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Evaluation of inflammatory markers in childhood-onset psychiatric disorders by using artificial intelligence architectures

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ABSTRACT

Objective: *One of the mechanisms proposed in the etiology of psychiatric disorders is the immunological and inflammatory processes. The aim of this study was to evaluate the neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and mean platelet volume (MPV) levels as an inflammatory marker in childhood-onset psychiatric disorders and to evaluate the inflammation parameters in the etiology.* ***Methods:*** *The hemogram data of 165 patients with early onset schizophrenia, bipolar disorder, depressive disorder and anorexia nervosa and 70 healthy children and adolescents were evaluated. In this study, artificial neural networks (ANN) are used for artificial intelligence-based computer aided system (CAS) design which can be able to help pediatric psychiatry specialists to diagnose easily and quickly. The data belonging to the patients were subjected to the normalization process in the designed system. Then, normalized data was entered to ANN and five outlets including four diseases and one test group were determined. The ANN model used has features of multilayer sensor network design. A three-tier cross validation method was used to test the success of the designed system. The three-tier cross-validation method is further divided into three parts. In each stage the first part was used for the test and the second and third parts was used for training.* ***Results:*** *The accuracy value of the model were calculated as 99%.* ***Conclusion:*** *These results show that the designed model gives robust and reliable results and can help the physicians in prediagnosis and differential diagnosis in clinical practice.* ***(Anatolian Journal of Psychiatry 2020; 21(3):301-309)***

Keywords: *artificial intelligence, childhood onset psychiatric disorder, monocyte/lymphocyte ratio, neutrophil/ lymphocyte ratio, platelet/lymphocyte ratio*

Çocukluk çağı başlangıçlı psikiyatrik hastalıklarda yapay zeka mimarileri ile inflamatuvar değerlendirme

ÖZ

Amaç: *Psikiyatrik hastalıklarda etiyopatogenezde öne sürülen mekanizmalardan biri immünolojik ve inflamatuvar süreçlerdir. Son yıllarda ucuz ve kolay bakılabilir bir yöntem olan hemogram verilerinin inflamatuvar belirteç olarak kullanılmasına olan ilgi giderek artmaktadır. Bu çalışmada çocukluk çağı başlangıçlı psikiyatrik bozukluklarda inflamatuvar belirteç olarak gündeme gelen nötrofil/lenfosit oranı, platelet/lenfosit oranı, monosit/lenfosit oranı ve ortalama trombosit hacmi düzeylerinin karşılaştırılması ile etiyolojide inflamasyon parametrelerinin değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *Çalışmada çocuk psikiyatrisi yataklı servisinde tedavi gören erken başlangıçlı şizofreni, bipolar bozukluk, depresif bozukluk ve anoreksiya nervozalı 165 hasta ve 70 sağlıklı çocuk ve ergenin hemogram verileri kullanıldı. Bu çalışmada çocuk psikiyatrisi uzmanlarının hastalara tanı koymada zaman ve hız bakımından*

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yardımcı olabilecek yapay sinir ağı (YSA) tabanlı bilgisayar destekli tanı sistemi (BDTS) tasarlandı. Tasarlanan sistemde ilk olarak hastaların verileri normalizasyon işlemine tabi tutuldu. Daha sonra normalize olan veriler YSA'nın girişine verilerek dört bozukluk ve bir test grubuna ilişkin beş çıkış belirlendi. Kullanılan YSA modeli Çok Katmanlı Algılayıcı Ağ Mimarisinin (ÇKAA) özelliklerine sahiptir. Tasarlanan sistemin başarısının sınanması için üç katmanlı çapraz doğrulama yöntemi kullanıldı. Bu yöntemin veri kümesi de üç parçaya ayrıldı. Her aşamada bir parça test için, ikinci ve üçüncü parçalar ise eğitim için kullanıldı. ***Sonuçlar:*** *Tasarlanan sistemin kullanılan veri setindeki bozuklukları sınıflandırmadaki doğruluk oranı %99 olarak hesaplandı.* ***Tartışma:*** *Bu sonuçlar bu modellemenin hızlı ve güvenilir bir yöntem olarak çocuk psikiyatrisinde yukarıda tanımlanan hasta grupları için ön tanı ve ayırıcı tanıda kullanılabileceğini göstermektedir.* ***(Anadolu Psikiyatri Derg 2020; 21(3):301-309)***

