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Post COVID-19: a narrative review of a new challenge

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Abstract

COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Though the majority of the patients infected with COVID-19 fully recover, persistent illness and symptoms have been identified among a considerable number of patients. This review summarizes the reported post COVID-19 symptoms, prevalence, and the predicting factors of post COVID-19 condition are also outlined. Post COVID-19 symptoms can range from fatigue, dyspnea, cough, sleep disorders, cognitive impairments, and anxiety or depression that last for weeks or months after the initial recovery. The prevalence of post COVID-19 symptoms varied highly, ranging from 0.42-98%. It can affect anyone with mild to severe acute infection, and females and older adults were found to be at greater risk of developing prolonged symptoms. Proper evaluation of risk involved in the subgroups of COVID-19 patients- would enable earlier diagnosis and better treatment and rehabilitation.

Keywords: *Post COVID-19 condition, post COVID-19 symptoms, persistent symptoms, prevalence symptoms*

INTRODUCTION

The Global context of COVID-19

Coronavirus disease (COVID-19), a highly contagious disease,[1,2] caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),[3–5] was responsible for more than 234 million confirmed cases and more than 4.8 million deaths globally.[6]

Patients who have been infected with COVID-19 are mostly asymptomatic or develop mild to moderate symptoms, whereas some may develop pneumonia as a potential complication.[7] The symptoms and severity of the individuals who have been infected with the disease vary across individuals,[8] as does the recovery time, which is known to be around 14 days for a patient with mild symptoms and 3-6 weeks for a patient with severe symptoms.[9]

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A historical perspective: the post corona viral disease

The survivors of the two viral disease outbreaks of the past two decades similar to the current COVID-19 pandemic, such as Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS), had systemic and neurologic complications, reduced lung function, reduced ability to exercise and mental health issues including stress, anxiety, and depression following hospital discharge.[10,11] Hence, it was anticipated that patients recovered from COVID-19 disease who experienced systemic and neurologic complications during the acute phase might experience these complications in their recovery phase, leading to post COVID-19 condition.[2,12]

The post COVID-19 condition

The range of fluctuating symptoms experienced and scarcity of documented evidence has made it challenging to have a comprehensive definition for the post COVID-19 condition. Thus, as of yet a consensual definition is less well defined.[7] However, of the varying definitions that have been used to define post covid symptoms that last for weeks to months, the National Institute for Clinical Excellence (NICE) defined post COVID-19 condition or "Long Covid" as persistence of COVID- 19 signs and symptoms, that continue to develop after acute COVID-19 can include both ongoing symptomatic COVID-19 and post COVID-19 syndrome. Furthermore, NICE describes ongoing symptomatic COVID-19 as signs and symptoms which persist from 4 to 12 weeks and post COVID-19 syndrome as signs and symptoms that arise during or after an infection consistent with COVID-19 and last for more than 12 weeks and are not explained by an alternative diagnosis.[13]

As per the Centers for Disease Control and Prevention (CDC), experiencing new, returning, or ongoing health problems for 4 or more weeks by people after initial infection with SARS- CoV-2 is described as the post COVID-19 condition.[9]

Associated symptoms and sequelae of post COVID-19 condition

Post COVID-19 symptoms are experienced as clusters of symptoms and can cause functional impairment in any system in the body, with more than 200 different[14] symptoms associated with 10 organ systems.[7] The most commonly reported symptoms are fatigue, shortness of breath (dyspnea), muscle weakness, cognitive dysfunction, sleep difficulties, anxiety, or depression.[3,7,15]

Most frequently identified post covid symptoms by major organ systems include, but are not limited to, general symptoms (fatigue, fever, pain), respiratory symptoms (breathlessness, cough), cardiovascular symptoms (chest tightness, chest pain, palpitation), neurological symptoms (cognitive impairment, headache, sleep disturbance, peripheral neuropathy symptoms, dizziness, delirium), gastrointestinal symptoms (abdominal pain, nausea, diarrhea, anorexia, and reduced appetite), musculoskeletal symptoms (joint pain, muscle pain), psychological/ psychiatric symptoms (symptoms of depression, symptoms of anxiety), ear, nose and throat symptoms (tinnitus, earache, sore throat, dizziness, loss of taste and/ or smell), dermatological symptoms (skin rash).[13,7,12]

Prevalence of post COVID-19 condition

The World Health Organization (WHO) states, one-quarter of individuals infected with SARS-CoV-2 experience symptoms of post COVID-19 condition for at least 30 days, and 1 in 10 experience symptoms that persist beyond 12 weeks.[16]

