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Relationship between Withdrawal Severity and Inflammation Parameters during the Detoxification Treatment of Alcohol Use Disorder

Alkol Kullanım Bozukluğunun Detoksifikasyon Tedavisi Sırasında Yoksunluk Şiddeti İle İnflamasyon Parametreleri Arasındaki İlişki

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Abstract

Objective: Alcohol withdrawal is a potentially life-threatening condition that could be seen after discontinuation or a decrease in alcohol consumption. Inflammatory processes take part in alcohol withdrawal duration. This study aimed to investigate the relationship between withdrawal severity and inflammation parameters.
Method: This retrospective study was performed via electronic health records in an alcohol and drug treatment center between August-2021 and August-2022. One hundred forty-one inpatients with alcohol use disorder and 134 controls were enrolled. Sociodemographic, clinical, and biochemical data of the participants were collected.
Results: The patients and the control group were similar in age, gender, and educational status. The patients' group had higher levels of neutrophils and lower levels of lymphocytes than the control group. Neutrophil-to-lymphocyte (NLR) and monocyte-to-lymphocyte ratio (MLR) levels were higher in the patients' group. The alcohol withdrawal severity of patients was positively correlated with NLR levels, MLR levels, the amount of daily alcohol, and years of heavy alcohol consumption.
Conclusion: NLR and MLR are inexpensive and easily accessible markers that could be used to estimate alcohol withdrawal severity.

Keywords: Alcohol-related disorders, inflammation, neutrophils, lymphocytes, withdrawal symptoms

Öz

Amaç: Alkol yoksunluğu, alkol alımının kesilmesinden veya azaltılmasından sonra görülebilen, potansiyel olarak yaşamı tehdit eden bir durumdur. İnflamatuar süreçler alkol yoksunluk süresinde yer alır. Bu çalışmada alkol yoksunluk şiddeti ile inflamasyon parametreleri arasındaki ilişkinin incelenmesi amaçlanmıştır.
Yöntem: Bu retrospektif çalışma Ağustos-2021 ve Ağustos-2022 tarihleri arasında bir alkol ve uyuşturucu madde tedavi merkezinde elektronik sağlık kayıtları üzerinden gerçekleştirilmiştir. Alkol kullanım bozukluğu olan 141 hasta ve 134 kontrol grubu çalışmaya dahil edilmiştir. Katılımcıların sosyodemografik, klinik ve biyokimyasal verileri toplanmıştır.
Bulgular: Hastaların ve kontrol grubunun yaş, cinsiyet ve eğitim durumu açısından benzer oldukları görülmüştür. Hasta grubunun, kontrol grubundan daha yüksek nötrofil seviyelerine ve daha düşük lenfosit seviyelerine sahip olduğu; nötrofil-lenfosit oranı (NLO) ve monosit-lenfosit oranı (MLO) düzeylerinin de hasta grubunda daha yüksek olduğu saptanmıştır. Hastaların alkol yoksunluk şiddetinin NLO düzeyleri, MLO düzeyleri, günlük alkol miktarı ve ağır alkol tüketim süresi ile pozitif korelasyon gösterdiği görülmüştür.
Sonuç: NLO ve MLO, alkol yoksunluk şiddetini tahmin etmek için kullanılabilecek ucuz ve kolay erişilebilir belirteçlerdir.

Anahtar kelimeler: Alkol ilişkili bozukluklar, inflammasyon, nötrofil, lenfosit, alkol yoksunluk semptomları

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Introduction

Alcohol is one of the most abused substances, and alcohol use disorder remains a common public health problem worldwide. Alcohol use disorder often shows relapses, leads to problems in the social and professional life of the individual, and contains many different risky situations for the person (1).

Alcohol use disorder is also associated with many pathologies, such as gastrointestinal, cardiovascular, and neuropsychiatric diseases, traffic accidents, injuries, suicide attempts, and alcohol withdrawal syndrome. Alcohol withdrawal syndrome (AWS) may occur when alcohol intake is stopped or reduced (2). Autonomic (e.g., tachypnea, tachycardia, elevated blood pressure), motor (e.g., ataxia, seizures, tremor, dysarthria), awareness (e.g., irritability, agitation, insomnia), and psychiatric symptoms (e.g., hallucinations, delusions, anxiety, affective instability) can be seen due to AWS (3). Elevated blood pressure increases the risk of adverse outcomes such as delirium tremens (DT) and should be carefully evaluated during the detoxification treatment (4).