Anahtar sözcükler: *Yapay zeka, çocukluk çağı psikiyatrik bozuklukları, monosit/lenfosit oranı, nötrofil/ lenfosit oranı, platelet/lenfosit oranı*

INTRODUCTION

The relationship between the brain and the immune system is related to each other in a wide range.[1,2]

It has been suggested that many different immunological and inflammatory mechanisms are mediated in different psychiatric disorders. A member of the immune system that mediates inflammation is leukocytes.[3] Neutrophils, a variety of leukocytes, are responsible for the secretion of chemical mediators in inflammation.[4] After neutrophil to lymphocyte ratio (NLR) has been shown to be an inflammatory marker,[3] as well as neutrophil quantity, these markers have increasingly been used in psychiatric disorders[5-8] and other medical conditions.[9-14] Other CBC parameters, including monocyte/lymphocyte ratio (MLR) and platelet/lymphocyte ratio (PLR) have also been used as inflammatory markers in several diseases including cardiovascular diseases,[15,16] psoriasis,[17] cancer,[18] and psychiatric diseases,[19,20] as well as NLR. The studies investigating the role of mean platelet volume (MPV) in inflammatory processes have also been conducted as well as the other CBC parameters. MPV was found to be an indicator of platelet activation.[21] In addition, it has been shown that MPV ratio increase in inflammatory diseases, which supports the relationship between MPV and inflammation.[22-25]

In the literature, many methods have been defined in the diagnosis of diseases. However, the diagnosis process can be long and costly with existing diagnostic systems. Today, computer aided systems (CAS) are frequently used in many applications such as control and system identification, image and voice recognition, estimation and prediction, fault analysis, medicine, communication, traffic, and production management. The use of CASs in diagnosing diseases can increase the ability of specialists to make decisions. In the literature, architectures such as artificial neural networks (ANN) are used frequently in artificial intelligence-based CAS design.[26-29] ANNs can make generalizations. They can product a response to any input data they have never used. Artificial neural networks, due to this ability to learn and generalize, have found wide application area in many fields of science. They have the ability to product solutions to complex problems.[27] The ANN learn through examples, similar to humans. Therefore, the data set is divided into two parts including training and test sets.[27-29]

In this study, a CAS was proposed by using artificial neural networks (ANN) in order to facilitate the classification of early onset schizophrenia, bipolar disorder, major depressive disorder, and anorexia nervosa. Two goals was proposed: 1. investigation of the relationship between early onset psychiatric diseases and inflammatory markers, 2. whether these parameters can be used in the preliminary diagnosis and differential diagnosis.

METHODS

This study was planned as a retrospective study. The data used for childhood onset psychiatric diseases were obtained by screening the files of the inpatients between 2017 and 2019 retrospectively through the hospital system of İnönü University, Turgut Özal Medical Center Child and Adolescent Psychiatric Clinic. Data of patients with early onset schizophrenia, bipolar disorder, depressive disorder and anorexia neurosis were included in the study according to DSM-5 criteria. Data from patients were compared with the control group consisted of healthy individuals matched by age and gender. Ethical approval is obtained from the Board of Scientific Research and Publication of İnönü University with the Decision No. 2019/7-3.

Inclusion criteria

CBC values used in the study were obtained from the first assays applied to the patients on

the first day of hospitalization. Patients with a known infection at the time of blood collection with symptoms of any disease such as fever, pain, diarrhea chronic disease, history of substance use or active psychiatric disease, which can be associated with substance use were excluded from the study. In addition, the patients with a history of trauma and surgery were excluded from the study. How long the patients on psychiatric medication used these drugs and the names of the drugs were noted in detail. The data of the patients who were used outside the psychiatric medicine were not included in the study. All patients who participated in the study had an acute attack. Patients with bipolar disorder were in manic attack period. Patients with leukocytosis or thrombocytosis suggestive of infection according to CBC data were excluded from the study.

Adolescents in the control group were examined by a child psychiatrist according to DSM-5 criteria. Individuals with any psychiatric or medical illness were excluded from the study. CBC data of healthy children and adolescents without any known psychiatric or medical illnesses were taken as control group. Children and adolescents included in the control group were matched with the patient group by age and gender.

