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**ORIGINAL ARTICLE**

# Evaluation of ADMA and Galectin 3 Levels in Predicting Cardiovascular Disease Risk in Patients with Bipolar Disorder

# Bipolar Bozukluğu Olan Hastalarda Kardiyovasküler Hastalık Riskini Öngörmede ADMA ve Galektin 3 Düzeylerinin Değerlendirilmesi

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**ABSTRACT**

**Aim:** Bipolar disorder (BP), a chronic disease, occurs in 1-5% of the population. BP patients have approximately twice as many cardiovascular disease (CVD)-related deaths than the general population. Asymmetric Dimethylarginine (ADMA) and Galectin 3 (Gal 3) can be biomarkers for determining CVD risk and the burden of chronic diseases. Myocardial performance index (MPI) is an echocardiographic parameter evaluating left ventricular (LV) systolic and diastolic functions. MPI also indicates CVD mortality risks. This study aims to investigate the relationship between the sociodemographic and disease-related characteristics of BP patients and the parameters evaluating CVD risks and chronic diseases.
**Material and Methods:** ADMA and N(G)-monomethyl L-arginine (L-NMMA) were measured from the sera from 75 BP patients admitted to Mazhar Osman Mood Center, Faculty of Medicine at Selcuk University and who were euthymic for at least 8 weeks. Simultaneously, echocardiography (ECG) was performed to obtain information about cardiac function.
**Results:** The study included 75 BP patients (52%, n=39 female; 48%, n=36 male). While 54.9% (n=39) had previously experienced psychotic symptoms, 45.1% (n=32) experienced no previous psychotic symptoms, and half had BP family members. Mean plasma ADMA values were 0.26±0.10 µm/L, the mean MPI values were 0.33±0.77, and the mean Gal 3 value was 895.66±721.29 pg/mL. There is a moderately significant positive correlation between age and MPI values ($r=0.588$, $p \leq 0.001$). There was a moderately significant negative correlation between age and Gal 3 values ($r=-0.493$, $p \leq 0.001$). No significant correlation was found between age and ADMA values. No statistically significant difference was observed in mean values of MPI, ADMA, and Gal 3 concerning the presence of psychotic symptoms.
**Conclusion:** No significant relationship was found between ADMA determining CVD risk, disease burden, and psychotic symptoms in BP patients. BP is a chronic disease and its episodic course increases with age and the increase in MPI and Gal 3 are consistent with the literature.