Alcohol also, directly and indirectly, affects the production and function of blood cells. Alcohol suppresses the production of blood cells and leads to cytopenia. It suppresses the ability of neutrophils to respond effectively to bacterial infections and causes susceptibility to infections. It also affects the platelets' functions and fibrinolysis, which leads to thrombophilia or hemophilia (5,6).

In recent years, inflammation and the immune system have been among the topics focused on the etiology of mental illnesses. Low-grade systemic inflammation is a weakened and sustained form of the inflammatory response in the body. Parameters that can be easily obtained from a complete blood count, such as neutrophil-lymphocyte ratio (NLR), platelets lymphocyte ratio (PLR), and monocyte lymphocyte ratio (MLR), are used as indicators of chronic low-grade inflammation (7). These low-grade indicators of systemic inflammation have been investigated in various mental illnesses such as schizophrenia, bipolar affective disorder, Alzheimer's Disease, and substance use disorders (8,9). There are a limited number of studies investigating the relationship between alcohol use disorder and inflammation parameters such as NLR and PLR, and conflicting results have been found in these studies. In one study, it was found that there was no relationship between alcohol and NLR, eosinophil lymphocyte ratio (ELR), and MLR (10). Contrary to these results, NLR and MLR were higher in patients with alcohol use disorders than healthy controls (11).

Low-grade systemic inflammation has also been claimed to be involved in developing elevated blood pressure (12). The monocyte levels and NLR are higher in non-dipper hypertension (13). During alcohol detoxification treatment, autonomic instability, e.g., hypertension, is an important prognostic factor (4).

Since low-grade systemic inflammation exists in hypertension and alcohol use disorder, it might be essential in autonomic instability during AWS. More studies should scrutinize the relationship between immune parameters such as NLR, MLR, PLR, and alcohol withdrawal severity. In the current study, we aimed to investigate NLR, MLR, and PLR levels during the alcohol detoxification treatment and the relationship between these inflammation parameters and alcohol withdrawal severity. We hypothesized that patients with alcohol use disorder have higher NLR and MLR levels, and alcohol withdrawal severity is correlated with NLR and MLR.

Method

Sample

In this retrospective study, 141 participants were recruited from the Alcohol and Substance Use Treatment Center of the Ankara Training and Research Hospital. The data from the hospital's medical records were reviewed for one-year (between August 2021 – August 2022), and the eligible subjects were included. The inclusion criteria were age 18 or above, having an Alcohol Use Disorder (AUD) diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), being hospitalized for alcohol detoxification

treatment, and having recorded blood biomarkers. The blood tests were performed within 24 hours of admission to the inpatient clinic.

One hundred thirty-four participants for the control group were recruited from the health board clinic, where people were admitted for different reasons and took a health report indicating they did not have any alcohol or substance use disorder or psychiatric diagnosis.

The exclusion criteria were any current inflammatory situation, e.g., COVID-19, cold, other infections, a rheumatological disease for all participants, and any psychiatric diagnosis for the control group. Individuals with incomplete data were omitted. The data of the study were collected anonymously; any personal data that could cause subject identification was not included. The ethics committee of the Ankara Training and Research Hospital hospital approved the study (21.09.2022-1032).

Procedure

The following data were recruited from the medical records; participants' age, gender, self-reported daily alcohol consumption as standard drinks, years of heavy alcohol consumption, comorbidities, substance use, needed benzodiazepine dose (5 mg or more as equivalent diazepam dose), alcohol withdrawal severity, and whether there was a need for anti-hypertensive medication during the detoxification treatment. Heavy alcohol consumption refers to risky alcohol use or higher levels of alcohol. 1 mg of lorazepam was considered as 5 mg diazepam equivalent dose (14). The maximum dose of needed benzodiazepine was taken into account.

Moreover, the following blood biomarkers were recruited; urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), iron, iron-binding capacity, transferrin, C-reactive protein (CRP), white blood cells (WBC), red blood cells (RBC), platelets (PLT), hemoglobin, mean corpuscular volume (MCV), neutrophil, lymphocyte, eosinophil, and basophil levels. After that, the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) were calculated.

In the 24 hours of the inpatient treatment, blood was drawn from the patients at 08:00 a.m. before breakfast. Also, the control group participants gave their blood samples early before breakfast. Blood samples were taken by venipuncture into EDTA-containing tubes (BD Vacutainer® K2E) for complete blood cell count (CBC) and plain tubes (BD Vacutainer® SST II Advance) for the rest of the biochemical parameters. CBC was calculated via fluorescent flow cytometry (XN-1000, Sysmex, Kobe, Japan), and biochemical parameters were calculated via Roche Cobas 6000 (Roche, Germany).

