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Evaluation of the macrophage migration inhibitory factor (MIF) -173 G/C variant in bipolar disorder

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Summary

Background: *This study aimed to study the genetic variant in the MIF −173 G/C in bipolar disorder (BD) by comparing genotype distributions of the MIF −173 G/C variant between patients and healthy controls, considering clinical parameters.*

Subjects and Methods: *A total of 104 patients with BD and 100 healthy volunteers were included in the study. The participants were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and sociodemographic and clinical data forms. The Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HAM-D), and The Clinical Global Impression Scale (CGI) were administered to patients with BD. Blood samples were collected from participants to isolate their deoxyribonucleic acid material (DNA). The MIF −173 G/C variant was determined using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis.*

Results: *The genotype distribution (GG, GC, CC) and allele frequencies (G, C) in the BD group significantly differed from those in the control group. The percentages of the GG genotype (p=.040) and G allele (p=.049) were significantly higher in the BD group compared to the control group. When comparing scale scores and clinical parameters (number of manic episodes, depressive episodes, total episodes, duration of disease, age of onset, and number of hospitalizations) based on MIF genotype distributions in patients with BD, the CGI-I score was significantly higher in the group with the GG genotype compared to the GC/CC group (p = .029).*

Conclusion: *The MIF −173 G/C variant might be associated with BD and treatment response. Additionally, possessing the GG genotype and G allele appears to be disadvantageous in terms of BD diagnosis and treatment resistance in the Turkish population.*

Keywords: *Bipolar disorder, treatment response, macrophage migration inhibitory factor, MIF, single-nucleotide polymorphism*

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INTRODUCTION

Bipolar disorder (BD) is a psychiatric disorder that can cause significant impairments in psychosocial and occupational function during episodes, have a chronic course, and is seen in approximately 1% of the world population (Avramopoulos et al., 2015). Although many studies have investigated biological, genetic, and psychosocial factors to explain the pathophysiology of BD, the etiology of BD has not yet been fully elucidated. An increasing number of studies show that inflammation may play an essential role in the pathophysiology of BD (Nursal et al., 2020; Pehlivan et al., 2020).

The traditional knowledge that the central nervous system (CNS) is protected from peripheral immune events by the blood-brain barrier has recently been discussed. Nowadays, studies about the brain both trigger and remain under the effect of the peripheral immune mechanisms suggest that the pro-inflammatory response may affect the formation of the symptoms in BD (Aytaç & Pehlivan, 2020). Indeed, studies have shown that the immune system cells in the patient's peripheral blood with BD show numerical and structural changes. It is thought that a systemic inflammatory change plays a role in the etiology of the disease. The high cytokine levels reported in both serum and cerebrospinal fluid (CSF) of patients may also vary depending on the type of possible immunogen exposed at the time of measurement (Kalelioğlu et al., 2017; Muneer, 2016). Thus, monitoring only cytokine levels of serum and CSF and disregarding the confounding factors mentioned above (a latent infection focus exposed during measurement, presence of concomitant autoimmune disease, etc.) can be misleading without considering the genetic background of the immunological systems and the role of underlying variants of the inflammation-related genes (Panaccione et al., 2015).

Macrophage migration inhibitory factor (MIF) is a potent cytokine that plays a crucial role in innate and adaptive immune responses and is implicated in the pathogenesis of various inflammatory and autoimmune diseases. The *MIF* gene is localized to the q11.23 region

on chromosome 22. In studies about the variants in the promoter region of the *MIF* gene, the –173 C allele in the rs755622 variant was associated with increased transcription activity and MIF protein production (Bucala, 2013a). In previous studies, it was seen that the *MIF* gene played an essential role in the pathophysiology of sepsis, acute respiratory distress syndrome, tuberculosis, and diabetes (Xu et al., 2013). Based on our previous study, which identified an association between *MIF* gene polymorphism and suicide attempts in patients with BD (Aytac et al., 2020), we believe that the relationship between *MIF* −173 G/C gene polymorphism and other clinical parameters in BD requires further detailed investigation. In this research, we hypothesized that the distribution of *MIF* −173 G/C gene polymorphism in patients with BD would differ significantly from that of the control group and could provide valuable insights into the prognosis of the disorder. A literature review indicates that the relationship between BD, its clinical parameters, and the *MIF* −173 G/C variants has not been explored in previous studies. To the best of our knowledge, this is the first study to comprehensively investigate the association between the *MIF* −173 G/C variant and the clinical features of BD.