Sixteen patients who did not meet the inclusion criteria were excluded. The CBC data of 165 patients and 70 healthy children and adolescents who met all inclusion criteria were used in this modeling study.

Statistical analysis

SPSS 22 software was used for statistical analysis of the data. Qualitative data is expressed as a percentage. One-way ANOVA test, Kruskal Wallis test and Pearson's chi-square test and reciever operator characteristics curve analysis were used to analyze the data. A value of $p<0.05$ was considered statistically significant.

Artificial neural networks

The computer on which the CAS is designed has a 2.8 GHz processor and 16 GB of memory. Program codes were written in MATLAB 2018 program.

In the designed CAS, the CBC parameters including leukocyte count, lymphocyte count, neutrophil count, monocyte count, platelet count, NLR, PLR, MLR, MPV, age and sex parameters were normalized and entered as ANN input parameters. Then, based on these data, the classification of early onset schizophrenia, bipolar disorder, depressive disorder and anorexia nervosa diseases were performed by using ANN. At first stage of the modelling the input data were normalized. These normalized data were applied to the ANN models to predict four diseases and one test group. Totally five output parameters were predicted. The ANN model is multi-layer perceptron. Three-fold cross validation test was used to calculate the performance of the designed CAS. In addition, accuracy was used as performance parameters. In three-fold cross validation method, the data set was divided into three parts. At each stage, the first part was used for the testing, and the second and third parts were used for the training. Thus, the accuracy rate of the designed CAS has been determined effectively.

RESULTS

Among the children and adolescents included in the study, the mean age for SCH was 15.70±1.28, 15.13±1.83 for BAD, 15.13±1.62 for AN, 15.89±1.39 for MDD, and 15.41±1.87 for control group. 57 SCH patients, 23 BD patients, 61 MDD patients, 24 AN patients and 70 healthy controls were included in the study. There were no statistically significant differences between the patient group and the control group in terms of gender and age ($p>0.05$). Thirty-five out of 165 patients included in the study were using a psychiatric drug.

The mean and standard deviation rates of hemogram parameters and the results of the analysis of the patient and control group are given in Table 1. There was a statistically significant difference between the groups in terms of leukocytes ($p=0.007$), lymphocytes ($p=0.001$), monocytes ($p<0.001$), neutrophils ($p=0.004$), MPV ($p<0.001$), NLR ($p=0.001$) and MLR ($p=0.001$). The post hoc test results revealed that the statistical difference was caused by AN-BAB, AN-SCH and AN-MDB binary subgroups for leukocytes; MDB-SCH and MDB-control binary comparisons for lymphocytes; AN-SCH, AN-MDB and AN-BAB for monocytes; AN-SCH and AN-BAB for neutrophils; Control-AN, Control-BAB and Control-MDB for MPV; AN-SCH AN-BAB, and MDB-SCH for NLR; and AN-SCH and AN-BAB for MLR.

The results of ROC analysis for NLR, MLR and PLR rates for bipolar disorder and schizophrenia patients are given in Table 2. The area under the curve for MLR and NLR was significant for bipo-

Table 1. Comparison of mean blood values

Parameters	Anorexia nervosa	Bipolar dis.	Schizophrenia	Major depr. dis.	Healthy control	p
Leukocytes	6.11±1.42	7.37±1.39	7.33±1.60	7.45±1.50	6.91±1.83	**0.007**
Lymphocytes	2.29±0.63	2.14±0.65	2.13±0.67	2.64±0.69	2.28±0.76	**0.001**
Monocytes	0.42±0.13	0.61±0.14	0.58±0.20	0.61±0.17	0.53±0.15	**<0.001**
Neutrophils	3.06±1.14	4.33±1.15	4.36±1.52	3.96±1.13	3.86±1.46	**0.004**
Platelets	255.16±66.41	261.08±54.58	270.82±53.5	291.57±54.02	267.08±67.75	0.058
MPV	9.72±1.56	10.07±1.40	9.04±1.60	10.17±1.09	8.52±1.47	**<0.001**
NLR	1.42±0.59	2.34±1.38	2.32±1.39	1.61±0.65	2.04±1.94	**0.001**
MLR	0.19±0.06	0.32±0.16	0.29±0.12	0.24±0.08	0.26±0.14	**0.001**
PLR	119.73±45.66	135.87±70.50	139.24±53.25	117.06±33.11	136.24±103.8	0.283

