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The Interplay of NLRP3, Gasdermin-D, and C-Reactive Protein in Predicting Depression in Long-COVID

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ABSTRACT

Patients with COVID-19 are at risk for long-COVID (LC) symptoms after recovery. LC is associated with neuropsychiatric disorders and inflammatory symptoms. Depression is an important symptom that affects the everyday life of patients. In the present study, we recruited the leucine-rich-containing family, pyrin domain-containing-3 (NLRP3), Gasdermin-D (GSDMD), and C-reactive protein as tools for prediction of depression in LC patients. Leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome overactivation brought on by severe acute respiratory syndrome in certain instances, cytokine storm is also caused by coronavirus 2 (SARS-CoV-2). Gasdermin-D (GSDMD) is cleaved by caspase-1 upon caspase-1 activation, which causes pyroptosis, an anticipated cell death. Patients with COVID-19 also have elevated levels of CRP, another biomarker. In patients with COVID-19, elevated CRP levels have been linked to higher mortality, inflammatory alterations in chest CT scans, and severe infection. A vital initial line of defense against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is innate immunity one However, dysregulated innate immune responses can be harmful, leading to an overabundance of proinflammatory cytokines that worsen tissue damage. As an intravascular effector of innate immunity, immunothrombosis refers to complicated networks of molecular pathways and cellular interactions functioning to restrict the survival and spread of pathogens. When pro-inflammatory cytokines like interleukin-6 (IL-6) are stimulated, the liver is the primary source of the acute-phase protein known as C-reactive protein (CRP). It is a proven biomarker for tracking COVID-19 patients' rates of inflammation. By attaching itself to pathogen surfaces and injured cells, CRP plays a crucial part in triggering the innate immune response. Serum levels of NLRP3, GSDMD, were measured using the ELISA technique. Depression symptoms were estimated using the Hamilton depression (HAMD). Results indicate a substantial rise ($p<0.001$) in median CRP levels in LC+Dep and LC groups compared to the control group. Serum NLRP3 levels were considerably higher ($p<0.001$) in the LC+Dep group compared to LC patients and the control group. The LC+Dep and LC groups had considerably greater GSDMD levels ($p<0.001$) than the control group, which had the lowest value. The partial correlation study among the study groups after controlling for age, weight, height, BMI, and smoking in LC patients showed significant correlation between total HAMD score and CRP, GSDRMD, and NLRP3. GSDMD has the best diagnostic ability for depression in LC patients at a cut-off value of 60.98 pg/ml indicating that the subjects may predict depression in LC patients with a significant sensitivity (69.8%) and specificity (69.9%). The present study revealed the importance of inflammation and NLRPs and GSDMD in the pathophysiology of the LC symptoms. DSDRMD is the best predictor for depression in LC patients.

