

# Intersections between pneumonia, lowered oxygen saturation percentage and immune activation mediate depression, anxiety and chronic fatigue syndrome-like symptoms due to COVID-19: a nomothetic network approach

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## Abstract

**Background:** COVID-19 is associated with neuropsychiatric symptoms including increased depressive, anxiety and chronic fatigue-syndrome (CFS)-like physiosomatic (previously known as psychosomatic) symptoms.

**Aims:** To delineate the associations between affective and CFS-like symptoms in COVID-19 and chest CT-scan anomalies (CCTAs), oxygen saturation (SpO<sub>2</sub>), interleukin (IL)-6, IL-10, C-Reactive Protein (CRP), albumin, calcium, magnesium, soluble angiotensin converting enzyme (ACE2) and soluble advanced glycation products (sRAGEs).

**Method:** The above biomarkers were assessed in 60 COVID-19 patients and 30 healthy controls who had measurements of the Hamilton Depression (HDRS) and Anxiety (HAM-A) and the Fibromyalgia and Chronic Fatigue (FF) Rating Scales.

**Results:** Partial Least Squares-SEM analysis showed that reliable latent vectors could be extracted from a) key depressive and anxiety and physiosomatic symptoms (the physio-affective or PA-core), b) IL-6, IL-10, CRP, albumin, calcium, and sRAGEs (the immune response core); and c) different CCTAs (including ground glass opacities, consolidation, and crazy paving) and lowered SpO<sub>2</sub>% (lung lesions). PLS showed that 70.0% of the variance in the PA-core was explained by the regression on the immune response and lung lesions latent vectors. Moreover, one common “infection-immune-inflammatory (III) core” underpins pneumonia-associated CCTAs, lowered SpO<sub>2</sub> and immune activation, and this III

core explains 70% of the variance in the PA core, and a relevant part of the variance in melancholia, insomnia, and neurocognitive symptoms.

Discussion: Acute SARS-CoV-2 infection is accompanied by lung lesions and lowered SpO<sub>2</sub> which both may cause activated immune-inflammatory pathways, which mediate the effects of the former on the PA-core and other neuropsychiatric symptoms due to SARS-CoV-2 infection.

**Keywords:** COVID-19, depression, chronic fatigue syndrome, inflammation, neuro-immune, psychiatry.

## Introduction

SARS coronavirus 2 (SARS-CoV-2) affected more than 157 million people worldwide as of late November 2020, with more than 3.27 million deaths until May, 2021 (Coronavirus-Resource-Center, 2021). SARS-CoV-2 infection has a broad clinical scope, ranging from asymptomatic infection, mild sickness, moderate upper respiratory tract disease, to severe viral pneumonia with respiratory failure and even death (Krishnan et al., 2021; Montenegro et al., 2021; Zhou et al., 2020). Chest imaging, especially computed tomography scan (CT-scan), is critical for the diagnosis, management, and follow-up of COVID-19 infection (Fang Y, 2020; Zhang et al., 2020a). CT scan anomalies (CCTAs), including ground-glass opacities (GGOs), pulmonary densification areas consistent with residual lesions, pneumonic consolidation, and crazy-paving trends are observed in 78.3% of RT-PCR test-proven COVID-19 patients and are associated with lower peripheral oxygen saturation (SpO<sub>2</sub>) (Al-Hakeim et al., 2021).

SARS-CoV-2 may cause an exaggerated host immune response which may result in lung pathology (Huang et al., 2020; Hui and Zumla, 2019) and organ dysfunctions which are caused by direct virus-induced tissue injury, a systemic inflammatory response and the synergistic effects of both (Darif et al., 2021). The severe lung injury and pulmonary inflammation due to COVID-19 are accompanied by elevated levels of pro-inflammatory cytokines including interleukin-6 (IL-6) and chemokines (Liu et al., 2020a; Mehta et al., 2020). IL-6 is one of the cytokines which causes the acute phase response with increased levels of positive and negative acute phase proteins (including increased levels of C-reactive protein C (CRP) and lowered levels of albumin (Tanaka et al., 2014). SARS-CoV-2 also causes the release of T-helper (Th)-1 pro-inflammatory and Th-2 anti-inflammatory and T-regulatory cytokines, such as IL-10, which has protective properties against lung injury (Huang et al., 2020) (Lindner et al., 2021). COVID-19 and increased CCTAs are accompanied by increased serum IL-6, CRP, and IL-10, and lowered albumin and oxygen saturation percentage (SpO<sub>2</sub>) (Al-Hakeim et al., 2021). Moreover, we detected increased levels of sRAGE (soluble receptor for advanced glycation end-products) and angiotensin converting enzyme 2 (ACE2) in COVID-19 patients (Al-Hakeim et al., 2021). sRAGEs are generated through proteolysis of the extracellular domain of RAGE or through alternative RNA splicing (Sterenczak et al., 2009; Zhang et al., 2008). Binding of AGEs to membrane RAGEs initiates the transcription of pro-inflammatory transcription factors (Macaione et al., 2007; Tobon-Velasco et al., 2014) with consequent production of IL-6 and other inflammatory mediators (Wang and Liu, 2016). sACE2 is cleaved from membrane-associated ACE2 and is consequently released into the extracellular environment (Lambert et al., 2005). The COVID-19 virus may bind with high affinity to human cells via ACE2 receptors leading to endocytosis of the virus (Pouya et al., 2020; Vlachakis et al., 2020).

COVID-19 is frequently associated with mental health symptoms. Depression is present in 27% of the admitted COVID-19 patients, anxiety in 67%, and sleep disorders in 63% (Yadav et al., 2021).

Another study reported an increased prevalence of depression (29.2%) in patients who experienced COVID-19 infection (Zhang et al., 2020b). Anxiety levels in patients with COVID-19 are associated with severity of the condition and comorbidities (Yadav et al., 2021). The effects of COVID-19 on mood symptoms are often described as being the consequence of psychological effects. Thus, not only people with COVID-19 but also people who had contact with COVID-19 infected individuals show increased levels of depression and anxiety (Cao et al., 2020; Oxley et al., 2020; Wang et al., 2020). In addition, self-isolation during lockdowns is associated with an increased prevalence of depressive and anxiety symptoms and this was explained by feelings of isolation (Gualano et al., 2020; Xiao et al., 2020a, b). Patients with either major depression or bipolar disorder show increased psychological distress in response to these SARS-CoV-2-associated phenomena (Van Rheen et al., 2020). Xiang et al. (Xiang et al., 2020) reported that COVID-19 patients are more likely to experience neuropsychiatric syndromes because of the stigma associated with the illness and anxiety over the infection's effect. Kornilaki (2021) (Kornilaki, 2021) reported that increased levels of depression, negative affect and anxiety as a results of the COVID-19 symptoms or due to the quarantine state.

Nevertheless, there is now evidence that mood disorders including depression and anxiety have an organic substrate and are characterized by activated immune-inflammatory pathways (Maes et al., 1990; Maes and Carvalho, 2018) including increased levels of proinflammatory (e.g., IL-6) and anti-inflammatory (e.g., IL-10) cytokines, and an acute phase response as indicated by higher levels of CRP and lowered levels of albumin (Maes, 1993; Maes et al., 1993). There is also evidence that these neuro-immune pathways have detrimental effects on gray and white matter neuroplasticity, thereby inducing the biobehavioral changes characteristic of mood disorders (Leonard and Maes, 2012). Therefore, it is appropriate to posit that mood symptoms due to COVID-19 are mediated at least in part by neuro-immune pathways. People with COVID-19 also frequently suffer from mental fatigue, physical fatigue, mild loss of concentration, neurocognitive deficits, headache and myalgia (Borges do Nascimento et al., 2020; Liu et al., 2020b; Zhang et al., 2020c; Zhu et al., 2020), symptoms which are reminiscent of Myalgic Encephalomyelitis / chronic fatigue syndrome (ME/CFS) (Maes and Twisk, 2010). As with mood disorders, patients with ME/CFS show activated neuro-immune pathways with increased levels of pro- and anti-inflammatory cytokines, an acute phase response and multiple signs of nitro-oxidative damage (Bjørklund et al., 2020b; Morris and Maes, 2013). Nevertheless, no research has delineated the immune pathways of affective and ME/CFS-like symptoms in people with COVID-19.

Hence, the aim of the present study was to delineate the associations between affective and ME/CFS-like symptoms and a) CCTAs and SpO<sub>2</sub>, and b) IL-6, IL-10, CRP, albumin, calcium, magnesium, sACE2, and sRAGE in COVID-19. The specific hypothesis is that mood and ME/CFS-like symptoms in COVID-19 are significantly and positively associated with CCTAs, IL-6, IL-10, CRP, sACE2 and sRAGEs, and negatively with SpO<sub>2</sub>, albumin, calcium, and magnesium.