Measure

Clinical Institute Withdrawal Assessment for Alcohol-Revised Version (CIWA-Ar)

The alcohol withdrawal severity of the patients was evaluated via the CIWA-Ar scale, developed in 1989. This scale investigates tactile, auditory, and visual disturbances, nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, headache, and orientation symptoms. It consists of 10 questions; the first nine items are 7-point Likert-type questions, the last item is 4-point Likert-type (score range: 0-67 points), and higher scores indicate more severe withdrawal symptoms (15). 0-7 points refer to mild withdrawal symptoms, 8-15 points refer to moderate withdrawal symptoms, and 16 points or above refer to severe withdrawal symptoms. Turkish version of the scale was used in the study (16).

Statistical Analysis

Research data were evaluated using SPSS (Statistical Package for Social Sciences for Windows v.22,0, SPSS Inc. Chicago, IL). The normality of the data was evaluated using the Kolmogorov-Smirnov test, skewness-kurtosis (z-score), histogram graphs, and detrended plot methods. Data showing a normal distribution were presented as mean, and standard deviation, while data not showing a normal distribution were presented as median, minimum, and maximum values. For pairwise group comparisons, independent

samples t-test was used if the data were normally distributed, and Mann Whitney U test was used if the data were not normally distributed. The Spearman correlation test was used for correlation analysis because the data did not follow a normal distribution. Binary logistic regression analysis was performed to determine possible predictors of moderate and severe withdrawal severity. The statistical significance level was accepted as $p<0.05$.

A power analysis was conducted using the data obtained in the study. For the variables examining the relationship between NLR score and CIWA-R score, the effect size was found to be small ($r = 0.166$) (effect sizes for bivariate correlation: Cohen's d: 0.1 = small effect size, 0.3 = medium effect size, 0.5 = large effect size). With a sample size of 141 patients, under 5% type I error, the power ($1-\beta$) was found to be 55% (0.51). G*Power Software version 3.1.9.4 (A flexible statistical power analysis program for the social, behavioral, and biomedical sciences) was used to calculate the power of the study.

Results

This study was carried out with 141 inpatients for alcohol use disorder and 134 participants for the control group. The median age of the participants was 46 (min: 19 - max: 73). 255 (92.7%) participants were male, and 20 (7.3%) were female. The patients and the control group were similar in age, gender, and educational status (for all $p>0.005$). The patients' duration of heavy alcohol consumption was an average of 15 years, and their average alcohol consumption was equivalent to 13 standard drinks a day. 17 (12.1%) patients were using substances in addition to alcohol. The patients' median inpatient treatment duration was 21 days, and the median CIWA-Ar score was 19. Various sociodemographic and clinical data of the participants are shown in Table 1.

Table 1. Sociodemographic and clinical data of the participants

Variable	Patients (n=141)	Control (n=134)	p
Age	46 (27-72)	45.5 (19-73)	.196[a]
Gender (male)	134 (95%)	121 (90.3%)	.131[b]
Educational status			
Primary school	99 (70.2%)	89 (66.4%)	.499[b]
High school or above	42 (29.8%)	45 (33.6%)	
Drug use other than alcohol	17 (12.1%)	-	-
Years of heavy alcohol consumption	15 (1-40)	-	-
Standard drinks a day	13 (2-30)	-	-
Days of inpatient treatment	21 (2-84)	-	-
CIWA-Ar	19 (3-51)	-	-
Needed diazepam equivalent dose (mg/day)	30 (0-60)	-	-

Categorical variables were shown as n (%). Normally distributed continuous variables were given as mean ± SD, and non-normally distributed continuous variables were expressed as median (min-max). SD: Standard deviation; min: minimum; max: maximum; n: number; %: percentage; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale; a: Mann-Whitney U test; b: Chi-Square test.

The patients' blood biomarkers, such as urea, creatinine, AST, ALT, GGT, iron, iron binding capacity, transferrin, and CRP levels, are shown in Table 2. The mean NLR and MLR of the patients were significantly higher than the control group ($p<0.001$ for both). Complete blood count parameters and NLR, PLR, and MLR values of the participants are shown in Table 3.

When the correlation analysis was performed, there was a positive correlation between NLR and CIWA-Ar, MLR, and PLR. MLR was positively correlated to NLR, PLR, and CIWA-Ar. No correlation was found between PLR and the other clinical parameters. A positive correlation was found between CIWA-Ar and NLR, and MLR in patients. Furthermore, CIWA-Ar also was positively correlated to the number of daily standard drinks, years of heavy alcohol consumption, days of hospitalization, and needed diazepam equivalent benzodiazepine dose. All the correlations are shown in detail in Table 4.

