Beta Endorphins, Interleukin 1 and Interleukin 38 in Covid Patients Associated with Neuropsychological Manifestations

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Abstract:

Background: Coronavirus was identified as a cause of a worldwide epidemic which led to millions of deaths globally. Although most COVID-19 patients have initially complained of respiratory insufficiency, the presence of neuropsychiatric manifestations is also reported frequently. These neuropsychiatric complications have emerged as a potential indicator of worsened clinical outcomes and poor prognosis [1]. This study aimed to detect the levels of βeta endorphins, interleukin 1, and interleukin 38 in the serum of COVID-19 patients and their relation to the development of neuropsychiatric symptoms.

Methods: a case-control study conducted on 50 COVID-19 patients and 40 healthy controls in the clinical pathology department, South Egypt Cancer Institute, Assiut University. Patients with Other respiratory diseases and previous neuropsychiatric disorders were excluded. All patients and control are assessed by using psychometric tests for anxiety and depression (Hamilton depression and anxiety). Serum interleukin 1 beta, interleukin 38 and Beta-endorphin were measured by ELISA.

Results: Our study showed that IL1 and β endorphins were higher in the serum of COVID patients as compared to controls. As for IL38 and β endorphins, COVID cases without neuropsychiatric manifestations had significantly higher IL38 levels and β endorphins than those with neuropsychiatric manifestations.

Conclusion: Neuropsychological assessment suggests a higher incidence of anxiety/depression among COVID-19 patients. This study indicates that serum IL-1, IL-38 & β-Endorphins levels were affected by COVID-19 infection, and may be involved in developing neuropsychiatric complications and could help in targeting a therapy toward this complication.

Keywords: Covid 19 –neuropsychiatric disorders- interleukin 1- intelekin38 – beta endorphins.

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Introduction:

Coronavirus was identified in early 2020 as the cause of a pneumonia epidemic affecting Wuhan, spreading rapidly across the world [1]. The signs and symptoms present at the illness onset may vary widely and involve various organ systems. Recent literature is beginning to shed light on the impact of COVID-19 on the nervous system and its neuropsychiatric sequelae. [2]. Although most COVID-19 patients have initially complained of respiratory insufficiency, the presence of neuropsychiatric manifestations is also reported frequently. They range from headache, anosmia, strokes, seizures, encephalopathy, altered mental status, depression, anxiety, and panic disorders. These neuropsychiatric complications have emerged as a potential indicator of worsened clinical outcomes and poor prognosis. The psychological disorders caused by COVID-19 have significant effects on the immune system, resulting in mast cell activation and generation of cytokines. They include cytokines with both proinflammatory (IL-1α, IL-1β, IL-18, IL-33, and IL-36) and anti-inflammatory (IL-37 and IL-38) effects.

[3]. IL-38 is the newest cytokine of the IL-1 family members. It is also a potential therapeutic cytokine that inhibits inflammation in viral infections including that caused by covid-19 [4].

β-Endorphin which is a morphine-like and an endogenous opioid peptide hormone is related to pain modulation and strongly linked to chronicity and severity of depression. The μ-opioid receptor which is a specific receptor for β-endorphin is upregulated by IL-1α and IL-1β. β-Endorphin stimulates chemotaxis of monocytes, their differentiation into macrophages, and production of reactive oxygen species, interleukin (IL)-1β, IL-10, interferon-γ, and tumor necrosis factor-α from macrophages. [5]. Our study aims to detect the levels of βeta endorphins, interleukin 1, and interleukin 38 in the serum of COVID-19 patients. In addition, to determine the relation between these cytokines and the development of neuropsychiatric symptoms among COVID-19 patients.

Patients and Methods:

The current study is a prospective study carried out in the clinical pathology department, South Egypt Cancer Institute, Assiut University. The patients of this study were admitted at Intensive Care Unit and Chest Department, Faculty of medicine, Assiut University between June 2021 and December 2022. The Assiut University Faculty of Medicine's medical ethical committee gave the research the thumbs up. We assessed the level of interleukin 1 beta, interleukin 38, and beta endorphin in ninety subjects (fifty COVID patients and forty healthy controls). The fifty Covid patients had positive throat swabs by real-time PCR which is a nuclear-derived method for detecting the presence of specific genetic material for corona virus. Patients were divided into two groups (group 1 included Covid-19 patients with neuropsychiatric manifestations and group 2 included those without neuropsychiatric manifestations). Patients were classified according to presence or absence of neurological symptoms. All patients and control are subjected to complete neurological examination and psychiatrically assessed by the most widely used psychometric test for anxiety and depression (Hamilton depression and anxiety). The Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) are psychological questionnaires used by clinicians to rate the severity of a patient's anxiety and depression, respectively. [6].