## Subjects and Methods

### Subjects

Between September and November 2020, sixty COVID-19 male patients aged 25 to 59 years were recruited at the Al-Sadr Teaching Hospital and Al-Amal Specialized Hospital for Communicable Diseases in Najaf governorate, Iraq. These hospitals are official quarantine facilities specializing in COVID-19 care in Iraq. All patients had acute respiratory syndrome (ARS) and were diagnosed with SARS-CoV-2 infection based on positive COVID-19 nucleic acid findings by reverse transcription real-time polymerase chain reaction (rRT-PCR), positive IgM, and ARS disease symptoms including

fever, breathing problems, cough, anosmia, and ageusia. The normal controls were males matched for age with the patients. We excluded controls and patients with pre-existing medical conditions, such as type 1 diabetes, and liver, kidney, and cardiovascular disease and cancer, and pre-existing neuro-psychiatric disease including dementia, Parkinson's disorder, multiple sclerosis, and axis-I psychiatric disorders including major depressive disorder, bipolar disorder, generalized anxiety disorder, and schizophrenia. The study was approved by the institutional ethics board of the University of Kufa (617/2020). Before taking part in this study, all participants and the guardians of COVID-19 patients gave written informed consent. The work was carried out in compliance with Iraqi and foreign ethics and privacy rules, as well as the World Medical Association Declaration of Helsinki, The Belmont Report, CIOMS Guideline, and International Conference on Harmonization of Good Clinical Practice, our IRB adheres to the International Guideline for Human Research Safety (ICH-GCP).

### *Clinical Measurements*

A senior psychiatrist assessed the 21-item Hamilton Depression Rating Scale (HDRS) score (Hamilton, 1960). We assessed the first 17 items to measure of severity of illness, while item 18 (diurnal variation) was used in composite scores (see below). Severity of anxiety symptoms was measured employing the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). In addition, three HDRS and two HAM-A subdomain scores were computed as explained previously (Almulla et al., 2021). The HDRS subdomain were a) the key depressive symptom domain (key HDRS), namely the sum of depressed mood + feelings of guilt + suicidal ideation (but without loss of work and activities); b) the physiosomatic symptom domain (physiosomatic HDRS), namely the sum of anxiety somatic + somatic symptoms, gastrointestinal + somatic symptoms, general + genital symptoms + hypochondriasis; and c) the melancholic symptom domain (melancholia HDRS), namely the sum of insomnia late + psychomotor retardation + diurnal variation + loss of weight. The HAM-A subdomain scores were a) the key anxiety symptom domain (key HAM-A), namely the sum of anxious mood + tension + fears + anxious behavior at interview; and b) the HAM-A physiosomatic symptom domain (physiosomatic HAM-A), namely the sum of somatic muscular + somatic sensory + cardiovascular symptoms + gastrointestinal symptoms + genitourinary symptoms + autonomic symptoms (but not the respiratory symptoms).

The same senior psychiatrist also assessed the Fibromyalgia and Chronic Fatigue Syndrome Rating (FF) scale (Zachrisson et al., 2002). This scale assesses 12 FF symptoms, namely FF1: muscle pain, FF2: muscular tension, FF3: fatigue, FF4: concentration difficulties, FF5: failing memory, FF6: irritability, FF7: sadness, FF8: sleep disturbances, FF9: autonomic disturbances, FF10: irritable bowel, FF11: headache, and FF12: a flu-like malaise. We used the total sum of all items as an index of overall severity of physio-somatic symptoms (Kanchanatawan et al., 2018). We also computed a purer physiosomatic FF score (physiosomatic FF) as the sum of FF1 + FF2 + FF3 + FF9 + FF10 + FF11 + FF12. Consequently, we computed the sum of all physiosomatic scores, namely z score of physiosomatic HDRS + z physiosomatic HAM-A + z physiosomatic FF. Moreover, we computed z composite scores reflecting cognitive impairments as: z HAM-A item 5 + z FF4 + z FF5. Finally, we also computed an insomnia z composite score as z HDRS items 4, 5 and 6 + z HAMA item 4 + z FF8. The diagnosis of tobacco use disorder (TUD) was made using the DSM-IV-RT criteria. Body mass index (BMI) was determined by dividing weight in kilograms by height in meters squared.

### *Measurements of biomarkers*

RT-PCR tests were conducted employing the Applied Biosystems® QuantStudio™ 5 Real-Time PCR System (Thermo Fisher Scientific) supplied by Life Technologies Holdings Pte Ltd.

(Marsiling Industrial Estate, Singapore) using the Lyra<sup>®</sup> Direct SARS-CoV-2 real-time RT-PCR Assay kits (Quidel Corporation, CA, USA). This kit offers a real-time RT-PCR assay for detecting human SARS-CoV-2 in viral RNA isolated from nasal, nasopharyngeal, or oropharyngeal swab specimens. The Assay is designed to detect the SARS-CoV-2 virus's non-structural Polyprotein (pp1ab). The procedures were carried out as stated in the kit's instruction manual.

Chest computed tomography anomalies (CCTAs) were measured using the SOMATOM Concept AS (Siemens, Munchen, Germany). We used the world standard nomenclature (Franquet, 2011; Hansell et al., 2008) to assess GGOs, regions of pulmonary densification associated with latent lesions, pneumonic consolidation, and crazy-paving trends (Kwee and Kwee, 2020)

After an overnight fast (at least 10 hours) and before having breakfast, we sampled blood between 7.30 and 9.00 a.m. Venous blood samples (5 mL) were taken and placed in sterile plain tubes. Samples that had been hemolyzed were rejected. The clotted blood samples were centrifuged for five minutes at 3000 rpm after ten minutes, and the serum was removed and transferred to three fresh Eppendorf tubes. IgG and IgM were measured in the sera of patients and controls using a qualitative ACON<sup>®</sup> COVID-19 IgG/IgM rapid screen. The kits have a 99.1% sensitivity and a 98.2% reliability. We only included patients with positive IgM tests. CRP was measured qualitatively and semi-quantitatively in human serum using a C-Reactive Protein (CRP) latex slide test (Spinreact<sup>®</sup>, Barcelona, Spain). We used Melsin Medical Co. (Jilin, China) ELISA kits to measure serum IL-6, IL-10, sRAGE, and sACE2. All analytes showed an inter-assay CV of < 12%. Biolabo<sup>®</sup>, Maizy, France, provided spectrophotometric kits to test total calcium, albumin, and magnesium.

### Statistical analysis

We used analysis of variance (ANOVA) to check whether there were differences in scale variables between diagnostic groups. The analysis of contingency tables (the  $\chi^2$ -test) was employed to check whether there were significant associations between nominal variables. To examine the associations between biomarkers and the clinical scores we used correlation matrices based on Pearson's product-moment correlation coefficients. To delineate the associations between diagnosis and biomarkers, we used univariate generalized linear model (GLM). Consequently, we conducted protected pairwise comparisons among treatment means. False discovery rate p-correction was used to correct for multiple comparisons (Benjamini and Hochberg, 1995). Multiple regression analysis was used to determine the most important biomarkers, which predict the rating scale scores, while allowing for the effects of demographic data (e.g. age and education). We used an automated stepwise method with a p-to-entry of 0.05 and a p-to-remove of 0.06. We checked  $R^2$  changes, multivariate normality (Cook's distance and leverage), homoscedasticity (with the White and modified Breusch-Pagan tests), and multicollinearity (using tolerance and variance inflation factor). All results of regression analyses were bootstrapped (5.000 samples) and the latter results are shown if the results are not concordant. All tests were two-tailed, and significance was set at  $p=0.05$ . All statistical analyses were performed using IBM SPSS windows version 25, 2017.

We used Smart Partial Least Squares (SmartPLS)-SEM path analysis (Ringle et al., 2012) to assess the multi-step multiple mediated paths between input variables (biomarkers and CCTAs) and the clinical rating scale scores. The latter was entered as a latent vector extracted from the different total and subdomain scores. Output variables that could not be combined in latent vectors were entered as single indicators. The primary input variables were entered (if possible) as one latent vector comprising CCTAs, GGOs, consolidation or other CCTAs, and SpO<sub>2</sub> (labelled as COVID-19 pneumonia). The biomarker data were considered to (partially) mediate the effects of COVID-19 pneumonia on the symptom domains. The input biomarker variables were (if possible) combined in



one latent vector reflecting immune activation (e.g. IL-6, CRP, IL-10, sRAGE, albumin, calcium) and the other biomarkers were entered as single indicators. The latent vectors were conceptualized as reflective models. We performed complete SmartPLS analysis using 5.000 bootstrap samples only when the inner/outer models complied with specific quality data: a) Confirmatory Tetrad analysis confirms that the latent vectors are not mis-specified as reflective models; b) the overall fit of the pathway model is adequate with SRMR < 0.08; c) the outer model latent vector loadings are > 0.666 at  $p < 0.001$ ; and d) the latent vectors show an accurate construct validity as indicated by an average variance extracted (AVE) > 0.5, Cronbach's alpha > 0.7, rho\_A > 0.8, and composite reliability > 0.7. Consequently, we conducted complete PLS path analysis on 5.000 bootstrap samples and computed path coefficients (with p value), outer model loadings, and specific indirect and total effects. We employed Blindfolding and PLSpredict with 10-fold cross-validation to check the predictive performance of the model (Shmueli et al., 2019). Predicted-Oriented Segmentation analysis, Multi-Group Analysis and Measurement Invariance Assessment were used to assess compositional invariance.

