

Predictors of Post Covid Syndrome among Covid Survivors Patients attending Post Covid Out-Patients Clinic

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ABSTRACT

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic remains a constant challenge for healthcare systems and affects the well-being of many individuals. The objective of the current study is to determine the parameters that can predict post COVID-19 sequele and incidence of post Covid sequele among Covid survivor's patients attending post covid outpatient clinic.

Patients and methods: This was a case control study carried out on 60 COVID-19 survivors whom were recovered from the acute illness and discharged for follow-up at the post covid out-patient clinic at Zagazig University. The sixty patients included in the study were divided to Group I: (Asymptomatic patients): include 30 patients whom were discharged for follow-up and in whom no significant symptoms or signs were reported during the study. Group II: (Symptomatic patients): include 30 patients whom were discharged for follow-up and in whom there were significant symptoms or signs during the study.

Results: There is statistically significantly association between initial parameters high (CRP, D-dimer, ferritin, LDH, IL6) and low Lymphocytes. Post covid degree of lung affection in chest CT scan where Grade ≥ 5 (severe lung affection) prevailed in 63.3% and 20% in those with and without post covid syndrome, respectively, while Grade < 2 (less sever lung affection) was more dominant in those without post covid (30% vs. 6.7%).

Conclusion: Persistence of symptoms is common after the acute phase of COVID-19 infection. Post covid syndrome occurs regardless of the disease severity. High CRP, LDH, ferritin, D-dimer, and IL6, low Lymphocytes and degree of lung affection at diagnosis of acute covid19 may be good predictors for the occurrence of post covid syndrome.

Keywords: Post covid Syndrome, COVID-19, COVID-19 Survivors.

INTRODUCTION

Respiratory viral diseases are associated with both acute and long-lasting psychopathological consequences in the survivors⁽¹⁾. Corona viruses are negatively stranded RNA viruses, which cause infections ranging from common colds to severe acute respiratory syndrome. Coronavirus exposure has also been implicated in neuropsychiatric diseases during and after Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks⁽²⁾.

SARS survivors reported psychiatric symptoms, including post-traumatic stress disorder (PTSD), depression, panic disorder, and obsessive-compulsive disorder (OCD) at 1 to 50 months follow up⁽³⁾. Moreover, sero-positivity for corona viruses associated with suicide and psychosis persisting one year after SARS⁽⁴⁾.

Despite passing months after the first case of COVID-19, scientists are facing long-term complications. This disease can cause heart failure, neurological diseases, such as stroke, and lung disease. Symptoms include fatigue and brain fog, which may be related to cytokines that cross the blood brain-barrier (BBB) and affect the brain. These symptoms should be seriously considered because they may reflect the post-viral syndrome associated with COVID-19. Moreover, difficulty in reading, insomnia, general myalgia, dry skin, and increased anxiety are other common symptoms⁽⁵⁾.

Common symptoms, such as cough, fever, dyspnea, musculoskeletal symptoms, and anosmia have been

seen in a large proportion of patients in a study in Italy. The patients who were discharged from the hospital were assessed, of whom 12.6% had no symptoms of COVID-19, 32% had one or two symptoms, and 55% had three or more. Also, 53% had fatigue, 43% dyspnea, 27% joint pain, and 21% chest pain. According to this study, 87.4% had persistence of at least one symptom especially fatigue and dyspnea⁽⁶⁾.

The aim of this study was to determine the parameters that can predict the post covid syndrome and determine the spectrum of the post covid syndrome among COVID-19 survivors attending the post covid syndrome outpatient clinic at Zagazig University Hospital.

PATIENTS AND METHODS

This was a case control study carried out on 60 COVID-19 survivors whom were recovered from the acute illness and discharged for follow-up at the post covid cases at chest out-patient clinic at Zagazig University Hospital.

Inclusion criteria: Adults > 18 years old. COVID-19 survivors who met World Health Organization (WHO) criteria for discontinuation of isolation (for symptomatic patients; 10 days after symptom onset, plus at least 3 additional days without symptoms), and those symptomatic patients who have had COVID-19 at least 3 months before.

Exclusion criteria: Pregnant and lactation women. Patients refuse to complete their follow up.

