

Altered serum interleukin-7 and interleukin-10 are associated with drug-free major depressive disorder

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Abstract

Background: Abnormal expression of inflammatory cytokines in major depressive disorder (MDD) suggests the activation of an inflammatory process. The pattern of alterations in cytokine levels is still ambiguous. The present study aimed to evaluate interleukin-7 (IL-7) and interleukin-10 (IL-10) for their involvement in the pathophysiology of MDD and determine their relationships with depression risk.

Methods: The study included 166 medication-free subjects: 84 MDD patients and 82 sex- and age-matched healthy controls (HCs). A qualified psychiatrist diagnosed patients and evaluated controls based on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5). Hamilton depression rating scale (Ham-D) was used to measure the severity of depression in MDD patients. Serum IL-7 and IL-10 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits.

Results: Compared with HCs, the serum levels of IL-7 were significantly decreased, whereas that of IL-10 increased in MDD patients. Moreover, the severity of depression is correlated with the altered levels of IL-7 and IL-10 in MDD patients. We found a negative correlation between IL-7 and Hamilton depression rating (Ham-D) scores ($r = -0.580, p < 0.05$), whereas there was a positive correlation between IL-10 and Ham-D scores ($r = 0.555, p < 0.05$).

Conclusions: The altered levels of serum IL-7 and IL-10 in MDD patients may represent a homeostatic mechanism that enhances the inflammatory process during depression. The alterations of these cytokine levels in MDD and their association with the severity of depression support them as promising, but there may still be controversial factors for understanding the pathophysiology of depression.

Keywords: IL-7, IL-10, interleukin-7, interleukin-10, major depressive disorder, MDD

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Introduction

Major depressive disorder (MDD) is a well-known, complex mood disorder in which up to 60% of patients may encounter treatment resistance that prolongs and worsens the cases.¹ This illness can become chronic or recurrent and lead to massive impairments in the ability to deal with an individual's daily responsibilities. This issue has turned into one of the main contributors to the global burden of disease.² Common features of MDD are sadness, apathy, irritability or

indifference. It is usually associated with a change of weight, sleep patterns, motor agitation or retardation, fatigue, impaired concentration, decision making, as well as feelings of shame or guilt and thoughts of death or dying.³ Depression that begins mostly in early adulthood is likely to be recurrent. It affects women more frequently than men, and unemployed people are at high risk.⁴

An incomplete understanding of the nature of depression might be the reason for the less

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effective treatment of MDD.⁵ For successful treatment of depression, the first step is to recognize the problem and make a correct diagnosis. But complicated neurophysiology of MDD affects the correct diagnosis of the specific condition, prediction of clinical outcomes in patients and our ability to produce newer, highly efficacious and safe antidepressants.⁶ The primary health care provider is the first person responsible for the diagnosis of depression, but evidence suggests that in most cases it remains unrecognized at this level due to poor understanding of the disease mechanism.⁷ Since the diagnosis of depression mostly depends on statements by patients, this leads to misdiagnosis and confusion.⁸ Evidence suggests that factors associated with the inflammatory process, neurotransmission, neurotrophs, neuroendocrine and metabolic systems could be used to recognize the mechanism of disease for individuals suffering from depression.⁹ The biological markers for understanding the pathophysiology of MDD are rare, and although there are few risk assessment factors, the findings are largely inconsistent.

Some recent evidence suggest that cell-mediated immunity plays an important role in the pathogenesis of MDD.¹⁰⁻¹² Interleukin-7 (IL-7) is a growth factor that is considered to be an immune-stimulatory substance, and a major homeostatic cytokine.¹³ Interleukin-10 (IL-10), which is an anti-inflammatory cytokine, increases during neuroinflammation and may be implicated in depression.¹⁴ IL-7 and IL-10 are both assumed to play a vital role in lymphocyte development since abnormal levels of these cytokines have been found in multi-analytic screening studies in the serum of psychiatric patients.¹⁵ There are many controversial studies found for these markers. Dahl *et al.* reported that serum IL-7 and IL-10 levels were significantly elevated in medication-free MDD patients compared with healthy controls (HCs).¹⁶ Wiener *et al.* showed higher serum levels of IL-10 in MDD patients than those of HCs through a cross-sectional study.¹⁷ In contrast, other studies found decreased serum IL-7 levels in MDD patients compared with HCs.¹⁸⁻²⁰ However, some authors also reported no significant difference in the production of IL-10 in MDD patients compared with HCs.²¹⁻²⁴ The above findings regarding IL-7 and IL-10 in MDD patients highlight the need to initiate further studies in this field. However, the existence of biological markers for the understanding of the