## Results

### *Socio-demographic and clinical data*

**Table 1** displays the socio-demographic data in the controls and two COVID-19 patient groups divided into those with normal to moderately reduced SpO<sub>2</sub> values ( $\geq 76\%$ ) and those with extremely low SpO<sub>2</sub> values ( $< 76\%$ ). Patients with SpO<sub>2</sub> < 76% are somewhat older than the other groups. No significant differences among these study groups were detected in BMI, education, residency, marital status, employment, and TUD. Patients with SpO<sub>2</sub> < 76% had higher total CCTAs, GGO, consolidation, crazy-paving and other chest abnormalities than COVID patients with SpO<sub>2</sub>  $\geq 76$ . The differences in CCTA, crazy-paving and other patterns remained significant after FDR p-correction (at  $p = 0.0133$ ). All COVID-19 patients were treated with vitamin C and D and this frequency was higher than in controls. More patients in the SpO<sub>2</sub> < 76% group were treated with dexamethasone than in the > 76% SpO<sub>2</sub> patient group. There were no significant differences in the treatment with Famotidine, Azithromycin, Meropenem, Heparin, and Clexane between both COVID-19 groups. All COVID-19 patients were on O<sub>2</sub> therapy and were receiving daily treatment with paracetamol and bromhexine.

### *Differences in biomarkers between COVID-19 subgroup and controls.*

Table 1 displays the measurements of the various biomarkers in the three study samples and shows substantial differences in all biomarkers, which remained significant after p-correction for FDR (at  $p = 0.0011$ ). There was a significant decrease in serum albumin, calcium, and magnesium in COVID-19 and increases in IL-6, CRP, IL-10, sRAGE, glucose and ACE2 as compared with normal controls. Moreover, serum IL-6, ACE2, albumin, magnesium, and calcium were significantly reduced in patients with SpO<sub>2</sub> < 76% as compared with patients with higher SpO<sub>2</sub> values.

### *Differences in clinical scores among the study groups.*

**Table 2** shows the measurements of the HDRS, HAM-A and FF total and subdomains scores in both COVID-19 subgroups and controls. All FF and HAM-A total and subdomain scores as well as the sum of all psychosomatic scores, and the cognitive and insomnia scores were significantly higher in COVID-19 patients than in controls. The total HDRS-17 and melancholia HDRS scores were significantly different between the three subgroups and increased from controls → COVID-19 with SpO<sub>2</sub>  $\geq 76\%$ . → COVID-19 with SpO<sub>2</sub> < 76%.

Table 1. Socio-demographic and clinical data of healthy controls (HC) and COVID-19 patients divided into those with SpO2 values  $\geq$  76% and with values  $<$  76%.

Variables	HC (n=30) <sup>A</sup>	COVID-19 with SpO2 $\geq$ 76% (n=33) <sup>B</sup>	COVID-19 with SpO2 $<$ 76% (n=27) <sup>C</sup>	F/FEPT/ $\chi^2$	df	p
Age (years)	47.1 $\pm$ 5.2 <sup>C</sup>	46.1 $\pm$ 9.3 <sup>C</sup>	51.6 $\pm$ 6.4 <sup>A,B</sup>	4.52	2/87	0.014
BMI (kg/m <sup>2</sup> )	28.13 $\pm$ 2.19	28.22 $\pm$ 5.45	28.22 $\pm$ 3.96	0.01	2/87	0.995
Education (years)	11.3 $\pm$ 4.5	11.9 $\pm$ 4.0	10.4 $\pm$ 2.90	1.05	2/85	0.355
Urban/Rural	27/3	10/23	7/20	4.05	2	0.132
Single/Married	2/28	5/28	1/26	FEPT	-	0.338
TUD No/Yes	10/20	10/23	11/16	0.74	2	0.690
SpO <sub>2</sub> (z scores)	1.034 $\pm$ 0.089 <sup>B,C</sup>	0.096 $\pm$ 0.494 <sup>A,C</sup>	-1.266 $\pm$ 0.453 <sup>A,B</sup>	245.98	2/87	$<$ 0.001
CCTA (%)	-	29.24 $\pm$ 25.19 <sup>C</sup>	44.07 $\pm$ 22.45 <sup>B</sup>	7.90	1/58	0.007
GGO (%)	-	17.42 $\pm$ 14.26	21.11 $\pm$ 10.32	3.88	1/58	0.054
Consolidation (%)	-	4.39 $\pm$ 7.04	6.67 $\pm$ 6.36	3.55	1/58	0.065
Crazy paving (%)	-	4.09 $\pm$ 4.91 <sup>C</sup>	7.96 $\pm$ 6.83 <sup>B</sup>	7.64	1/58	0.008
Other CT abnormalities (%)	-	3.33 $\pm$ 3.89 <sup>C</sup>	8.70 $\pm$ 7.42 <sup>B</sup>	12.18	1/58	0.001
IL-6 (z scores)	-0.875 $\pm$ 1.019 <sup>B,C</sup>	0.665 $\pm$ 0.765 <sup>A,C</sup>	0.160 $\pm$ 0.267 <sup>A,B</sup>	32.83	2/87	$<$ 0.001
CRP (z scores)	-0.840 $\pm$ 0.001 <sup>B,C</sup>	0.282 $\pm$ 1.060 <sup>A</sup>	0.588 $\pm$ 0.878 <sup>A</sup>	25.67	2/87	$<$ 0.001
IL-10 (z scores)	-1.056 $\pm$ 0.741 <sup>B,C</sup>	0.624 $\pm$ 0.629 <sup>A</sup>	0.411 $\pm$ 0.606 <sup>A</sup>	58.05	2/87	$<$ 0.001
sRAGE (z scores)	-1.106 $\pm$ 0.780 <sup>B,C</sup>	0.691 $\pm$ 0.602 <sup>A</sup>	0.0385 $\pm$ 0.359 <sup>A</sup>	75.41	2/87	$<$ 0.001
ACE2 (z scores)	-0.657 $\pm$ 0.959 <sup>B,C</sup>	0.628 $\pm$ 0.774 <sup>A,C</sup>	-0.038 $\pm$ 0.813 <sup>A,B</sup>	17.92	2/87	$<$ 0.001
Albumin (z scores)	0.897 $\pm$ 0.667 <sup>B,C</sup>	-0.199 $\pm$ 0.883 <sup>A,C</sup>	-0.754 $\pm$ 0.631 <sup>A,B</sup>	36.84	2/87	$<$ 0.001
Magnesium (z scores)	0.527 $\pm$ 0.959 <sup>B,C</sup>	0.010 $\pm$ 0.973 <sup>A,C</sup>	-0.598 $\pm$ 0.734 <sup>A,B</sup>	11.02	2/87	$<$ 0.001
Calcium (z scores)	1.054 $\pm$ 0.580 <sup>B,C</sup>	-0.301 $\pm$ 0.609 <sup>A,C</sup>	-0.803 $\pm$ 0.723 <sup>A,B</sup>	66.39	2/87	$<$ 0.001
Zinc (50mg/day) No/Yes	16/14	0/33	0/27	FEPT	-	$<$ 0.001
Vitamin D No/Yes	25/5	0/33	0/27	FEPT	-	$<$ 0.001
Vitamin C No/Yes	16/14	0/33	0/27	FEPT	-	$<$ 0.001
Dexamethasone No/Yes	-	8/25	1/26	FEPT	-	0.033
Famotidine No/Yes	-	10/23	13/14	2.00	1	0.157
Azithromycin No/Yes	-	11/22	14/13	2.10	1	0.148
Meropenem No/Yes	-	22/11	13/14	2.10	1	0.148
Heparin No/Yes	-	11/22	14/13	2.10	1	0.148
Clexane No/Yes	-	22/11	13/14	2.10	1	0.148
O2 therapy No/Yes	-	0/33	0/27	-	-	-

Bromhexin	No/Yes	-	0/33	0/27	-	-	-
Paracetamol	No/Yes	-	0/33	0/27	-	-	-

All results are shown as mean (SD); <sup>A, B, C</sup>: pairwise comparisons between group means; FEPT: Fisher’s exact probability test. BMI: body mass index, TUD: tobacco use disorder, CCTA: chest CT scan abnormalities, sRAGE: soluble receptor for advanced glycation end-products, sACE2: soluble angiotensin converting enzyme 2, GGO: ground-glass opacities, IL-6: interleukin (IL)-6, CRP: C-reactive protein, SpO2: oxygen saturation percentage.

**Table 2.** Measurements of affective and physiosomatic symptom scores in healthy controls (HC) and COVID-19 patients divided into those with SpO2 values  $\geq 76\%$  and with values  $< 76\%$ .