The studied patients included in the study were divided into two groups; **Group I** (Patients with post covid): include 30 patients whom were discharged for follow-up and in whom there were significant symptoms or signs during the study duration. **Group II** (Patients without post covid): include 30 patients whom were discharged for follow-up and in whom no significant symptoms or signs were reported during the study duration.

Revision of medical records and reporting that were done to all patients such as; history taking, complete medical examination and laboratory Investigations: (A) Biochemical Parameters [Complete blood cell count (CBC) including differential white blood cell (WBCs) count, Serum Ferritin, Serum IL-6, Serum cardiac troponin I (cTnI), Blood urea nitrogen (BUN) and Serum Creatinine, Serum Aspartate aminotransferase (AST) and alanine, aminotransferase (ALT), Serum procalcitonin (PCT), Serum C-reactive protein (CRP) and Serum lactate dehydrogenase (LDH)]. (B) Coagulation Indicators including Platelet counts, D-dimer, Fibrinogen, PT, PTT.

Follow up:

Group I (Patients with post covid patients):

All patients were offered a comprehensive assessment including collection of detailed medical history including thorough medical history and complete physical examination (local and general examination). Reverse transcriptase-polymerase chain reaction assay of nasopharyngeal and oropharyngeal swab (RT-PCR) was done if any symptoms or signs suggesting COVID-19 to exclude re-infection.

Special questionnaire to inquire about the current health status of patients and their persistent symptoms in the post covid period and contacted all eligible patients, this survey aimed to detect the presence of post covid syndrome, the questionnaires were filled out by trained independent physicians; the information included, age, sex, co-morbid diseases; characteristics of acute COVID-19, history of hospitalization, length of hospital stay, and need for intensive care unit, Baseline and follow-up inflammatory markers, duration since symptoms onset, presence of persistent symptoms after recovery, and symptoms of patients were grouped by the system as general, respiratory, cardiovascular, neuropsychiatric, dermatologic, gastrointestinal and genitourinary. Participants were asked to score each symptom from 0 to 10.

Group II (Patients without post covid group): Patients were offered simple investigations including: complete blood count with or without monthly chest x-ray as routine follow up.

Ethical consent:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was taken from all participants. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data was collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Qualitative data was expressed as absolute frequencies (number) and relative frequencies (percentage), and quantitative data was expressed as the mean and SD, and median (range). Descriptive statistics were used to describe demographic and key clinical characteristics of the study population according to sex and time elapsed from hospital discharge.

Chi square test (χ^2) to calculate difference between two or more groups of qualitative variables. Mann Whitney test was used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. P value was set at ≤ 0.05 for significant results and ≤ 0.001 for high significant result.

RESULTS

The current study included 30 patients with post covid sequale and other 30 without post covid sequale. They were 17 (56.7%) males in **Group I** and 16 (53.3%) males in **Group II**.

There was statistically significant difference between both groups regarding, BMI > 25 kg/m², diabetes mellitus, asthma and COPD (all are higher in those with post covid group), while no statistically significant difference between both groups regarding gender, or other co-morbidities.

Table (1): Characteristics of all the studied participants.

Parameter	Groups		Test	
	Patients with post covid syndrome group	Patients without post covid syndrome group	χ^2	P-value
	N= 30 (%)	N= 30 (%)		
Male gender	17 (56.7%)	16 (53.3%)	0.067	0.795
BMI>25 kg/m ²	14 (46.7%)	6 (20%)	4.8	0.028*
Diabetes mellitus	13 (43.3%)	6 (43.3%)	5.079	0.02
DM on insulin	10/13 (76.9%)	3/6 (50%)	Fisher	0.32
Hypertension	6 (20%)	9 (30%)	0.8	0.371
COPD	4 (13.3%)	0 (0%)	4.28	0.038*
Asthma	7 (23.3%)	1 (3.3%)	5.192	0.023*
IHD	0 (0%)	2 (6.7%)	Fisher	0.492
Hypothyroidism	0 (0%)	5 (16.7%)	Fisher	0.052

χ^2 : Chi square test *p<0.05 is statistically significant.

