Elevated Serum IL-2 Levels are Associated With Major Depressive Disorder: A Case-Control Study

Farhana Islam Suhee, Mohammad Shahriar,
Sardar Mohammad Ashraful Islam, Mohiuddin Ahmed Bhuiyan
and Md. Rabiul Islam

Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh.

ABSTRACT

OBJECTIVES: Numerous earlier studies have stated an association between major depressive disorder (MDD) and altered expression of inflammatory process. However, it still needs to determine whether the alteration of cytokines is the causative factor or a consequence of this disorder. Therefore, we attempted to evaluate the role of the pro-inflammatory cytokine IL-2 in the pathophysiology of depression.

METHODS: We collected blood samples from 111 MDD patients and 112 healthy controls (HCs) matched by age and sex. Diagnostic and statistical manual of mental disorders (DSM-5) score was used to assess study participants. We determined the severity of depression using the Hamilton Depression (Ham-D) rating scale. We assayed serum levels of IL-2 using the Enzyme-Linked Immunosorbent Assay (ELISA) kit.

RESULTS: Elevated levels of IL-2 were detected in MDD patients than HCs (29.79 ± 6.18 and 12.77 ± 4.84 pg/ml, $P < 0.05$). We observed a higher level of IL-2 in female MDD patients compared to female HCs (31.98 ± 8.34 and 7.76 ± 0.36 pg/ml, $P < 0.05$). We witnessed a sex-specific correlation between the serum IL-2 levels and the Ham-D score and found that the females with higher Ham-D scores had higher serum IL-2 levels. Moreover, the ROC curve represented the good diagnostic performance of serum IL-2 levels as a biomarker with sensitivity and specificity values of 83.7% and 80.4%, respectively.

CONCLUSIONS: The current study findings indicate that elevated serum IL-2 levels are associated with MDD. This alteration may be the cause of triggering depression or a result of the activated inflammatory process during the depression. Therefore, we recommend further interventional research to clarify the actual reasons for these altered IL-2 levels in MDD patients.

KEYWORDS: Major depressive disorder, depressive disorder, depression, IL-2, cytokine

Introduction

Major depressive disorder (MDD) is a chronic medical condition recognized as a crucial problem globally due to its ever-increasing rate of prevalence and its impact on disability, morbidity, and mortality.[1] According to WHO, depression affects approximately 280 million people worldwide[2] and will become a prime cause of disability by 2030.[3,4] Persistent changes in daily life functions, including lack of sleep, loss of appetite, diminished psychomotor activity, and, most importantly, low mood, occur in people with MDD and last for at least 2 weeks.[5] The younger generation tends to develop depression more often, though females are more vulnerable to it than males.[6-8] MDD is an intricate illness as multiple factors influence the occurrence of MDD, including biological, hereditary, medical comorbidity, and environmental adversity such as violence, abuse, or poverty.[9-14] Although the origin of this multifactorial disorder is still uncertain, a few biological events such as HPA axis deregulation,[15] alteration in pro-inflammatory and anti-inflammatory cytokines,[16-18] down-regulation of neurotransmitters, and abnormal glutamatergic activity are assumed to be associated with the pathophysiology of MDD.[19] As a result of the heterogenetic symptoms and uncertain

origin, it is very challenging to diagnose MDD based on the patient interview and subjective assessment by psychiatrists.[20,21] It eventually leads to misdiagnosis and inadequate treatment for MDD patients. So, current studies are trying to identify traceable peripheral biomarkers that can aid in a more accurate diagnosis and better treatment regime for MDD patients.

Extensive studies on MDD patients have discovered a relationship between the disorder and altered expression of cytokines.[22-26] Our earlier studies on MDD patients have also found altered cytokine responses among MDD patients, emphasizing the intriguing role of inflammation in the pathogenesis of neuropsychiatric diseases like MDD.[27-30] Altogether, these findings hint at the possibility of acknowledging inflammatory cytokines as prospective biomarkers for diagnosis and treatment response of MDD patients.

