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Correlation Between Interleukin-6 Serum Level and Olfactory Dysfunction Severity in COVID-19 Patients in Egypt

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ABSTRACT

Background and aim: Olfactory disorders [OD], which include anosmia and hyposmia, are one of the most common clinical symptoms of COVID-19. It may be the first or the only symptom. Interleukin [IL]-6, an inflammatory mediator, is produced during the initial stage of inflammation. Its release as a defense mechanism could be responsible for COVID-19 symptoms and OD as well as their severity, so the aim of this study was to analyze the relation between IL-6 and OD status and severity of disease among COVID-19 patients.

Patients and Methods: The study included 96 individuals attending the ear, nose, and throat [E.N.T.] clinics of the military hospitals. They were divided into 2 groups [48 COVID-19 patients and 48 controls]. Interleukin-6 was measured in both groups together with olfactory function and disease severity.

Results: Interleukin-6 levels were statistically higher among COVID-19 patients with OD when compared to COVID-19 patients without OD. A higher level of IL-6 was associated with poor olfactory function and higher COVID-19 disease severity.

Conclusion: There might be a directly proportionate relationship between the level of IL-6 and the olfactory dysfunction. Anosmia might be associated with a higher level of IL-6 than hyposmia. IL-6 could be considered a valid prognostic factor for COVID-19 as well as olfactory dysfunction.

Keywords: Interluekin-6; COVID-19; Olfactory; Anosmia.

INTRODUCTION

The World Health Organization first identified the coronavirus disease 2019 [COVID-19] in China in December 2019 and declared it a pandemic in March 2020 [1]. Coronaviruses are enveloped, non-segmented, positive-sense, single-stranded RNA viruses with a genome of 26–32 kilobases, which encodes four structural proteins, including the spike, envelope, membrane and nucleocapsid proteins [2].

The innate immune response to corona-viruses is induced in response to the recognition of their positive-sense RNA genomes. This results in the production of type I interferons, which regulate the expression and induction of pro-inflammatory cytokines and chemokines. Specifically, the severe acute respiratory syndrome coronavirus 2 [SARS- CoV-2] infection was associated with increased production of the T helper cell type 1 pro-inflammatory cytokines [IL-1, IL-6, interferon gamma, IL-12] and chemokines. Interleukin 6 has both anti-inflammatory and pro-inflammatory properties. It is produced by the human IL-6 gene. But in the light of the greater coronavirus epidemic, an inflammatory marker called IL-6 can be used to indicate a severe COVID-19 infection with a poor prognosis [3].

The term "normosmia" refers to normal olfactory function. The three types of quantitative abnormalities are dysgeusia [a distortion of the sense of taste], anosmia, and hyposmia [a reduction in smell or altered sensation of smell]. Parosmia is a change in how fragrances are normally perceived, such as when a familiar scent is misperceived or when something that usually smells good turns bad [4].

Cough and fever are the typical initial symptoms of COVID-19 patients, and a chest computed tomography scan may show parenchymal abnormalities. Anosmia and dysgeusia have been observed in 33 to 80% of COVID-19 patients. There was a documented 11–40% correlation between anosmia, hyposmia, dysgeusia, and other upper respiratory tract infections, primarily because of nasal secretions and congestion. Anosmia associated with COVID-19 is distinct from anosmia associated with other upper respiratory tract infections in that it develops suddenly and doesn't depend on the presence of nasal congestion or blockage [5].

Only a small number of authors have looked at the relationship between the severity of olfactory abnormalities and blood levels of IL-6 prior to the COVID-19 pandemic. They discovered a directly proportional association that was statistically significant. These findings provide credence to the idea that IL-6 may be involved in the pathogenesis causing these olfactory dysfunctions. Contrary to what has been reported in COVID-19 patients, where the severity of olfactory impairment appears to be inversely proportional to the severity of COVID-19 and therefore likely inversely proportional to serum IL-6 levels, these levels were assumed to primarily reflect the severity of COVID-19 pneumonia and other major organ involvement as a direct proportional link [6].

Anosmia, hyposmia, ageusia [the complete lack of taste], and/or dysgeusia could be related to COVID-19. Thus, this study aimed to analyze the association between IL-6 and COVID-19 in terms of the development and severity of OD among COVID-19 patients.