Regarding the presenting symptoms during post covid follow up period, dyspnea and fatigue were the most dominant symptoms in 70% and 60% of patients respectively, while skin lesions were the lowest (3.3%), while other symptoms were as follow; anosmia, myalgia, headache, amnesia, diarrhea, visual disturbance, fever, cough and chest pain were 36.7%, 63.3%, 36.7%, 40%, 6.7%, 10%, 30%, 46,7 and 30% respectively as showed in table 2.

Table (2): Distribution of presenting symptom in the post covid group.

Variable	N=30	%
Fatigue	18	60%
Anosmia	11	36.7%
Myalgia	19	63.3%
Dyspnea	21	70%
Cough	14	46,7
Headache	11	36.7%
Amnesia	12	40%
Diarrhea	2	6.7%
Skin features	1	3.3%
Visual disturbance	3	10%
Fever	9	30%
Chest pain	9	30%

Table 3 shows that there was statistically significant difference between both groups as regard initial laboratory assessment during COVID-19 attack where, D-dimer, LDH, CRP, serum ferritin and interleukin-6 which were significantly higher in those with post covid than in those without post covid while lymphocytes were lower in patients with post covid than in those without post covid. There was no statistically significant difference between both groups neutrophils count.

Table (3): Initial laboratory parameters among both groups.

Parameter	Groups		Test	
	Patients with post covid syndrome group	Patients without post covid syndrome group	Z	P
	Mean±SD	Mean±SD		
Neutrophil%	3.5 ± 0.61	3.5 ± 0.71	-1.187	0.235
Lymphocytes%	0.9 ± 0.3	1.75 ± 0.4	-2.322	0.02*
D dimer/Ug/ml	2.15 ± 0.5	0.3 ± 0.051	-3.072	0.002*
CRP/mg/dl	64.32 ± 4.32	4.3 ± 0.92	-3.211	0.001**
Ferritin/ng/ml	540 ± 18.3	145 ± 33.61	-3.551	<0.001**
LDH/U/L	1136.75 ± 256.42	224 ± 51.51	-2.405	0.016*
IL-6/pg/L	57 ± 12.62	10.3 ± 2.22	-3.654	<0.001**

*p<0.05 is statistically significant Z Mann Whitney test IQR interquartile range **p<0.001 is statistically highly significant.

Table 4 shows that the AUC of D-dimer was 0.73 [Cutoff= ≥ 0.445] for distinguishing patients with post covid syndrome from those without, with 66.7% sensitivity and 73.3% specificity. Moreover, CRP showed 76.7% sensitivity and 73.3% specificity with AUC of 0.741. Meanwhile, the AUC of ferritin for differentiating both groups was 0.767 with 80% sensitivity and 73.7% specificity. Also, LDH showed 73.3% sensitivity and 66.7% specificity with AUC of 0.674 for distinguishing both groups. Finally, the AUC of IL-6 was 0.774 [Cutoff= ≥ 14.75] for distinguishing patients with post covid syndrome from those without, with 86.75% sensitivity and 63.3% specificity.

Table (4): The role of studied markers in prediction of post covid syndrome among studied patients.

Markers	AUC	Cutoff	Sensitivity	Specificity	Accuracy	P-value
D-dimer/Ug/ml	0.73	≥ 0.445	66.7%	73.3%	70%	0.002*
CRP/mg/dl	0.741	≥ 6.51	76.7%	73.3%	75%	<0.001**
Ferritin/ng/ml	0.767	≥ 393.5	80%	73.7%	76.7%	<0.001**
LDH/U/L	0.674	≥ 278	73.3%	66.7%	70%	0.02*
IL-6/pg/L	0.774	≥ 14.7	86.6%	63.3%	75%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value ** $p \leq 0.001$ is statistically highly significant * $p < 0.05$ is statistically significant

Table 5 shows pulmonary CT scan presentation of both groups regarding the degree of lung affection where Grade ≥ 5 (more sever lung affection) prevailed in 63.3% and 20% in those with and without post covid syndrome respectively while Grade < 2 (less sever lung affection) was more dominant in those without post covid syndrome (30% vs. 6.7%).