MPV: Mean platelet volüme; NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; PLR: Platelet/lymphocyte ratio

Tablo 2. NLR, MLR and PLR ROC analysis results for BD, Sch and MDD patients

Values	Area	Std. error	p	95% Confidence interval Lower	Upper
Bipolar disorder (BD)					
NLR	0.640	0.061	**0.038**	0.520	0.761
MLR	0.644	0.063	**0.033**	0.521	0.768
PLR	0.506	0.066	0.930	0.377	0.635
Schizophrenia (Sch)					
NLR	0.612	0.050	**0.028**	0.514	0.710
MLR	0.603	0.050	**0.043**	0.505	0.702
PLR	0.560	0.051	0.238	0.460	0.660
Major depressive disorder (MDD)					
NLR	0.454	0.050	0.371	0.356	0.553
MLR	0.513	0.051	0.802	0.351	0.550
PLR	0.450	0.051	0.332	0.413	0.613

NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; PLR: Platelet/lymphocyte ratio

lar patients and the area under the curve for NLR and MLR was significant for patients with schizophrenia.

Cut off values of different sensitivity and specificity values were found for each disease group. For example, the NLR rate was 3.89 in SCH patients and the sensitivity was 5% (cut off: 5.37). The LR value for the BAD group was 3.08, whereas the sensitivity for MLR was 12% (cut off: 4.79). When the cut-off values of the significant variables for each patient group were examined, the LR (+) values were below 2 in the cut off values which have a high direct positive ratio for all parameters, i.e. false positivity rates increase. On the other hand true positive rates were found to be very low in high LR (+) values. The use of MLR and NLR as a diagnostic test for bipolar and schizophrenia patients was found to be based on poor evidence. The result of the statistical evaluations showed that measured variables have different effects on the decision making for these diseases. However, each variable was evaluated individually for each disease group. Similarly, in the literature, it is seen that a single variable is insufficient in explaining these diseases and there is no biomarker that can be used in the preliminary diagnosis of psychiatric diseases. However, in this study, an Artificial Neural Network (ANN) based Computer Aided Diagnostic System (BDTS) was designed. In the designed model, an artificial intelligence based decision support system was created to help specialists in the diagnosis of the diseases by evaluating 11 variables and the complex relationship between these variables, instead of a single variable as in other statistical methods. In this way, reliability has increased significantly. ANN parameters are given in Table 3. The classification results of the simulation designed for the diagnosis of the disease depending on the

Table 3. ANNs model and training parameters

Architecture	
The number of layers	3
The number of neuron on the layers	Input: 11, Hidden: 12, Output: 1
The initial weights and biases	Random
Activation functions	Tangent-Sigmoid Linear
Training parameters	
Learning rule	Levenberg-Marquardt Back-Propagation
Learning rate	0.01
Mean-squared error	0.0000001
Maximum epochs number	3000