PATIENTS AND METHODS

Research design and setting

This was a case-control study conducted in the E.N.T. clinics of military hospitals [Kobri El Qobba military complex, Ghamra military hospital, Elmaadi military complex, and El Galaa military complex] from January 2022 to June 2022.

Participants

COVID-19 patients of both genders with olfactory dysfunction [anosmia or hyposmia] and ages at time of study ranging from 20 to 70 years old were included in the study.

On the other hand, patients who had psychiatric or neurological disorders, previous surgery or radiotherapy for any oral or nasal pathologies, or any history of nasal pathologies such as allergic rhinitis or nasal polyposis, were all excluded from the study, as were any patients with a smoking history.

Accordingly, 48 eligible COVID-19 cases agreed to participate. An equal number of age- and sex-frequency-matched controls [n = 48] were chosen from patients presenting to the E.N.T. clinic, provided that they had no COVID-19 clinical infection.

Methods

COVID-19 cases were classified according to disease severity into mild, moderate, and severe groups in terms of signs, symptoms, O2 saturation, and chest CT scan findings **[Table 1]**.

Table [1]: Classification of COVID-19 severity

Mild	Mild symptoms of fever, cough, weakness, headache and sore throat. Normal O_2 saturation and normal CT chest [no hypoxia no pneumonia]
Moderate	O_2 saturation < 92 and chest CT showed lung infiltrate less than 50% [pneumonia without hypoxia].
Severe	O_2 saturation ≤ 92, respiratory rate > 30 breath\min, chest CT showed lung infiltrate ≥ 50% [pneumonia with hypoxia responding to oxygen therapy].

For all 96 participants, the following was carried out:

1. Measurement of serum IL-6: serum IL-6 was measured using enzyme-linked immunosorbent assay test using peripheral blood samples with a fully automated Elecsys system on a Cobas e801 platform [Roche Diagnostics, Basel, Switzerland]. In the first step, IL-6 within a monoclonal anti-human IL-6 antibody linked to gold binds to the sample. The IL-6/conjugate combination kept moving through the analytical membrane. A band that was correlated with the sample's IL-6 levels in terms of intensity became apparent. After 20 minutes, the results were available. They were analyzed using densitometry. The sample's IL-6 content and the test band's amplitude were associated. Utilizing a PicoScan® densitometry technology that measures IL-6 concentrations at a 30 40 cm resolution. This device quantitatively detects the strength of the test band and computes IL-6 concentrations using a standard curve [sensitivity range 50-10,000pg/mL of IL-6] **[Figure 1]**.

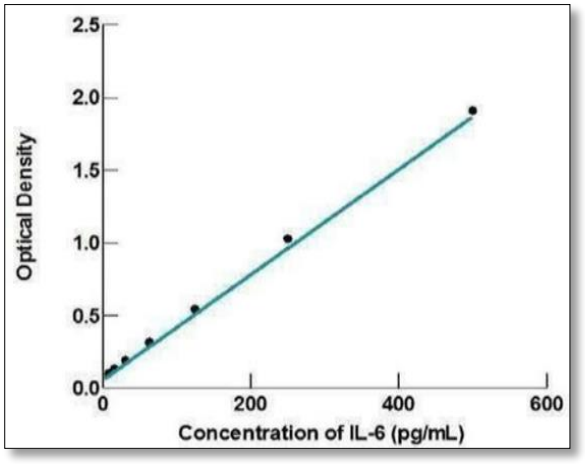

Figure [1]: A photograph showing the standard curve of IL-6.

2. The psychophysical test [sniffin stick test] [6] that comprised 3 subtests, resulting in 4 scores: T threshold score, D discrimination score, I identification score and TDI global olfactory score**.** Each subtest corresponds to a specific module that can be acquired separately. The test uses felt pens with antibacterial agent and 4 cc of odorant fluid or material dissolved in propylene glycol impregnated on the tips**.** The test was conducted in a calm, well-ventilated space. The subject only saw each pen once, for 3 to 4 seconds, roughly 2 cm from the nostril's border. After a brief verbal instruction, the patient was instructed to smell no more than twice before the pen's cover was promptly replaced. The [T] threshold test had 48 pens in total, divided into 16 triplets, each with a red number from 1 to 16. Each triplet has 3 pens that could be identified by the color of their cap: blue [Impregnated with solvent only], green [Impregnated with solvent only], and red [Impregnated with BUT/PEA diluted in solvent].