Variables	HC (n=30)	COVID-19 with SpO2 $\geq 76\%$ (n=33) <sup>B</sup>	COVID-19 with SpO2 $< 76\%$ (n=27) <sup>C</sup>	F/ $\chi^2$	df	p
Key HDRS	0.63 $\pm$ 0.67 <sup>B,C</sup>	2.94 $\pm$ 1.44 <sup>A</sup>	2.74 $\pm$ 1.16 <sup>A</sup>	37.71	2/87	<0.001
Physiosomatic HDRS	1.83 $\pm$ 0.91 <sup>B,C</sup>	4.52 $\pm$ 1.50 <sup>A</sup>	4.82 $\pm$ 1.62 <sup>A</sup>	42.32	2/87	<0.001
Melancholia HDRS	0.70 $\pm$ 0.84 <sup>B,C</sup>	2.24 $\pm$ 1.39 <sup>A,C</sup>	2.96 $\pm$ 1.43 <sup>A,B</sup>	24.88	2/87	<0.001
Total HDRS	5.17 $\pm$ 1.56 <sup>B,C</sup>	15.73 $\pm$ 2.97 <sup>A,C</sup>	17.63 $\pm$ 2.17 <sup>A,B</sup>	243.65	2/87	<0.001
Physiosomatic FF	2.77 $\pm$ 1.14 <sup>B,C</sup>	13.30 $\pm$ 4.10 <sup>A</sup>	13.59 $\pm$ 4.09 <sup>A</sup>	98.17	2/87	<0.001
Total FF	6.57 $\pm$ 1.61 <sup>B,C</sup>	22.55 $\pm$ 6.48 <sup>A</sup>	22.85 $\pm$ 5.59 <sup>A</sup>	101.32	2/87	<0.001
Key HAM-A	0.70 $\pm$ 0.75 <sup>B,C</sup>	4.09 $\pm$ 1.49 <sup>A</sup>	3.70 $\pm$ 1.35 <sup>A</sup>	67.57	2/87	<0.001
Physiosomatic HAM-A	0.40 $\pm$ 0.56 <sup>B,C</sup>	3.46 $\pm$ 1.89 <sup>A</sup>	3.41 $\pm$ 1.62 <sup>A</sup>	41.72	2/87	<0.001
Total HAM-A	2.47 $\pm$ 1.63 <sup>B,C</sup>	12.67 $\pm$ 3.41 <sup>A</sup>	12.74 $\pm$ 2.61 <sup>A</sup>	145.55	2/87	<0.001
All physiosomatic (z scores)	-1.24 $\pm$ 0.20 <sup>B,C</sup>	0.59 $\pm$ 0.55 <sup>A</sup>	0.66 $\pm$ 0.59 <sup>A</sup>	151.10	2/87	<0.001
Cognitive symptoms (z scores)	-0.48 $\pm$ 0.70 <sup>B,C</sup>	0.32 $\pm$ 1.23 <sup>A</sup>	0.15 $\pm$ 0.76 <sup>A</sup>	6.04	2/87	0.003
Insomnia symptoms (z scores)	-0.67 $\pm$ 0.70 <sup>B,C</sup>	0.22 $\pm$ 1.10 <sup>A</sup>	0.48 $\pm$ 0.75 <sup>A</sup>	13.76	2/87	<0.001

All results are shown as mean  $\pm$  SD; <sup>A, B, C</sup>: pairwise comparisons between group means; FF: Fibromyalgia and Chronic Fatigue Syndrome Rating Scale, HDRS: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale.



*Correlations between rating scale scores and biomarkers.*

**Table 3** shows the intercorrelation matrix between the total HDRS, FF, and HAM-A scores and CCTAs, SpO<sub>2</sub>, and the biomarkers in the total study group. The HDRS, FF and HAM-A scores showed positive significant associations with CCTAs, CRP, IL-6, IL-10, sRAGE, and ACE2, and inverse correlations with SpO<sub>2</sub>, albumin, magnesium and calcium.

*Prediction of the Hamilton Depression Rating Scale (HDRS) scores.*

The results of multiple regression of the HDRS total and subdomain scores on the measured biomarkers as dependent variables are presented in **Table 4**. Regression #1 shows that 72.6% of the variance in the total HDRS score could be explained by the regression on sRAGE and CCTA (all positively associated) and SpO<sub>2</sub> (inversely associated). Regression #2 shows that 65.7% of the variance in the total HDRS score could be explained by regression on sRAGE (positively) and calcium (negatively). A significant part of the variance in the key HDRS scores (39.5%) could be explained by the regression on the IL-6 (positively) and calcium (inversely). Regression #4 shows that 43.3% of the variance in the physiosomatic HDRS symptoms could be explained by the regression on CCTA and IL-10 (both positively). **Figure 1** shows the partial regression plot of the physiosomatic HDRS score on the CCTAs values after adjusting for IL-10. Furthermore, IL-10 and CRP explained 30.8% of the variance in the physiosomatic HDRS score (Regression #5). A significant part of the variance (36.2%) in the melancholia HDRS scores could be explained by the regression on calcium and SpO<sub>2</sub>.

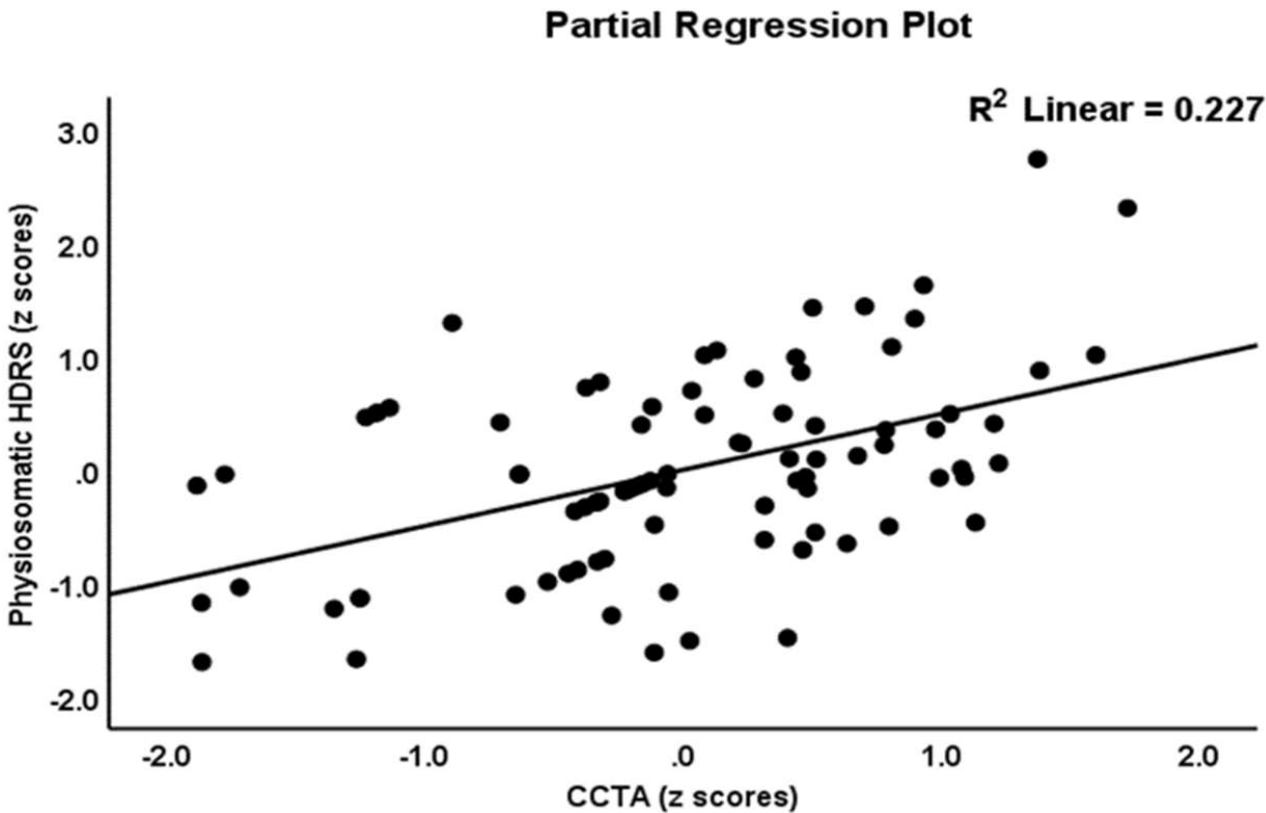


Figure 1. Partial regression of the physiosomatic component of the Hamilton-Depression-Rating-Scale (HDRS) score on the total chest CT scan anomalies (CCTAs).

**Table 3.** Intercorrelation matrix between affective and physiosomatic rating scale scores, Chest CT scan anomalies (CCTAs), blood oxygen saturation percentage (SpO2), and diverse biomarkers.

	Total HDRS	Total FF	Total HAM-A
Total HDRS	-	0.706*	0.737*
Total FF	0.706*	-	0.856*
Total HAM-A	0.737*	0.856*	-
CCTAs	0.668*	0.500*	0.594*
SpO2	-0.728*	-0.715*	-0.712*
Interleukin-6	0.480*	0.584*	0.587*
C-Reactive Protein	0.547*	0.555*	0.566*
Interleukin-10	0.532*	0.521*	0.594*
Soluble advanced glycation end-product receptor	0.527*	0.571*	0.607*
Soluble angiotensin converting enzyme 2	0.322*	0.445*	0.468*
Albumin	-0.561*	-0.554*	-0.562*
Magnesium	-0.457*	-0.401*	-0.444*
Calcium	-0.690*	-0.671*	-0.648*

FF: Fibromyalgia and Chronic Fatigue Syndrome Rating Scale, HDRS: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale.

\*All significant at  $p<0.001$  (n=90).

**Table 4.** Results of multiple regression analyses with the Hamilton Depression Rating Scale (HDRS), total and subdomain, scores as dependent variables and biomarkers as explanatory variables.