Keywords: Long COVID, Pyroptosis, Inflammation, Depression, Thrombosis

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I. INTRODUCTION

In March of 2020, the World Health Organization identified the new coronavirus, commonly known as SARS-CoV-2, that causes COVID-19 to be a pandemic.[1] The most recent outbreak of corona virus disease 2019 (currently known as COVID-19) has raised concerns about the potential health risks to humans, this virus has the potential to cause severe respiratory disease in humans. It emerged from Wuhan, the provincial capital of Hubei, China, on December 29, 2019.[2] A vital initial line of defense against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is innate immunity [3]. Dysregulated innate immune responses can be harmful, leading to an overabundance of proinflammatory cytokines that worsen tissue damage. [4] SARS-CoV-2 infection promotes the overproduction of inflammatory cytokines with a range of biological functions; these cytokines encourage positive feedback on inflammatory areas and draw immune cells to them. This "cytokine storm" is a potentially lethal systemic inflammatory disorder that is typified by elevated levels of circulating cytokines and immune cell hyperactivity. These factors may cause coagulopathy or thrombosis associated with COVID-19.[5, 6] People with a history of suspected or confirmed SARS-CoV-2 infection are susceptible to long-COVID (LC).[7] It is distinguished by symptoms that don't go away with another diagnosis and last for at least two months. Common symptoms include fatigue, dyspnea, cognitive impairment, and others frequently interfere with day-to-day functioning [8]. The symptoms may persist from the first illness, appear after the initial recovery following an acute episode of COVID-19, or be new. Additionally, symptoms may alter or recur over time. [7, 9] The most frequently reported symptoms associated with LC are chronic fatigue, dyspnea, affective symptoms (anxiety and depression), and cognitive impairments [10-12]. There is previous evidence that viral infections are related to the development of fatigue, severe depression, and anxiety [13, 14]. Within six months following the onset of the first COVID-19 symptom, about one-third of COVID-19 survivors experience neuropsychiatric symptoms, such as sleeplessness, anxiety, or depression [15]. Therefore, it is necessary to study the biomarkers that are related to the pathophysiology of depression LC and may predict depression earlier in order to treat these symptoms and prevent further consequences. Previous research showed that leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome over-activation brought on by severe acute respiratory syndrome in certain instances, cytokine storm is also caused by coronavirus 2 (SARS-CoV-2). [16, 17] The pro-inflammatory cytokines interleukin (IL)-1β and IL-18 are cleaved by the NLRP3 inflammasome of the Nod-like receptor (NLR) family of proteins. These interleukins exhibit a strong inflammatory association with a number of central neurological disorders, such as epilepsy, Parkinson's disease, Alzheimer's disease, and chronic inflammatory demyelinating polyradiculoneuropathy. [18] As an intravascular effector of innate immunity, immune-thrombosis refers to complicated networks of molecular pathways and cellular interactions functioning to restrict the survival and spread of pathogens.[19] The immune-mediated stimulation of coagulation in sterile environments is referred to as thromboinflammation. Immune cell activation sustains these processes by releasing a variety of proinflammatory mediators, with platelets and the endothelium playing a critical role. These mediators work in concert to trigger the activation of blood coagulation factor.[20] clinical data pointing to the leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome pathway's involvement in COVID-19's atherothrombotic etiology.[20] When pro-inflammatory cytokines like interleukin-6 (IL-6) are stimulated, the liver is the primary source of the acute-phase protein known as C-reactive protein (CRP). It is a proven biomarker for tracking COVID-19 patients' rates of inflammation. By attaching itself to pathogen surfaces and injured cells, CRP plays a crucial part in triggering the innate immune response, which in turn triggers the complement system and phagocytosis.[21]

Critical COVID-19 individuals had much higher serum gasdermin D (GSDMD) levels than mild to moderate cases [31]. Elevated blood GSDMD levels in COVID-19 patients were associated with a critical respiratory status and an area of consolidation on chest CT images. [22] GSDMD is cleaved by caspase-1 upon caspase-1 activation, which causes pyroptosis, an anticipated cell death. [23] N-terminal GSDMD generates membrane holes that permit IL-18 and IL-1β to penetrate the extracellular area and initiate further autocrine, paracrine, and endocrine immune responses. [23] Pyroptosis on the other hand, is a kind of inflammatory cell death that involves cell lysis and the release of cytokines and other inflammatory mediators. Pyroptosis is a caspase-dependent process that causes GSDMD pore development [24]. It was determined that the primary executor of pyroptosis was GSDMD, a protein belonging to the gasdermin family [25]. Cleaving GSDMD by NLRP3 triggers this inflammatory cell death. This causes a number of cellular events, such as cytoplasmic swelling, plasma membrane rupture, and nucleus consolidation with cytoplasmic contents released into the extracellular space [26, 27]. Patients with COVID-19 also have elevated levels of C-reactive protein (CRP), another biomarker. In patients with COVID-19, elevated CRP levels have been linked to higher mortality, inflammatory alterations, and severe infection. [28] In the present study, serum levels of CRP, GSDRMD, and NLRP3 were measured in the LC patients with severe depression and LC patients without depression as tools for prediction of depression in LC patients.