Aims of The Study

This study aims to evaluate the relationship between the clinical features of BD and the *MIF* −173 G/C variant by comparing the genotype distributions of this variant between patients with BD and healthy controls, with a specific focus on clinical parameters.

SUBJECTS AND METHODS

1) Patient Selection:

One hundred and four patients with BD were consecutively followed at the outpatient clinic of Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital from January to June 2018. Additionally, 100 healthy volunteers were included in this case-control study for comparison. The study was approved by the Local Committee of Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital (07.11.2017/81). The participants were thoroughly informed about the study's purpose, method, and procedures, and written consent was obtained from all participants. The interview was initiated by filling out data forms that included sociodemographic and clinical information. Afterward, the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) was used to confirm the diagnosis according to DSM-IV-TR criteria, and the presence of any psychiatric diagnosis was decided as the basis for exclusion from the study in the healthy control group. The Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HAM-D), and the Clinical Global Impression Scale (CGI) were administered to patients with BD.

Inclusion and Exclusion Criteria:

Subjects of 18 to 65 years of age, of either gender, were literate, agreed on the participation in the study, diagnosed with a BD according to the SCID-I interview, had no other systemic/neurological disease that may affect cognitive functions (dementia, epilepsy, Parkinson disease, head trauma accompanied by loss of consciousness) included in the study.

We excluded subjects who had mental retardation, neurodevelopmental disorders such as autism, a diagnosis of axis-1 disorder other than BD as a result of the SCID-I interview, a BD secondary to a general medical condition, dementia, or brain damage.

Diagnostic Tools And Scales

a) Sociodemographic and Clinical Characteristics Data Form:

This data form is a detailed interview prepared by the researchers, which includes questions about clinical information such as sociodemographic characteristics, family history, disease history, and complaints related to BD.

b) Structured Clinical Interview for DSM-IV-TR (SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders):

First et al. developed the SCID-I in 1997, a structured interview chart for diagnosing Axis I disorders according to DSM-IV-TR diagnostic criteria (Spitzer et al., 1992). Çorapçıoğlu et al. conducted adaptation and validity-reliability studies of SCID-I for the Turkish population in 1999 (Çorapçıoğlu et al., 1999).

c) Hamilton Depression Rating Scale (HAM-D):

HAM-D was developed by Hamilton to evaluate the severity of depression in patients diagnosed with depression (Hamilton, 1960). A Turkish validity-reliability study was performed by Akdemir et al. (Akdemir et al., 1996).

d) Young Mania Rating Scale (YMRS):

Young et al. developed YMRS in 1978 to evaluate the severity and change in manic conditions (Young et al., 1978). A Turkish validity-reliability study was performed by Karadağ et al. (Karadağ et al., 2001).

e) Clinical Global Impression Scale (CGI):

CGI was developed by Guy in 1976 to evaluate the course of all psychiatric disorders at any age for clinical research purposes (Guy, 1976). This three-dimensional semi-structured scale is used during the semi-structured interview to assess the severity of disease (CGI-S) and response to treatment of people with psychiatric disorders (CGI-I).

2) DNA Analyses:

Blood samples were obtained from participants at the Istanbul Faculty of Medicine Laboratory of Medical Biology to isolate their deoxyribonucleic acid (DNA) material. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to determine the *MIF* −173 G/C variant. PCR was performed using forward (5′-ACTAAGAAAGACCCGAGGC-3′) and reverse (5′-GGGGCACGTTGGTGTTTAC-3′) primers. The PCR product contains two restriction sites for allele C (205 bp, 62 bp, and 63 bp), whereas one of these sites is destroyed in the presence of allele G, resulting in fragments of 268 bp and 62 bp (Ekşi et al., 2017).