Dependent Variables	Explanatory Variables	$\beta$	t	p	F model	df	p	R <sup>2</sup>
#1. Total HDRS	Model				75.81	3/86	<0.001	0.726
	SpO2	-0.403	-5.03	<0.001				
	sRAGE	0.331	4.76	<0.001				
	CCTA	0.266	3.25	0.002				
#2. Total HDRS	Model				83.34	2/87	<0.001	.657
	Calcium	-0.518	-6.86	<0.001				
	sRAGE	0.398	5.27	<0.001				
#3. Key HDRS	Model				28.44	2/87	<0.001	.395
	Calcium	-0.446	-4.86	<0.001				
	IL-6	0.294	3.20	0.002				
#4. Physiosomatic HDRS	Model				33.15	2/87	<0.001	0.433
	CCTA	0.493	5.06	<0.001				
	IL-10	0.239	2.45	0.016				
#5. Physiosomatic HDRS	Model				19.34	2/87	<0.001	0.308
	IL-10	0.401	3.93	<0.001				
	CRP	0.235	2.30	0.024				
#6. Melancholia HDRS	Model				24.73	2/87	<0.001	0.362
	SpO2	-0.335	-2.80	0.006				
	Calcium	-0.318	-2.66	0.009				

sRAGE: soluble advanced glycation end-product receptor, sACE2: soluble angiotensin converting enzyme 2, IL-6: interleukin (IL)-6, CRP: C-reactive protein, CCTA: chest CT scan abnormalities, SpO2: oxygen saturation percentage.

### Prediction of the FF scale scores.

**Table 5** shows the results of multiple regression analyses with the FF total and subdomain scores as dependent variables and the biomarkers as explanatory variables. We found that 64.3% of the variance in the total FF score could be explained by the regression on IL-6 and sRAGE (both positively) and SpO<sub>2</sub> (negatively) (Regression #1). Regression #2 shows that 59.8% of the variance in the FF total score could be explained by the regression on the sRAGE, CRP, and IL-6 (all positively) and calcium (inversely). Regression #3 showed that 61.6% of the variance in the physiosomatic FF symptoms could be explained by the regression on IL-6 and sRAGE (both inversely) and SpO<sub>2</sub> (positively). **Figure 2** shows the partial regression plot of the physiosomatic FF score on SpO<sub>2</sub> after adjusting for IL-6 and sRAGE. Regression #4 showed that 56.3% of the physiosomatic FF symptoms could be explained by the regression on IL-6 and sRAGE (positively) and calcium (inversely). Regression #5 showed that 46.2% of the variance in the fatigue score could be explained by the regression on sRAGE (positively) and SpO<sub>2</sub> (inversely). Regression #6 showed that 47.0% of the variance in the fatigue score could be explained by the regression on CRP and sRAGE (positively) and calcium (negatively).

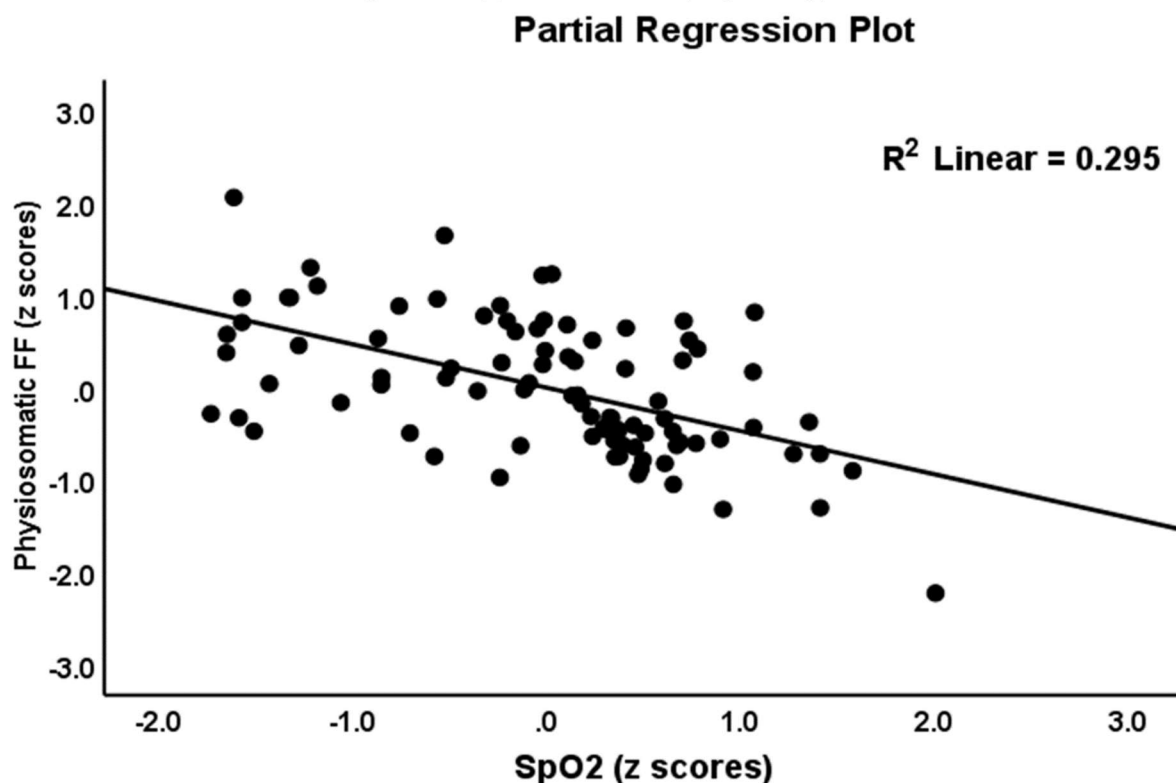


Figure 2. Partial regression of the pure physiosomatic component of the Fibromyalgia and Chronic Fatigue Rating Scale (FF) score on oxygen saturation percentage (SpO<sub>2</sub>)

### Prediction of the HAM-A score.

**Table 6** shows the results of multiple regressions of the HAM-A total and subdomain scores on the biomarker levels while allowing for the effects of demographic data. Regression #1 shows that 68.0% of the variance in the total HAM-A score could be explained by the regression on sRAGE and GGO (both positively), and SpO<sub>2</sub> and calcium (both inversely). **Figure 3** shows the partial regression of the total HAM-A on sRAGE levels. The combination of sRAGE (positively) and calcium (negatively) explained 62.1% of the variance in the total HAM-A score (Regression #2). sRAGE and

GGO explained 48.9% of the variance in the key HAM-A scores (Regression #3) and sRAGE and calcium explained 43.7% of the variance in the key HAM-A scores (regression #4). Regression #5 shows that sRAGE and GGO (both positively) and calcium (negatively) explained 41.9% of the variance in the physiosomatic HAM-A score. In regression #6 we found that 38.3% of the variance of the physiosomatic HAM-A scores could be explained by sRAGE (positively) and calcium (negatively). Finally, we also examined the regression of the sum of all physiosomatic symptoms on the biomarkers and found that sRAGE and GGO (positively) and SpO2 (inversely) explained 62.9% of its variance.

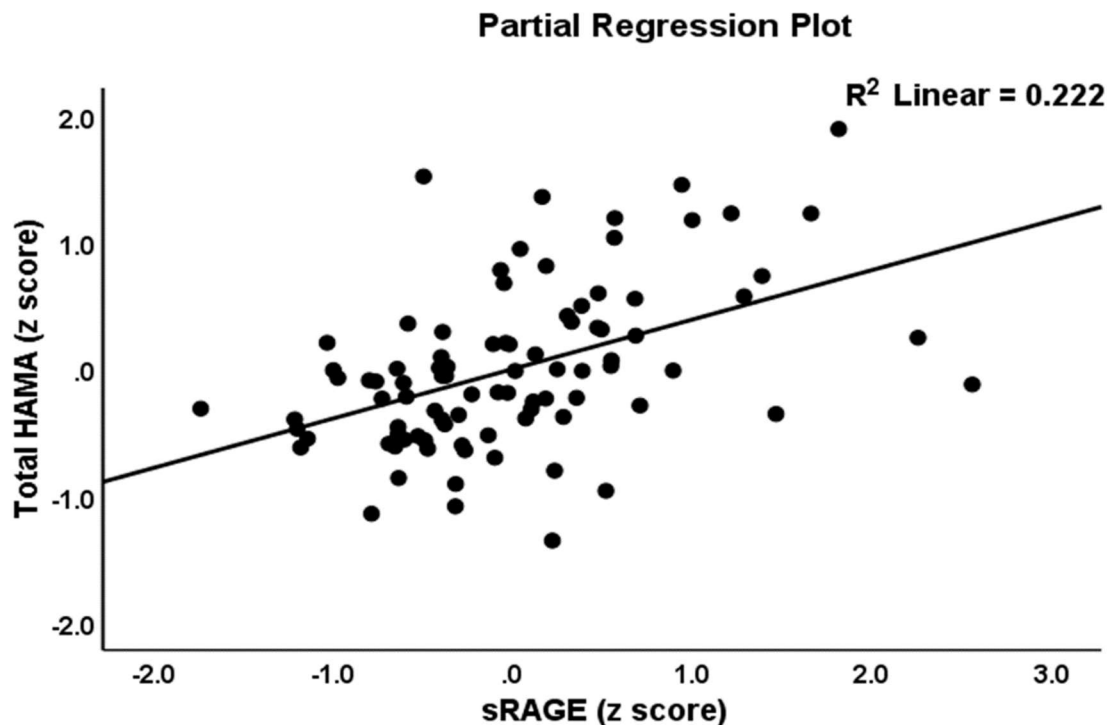


Figure 3. Partial regression of the total Hamilton Anxiety Rating Scale (HAMA) on levels of soluble receptor for advanced glycation products (sRAGE).



