Predictors of Long Covid 19 Syndrome

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ABSTRACT

Background: Symptoms of covid persist in most cases with development of a multisystem syndrome called long covid syndrome.

Objective: The aim of the work was to evaluate symptoms that persist after the acute stage of the disease in a cohort of patients with confirmed or suspected COVID 19 and to define the predictors for long COVID syndrome.

Patients and method: This retrospective study involved 164 patients with previously confirmed or highly suspected COVID 19 and still attending to the post covid outpatient clinic in El-Minia University Chest Hospital complaining from persistence of symptoms or for regular follow up. Their data was obtained from their previous medical reports.

Results: Post Covid 19 symptoms were found in about 86 % of the studied patients with 42.7% reported neuropsychiatric symptoms and 26.8% reported respiratory symptoms. The most common reported symptoms in non-severe cases were the anxiety disorders (18.9%), followed by chronic fatigue and neuropathy (15.2%), while chronic dyspnea in 9.8% mostly in severe cases, while vertigo and headache in 9.1%, musculoskeletal symptoms in 6.1% and skin lesions in 3.7%.

Conclusion: It could be concluded that **p**ersistence of symptoms is very common after acute Covid 19 infection. Chronic dyspnea was reported more frequently in severe cases while anxiety reported mostly by patients with mild disease.

Keywords: Long covid syndrome, Post covid syndrome, Persistent symptoms, chronic fatigue syndrome.

INTRODUCTION

A novel coronavirus (nCoV) disease (COVID-19) has been defined as a pandemic health problem caused by a newly discovered SARS COV-2 virus. Post covid-19 ("long covid") is a multisystem syndrome, occurring even after a mild acute illness. The patients remain suffering from multiple neuropsychiatric and respiratory symptoms as chronic dyspnea 'lung burn', tachycardia and loss of smell or taste accompanied by chronic fatigue – but not always [1]. The symptoms may be constantly persistent or fluctuate. It may take days till feeling well but may recur sometimes following exertion and sometimes for no apparent reason [2].

Greenhalgh *et al.* [3] define the post-acute covid-19 symptoms that extending beyond three weeks from the onset of first symptoms and chronic covid-19 which extend beyond 12 weeks.

The aim of the present study was to evaluate symptoms that persist after the acute stage of the disease in a cohort of patients with confirmed or suspected COVID 19 and to define the predictors for long COVID syndrome.

PATIENTS AND METHODS

For the purpose of this study, we used the definition of post COVID 19 syndrome as symptoms that persist for beyond 3 months from the start of the disease.

This retrospective study included a total of 164 patients with previously confirmed or highly suspected COVID 19 attending at the Post Covid Outpatient Clinic, El-Minia University Chest Hospital,

complaining of persistence of symptoms or for regular follow up.

Their data was obtained from their previous medical reports. Demographic data, comorbidities, the initial presenting symptoms, and laboratory finding were recorded.

The severity of the cases was defined based on the criteria established by China's National Health Commission [4]: 1- Mild: minor symptoms only, without evidence of pneumonia by chest X-ray. 2- Moderate: Fever and respiratory symptoms are present, and there is evidence for pneumonia by chest X-ray, (both groups classified also as non-severe cases). 3- Severe: Defined by any of the following conditions. 1) Dyspnea, respiratory rate ≥30 /min, 2) resting hypoxia SaO2 $\leq93\%$, 3) PaO2/FiO2 ≤300 mmHg. 4. Critical: the presence of any of the following conditions. 1) Respiratory failure, require mechanical ventilation, 2) shock, 3) other acute organ failure. (Both groups classified also as a severe cases).

Ethical consent:

An approval of the study was obtained from Minya University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation. 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

The analysis of the data was carried out using the IBM SPSS 20.0 statistical package software. Data were expressed as mean, standard deviation (SD), minimum and maximum of range for quantitative parametric measures and median (range) for non-parametric data, in addition to both number and percentage for categorized data. To assess potential risk factors for the occurrence of post COVID-19 symptoms, a forward-stepwise binary logistic regression analysis was performed. For all analyses, a P value less than 0.05 was considered statistically significant.

