Journal of Dependence bağımlılık Dergisi

ARAŞTIRMA | RESEARCH
Bağımlılık Dergisi, 2025; 26(3):277-285
Doi: 10.51982/bagimli.1581177

The Role of Neutrophil-Lymphocyte Ratio in Predicting Alcohol Withdrawal-Induced Seizures in Patients with Alcohol Use Disorder

Alkol Kullanım Bozukluğu Olan Hastalarda Alkol Yoksunluğuna Bağlı Nöbetlerin Öngörülmesinde Nötrofil-Lenfosit Oranının Rolü

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Abstract

Objective: Alcohol withdrawal seizures are a medical condition, potentially life-threatening, that can occur after the cessation or reduction of alcohol consumption. Inflammatory changes play a major role in alcohol withdrawal symptoms (AWS). The neutrophil-lymphocyte ratio (NLR) is an accessible and straightforward method that can alert clinicians to possible risks in certain clinical conditions and support diagnosis. This study aimed to investigate whether NLR scores would contribute to the prediction of seizure development in patients with AWS.

Method: This study was conducted through electronic health records at Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery- Specific Care Unit of Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM). Thirty patients with alcohol withdrawal seizures (SZ+) and sixty-five alcohol use disorder patients without seizures (SZ-) were enrolled. The participants' biochemical, sociodemographic and clinical data were collected.

Results: The SZ+ group and SZ- group showed similarities in terms of age, mean duration of alcohol use and gender. Neutrophil levels were higher and lymphocyte levels were lower in the SZ+ group compared to the SZ- group. NLR found higher in SZ+ group. This difference between the two groups was significant.

Conclusion: NLR is a low-cost, widely available marker that can be used to predict alcohol withdrawal seizures.

Keywords: Alcohol use disorder, alcohol withdrawal seizures, neutrophil-lymphocyte ratio, inflammation

Öz

Amaç: Alkol yoksunluğu nöbetleri, potansiyel olarak hayatı tehdit eden, alkol tüketiminin kesilmesi veya azaltılmasından sonra ortaya çıkabilen tıbbi bir durumdur. Alkol yoksunluğu semptomlarında (AYS) inflamatuvar süreçler önemli rol oynamaktadır. Nötrofil-lenfosit oranı (NLO), klinisyenleri belirli klinik durumlarda olası risklere karşı uyarabilen ve tanıyı destekleyen erişilebilir ve basit bir yöntemdir. Bu çalışmanın amacı, NLO skorlarının AYS olan hastalarda nöbet gelişiminin öngörülmesine katkıda bulunup bulunmayacağını araştırmaktır.

Yöntem: Bu çalışma, hastanemiz Alkol ve Madde Bağımlılığı Araştırma, Tedavi ve Eğitim Merkezi (AMATEM) Özel Bakım Ünitesi'nde elektronik sağlık kayıtlarının incelenmesi ile gerçekleştirilmiştir. Alkol yoksunluk nöbeti geçiren otuz hasta (N+) ve nöbet geçirmeyen altmış beş alkol kullanım bozukluğu hastası (N-) çalışmaya dahil edilmiştir. Katılımcıların biyokimyasal, sosyodemografik ve klinik özellikleri ile ilgili veriler toplanmıştır.

Bulgular: N+ grubu ve N- grubu yaş, ortalama alkol kullanım süresi ve cinsiyet açısından benzerlik göstermiştir. N+ grubunda N- grubuna göre daha yüksek nötrofil ve daha düşük lenfosit seviyeleri saptandı. NLO, N+ grubunda daha yüksek bulundu. İki grup arasındaki bu fark istatistiksel olarak anlamlıydı.

Sonuç: NLO, alkol yoksunluğu nöbetlerini öngörmek için kullanılabilecek düşük maliyetli, yaygın olarak ulaşılabilen bir belirteçtir.