Table (5): The degree of lung affection in chest CT scan during covid illness:

Parameter	Groups		Test	
	Patients with post covid syndrome group	Patients without post covid syndrome group	χ^2	P-value
	N=30 (%)	N=30 (%)		
CT scan				
<2	2 (6.7%)	9 (30%)	12.016	0.001**
≥ 2 -<5	9 (30%)	15 (50%)		
≥ 5	19 (63.3%)	6 (20%)		

χ^2 : Chi square for trend test ** $p \leq 0.001$ is statistically highly significant

Table 6 showed that there is statistically significant relation between CT scan and dyspnea (76.2% of those with dyspnea had CT score ≥ 5 versus 33.3% in those without dyspnea). There is statistically significant relation between CT scan and cough where 92.9% of those with cough had score ≥ 5 .

Table (6): Relation between post covid symptoms of lung and initial Chest CT scan.

CT	Dyspnea		Cough	
	Absent N (%)	Present N (%)	Absent N (%)	Present N (%)
<2	2 (22.2%)	0 (0%)	2 (12.5%)	0 (0%)
2 - <5	4 (44.4%)	5 (23.8%)	8 (50%)	1 (7.1%)
≥ 5	3 (33.3%)	16 (76.2%)	6 (37.5%)	13 (92.9%)
χ^2	6.808		8.772	
P-value	0.009*		0.003*	

χ^2 : Chi square for trend test * $p < 0.05$ is statistically significant

Table 7 shows different modalities of therapeutic management, there was statistically significant difference between both groups, where the use of nebulizer was higher (86.7% vs. 40%) in the post covid syndrome group. Also, there was statistically significant difference between both groups, regarding the use of corticosteroids (dexamethazone and solucortif) which were higher in the post covid syndrome group (53.3% vs. 20% and 40% vs. 26.7%) respectively. As regard the need for ventilatory support there was statistically significant difference between both groups, where in the post covid syndrome group the need for such support was higher than in those without post covid syndrome. On the other hand there was no statistically significant difference between both groups regarding the use of vaso-pressors or antiviral therapy.

Table (7): Different therapeutic management at post covid syndrome period.

Parameter	Groups		Test	
	Patients with post covid syndrome group	Patients without post covid syndrome group	χ^2	P-value
	N= 30 (%)	N= 30 (%)		
Nebulizer Pulmocort/Atrovent	26 (86.7%)	12 (40%)	MC	<0.001**
Corticosteroids:				
No	2 (6.7%)	16 (53.3%)	MC	<0.001**
Dexamethazone	16 (53.3%)	6 (20%)		
Solucortif	12 (40%)	8 (26.7%)		
Vasopressor	2 (6.7%)	0 (0%)	Fisher	0.492
Antiviral	15 (50%)	15 (50%)	0	>0.999
Ventilatory aids:				
No	7 (23.3%)	26 (86.7%)	MC	<0.001**
Simple mask	10 (33.3%)	0 (0%)		
Reservoir	4 (13.3%)	0 (0%)		
CPAP	9 (30%)	4 (13.3%)		

*p<0.05 is statistically significant MC Monte Carlo test **p<0.001 is statistically highly significant.

DISCUSSION

In the current study, no long-term data on large scale were observed of patients of COVID-19 patients with persistent symptoms and long term sequale. Our results allowed outlining a group of patients with present long-lasting sequelae, up to 6 months, in the post covid period.

NICE guideline currently defines post covid syndrome as the persistence of signs and symptoms for more than 3 months after infection, in the absence of an alternative diagnosis (National Institute for Health and Care Excellence, 2020) (7). The most common frequent clinical presentation after COVID-19 are abnormal lung functions prevalently with persistent dyspnea, smell and taste disturbances, general neurological decay and chronic fatigue. Other common symptoms include joint pain and chest pain. These symptoms may recur for weeks or months following initial recovery (8). Therefore, the aim of this study was to determine the parameters that can predict post covid-19 sequale and to determine the spectrum and incidence of post covid sequale among COVID-19 survivors attending post covid outpatient clinic. The population of the current study, was male gender (56.7%) in patients with post covid syndrome group and (53.3%) in patients without post covid syndrome group with no significant difference. Which is in accordance with **Peckham et al.** (9) who reported that, male sex was associated with higher risk of severe COVID-19. On the other hand, **Desgranges et al.** (10) identified female gender as a predictor for the post covid syndrome, in particular for persistent fatigue and smell or taste disorder.