Patients who have the most severe illness in the initial phase of the infection, especially those who require an intensive care unit (ICU) admission, are more likely to experience long-term health consequences.[12]

Furthermore, the prevalence of post COVID-19 symptoms also varies with increasing age, previous health status, presence of comorbidities, and the number of symptoms in the acute phase.[10,17] Moreover, double vaccination reduces the risk of post COVID-19 condition by reducing the chance of becoming infected.[18]

The burden of post COVID-19 condition

Individuals who experience the post COVID-19 condition have reduced cognitive and physical status, resulting in difficulties in returning to the normal state of health and have resulted in increased health care utilization and supportive needs significantly impacting their lives and their livelihoods,[7] including limitations in their ability to perform daily activities, and difficulty returning to their jobs.[19] Moreover, it has an impact on mental health and may face significant economic

consequences by those who have been affected, their families, and by society and may place a substantial burden on the health system.[12,14,19]

As the number of individuals recovering from COVID-19 grows, concerns over their health-related issues after being discharged from the hospital have increased.[1] Though the majority of the patients infected with COVID-19 fully recover, persistent illness and symptoms remain among a considerable fraction of patients for weeks or months even after the initial recovery.[3,13,1] Evaluation of symptoms, factors associated and pathophysiology of the post COVID-19 condition is essential in delivering better healthcare for the patients to manage the condition and prevent the condition in future patients. Hence this narrative review focused on published observational studies investigating post COVID-19 condition in severe and mild COVID-19 infected patients.

METHODS

A literature search was performed in PubMed to identify studies on post COVID-19 condition, the keywords used in the search were “SARS-CoV-2”, “COVID-19”, “long COVID”, “COVID-19 sequelae”, “severe acute respiratory syndrome coronavirus 2”, “post COVID-19 symptoms”, “post COVID syndrome”, “post-acute COVID-19 syndrome”, “persistent symptoms”, “PASC”, “PCS”, “fatigue”, “shortness of breath”, “anosmia”, “persistent symptoms”, “home isolates”. First, the titles and abstracts of the resulting citations were screened, then the relevant articles were selected after reading the full text. Finally, the extracted data were tabulated and the findings of selected articles were summarized and discussed.

Eligibility criteria

Studies that met the following criteria were included, observational studies that reported on post COVID-19 symptoms and prevalence, published in English, and not a review.

RESULTS

Altogether 15 articles were included in the review. These were conducted in the United Kingdom(n=4), USA(n=2), Italy(n=2), Germany(n=1), France(n=1), China(n=2), Spain(n=1), Norway(n=1) the Netherlands(n=1). The length of follow-up ranged from four weeks to 6 months. The sample size of the studies ranged from 100 to 236,379 patients, and 6 studies included both severe and non-severe patients. Of the 15 studies, 10 were cohort studies, one was a cross sectional study, others were described as single-center clinical survey, prospective single center follow up study, and retrospective and prospective observational studies. The studies included in this study are summarized in Table 1.

Table 1. Summary of findings on the prevalence of post COVID-19

Reference, country and study design	Follow up periods	Sample size and mean age	H/ NH	severity	Symptoms								
					Respiratory	General	Cardiovascular	Neurological	Gastrointestinal	Musculoskeletal	Psychological	Dermatological	Others
Huang *et al.* 2021 Prospective, cohort study in Wuhan, China	6 months post symptoms onset	n = 1733 who were discharged from the hospital with a median age of 57	H	Severe	-	Fatigue or muscle weakness 81%	Palpitation 11% Chest pain 4%	Headache 3% Dizziness 8% Sleep disorder 26%	Decrease appetite 9% Diarrhea/ vomiting 4%	Joint pain 15%	-	Hair loss 24% Skin rash 3%	Taste disorder 7% Smell disorder 12% Sore throat 4%
				Non-severe	-	Fatigue or muscle weakness 66%	Palpitation 11% Chest pain 9%	Headache 2% Dizziness 8% Sleep disorder 27%	Decrease appetite 10% Diarrhea/ vomiting 6%	Joint pain 12%	-	Hair loss 22% Skin rash 4%	Smell disorder 13% Taste disorder 9% Sore throat 5%
Garrigues *et al*. 2020 Prospective, single center follow up study in France	3-4 months post admission	n = 120 who were discharged from a hospital with a median age of 63.2	H	Severe	Cough 25% Dyspnea 50%	Fatigue 58.3%	Chest pain 8.3%	Attention disorder 16.7% Memory loss 20.8% Sleep disorder 33.3%	-	-	-	Hair loss 25%	Ageusia 16.7% Anosmia 8.3%