**Table 5.** Results of multiple regression analysis with the Fibromyalgia and Chronic Fatigue Rating Scale (FF), total and subdomain, scores as dependent variables and chest CT scan anomalies (CCTAs), oxygen saturation percentage (SpO2), and biomarkers as explanatory variables.

Dependent Variables	Explanatory Variables	$\beta$	t	p	F model	df	p	R <sup>2</sup>
#1. Total FF	Model				51.64	3/86	<0.001	0.643
	SpO2	-0.478	-6.32	<0.001				
	sRAGE	0.271	2.99	0.004				
	IL-6	0.223	2.66	0.009				
#2. Total FF	Model				31.60	4/85	<0.001	0.598
	sRAGE	0.273	2.75	0.007				
	Calcium	-0.341	-3.41	0.001				
	CRP	0.189	2.17	0.033				
	IL-6	0.192	2.12	0.037				
#3. Physiosomatic FF	Model				45.933	3/86	<0.001	0.616
	SpO2	-0.470	-6.00	0.000				
	IL-6	0.246	2.83	0.006				
	sRAGE	.237	2.52	0.014				
#4. Physiosomatic FF	Model				37.00	3/86	<0.001	0.563
	Calcium	-.399	-4.63	0.000				
	sRAGE	.263	2.60	0.011				
	IL-6	.240	2.58	0.011				
#5. Fatigue	Model				37.33	2/87	<0.001	0.462
	sRAGE	.451	4.91	<0.001				
	SpO2	-.352	-3.54	0.001				
#6. Fatigue	Model				25.41	3/86	<0.001	0.470
	sRAGE	.401	4.07	<0.001				
	CRP	.207	2.10	0.039				
	Calcium	-.207	-2.02	0.046				

sRAGE: soluble advanced glycation end-product receptor, sACE2: soluble angiotensin converting enzyme 2, IL-6: interleukin (IL)-6, CRP: C-reactive protein.

**Table 6.** Results of multiple regression analysis with the Hamilton Anxiety Rating Scale (HAM-A), total and subdomain, scores as dependent variables and chest CT scan anomalies (CCTAs), oxygen saturation percentage (SpO<sub>2</sub>), and biomarkers as explanatory variables.

Dependent Variables	Explanatory Variables	β	t	p	F model	df	p	R <sup>2</sup>
#1. Total HAM-A	Model				45.15	4/85	<0.001	0.680
	sRAGE	0.391	4.93	<0.001				
	SpO <sub>2</sub>	-0.220	-2.35	0.021				
	GGO	0.192	2.23	0.029				
	Calcium	-0.186	-2.03	0.046				
#2. Total HAM-A	Model				71.18	2/87	<0.001	0.621
	sRAGE	0.499	6.28	<0.001				
	Calcium	-0.392	-4.93	<0.001				
#3. Key HAM-A	Model				41.61	2/87	<0.001	0.489
	sRAGE	0.433	4.66	<0.001				
	GGO	0.356	3.82	<0.001				
#4. Key HAM-A	Model				33.77	2/87	<0.001	0.437
	sRAGE	0.511	5.28	<0.001				
	Calcium	-0.222	-2.29	0.024				
#5. Physiosomatic HAM-A	Model				20.67	3/86	<0.001	0.419
	sRAGE	0.301	2.85	0.006				
	GGO	0.249	2.29	0.024				
	Calcium	-0.215	-1.99	0.050				
#6. Physiosomatic HAM-A	Model				27.06	2/87	<0.001	0.383
	sRAGE	0.388	3.83	<0.001				
	Calcium	-0.312	-3.08	0.003				
#7. Sum all physiosomatic symptoms	Model				48.69	3/86	<0.001	0.629
	GGO	0.301	3.32	0.001				
	sRAGE	0.335	4.06	<0.001				
	SpO <sub>2</sub>	-0.303	-3.47	0.001				

GGO: ground glass opacities, sRAGE: soluble advanced glycation end-product receptor, sACE2: soluble angiotensin converting enzyme 2, IL-6: interleukin (IL)-6, CRP: C-reactive protein.

### *Results of PLS analyses*

**Figure 4** shows a first PLS model conducted on 5.000 bootstrap samples. Melancholia, cognitive symptoms and insomnia could not be included in the same latent vector (due to low loadings) and, therefore, were entered as single indicators. One latent vector could be extracted from the key HDRS and HAM-A scores and the three psychosomatic domains as well (labeled physio-affective or PA-core). We were also able to combine all biomarkers into one latent vector (labeled as immune response), except sACE2 and magnesium which were entered as single indicators. We were able to extract one latent vector from CCTAs, crazy paving, consolidation, GGO, and other CCTAs, SpO<sub>2</sub>, and infection (a positive PCR test and IgM antibodies), labeled COVID-19 pneumonia. The construct reliabilities of the three latent vectors are good with AVE > 0.655, Cronbach  $\alpha$  > 0.881, rho A > 0.873, and composite reliability > 0.904. The outer model loadings on the three latent vectors were > 0.721 at  $p < 0.0001$ . The model fit was good with SRMR=0.050. CTA showed that the outer models were not mis-specified as reflective models. The construct cross-validated redundancies of the immune response (0.387) and PA-core (0.449) latent vectors were more than adequate. Full compositional invariance was obtained as indicated by the results of Prediction-Oriented Segmentation analysis, Measurement Invariance Assessment and Multi-Group Analysis. The  $Q^2$  Predict values of all construct indicators were positive which suggests that they outperform the most naïve benchmark. We found that 70.0% of the variance in the PA-core was explained by the regression on the immune response and pneumonia latent vectors. We found that the immune response explained 29.2% of the variance in melancholia and 9.7% of the variance in cognitive symptoms. Moreover, 28.7% of the variance in insomnia was explained by pneumonia and BMI (both positively associated). A large part the variance in the immune response (62.0%) was explained by the pneumonia latent vector. There were significant specific indirect effects of the latter on the PA-core ( $t=4.74$ ,  $p < 0.001$ ), melancholia ( $t=7.50$ ,  $p < 0.001$ ), cognitive symptoms ( $t=3.89$ ,  $p < 0.001$ ), magnesium ( $t=4.50$ ,  $p < 0.001$ ) and ACE2 ( $t=7.87$ ,  $p < 0.001$ ), which were all mediated by the immune response latent vector.

**Figure 5** shows a second PLS path analysis in which we have combined the immune response and pneumonia indicators into one latent vector named the infection-immune-inflammatory (III) core. The model fit (SRMR=0.051) was adequate and the construct reliability was adequate with AVE = 0.613, Cronbach  $\alpha$  = 0.947, rho A > 0.954, and composite reliability > 0.953 and all III core loadings were all > 0.701 (except IL-6) at  $p < 0.0001$ . This vector was not mis-specified as a reflective model. We found that this III core predicted the PA-core and other single indicator symptoms as well.