According to decreasing concentrations, red pens were impregnated with N-butanol or phenylethyl alcohol [BUT/PEA] dissolved in an odourless solvent. Only solvent was used to impregnate blue and green pens. The patient was asked to pick out the BUT/PEA pen from the group of the three pens that were displayed. The patient must make a decision, choosing one of the three pens each time. The subject of this exam must conduct it with their eyes closed or their vision covered. The most strongly scented red pen [with the highest BUT/PEA concentration] was used first in the test. A blue or green pen, which should ostensibly have no odor, was provided after thirty seconds. The test then involved presenting triplets of pens with progressively lower BUT/PEA concentrations [increasing number]. Each triplet's three pens must be displayed in a different order. The two triplets of pens should be separated by a 30-second period. The patients' responses were recorded on the grid as correctly identified [+] or not identified [-]**.**

The turning points were the level of focus required for the patient to respond correctly twice in a row [++]. Next, the examiner displayed the until a first error [+-] was noticed, triplets of pens matching to the immediately lower concentration were used [2nd turning point]. Then, until two right responses [++] were received, a higher concentration was shown [3rd turning point]. In this manner, the test continued to fill in the grid from left to right. Finally, 7 points in total were earned. The average of the previous four turning points was

used to define the olfactory T-threshold **[Table 2] and [Figure 2]**.

Table [2]: Turning point interpretation

First turning point	Correctly identified the smell.
Second turning point	First error observed
Third turning point	Correctly identified with high concentration

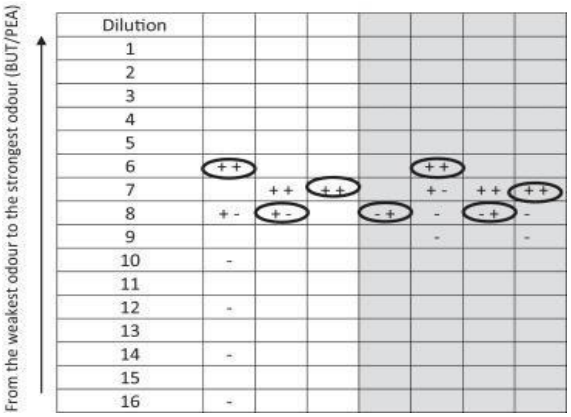

Figure [2]: Photographs showing Threshold

The [D] discrimination: green numerals from 1 to 16 were presented as 16 triplets of pens for this test. The blue and red pens were both impregnated with the same smell, but the green pens of each triplet had a different scent. The participant had to decide which of the triplet pens smelt different from the other two in order to complete the task. Different arrangements of the pens were displayed. Between any two pens of the same triplet, there was a 3 second gap, and between any two sets of triplets, there was a 30 second gap. Each test required a response from the respondent, who was required to maintain eye closure or wear a blindfold. The discrimination score was determined by how many of the 16 responses were accurate.

The [I] identification test: There were 16 blue pens with black numbers on them. Each pen was only offered once. To prevent olfactory desensitization, a gap of at least 30 seconds was kept between each exposure. The individual is compelled to pick one of four options from a list for each odorant pen. Blinded conditions were not required for this test. The number of accurate responses was reflected in the identification score [I]. **The TDI score:** The previous three scores were added to create this overall olfactory score. Functional anosmia was first classified as a TDI score ≤ 16.5, Hyposmia was defined as a TDI score between these two levels [16.5- 30.5] and normosmia as a score > 30.5**.**

Statistical analysis

SPSS [statistical software for social science] version 26.0 was used to analyse the data on an IBM compatible computer **[SPSS Inc., Chicago, IL, USA].** Chi square was used to assess the qualitative data, which was presented as numbers and percentages. Shapiro Wilks test was used to determine the normality of quantitative data, assuming normality at $P > 0.05$. If quantitative data were regularly distributed, Student's t test was used; otherwise, Both the Kruskal Wallis test and the Mann-Whitney U test were utilised. Mean, standard deviation, and range were the formats used to present quantitative data. The accepted level of significance in this investigation was 0.05 [$P < 0.05$ was regarded as significant].