Table 2. Blood biomarkers of patients (n=141)

Biomarker	Results	Reference intervals
Urea (mg/dL)	24 (9-76)	19-44
Creatinine (mg/dL)	0.80 ± 0.14	<1.2
AST (IU/L)	28 (13-317)	0-37
ALT (IU/L)	28 (8-508)	0-41
GGT (IU/L)	70 (22-1874)	0-71
Serum iron (µg/dL)	103 (13-353)	59-158
Total iron binding capacity (µg/dL)	214.90 ± 87.50	112-346
Transferrin (g/L)	2.2 (1.5-3.5)	2.2-4
CRP (mg/dL)	4 (0.3-51)	<5

Normally distributed continuous variables were given as mean ± SD, and non-normally distributed continuous variables were expressed as median (min-max). SD: standard deviation; min: minimum; max: maximum; n: number; mg: milligram; L: liter; dL: deciliter; IU: international unit; µg: microgram; g: gram; mg: milligram.

Table 3. Complete blood count parameters and NLR, PLR, and MLR values of the participants

Variable	Patients (n=141)	Control (n=134)	p
WBC count (10^3/µL)	7.4 (3.4-21.7)	7.3 (3-12.8)	.736[a]
RBC count (10^6/µL)	4.64 ± 0.65	5.31 ± 0.48	<.001[b]
HGB (g/dl)	14.9 (10.1-17.9)	15.8 (5.6-18.1)	<.001[a]
HTC (%)	42.7 (11.9-52.8)	46.4 (4.3-54.3)	<.001[a]
MCV (fL)	92.1 (40.2-115.9)	87.3 (67.2-95.6)	<.001[a]
RDW (%)	13.5 (11.7-20.8)	12.6 (11.1-17.9)	<.001[a]
PLT (10^3/µL)	237 (68-879)	260.5 (116-422)	.002[a]
Neutrophil (10^3/µL)	4.3 (1.5-14.4)	4.1 (2-8.9)	.050[a]
Lymphocyte (10^3/µL)	2 (0.7-5.4)	2.2 (0.6-5.7)	.001[a]
Monocyte (10^3/µL)	0.66 ± 0.24	0.60 ± 1.15	.031[b]
Basophil (10^3/µL)	0.05 (0-0.1)	0.04 (0-0.1)	.231[a]
Eosinophil (10^3/µL)	0.1 (0-2.9)	0.1 (0-0.7)	.366[a]
NLR	2.1 (0.9-12.2)	1.8 (0.6-5.2)	<.001[a]
PLR	112.8 (41.5-376)	114 (58.6-241.7)	.668[a]
MLR	0.3 (0.1-1.1)	0.2 (0.1-1.2)	<.001[a]

Normally distributed continuous variables were given as mean ± SD, and non-normally distributed continuous variables were expressed as median (min-max). min: minimum; max: maximum; a: Mann Whitney U test; b: independent samples t-test; WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HTC: hematocrit; MCV: mean corpuscular volume; RDW: red cell distribution width, PLT: platelet; NLR: neutrophil-lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio, g: gram; dL: deciliter; µL: microliter; fL: femtoliter; %: percentage.

Table 4. Correlations between NLR, PLR, MLR, and various variables associated with alcohol use disorder in patients' group (n=141)

	1	2	3	4	5	6	7	8
1. NLR	1							
2. PLR	0,520**	1						
3. MLR	0,569**	0,378**	1					
4. Std. drinks a day	0,091	0,036	0,114	1				
5. Years of alcohol	0,030	-0,071	0,072	0,107	1			
6. CIWA-Ar	0,166*	0,011	0,168*	0,347**	0,224**	1		
7. Days of hosp.	0,144	0,102	0,140	0,060	0,182*	0,185*	1	
8. DZ dose	0,199	-0,013	0,152	0,230**	0,092	0,994**	0,186*	1
9. CRP	0.128	-0.78	0.205*	0.119	0.263**	0.098	0.077	0.039

r: correlation coefficient; *: <0.05; **: <0.01; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; MLR: monocyte lymphocyte ratio; Std.: standard; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale; hosp: hospitalization; DZ dose: needed diazepam equivalent benzodiazepine dose.