Inflammatory cytokines are small proteins produced by many cells involved in the immune system, although the predominant cells are T cells and macrophages.[31] The concept of neuroimmune communication has been reported by various immunologists, pointing to the possible access of peripheral cytokines to the central nervous system (CNS) system through the permeable blood-brain barrier or via transporters present

on the endothelium of the brain.[32,33] These cytokines seem to exert few effects in the CNS. Astrocytes and microglia, the cells of the CNS, are also responsible for producing cytokines in response to peripheral inflammation.[34] Many reports claim that the elevation of peripheral cytokines may lead to reduced neurotransmitter availability by stimulating the indoleamine 2,3-dioxygenase (IDO) pathway in glial cells, impaired neuroplasticity by causing hippocampal changes, neuro-degeneration by suppressing brain-derived neurotrophic factor (BDNF) activity, and neuroinflammation, all of which ultimately contribute to the pathophysiology of depression.[34-36] Another prominent pathway thought to be involved in depression is the hypothalamus-pituitary-adrenal (HPA) axis, which appears to be over-activated as a result of cytokine elevation.[37,38] Continuous cytokine elevation enables cortisol levels to increase by activating the HPA axis and causing glucocorticoid resistance, which eventually leads to the development of MDD.[39] Furthermore, increased cytokine levels boost the expression of transporters for serotonin reuptake and promote the activity of IDO, thereby strengthening the kynurenine pathway responsible for reduced serotonin levels.[40,41] Augmented inflammation also leads to mental deterioration and is thought to be the cause of the cognitive damage seen in depression.[42] Mounting evidence from previous observations suggests that cytokines like IL-1, C reactive protein (CRP), IL-6, and tumor necrosis factor (TNF)-alpha, are certainly altered in MDD, confirming the involvement of altered cytokine responses in the pathophysiology of MDD.[43,44]

IL-2 is one of the mediators of the inflammatory responses known as a pro-inflammatory cytokine that promote inflammation and is involved in the pathophysiology of depression. Inflammatory pathway mediates a connection between sickness behavior and clinical depression.[45] Rodent studies reported that the administration of pro-inflammatory cytokines induced depressive-like behaviors suggesting the association between depression and inflammation.[46] Elevated IL-2 levels cause the degradation of the tryptophan (TRP) enzyme, a precursor of serotonin production through the IDO pathway, and thereby lead to depression. The IDO pathway has a subsequent role in the formation of neurotoxic metabolites, causing neuro-degeneration and triggering depression.[47] Additionally, IL-2 imparts a role in the activation of other cytokines, such as IL-6, TNF-alpha, and IFN, which inhibit the production of TRP by activating the IDO pathway.[48] In addition, another study has claimed that increased IL-2 levels hyper-activate the HPA axis, thus raising cortisol levels and triggering depression in people.[49] A group of authors observed elevated levels of serum IL-2 in MDD patients in their studies.[50-52] Contrarily, a few studies claimed reduced levels of IL-2 in the serum of MDD patients.[53,54]

Previous investigators have reported varied opinions on the role of IL-2 in depression. A meta-analysis reported that IL-2 level is not associated with MDD.[55] As a result, the existence of IL-2 as a potential biomarker is not confirmed yet. However, a link between MDD and IL-2 might help to recognize IL-2 as an early risk assessment indicator, which would contribute to identifying the group of patients having the highest risk of developing MDD. So, we designed this study on the Bangladeshi population to observe the alteration of IL-2 in MDD patients. Therefore, we attempted to compare the serum IL-2 levels between MDD patients and HCs. Simultaneously, we tried to explore the sex-specific correlation of altered IL-2 levels with the severity of the disease.

Method

Study design and participants

This study was a case-control study and we applied power calculation formula to calculate the sample size in this study. We estimated our sample size considering the confidence level, acceptable margin of error, and prevalence. Following the estimation, we needed to recruit 100 patients to attain better statistical power. Therefore, we recruited 111 drug-free MDD patients who were suffering from depressive symptoms for at least 2 weeks. Also, we included 112 HCs matched by age-and sex with patients. The age limit of study participants was between 18 and 60 years. We enrolled all the patients from a hospital in Bangladesh. The recruited patients were aware of the motive of this study. The entire study was conducted from January 1, 2022 to June 30, 2022. Before sample collection, we took written permission from each of them. A qualified psychiatrist diagnosed the MDD patients following the diagnostic and statistical manual of mental disorders (DSM-5). The severity of depression was determined using the Hamilton Depression rating scale (Ham-D) scores. We recruited those patients whose Ham-D scores were more than 7. This study excluded patients with comorbidities like cardiovascular and endocrine diseases and infectious diseases. The study also did not include participants involved in alcohol or other substance abuse or having other mental disorders. Besides that, the HCs were also evaluated based upon DSM-5 criteria and matched with the MDD cases. We assessed the controls using the same process and questionnaire as the cases. The general information, including the socio-demographic profile of MDD patients and HCs, was obtained appropriately using a predesigned questionnaire. Prior to our main study, we conducted a pilot test on a 10% population of our total sample size using our questionnaire.