**Keywords:** ADMA, bipolar disorder, cardiovascular risk galectin 3, myocardial perfusion

**ÖZ**

**Amaç:** : Bipolar bozukluk (BB) toplumda %1-5 arasında görülen kronik seyirli bir hastalıktır. BB hastalarında genel popülasyonun yaklaşık iki katı kardiyovasküler hastalık kaynaklı ölüm olduğu bildirilmiştir. Son yıllarda karsiyovasküler hastalık riskini tespit etmek için ADMA ve metabolitleri, kronik hastalıklarda hastalık yükünü tespit etmek amaçlı galektin 3 düzeylerinin biyobelirteç olabileceği bildirilmiştir. Kardiyovasküler mortalite riskini gösteren miyokardiyal performans indeksi (MPI), sol ventrikül (SV) sistolik ve diyastolik fonksiyonunun değerlendirilmesinde kullanılan ekokardiyografik bir parametredir. Bu çalışma bipolar bozukluk tanılı hastanın sosyodemografik ve hastalığa ait özelliklerinin kardiyovasküler ve kronik hastalık riskini değerlendiren parametrelerle ilişkisi araştırmayı hedeflemektedir.
**Yöntem:** Selçuk Üniversitesi Tıp Fakültesi Mazhar Osman Duygudurum merkezine başvurmuş 18-65 yaş arası en az 8 haftadır ötimik olan bipolar bozukluk tanılı 75 hastanın rutin tahlillerinden istenen kanlardan arta kalan serum örneklerinden ADMA, L-NMMA, ölçülmüş ve eş zamanlı olarak kardiyak fonksiyon hakkında bilgi edinme amacıyla EKO yapılmış ve Miyokard performans indeksi hesaplanmıştır.
**Bulgular:** Çalışmaya 75 bipolar bozukluk tanılı hasta dahil edilmiştir. Hastaların %52'i (n:39) kadın , %48'i (n:36 ) erkek idi. Hastaların %54,9'u (n:39) daha önce psikotik belirtiler yaşamışken , %45,1'i (n:32) daha önce psikotik belirti yaşamamış idi. Hastaların yarısının aile bireylerinde de bipolar bozukluk mevcuttu. Hastaların plazma ADMA değerlerinin ortalaması 0,26±0,10µM/l, MPI değerlerinin ortalaması 0,33±0,77, galektin 3 değerinin ortalaması 895,66±721,29 pg/ml'di. Hastanın yaşı ile MPI değeri arasında pozitif yönde orta derecede anlamlı bir ilişki bulunmaktadır ($r=0.588$, $p \leq 0.001$).Hastanın yaşı ile Gal 3 değeri arasında negatif yönde orta derecede anlamlı bir ilişki bulunmaktadır ($r=-0.493$, $p \leq 0.001$). Hastanın yaşı ile ADMA değerleri arasında anlamlı bir ilişki saptanmamıştır. psikotik belirti varlığına göre MPI, ADMA, Gal 3 ortalama değerlerinde istatistiksel olarak anlamlı farklılık gözlenmemiştir.
**Sonuç:** Bu çalışmada bipolar bozukluk hastalarında hastalık yükü ve psikotik belirti ile kardiyovasküler hastalık riskini belirlemede önemli olan ADMA arasında anlamlı ilişki bulunmamıştır. Bipolar bozukluğun kronik seyirli bir hastalık olması yaşla birlikte artan epizodik seyirle birlikte MPI ve galektin 3 parametrelerinde artış görülmesi literatür ile uyumlu bulunmuştur.

**Anahtar kelimeler:** ADMA, bipolar bozukluk, galektin 3, miyokard perfüzyon, kardiyovasküler risk

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## INTRODUCTION

Bipolar disorder (BD) is a mood disorder characterized by chronic, recurrent episodes of mania and depression. Its lifetime prevalence varies between 1% and 5% (1). BD negatively affects the social and professional quality of life of affected individuals. In addition, it has been reported that the life expectancy of BD patients is shortened by 9 to 20 years compared to the general population (2). One of the most important reasons for this is the increased risk of other medical diseases. Cardiovascular diseases (CVDs) are the leading cause of death from medical causes for patients diagnosed with BD (3). In a 20-year follow-up study of 17,101 patients diagnosed with BD in Sweden, it was reported that 38% died due to CVD (4). In a similar study conducted in Norway, it was shown that 33% of patients diagnosed with BD died due to cardiovascular causes in a 33-year follow-up study (5). A 9-year follow-up study of 1300 patients diagnosed with BD in our country also confirms these rates, and it was published that 34.8% of the patients died due to CVD (2).

Nitric oxide (NO) is an endothelial-derived neuromodulator. NO provides potent vasodilator activity via Gluergic activation and mediates the link between neuronal activity and cerebral blood flow (6). It has also been reported that NO has an antiproliferative effect on the myocardium, which also protects against the development of left ventricular hypertrophy. NO concentration fluctuates in the low range, making it a difficult molecule to measure (7). Asymmetric dimethylarginine (ADMA) is an inhibitor of the endogenous nitric oxide synthase (NOS) enzyme. ADMA reduces NO production and can consequently lead to endothelial dysfunction and cardiovascular events. With a better understanding of the pathophysiology of atherosclerosis, especially the central role of endothelial dysfunction, it has been shown that elevated ADMA levels are also associated with heart failure, left ventricular hypertrophy, and increased carotid artery intima-media thickness, and based on all these, it has been thought that plasma ADMA levels can be used as a cardiovascular risk marker (8). In a study conducted in healthy individuals, the reference ranges for ADMA values were 0.22 to 0.69 micromol/l (9).