Procedures For Blood Samples

Two cc blood samples were collected with ethylene diamine tetraacetic acid (EDTA) tubes to obtain the DNA of 104 patients with BD and 100 healthy volunteers. Generally, a three-step pathway is used to detect gene variants: genomic DNA isolation, amplification of target gene region by PCR, restriction enzyme digestion, and application of an agarose gel electrophoresis method for visualization of the obtained product.

After the genomic DNA was isolated with the GeneMark Plus Blood Genomic DNA Purification Kit, reproduction of the desired region of DNA was carried out via PCR using artificially prepared oligonucleotide primers.

The *MIF* −173 G/C variant was determined using the PCR-RFLP method (Ekşi et al., 2017). At the end of the procedure, 10 µl of the PCR product was taken, and electrophoresis was performed using a 2% agarose gel. The DNA samples containing *MIF* −173 G/C polymorphic bands were examined under ultraviolet light. Ten percent of the samples were randomly selected for validation, and the method was verified using this subset.

3) Statistical Analyses:

Statistical analysis was performed using IBM SPSS version 21.0 (IBM Corp. released 2012; Armonk, NY, USA). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage. Pearson chi-square test or Fisher's exact test was used for the comparison of discrete variables. The odds ratio (OR) and the 95% confidence interval (CI) were also calculated. The Shapiro-Wilk test evaluated the suitability of continuous variables to normal distribution. Intergroup comparisons of continuous variables were conducted using the Mann-Whitney U test. Genotype distributions in both the patients and the healthy controls were analyzed according to the Hardy-Weinberg Equilibrium (HWE) (mid-p adjustment). Statistical significance was accepted as $p < 0.05$ for the results of all analyses.

RESULTS

One hundred and four patients with BD (62 female/42 male) were evaluated according to their clinical parameters and scale scores, as shown in Table 1.

Table 1: The Clinical Parameters and Scale Scores of Patients

	Bipolar Disorder (N:104)
	Mean ± SD
Age of onset (year)	25.68±8.51
Duration of disease (year)	15.73±10.49
Number of Hospitalization	3.28±4.2
Dep. episode	1.17±2.32
Manic episode	4.02±4.58
Total episode	5.57±5.25
HAM-D	14.78±9.09
YMRS	9.39±10.87
CGI-S	4.96±0.94
CGI-I	2.18±0.87

(Abbreviations: SD, standard deviation; dep., depressive; HAM-D, hamilton depression rating scale; YMRS, young mania rating scale; CGI-S, clinical global impression scale-severity; CGI-I, clinical global impression scale-improvement)

The clinical specifiers of the patients are presented in Table-2. The mean age of the BD patient group was 41.41±11.56. According to the *MIF* −173 G/C genotype distribution, 78.8 % (n=82) of the patients diagnosed with BD had GG, 19.2 % (n=20) had GC, and 1.9 %

(n=2) had CC genotypes. When the *MIF* −173 G/C genotype (GG, GC, CC) and the allele frequencies (G, C) of patients with BD were compared with the control group, the *MIF* genotype distribution of BD was found to be significantly different from the control group (OR: 0.521, 95%Cl: 0.278-0.975; p=.040). The percentage of the GG genotype was found to be statistically higher in the BD group compared to the control group. The *MIF* −173 G/C allele frequency of the BD group was also significantly different from the control group (OR: 0.575, 95%Cl: 0.330-1.001; p=.049). The percentage of the G allele was found to be statistically higher in the BD group than in the control group (Table 3).