Results:

Demographic data of both groups is illustrated in Table 1. The median age of the studied cases was 42 years, with a range from 9 years up to 73 years old. Out of 50 studied cases, 28 (56%) were males while 22 (44%) were females, with a male to female ratio of 1.2:1. Out of 50 studied cases, 16 cases (32%) were smokers. There was no significant difference as regard age, sex, and smoking between patients and controls. The median age of Covid-19 cases with neuropsychiatric manifestations was 42 years, with a range from 9 years up to 73 years old. Out of 25 cases with neuropsychiatric manifestations, 14 cases (56%) were males while 11 cases (44%) were females, with a male to female ratio of 1.2:1 which was the same ratio in those without neuropsychiatric manifestations. In patients with neuropsychiatric manifestations, 9 cases (36%) were smokers versus 16 cases (64%) were nonsmokers. In patients without neuropsychiatric manifestations, 7 cases (28%) were smokers and 18 cases (72%) were nonsmokers with no statistical significance (P value 0.544).

According to the clinical presentation, the majority of the studied cases were presented with Sore throat followed by Cough. Fatigue was observed in (70%) , Fever in (68%) and Dyspnea in (68%). Four cases (8%) presented with fine tremors, three cases (6%) with numbness in the lower limb, two cases (4%) with slurred speech, and two cases (4%) with lower limb weakness. Photophobia was documented in one case only (2%).

By comparing the clinical presentation of Covid-19 cases with neuropsychiatric manifestations and those without neuropsychiatric manifestations, there was no significant difference between the two groups, except for Headache, Loss of taste, and Loss of smell were significantly more frequent in COVID cases with neuropsychiatric manifestations than Covid cases without neuropsychiatric manifestations (0%) with a significant P value (P value < 0.001). Table 2

Table 3 showed HAM scales between studied groups, by comparing HAM-A and HAM-D scales between COVID-19 cases and controls, COVID cases presented with higher HAM-A and HAM-D scores than controls. By comparing HAM-A and HAM-D scales between the two groups of COVID patients, there was a significantly higher HAM-A and HAM-D scores in COVID patients with neuropsychiatric manifestations than in those without neuropsychiatric manifestations P value (< 0.001). Table 3

IL1β, IL38 & Beta endorphins detection:

Our study showed that IL38 is lower in COVID patients when compared to controls but of no statistical significance. There is a statistically significant increase of IL1 beta and Beta Endorphins in the serum of COVID patients when compared to controls with P value (<0.001).

IL1 beta is higher in patients without neuropsychiatric manifestations than in those with neuropsychiatric manifestations but of no statistical significance. As regard IL38 and β endorphins, Covid cases without neuropsychiatric manifestations had significantly higher IL38 levels and β endorphins than Covid cases with neuropsychiatric manifestations Table 4.

Correlation between the studied biomarkers and patient's characteristics:

Our study found that there is a statistically significant weak negative correlation between interleukin 38 levels and age of the studied participants. (r = -0.284, p = 0.045) Another significant weak

negative correlation was observed between beta endorphin level and leucocyte count in the studied participants (r = -0.283, p = 0.046). Also, there is a statistically significant weak negative correlation between interleukin 1 beta level and D-dimer level in the studied participants (r = -0.284, p = 0.046) Table 5

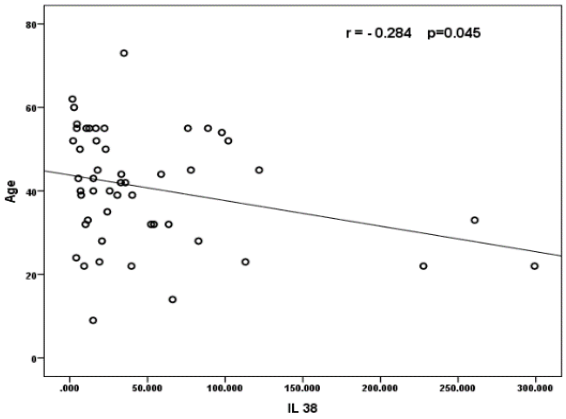

Figure 1 Scatter plot diagram showing the correlation between IL 38 and age of the studied COVID-19 cases.