pathophysiology of depression is still unknown. Taking all the above evidence and findings together, the present study evaluated inflammatory cytokines in major depression. The aim of this study was, first, to investigate serum IL-7 and IL-10 levels in MDD patients and HCs. Second, in case of any alteration in these levels, we aimed to determine the association between the altered cytokine levels and the severity of depression. Third, our objective was to detect the involvement of cytokine levels in depression risk.

Methods

Study population

A total of 84 MDD patients and 82 sex- and age-matched HCs took part in this study. All patients were recruited from the Department of Psychiatry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, and all HCs were taken from different parts of Dhaka. The study participants were screened by a qualified psychiatrist before entering the study. This screening was conducted in five steps: (1) a standard psychiatric interview; (2) a structured clinical interview following the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5); (3) severity assessment through the Hamilton depression rating (Ham-D) scale; (4) a detailed assessment of previous psychiatric illness; and (5) a sociodemographic status recorded using predesigned questionnaires. MDD patients suffering from depressive symptoms for at least 2 weeks or longer were included in this study. Exclusion criteria were the use of illegal drugs, alcohol or substance abuse within the past 6 months, history of heart disease, kidney or inflammatory diseases, acute or chronic infection and major somatic disorders. As antidepressant or antipsychotic drugs could interfere with serum cytokine levels, all the study participants were free of medications for at least 1 week before the examination. Written consent was taken from all study participants and the study was approved by the ethical review committee of BSMMU (approval number: BSMMU/2019/3507).

Blood sample collection and cytokine measurement

Blood samples (5 ml) were collected from the cephalic vein and serum probes were immediately centrifuged at $1000 \times g$ for 15 min. The supernatant

was aliquoted in non-absorbing 300µl polypropylene tubes and stored at -80°C until cytokine measurement. The serum IL-7 and IL-10 levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (BosterBio, USA) according to the manufacturer's instructions. Briefly, 100µl of serum sample or standard solution was added to the appropriate wells of the 96-well microtiter plate. The plate was covered and incubated at room temperature for 120 min. Then, the cover was removed to discard the liquid in the wells. Then, 100µl of the biotinylated anti-human antibody of the respective cytokine was dispensed into each well with thorough mixing. The plate was again covered with a plate sealer and incubated at room temperature for 90 min. The contents of each well were aspirated, followed by three rinses with 300µl of wash buffer. Avidin–biotin–peroxidase complex (100µl) was added to each well and the plate was incubated at room temperature for 40 min. The contents of each well were again aspirated, followed by five rinses with 300µl of wash buffer. Then, 90µl of color developing reagent tetramethylbenzidine (TMB) was added into each well and the plate was incubated in the dark for 30 min at room temperature. The reaction was stopped with the addition of 100µl stop solution and absorbance was read at 450 nm immediately. The serum levels of IL-7 and IL-10 were expressed as pg/ml. The minimum detectable doses for serum IL-7 and IL-10 were <1 pg/ml and <0.5 pg/ml, respectively.

Statistical analysis

Data for serum IL-7 and IL-10 levels were tested for normality. The distribution pattern of the data was centrally grouped about the mean but not skewed significantly. An independent sample *t*-test was applied to compare between MDD patients and HCs. The serum levels of IL-7 and IL-10 were expressed as the mean \pm standard error of the mean (mean \pm SEM). Spearman's correlation analysis and scatter plot graphs were applied to obtain the relationship between the analyzed cytokines and the severity of depression. Box plot graphs were used to show the changes in serum cytokines between the groups. Receiver operating characteristic (ROC) curve analysis was performed to get the diagnostic or predictive value of altered cytokines in depression. Statistical significance was set at a *p*-value of less than 0.05 for all analyses. Statistical analysis was done using the statistical software package SPSS version 23.0 (IBM Corp., Armonk, NY).