				Non-severe	Cough 14.6%% Dyspnea 40%	Fatigue 54.2%	Chest pain 11.5%	Attention disorder 29.2% Memory loss 37.5% Sleep disorder 30.2%	-	-	-	Hair loss 18.8%	Ageusia 9.4% Anosmia 14.6%
Halpin *et al*. 2021 A cross sectional evaluation in the UK	1-2 months post discharge	n = 100 severe and non-severe patients with a median age of 58.5 and 70.5 who were discharged from a University hospital	H	Severe	Breathlessness 66%	New fatigue 72%	-	PTSD 47% Concentration issues 34%	-	-	-	-	-
				Non-severe	Breathlessness 60%	New fatigue 72%	-	PTSD 23.5% Concentration issues 33.8%	-	-	-	-	Speech & swallow deficit 42.6%
Wang *et al.* 2020 Prospective cohort study in Wuhan, China	1 month after discharge	n = 147 who were discharged from Tongji hospital with a median age of 49	H	Severe	Cough 23.19% Dyspnea 13.04%	Fever 7.25% Fatigue 7.25%	Chest tightness 5.8% Chest pain 1.45% Palpitation 1.45%	-	-	-	-	-	-

				Non-severe	Cough 40.32% Dyspnea 1.61%	Fever 3.23% Fatigue 7.25%	Chest tightness 6.45% Chest pain 4.84% Palpitation 3.23%	-	-	-	-	-	-
Lorenzo *et al.* 2020 Retrospective and prospective cohort study in Milan, Italy	1 month after discharge	n = 185 patients with a median age of 57 who discharged from San Raffle University Hospital	H	Severe	Mild dyspnea 18.6%	-	Cognitive impairment 18.6%	Insomnia 24.6% Anxiety 25.4% PTSD 14.3%	-	-	-	-	-
				Non-severe	Mild dyspnea 18.6%	-	Cognitive impairment 28.6%	Insomnia 24.6% Anxiety 25.4% PTSD 14.3%	-	-	-	-	-
Moreno -Perez *et al.* 2021 Prospective cohort study in Spain	2-3 months post covid onset	n = 277 who survived and discharged from emergency department with a median age of 56	H	Severe Non-severe	Dyspnea 34.4% Cough 21.3%	Fatigue 34.8%	-	Headache 17.8%	Diarrhea 10.5%	Joint pain 19.6% Muscular pain 19.6%	-	-	Loss of taste/smell 21.4%
Carfi *et al*. 2020 Single center, clinical and survey in Italy	60.3 days	n= 143 patients with a median age of 56.5 discharge	H	Severe	Dyspnea 43.4%	Fatigue 53.1%	Chest pain 21.7%	-	-	-	Joint pain 27.3%	-	-

		after recovery from COVID-19											
Taquet *et al.* 2021 Retrospective cohort study in the United State	6 months	n= 236,379 survivors of COVID-19 with a median age of 46	H	Severe	-	-	-	-	Mood disorder 4.22% Anxiety disorder 7.11% Psychotic disorder 0.42%	-	-	-	-
Ayoubkhani *et al*. 2021 Observational retrospective cohort study in the UK	140 days	n= 47,780 patients with a median age of 64.5 discharge following COVID-19	H	Non-severe	Respiratory disease 29.6%	-	-	-	-	-	-	-	-
Davis *et al.* 2021 International cohort study in the UK	7 months	n = 3762 responded from 56 countries (out of responders 44% were sought for hospital based care)	NH	Non-severe	-	-	-	Cognitive dysfunction 88% Headache 77% Memory impairments 72.8%	-	-	-	-	Taste and smell disorder 57.6%
Blomberg *et al*. 2021 Prospective cohort study) in Norway	6 months	n = 312 COVID-19 confirmed hospitalized patient and home isolated patient (out of 65 were hospitalized)	NH	Non-severe	Dyspnea 15%	Fatigue 30%	Palpitation 6%	Concentrated problem 19% Memory problem 18%	-	-	-	-	Disturbed taste/ smell 27%