Ethical considerations

The study proposal was approved by the Armed Forces College of Medicine Ethical Review Committee **[IRB: 37; meeting: September 25, 2021; serial number: 69].** Verbal informed consent was obtained from all participants before enrollment in the study. The study conformed to the requirements of the Revised Helsinki Declaration of Biomedical Ethics. The policy of data confidentiality was strictly followed.

RESULTS

A total of 96 participants were enrolled in our study, including 48 patients with COVID-19 and 48 controls. The patient age ranged between 20 and 70 years. Females represented 43.8% and 52.1% of COVID-19 and control groups respectively. There were no significant differences between COVID-19 and Control groups regarding age or gender [Table 3].

The severity of COVID-19 was mild in 20 patients [41.7%], moderate in 18 patients [37.5%] and severe in 10 patients [20.8%]. The interleukin-6 was significantly increase in the COVID-19 than control group [14.1±4.9 vs 2.9±1.1 pg/ml respectively, $p < 0.001$].

Regarding olfactory function, the mean TDI was 12.8 ± 10.2, ranging between 1.1 and 36. In the control group, the average TDI was 36.5 ± 2.7, ranging between 31 and 41. The mean threshold component was 4.3 ± 3.7 in the COVID-19 group and 10.2 ± 2.9 in the control group. The mean discrimination component was 4.1 ± 3.5 in the COVID-19 group, while it was 13 ± 1.7 in the control group. The mean

identification component was 4.2 ± 3.7 in the COVID-19 group and 13.2 ± 3.8 in the control group. The control group had a significantly higher mean TDI, threshold, discrimination, and identification than the COVID-19 group [36.5, 10.2, 13.0, and 13.2 versus 12.8, 4.3, 4.1, and 4.2, respectively [P-value < 0.001]] [Table 4].

The percentage of abnormal olfactory function associated with COVID-19 was 83.3%. In the COVID-19 group, 36 [75%] patients were diagnosed with anosmia, 12[25%] were diagnosed with hyposmia**.** On the other hand, all patients in the control group had normal olfactory function.

Relation between IL-6 and olfactory dysfunction in the COVID-19 Group [table 5]: The mean IL-6 level was 17.4 ± 11.3 pg/ml [range,6.2 – 44.2] and 9.7 ± 1.7 pg/ml [range, 8.0 – 12.0] in COVID-19 patients presenting with anosmia and hyposmia, respectively. On the other hand, patients with normal olfactory function had lower levels of IL-6 with a mean 4.7 ±0.6 pg/ml [range, 3.8 – 5.5]. As shown in table [5], the difference in IL-6 levels among patients with anosmia, hyposmia, and normosmia was statistically significant [P-value = 0.004].

There was an inverse relation between IL-6 levels and components of Sniffin's score [Table 6]. Higher IL-6 levels were associated with lower threshold, discrimination, identification and TDI scores and poor olfactory function. The correlations were statistically significant [P <0.0001] [Figure 3]. Relation between IL-6 and disease severity in the COVID-19 Group: In the COVID-19 group, the mean IL-6 level was 6.8 ± 2.1 pg/ml [range, 3.8– 9.9] in the mild disease, 11.9 ± 4.7 pg/ml [range, 6.2 – 19.7] in moderate disease, and 32.7 ± 8.2 pg/ml [range, 17.5 – 44.2] in the severe disease. As shown in table 7, the difference in IL-6 levels among patients having mild, moderate, and severe COVID-19 was statistically significant [P-value < 0.001]. [Table 7]. A correlation analysis showed a positive relation between IL-6 levels and disease clinical stage. Therefore, higher IL-6 levels are associated with more severe disease. The correlation was statistically significant [P-value < 0.05] [figure 4].