II. METHODS AND MATERIAL

Participants and Methods

Participants

From March until May 2024, we recruited 100 individuals with LC and 50 healthy controls for this research. The subjects were collected from Al-Sader medical city, Najaf governorate, Iraq. LC was identified using the World Health Organization's (WHO) criteria [29]. The criteria suggest that the patients must have a verified COVID-19 infection and have at least two symptoms that impact their everyday activities: cognitive impairment, achy muscles, loss of taste or smell, exhaustion, memory or concentration problems, and emotional symptoms. In addition, at least two months should pass between symptoms, and symptoms need to last past the acute stage or show up two to three months later [29]. Patients groups were divided into two groups according to the results of the total HAMD score into LC patients with depression (LC+Dep group, HAMD≥17), and LC without severe depression (LC group, HAMD<17). According to age, gender, and BMI, the controls were chosen from the same area of LC patients. All individuals provided written informed permission before their involvement in our study. Our study, which was authorized by the Training and Human Development Center of the Najaf Health Directorate and the institutional ethical board, was given the number 4316/2024. The current study was designed and carried out under international and Iraqi ethical and privacy standards, such as the World Medical Association's Declaration of Helsinki, and the International Conference on Harmonization of Good Clinical Practice. Participation in the control group was restricted to those with a Hamilton Depression Rating Scale (HAMD) score of less than 7. Only those with a COVID-19 infection who did not exhibit any LC symptoms were considered controls. The study excluded any participants with substance use disorders (apart from tobacco use disorder (TUD), neurodegenerative and neuroinflammatory diseases, including Parkinson's or Alzheimer's disease, multiple sclerosis, stroke, chronic fatigue syndrome, renal or hepatic disorders, or systemic (auto immune diseases, including psoriasis, inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes mellitus, or systemic lupus erythematosus), was also excluded from the study. Participants were also not allowed to participate in the trial.

Methods

A fasting blood sample of five milliliters was taken at around 9:00 a.m. Following a 10-minute break, the clotted blood samples underwent a 5-minute centrifugation at 1200Xg. Afterwards, the serum was divided and transferred to three Eppendorf tubes. In the experiment, hemolyzed samples were not utilized. After that, these tubes were thawed for testing and stored in a refrigerator at -80 °C. We measured blood human NLRP3, and GSDMD, using ELISA kits that are ready to use and supplied by Nanjing Pars Biochem Co., Ltd. (Nanjing, China). All ELISA kits have intra-assay coefficients of variation (CV) below 10%. We applied sample dilutions as required according to the kit's procedures. (Nanjing, China) to assess serum levels of NLRP3, GSDMD. The Spinreact® latex slide assays (Barcelona, Spain) were used to measure the levels of CRP in human serum.

Biostatistics

The Kolmogorov-Smirnov test was used to examine the distribution types of the results group. The findings for normally distributed variables were expressed as mean ± standard deviation. Continuous variable differences across groups were examined using analysis of variance (ANOVA), while correlations between nominal variables were examined using contingency tables (χ^2-test). The two research groups' biomarkers were compared using the Mann-Whitney U test (MWUT). To examine the relationships between the variables, we controlled the analysis for age, weight, height, BMI, and smoking in LC patients to compute the partial coefficient which is more informative than the simple correlation coefficient. Receiver operating characteristics (ROC) analysis was employed to evaluate the diagnostic efficacy of the identified biomarkers. Youdin's statistics, cut-off points, sensitivities, and specificities are calculated variables. The tests were conducted using a 2-tailed approach, and a p-value of 0.05 was used to determine statistical significance. The statistical studies were conducted using IBM SPSS Windows version 25, released in 2017.