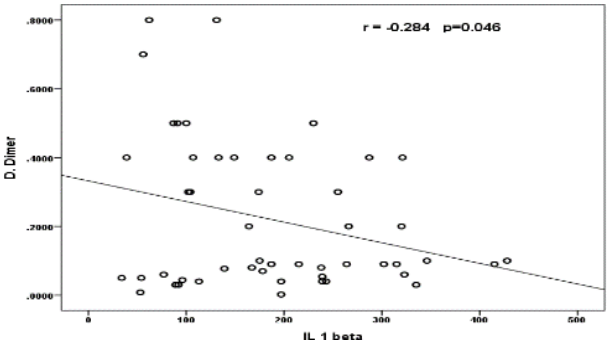

Figure 2 Scatter plot diagram showing the correlation between IL 1 beta and D. Dimer among the studied COVID-19 cases.

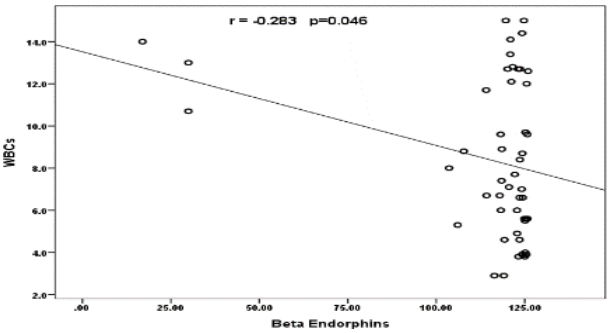

Figure 3 Scatter plot diagram showing the correlation between Beta Endorphins level and WBCs count among the studied COVID-19 cases.

Table 1 Demographic data of the studied participants

Demographic data	COVID cases (n=50)	Controls (n=40)	P value
Age (years)			0.215
• Mean ± SD	40.84 ± 13.68	37.75 ± 8.45	
• Median (range)	42 (9 – 73)	40 (16 – 52)	
Sex, n (%)			0.887
• Male	28 (56.0%)	23 (57.5%)	
• Female	22 (44.0%)	17 (42.5%)	
Smoking, n (%)			0.062
• No	34 (68.0%)	34 (85.0%)	
• Yes	16 (32.0%)	6 (15.0%)	
Demographic data	**COVID with neuropsychiatric (n=25)**	**COVID without neuropsychiatric (n=25)**	**P value**
Age (years)			0.098
• Mean ± SD	40.84 ± 13.68	37.64 ± 12.09	
• Median (range)	42 (9 – 73)	39 (14 – 56)	
Sex, n (%)			1
• Male	14 (56.0%)	14 (56.0%)	
• Female	11 (44.0%)	11 (44.0%)	
Smoking, n (%)			0.544
• No	16 (64.0%)	18 (72.0%)	
• Yes	9 (36.0%)	7 (28.0%)	

Quantitative data are presented as mean ± SD and median (range); qualitative data are presented as number (percentage). P value is significant ≤0.05.

Table 2 Clinical presentation of the studied COVID infected cases with and without neuropsychiatric comorbidities

Clinical presentation	Total cases (n=50)		COVID with neuropsychiatric, n =25		COVID without neuropsychiatric, n=25		P value
Sore throat	44	(88.0%)	22	(88.0%)	22	(88.0%)	1
Cough	42	(84.0%)	23	(92.0%)	19	(76.0%)	0.247
Fatigue	35	(70.0%)	17	(68.0%)	18	(72.0%)	0.758
Fever	34	(68.0%)	14	(56.0%)	20	(80.0%)	0.069
Dyspnea	34	(68.0%)	16	(64.0%)	18	(72.0%)	0.544
Headache	21	(42.0%)	21	(84.0%)	0	(0.0%)	<0.001
Loss of taste	17	(34.0%)	17	(68.0%)	0	(0.0%)	<0.001
Loss of smell	17	(34.0%)	17	(68.0%)	0	(0.0%)	<0.001
Diarrhea	3	(6.0%)	1	(4.0%)	2	(8.0%)	1
Numbness in lower limb	3	(6.0%)	3	(12.0%)	0	(0.0%)	0.235
Slurred speech	2	(4.0%)	2	(8.0%)	0	(0.0%)	0.490
Lower limb weakness	2	(4.0%)	2	(8.0%)	0	(0.0%)	0.490
Photophobia	1	(2.0%)	1	(4.0%)	0	(0.0%)	1