Table 2: The Clinical Specifiers of Patients with Bipolar Disorder

Clinical Specifiers		**N**	**%**
Atypical Features	No	82	79
	Yes	22	21
Mixed Features	No	80	77
	Yes	24	23
Seasonal Pattern	No	58	55.7
	Yes	46	44.3
Hist. of Rapid Cyc.	No	75	72.1
	Yes	29	27.9
Psychotic Depression	No	88	84.6
	Yes	16	15.4
Psychotic Mania	No	55	52.9
	Yes	49	47.1
Postpartum Onset	No	94	90.4
	Yes	10	9.6

(Abbreviations: hist., history; cyc., cycling)

Comparing the scale scores (HAM-D, YMRS, CGI-S, CGI-I) and clinical parameters (number of manic episodes, depressive episodes, total episodes, age of onset, duration of disease and number of hospitalizations) regarding the *MIF* −173 G/C genotype (GG, GC/CC) distributions in patients with BD, the CGI-I score was significantly different between the groups of *MIF* −173 G/C genotype (p=.029) (Table 4). The CGI-I score of the group containing the genotype of the mutation allele (GC/CC) was statistically lower than the group containing the GG genotype. Also, comparing the *MIF* −173 G/C genotype and allele frequency distributions between the two groups according to the presence of clinical specifiers (psychotic features, atypical features, seasonal pattern, mixed features, rapid cycling history, peripartum onset) in the BD patient group, it was shown that there were no statistically significant differences in terms of clinical specifiers (p>.05) (data not shown).

DISCUSSION

The data analysis of our study, which included 204 participants (104 BD patients and 100 healthy volunteers), revealed that the *MIF* −173 G/C genotype and allele frequency distributions in the BD group were significantly different from those in the control group. The percentage of GG genotype and G allele of the BD group was found to be statistically higher than the control group. Many studies conducted on BD patients have shown increased levels of pro-inflammatory markers, both in the blood and in the CNS. The studies usually focused on the peripheral cytokine levels of BD patients. Although the results were conflicting, the patients with BD had higher

Table 3: Comparison of MIF –173G/C Genotype Distribution of Patients with the Control Group

	Genotype	**Bipolar Disorder**		**Healthy Control**		**OR**	**95% CI**	**p**
		n = 104	(%)	n = 100	(%)			
MIF	GG	82	(78.8)	66	(66)	0.521*	0.278-0.975*	**.040***
	GC	20	(19.2)	31	(31)	1.887*	0.989-3.600*	.052*
	CC	2	(1.9)	3	(3)	0.634[&]	0.104-3.876[&]	.678[&]
Allele								
	G	184	(88.5)	163	(81.5)			
	C	24	(11.5)	37	(18.5)	0.575*	0.330-1.001*	**.049***
HWE mid-p		0.482		0.869				

Abbreviations: OR, odds ratio; CI, confidence interval; *Pearson chi-square; [&]Fisher's Exact Test;
HWE mid-p, Hardy-Weinberg equilibrium mid-p adjustment.

Table 4: Comparison of Scale Scores and Clinical Parameters According to *MIF* –173G/C Genotype Distribution in Patients

	GG		GC/CC		p*
	Median (min-max)	**Mean ± SD**	**Median (min-max)**	**Mean ± SD**	
HAM-D score	14(0-41)	15.62 ±9.38	11(0-26)	11.68±7.31	.093
YMRS score	6.5(0-42)	9.89±10.84	1(0-35)	7.54±11.01	.104
CGI-S score	5(2-7)	4.97±0.91	5(3-7)	4.90±1.06	.781
CGI-I score	2(1-5)	2.28±0.87	2(1-3)	1.81±0.79	**.029**
Dep. episode	0(0-10)	1.32±2.50	0(0-6)	0.59±1.33	.224
Manic episode	2(0-21)	3.86±4.29	3(1-21)	4.63±5.61	.581
Total episode	4(1-23)	5.53±4.96	3.5(1-27)	5.72±6.33	.825
Age of onset	24(13-52)	26.09±8.83	24(10-34)	24.1±7.16	.641
Duration of disease	13.5(0.5-40)	15.05±10.05	20(2-40)	18.27±11.87	.256
Number of hospt.	2(0-21)	3.39±4.14	2(0-21)	2.90±4.47	.594

* Mann Whitney U test
(Abbreviations: SD, standard deviation; min, minimum; max, maximum; CGI-S, clinical global impression scale-severity; CGI-I, clinical global impression scale-improvement; HAM-D, hamilton depression rating scale; YMRS, young mania rating scale; dep., depressive; hospt., hospitalization)

serum concentrations of IL-1β, a soluble IL-2 receptor (sIL-2R), IL-4, sIL-6R, TNF-α, and sTNF-R1 compared to the healthy control group (Gonzalez et al. 2017).