III. RESULTS AND DISCUSSION

Comparison study between long-COVID patients and the control groups

Table-1 shows the demographic and clinical characteristics of healthy controls and long-COVID patients groups with depression (LC+Dep) and without depression (LC). There is no significant difference between groups in age, residency, education years, weight, height, BMI, and marital status. The results showed a significant decrease ($p<0.001$) in the SPO2 percentage in LC patients compared with the control group. At the same time, body temperature was significantly increased ($p<0.001$) in the patients than in the control group.

Comparison in CRP between patients and Controls

The results showed a significant increase ($p<0.001$) in the median serum levels CRP [5.94(3.925-6.2) mg/l] in Long-COVID patients in comparison with the control group [2.815(1.743-3.95) mg/l].

The median serum levels of GSDMD [54.673(39.057-76.849) pg/ml] were significantly higher ($p<0.001$) in Long COVID patients than in the control group [31.547(24.073-42.925) pg/ml].

The median serum levels of NLRP3 in Long COVID patients were found to be significantly higher ($p<0.001$) at [35.522 (28.228-42.241)] pg/ml compared to [26.594 (23.158-30.596)] pg/ml in the control group.

Correlation study

The results of the correlation between the serum biomarkers and psychiatric scales in long COVID patients are presented in Table -3.

The results showed significant correlation in GSDMD with CRP and NLRP3 P>0.05 while all biomarkers significant correlation with HAMD Total, and invers correlation of SpO2 with CRP, GSDMD and NLRP3.

The results in Table-5 showed that the increase in GSDMD level higher cut-off value (60.98 ng/ml) indicates that the subjects may Long COVID with a significant sensitivity (0.698%) and specificity (0.699%), utility for prediction of Long COVID (p=<0.001). While NLRP3 has cut-off value (35.27), sensitivity (0.512%) and specificity (0.508%). The results in Table-5 showed that CRP no significant in Long COVID (p=0.974).

Study of diagnostic ability of the measured biomarkers for prediction of Long COVID patients

To examine the diagnostic abilities of the measured biomarkers for diagnosis of Long COVID patients, the receiver operating characteristics (ROC) study was carried out to estimate the sensitivity and specificity at each concentration. The ROC curves for the measured parameters are plotted in Figure.3 While, the results of analysis are presented in Table -5.

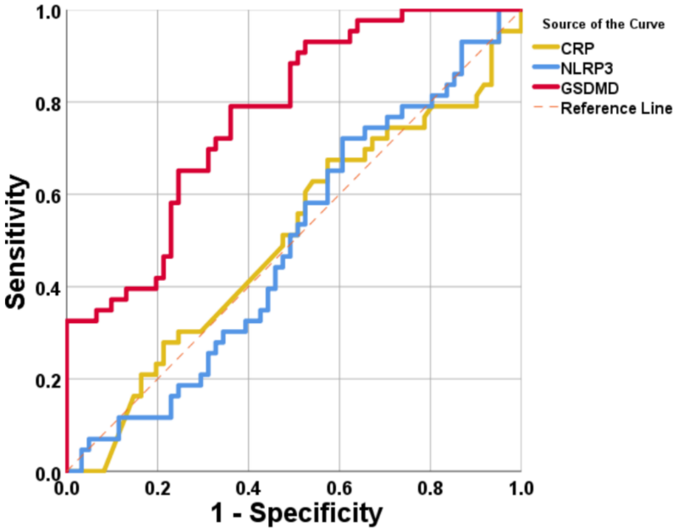

Figure -1. Receiver operating characteristic curves of the NLRP3, GSDMD, CRP and their ratio in prediction of Long COVID

Table 1: Demographic and clinical characteristics of long-COVID patients (with (LC+Dep) and without depression (LC) and control groups.