Results

The sociodemographic profile of the study population is presented in Table 1. Age, sex, and body mass index (BMI) did not differ significantly between the MDD patients and HCs. Clinical outcomes and laboratory findings are shown in Table 2, where the patients with MDD have significantly lower levels of IL-7 ($p < 0.05$) and higher levels of IL-10 ($p < 0.05$) compared with HCs. These alterations of serum cytokine levels are displayed graphically in Figure 1. Both pro-inflammatory (IL-7) and anti-inflammatory (IL-10) cytokines were found to be higher in female patients compared with male patients. The serum IL-7 levels were negatively correlated ($r = -0.580$, $p < 0.05$) with Ham-D scores, whereas serum IL-10 levels were positively correlated ($r = 0.555$, $p < 0.05$) with Ham-D scores in MDD patients (Table 3). Moreover, the serum IL-7 and IL-10 were inversely correlated ($r = -0.383$, $p < 0.05$) in MDD patients; however, the serum IL-7 levels were positively correlated with Ham-D scores in HCs ($r = 0.486$, $p < 0.05$). Graphical illustrations of these correlations between serum cytokine levels and Ham-D scores are presented in Figure 2. The serum cytokine levels of MDD patients were not correlated with their age, education, smoking or area of residence. The ROC curves of IL-7 and IL-10 were plotted, and cut-off points were detected as 332.90 pg/ml and 44.0 pg/ml, respectively (Figure 3).

Discussion

In the present study, a pro-inflammatory cytokine, IL-7, was significantly lower and anti-inflammatory cytokine, IL-10, was significantly higher in MDD patients than in HCs. The major correlations were observed between altered levels of serum cytokines and the severity of depression. The inflammatory system is extremely complex and numerous biomarkers represent different aspects of this system. Several mechanisms could link cytokine-mediated immune activation to the pathophysiology of depression, including cytokine receptor activation of neurons,²⁵ increased expression of serotonin transporters,²⁶ kynurenine pathway activation,²⁷ reduced neuronal growth factors,²⁸ activation of the hypothalamic–pituitary–adrenal axis²⁹ and alterations in the synthesis, release and reuptake of neurotransmitters.³⁰ IL-7 is essential for lymphocyte development and survival.³¹ T cells and natural killer (NK) cells are important contributors to the cell-mediated immune response. Abnormal numbers

Table 1. The sociodemographic profile of the study population.

Parameters	MDD patients (n=84)			Healthy controls (n=82)			p-value
	n	%	Mean ± SEM	n	%	Mean ± SEM	
Age in years							
18–24	5	5.95	34.13 ± 1.50	7	8.54	32.68 ± 1.83	0.689
25–34	42	50.00		44	53.66		
35–44	26	30.95		22	26.83		
45–60	11	13.10		9	10.98		
Gender							
Male	26	30.95		35	42.68		0.272
Female	58	69.05		47	57.32		
Marital status							
Unmarried	37	44.05		39	47.56		0.741
Married	47	55.95		43	52.44		
BMI (kg/m ²)							
Below 18.5 (CED)	8	9.52	25.18 ± 0.90	4	4.88	24.50 ± 0.81	0.575
18.5–25 (normal)	45	53.57		48	58.54		
Above 25 (obesity)	31	36.90		30	36.59		
Education level							
Illiterate	8	9.52		9	10.98		0.857
Primary	24	28.57		20	24.39		
Secondary	39	46.43		42	51.22		
Graduate and above	13	15.48		11	13.41		
Occupation							
Service	7	8.33		8	9.76		0.147
Business	3	3.57		4	4.88		
Housekeeper	32	38.10		30	36.59		
Unemployed	15	17.86		14	17.07		
Others	27	32.14		26	31.71		
Economic impression							
Lower	26	30.95	30.03 ± 1.57	25	30.49	31.15 ± 1.63	0.573
Middle	45	53.57		42	51.22		
Higher	13	15.48		15	18.29		