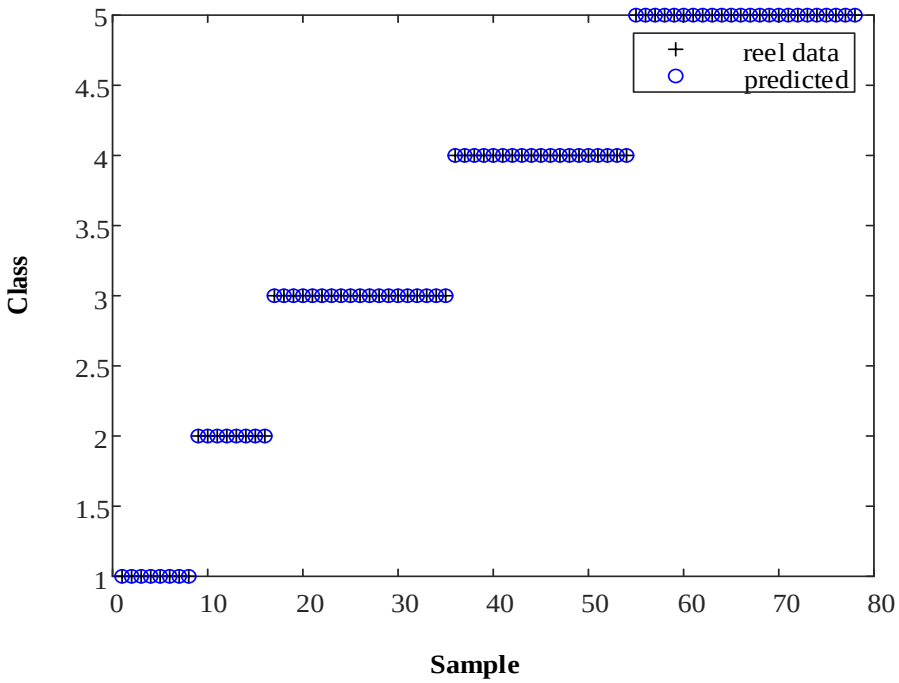

Figure 1. Simulation results of the designed CAS (1: Anorexia Nervosa, 2: Bipolar disorder manic attack, 3: Early onset schizophrenia, 4: Depressive disorder, 5: Healthy control group)

input parameters are presented in Figure 1, the horizontal axis shows the sample number in dataset. The numbers 1, 2, 3, 4, 5 in the vertical axis indicate output labels such as anorexia nervosa, bipolar disorder, early onset schizophrenia, depressive disorder and healthy control group, respectively. In Figure 1, '+' shows the actual data 'o' shows the predicted data. In the simulation results interlocking of '+' and 'o' symbols means that CAS classifies diseases successfully.

The training performance graph of ANN CAS model is given in Figure 2. The accuracy value of the model were calculated as 99%.

DISCUSSION

One of the features of childhood-onset psychiatric disorders is the variability of the clinical picture, therefore, the diagnosis process becomes more difficult. Faster and more reliable tools are needed for a diagnosis. Moreover, as discussed below, in the literature only one or two kinds of parameters are studied in the differential diagnosis of diseases. Therefore, it is controversial to use the data obtained in the primary diagnosis and differential diagnosis. In the CAS system designed in this study, the accuracy rate in the diagnostic process was determined as 99% with 11 different input parameters. The aim of this

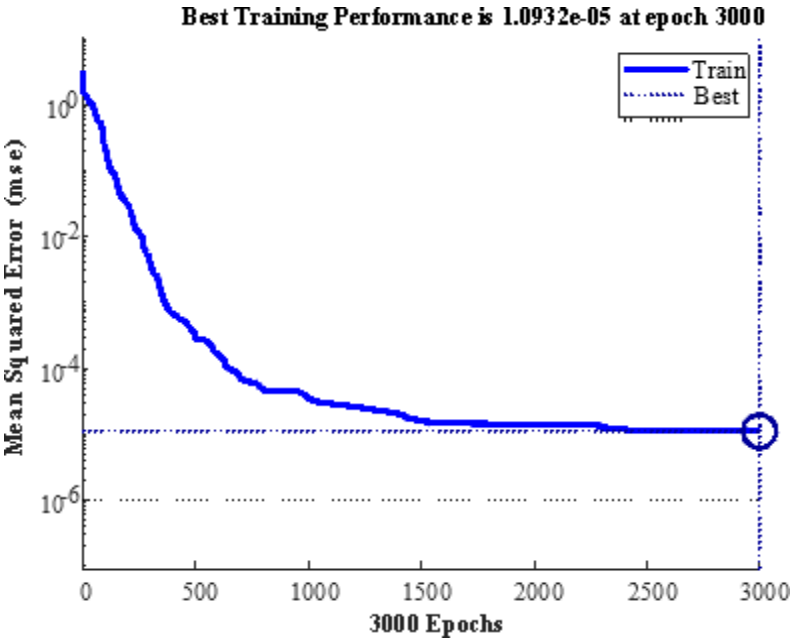

Figure 2. Training performance

study is to introduce a practical, fast and reliable diagnostic system to psychiatrists by using CAS, which is based on CBC parameters, which is a cheap and easily accessible method. The results of the study showed that the use of 11 parameters together, significantly increased reliability.

