
RT	**2**	**11**	
LT	**26**	**9**	**0.039**
BI	**23**	**6**	
LOCATION			
SKULL BASE	**40**	**19**	**0.1**
NON SKULL BASE	**29**	**7**	
WBC	**6838(3800-9900)**	**7188(5100-9800)**	**0.29**
LYMPHOCYTE	**1803(522-3562)**	**2009(366-5635)**	**0.497**
NEUTROPHIL	**4499(1920-8578)**	**4737(1909-7191)**	**0.0032**
PLATLET $\times 10^3$	**225.2(109.0-410.0)**	**227.6(138.0-326.0)**	**0.086**
MONOCYTE	**374(62-914)**	**352(83-591)**	**0.006**
RBC $\times 10^6$	**4.47(3.16-5.61)**	**4.33(2.82-6.08)**	**0.62**
NLR	**3.56(5.77-16.4)**	**3.86(3.38-19.6)**	**0.49**
PLR	**148(59.5-535)**	**159(24.5-519)**	**0.095**
LMR	**5.91(1.1-23.5)**	**5.93(2.1-12.8)**	**0.009**

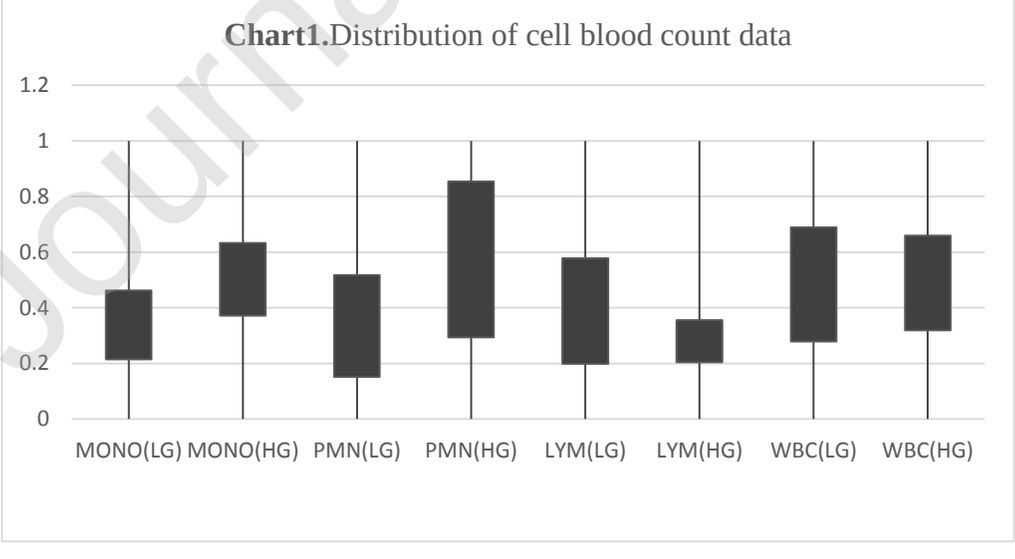
NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; AGR, Albumin-to-globulin ratio.

Table2.

Specifications of artificial neural network designed to determine tumor grade

$Recall^-$	$Recall^+$	$Precision^-$	$Precision^+$	$F\_Measure^-$	$F\_Measure^+$	MCC	AUC
0.7142	0.8461	0.4545	0.9428	0.5554	0.8918	0.4719	0.694

0≤ F_Measure ≤1, -1 ≤MCC ≤+1; MCC: Matthews Correlation Coefficient; AUC: Area Under the Curve