(Continued)

Table 1. (Continued)

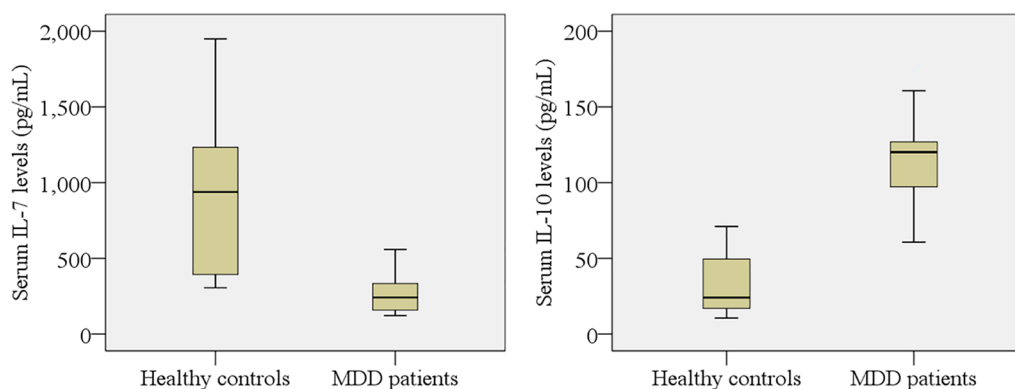
Parameters	MDD patients (n = 84)			Healthy controls (n = 82)			p-value
	n	%	Mean ± SEM	n	%	Mean ± SEM	
Area residence							0.932
Urban	29	34.52		30	36.59		
Rural	55	65.48		52	63.41		
Smoking history							0.739
Non-smoker	60	71.43		60	73.17		
Smoker	24	28.57		22	26.83		

BMI, body mass index; CED, chronic energy deficiency; MDD, major depressive disorder; SEM, standard error of the mean.

Table 2. Clinical outcomes and laboratory findings of the study population.

Parameters	MDD patients (n = 84)	Healthy controls (n = 82)	p-value
	Mean ± SEM	Mean ± SEM	
Ham-D score	20.15 ± 0.42	4.74 ± 0.65	0.000
Serum IL-7 (pg/ml)	265.16 ± 49.39	918.20 ± 233.20	0.001
Serum IL-10 (pg/ml)	119.2 ± 23.71	33.44 ± 5.53	0.008

Ham-D, 17-item Hamilton depression rating scale; IL-7, interleukin-7; IL-10, interleukin-10; MDD, major depressive disorder; SEM, standard error mean. Significant p-values are shown in bold.

**Figure 1.** Variations of serum interleukin-7 (IL-7) and interleukin-10 (IL-10) among the study population. There is a significant difference between patient and control groups at a 95% confidence interval (CI). MDD, major depressive disorder.

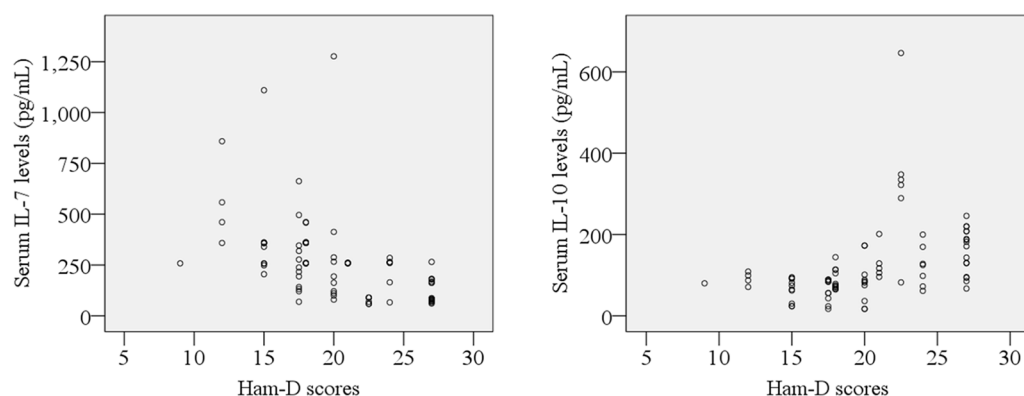
and functions of T cells and NK cells have been reported in MDD patients.³² Therefore, through the regulation of T cells, which secrete lymphokines, IL-7 also participates in the cascade possibly by contributing to the hypothesized