Anahtar kelimeler: Alkol kullanım bozukluğu, alkol yoksunluk nöbeti, nötrofil-lenfosit oranı, inflamasyon

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Received /Gönderilme tarihi: 16.11.2024 | Accepted /Kabul tarihi: 17.02.2025

Introduction

Alcohol use disorder (AUD) is a chronic disorder characterized by the persistent engagement of the mind with alcohol use, repetitive use, using more than intended, and negative internal experiences when stopped (1,2). The main diagnostic criteria include overwhelming cravings, inability to control alcohol intake, excessive or prolonged use, unsuccessful attempts to quit, and withdrawal symptoms like tremors, sweating, and palpitations upon cessation (1). AUD is prevalent in developed countries where alcohol is inexpensive, easily available and widely marketed. It is typical for common, mild disorders to resolve during early adulthood. However, more serious disorders have the potential to become chronic and necessitate long-term attention from both a medical and psychological perspective. (3). According to the World Health Organization's report published in 2018, harmful alcohol use accounts for 7.1% of men and 2.2% of women globally and results in 3 million deaths worldwide annually, which represents 5.3% of all deaths. Along with significant health problems that can threaten life, AUD is a disorder that causes social and economic problems in society (4). Harmful alcohol use is a pattern of drinking that causes clear mental or physical harm, including impaired judgment or behavior, leading to personal or social consequences. This pattern must persist for at least one month or recur over twelve months, without meeting criteria for another alcohol-related mental disorder. Unlike alcohol dependence, it does not involve tolerance, cravings, loss of control, or withdrawal symptoms. This diagnostic distinction is made in the ICD-10 classification and in the DSM-5, both of these definitions fall under the diagnosis of AUD (5). Mental disorders that may occur due to alcohol use include intoxication, withdrawal, intoxication delirium, withdrawal delirium, dementia, persistent amnestic disorder, psychotic disorder, mood disorder, anxiety disorder, sexual dysfunction and sleep disorder, depending on the effects of the substance (6).

One of the significant problems caused by AUD is withdrawal symptoms. Alcohol withdrawal is a possible life-threatening condition caused by glutamate hyperactivity (7). In individuals with a history of chronic alcohol use, there is an increase in glutamate activity, which serves to compensate for the elevated GABA activity associated with alcohol consumption (8). Alcohol withdrawal symptoms (AWS) occur after a decrease or cessation of alcohol intake and include autonomic instability (symptoms such as tachycardia, hypertension, fever, hypothermia, sweating, and flushing), seizures, tremors, nausea, vomiting, headache, and hallucinations (9). In 3-5% of cases, withdrawal progresses to seizures and delirium tremens (DT), life-threatening complications requiring urgent care (10).

There is a complicated and many-sided relationship between alcohol and seizures. Unlike intoxication, where seizures are rare, withdrawal can trigger isolated or clustered seizures, often when blood alcohol levels reach zero or decrease significantly. However, they can also occur at an earlier stage when there is still a residual amount of alcohol present in the bloodstream (11). Alcohol affects the brain by altering ion fluxes through glutamate, NMDA, and GABA receptors and raising the seizure threshold. Therefore, reducing or stopping alcohol use will lower the seizure threshold. Alcohol withdrawal seizures often occur as generalized tonic-clonic seizures within 6-48 hours after reducing or quitting alcohol use (12,13). While alcohol withdrawal seizures are often self-limiting and benign in nature, they can be challenging to treat. Following these seizures, status epilepticus or DT may develop, and serious injuries can occur due to falls. The diagnosis of alcohol withdrawal seizures in heavy drinkers is made by exclusion. The drinking history in such cases should be coherent with long-term heavy alcohol use, and the clinical and laboratory findings should be consistent with uncomplicated alcohol withdrawal (11). There is limited data available to predict the development of seizures in alcohol withdrawal syndrome. A score of 15 or more on the CIWA-AR scale (Clinical Institute Withdrawal Assessment for Alcohol), which indicates the severity of AWS, is the most important predictor of seizure development (14–16). Although the severity of AWS is essential in predicting alcohol withdrawal seizures, the desired level has not yet been achieved in this regard (17). Furthermore, no specific laboratory findings support this seizure risk assessment or predict risk, demonstrating the need for such a laboratory finding.