Table [3]: Patient characteristics

		COVID-19 [n = 48]	Control [n = 48]	P value
Age [years]	Mean ± SD	46.2 ±15.5	47.4 ±14.3	>0.05
	Min-Max.	20-70	22-70	
Gender [n, %]	Females	21[43.8%]	25 [52.1%]	0.414
	Males	27 [56.3%]	23[47.9%]	

Table [4]: Comparison of the olfactory function between the study groups [N = 96]

	COVID-19 [N = 48]		Control [N = 48]		P-value[#]
	Mean	**SD**	**Mean**	**SD**	
TDI	12.8	10.2	36.5	2.7	< .001
Threshold	4.3	3.7	10.2	2.9	< .001
Discrimination	4.1	3.5	13.0	1.7	< .001
Identification	4.2	3.7	13.2	3.8	< .001

Table [5]: Relation between IL-6 and Olfactory Function among COVID-19 patients [N = 48]

	IL-6 [pg/ml]			
Olfactory Function	**Mean**	**SD**	**Range**	**P-value**
Anosmia	17.4	11.3	6.2 – 44.2	**0.004***
Hyposmia	9.7	1.7	8.0 – 12.0	

Table [6]: Correlation analysis between IL-6 Levels and Sniffin's score

	IL-6 level	*P*-value
Sniffin's score	**Correlation Coefficient**	
TDI	-0.598	< 0.001
Threshold	-0.664	< 0.001
Discrimination	-0.511	< 0.001
Identification	-0.491	< 0.001

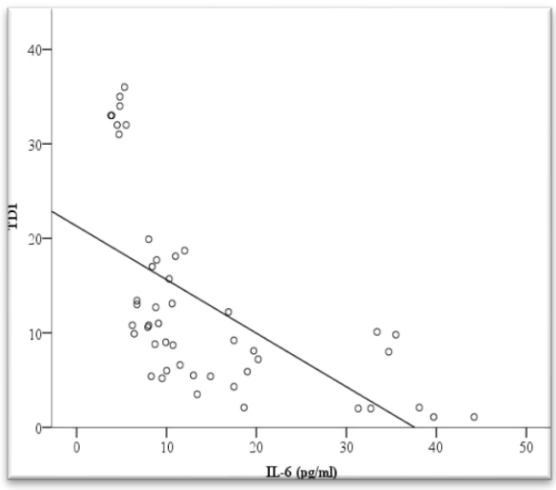

Figure [3]: Scatter plot showing the correlation between IL-6 and TDI Score.

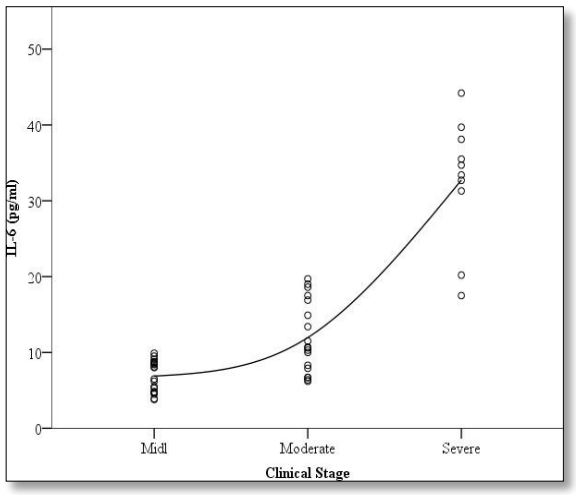

Figure [5]: Correlation between IL-6 and the severity of COVID-19.

Table [7]: Comparison of IL-6 level according to disease severity among COVID-19 patients [n = 48]

COVID-19 severity	IL-6 level			P-value
	Mean	SD	Range	
Mild	6.8	2.1	3.8 – 9.9	< 0.001*
Moderate	11.9	4.7	6.2 – 19.7	
Severe	32.7	8.2	17.5 – 44.2	

DISCUSSION

The COVID-19 pandemic has continued for approximately three years, imposing severe burdens on the global health care systems and economic stability [6]. Also, an increasing number of studies have found that OD, which include anosmia and hyposmia, are among the most common clinical symptoms of COVID-19 [7, 8].

Reports had shown that OD symptomatizes in 33–80% of patients with COVID-19 [9, 10], which seemed to be higher than that of a common cold or influenza [11].

Kaye *et al.* [12] reported that 26.6% of COVID-19 patients presented with anosmia initially, while 73% of them presented with anosmia during the disease course.

Cazzolla *et al.* [13] reported that 65.7% of COVID-19 patients presented with isolated olfactory dysfunctions, 25.4% with isolated taste disorders, and only 8.95% with combined smell and taste disorders.