Genome-wide association studies (GWAS) and linkage studies have reported genes related to brain-derived neurotrophic factor (*BDNF*), the voltage-dependant calcium channel α-1 subunit (*CACNA1C*), catechol-O-aminotransferase (*COMT*), cyclic-AMP response element-binding (*CREB*), ankyrin-G and the apoptotic genes like *FAS*, *BAK*, and *APAF-1* to be associated with BD (Dodd et al. 2015). When reviewing the literature on inflammation-related gene variants, Ucok et al. reported that the frequencies of HLA-A10, HLA-A29, HLA-B7, HLA-B16, and HLA-B21 were higher in BD patients compared to the control group (Ucok et al. 2005). In one study related to the topic, the *IFN-γ* +874 T/A (rs2430561) gene variant was analyzed in 106 patients with BD type-1 and 109 control. The genotype distribution of the *IFN-γ* +874 T/A variant was found to be significantly different between the patients and control group (Nayeri et al., 2019).

Increasing evidence suggests that *MIF* gene variants play a significant role in the pathogenesis of depression and schizophrenia. In our previous study examining the *MIF* −173 G/C polymorphism in patients diagnosed with schizophrenia, although there was no statistically significant difference in the distribution of the *MIF* −173 G/C gene polymorphism between the patient and control groups, we found that the *MIF* −173 G/C gene polymorphism may be associated with the age of illness onset and impaired insight in patients with schizophrenia (Aytac et al., 2021). Musil et al. found that patients with depression had significantly elevated serum MIF and reduced serum TGF-β concentrations compared to the control group. They suggested that MIF is a promising new candidate in the neuro-immune interaction that may be related to depressive symptoms, altered immune system, and hypothalamic–pituitary–adrenal (HPA) axis (Musil et al., 2011). Similar results have been reported in a study conducted on pregnant women, where an association was determined between depressive symptoms and increased serum levels of MIF (Christian et al., 2010). Again, Okazaki et al. reported that serum MIF levels were significantly higher in patients with schizophrenia than in controls and were positively correlated with the antipsychotic dose. These high levels of MIF in serum may potentially be biomarkers for schizophrenia, as mentioned in the previous studies, and the association with the antipsychotic dose may be explained with an alternative etiological mechanism besides the dopamine antagonist effect in the treatment (Okazaki et al., 2018).

As known, the CGI-I is used to evaluate how much the patient's illness has improved or worsened relative to

a baseline state at the beginning of the treatment (Busner & Targum, 2007). When we classified the groups according to the presence of mutation alleles (GG, GC/CC) (homozygosis normal, heterozygosis/ homozygosis mutant), the CGI-I score of the group containing the genotype of mutation allele (GC/CC) was statistically lower than the group containing genotype of GG. This result indicated that the treatment response was better in the group carrying the genotype with the mutant allele. The *MIF* −173 G allele, a low-expression variant, may be linked to disrupted immune regulation. While high-expression *MIF* variants often worsen disease outcomes, their effects are disease-specific, with some studies showing reduced susceptibility in certain conditions, as in our study (Bucala, 2013b). In BD, the low expression of *MIF* linked to the G allele could impair immune balance, contributing to inflammation-related pathophysiology and treatment resistance, highlighting the complex, disease-dependent role of *MIF* polymorphisms (Sumaiya et al., 2022).

BD itself appears to be the most inheritable disease among all psychiatric disorders, but genetic studies of treatment response are predominantly related to predictors of lithium response. Some studies provide evidence supporting the anti-inflammatory effects of lithium through various mechanisms (Nassar & Azab, 2014). Lithium reduces the synthesis of pro-inflammatory enzymes and molecules (IL-1, TNF-α, PG, NO, iNOS, COX-2, and PLA2) during treatment and organizes in vitro microglial activity. It was also shown that valproic acid down-regulates the arachidonic acid signal cascade by inhibiting COX-1 and COX-2 synthesis in the rat brain, similar to lithium. Thus, valproate and other antiepileptic agents used as mood stabilizers (carbamazepine, lamotrigine, oxcarbazepine, and topiramate) have been shown to significantly reduce cytokine synthesis in vitro (Nassar & Azab, 2014; Panaccione et al., 2015).