Qualitative data are presented as number (percentage). P value is significant ≤0.05.

Table 3 HAM-A and HAM-D scales between the studied participants

Neuropsychiatry scales	**COVID cases (n=50)**	**Controls (n=40)**	**P value**
HAMA			
• Mean ± SD	16.36 ± 4.59	12.60 ± 2.99	**<0.001**
• Median (range)	16 (5 – 27)	12 (6 – 18)	
• Mild severity (<=17)	32 (64.0%)	39 (97.5%)	**<0.001**
• Mild to moderate severity (18 - 24)	16 (32.0%)	1 (2.5%)	
• Moderate to severe (25 - 30)	2 (4.0%)	0 (0.0%)	
HAMD			
• Mean ± SD	6.16 ± 1.86	4.73 ± 1.68	**0.001**
• Median (range)	6 (2 – 10)	5 (2 – 7)	
• Normal (0 - 7)	38 (76.0%)	40 (100.0%)	**0.001**
• Mild depression (8 - 16)	12 (24.0%)	0 (0.0%)	
• Moderate depression (17 - 23)	0 (0.0%)	0 (0.0%)	
• Severe depression (>=24)	0 (0.0%)	0 (0.0%)	
Neuropsychiatry scales	**COVID with neuropsychiatric, n =25**	**COVID without neuropsychiatric, n=25**	**P value**
HAMA			**<0.001**
• Mean ± SD	19.12 ± 4.03	13.60 ± 3.32	
• Median (range)	19 (11 – 27)	14 (5 – 19)	
• Mild severity (<=17)	9 (36.0%)	23 (92.0%)	**<0.001**
• Mild to moderate severity (18 - 24)	14 (56.0%)	2 (8.0%)	
• Moderate to severe (25 - 30)	2 (8.0%)	0 (0.0%)	
HAMD			
• Mean ± SD	7.32 ± 1.60	5.00 ± 1.29	**<0.001**
• Median (range)	7 (4 – 10)	5 (2 – 7)	
• Normal (0 - 7)	13 (52.0%)	25 (100.0%)	**<0.001**
• Mild depression (8 - 16)	12 (48.0%)	0 (0.0%)	
• Moderate depression (17 - 23)	0 (0.0%)	0 (0.0%)	
• Severe depression (>=24)	0 (0.0%)	0 (0.0%)	

Data are presented as mean ± SD and median (range), or number (percentage). P value is significant ≤0.05.

Table 4: The studied biomarkers between the studied participants

Biomarkers	COVID cases (n=50)	Controls (n=40)	P value
IL1beta			**<0.001**
• Mean ± SD	186.40 ± 100.89	106.25 ± 65.79	
• Median (range)	176.5 (34 – 428)	96 (18 – 258)	
IL38			0.082
• Mean ± SD	48.41 ± 63.59	52.17 ± 38.30	
• Median (range)	23.6 (1.67 – 299.26)	41.8 (0.83 – 167.28)	
Beta Endorphins			**<0.001**
• Mean ± SD	115.44 ± 23.49	101.78 ± 32.56	
• Median (range)	122.8 (16.97 – 125.92)	115.42 (16.97 – 123.85)	
Biomarkers	**COVID with neuropsychiatric, n =25**	**COVID without neuropsychiatric, n=25**	**P value**
IL1beta			0.125
• Mean ± SD	168.48 ± 109.13	204.32 ± 90.57	
• Median (range)	139 (34 – 428)	197 (53 – 415)	
IL38			**0.023**
• Mean ± SD	34.69 ± 59.92	62.12 ± 65.39	
• Median (range)	16.7 (1.67 – 299.26)	39.6 (2.07 – 260.70)	
Beta Endorphins			**0.010**
• Mean ± SD	115.15 ± 21.24	115.73 ± 25.99	
• Median (range)	119.6 (16.97 – 125.8)	124.1 (29.9 – 125.9)	

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage). P value is significant ≤0.05.