In the studies, leukocyte count, monocyte count, neutrophil count, lymphocyte count, NLR, MLR, PLR, MPV parameters have been used as inflammatory biomarkers. In the study of Cakır et al., neutrophil count, lymphocyte count and NLR were found to be significantly higher in bipolar patients.[30] In a multicenter study, conducted by Semiz et al. blood parameters of schizophrenic patients and healthy individuals were compared. In this study, neutrophil, lymphocyte, and NLR were found to be significantly higher in the schizophrenia group than the healthy control group, similar to the results in bipolar patients.[31] In another study, NLR level in adult schizophrenia patients was investigated and NLR levels were found to be significantly higher in schizophrenia patients. In the same study, neutrophil and lymphocyte levels were found to be significantly higher in schizophrenic patients, and the ROC analysis for the neutrophil/lymphocyte ratio showed 76% sensitivity and 77% specificity for LR (+) 3.34, cut off norm 1.98, and the area under the curve was 0.885. In this study, the diagnostic value of NLR was emphasized.[7] Özdin et al. in their study compared NLR, MLR and PLR levels in adult schizophrenia patients at different stages of the disease; they found that, NLR, MLR and PLR levels were significantly higher in remission period compared to the control group, and these levels were significantly higher in patients with relapse than those in remission period. MLR and PLR levels were found to be important markers.[32] In a prospective study on bipolar patients, it was found that higher NLR and PLR levels were associated with more anxiety and lower functions, more frequent attacks and more frequent hospitalization.[33] In another meta-analysis, NLR and PLR were investigated in patients with mood disorders. It was found that people with bipolar disorder had higher NLR and PLR compared to healthy control group.[34] In a retrospective study of NLR, MLR, PLR ratio in patients with schizophrenia and bipolar disorder, all rates for both groups were found to be significantly higher.[19] In a study evaluating the rates of NLR and PLR in outpatients and inpatients at different levels of major depression, higher PLR levels were found in psychotic depression cases.[35]

Regarding MPV, there are limited studies examining the relationship between MPV levels and psychiatric disorders. In a study comparing ADHD patients with the healthy control group, MPV rates were found to be higher in ADHD patients and it was suggested that it could be used as an inflammatory marker in the pathophysiology of ADHD.[36] In a study conducted on

patients with schizophrenia, unipolar depression, and bipolar disorder, it was found that there were significant differences for platelets and MPV values between study groups. A significant percentage of patients with bipolar disorder had abnormal (too low or too high) number of platelets and positive correlation between age and MPV levels was found in patients with schizophrenia.[37] In another study MPV and NLR levels have been associated with the type of suicide attempt.[38] MPV values were examined in various psychiatric disorders such as schizophrenia, panic disorder and generalized anxiety disorder. Significant differences were found between patients with generalized anxiety disorder (GAD) and control groups.[39] In the anxiety group, MPV was significantly higher and platelet count was significantly lower. The area under the ROC curve of MPV levels for GAD is 0.655. Ransing et al., in their study conducted in 2017, found that patients with panic disorder had higher MPV and higher platelet distribution width.[40]

CBC studies were predominantly focused on adult patients. The findings for childhood onset psychiatric disorders are limited and contradictory results have been reported. Bustan et al. in their study conducted on psychotic adolescents, found that NLR and leucocyte amount were higher in those patients and NLR was significantly decreased in remission period.[8] The results indicate that psychosis is associated with higher levels of peripheral inflammation markers in the early period of the disease and levels of these markers decrease in clinical remission. In another study, in the autism spectrum disorder (ASD) NLR levels were found to be significantly higher than the control group and the importance of inflammation in the etiology was emphasized. In this study, high neutrophil counts, low platelet and lymphocyte counts were found in ASD patients and it was suggested that NLR could be indicator for ASD.[41] In the study conducted by Cevher et al. on bipolar adolescents in the euthymic stage, there was no difference in NLR and PLR compared to healthy children. They interpreted these results to be due to lower inflammatory response in the euthymic phase of bipolar disorder.[42]

In patients with anorexia nervosa, the number of studies evaluating CBC data is significantly lower than in other patient groups. Moderate changes in CBC values were observed on admission and most of these changes were reversible after weight gain. Patients with more weight loss, those with lower body mass index (BMI), and those with a history of psychotropic drug use are more likely to develop these hematological abnormalities.[43] In addition, it has been emphasized that altered immune response in chronic anorexia nervosa patients may lead to an increase in infection risk and mortality rates.[43]

In the studies, a suitable cut off value for NLR ratio was not reported. In some studies, patients were categorized according to NLR intervals.[44] In a recent study on a non-geriatric healthy group, the cut-off value for NLR was reported between 0.78 and 3.53.[45] However, although differences in CBC data are detected in different psychiatric disorders, it is unclear at which stages NLR or other CBC parameters can be used in the diagnostic process. The accuracy rate of the designed system is calculated as 99%. This ratio revealed that the system designed based on CBC data can be used as a quick and reliable tool in early childhood psychiatric disorders.