Parameter	Control (n=57)	LC (n=61)	LC+Dep. (n=43)	F/χ^2	P
Age yrs.	39.825±9.008	41.836±9.689	40.605±8.707	0.718	0.490
Weight kg	82.228±10.767	86.098±13.581	81.767±11.598	2.152	0.120
Height cm	171.842±6.573	174.082±7.036	171.256±7.944	2.395	0.095
BMI kg/m^2	27.814±3.105	28.413±4.169	27.89±3.555	0.460	0.632
Single/Married	3/54	4/57	2/41	0.192	0.909
Smoking No/Yes	43/14	40/21	34/9	2.653	0.265
Rural/Urban	10/47	10/51	6/37	0.238	0.888
Employment No/Yes	7/50	13/48	4/39	3.347	0.188
Education years	13.237±2.822	14.370±2.623	13.880±2.970	2.178	0.117
Highest Body temp. ºC	38.407±0.392 ^{B,C}	39.056±0.639 ^{A}	39.063±0.76 ^{A}	21.524	<0.001
SpO2 %	91.368±2.454 ^{B,C}	82.852±6.916 ^{A}	80.628±8.952 ^{A}	40.900	<0.001
HAMD	4.842±1.544 ^{B,C}	12.639±1.932 ^{A,C}	19.837±3.078 ^{A,C}	583.491	<0.001

^{A,B,C}: Pair-wise comparison. Results are expressed as mean ± standard deviation for normally distributed data. Binomial data were expressed as ratios and analyzed by Chi-squared test. *p. probability value,* and BMI. Body mass index. *F/χ^2: F-statistics value for continuous variables or Chi-square statistic value for binominal variables*.

Table 2. The results of serum CRP, NLRP3, GSDMD in long-COVID patients and control groups

Parameter	Control	LC	LC+Dep.	p
CRP mg/l	2.84 (1.745_4.04)^{B,C}	5.57 (3.845_6.125) ^{A}	5.94 (3.79_6.21) ^{A}	<0.001
NLRP3 pg/ml	26.594 (23.158_30.596) ^{B,C}	35.023 (26.723_48.917) ^{A}	35.522 (28.228_42.241) ^{A}	<0.001
GSDMD pg/ml	31.547 (24.073_42.925) ^{B,C}	43.509 (28.166_71.912) ^{A,C}	54.673 (39.057_76.849) ^{A,B}	<0.001

^{A,B,C} : Pair-wise comparison

Table 3: The partial correlation study among the patient's group in the serum biomarkers and psychiatric scales , SpO2 and smoking expressed as correlation coefficient (p-value).

Parameters	CRP	NLRP3	GSDMD
CRP	1(0)	0.119(0.143)	0.175(0.009)
NLRP3	0.119(0.143)	1(0)	0.239(0.003)
GSDMD	0.155(0.056)	0.239(0.003)	1(0)
HAMD Total	0.305(<0.001)	0.306(<0.001)	0.280(<0.001)
Highest Body temp.	0.182(0.024)	0.076(0.354)	0.180(0.026)
SpO2	-0.311(<0.001)	-0.291(<0.001)	-0.216(0.007)
Smoking	-0.030(0.711)	-0.103(0.204)	0.084(0.299)

Table 4: Receiver operating characteristic-area under curve (AUC) analysis of NLRP3, GSDMD, CRP and their ratio in prediction of Long COVID

Test	Cut-off	Sensitivity %	Specificity %	Youden's J statistic	AUC (95% CI)	p-value
GSDMD pg/ml	60.98	0.698	0.699	0.397	0.77(0.68-0.86)	<0.001
CRP mg/l	5.76	0.512	0.525	0.037	0.50(0.39-0.62)	0.974
NLRP3 pg/ml	35.27	0.512	0.508	0.021	0.49(0.38-0.60)	0.882