Table 5: Correlation between the studied biomarkers and patient's characteristics among whole studied cases

Variables		IL 1 beta	IL 38	Beta Endorphins
IL 38	r	0.140		
	p	0.331		
Beta Endorphins	r	0.217	0.111	
	p	0.131	0.444	
Age	r	-0.102	-0.284	-0.131
	p	0.481	**0.045**	0.365
HAM A score	r	-0.187	-0.262	0.050
	p	0.193	0.066	0.733
HAM D score	r	-0.062	-0.174	-0.015
	p	0.669	0.226	0.919
WBCs	r	0.203	-0.059	-0.283
	p	0.157	0.685	**0.046**
Hemoglobin	r	0.113	-0.162	0.075
	p	0.434	0.261	0.606
Platelets count	r	0.238	0.067	0.055
	p	0.095	0.644	0.707
Ferritin	r	-0.031	0.142	-0.113
	p	0.829	0.325	0.435
CRP	r	0.054	0.085	0.149
	p	0.711	0.559	0.303
D. Dimer	r	-0.284	-0.017	-0.140
	p	**0.046**	0.905	0.331

Discussion:

The world is facing one of its worst infectious disease pandemics in history, the coronavirus. SARS-CoV-2 was identified as the cause of an outbreak of a severe pneumonia-like disease, currently known as Covid-19. Although the main risk of COVID-19 is to cause injuries to the upper and lower respiratory tract and lungs, other organs are also affected, including CNS leading to a variety of neuropsychiatric symptoms including headache, malaise and unstable walking, cerebral hemorrhage, depression, delirium and memory impairment. These psychological symptoms become more obvious with quarantine, which is one of the most common protections against virus infections. COVID 19 pandemic had a dramatic impact in global poverty and led to a considerable number of disabilities and deaths all over the world.

In the current study, the mean age of the studied COVID-19 patients was 40.84 ± 13.68 and ranged from 9 to 73 years. In our study, there was no sex predilection among the studied cases with a male-to-female ratio of 1.2:1. In line with this finding, the current worldwide data report similar numbers of diagnosed cases in women and men (1:1.1 ratio) [7]. Docherty et al. showed that age is a major factor in determining the risk of severe illness outcomes, so data on the age distribution of infected persons can help guide expectations about demands on hospital resources [8]. Bhopal, 2020 concluded that in addition to age group, we need to stratify cases by sex which is important for designing effective interventions [9].

In this study, sore throat is the commonest presentation among the studied participants, followed by cough, fatigue, fever, headache, loss of taste, and loss of smell. The most common neurologic and psychiatric manifestations among the studied participants included headache, loss of taste, and loss of smell in 84%, 68%, and 68% respectively.

In a systematic review of the literature, authors observed that the main symptoms among COVID-19-infected patients were fever, cough, dyspnea, malaise, fatigue, and sputum/secretion. Neurological symptoms, dermatological manifestations, anorexia, myalgia, sneezing, sore throat, rhinitis, headache, chest pain, and diarrhea were other common symptoms. The least frequent sign/symptom was hemoptysis [10].

Nalleballe et al. revealed that the most common neurologic manifestations were headaches, sleep disorders, encephalopathy, myalgia, pain, loss of taste and smell, stroke, transient ischemic attack (TIA), dizziness, extrapyramidal and movement disorders, seizures, polyneuropathy, and nerve root and plexus disorders [11].

According to (HAM-A) and (HAM-D) scales, we observed that COVID-19 patients suffered from a higher rate of depression [12 cases with mild depression (24.0%)], and anxiety [mild (64.0%), mild to moderate severity (32.0%), and moderate to severe (4.0%)] as compared to matched controls. Additionally, we observed significantly higher means of HAM-D and HAM-A among COVID-19 patients with neuropsychiatric manifestations compared with those with no neuropsychiatric manifestations. These findings are similar to Rogers et al. 2020 results which demonstrated that there is link between the development of depression, anxiety, and neuropsychiatric manifestations in the COVID-19 pandemic [12].