Cognition and behavior are mediated by glutamate. Neuroinflammation affects glutamate's metabolism and alters its transporters' function, leading to cognitive, behavioral, and psychiatric disorders (18). The neutrophil-lymphocyte ratio (NLR) is a reliable inflammatory marker that reflects systemic and autonomic nervous system dysregulation and affected by inflammatory cytokines and endocrine effects of the hypothalamic pituitary axis (19,20). Increased NLR in psychiatric disorders such as DT, opioid use disorder, bipolar disorder, schizophrenia and depression confirms the association of neuroinflammation with psychiatric disorders as well as other medical conditions (21–24). Inflammation occurs in mood disorders, and NLR may be one of the useful markers in detecting this activation (25). NLR is an accessible and straightforward method that can alert clinicians to possible risks in certain clinical conditions and support the clinic diagnostically. Normal NLR is between 1-2. Values greater than 3 and less than 0.7 are considered pathological. While NLR is higher in individuals with AUD compared to healthy controls, it is even higher in those developing DT compared to those who do not (23,26). Additionally, there is a relationship between epileptic seizures and systemic inflammation and NLR was found higher in individuals diagnosed with epilepsy compared to those without alcohol use disorder (27–29).

However, research on NLR and alcohol withdrawal seizures is limited, with some studies examining seizures as part of DT. The severity of withdrawal symptoms is a clinically important factor in predicting seizures due to alcohol withdrawal, but there are currently insufficient specific laboratory findings to support this clinical data or to help predict risk. Consequently, there is an unmet need for such laboratory findings. In this study, we aimed to determine whether NLR levels would contribute to predicting seizure development in patients with AWS.

Method

Procedure

Our study was a retrospective study planned to involve the examination of medical records of the patients with AUD who were hospitalized at Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery- Specific Care Unit of Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM). AMATEM is a structured unit for addiction, and the Specific Care Unit is a sub-unit set up to manage alcohol withdrawal symptoms and potential problems related to alcohol cessation, such as DT and alcohol withdrawal seizures. Since the hospital where the study was conducted is a training and research hospital, the informed consent form filled out by the inpatients during hospitalization includes the information that they will allow the use of their medical data in retrospective studies by keeping their personal information confidential in the scientific researches to be carried out, this information is given in detail to the individuals and they are hospitalized, and in our study, the individuals who approved this informed consent form were included in the study. Permission for the study was obtained from the University of Health Sciences Hamidiye Scientific Research Ethics Committee (meeting number: 2024/9, dated August 22, 2024; decree number: 9/6).

Sample

The study sample consisted of individuals aged 18-65 years who received inpatient AUD treatment between June 2017 and June 2024 and were in the first 14 days of alcohol cessation. Medical records of patients meeting the inclusion criteria were reviewed by complete blood count (CBC) to evaluate the relationship between NLR and clinical presentation. Sociodemographic data, clinical findings, medical history, and routine laboratory findings obtained on the first day of hospitalization and if available, tests performed within 24 hours before the seizure prior to hospitalization were also evaluated. The NLR values included in the evaluation were those obtained within the last 24 hours before the seizure, whether the seizure occurred before or after hospitalization.

We found that 759 patients were admitted to our clinic for AUD treatment. One hundred and seventy-six patients were excluded because they completed their detoxification treatment as outpatients. The meticulous

application of our exclusion criteria resulted in the exclusion of fifty-seven patients due to infectious findings during hospitalization, 77 patients due to comorbid substance use, 37 patients due to comorbid benzodiazepine/pregabalin/gabapentin use, 21 patients due to a diagnosis of epilepsy, 11 patients due to inflammatory or rheumatologic diseases that may affect NLR, and 35 patients due to bipolar disorder or psychotic disorders known to affect NLR. Of the remaining 355 patients, 48 had alcohol withdrawal seizures, and 18 were excluded because they had no CBC evaluated before the seizure. It was observed that these 18 patients were patients who were diagnosed with seizures in another healthcare institution and referred to our clinic; it was not possible to find out whether pre-seizure examinations were performed in the relevant clinic. Additionally, patients with electrolyte imbalances that could lead to seizures, such as hypoglycemia, hypomagnesemia, and hyponatremia, were not included in the study. Thus, 30 patients were included in the seizure group (SZ+). Power analysis was performed with the G*Power statistical program (ver.3.1.9.7). When Cohen's d effect size of 0.8 (large), type I error rate of 0.05 and power of 0.95 were considered and allocation ratio N2/N1=2 were accepted, it was calculated that 26 patients were required for SZ + group and 52 patients were required for SZ - group for independent variables t-test. Sixty-five patients were included for the control group (SZ-) versus the patient group were randomly selected from 307 patients without seizures. The data were analyzed via SPSS version 24.