It has been reported that the *BDNF* gene plays a role in the pathogenesis of BD and the *BDNF* variant (rs6265) has been associated with lithium response (Dmitrzak-Weglarz et al. 2008). In different studies, *NTRK2* variants have been involved in genetic factors underlying BD in GWAS and found to be related to lithium response (Salloum et al., 2014). Mamdani et al. reported that there was an association between variants in *CREB1* (*CREB1-1H* SNP (G/A change, $p < 0.002$) and the *CREB1-7H* SNP (T/C change, $p < 0.002$)) and lithium response on a sample consisting of 258 patients diagnosed with BD followed over three years (Mamdani et al. 2008). In another study, it was reported that glycogen synthase kinase 3β (*GSK3B*) variants might be associated with BD type-1 and the therapeutic response to lithium in a cohort of 138 Taiwanese subjects diagnosed with BD (Lin et al., 2013). In summary, although *HLA-A3*, *HLA-B5*, *BDNF*, *5-HTTLPR*, *GSK-3β*, *CREB1*, *ACCN*, *CACNG2*, *GADL-1*, and *GSK-3β* gene variants are thought to be related to response to lithium treatment, *DRD2*, *DRD3*, *DRD4*, *GABRA1*, *PLCG1-5*, *PLCG1-8*, *mtDNA 5178*, *SCL4A10*, and *INPP1* variants were found to be unrelated with the treatment response (Bozkurt et al., 2018). When we look at the studies about *MIF* gene and treatment response of psychiatric disorders, in the Genome-based Therapeutic Drugs for Depression (GENDEP) project, serum MIF levels were significantly higher in patients who responded to treatment than in patients who had treatment-resistant depression. Again, serum MIF levels were reported to be higher in patients with depression than in the control group. (Cattaneo et al., 2013).

Considering the limitations of the study, the small sample size reduces its power, and the case-control design, which prevents the establishment of causality, should be noted. Additionally, while our study focused on the *MIF* –173G/C variant, the functional *MIF* –794 $CATT_{5–8}$ microsatellite variant was not examined, nor were serum MIF levels measured—both of which could have provided valuable insights. However, the study also has several strengths. It is the first to explore the relationship between the *MIF* –173G/C gene variant and clinical characteristics in patients diagnosed with BD. The inclusion of patients regularly followed up at the Community Mental Health Center ensured a more stable clinical profile and reliable data collection. Moreover, by sampling from a specific region, the study minimized the confounding effects of diverse environmental factors, providing a more homogeneous environmental context for clearer analysis.

In conclusion, we found that the *MIF* −173 G/C variant may be associated with BD and treatment response. Furthermore, our study revealed that the presence of the GG genotype and G allele was disadvantageous in terms of both the risk of BD diagnosis and treatment resistance in the Turkish population. In the future, exploring the interaction between the *MIF* gene and other genes involved in immune response, neuroinflammation, and neuroplasticity could provide deeper insights into the mechanisms linking *MIF* with BD. Functional studies examining how different *MIF* gene variants impact protein expression, cytokine levels, and neuronal function may offer valuable information for developing targeted therapies. Furthermore, expanding research on *MIF* gene variants to diverse populations could help determine whether the associations observed in the Turkish population are globally consistent, thereby enhancing our understanding of the genetic and environmental factors influencing BD.

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Ethical Standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation, as well as the Helsinki Declaration of 1975, as revised in 2013 (Association 2013).

References

Akdemir, A., Örsel, S., Dağ, İ., Türkçapar, H., İşcan, N., & Özbay, H. (1996). Hamilton Depresyon Derecelendirme Ölçeği (HDDÖ)'nin geçerliği, güvenirliği ve klinikte kullanımı. *Psikiyatri Psikoloji Psikofarmakoloji Dergisi, 4*, 251-259.