Galectin-3 (Gal 3), a beta-galactoside-binding lectin, is expressed in a variety of cell types, including epithelial and inflammatory cells, and plays a role in important cellular processes such as adhesion, apoptosis, inflammation, and differentiation (10). Gal 3 also appears to regulate central pathways involved in the etiology of many diseases, including fibrosis, inflammation, cancer progression, and metabolic disorders (11). Recent studies have shown that Gal 3 may be an important regulator of lipogenesis, hyperglycemia, and obesity-associated inflammation. Nayor et al found that plasma Gal 3 concentrations were positively associated with several cardiometabolic traits, including abdominal adiposity, dyslipidemia, and hypertension in cross-sectional analyses. Based on these findings, it has been suggested that Gal 3 may affect the risk of CVD through its potential effects on cardiometabolic pathways (10).

Myocardial performance index (MPI) is an easily obtained parameter that reflects both systolic and diastolic functions of the myocardium and is closely related to invasive measurements. MPI is a numerical value obtained using cardiac time intervals. This numerical value is obtained by dividing

the sum of isovolumic contraction time and isovolumic relaxation time by ejection time. It reflects both the systolic and diastolic functions of the myocardium. MPI has been shown to predict morbidity and mortality due to idiopathic dilated cardiomyopathy, cardiac amyloidosis, and primary pulmonary hypertension (12). It is associated with morbidity and mortality in CVDs. In a study, the MPI value in healthy people was determined as 0.39±0.05 (13).

This study aims to investigate the role of Asymmetric Dimethylarginine (ADMA) and Gal-3 levels and myocardial performance index (MPI) in predicting CVD risk in BD patients. It is well established that individuals with BD have higher cardiovascular mortality rates compared to the general population. Therefore, this study seeks to evaluate the relationship between these biomarkers, disease burden, and cardiac function, assessing their potential prognostic and diagnostic significance.

## MATERIAL and METHODS

ADMA, L-NMMA, arginine, citrulline, ornithine, homoarginine, and methylarginine levels were measured from the remaining serum samples from the routine blood tests of 75 patients diagnosed with BD admitted to Selcuk University, Faculty of Medicine, Mazhar Osman Emotion Center and who have been euthymic for at least 8 weeks, and echocardiography (ECG) was performed simultaneously to obtain information about cardiac function and Myocardial performance index was calculated. Patients with chronic hypertension and blood pressure that cannot be controlled with treatment and those with an ejection fraction below 50% were excluded from the study.

Metabolic parameters in the blood taken from the patients were studied from the remaining serums from the blood sample taken from the antecubital vein after 12 hours of fasting. Blood samples were taken in the laboratory in the morning hours after at least 10 hours of fasting, and the remaining plasma was transferred to plastic tubes after centrifugation and stored at -80° C until processing. Blood samples were analyzed using Electrospray ionization (ESI method) in the Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS ABSCIEX API 3200) device in the Biochemistry Metabolism Laboratory of Selcuk University Faculty of Medicine. 100 microliters of d7-ADMA dissolved in methanol were added to 200 microliters of serum sample and after centrifugation at 13000 rpm for 10 min, the supernatant was separated and evaporated under nitrogen gas at 60 C. 200 microliters of butanol containing 5% acetyl chloride was added. It was kept at 60 C for 20 min. After evaporation under nitrogen gas, 40 microliters were dissolved in a 10% methanol/water mixture containing 0.1% formic acid and injected into the device. Gal 3 and nitrite/nitrate tests were performed with a commercial ELISA kit from the remaining serum samples.

A tube of blood was collected from the volunteers included in the study to measure arginine and arginine metabolites, L-NMMA, SDMA, ADMA, and Gal 3, and ECG was performed by a cardiologist simultaneously. ECG imaging in the study Transthoracic ECG was performed by a cardiologist experienced in ultrasonography, using a dedicated ultrasound device (Vivid E9, GE Vingmead, Horten, Norway) and M5S cardiac sector probe (1.5–4.5 MHz), as recommended by the American Society

of Echocardiography for transthoracic studies.

### Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 software. Descriptive findings were presented with mean, standard deviation, minimum, and maximum for numerical variables; and frequency and percentage for categorical variables. The conformity of numerical variables to normal distribution was assessed using the Kolmogorov-Smirnov test. If the number of measurements in each group was 30 and above and/or if they were normally distributed, they were considered parametric; otherwise, they were considered non-parametric. Since parametric conditions were provided in the comparison of MPI, ADMA, and Gal 3 values according to gender, age groups, presence of psychotic symptoms in the first episodic attack, and presence of a disease in the family history; t-test was used in independent groups. The relationship between the numerical variable age and MPI, ADMA, and Gal 3 values was assessed using the Pearson correlation test. The cases where the type-1 error level was below 5% were interpreted as the diagnostic value of the test being statistically significant.

## RESULTS

The study included 75 patients diagnosed with BD, aged 18-65, who had been euthymic for at least eight weeks and applied to the Mazhar Osman Mood Center of the Faculty of Medicine at Selcuk University. Descriptive findings of the patients participating in the study are presented in Table 1.

**Table 1.** Descriptive findings of categorical variables in the study group

| Variables | | Number (n) | Percent (%) |
|---|---|---|---|
| **Sex (n=75)** | **Female** | 39 | 52.0 |
| | **Male** | 36 | 48.0 |
| **Marital Status (n=74)** | **Single** | 27 | 36.5 |
| | **Married** | 40 | 54.1 |
| | **Widow** | 1 | 1.4 |
| | **Divorced** | 6 | 8.1 |
| **First Disease Episode (n=73)** | **Manic Episode** | 35 | 47.9 |
| | **Depression** | 35 | 47.9 |
| | **Hypomania** | 2 | 2.7 |
| | **Others** | 1 | 1.4 |
| **Psychotic Episode (n=71)** | **No** | 39 | 54.9 |
| | **Yes** | 32 | 45.1 |
| **Psychiatric Illness History (n=68)** | **No** | 34 | 50.0 |
| | **Yes** | 34 | 50,0 |

The mean plasma ADMA values of the patients were 0.26±0.10μM/l, the mean MPI values were 0.33±0.77, and the mean Gal 3 value was 895.66±721.29 pg/ml. Descriptive findings of numerical variables in the study group are presented in Table 2.

A comparison of MPI, ADMA, and Gal 3 values by gender is presented in Table 3. No statistically significant difference is observed in the mean MPI and ADMA values by gender. The mean Gal 3 was found to be 729.92 in women and 1075.21 in men. The mean Gal 3 was found to be statistically significantly higher in men than in women (p=0.040).

**Table 2.** Descriptive findings of numerical variables in the study group

| Variables | n | Min. | Max. | Mean | SD |
|---|---|---|---|---|---|
| **Age** | 75 | 17 | 63 | 34.87 | 11.615 |
| **MPI** | 75 | 0.17 | 0.63 | 0.3311 | 0.07700 |
| **ADMA** | 75 | 0.116 | 0.620 | 0.26504 | 0.101423 |
| **L-NMMA** | 75 | 0.00975 | 0.26700 | 0.0303168 | 0.02980021 |
| **Gal-3** | 75 | 107.895 | 2932.358 | 895.66621 | 721,299169 |

Asymmetric dimethylarginine (ADMA) levels are expressed in µm/L (micromolar per liter), and galectin-3 (Gal-3) levels are presented in pg/mL (picogram per milliliter). L-NMMA: N(G)-monomethyl L-arginine, MPI: Myocardial performance index, SD: Standard deviation