Statistical Analysis

In order to determine whether the variables were normally distributed, they were analyzed using the Kolmogorov-Smirnov test. For categorical variables, descriptive analyses were presented using numbers and percentages, for normally distributed variables, mean and standard deviation; and for non-normally distributed variables, median and interquartile range. A comparative analysis was conducted between patients with and without alcohol withdrawal seizures, employing chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous variables that followed a normal distribution. The p-value of less than 0.05 was considered significant.

Table 1. Differences of sociodemographic and clinical data between SZ + and SZ- groups

Variables			**SZ+ (n=30)**	**SZ- (n=65)**
Age		M ± SD	45.4 ± 11.2	42.6 ± 11
Gender (Female)		n (%)	2 (6.7)	9 (13.8)
Duration of use (years)		M ± SD	20.80 ± 12.86	20.86 ± 10.91
Attempt to quit		M ± SD	7 ± 3.07	4.75 ± 2.85
Marital status	Married	n (%)	12 (40)	38 (58.5)
	Single		11 (36.7)	15 (23.1)
	Divorced		6 (20)	11 (16.9)
	Widowed		1 (3.3)	1 (1.5)
Education status	Elementary school	n (%)	5 (16.7)	15 (23.1)
	Middle school		9 (30)	23 (35.4)
	High school		15 (50)	21 (32.3)
	Bachelor's degree		1 (3.3)	6 (9.2)
Working status	Working	n (%)	10 (33.3)	21 (32.3)
	Not working		14 (46.7)	30 (46.2)
	Retired		6 (20)	14 (21.5)
Additional medical condition	None	n (%)	27 (90)	61 (93.8)
	Hypertension		2 (6.7)	4 (6.2)
	Diabetes Mellitus		1 (3.3)	0 (0)
Past seizures		n (%)	4 (13.3)	0 (0)

n: number; M: mean; SD: standard deviation; SZ+: patient with alcohol withdrawal seizures; SZ-: patient without alcohol withdrawal seizures

Results

In our study, 95 patients (30 patients of the SZ+ group and 65 patients of the SZ- group) were included. The sample consisted of 84 (87.5%) males and 11 (11.5%) females, with a mean age of 43.5 ± 11.1 years. There was no significant age difference between the two groups. While the mean duration of alcohol use was similar in both groups (SZ +: 20.80±12.86 years, SZ -: 20.86±10.91 years), the mean number of quit attempts was higher in the SZ + group (SZ +: 7±3.07, SZ -: 4.75±2.85). Another important finding was that 4 out of 30 people in the SZ+ group had a history of alcohol withdrawal seizure, while none of the 65 people in the SZ- group had a history of seizure. Additional sociodemographic data and clinical characteristics of the patients and comparison of these data between the SZ+ and the SZ- groups are presented in Table 1.

Neutrophil levels were significantly higher in the SZ+ group than SZ- group ($p<0.05$). In contrast with neutrophile levels, lymphocyte levels were significantly lower in the SZ+ group. NLR was significantly higher in the SZ+ group. In addition, platelet count and hemoglobin were found to be lower in the SZ+ group and this difference was statistically significant. No significant difference was found between C Reactive Protein (CRP) and total leukocyte count (Table 2).