Many other studies demonstrated that depression and anxiety are higher in COVID-19 patients than usual. [13,14]. This could be explained by various stressors during isolation, including fear of severe disease and a fear of infecting others which lead to several psychological distresses, including anxiety, depression, and insomnia [15].

Our study showed that statistically significant increase of IL1 beta in the serum of COVID patients when compared to controls

Mardi et al., 2021 showed that IL-1 played a pivotal role in the induction of cytokine storm due to dysregulated immune responses [16]. In line with our study, elevated concentrations of interleukin-1β (IL-1β) was reported in COVID-19 patients [17,18].

Another interesting finding in the current study is that IL38 level was significantly higher among COVID-19 patients without neuropsychiatric manifestations compared with those with neuropsychiatric manifestation. In agreement with our study, Gao et al observed lower levels of IL-38 among severely ill patients compared to patients with non-severe disease. [19]. IL-38 may have a protective role against immune system overactivity.

In the current study, we observed that β-endorphin level was significantly higher among COVID-19 patients compared to matched controls, and also was significantly higher among COVID-19 without neuropsychiatric manifestations compared with those with neuropsychiatric manifestations. This finding could be explained by the fact that β-Endorphins, along with other opioids, appear to attenuate cyclic adenosine monophosphate levels and decrease calcium uptake. The peptide is typically released to the periphery in response to a painful or stressful event, where they inhibit somatosensory fibers, with a focus on nociceptors. [20].

In our study, correlation analysis revealed a negative correlation between IL-38 and age ($r = -0.284$, $p = 0.045$).

In contrast to our finding, De Graaf et al. didn't find a correlation between IL-38 and the age of the studied participants, while he observed a negative correlation between IL-38 and BMI in a sex-dependent manner and a positive correlation between IL-38 plasma concentrations and d-dimer in men only with no relationship with CRP, LDH, ferritin, and creatinine levels. [21].

On the other hand, Al-bassam et al. observed a significant negative correlation between IL-38 and Hb levels, while it was positively correlated with BUN and uric acid [22].

We consider several explanations for the discrepancies between our data and those reported by other studies. First, the expression of IL-38 during an infection may change, and thus the timing of the blood

draw is relevant. Furthermore, different ethnicities and ages of the studied patients may contribute to the opposing observations between our and Al-bassam's & Gao's studies.

Another significant negative correlation was observed between beta endorphin level and total leucocyte count in the studied participants (r = - 0.283, p = 0.046). This finding could be explained by the fact that leukocytes are a rich source of endogenous opioid peptides that inhibit nociceptive transmission by binding to peripheral opioid receptors. During inflammation, leukocytes are recruited to the site of damage. Upon stimulation with mediators such as interleukin-1 (IL-1), corticotrophin-releasing factor (CRF), or norepinephrine, they release opioid peptides (i.e., β-endorphin), which exert an anti hyperalgesic effect in inflamed tissues. [23].

There is also a statistically significant weak negative correlation between interleukin 1 beta level and D. dimer level in the studied participants (r = -0.284, p = 0.046). Elevated d-dimer is a prognostic marker for severe COVID-19, as well as for thrombotic complications. The negative correlation between IL-1 and d-dimer may reflect an ongoing attempt of the immune system to limit d-dimer or the breakdown of an established clot, resulting in a reduction of circulating d-dimer. [24].

Study limitations and recommendations

We recommend further larger multi-center studies to confirm the current findings due to the relatively small sample size. We also recommend periodical examinations and follow up for infected COVID-19 patients to document developing neuropsychiatric complications with earlier and proper management to improve the patient's outcome and achieve a better quality of life.

Conclusion:

Neuropsychological assessment suggests a higher incidence of anxiety and depression, among COVID-19- infected patients. Our study revealed that COVID cases without neuropsychiatric manifestations had significantly higher IL38 and β endorphin levels than COVID cases with neuropsychiatric manifestations. This may give an idea about the role of these biomarkers in the development of COVID-19 neuropsychiatric complications and highlight the association of these markers with the severity of COVID-19 infection. These findings also support the role of endorphin release therapy in management of COVID cases associated with neuropsychiatric complications and confirm the role of IL38 as a therapeutic cytokine in management of severe COVID 19 infections.

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