Sample collection and processing

We communicated with the MDD patients and obtained their permission for sample collection. With their approval, 5 ml of blood was withdrawn from each MDD patient and preserved in the falcon tube for 1 hour at room temperature. Then we placed the falcon tube in a centrifuge machine and ran it for 15 minutes at 3000 rpm. After that, we observed a supernatant

serum in the upper portion of the falcon tube. The serum was separated, collected in an Eppendorf tube, and kept at –80°C for analysis.

Sample analysis

We used the Human IL-2 ELISA Kit EZ-Set as instructed in the protocol to quantify the concentration of our targeted marker, IL-2, in the serum (Boster Bio, USA). We did the following operations to analyze the cytokine IL-2 following procedure described in our earlier articles.[56,57] In a 96-well micro-plate, we first deposited 100 µl of sample and reference in the suitable wells. We placed the plates for incubation at room temperature for 2 hours and then washed the liquid out of the wells. Subsequently, we added 100 µl of biotinylated goat anti-human IL-2 polyclonal antibody to each well. After resealing, we placed these plates inside the incubators at 37°C for 60 minutes. Afterward, we removed the liquid and rinsed the dish three times using 300 ml of Phosphate Buffer Solution (PBS). After that, we added 100 µl of the avidin-biotin-peroxidase complex (ABC) to the wells and incubated them for another 30 minutes at 37°C. We rinsed each plate five times with 300 ml of PBS after the content was aspirated again. We kept plates in the dark for incubation at room temperature for 2 hours after we added 90 µl of Tetramethyl-benzidine. Following this step, we incorporated 100 µl of stop solution to halt the reaction and took the absorbance at 450 nm. Finally, with the help of these absorbance values, we determined the concentration of serum IL-2 and denoted the values as pg/ml. We conducted the entire experiment with the assistance of the same research personnel to minimize the variability.

Statistical analysis

After our data collection, we compiled all the data in Excel 2016 and completed the data processing. For data analysis, we used the IBM SPSS Statistics version 25 and performed the Sample *t*-test and Pearson's correlation test to compare all the variables of the study parameters and also identified the correlation between Ham-D scores and IL-2 levels using Pearson's correlation test. We represented our main findings visually using box plots and scatter plot graphs. In addition, we did the ROC curve analysis to assure the diagnostic performance of altered IL-2 levels. We set the *P*-value at 0.05 or below and considered the results significant according to this *P*-value.

Results

Sociodemographic profile of study participants

In Table 1, we displayed the sociodemographic profile of our study participants. In accordance with our findings, there were no significant differences in age (patients: 31.05 ± 1.07, controls: 30.92 ± 0.89, $P = 0.928$), sex (male/female: 37/74, 50/62 corresponded with patients and controls, $P = 0.129$), or BMI (patients: 23.44 ± 0.36, controls: 24.11 ± 0.33, $P = 0.186$)

between MDD patients and HCs. There were more female participants (patients: 66.67%, controls: 55.36%) than male participants (patients: 33.33%, controls: 44.64%). We observed that most MDD subjects were from lower economic statuses and urban areas and were non-smokers.

Clinical and laboratory findings

Our findings expressed significant differences between patients and controls in their DSM-5 scores (patients: 7.56 ± 0.11, controls: 2.02 ± 0.13, $P \leq 0.001$) and Ham-d scores (patients: 17.50 ± 0.46, controls: 3.80 ± 0.29, $P \leq 0.001$) as presented in Table 2. In this investigation, we found that the serum IL-2 levels of MDD patients were significantly higher than those of HCs (patients: 29.79 ± 6.18, controls: 12.77 ± 4.84, $P \leq 0.031$), as shown in Figure 1. Furthermore, we observed a higher level of serum IL-2 in female patients (patients: 31.98 ± 8.34, controls: 7.76 ± 0.36, $P \leq 0.007$). The serum IL-2 levels also expressed a sex-specific correlation with the Ham-D score, where higher serum IL-2 levels were observed in female patients with higher Ham-D scores (Figure 2).