World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA, 310*, 2191-2194.

Avramopoulos, D., Pearce, B. D., McGrath, J., Wolyniec, P., Wang, R., Eckart, N., et al. (2015). Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation. *PloS One, 10*, e0116696.

Aytac, H. M., Oyaci, Y., Yazar, M. S., Erol, A., & Pehlivan, S. (2020). Association of MIF and MBL2 gene polymorphisms with attempted suicide in patients diagnosed with schizophrenia or bipolar disorder. *Journal of Clinical Neuroscience, 78*, 264-268.

Aytac, H. M., Oyaci, Y., Yazar, M. S., & Pehlivan, S. (2021). Macrophage migration inhibitory factor-173 G/C polymorphism is associated with the age of onset and insight in Schizophrenia in the Turkish population. *Neurological Research, 43*, 977-984.

Aytaç, H. M., & Pehlivan, S. (2020). Viral Pandemics as Possible Psycho-immunological Causes of Psychiatric Symptoms: From Past to Present. *Sağlık Bilimlerinde İleri Araştırmalar Dergisi, 3*, 92-98.

Bozkurt, H. T., Erbasan, V., Eğilmez, Ü., Şen, B., Aydın, M., & Altınbaş, K. (2018). Clinical, Biological and Genetic Predictors of Lithium Treatment Response. *Current Approaches in Psychiatry/Psikiyatride Güncel Yaklaşımlar, 10*.

Bucala, R. (2013a). MIF, MIF alleles, and prospects for therapeutic intervention in autoimmunity. *Journal of Clinical Immunology, 33*, 72-78.

Bucala, R. (2013b). MIF, MIF alleles, and prospects for therapeutic intervention in autoimmunity. *Journal of Clinical Immunology, 33*, 72-78.

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont), 4*, 28.

Cattaneo, A., Gennarelli, M., Uher, R., Breen, G., Farmer, A., Aitchison, K. J., et al. (2013). Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology, 38*, 377.

Christian, L. M., Franco, A., Iams, J. D., Sheridan, J., & Glaser, R. (2010). Depressive symptoms predict exaggerated inflammatory responses to an in vivo immune challenge among pregnant women. *Brain, Behavior, and Immunity, 24*, 49-53.

Çorapçıoğlu, A., Aydemir, Ö., Yıldız, M., Esen, A., & Köroğlu, E. (1999). *DSM-IV Eksen I Bozuklukları (SCID-I) için yapılandırılmış klinik görüşme, klinik versiyon*. Ankara: Hekimler Yayın Birliği.

Dmitrzak-Weglarz, M., Rybakowski, J. K., Suwalska, A., Skibinska, M., Leszczynska-Rodziewicz, A., Szczepankiewicz, A., & Hauser, J. (2008). Association studies of the BDNF and the NTRK2 gene polymorphisms with prophylactic lithium response in bipolar patients. *Pharmacogenomics, 9*, 1595-1603.

Dodd, S., Fernandes, B. S., & Dean, O. M. (2015). Future Directions for Pharmacotherapies for Treatment-resistant Bipolar Disorder. *Current Neuropharmacology, 13*, 656-662.

Ekşi, F., Pehlivan, S., Erdoğan, M. B., Bayram, A., Oğuzkan-Balcı, S., Yamak, B., & Pehlivan, M. (2017). MBL2 and MIF gene polymorphisms in cardiovascular patients with atherosclerotic lesions undergoing heart valve replacement. *Biotechnology & Biotechnological Equipment, 31*, 1173-1177.

Gonzalez, S. D., Williams, A. J., Blacker, C. J., Voort, J. L. V., Schak, K. M., Nemeroff, C. B., et al. (2017). Putative biological predictors of treatment response in bipolar disorders. *Personalized Medicine in Psychiatry, 1*, 39-58.

Guy, W. (1976). Clinical global impression. In *Assessment manual for Psychopharmacology* (pp. 217-222).