**Table 3.** Comparison of MPI, ADMA, and Gal 3 values by gender

| Variables | | n | Mean | SD | p |
|---|---|---|---|---|---|
| **MPI** | **Female** | 39 | 0.3413 | 0.08339 | 0.234 |
| | **Male** | 36 | 0.3200 | 0.06887 | |
| **ADMA** | **Female** | 39 | 0.25628 | 0.094370 | 0.440 |
| | **Male** | 36 | 0.27453 | 0.109094 | |
| **Gal 3** | **Female** | 39 | 729.92533 | 591.560909 | 0.040 |
| | **Male** | 36 | 1075.21883 | 810.120624 | |

Independent groups t-test. ADMA: Asymmetric dimethylarginine, Gal 3: Galectin 3, MPI: Myocardial performance index, SD: Standard deviation

**Table 4.** Comparison of MPI, ADMA, and Gal 3 values in terms of age

| Variables | | n | Mean | SD | p |
|---|---|---|---|---|---|
| **MPI** | **≤ 35 years** | 39 | 0.2997 | 0.05055 | 0.001 |
| | **≥ 36 years** | 36 | 0.3650 | 0.08650 | |
| **ADMA** | **≤ 35 years** | 39 | 0.26885 | 0.102669 | 0.738 |
| | **≥ 36 years** | 36 | 0.26092 | 0.101344 | |
| **Gal 3** | **≤ 35 years** | 39 | 1226.24500 | 817.617975 | 0.001 |
| | **≥ 36 years** | 36 | 537.53919 | 347.151956 | |

Independent groups t-test. ADMA: Asymmetric dimethylarginine, Gal 3: Galectin 3, MPI: Myocardial performance index, SD: Standard deviation

**Table 5.** Relationship between patient's age, and values of MPI, ADMA, and Gal 3

| Variables | | MPI | ADMA | Gal 3 |
|---|---|---|---|---|
| **Age** | **Correlations (r)** | 0.588 | -0.060 | -0.493 |
| | p | ≤0.001 | 0.609 | ≤0.001 |
| | n | 75 | 75 | 75 |

Pearson correlation test. ADMA: Asymmetric dimethylarginine, Gal 3: Galectin 3, MPI: Myocardial performance index

MPI average was determined as 0.29 in the group under 35 years of age, and the MPI average was determined as 0.36 in the group 36 years of age and above. MPI average was statistically significantly higher in the group 36 years of age and above compared to the group 35 years of age and below (p=0.001). Gal 3 average was determined as 1226 in the group under 35 years of age, and Gal 3 average was determined as 537 in the group 36 years of age and above. Gal 3 average was statistically significantly higher in the group 35 years of age and below compared to the group 36 years of age and above (p=0.001). A comparison of MPI, ADMA, and Gal 3 values according to age is presented in Table 4.

There is a moderately significant positive relationship between patient age and MPI value (r=0.588, p≤0.001). (Note: when one ıncreases, the other ıncreases)There is a moderately significant negatıve relationship between patient age and Gal 3 value (r=-0.493, p≤0.001). (note: when one ıncreases, the other decreases). No significant relationship was found between patient age and ADMA values. The relationship between patient age and MPI, ADMA, and Gal 3 values is presented in Table 5 with Pearson correlation coefficient values.

No statistically significant difference was observed in the mean values of MPI, ADMA, and Gal 3 according to the presence of psychotic symptoms in the first episodic attack. A comparison of MPI, ADMA, and Gal 3 values according to the presence of psychotic symptoms in the first episodic attack is presented in Table 6.

## DISCUSSION

It has been reported that the risk of death from CVD is almost doubled in BD compared to the general population. Obesity, hypertension, diabetes mellitus, and hyperlipidemia risk factors are shown as a risk factor for CVD mortality in BD , but a biomarker that evaluates CVD risk is not yet available (14). In this study, the relationship between the sociodemographic and disease-related characteristics of 75 patients diagnosed with BD and the parameters evaluating CVD and chronic disease risk were investigated.