Limitations

Some of the patients included in the study were using psychiatric medication when the blood samples were collected. The most important limitation of this study is that it has not been performed completely during the drug-free period.

Authors's contributions: *I.U.: data acquisition, data analysis, writing manuscript; O.O.: data acquisition, writing manuscript; B.K.T.: data acquisition, data analysis, writing manuscript; B.M.: data acquisition, writing manuscript; A.A.: data acquisition, writing manuscript; K.Y.: data acquisition, writing manuscript; B.M.: provided the outlines for the presentation of the study, supervised the study process, edited the final manuscript; A.A.: provided the outlines for the presentation of the study, supervised the study process, edited the final manuscript.*

REFERENCES

1. *Quan N, Banks WA. Brain-immune communica-tion pathways. Brain Behav Immun 2007; 21:727-735.*
2. *Takahashi A, Flanigan ME, McEwen BS, Russo SJ. Aggression, social stress, and the ımmune system in humans and animal models. Front Behav Neurosci 2018; 12:1-16.*

3. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001; 102:5-14.
4. Nathan C. Neutrophils and immunity: Challenges and opportunities. Nat Rev Immunol 2006; 6:173-182.
5. Demir S, Atli A, Bulut M, İbiloğlu AO, Güneş M, Kaya MC, et al. Neutrophil-lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat 2015; 11:2253-2258.
6. Demircan F, Gözel N, Kılınç F, Ulu R, Atmaca F. The ımpact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. Neurol Ther 2016; 5(1):27-33.
7. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. Neuropsychiatr Dis Treat 2016; 12:1999-2005.
8. Bustan Y, Drapisz A, Ben Dor DH, Avrahami M, Schwartz-Lifshitz M, Weizman A, et al. Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for early association between inflammation and psychosis. Psychiatry Res 2018; 262:149-153.
9. Duksal F, Alaygut D, Güven AS, Ekici M, Oflaz MB. Neutrophil-lymphocyte ratio in children with familial Mediterranean fever : Original article 2015; 2(1):20-23.
10. Gao S-Q, Huang L-D, Dai R-J, Chen D-D, Hu W-J, Shan Y-F. Neutrophil-lymphocyte ratio: a controversial marker in predicting Crohn's disease severity. Int J Clin Exp Pathol 2015; 8:14779-14785.
11. Mentis AA, Kyprianou MA, Xirogianni A, Kesanopoulos K. Neutrophil-to-lymphocyte ratio in the differential diagnosis of acute bacterial meningitis 2016; 35(3):397-403.
12. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther 2016; 14:573-577.
13. Shi L, Qin X, Wang H, Xia Y, Li Y, Chen X, et al. Elevated neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio and decreased platelet-to-lymphocyte ratio are associated with poor prognosis in multiple myeloma. Oncotarget 2017; 8:18792-18801.
14. Wang Y, Fuentes HE, Attar BM, Jaiswal P, Demetria M. Pancreatology Evaluation of the prognostic value of neutrophil to lymphocyte ratio in patients with hypertriglyceridemia-induced acute pancreatitis. Pancreatology 2017; 17(6): 893-897.
15. Ayça B, Akin F, Çelik Ö, Yüksel Y, Öztürk D, Tekiner F, et al. Platelet to lymphocyte ratio as a prognostic marker in primary percutaneous coronary intervention. Platelets 2015; 26:638-644.
16. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017; 111:176-181.
17. Kim DS, Shin D, Lee MS, Kim HJ, Kim DY, Kim SM, et al. Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis 2016; 43(3):305-310.
18. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Lung Cancer Neutrophil-to-Lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017; 111:176-181.
19. Özdin S, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet- lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients – a retrospective file review. Nord J Psychiatry 2017; 71:509-512.
20. Kalelioglu T, Akkus M, Karamustafalioglu N, Genc A, Genc ES, Cansiz A, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. Psychiatry Res 2015; 228:925-927.
21. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: Methodological issues. Platelets 2002; 13:301-306.
22. Yazici S, Yazici M, Erer B, Erer B, Calik Y, Ozhan H, et al. The platelet indices in patients with rheumatoid arthritis: Mean platelet volume reflects disease activity. Platelets 2010; 21:122-125.
23. Unal M, Unal M. Platelet mass index is increased in psoriasis. A possible link between psoriasis and atherosclerosis. Arch Med Sci Atheroscler Dis 2016; 6(1)1:145-149.
24. Yavuz S, Ece A. Mean platelet volume as an indicator of disease activity in juvenile SLE. Clin Rheumatol 2014; 33:637-641.
25. Fan Z, Tang S. Mean platelet volume and platelet count are elevated in patients with subacute thyroiditis. Clin Lab 2017; 63(9):1487-1492.
26. Chyzhyk D, Savio A, Graña M. Computer aided diagnosis of schizophrenia on resting state fMRI data by ensembles of ELM. Neural Networks 2015; 68:23-33.
27. Ari A, Hanbay D. Deep learning based brain tumor classification and detection system. Turkish J Electr Eng Comput Sci 2018; 26:2275-2286.
28. Das R, Turkoglu I, Sengur A. Diagnosis of valvular heart disease through neural networks ensembles. Comput Methods Programs Biomed 2009; 93:185-191.