depression-related lymphokine suppression.³³ Since IL-7 is a major regulator of T cell functioning, its measurement could be a potent indication of depression-related T cell alterations. Our finding that decreased serum IL-7 levels

Table 3. Spearman's correlation among various research parameters among the study population.

Correlation parameters	MDD patients (n = 84)		Healthy controls (n = 82)	
	r	p-value	r	p-value
Age and IL-7	-0.015	0.934	-0.257	0.073
BMI and IL-7	0.230	0.206	-0.054	0.827
Education and IL-7	0.050	0.784	0.322	0.178
Income and IL-7	0.149	0.415	0.166	0.496
Smoking and IL-7	0.083	0.652	-0.361	0.129
Ham-D and IL-7	-0.580	0.000	0.486	0.035
Age and IL-10	0.078	0.672	0.107	0.662
BMI and IL-10	-0.106	0.567	0.191	0.433
Education and IL-10	0.053	0.775	-0.068	0.781
Income and IL-10	-0.137	0.454	0.295	0.220
Smoking and IL-10	0.038	0.838	0.176	0.471
Ham-D and IL-10	0.555	0.001	-0.012	0.960
IL-7 and IL-10	-0.383	0.030	-0.051	0.837

Ham-D, Hamilton depression rating scale; IL-7, interleukin-7; IL-10, interleukin-10; MDD, major depressive disorder; r, correlation coefficient. Negative values specify the opposite correlation. Significant p-values are shown in bold.

**Figure 2.** Scatter plot of serum interleukin-7 (IL-7) and interleukin-10 (IL-10) with Hamilton depression rating (Ham-D) scores among major depressive disorder patients.

are associated with the severity of depression is consistent with past studies. Lehto *et al.* found that serum IL-7 levels were decreased in MDD patients compared with HCs, which supports the present study findings.¹⁸ Another study by Grosse *et al.* found that IL-7 levels were lowered in MDD patients compared with those of HCs.²⁰ Gaarden *et al.* found lowered plasma levels of

IL-7 in depressed patients compared with non-depressed controls through a cross-sectional study.¹⁹ Similar to our findings, one study revealed that serum IL-7 levels were significantly, but inversely, associated with the severity of depression among geriatric patients.³⁴ Moreover, inflammatory processes and oxidative stress are positively correlated with the severity of drug-naïve