Many studies have reported that ADMA and its metabolites are higher in psychiatric diseases compared to healthy controls It is thought that ADMA causes vasocontraction

**Table 6.** Comparison of MPI, ADMA, and Gal 3 values by the presence of psychotic symptoms

| Variables | Psychotic Symptoms BD | n | Mean | SD | p |
|---|---|---|---|---|---|
| **MPI** | No | 39 | 0.3351 | 0.08448 | 0.514 |
| | Yes | 32 | 0.3231 | 0.06606 | |
| **ADMA** | No | 39 | 0.26892 | 0.111274 | 0.632 |
| | Yes | 32 | 0.25731 | 0.087591 | |
| **Gal 3** | No | 39 | 894.80041 | 800.664734 | 0.752 |
| | Yes | 32 | 950.60347 | 653,874374 | |

Independent groups t-test. BD: Bipolar disorder, ADMA: Asymmetric dimethylarginine, Gal 3: Galectin 3, MPI: Myocardial performance index

by inhibiting NOS, and with this effect, it reduces cerebral blood flow and may cause the emergence of psychiatric diseases (15). In a manic episode, ADMA levels in the plasma of 30 patients with BD and 30 healthy volunteers were compared and ADMA levels in the patients in the episode were found to be significantly higher than in the healthy volunteers (16). In a study comparing plasma ADMA values of 78 patients with psychosis and 30 healthy volunteers, changes in plasma ADMA concentrations after antipsychotic treatment were evaluated in the patient group, and a decrease in plasma ADMA levels was shown in the patient group after antipsychotic drug treatment. It was thought that antipsychotic treatment caused a decrease in ADMA levels (17). When the values in the study of Deneva-Koycheva, T.I. et al. evaluating plasma ADMA levels in healthy individuals were taken as reference, no significant difference was found between plasma ADMA levels between healthy individuals and the patients in our study (9). This may be because the patients were in the euthymic period and under antipsychotic treatment and the sample size was small. The patients were divided into two groups: psychotic and non-psychotic, and no statistically significant difference was found between the groups. In the study conducted by Zincir S., as in this study, no relationship was found between plasma ADMA concentrations and the clinical type and severity of the disease (18).

The study found a statistically significant relationship between increasing age and Gal 3. Although it was stated that galectin is a stable biomarker and is not affected by variables such as age, it has been reported that it increases in chronic diseases (19). Since BD is a chronic disease that affects the system, Gal 3 levels may have increased with age. MPI is a parameter OF ECG used to evaluate left ventricular systolic and diastolic function. It has previously been shown that MPI predicts morbidity and mortality due to idiopathic dilated cardiomyopathy, cardiac amyloidosis, and primary pulmonary hypertension. A recent study on patients with heart failure found that this index is a strong predictor of CVD mortality (12). There are studies indicating that it is a predictor of CVD mortality independent of CD risk factors in elderly male individuals (20). In this study, it was observed that there was an increase in MPI value as age increased.

This study has attempted to emphasize the importance of biomarker studies in a group such as BD, where CVD-related deaths are higher than the general population. When the literature is examined, it is seen that the studies on this subject are insufficient. This study is important in terms of investigating the psychopathologies of CVDs in BD, which is a chronic disease affecting multiple systems.

## CONCLUSION

In this study, it was found that ADMA levels were not directly associated with CVD risk in patients with BD. A significant positive correlation was observed between age and myocardial performance index (MPI), suggesting that cardiac function may deteriorate with aging. Additionally, a significant negative correlation was identified between age and Gal 3 levels ($r=-0.493$, $p\leq0.001$), indicating that Gal-3 levels decrease with advancing age.

Considering that Gal-3 is associated with chronic disease burden, this variation may reflect age-related physiological changes. Moreover, no significant differences were found in MPI, ADMA, or Gal-3 levels based on the presence of psychotic symptoms. These findings highlight the potential role of biomarkers in c risk assessment in patients with BD and provide insights for future research.

**Limitations:** The limitations of the study include the fact that it was a single-center study, the small sample size, and the lack of healthy controls.

**Ethical Approval:** This study was approved by the Selcuk University Faculty of Medicine Local Ethics Committee on 04.03.2019 with decision number 2029/64.

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