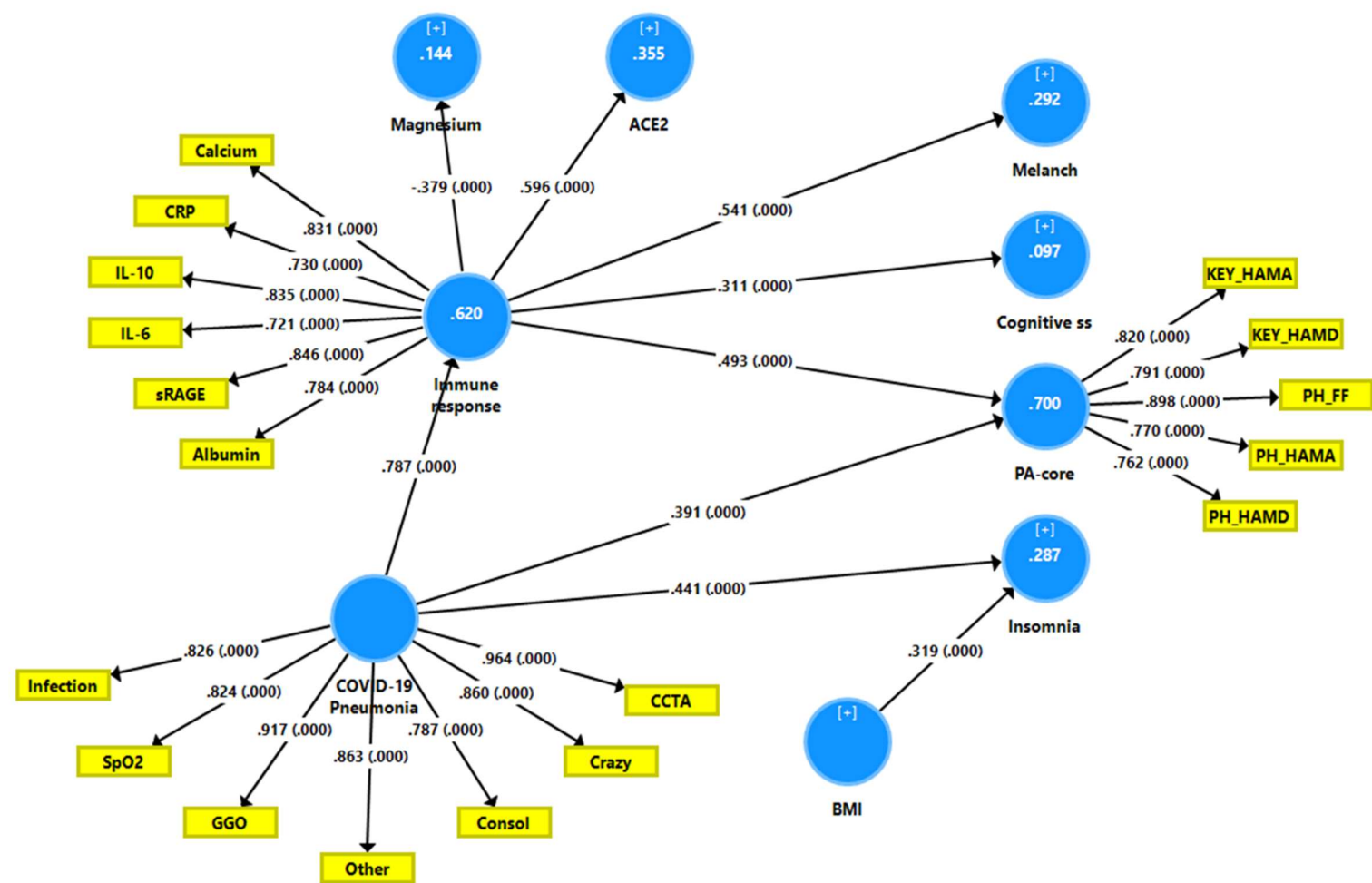


Figure 4. Results of Partial Least Squares (PLS)-SEM analysis with the PA-core (the physio-affective core), melancholic and cognitive symptoms and insomnia as output variables. The pathology of COVID-19 including chest CT scan anomalies (CCTAs), ground glass opacities (GGOs), crazy paving (crazy), consolidation (consol), other CCTAs (other) and lowered oxygen saturation (SpO2) as input variables. The immune response as indicated by a latent vector extracted from calcium, CRP (C-reactive protein), IL-10 (interleukin-10), IL-6, sRAGEs (soluble receptor for advanced glycation end products) and albumin (partially) mediates the effects of COVID-19 on neuropsychiatric symptoms. Lowered magnesium and increased angiotensin converting enzyme 2 (ACE2) are spin-offs of the immune response. Figures in the circles indicate explained variance. Shown are path coefficients or latent vector loadings with accompanying p-values.

KEY\_HAMA: key anxiety symptoms of the Hamilton Anxiety Rating Scale.  
KEY\_HAMD: key depressive symptoms of the Hamilton Depression Rating Scale.  
PH-HAMA/PH-HAMD: physiosomatic symptoms of HAMA/HAMD, respectively.  
PH\_FF: physiosomatic symptoms of the Fibromyalgia and Chronic Fatigue Rating Scale (FF).

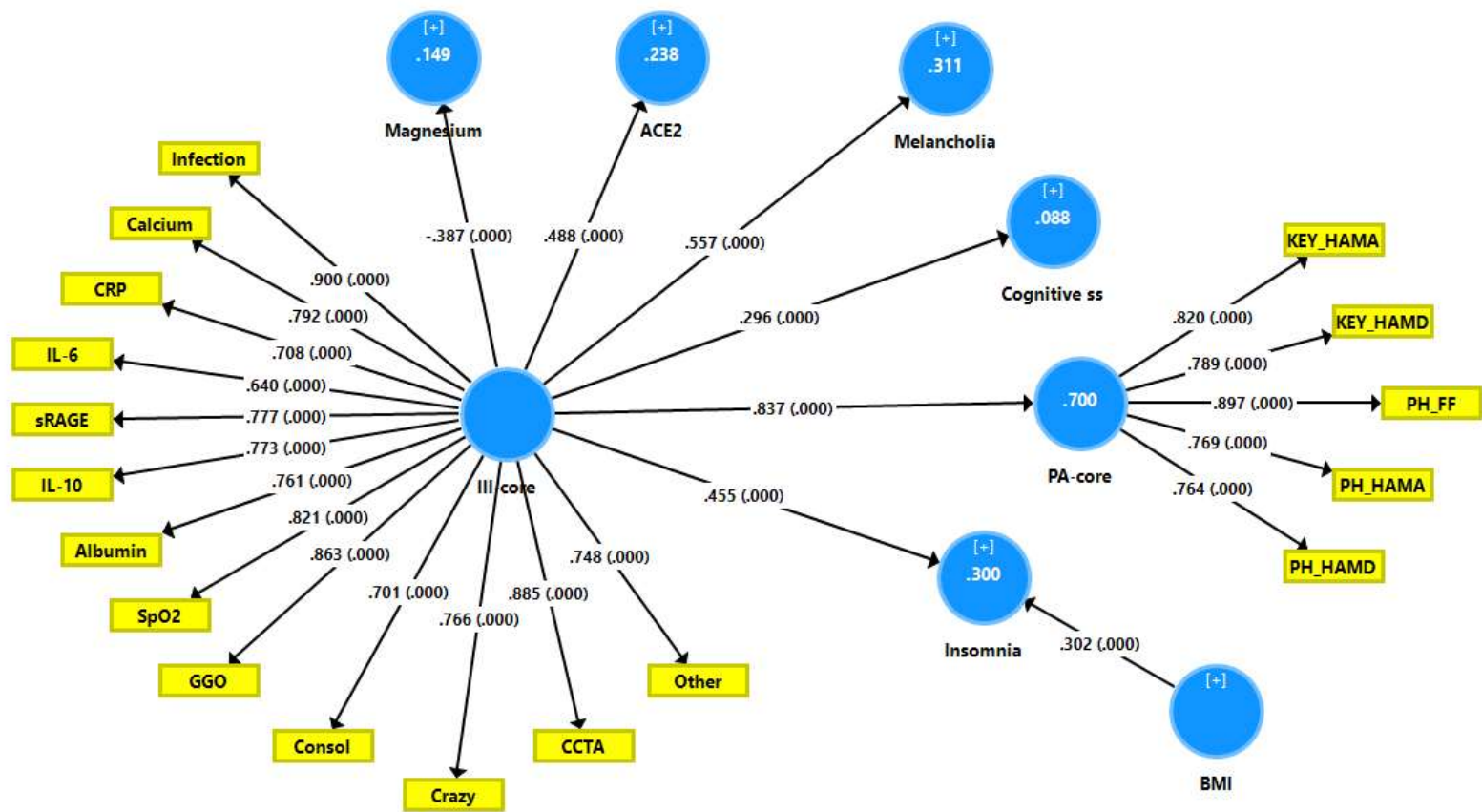


Figure 5. Results of Partial Least Squares (PLS)-SEM analysis with the PA-core (the physio-affective core), melancholic and cognitive symptoms and insomnia as output variables. Input variable is a latent vector named the infection-immune-inflammatory (III) core extracted from chest CT scan anomalies (CCTAs), ground glass opacities (GGOs), crazy paving (crazy), consolidation (consol), other CCTAs (other), lowered oxygen saturation (SpO2), calcium, CRP (C-reactive protein), IL-10 (interleukin-10), IL-6, sRAGEs (soluble receptor for advanced glycation end



products) and albumin (partially). Lowered magnesium and increased angiotensin converting enzyme 2 (ACE2) are spin-offs of this III core but are not associated with neuro-psychiatric symptoms.

Figures in the circles indicate explained variance. Shown are path coefficients or latent vector loadings with accompanying p-values.

KEY\_HAMA: key anxiety symptoms of the Hamilton Anxiety Rating Scale.

KEY\_HAMD: key depressive symptoms of the Hamilton Depression Rating Scale.

PH-HAMA/PH-HAMD: physiosomatic symptoms of HAMA/HAMD, respectively.

PH\_FF: physiosomatic symptoms of the Fibromyalgia and Chronic Fatigue Rating Scale (FF).

## Discussion

### *COVID-19, affective and physiosomatic symptoms*

A first major finding of this study is that COVID-19 is associated with increased levels of affective (including key depression and anxiety and melancholia) and physiosomatic FF symptoms as well as cognitive symptoms and insomnia. Because we have excluded patients with primary major depression, bipolar disorders and anxiety disorders, this association can best be described as depression, anxiety and physiosomatic (or ME/CFS-like) symptoms due to COVID-19. These findings extend the reports mentioned in our Introduction depicting the appearance of those symptoms in people with COVID-19. Depression was shown to be present in 8.3% to 48.3% of COVID-19 patients (Gao et al., 2020; Huang and Zhao, 2020; Ozamiz-Etxebarria et al., 2020). Other studies also reported increased levels of depression, distress, fear, sleep disorders, and suicidality in patients with COVID-19 (Luo et al., 2020; Qiu et al., 2020). Patients who are infected (or suspected of being infected) with COVID-19 can experience extreme emotional and behavioral reactions such as terror, boredom, isolation, anxiety, insomnia, or frustration (Shigemura et al., 2020). In COVID-19 patients, increased levels of fatigue are observed with a prevalence between 17.5% (Simani et al., 2021) and 53.6% (Qi et al., 2020). Chronic fatigue is also a key symptoms of the long (late) COVID-19 syndrome (Islam et al., 2020) (Décary et al., 2021).