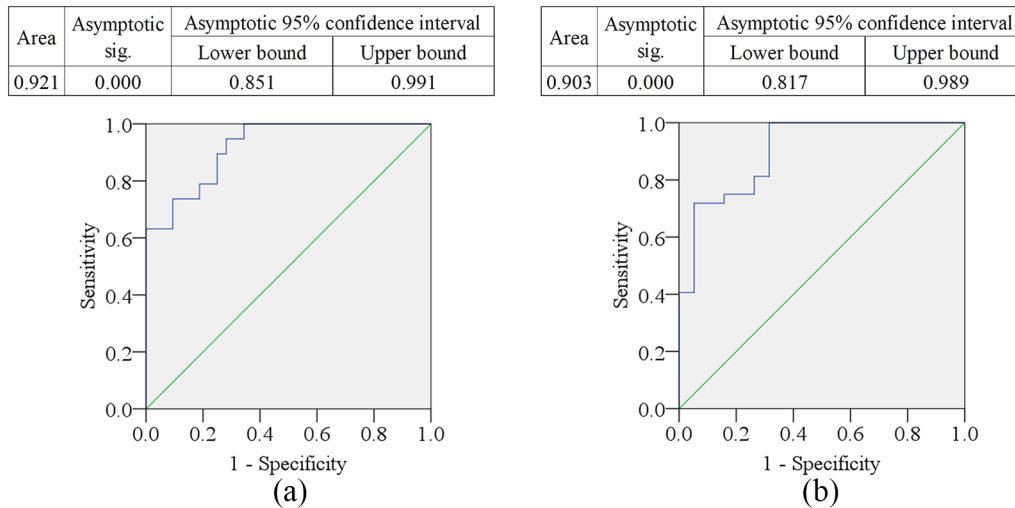


Figure 3. Receiver operating characteristic (ROC) curves: (a) interleukin-7 (IL-7) and (b) interleukin-10 (IL-10). The cut-off point was detected as 332.90 pg/ml for IL-7 and 44.00 pg/ml for IL-10.

MDD patients.²³ Also, significantly positive correlations between anxiety measures and serum levels of IL-1 α , IL-6, IL-8 and IFN- γ were seen.^{35,36}

In contrast, IL-10 is elevated in response to acute immune challenge. These changes have been considered in terms of the imbalance between individual pro- and anti-inflammatory cytokines and the Th1 and Th2 imbalance in major depression.³⁷ IL-10 increases due to inflammation induced by psychological or physiological stress.³⁸ The elevated IL-10 may implicate a fine-tuned integrated activation linked to depression. Imbalanced interactions between different cytokines and immune pathways could be an underlying mechanism for the pathophysiology of MDD.³⁹ Thus, theoretically, this effect may occur secondarily to an overall reduction of peripheral inflammation promoted by antidepressants. Brunoni *et al.* found that antidepressants significantly decreased peripheral levels of IL-10.⁴⁰ However, it is difficult to determine the specific mechanisms involved. Certain cytokines may play a unique role in the pathophysiology of depression, while others could represent secondary factors not related directly to depression. In agreement with our findings, increased serum IL-10 levels and their correlation with the severity of depression were reported by some past research. One study found that antidepressant drug-naïve MDD patients had significantly elevated serum IL-10 levels compared with HCs.⁴¹ In another two recent studies, Müller *et al.* and Dahl *et al.* demonstrated the increased levels of IL-10 in

MDD patients compared with HCs.^{16,42} Wiener *et al.* also found the elevated levels of serum IL-10 in MDD patients compared with HCs through a cross-sectional study.¹⁷ In addition, increased levels of IL-10 were found in drug-naïve MDD patients and the levels were normalized after antidepressant treatment.⁴³ Moreover, a recent meta-analysis showed elevated levels of IL-10 in MDD patients compared with HCs.⁴⁴ The elevated levels of serum IL-10 can be explained by the study of Iacob *et al.*, in which the increased expression of the IL-10 gene in MDD patients was observed and the severity of depression was also positively associated with increased IL-10 expression.⁴⁵

Another finding of the present study is ROC curve analysis (Figure 3), which was used to quantify the predictive performance of altered cytokine levels. Accuracy is measured by the area under the ROC curve (AUC), with ranges as follows: 0.9–1.0 = excellent, 0.8–0.9 = good, 0.7–0.8 = fair, 0.6–0.7 = poor and <0.6 = not useful.⁴⁶ Several previous studies identified the altered serum levels of IL-7 and IL-10 in MDD patients, but these cannot be used to assess depression risk due to their lack of predictive performance.^{41,42,47} AUC of IL-7 was 0.921, which was significant ($p < 0.001$), and lower values were assigned as the disease state. Similarly, the AUC of IL-10 was 0.903, which was also significant ($p < 0.001$) where higher values were assigned as the disease state. ROC analysis showed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to be 89.5%, 75%, 78.6% and 87.5% for

IL-7, respectively, while these were 81.3%, 73.7%, 76.0%, and 79.4% for IL-10, respectively. As MDD is a multifactorial condition predisposed by environmental and genetic aspects,⁴⁸ it is essential to define biological factors for the evaluation of depression risk.