Regarding the BMI in our study, there is statistically significant difference between both groups regarding, BMI>25 kg/m². This coping with other studies such that **Desgranges et al.** (10) who found that obesity was an independent predictor for the presence of any long-term symptom, fatigue, and dyspnea. Our study revealed that, there is statistically significant

difference between both groups regarding, diabetes mellitus, asthma and COPD (all are higher in those with post covid syndrome). While no statistically significant difference between both groups regarding other comorbidities.

This is in accordance with **Mady et al.** (11) who found significant association between presences of comorbidities and post covid syndrome symptoms. Diabetes was significantly associated with fatigue, bronchial asthma with anxiety. Ischemic heart disease and hypertension were significantly associated with the persistence of dry cough. These findings are in accordance with previous study (12).

In our study, regarding the presenting symptoms in the post covid syndrome group, dyspnea and fatigue were the most dominant symptoms in 70%, 60% of patients respectively while skin lesions were the lowest (3.3%), while other symptoms were as follow; anosmia, myalgia, headache, amnesia, diarrhea, visual disturbance, fever, cough and chest pain were 36.7%, 63.3%, 36.7%, 40%, 6.7%, 10%, 30%, 46.7% and 30%, respectively. Two studies, evaluating more than 100 laboratory-confirmed COVID-19 outpatients, reported the prevalence of symptoms lasting more than 6 months after diagnosis: 33–46% participants with at least one symptom, 14–22% with fatigue, 8% with dyspnea, and 14–15% with change in sense of smell or taste (13,14).

Kayaaslan et al. (15) reported that, more than half of the patients having persistent symptoms had three or more symptoms. They detected respiratory symptoms (particularly dyspnea) as the second common complaint. However, patients scored their dyspnea as 4 based on the scale, and only one-third of patients with respiratory complaints needed to visit a healthcare center. Also, **Kayaaslan et al.** (15) reported that a considerable part of the patients suffered from neuropsychiatric disorders such as concentration or memory deficit, insomnia or hypersomnia, headache, and new-onset depression, and anxiety even 20 weeks

after infection. COVID-19 has also different cutaneous manifestations. They inquired patients about hair loss, and of participants in their study, 18% complained of hair loss.

In the present study, there was statistically significant difference between groups where, D-dimer, LDH, CRP, serum ferritin and interleukin-6 which were significantly higher in those with post covid syndrome than in those without post covid syndrome while lymphocytes were lower in patients with post covid syndrome than in those without post covid syndrome. There was no statistically significant difference between both groups neutrophils count.

High levels of inflammatory markers and lymphopenia related to the severe condition may explain the persistence of symptoms (16,17). In general, organ damage, inflammatory response, immune mechanisms, re-infection, are thought to be the causes of post covid syndrome (3,18).

This agrees with **Maamar et al.** (19) who has shown slightly but significantly higher values of serum CRP, fibrinogen and neutrophil count in patients with PCS. CRP serum level in the range of chronic inflammation has shown a significant relationship with PCS. Interestingly, this association has been noted only in men. CRP is an acute-phase protein produced by hepatocytes, and cytokines such as IL-6 play a key role in stimulating its synthesis (20). Fibrinogen, as well as CRP, serum amyloid A (SAA) and haptoglobin, are closely linked to IL-6 activation, hence higher levels of fibrinogen may be a reflection of the events driven by the production of IL-6 during COVID-19 infection.

Despite different study design, our results are consistent with **Lopez-Leon et al.** (21) who conducted meta-analysis of the long-term effects of COVID-19. They found residual elevation of CRP, D-dimer, and ferritin associating post covid syndrome related symptoms despite the heterogeneity of their data.

In the present study, there was statistically significant between both groups regarding the degree of lung affection in chest CT scan where Grade ≥ 5 (more sever lung affection) prevailed in 63.3% and 20% in those with and without post covid syndrome respectively while Grade < 2 (less sever lung affection) was more dominant in those without post covid syndrome (30% vs. 6.7%).