Table 2. Comparisons of relevant laboratory results between SZ + and SZ- groups

Variables		SZ+ (n=30)	SZ- (n=65)	p
Neutrophils	M±SD (min-max)	5.37 ± 2.65 (1.45-14.40)[a]	3.90 ± 1.50 (1.66-9.09)[a]	.007*
Lymphocytes	M±SD (min-max)	1.77 ± .94 (.56-5.08)[a]	2.83 ± 1.02 (.90-5.63)[a]	<.001*
NLR	M±SD	3.70 ± 2.55	1.49 ± .62	<.001*
Leukocytes	M±SD (min-max)	7.40 ± 3 (2.20-16.20)[a]	7.54 ± 2.15 (3.95-12.41)[a]	.388
Platelet	M±SD (min-max)	173 ± 108 (45-507)[a]	219 ± 71 (73-407)[a]	.039*
Hemoglobin	M±SD (min-max)	12.81 ± 1.72 (8.90-16.20)[b]	13.85 ± 2.48 (7.50-18.10)[b]	.041*
CRP	M±SD (min-max)	6.98 ± 5.86 (.50-24.60)[c]	8.76 ± 9.10 (.02-42)[c]	.258

n: number; M: mean; SD: standard deviation; min: minimum value; max: maximum value; SZ+: patient with alcohol withdrawal seizures; SZ-: patient without alcohol withdrawal seizures; NLR: Neutrophil-Lymphocyte Ratio; CRP: C Reactive Protein; p: p value for significance (2-tailed); *: statistically significant; [a] x1000/mm^3; [b] g/dL; [c] mg/L; The statistical method employed was the independent variables t-test.

In the analyses in which SZ +, SZ - groups and the total number of patients were evaluated separately, no significant correlation was found between neutrophil, lymphocyte and NLR values and age. Similarly, no significant correlation was found between these values and different genders. No correlation was found between these ratios and other descriptive data.

Discussion

To the best of our knowledge, this is the first study to examine the link between alcohol withdrawal seizures and NLR in AUD patients. AUD is a chronic, relapsing disorder where attempts to quit often lead to heavy drinking upon relapses. Withdrawal can trigger CNS hyperexcitability, autonomic instability, motor issues, and, in severe cases, seizures or DT. While alcohol withdrawal seizures are usually benign, they can cause serious injuries, status epilepticus, or DT, leading to stigma and anxiety (30–33). Despite the clinical importance of withdrawal severity in seizure risk, no specific laboratory markers exist, highlighting the need for reliable predictors like NLR, which this study aims to evaluate.

In our study, the mean NLR score was significantly higher in AUD patients with alcohol withdrawal seizures compared to those without seizures and this result was in line with another study conducted in Turkiye (23). In this study, Yıldırım et al. examined whether NLR could be used to predict the risk of developing DT in people with AUD and found that NLR was significantly higher in AUD patients who developed DT compared to those who did not develop DT. In our study, we aimed to investigate whether NLR can be used in the prediction of alcohol withdrawal seizures similar to this study. There are no other studies in the literature

evaluating the relationship between alcohol withdrawal seizures and NLR in patients with AUD. However, some studies suggest a number of markers to predict complications related to alcohol withdrawal. Huang et al. showed that there was a difference in serum brain-derived neurotrophic factor (BDNF) levels between AUD with DT and AUD without DT. In their study, baseline BDNF levels were found to be significantly lower in the DT group, intermediate in the AUD group without DT and highest in the group without AUD diagnosis. In addition, BDNF levels increased significantly after 1 week of alcohol abstinence for both groups with AUD diagnosis (34). The results of a study by Schreiber et al. showed that elevated Carbohydrate-deficient transferrin (CDT) (a serum transferrin derivative produced by the liver) and especially the γ-glutamyltransferase-CDT derived Anttila-Index at the time of intensive care unit (ICU) admission were associated with increased risk of alcohol related delirium, longer duration of delirium and higher hospital mortality. The researchers pointed out that these markers may have a potential role in predicting alcohol withdrawal delirium and other possible complications (35). Bleich et al. found that patients with alcohol withdrawal seizures had significantly higher plasma homocysteine levels than patients with AUD without seizures and stated that homocysteine would be useful in predicting such risks (36). However, inconsistent results were encountered in subsequent studies and meta-analyses.

Melamud et al. found that increases in inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) was more prominent in AWS patients with DT than in those without DT. Cluster analysis in this study showed that there is a subgroup of patients with evidence of high inflammation and that such a subgroup is more frequently associated with DT (37). In this study, it was also observed that total leukocyte count, hemoglobin and CRP levels did not show a significant difference in the DT group compared to the non-DT group, which is similar to the CRP and total leukocyte count findings of our study. In contrast, low hemoglobin levels were found in the SZ+ group in our study. In this respect, further studies are needed to evaluate the relationship between seizures due to alcohol withdrawal and hemoglobin levels.