RESULTS

Table (1): after revising 164 patients with post covid symptoms 90 male and 74 female with different age groups from 17 to 82 years, with 21% with hypertension, 20% with DM, 7% with IHD and 5% with CKD and bronchial asthma. From their medical reports, the patients were classified according to disease severity into mild (50%), moderate (37%), severe (8%) and critical (5%). The patients were also classified according to the initial presenting symptom into dry cough (28.7%), anosmia (25.6%), dyspnea (18.3%), GIT symptoms (17.1%) and fever (10.4%).

Table (1): Sociodemographic and clinical data of studied patients:

	Total (N=164)
Age (years)- Median (Range)	50 (17-82)
Sex	
Female	74 (45.1%)
Male	90 (54.9%)
Comorbidities	
Smoking	47 (28.7%)
Hypertension	35 (21.3%)
Diabetes Mellitus	33 (20.1%)
Chronic Kidney Disease	8 (4.9%)
Bronchial Asthma	8 (4.9%)
Ischemic Heart Disease	12 (7.3%)
Cancer	10 (6.1%)
Female	74 (45.1%)
Case classification	
Mild	82 (50.0%)
Moderate	61 (37.2%)
Severe	13 (8%)
Critical	8 (5%)
Initial presenting symptom	
Dyspnea	30 (18.3%)
Dry cough	47 (28.7%)
Anosmia	42 (25.6%)
GIT symptoms	28 (17.1%)
Fever	17 (10.4%)

Table (2): it shows the median of variable hematological and biochemical laboratory investigations including: CBC, Neutrophil-Lymphocyte Ratio (NLR), Neutrophil to lymphocyte ratio (NLR), liver enzymes, renal function, serum LDH, ferritin, CRP and D-dimer.

Table (2): Laboratory findings among the studied group:

	Total (N=164)
Hemoglobin level (g/dl) Mean±SD	12.1±2
Plateletes (x10³/cumm) Median (	231
WBCs (x10³/cumm) Median	6.8
Neutrophil % Mean±SD	62.7±3.4
Neutrophil count (/cumm) Median	4160
Monocytes % Median	5
Monocytes count (/cumm) Median	325
Lymphocytes % Median (Range)	23
Lymphocytes count(/cumm) Median	1615
NLR- Median	2.6
LMR- Median	4.9
ALT (U/L) **Mean±SD**	327
AST (U/L) **Mean±SD**	31.3±20.6
Urea (mg/dl) **Mean±SD**	46±.7
Creatinine (mg/dl) **Mean±SD**	1.5±0.08
CRP (mg/l) Median	17
LDH (U/L) Median	350
Ferritin (ng/ml) Median	253.5
D-dimer (mg/l) Median	0.5

WBCS= white blood cells, NLR= neutrophil lymphocytes ratio, LMR= lymphocytes monocytes ratio, ALT=alanine transaminase, AST=aspartate transaminase, CRP= C-reactive protein, LDH=lactate dehydrogenase.

Table (3); post Covid 19 symptoms were reported in about 79 % of the studied patients. About 42.7% of the studied cohort reported neuropsychiatric symptoms and 26.8% of the patients reported respiratory symptoms with predilection of anxiety in non-severe cases (p value **0.015)** and chronic dyspnea in severe cases (p value **0.001).**

Table (3): Prevalence post covid symptoms in the studied patients with body systems affection:

	Total	Non-severe (N=143)	Severe (N=21)	*P* value
Post-COVID fatigue and neuropathy				
Yes	25 (15.2%)	24 (16.8%)	1 (4.8%)	0.204
No		119 (83.2%)	20 (95.2%)	
Vertigo and headache				
Yes	15 (9.1%)	15 (10.5%)	0 (0.0%)	0.221
No		128 (89.5%)	21 (100.0%)	
Flaring of asthma				
Yes	14 (8.5%)	13 (9.1%)	1 (4.8%)	>0.99
No		130 (90.9%)	20 (95.2%)	
Anxiety symptoms				
Yes	31 (18.9%)	31 (21.7%)	0 (0.0%)	**0.015***
No		112 (78.3%)	21 (100.0%)	
Arthralgia				
Yes	10 (6.1%)	10 (7.0%)	0 (0.0%)	0.364
No		133 (93.0%)	21 (100.0%)	
Skin lesions				
Yes	6 (3.7%)	5 (3.5%)	1 (4.8%)	0.567
No		138 (96.5%)	20 (95.2%)	
Dry cough				
Yes	14 (8.5%)	13 (9.1%)	1 (4.8%)	>0.99
No		130 (90.9%)	20 (95.2%)	
Chronic dyspnea				
Yes	16 (9.8%)	9 (6.3%)	7 (33.3%)	**0.001***
No		134 (93.7%)	14 (66.7%)	
System affected				
Respiratory		44 (26.8%)		
CNS		70 (42.7%)		
Skin		6 (3.7%)		
Musculoskeletal		10 (6.1%)		
No		34 (20.7%)		

Table (4); by applying univariate binary logistic regression analysis, it was found that smoking and disease severity are significantly associated with chronic dyspnea while chronic fatigue associated with DM.