Unfortunately, the previous studies could not suggest new therapeutic approaches based on their findings of altered serum cytokine levels in MDD patients.^{16,19,42} In a study by Bschor *et al.* it was found that 30–50% of MDD patients do not respond to traditional antidepressant therapy.⁴⁹ The explanation could be a lack of efficacy or intolerable side effects.⁵⁰ Kopschina Feltes *et al.* observed that depressive patients have underlying immune deregulation that could explain the lack of therapeutic benefit from antidepressants and treatment resistance.⁵¹ The high rate of treatment resistance, the rising suicide risk in unresponsive MDD patients, together with the overwhelming economic costs to society, constitutes the basis of the search for new therapeutic agents that aim to improve the quality of life or even cure these patients.⁵² Furthermore, studies have demonstrated that the levels of pre-treatment biomarkers can be valuable predictors of treatment response, selection of the best treatment to be applied and indicators of possible treatment resistance to conventional antidepressant drugs.⁵¹ Evidence suggests that patients who have recovered from the depressive episode have normalized levels of pro- and anti-inflammatory cytokines after treatment.¹⁶ Based on the present study findings, we can suggest some new treatment approaches for depression. Both mind–body therapies (MBTs) and exercise are non-pharmacological augmentative strategies that can decrease stress levels and modulate immunity, increasing the quality of life of MDD patients. An increase in the pro-inflammatory cytokines is induced by laborious exercise. This release is balanced by the secretion of cytokine inhibitors (IL-1ra, sTNF-r1 and TNF-r2) and the anti-inflammatory cytokine IL-10.⁵³ Besides MBTs, other lifestyle changes, such as dietary interventions, could have a beneficial effect on MDD. For example, nutrients like zinc and omega-3 fatty acids have been shown to have beneficial effects on depression.^{54,55} These nutrients may exert an affect through interaction with inflammatory pathways.⁵⁶ Moreover, inhibiting the effects of cytokines with monoclonal antibodies is a promising therapeutic approach, though at present it is associated with the risk of potentially serious side effects.⁵⁷ NK cells are

innate immune cells that have strong cytolytic function against physiologically stressed cells.⁵⁸ Grosse *et al.* have shown various signs of NK and T cell defects in patients with MDD.²⁰ For a better clinical outcome, NK cell-based immunotherapeutic strategies can be applied to improve the function of NK cells. NK cell immunotherapy offers several advantages. First, the use of NK cells will bypass the need for antigen-specific T cells. Second, NK cells can secrete pro-inflammatory cytokines rapidly that can potentiate the adaptive immune response.⁵⁹ Lastly, NK cells have a relatively short lifespan and are easy to isolate and manipulate. Hence, the possibility of overexpansion of transferred NK cells in the recipient's body is minimized. Also, the metabolic reprogramming of NK cells may improve depression through cytokine therapy. For example, IL-10 is also a potent inducer of NK cell proliferation, cytotoxic function and IFN- γ production in combination with IL-18.⁶⁰ Therefore, it seems that suppression of particular inflammatory cytokines may be necessary for clinical recovery from depression, and as a consequence reduction in inflammation might not happen in depressed patients who fail to respond to treatment.

Due to the limited sample size, we did not exclude participants with a smoking habit, which might interrupt cytokine analyses. Also, we did not consider food habits, physical activity or sleep patterns in this study, as these would have reduced the statistical power by decreasing sample size further. The main limitation of the present study is that our test is not specific to depression. In addition, we did not investigate the impact of antidepressant medications on our study parameters. Therefore, our findings should be treated as preliminary, and to establish them further studies with a more homogeneous and larger population is recommended in this field.

In conclusion, this study of altered serum cytokine levels in MDD patients may demonstrate a connection between levels of IL-7 and IL-10 and the severity of depression. These results, along with their predictive performance, could be used to measure the depression risk and probable therapeutic approaches.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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