Patients were divided into two groups based on their CIWA-Ar scores: those experiencing mild withdrawal symptoms (CIWA-Ar<8) and those experiencing moderate to severe withdrawal symptoms (CIWA-Ar≥8). Logistic regression analysis was performed to identify potential predictors of moderate to severe withdrawal severity by using enter method. Withdrawal severity was the dependent variable, and NLR, MLR, CRP, monocyte, and eosinophil levels (parameters with significance p<0.200 in bivariate analyses) were included as independent variables. Our model was valid, and the model fit was good (Hosmer and Lemeshow test X^2:5.7653, df:4, p: 0.457). As a result of the regression analysis, none of the inflammation parameters predicted moderate to severe withdrawal severity (Table 5).

Table 5. Logistic regression analysis results to determine possible predictors of moderate and severe withdrawal severity.

Variables	*p*	Exp (β)	95% CI for Exp (β)	
			Lower	Upper
NLR	0.514	1.350	0.547	3.330
MLR	0.604	0.164	0.000	15.129
CRP	0.093	0.972	0.945	1.999
Monocyte	0.268	10.327	0.166	64.453
Eosinophil	0.202	0.008	0.000	0.461

p: statistical significance level; Exp (β): Odds ratio (exponential ratio of the β coefficients in the regression equation); 95% CI: 95% confidence interval; NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; CRP: C-reactive protein.

Discussion

Our study found changes in blood cell counts and ratios in alcohol use disorder compared to the control group. Patients with alcohol use disorder had higher NLR and MLR. Furthermore, there were positive correlations between alcohol withdrawal severity and NLR, MLR, years of heavy alcohol consumption, self-reported daily alcohol consumption as standard drinks, and needed benzodiazepine dose (5 mg or more as diazepam equivalent dose).

Alcohol consumption interferes with leukocyte production and function, and neutropenia and proneness to infections can be seen in patients with alcohol use disorder (2,5). Alcohol also interferes with monocyte production and function (5). During alcohol withdrawal syndrome, the process involves inflammation (17). Oxidative stress was found to be correlated with early alcohol withdrawal severity (18). In clinical practice, all the inflammation markers regarding cost and feasibility issues may not be available. At this point, inexpensive and simply usable biomarkers for inflammation (19), such as NLR, MLR, or PLR, become meaningful.

Neutrophils have significant roles in the immune system's first line; elevated NLR often means elevated neutrophil levels and decreased lymphocyte levels (7). During chronic alcohol consumption, neutrophils tend to be depressed, and increased neutrophil levels after alcohol cessation may also be a rebound increase (19). NLR was shown to be a prognostic factor for mortality and morbidity (7). In alcohol withdrawal syndrome, NLR was found to predict DT (19), and the optimal cut-off value of NLR for predicting DT was calculated as 2.67. In another study, alcohol withdrawal severity was correlated to NLR (20); similar results were found in our research.

During alcohol withdrawal, alleviated macrophage infiltration in subcutaneous adipose tissue was shown in one study (21). Another study showed that excessive drinkers had higher levels of monocyte activation (22). Although MLR was also investigated in several studies to show the inflammatory process as NLR, a limited number of studies explicitly investigated MLR in alcohol withdrawal. MLR of the patients with alcohol use disorder was higher than healthy controls in one study (11). Similar to this study, our study found higher MLR levels in alcohol use disorder patients than in the control group.

The alcohol withdrawal severity is essential for the prognosis of alcohol withdrawal treatment. The amount of alcohol consumed tends to increase the severity of alcohol withdrawal (23). In our study, supporting the

literature, a positive correlation was found between the amount of alcohol consumed daily, the years of heavy alcohol consumption, and the severity of alcohol withdrawal.The higher withdrawal severity correlates with a higher risk of complications, such as delirium tremens and seizures (19). Our study found a positive correlation between alcohol withdrawal severity and NLR and MLR; higher NLR and MLR showed higher alcohol withdrawal severity.

This research has several limitations that need to be acknowledged. First of all, the retrospective and cross-sectional design of the study is a limitation. Secondly, the study was performed in a single center, so it reduces the generalizability of the results. Third, infectious and rheumatologic diseases were diagnosed upon patients' anamnesis and physical examination; objective tests were not performed. And some parameters, e.g., body mass index or smoking status, were not considered, which could affect the inflammatory process, which is a limitation.

Furthermore, a relatively small number of patients, resulting in a power (1-β) of 50%, was a limitation. The sample size makes it challenging to generalize the study results. This limitation can be overcome with future studies that involve a larger sample size. Finally, this study was conducted through electronic health records, so the reliability of the data cannot be guaranteed.

Despite these limitations, our findings suggest that a complete blood count test is an inexpensive and accessible tool that is easily applied, and its clinical benefits are promising. Further studies should investigate our study's findings in other locations and cultures to generalize these findings, and prospective studies are needed.

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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.
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