Nevertheless, our study shows that in the acute phase of COVID-19, the appearance of affective (including key depressive and key anxiety symptoms) and physiosomatic FF symptoms is strongly interrelated and that this symptomatic response to COVID-19 is additionally characterized by the appearance of melancholia, cognitive symptoms, and insomnia. Furthermore, it appears that the key depressive, key anxiety and physiosomatic FF symptoms belong to a same underlying core and, therefore, that these symptoms are reflective manifestations of the same underlying phenomenon, which can best be described as the “physio-affective core”. It is interesting to note that such a core was also established in schizophrenia, major depression, ME/CFS, and somatoform disorder (Anderson and Maes, 2014; Kanchanatawan et al., 2019; Maes et al., 2021). On the other hand, melancholia, insomnia and cognitive symptoms do not belong to this common physio-affective core.

As described in the Introduction, the correlations between COVID-19 and affective and physiosomatic symptoms are often conceptualized as a consequence of psychological effects including the stigma that is associated with the infection, anxiety about possible adverse effects of the infection, the social isolation and reduction in social experiences, and the unemployment linked with quarantine or lockdown (Benke et al., 2020; Brooks et al., 2020; Kornilaki, 2021; Xiang et al., 2020). Nevertheless, as we will discuss in the following section, the physio-affective core, melancholic and cognitive symptoms, and insomnia are the consequence of infection, pneumonia, and the immune response in COVID-19.

### *Effects of pneumonia on affective and physiosomatic symptoms.*

The second major finding of this study is that the different CCTAs and lowered SpO<sub>2</sub>% were significantly associated with the appearance of the physio-affective core as well as with melancholia, cognitive symptoms and insomnia. Many (up to 70%) RT-PCR test positive COVID-19 patients show CCTAs (Adams et al., 2020), which indicate lung inflammation, bronchiolitis, pneumonia and lung fibrosis (Sadhukhan et al., 2020). In our study, the presence of CCTAs is strongly associated with lowered SpO<sub>2</sub> indicating that pneumonia and lung lesions may cause decreased peripheral oxygen saturation, which is often decreased in COVID-19 patients and especially in those with more severe

illness (Dai et al., 2020; Luks and Swenson, 2020). Silent hypoxia is one of the key symptoms of COVID-19, albeit it is not always the first symptom (Bouttell et al., 2020). In a recent study, the abnormalities in lung radiography such as presence of bilateral opacities, multifocal opacities, or any upper or middle zone opacity were associated with supplemental oxygen requirement (Ong et al., 2021).

There is some evidence that bronchitis and pneumonia are associated with major depressive symptoms (Adams et al., 2008; Seminog and Goldacre, 2013). In addition, patients with comorbid pneumonia and depression show a poorer treatment outcome as compared with patients without depression (Kao et al., 2014). On the other hand, depression is also a risk factor of hospitalization due to pneumonia (Davydow et al., 2014). According to the American Lung Association, low energy, fatigue, gastro-intestinal symptoms, neurocognitive impairments, and loss of appetite are typical symptoms of pneumonia (Niederman et al., 1993). Low blood oxygen levels or hypoxemia is also associated with depression and fatigue (Zhao et al., 2017).

*The effects of pneumonia are partly mediated by immune activation.*

The third major finding of this study is that the effects of pneumonia and lowered SpO<sub>2</sub> on the physio-affective core are partially mediated by the immune response and that pneumonia has also direct effects on this common core, suggesting that another process not mediated by immune activation may be involved. Furthermore, the effects of pneumonia on cognition and melancholia are completely mediated by immune activation. In the present study, the immune response was conceptualized as a common core underpinning the plasma levels of IL-6, IL-10, CRP, sRAGE (all increased), albumin and calcium (both decreased). Our results indicate that the acute phase and immune responses in COVID-19 are strongly associated with the physio-affective core. There is now evidence that affective disorders and ME/CFS are accompanied by an immune response (Bjørklund et al., 2020a; Gerwyn and Maes, 2017; Morris and Maes, 2013) and that the latter and its consequences may mechanistically explain symptoms of the physio-affective core and cognitive impairments (Kanchanatawan et al., 2019; Leonard and Maes, 2012; Morris and Maes, 2013). Interestingly, plasma levels of IL-6 and IL-10 in the acute phase of a virus infection have been shown to predict the progression of chronic fatigue (Russell et al., 2019).

In our study, lowered calcium is another component of the immune response latent vector in COVID-19 that is associated with the physio-affective core. Lowered calcium levels are frequently detected in COVID-19 with non-severe and severe illness (Di Filippo et al., 2021; Pal et al., 2020) and are often associated with severity of illness (Sun et al., 2020; Yang et al., 2021). Moreover, very low calcium values are associated with the severity of ARS (Sun et al., 2020) and the inflammatory response (Di Filippo et al., 2021; Di Filippo et al., 2020). Lowered calcium levels may be found during viral infections because albumin, which is lowered during the acute phase response, binds calcium and because viruses may utilize Ca<sup>2+</sup> signals (Deng et al., 2012; Nieto-Torres et al., 2015; Zhou et al., 2009). Lowered calcium is frequently observed in patients with affective disorders and is associated with severity of depressive and psychosomatic symptoms (Al-Dujaili et al., 2019). Hypocalcemia is accompanied by a variety of psychosomatic symptoms including muscle tension, pain and cramps, cognitive impairments, and cardiovascular and respiratory symptoms (Bove-Fenderson and Mannstadt, 2018). Although magnesium is partly bound to albumin and is decreased in our COVID-19 patients, especially in those with extremely low SpO<sub>2</sub> values, no associations with the physio-affective core or any other symptoms could be found after considering the role of the immune response. Nevertheless, magnesium deficiency may be accompanied by fatigue, lethargy, weakness, loss of appetite, numbness, muscle cramps, fibromyalgia-like symptoms, depression, and irritability (Ismail et al., 2018).

As described in the Introduction, binding of AGEs to the RAGEs on membranes initiates an immune-inflammatory response with elevated production of IL-6 and other cytokines (Macaione et al., 2007; Tobon-Velasco et al., 2014; Wang and Liu, 2016) and this response mediates not only inflammation, but also cell proliferation, migration, apoptosis, and microtubule stabilization (Xie et al., 2013) and this explains that the RAGE pathway is essential in COVID-19 progression (Yalcin Kehribar et al., 2021). The increased levels of sRAGEs in COVID-19 may be explained by proteolysis of the extracellular domain of RAGE (Sterenczak et al., 2009; Zhang et al., 2008), suggesting that increased sRAGE plasma levels in COVID-19 may reflect increased expression of membrane RAGEs. Interestingly, sRAGEs have anti-inflammatory properties by attenuating the binding to membrane RAGE (Oczypok et al., 2017; Sternberg et al., 2008; Yang et al., 2014). In major depression and bipolar disorder, sRAGE levels were significantly lower as compared with controls (Emanuele et al., 2011), suggesting that lowered levels could contribute to the immune response in mood disorders. As such, the increased sRAGE levels in our study are probably an indicant of the immune response in COVID-19, rather than mediating the effects of pneumonia on the physio-affective core. Hypoxia may upregulate ACE2 gene expression and protein levels in lung and kidney which may contribute to the severity of COVID-19 (Shenoy et al., 2020). Nevertheless, the increased ACE2 levels established in our study were not associated with any affective or physiosomatic scores after considering the role of the immune response.

Importantly, our PLS analysis showed that one common “infection-immune-inflammatory core” underpins pneumonia-associated lung lesions, lowered SpO<sub>2</sub> and immune activation, and that this core explains 70% of the variance in the physio-somatic core, and a relevant part of the variance in melancholia (31.1%), insomnia (30% when shared with BMI) and neurocognitive impairments (8.8%). As such, we may conclude that acute SARS-CoV-2 infection is often accompanied by lung lesions and lowered SpO<sub>2</sub> which both are known to induce immune-inflammatory pathways (Sadhukhan et al., 2020) and that the increased incidence of neuro-psychiatric symptoms in COVID-19 should be attributed at least in part to the infection-immune-inflammatory core of COVID-19. Moreover, SARS-CoV-2 can infect the brain, causing neuroinflammation (Pan et al., 2020) and this is believed to be another source of neuropsychiatric symptoms including chronic fatigue after recovery (Mandal et al., 2021).

### *Limitations.*

The results of the current study should be interpreted with regard to the limitations. First, this is a case-control study and, therefore, no firm causal relationships may be established. Second, it would have been even more interesting if we had assayed a set of neurotoxic immune biomarkers which are known to cause affective symptoms, including TNF- $\alpha$  and IL-1 signaling biomarkers, some chemokines, and oxidative stress biomarkers.

### *Conclusions.*

In COVID-19, one common core underpins lung lesions, lowered SpO<sub>2</sub>, and immune activation as indicated by increased plasma IL-6, IL-10, CRP, and sRAGE, and lowered albumin and calcium levels. This common “infection-immune-inflammatory core” explains a larger part of the variance in the physio-affective core, melancholic symptoms, insomnia, and neurocognitive complaints. Activated immune-inflammatory pathways mediate the effects of SARS-CoV-2 infection and pneumonia on the neuropsychiatric symptoms established in COVID-19.

## Acknowledgements

The authors thank the staff of the CCU unit and the internal medicine clinic in Al-Sadr Teaching Hospital-Najaf City-Iraq for their help in the collection of samples. Also, we acknowledge the highly skilled work of the staff of Asia Laboratory in measuring the biomarkers.

## Declaration of interest

The authors have no financial conflict of interests.

## Funding

There was no specific funding for this specific study.

## Authorships.

All authors contributed significantly to the paper and approved the final version.

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