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry, 23*, 56-62.

Kalelioğlu, T., Genç, A., & Karamustafalıoğlu, N. (2017). İki Uçlu Bozukluk ve İnflamasyon. *Journal of Mood Disorders, 7*.

Karadağ, F., Oral, E. T., Aran, Y., & Erten, E. (2001). Young mani derecelendirme ölçeğinin Türkiye'de geçerlik ve güvenilirliği. *Türk Psikiyatri Dergisi, 13*, 107-114.

Lin, Y. F., Huang, M. C., & Liu, H. C. (2013). Glycogen synthase kinase 3beta gene polymorphisms may be associated with bipolar I disorder and the therapeutic response to lithium. *Journal of Affective Disorders, 147*, 401-406.

Mamdani, F., Alda, M., Grof, P., Young, L. T., Rouleau, G., & Turecki, G. (2008). Lithium response and genetic variation in the CREB family of genes. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*, 500-504.

Muneer, A. (2016). Bipolar disorder: role of inflammation and the development of disease biomarkers. *Psychiatry Investigation, 13*, 18.

Musil, R., Schwarz, M., Riedel, M., Dehning, S., Cerovecki, A., Spellmann, I., et al. (2011). Elevated macrophage migration inhibitory factor and decreased transforming growth factor-beta levels in major depression—no influence of celecoxib treatment. *Journal of Affective Disorders, 134*, 217-225.

Nassar, A., & Azab, A. N. (2014). Effects of lithium on inflammation. *ACS Chemical Neuroscience, 5*, 451-458.

Nayeri, M. F., Talaei, A., Afshari, J. T., Nikpoor, A. R., Talaei, A., & Ganjali, R. (2019). Association between IFN-γ+ 874 T/A (Rs2430561) Polymorphisms and Bipolar 1 Disorder: A Study in an Ethnic Iranian Population. *Reports of Biochemistry & Molecular Biology, 8*, 1.

Nursal, A. F., Aytac, H. M., Yazar, M. S., Oyaci, Y., Pehlivan, M., & Pehlivan, S. (2020). TNF-α-308 G/A variant may be associated with bipolar disorder in a Turkish population. *Archives of Clinical Psychiatry, 47*, 176-179.

Okazaki, S., Hishimoto, A., Otsuka, I., Watanabe, Y., Numata, S., Boku, S., et al. (2018). Increased serum levels and promoter polymorphisms of macrophage migration inhibitory factor in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 83*, 33-41.

Panaccione, I., Spalletta, G., & Sani, G. (2015). Neuroinflammation and excitatory symptoms in bipolar disorder. *System, 36*, 40.

Pehlivan, S., Aytac, H. M., Ciftci, H. S., Oyaci, Y., Pehlivan, M., & Nursal, A. F. (2020). Investigating the eNOS and IFN-γ Gene Variants Susceptible to Bipolar Disorder or Schizophrenia in a Turkish Cohort. *Psychiatry and Clinical Psychopharmacology, 30*, 354-361.

Salloum, N. C., McCarthy, M. J., Leckband, S. G., & Kelsoe, J. R. (2014). Towards the clinical implementation of pharmacogenetics in bipolar disorder. *BMC Medicine, 12*, 90.

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry, 49*, 624-629.

Sumaiya, K., Langford, D., Natarajaseenivasan, K., & Shanmughapriya, S. (2022). Macrophage migration inhibitory factor (MIF): a multifaceted cytokine regulated by genetic and physiological strategies. *Pharmacology & Therapeutics, 233*, 108024.

Ucok, A., Akar, U., Polat, A., & Yazici, O. (2005). Human leukocyte antigen alleles in patients with bipolar disorder in Turkey. *European Psychiatry, 20*, 83.

Xu, L., Li, Y., Sun, H., Zhen, X., Qiao, C., Tian, S., & Hou, T. (2013). Current developments of macrophage migration inhibitory factor (MIF) inhibitors. *Drug Discovery Today, 18*, 592-600.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry, 133*, 429-435.

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