Diagnostic performance of altered IL-2

ROC curve analysis was used to evaluate the diagnostic performance of altered IL-2 (Figure 3). From this analysis, we observed that area under the curve (AUC) of serum IL-2 was 0.801 at a cut-off value of 7.35 pg/ml (Table 3). Also, sensitivity, specificity, positive prospective value (PPV), and negative prospective value (NPV) of serum IL-2 were 83.7%, 80.4%, 81.9%, and 80.6%, respectively as presented in Table 3. According to the results of the ROC analysis, serum IL-2 levels indicate good predictive performance for the risk evaluation of MDD.

Discussion

There are currently no laboratory-based methods available to predict or diagnose MDD. So, establishing a rational link between IL-2 and MDD might aid in predicting or developing better treatment approaches for MDD. According to our study findings, we found variability in the mean value of serum IL-2 levels between the MDD and HC groups. Our study found that compared to HCs, there was an elevation in the serum IL-2 levels among MDD patients. This result supports the involvement of altered cytokine levels in depression. Another finding was a sex-specific correlation between IL-2 and Ham-D scores, where we witnessed higher levels of IL-2 present in female patients with higher Ham-D scores.

Our study observed that MDD is more common in women than men, and young adults are likely to be affected by MDD more often than older people. Other studies also found a correlation between gender differences and MDD and observed that women are at the highest risk of MDD than men.[58,59] Other than gender differences, the prevalence of MDD is more in young people and seems to be less in older ones.[59,60]

Table 1. Socio-demographic profile of the study population.

CHARACTERISTICS	MDD PATIENTS (N = 111) (%)	HEALTHY CONTROLS (N = 112) (%)	P-VALUE
	MEAN ± SEM	MEAN ± SEM	
Age in y	31.05 ± 1.07	30.92 ± 0.89	0.928
18-25	43 (38.74)	40 (35.71)	
26-35	41 (36.94)	44 (39.29)	
36-45	12 (10.81)	17 (15.18)	
46-60	15 (13.51)	11 (9.82)	
Sex			0.129
Male	37 (33.33)	50 (44.64)	
Female	74 (66.67)	62 (55.36)	
Marital status			0.896
Married	66 (59.46)	66 (58.93)	
Unmarried	45 (40.54%)	46 (41.07%)	
BMI (kg/m²)	23.44 ± 0.36	24.11 ± 0.33	0.186
Below 18.5 (CED)	7 (6.31)	2 (1.79)	
18.5-25 (normal)	65 (58.56)	71 (63.39)	
Above 25 (obese)	39 (35.13)	39 (34.82)	
Education level			0.071
Illiterate	11 (9.91)	5 (4.47)	
Primary level	35 (31.53)	28 (25.00)	
Secondary level	40 (36.04)	39 (34.82)	
Graduate and above	25 (22.52)	40 (35.71)	
Occupation			<0.001
Business	2 (1.80)	0 (0.00)	
Service	18 (16.22)	56 (50.00)	
Retired	3 (2.70)	0 (0.00)	
Unemployed	33 (29.73)	5 (4.47)	
Student	26 (23.42)	40 (35.71)	
Others	29 (26.13)	11 (9.82)	
Economic impression			0.002
High	5 (4.50)	21 (18.75)	
Medium	21 (18.92)	20 (17.86)	
Low	85 (76.58)	71 (63.39)	
Smoking habit			0.067
Yes	10 (9.01)	20 (17.86)	
No	101 (90.99)	92 (82.14)	

(Continued)

CHARACTERISTICS	MDD PATIENTS (N = 111) (%)	HEALTHY CONTROLS (N = 112) (%)	P-VALUE
	MEAN ± SEM	MEAN ± SEM	

Table 1. (Continued)