Table (4): Univariate logistic regression analyses for post COVID-19.

Dependent variable	Variable	Crude OR (95% CI)	*p* value
Chronic dyspnea	**Age (years)**	1.04 (1-1.09)	**0.04***
	Smoking	3.72 (1.3-10.68)	**0.015***
	WBCs (x10³/cumm)	1.13 (1.03-1.24)	**0.011***
	Neutrophil (/cumm)	1.07 (1.02-1.11)	**0.005***
	Neutrophil count (/cumm)	1 (1-1)	**0.004***
	NLR	1.18 (1.05-1.32)	**0.005***
	LDH (U/L)	1 (1-1)	**0.025***
	Ferritin (ng/ml)	1 (1-1)	**0.006***
	Severity	7.44 (2.4-23.06)	**0.001***
Fatigue	**DM**	6.45 (2.58-16.12)	**<0.001***
Vertigo and headache	**CRP (mg/l)**	1.01 (1-1.02)	**0.009***
Anxiety	**Age (years)**	1 (0.9-1)	**0.034***
	BA	4.8 (1.1-20.3)	**0.034***
	WBCs (x10³/cumm)	0.9 (0.8-1)	**0.02***
	Neutrophil count (/cumm)	1 (1-1)	**0.041***
	Monocytes count (/cumm)	1 (1-1)	**0.016***
	LMR	1.1 (1-1.1)	**0.019***
Skin lesions	**IHD (mg/dL)**	7.4 (1.21-45.41)	**0.031***
	Monocytes count (/cumm)	1 (1-1.01)	**0.011***
Dry cough	**Age (years)**	1.05 (1-1.09)	**0.045***
	HTN (g/dl)	3.13 (1.01-9.72)	**0.049***
	IHD (mg/dL)	4.27 (1.01-18.1)	**0.049***

Table (5); multivariate analysis found that anxiety symptoms clearly associated with bronchial asthma, while ischemic heart diseases leads to dry cough and chronic dyspnea was highly associated with smoking and disease severity.

Table (5): Multivariate logistic regression analyses for post COVID-19 symptoms:

Dependent variable	Variable	Crude OR (95% CI)	P value
Anxiety	Age (years)	0.97 (0.94-1)	**0.037***
	BA	5.67 (1.21-26.55)	**0.028***
Skin lesions	Monocytes count	1 (1-1.01)	**0.02***
Dry cough	IHD	4.27 (1.01-18.10)	**0.049***
Chronic dyspnea	Smoking	3.73 (1.17-11.86)	**0.026***
	Ferritin	1 (1-1)	**0.01***
	Disease severity	5.8 (1.76-19.12)	**0.004***

DISCUSSION

Persistence of symptoms for variable period of time after acute covid-19 infection has been reported in several studies. **Greenhalgh et al.** [3] defined post-acute covid-19 as extending beyond three weeks from the onset of first symptoms and chronic covid-19 as extending beyond 12 weeks. Persistence of symptoms after acute covid-19 is not limited to patients with severe infection but studies also reported that even those patients with mild disease may experience long term symptoms. The most common reported symptoms were cough, fatigue, dyspnea, chest pain, fever, neurocognitive dysfunction, headache and many other symptoms [5, 6]. The persistence of symptoms following the acute stage of the diseases is not specific for COVID-19. Many other infectious diseases can result in symptoms that last for prolonged time [7, 8].