*: The decrease in these biomarkers is a predictor of Long COVID

V. DISCUSSION

The SPO2 % in acute phase COVID-19 patients were significantly lower ($p<0.001$) than in the control group, according to the data. The patients' body temperature was substantially higher ($p<0.001$) than that of the controls, although there was no significant difference in age, height, weight, BMI, smoking, rural/urban location, or education. A primary indicator of the innate immune response, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome system is now thought to be a major cause of endothelial dysfunction and vascular inflammation.[20] as well as an important contributor to certain illnesses, such as atherosclerosis and other cardiovascular disorders.[21] conditions including COVID-19 obstructive sleep apnea [22] or diabetic mellitus Following an initial priming phase to boost certain cellular components of the system, like NLRP3 or pro-IL-1β, the inactive precursor of interleukin-1β, the inflammasome must come together to form a functional multi-protein structure that includes NLRP3 and additional proteins, such as the adaptor molecule apoptosis-associated speck-like protein (ASC). [23]

Mild, moderate, and severe post-recovery COVID-19 patient groups showed substantially different body weight reduction ($p < 0.0005$); the average body weight loss for the mild–moderate group was 4.17 ± 1.95, whereas the severe groups was 4.17 ± 1.95 [24] .60.7% of the variance in the physio-affective phenome of Long COVID is predicted by female sex, lower SpO2, and increased body temperature during the acute phase. [25] Longer hospital stays and severe COVID-19 pneumonia were associated with higher plasma CRP levels. [26] Elevated CRP levels have been linked to greater mortality in COVID-19 patients, severe infection, and inflammatory abnormalities on chest CT scans. [18]

Significant correlations between inflammatory markers and CRP-measured inflammation were discovered in our investigation. An elevated LMR was linked to an elevated CRP, indicating heightened inflammation. According to these findings, increased (lymphocyte/monocyte ratio-LMR) LMR, a measure of the intensity of the inflammatory process, is linked to elevated CRP, an inflammatory marker. The significance of tracking these markers in evaluating and managing patients' inflammatory processes is underscored by these correlations. [27] In COVID-19, systemic inflammation as determined by CRP is closely linked to Venous thrombo-embolism (VTE), acute kidney injury (AKI) , critical illness, and death. [28]

NLRP3 levels in the septic shock group were considerably greater than those in the healthy control group.[29] Pyroptosis, an inflammatory programmed cell death mechanism that occurs in T cells, can result from NLRP3 activation. Gasdermin D (GSDMD) cleavage by caspase 1, 4, 5, and/or 11 initiates this inflammatory cell death, which leads to a sequence of cellular events such as cytoplasmic swelling, plasma membrane rupture, and nucleus consolidation with cytoplasmic contents released into the extracellular space. [30] Pyroptosis may be intricately connected to the pathophysiology of autoimmune disorders [31] and SARS-CoV-2 infection.[32]

An essential factor in the innate immune system's recognition of pathogens, especially viral infections, is the NLRP3 inflammasome In lipopolysaccharide-primed macrophages, the SARS-CoV 3a protein triggers the NLRP3 inflammasome, resulting in 3a-mediated IL-1β production linked to K^+ efflux and mitochondrial reactive oxygen species.[33]

The development of the NLRP3 inflammasome and the subsequent upregulation of gasdermin D, downstream Caspase-1, and inflammatory cytokines (IL-1β, IL-18, IL-6, and TNF-α) with the resulting lung tissue damage in COVID-19 cases suggested that an overreactive immune response may be the primary cause of this dysregulation. Numerous underlying medical illnesses are linked to NLRP3 inflammasome-related inflammatory diseases after SARS-COV-2 infection because of the influence on physiologic changes and genetics. [34] Showed that higher BT during acute COVID-19 predicted increased CRP and decreased antioxidant defenses, including zinc, in long COVID, whereas decreased SpO2 during the acute phase predicted decreased Gpx and increased NO generation in long COVID patients.[35] Significant immune cell recruitment and elevated levels of inflammatory markers, such as C-reactive protein, ferritin, and cytokines, linked to a hypercoagulation state, are characteristics of the inflammatory responses in severe COVID-19 individuals. [36]

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