In the present study, we targeted 48 patients already diagnosed with COVID-19 as well as OD [anosmia or hyposmia]. They were not known to have had previous ODs before the COVID-19 attack.

Vaira *et al.* [5], using the Sniffin`s test, and reported that the TDI score in the COVID-19 patients was significantly lower as compared to the controls. They also found that the prevalence of OD in COVID-19 patients was significantly higher [26.5%] when compared to controls [3.5%].

Vaira *et al.* [14] using the same method, reported no significant difference in TDI score among different COVID-19 severity groups. The present study had comparable findings, as a statistically significant decrease was found in the TDI score of COVID-19 patients in comparison to the controls [P < 0.001].

It was established that IL-6, an inflammatory mediator, is produced during the initial stage of inflammation as a host defense mechanism against infection. It is one of the cytokines that are released during the cytokine storm in COVID-19 patients. It is suggested that the cytokine storm resulted in severe tissue damage with a bad prognosis, especially in the respiratory system [15]. Thus, excessive release of IL6 during fighting the COVID-19 disease affects the

different body tissues. As a result, IL-6 could be responsible for OD due to olfactory system affection. A number of clinical studies reported that the serum level of circulating IL-6 was significantly higher among the COVID-19 patients from the severe to the critical stage [16,17].

Another study showed evidence that serum levels of IL-6 above 24.3 pg/ml might be associated with severe pneumonia in COVID-19 patients [18].

In their report, **Han and his colleagues [15]** and **El-shabrawy and associates [17]** stated that IL-6 was significantly higher in COVID-19 patients as compared to the controls. They concluded that IL6 was released as a host defense mechanism against the COVID-19.

In addition, **Vira *et al.* [14]** have mentioned a significant direct proportional relationship between the concentration of IL-6 and the severity of COVID-19. The more the IL-6, the more the disease severity. Our results, also demonstrated a significantly higher level of IL-6 in COVID-19 patients in comparison to the controls [$P < 0.001$]. Our results strongly support the idea that IL-6 might be a major contributing factor in the cytokine storm in the pathogenesis of COVID-19.

In addition, our results demonstrated a significant positive correlation between the level of IL-6 and COVID-19 severity. It was noticed clinically that the OD was not evident in all patients with COVID-19, even in the severe form, although they had an elevated level of IL-6, as mentioned before. Therefore, it could be believed that the severity of COVID-19 disease was inversely correlated to the OD. The greater the COVID-19 severity [the higher the IL-6 level], the less the OD.

Lechien *et al.* [19] had highlighted this point, with the justification that in severe COVID-19 disease, IL-6 levels should be very high, resulting in tissue damage without affection of the olfactory function. Our results found a significant relationship between the level of IL-6 and the different levels of ODs [anosmia versus hyposmia]. We can say that the more IL6, the more olfactory dysfunction**.**

In our minds, our study presented a new opinion explaining the relation between the level of IL-6 and OD severity. We proposed that IL-6 was released in a certain amount in every patient having COVID-19. However, it seems that SARS CoV-2, for some reason, selects certain tissues upon infection. It might select the lung tissues, the olfactory mucosa, or even other body tissues. This opinion explains why the IL-6 level is high in both severe COVID-19 symptoms with mild OD and mild COVID-19 symptoms with severe OD.

Cazzolla *et al.* [13] reported a statistically significant correlation between the decrease of IL-6 levels and the improvement of smell. Therefore, the serum IL-6 level could be considered an adverse prognostic factor for OD and hence COVID-19 disease. In other words, it can be considered a biomarker for prediction of ongoing COVID-19 disease and/or OD. We recommend assessing the IL-6 level in patients with COVID-19, which could harbor a prognostic value.

In conclusion, the pathogenesis of COVID-19 and its severity, as well as the olfactory dysfunction [anosmia and hyposmia], might be related to cytokines such as IL-6. The level of IL-6 was directly proportionate to the severity of COVID-19 and the resulting olfactory dysfunction. Anosmia was associated with a higher level of IL-6 than hyposmia. IL-6 could be considered a prognostic factor for COVID-19 as well as olfactory dysfunction.

Limitations of the study

The case-control design could have exposed the results to recall, response, and/or personal bias. Besides the small number of patients representing another limiting step.

Declarations

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Authors' contributions: All authors contributed equally in this work.

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