In the present study, post Covid 19 symptoms presented mainly with neuropsychiatric symptoms then respiratory symptoms. The most common reported symptoms in our cohort of patients were the anxiety disorders (18.9%) which include tachycardia, sweating with occasional panic attacks in previously normal individuals, followed by chronic fatigue and neuropathy (15.2%) (Tingling, numbness and tremors in the extremities). Chronic dyspnea was present in 9.8% and it was associated with persistent abnormal radiological finding, vertigo and headache was present in 9.1%. Arthralgia and myalgia were present in 6.1%. A skin lesion distributed mostly on limbs and back was present in 3.7%.

Our results are comparable with those reported by **Carfi et al.** [9] in a cohort of hospitalized COVID-19 patients; they reported that 87% of the patients reported one or more symptoms for two months after the onset of initial symptoms. Similarly, **Goertz et al.** [10] in a survey study of patients with suspected or confirmed COVID-19 found that the majority of the patients still experience variable symptoms at 3 months after the onset of the disease.

Garrigues et al. [11] evaluated 120 hospitalized patients with COVID-19, follow up of those patients after 100 day of their discharge revealed that fatigue was present in 55%, dyspnea was reported by 42% and loss of memory were complained by 34% of the studied cohort. In another study carried out by **Zhao et al.** [12], the most common symptoms reported by patients at 3 month follow up were GI symptoms (30.91%); headache (18.18%); fatigue (16.36%); dyspnea in 14.55%, cough and sputum in1.81%; disturbance in taste sensation in 4%.

Savarraj et al. [13] found that at 3 month follow up 71% of the patients complaining of neurological symptoms with pain was the most reported symptoms (64%) followed by fatigue (42%) and cognitive symptoms (12%).

At present the mechanisms behind the persistence of symptoms in post-acute COVID-19 are still uncertain. Many possibilities could be responsible for example, persistent viraemia and autoimmune reaction. Inflammatory reaction could also be implicated.

In this study and after applying univariate binary logistic regression analysis to assess the possible risk factors for post covid symptoms, it was found that smoking and disease severity are significantly associated with chronic dyspnea with odds ratio 3.72, 7.44 respectively and p value 0.015, 0.001 with significant association also with age, WBCs, neutrophil count, and percentage, NLR, LDH and serum ferritin with odds ratio 1 for each of them.

Previous studies had shown conflicting results regarding the association between the severity of the diseases and development of chronic post-COVID19 symptoms. While **Carvalho-Schneider et al.** [14] showed an association between the severity of the diseases and the development of chronic symptoms some other studies found no significant association [15, 11]. In our study we found that disease severity was significantly associated with persistence of dyspnea at 3 month follow up.

Some studies have evaluated the risk factors for the persistence of symptoms in post-acute COVID-19. The presence of dyspnea in the acute phase of the disease and having Asthma or chronic lung disease was associated with the risk of having chronic dyspnea in two studies [14, 16].

In the current study we found significant association between presences of comorbidities and post COVID-19 symptoms. Diabetes was significantly associated with fatigue with odds ratio 6.45 and p value < 0.001, bronchial asthma with anxiety with 4.8 odds ratio and 0.034 p value. Ischemic heart disease and hypertension were significantly associated with the persistence of dry cough (4.27, 3.13) odds ratio respectively and 0.049 p value. These findings are in accordance with previous study [17].

Multivariate logistic regression analyses showed that young age and bronchial asthma were predictors for the occurrence of anxiety disorder (0.97, 5.67) odds ratio and (0.037, 0.028) p value. Smoking, elevated serum

ferritin and disease severity are predictors for the persistence of dyspnea with (3.73, 1, 5.8) odds ratio respectively and p value (0.026, 0.01, 0.004). IHD was predictors of cough 4.27 odds ratio and 0.049 p value and elevated monocytes count was a predictor for the presence of skin lesion.

Our results are in accordance with some other studies **De Lorenzo et al. [15], Halpin et al. [18], Mazza et al. [19], Taquet et al. [20]** they found that ;younger age, being of female gender, or previous diagnosis of a psychiatric disorder are being risk factors the persistent psychiatric symptoms.

CONCLUSION

It could be concluded that persistence of symptoms is common after the acute phase of COVID 19 infection. Post covid syndrome occurs regardless of the disease severity. Neuropsychiatric symptoms were the commonest reported symptoms. Anxiety disorder was reported more in patients with mild disease. The young age and presence of bronchial asthma were predictors for the occurrence of anxiety. Severity of the disease, serum ferritin level and smoking were predictors for post COVID dyspnea.

Conflict of interest: Nil.

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