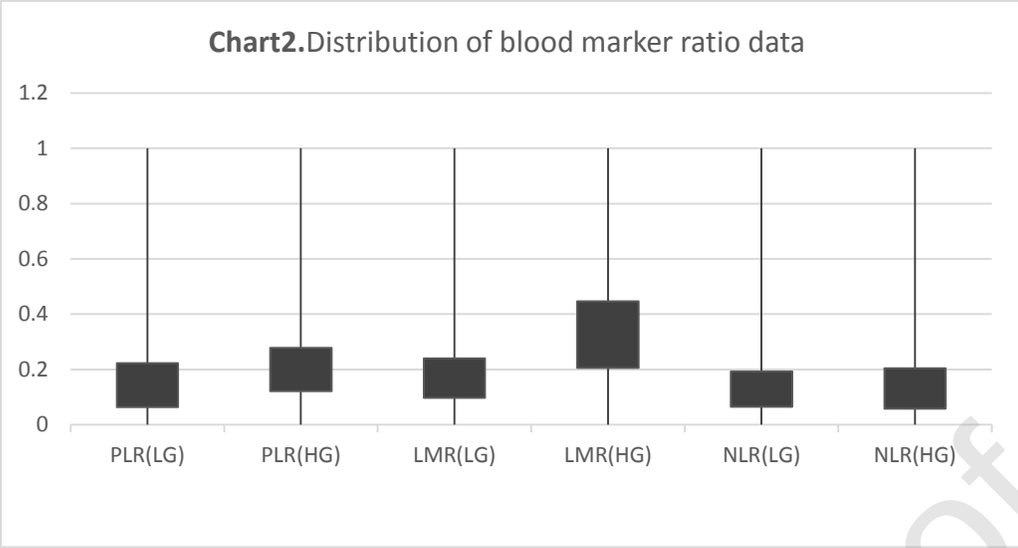


Chart 3. Impact of data as one dimention

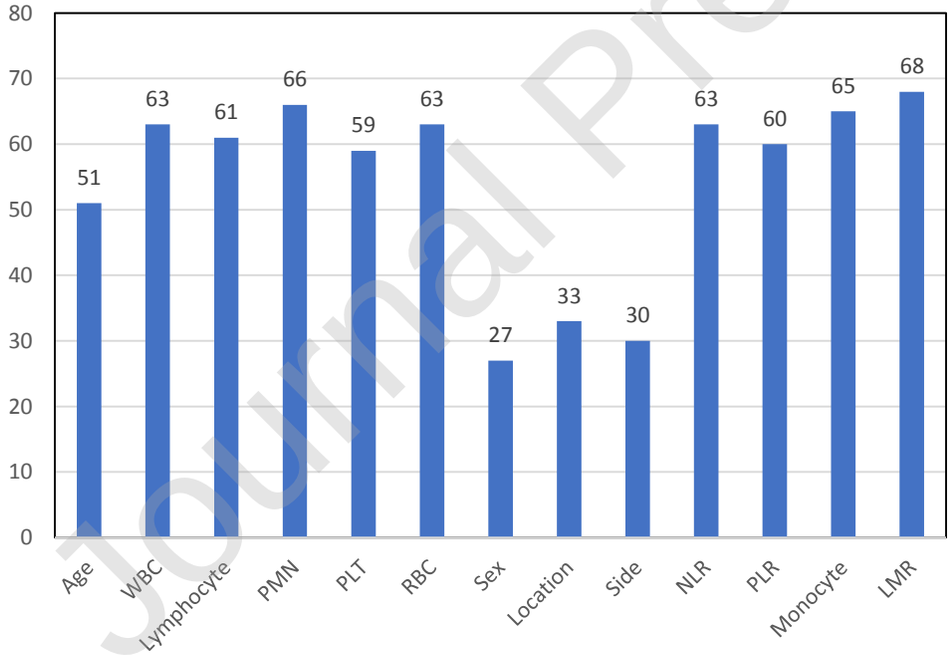


Chart 4. Diagram of efficiency after 50 training session

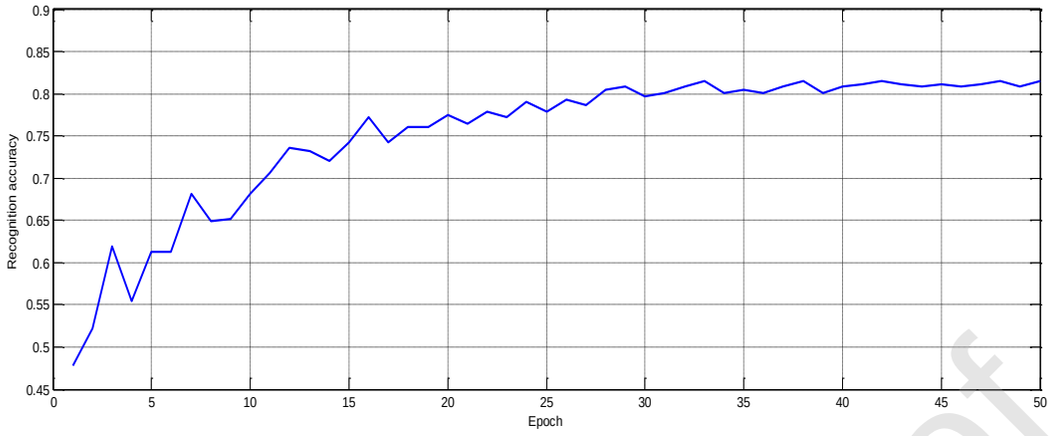


Chart 5. Diagram of Mean squared error(MSE) after 50 training course