Another finding of our study was that platelet count was lower in the SZ+ group compared to the SZ- group. In a systematic review and meta-analysis, both baseline low platelet count and serum potassium levels were shown to be predictive for the occurrence of DT and seizures, and higher baseline serum GGT levels were consistently associated with alcohol withdrawal seizures (38). Our finding of low platelet levels in this group is consistent with the literature.

Alcohol affects the brain by modifying ion flows through glutamate, NMDA, and GABA receptors and increases the seizure threshold. Accordingly, reduction or cessation of alcohol use will decrease the seizure threshold (12,13). In addition, it is known that inflammation is higher in people with epilepsy than in those without epilepsy, regardless of alcohol use. Although the cause-and-effect relationship has not yet been established, the fact that inflammation is significantly increased in these individuals and that inflammatory biomarkers change in the inflammation-indicating direction during seizure periods is important in predicting seizure risk. NLR is also a marker that may be effective in predicting seizures in epilepsy (27,39–41). Elevated NLR is linked to autonomic nervous system dysregulation and systemic inflammation and is influenced by inflammatory cytokines (19,20). Similarly to epilepsy, neuroinflammation also occurs in psychiatric disorders such as DT, opioid use disorder, bipolar disorder, schizophrenia and depression and NLR may be one of the useful markers in detecting this activation (21,22). These results suggest that neuroinflammation is an important factor in alcohol withdrawal seizures, as in other psychiatric disorders or epilepsy.

The present study revealed no statistically significant correlation between neutrophil, lymphocyte and NLR values and age in the analyses in which SZ +, SZ - groups and total patients were evaluated separately. When the literature is evaluated, we see that there is a positive correlation between age and neutrophil count and NLR, and a negative correlation with lymphocyte count (42,43). The findings of our study are not consistent with the literature. This result may be due to the fact that the sample is relatively small and may not reflect the general population.

In the present study, NLR was found to be significantly higher in AUD patients with alcohol withdrawal seizures compared to those without seizures, suggesting the possible usefulness of NLR in helping to predict

seizure risk in these patients. The fact that NLR is an easily accessible and inexpensive marker is also an important advantage. Such an easily accessible prediction of seizure risk will help these individuals to receive prophylactic treatment at appropriate doses and thus facilitate preventive measures against possible morbidity and mortality.

Our study has some limitations. Regarding the factors, mainly infections that could affect the CBC, we could not have captured a purely unaffected group of patients during the pandemic. The COVID-19 pandemic caused significant problems in our hospital, as in many parts of the world during some of the period covered by the study, and undetected subclinical COVID-19 infections may have affected the results. One of the study's shortcomings is that it did not detect gender differences. Although the results were significant when the patient group was evaluated collectively, the small number of female patients is insufficient to evaluate gender differences and their effect on the results. In terms of the mean age of the patients, our study's results were similar to those of other studies conducted in Turkiye on AUD patients (23,44), and the evaluation was made without making any distinction between young and old patient groups. In addition, the lack of availability of symptom severity scores in this retrospective study is another important limitation. We suggest that evaluating the level of effectiveness of NLR in determining the risk of epileptic seizures in different age groups would be helpful to our understanding of the inflammation process in AUD. Studies with larger participation are needed to evaluate whether the predictive value of NLR varies between young and elderly patient groups. Future studies should also carry out designs that would reveal gender-related differences.

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Yazar Katkıları: Tüm yazarlar ICMJE'in bir yazarda bulunmasını önerdiği tüm ölçütleri karşılamışlardır
Etik Onay: Bu çalışma için ilgili Etik Kuruldan etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir

Author Contributions: All authors met criteria recommended by ICMJE for being an author
Ethical Approval: Ethical approval was obtained for this study from relevant Ethics Committee.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors have declared that there is no conflict of interest.
Financial Disclosure: Authors declared no financial support.