Moreno-Pérez et al. (22) evaluated 277 patients face-to-face 10–14 weeks after disease onset and reported that although they detected post covid syndrome in half of the patients recovered from COVID-19, radiological and spirometric changes were mild and present in less than one-fourth of patients.

Lopez-Leon et al. (21) reported that in their systematic review and meta-analysis, abnormalities in CT lung scans persisted in 35% of patients even after 60–100 days from the initial presentation. Although most of the available studies do not include baseline pulmonary dysfunction or radiographic abnormalities, findings indicate improvement or resolution of

abnormal CT findings. In this study, there is statistically significant relation between CT scan and dyspnea (76.2% of those with dyspnea had CT score ≥ 5 versus 33.3% in those without dyspnea). There is statistically significant relation between CT scan and productive cough where 92.9% of those with cough had score ≥ 5 .

Persistent opacities in $\geq 10\%$ of one or more lung parenchyma zones, as assessed by CT, were present in approximately one in four participants after 3 months. Compared with reports after 4 weeks of follow-up in another cohort **Huang et al.** (23), this finding suggests that COVID-19 related GGO may resolve without development of persistent fibrosis. However, some of these CT findings may persist and gradually develop into fibrotic changes, as reflected by the finding of parenchymal bands in one-fifth of our study population (24). The present study showed that, there was statistically significant difference between both groups, where in the post covid syndrome group the use of nebulizer was higher (86.7% vs. 40%). There was statistically significant difference between both groups, regarding the use of corticosteroids which were higher in the post covid syndrome group (53.3% vs. 20% and 40% vs. 26.7%) respectively. This finding was proven in other studies like that of **Zha et al.** (25) who reported a longer duration of symptoms among patients who was 2 and 4-fold higher with antibiotics and corticosteroids treatment, respectively, moreover received corticosteroids compared to other COVID-19 patients.

The probability of post covid syndrome symptoms, antiviral and anticoagulant therapy was significantly associated with persistence of COVID-19 symptoms. This is expected as these drugs are prescribed for severe and critical cases (26).

No studies evaluated a definite cutoff values for certain laboratory parameters to predict the possibility of occurrence of post covid syndrome, in the present study the best cutoff of D-dimer for prediction of post covid syndrome is ≥ 0.445 with area under curve 0.73, sensitivity 66.7%, specificity 73.3%, positive predictive value 71.4%, negative predictive value 68.8% and overall accuracy 70% ($p=0.002$).

The best cutoff of CRP for prediction of post covid syndrome is ≥ 6.51 with area under curve 0.741, sensitivity 76.7%, specificity 73.3%, positive predictive value 74.2%, negative predictive value 75.9% and overall accuracy 75% ($p<0.001$).

The best cutoff of serum ferritin in prediction of post covid syndrome is ≥ 393.5 with area under curve 0.767, sensitivity 80%, specificity 73.3%, positive predictive value 75%, negative predictive value 78.6% and overall accuracy 76.7% ($p<0.001$).

The best cutoff of LDH in prediction of post covid syndrome is ≥ 278 with area under curve 0.674, sensitivity 73.3%, specificity 66.7%, positive predictive value 68.8%, negative predictive value 71.4% and overall accuracy 70% ($p<0.05$). The bet cutoff of IL-6 in prediction of post covid syndrome is ≥ 14.75 with area under curve 0.774, sensitivity 86.7%, specificity 63.3%,

positive predictive value 70.3%, negative predictive value 82.6% and overall accuracy 75% ($p < 0.0$).

Although higher values could be present in a lot of patients without post covid and lesser values could be present in patients with post covid but the present study intended to shed the light upon these parameters which are simple and requested routinely for covid patients and may be attractive for health worker attention to pay more attention for such patient during the hospital stay and also for patient education after discharge and to confirm the follow up schedule for such group of patients to avoid the occurrence of long term sequelae of covid.

In conclusion, post covid syndrome occurs regardless of the disease severity. The use of corticosteroids, nebulizer use, ventilatory aids use, lymphocytes, D-dimer, CRP, ferritin, LDH, and IL-6. The severity of lung affection in CT scan can be a good predictors for the occurrence of post covid syndrome.

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