29. *Bajaj V, Pawar M, Kumar Meena V, Mukesh M, Abdulkadir K, Guo Y. Computer-aided diagnosis of breast cancer using bi-dimensional empirical mode decomposition. Neural Comput Appl 2019; 31:3307-3315.*
30. *Çakir U, Tuman TC, Yildirim O. Increased neutrophil/lymphoctye ratio in patients with bipolar disorder: A preliminary study. Psychiatr Danub 2015; 27:180-184.*
31. *Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub 2014; 26:220-225.*
32. *Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res 2019; 271:131-135.*
33. *Melo MCA, Garcia RF, de Araújo CFC, Abreu RLC, de Bruin PFC, de Bruin VMS. Clinical significance of neutrophil-lymphocyte and platelet-lymphocyte ratios in bipolar patients: an 18-month prospective study. Psychiatry Res 2019; 271:8-14.*
34. *Gennaro M, Lucchi S, Grazia A, Tringali M, Rossetti A, Rossana E, et al. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2018; 84:229-236.*
35. *Kayhan F, Gündüz Ş, Ersoy SA, Kandeğer A, Annagür BB. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res 2017; 247:332-335.*
36. *Avcil S. Evaluation of the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as inflammatory markers in children with attention-deficit hyperactivity disorder. Psychiatry Clin Neurosci 2018; 72:522-530.*
37. *Wysokiński A, Szczepocka E. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res 2016; 237:238-245.*
38. *Orum MH, Kara MZ, Egilmez OB. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. J Immunoass Immunochem 2018; 39: 647-659.*
39. *Almis BH, Aksoy I. Mean platelet volume level in patients with generalized anxiety disorder. Psychiatry and Clinical Psychopharmacology 2018; 28(1):43-47.*
40. *Ransing RS, Patil B, Grigo O. Mean platelet volume and platelet distribution width level in patients with panic disorder. J Neurosci Rural Pract 2017; 8:174-178.*
41. *Kutlu A, Cevher Binici N. Does increased neutrophil-lymphocyte ratio predict autism spectrum disorder? Anadolu Psikiyatr Derg 2018; 19:607-614.*
42. *Cevher Binici N, Alşen Güney S, İnal Emiroğlu FN. Neutrophil-lymphocyte and platelet-lymphocyte ratios among adolescents with bipolar disorder: A preliminary study. Psychiatry Res 2018; 269:178-182.*
43. *Bühren K, Gärtner L, Kennes LN, Seitz J, Hagenah U, Herpertz-Dahlmann B. Hämatologische Veränderungen bei Anorexia nervosa im Kindes- und Jugendalter. Z Kinder Jugendpsychiatr Psychother 2014; 42:19-26.*
44. *Azab B, Camacho-rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects PLoS One 2014; 9(11):1-6.*
45. *Forget P, Khalifa C, Defour JP, Latinne D, van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes 2017; 10:1-4.*