CHARACTERISTICS	MDD PATIENTS (N = 111) (%) MEAN ± SEM	HEALTHY CONTROLS (N = 112) (%) MEAN ± SEM	*P*-VALUE
Residence area			0.831
Rural	38 (34.23)	40 (35.71)	
Urban	73 (65.77)	72 (64.29)	
Previous history of MDD			<0.001
Yes	63 (56.76)	0 (0.00)	
No	48 (43.24)	112 (100.00)	
Family history of MDD			<0.001
Yes	35 (31.53)	1 (0.89)	
No	76 (68.47)	111 (99.11)	

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

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

PARAMETERS	MDD PATIENTS (N = 111) MEAN ± SEM	HEALTHY CONTROLS (N = 112) MEAN ± SEM	*P*-VALUE
Age (years)	31.05 ± 1.07	30.92 ± 0.89	0.928
Male (P/C:37/50)	29.86 ± 1.51	31.78 ± 1.26	0.333
Female (P/C:74/62)	31.65 ± 1.42	30.25 ± 1.26	0.464
BMI (kg/m^2)	23.44 ± 0.36	24.11 ± 0.33	0.186
Male (P/C:37/50)	23.01 ± 0.55	23.42 ± 0.40	0.532
Female (P/C:74/62)	23.67 ± 0.47	24.64 ± 0.50	0.166
DSM-5 score	7.56 ± 0.11	2.02 ± 0.13	<0.001
Male (P/C:37/50)	7.59 ± 0.21	2.04 ± 0.20	<0.001
Female (P/C:74/62)	7.54 ± 0.13	2.00 ± 0.16	<0.001
Ham-D score	17.50 ± 0.46	3.80 ± 0.29	<0.001
Male (P/C:37/50)	16.86 ± 0.72	3.74 ± 0.48	<0.001
Female (P/C:74/62)	17.83 ± 0.59	3.85 ± 0.36	<0.001
Serum IL-2 (pg/ml)	29.79 ± 6.18	12.77 ± 4.84	0.031
Male (P/C:37/50)	25.55 ± 8.39	19.19 ± 11.02	0.667
Female (P/C:74/62)	31.98 ± 8.34	7.76 ± 0.36	0.007

Abbreviations: BMI, body mass index, DSM-5, diagnostic and statistical manual for mental disorders, fifth edition; Ham-D, 17-item Hamilton depression rating scale; IL-2, interleukin-2; MDD, major depressive disorder; P/C, patients/control; SEM, standard error mean.

An association between marital dissatisfaction and depressive symptoms has been observed in previous studies, although it is still obscure whether this marital role is the cause or the consequence of these symptoms.[61] Maximum MDD participants seem to have lower financial conditions, which aligns with the perceptions of other studies.[62-64] Moreover, previous history and family history can also contribute to the occurrence of future MDD episodes in individuals.[65]
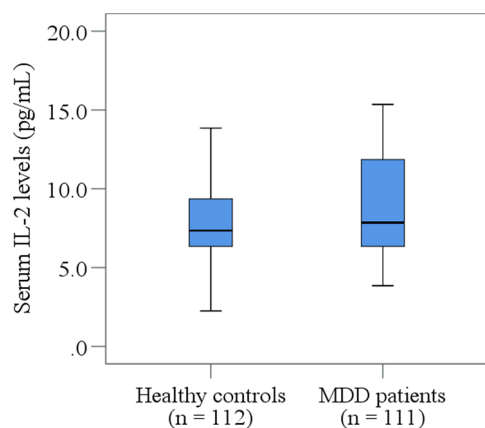
Figure 1. Distribution of serum IL-2 levels in MDD patients and healthy controls. Boxplot graphs showing the median, maximum and minimum value range.
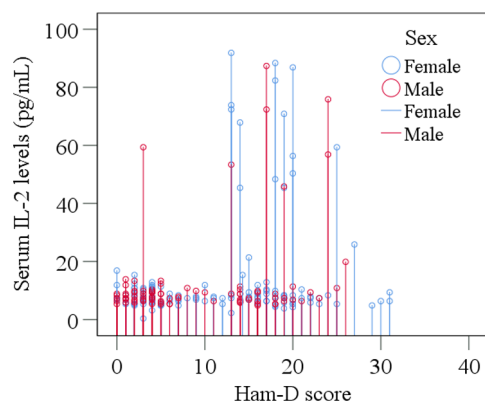

Figure 2. Sex-specific scatter plot graphs showing association and mean difference of serum IL-2 levels with Ham-D scores of study participants.

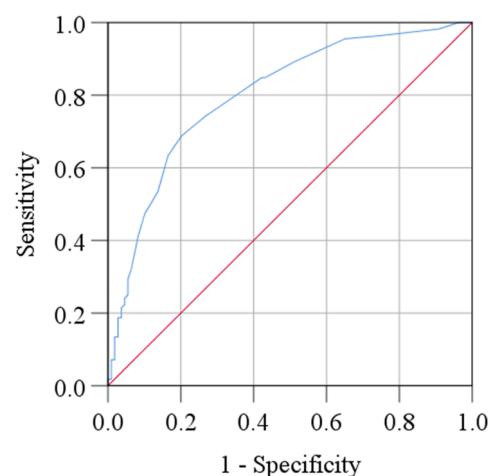| Area	Std. error	Asymptotic sig.	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.801	0.030	<0.001	0.742	0.859

Figure 3. Receiver operating characteristic (ROC) curve for serum IL-2. The cut-off point was detected as 7.35 pg/ml.

Few previous findings have shown consistency with our results. A study conducted by Chen et al on 25 MDD patients and 20 HCs, observed that MDD patients exhibited elevated serum IL-2 levels than HCs establishing a considerable positive correlation between serum cortisol and IL-2, as well as ACTH and IL-2. It can be due to the hypothesis that the elevated IL-2 level raises the cortisol levels that strengthen the kynurenine pathway and results in neurotoxic metabolites, which may contribute to depression in individuals. Chen et al[50] also observed a correlation between altered IL-2 levels and Ham-D scores. Similarly, Shelton et al[52] asserted in their study that elevated levels of IL-2 were found after comparing 64 depressed patients to 204 non-depressed individuals. Additionally, Schmidt et al[51] did a study on 135 MDD patients and 50 controls and revealed that MDD patients had higher IL-2 levels compared to HCs, suggesting the association of the inflammatory process with MDD. On the contrary, 2 studies showed the opposite of our findings. Kim et al[53] also conducted a case-control study on 48 MDD subjects and 63 HCs and experienced reduced serum IL-2 levels in MDD subjects compared to controls. Similarly, Pavón et al[54] observed lower levels of serum IL-2 in MDD patients after their study.

The current study has a few competitive advantages, which makes it more distinctive and substantial. The use of the ROC curve analysis in this study assures the accuracy of the diagnostic performance of altered IL-2 levels. The ROC curve has a range of values between 0.9 and 1.0, 0.8 and 0.9, 0.7 and 0.8, and 0.6 and 0.7, respectively, which denotes excellent, good, fair, bad, and not useful performance for this analysis.[66] For this study, the AUC value falls between 0.8 and 0.9 ranges, representing the good diagnostic performance of altered IL-2 levels. We determined the cut-off value at 7.35 pg/ml for ROC curve analysis. Although previous studies on MDD patients reported altered serum IL-2 levels, their studies lack predictive performance analysis and precise cut-off value consideration.[50-52] Another unique attribute is that this study demonstrates how altered IL-2 levels and disease severity are correlated, which previous studies have missed out on.[51,52]

There have been no prescribed therapeutic approaches proposed to date that can act on peripherally altered cytokine levels in MDD patients. It has been stated in many earlier studies that around 30% to 50% of MDD patients show no response to antidepressants.[67] It could be because these antidepressants only work to restore neurotransmitter balance or antagonize the transporter of neurotransmitters and do not affect the underlying cause of MDD. According to in vitro investigations, antidepressants have shown a varying effect on cytokine levels in MDD patients.[68] Previous studies demonstrate that antidepressants including duloxetine, mirtazapine, citalopram, paroxetine, fluoxetine, sertraline, amitriptyline, clomipramine, escitalopram have shown varied influences on the altered serum IL-2 level.[69-72] As a result of these trials, it is evident that antidepressants alone cannot normalize the level. As antidepressants have contradicting role in reducing the elevated IL-2 level, a few

Table 3. Receiver operating characteristic curve analysis of serum interleukin-2.

PARAMETERS	CUT-OFF VALUE (PG/ML)	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUC	95% CI		*P*-VALUE
							LOWER BOUND	UPPER BOUND	
Interleukin-2	7.35	83.7	80.4	81.9	80.6	0.801	0.742	0.859	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

therapeutic strategies have been in trials as optional approaches to minimize the level of pro-inflammatory cytokines that eventually reduces depressive symptoms.[73] In a study by Akhondzadeh et al[74], the administration of Celecoxib is found favorable to MDD patients with elevated pro-inflammatory cytokines. Raison et al[75] discovered Infliximab as another treatment option for MDD patients having significant inflammation. Soczynska et al[76] observed that Minocycline had pleiotropic anti-inflammatory action in their study. Authors hypothesized that Minocycline could control the cytokine levels and activate neuroprotective agents released by astrocytes of the CNS, helping to manage depressive symptoms in MDD.[77] A few supplements, like omega fatty acid, vitamin B12, and zinc, have been shown to exert beneficial effects on depressed patients. Omega-3 fatty acids might help depression by controlling the corticotropin factor and prompting the serotonergic pathway.[78] MDD patients (about 10%-30%) with folate deficiency showed a dissatisfying response to antidepressants.[79] Ranjbar et al found that zinc with the antidepressant SSRI exhibited a beneficial effect among MDD patients.[80] Our previous studies also discovered that an imbalance of cytokines, antioxidants, and macro minerals might have an association with depression, which suggests that intake of these supplements might be beneficial for MDD patients.[81-86]

The sample size and the data collection method were 2 of the primary advantages of this study. Previous researchers conducted their studies on a small scale. Therefore, the variance we observed in the mean value of IL-2 is more reliable than others. Further strengths include the absence of the influence of other confounding factors like age, sex, BMI, and smoking history, as we matched both cases and controls firmly. So, the altered level of cytokines was not interfered with by these factors. The statistical and sample design of this study was also one of the positive aspects of this study. Lastly, ROC curve analysis focusing on predictive performance has assured us that altered IL-2 levels are linked with MDD.

Limitation of the study

A few limitations were present in this study like we only assessed the pro-inflammatory cytokine IL-2 levels in the MDD patients and HCs once due to the short timeframe of our analysis; sampling at multiple stages of the MDD phase would have provided a more accurate picture of the results. We did not consider the average duration of the disease. We also

could not match a few sociodemographic variables between MDD patients and HCs in this study. Additionally, the impact of any medications, dietary, or lifestyle behaviors, such as food or exercise, was also disregarded. Specifically, food mediates benefits to depressive symptoms and including avoided onset of symptoms. A study reported that higher intake of nutrition-rich dairy products benefits to depressive symptoms among adults.[87] Another study showed that saffron supplementation could be an option for effective intervention of symptoms of depression and anxiety.[88] Therefore, we recommend further studies considering the above-mentioned factors including the sociodemographic variables on a larger and more homogeneous population to measure the actual association of IL-2 with depression. We would also suggest that further studies must address the role of medication use, lifestyle behaviors, dietary factors, and sleep patterns in MDD patients.

Conclusion

The current study observed elevated serum IL-2 levels among MDD patients and a sex-specific finding that altered IL-2 levels and the severity of the disease are significant in only female MDD patients. So, it is possible to consider IL-2 as a valuable indicator to assess the risk of MDD and develop novel treatments for patients if further studies align with ours. However, this is yet to confirm whether these alterations are the consequence of the disease or the cause. Therefore, we advise researchers to conduct further interventional studies on MDD patients to define the actual role of IL-2 as a risk assessment indicator for MDD.

Author Contributions

Farhana Islam Suhee and Mohammad Shahriar: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Sardar Mohammad Ashraful Islam and Mohiuddin Ahmed Bhuiyan: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Md. Rabiul Islam: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data Availability Statement

All the relevant data and information will be available from the corresponding author upon reasonable request.

Ethics Approval Statement

We received approval for this study from the Research Ethics Committee, approval No: UAP/REC/2022/104, University of Asia Pacific. We followed the Declaration of Helsinki to conduct this case-control study. We obtained written consent from all patients/participants.

Supplemental Material

Supplemental material for this article is available online.

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