		with a median age of 46						Headache 11% Dizziness 10%					
Augustin *et al*. 2021 Longitudinal prospective cohort study in Germany	7 months	n = 958 patients with confirmed mild or asymptomatic COVID -19 with a median age of 43	NH	Non-severe	Shortness of breath 13.6%	Fatigue 14.2%	-	Headache 3.4%	-	-	-	-	Anosmia 14.7% Ageusia 11.0%
Sudre *et al.* 2020 Prospective observational cohort study in the UK	28-56 days	n= 4,182 users of the COVID symptom study	NH	Non-severe	-	Fatigue 97.7%	-	Intermittent headache 91.2%	-	-	-	-	-
Goërtz *et al*. 2020 Prospective observational study in the Netherland and Belgium	Median of 79±17 days	n = 2113 Facebook group for coronavirus patients with persistent complaints (out of which 112 were hospitalize d) with a median age of 47	NH	Non-severe	Dyspnea 87%	Fatigue 93.3%	Chest tightness 71.9% Cough 68.1%	Headache 79.1% Dizziness 49.6%	-	Muscle pain 71%	-	-	Sore throat 54.5%
Tenforde *et al.* 2020 Retrospective observational study in the United State	14-21 days	n= 274 outpatient with a median of 42.5	NH	Non-severe	Dyspnea 29% Cough 43%	Fatigue 35%	-	-	-	-	-	-	-

H- Hospitalized NH- Non hospitalized

Prevalence of Post covid-19 symptoms

In most of the studies post COVID-19 symptoms were measured by administering a survey questionnaire, some studies have used validated measurements such as the modified British Medical Research Council (mMRC) dyspnea scale, and Women's Health Initiative Insomnia Rating Scale(WHIIRS) and a few have used both. More than 20 different symptoms were reported across all included studies. Fatigue was the most frequently reported symptom among studies followed by dyspnea, cough, headache, and smell or taste disorders.

Patients with severe COVID-19 were highly likely to experience symptoms at least 2-months post discharge. An Italian study by Carfi *et al.* examined 143 patients, of these 73% were diagnosed with interstitial pneumonia, found that only 18% were free from any COVID-19 related symptom, 32% had one or two symptoms and 55% reported having three or more symptoms at a mean duration of 60 days.[20] A study by Wang *et al.* found that 48.09% of patients had one or more symptoms in the first and second week following discharge.[1]

Goertz *et al.* found that more than 99% of non-severe individuals had persistent symptoms even 79 days after the infection.[15] Ayoubkhani *et al.* reported nearly one third of individuals who were discharged from hospital after the acute infection was readmitted and the readmission rate was four times higher. 1 in 10 died post discharged and the rate was greater than the controls.[19]

A large cohort study of COVID-19 infected patients from Germany that were prospectively followed up for 7 months reported that the presence of at least one characteristic symptom at four months was 28%, and 35% at seven months post-acute infection.[14] Huang *et al.* showed that 76% of the adult patients discharged from the hospital reported having at least one symptom at 6 months follow up with the most common symptoms being fatigue, muscle weakness, and sleep difficulties.[3] In a cohort of 4182 COVID-19 infected patients, 13.3% of individuals had symptoms lasting beyond 28 days and 2.3% had symptoms persisting over 12 weeks.[7]

Persistent symptoms

A wide spectrum of post covid-19 symptoms was reported across studies beyond the acute illness, with the most frequently revealed symptoms being general, neurological, and pulmonary symptoms.

A study by Goertz *et al.* reported that 93.9% of non hospitalised patients had fatigue at 3 months following symptom onset.[15] Fatigue was the most commonly reported symptom after acute COVID-19 among other studies.[20,12] Moderate or severe fatigue was more frequently reported in female patients with non-severe COVID-19.[12]

Dyspnea was one of the most frequently reported respiratory symptoms among studies. Garrigue *et al.* reported that 50% and 40% of severe and non-severe COVID-19 patients respectively experienced dyspnea following 110 days post discharge.[15]

Augustine *et al.* reported anosmia (14.7%) was the most common symptom, and ageusia (11%) persisted even after a median of 6.8 months following initial infection.[14]

A study from UK by Sudre *et al.* disclosed that cardiac symptoms including palpitation, tachycardia, neurological symptoms (concentration deficits, memory issues, tinnitus, earache), and peripheral neuropathy symptoms were the most common symptoms among individuals with symptoms persisting beyond 28 days compared with those with alleviated symptoms within 10 days.[21]

In a study by Taquet *et al.* that assessed neurological and psychiatric symptoms in patients with COVID-19 compared with matched controls diagnosed with other respiratory tract infections reported increased rates in neurological or psychiatric symptoms at 6-months disease onset. The first diagnosis of mood disorder was 4.22%, anxiety, and psychotic disorder were 7.11% and 0.42% respectively. In the overall cohort, neurological or psychiatric symptoms were reported to occur in 33.62% of patients whereas in patients who received intensive therapy unit treatments this was reported to be 46.2% highlighting the need for follow up of patients who required ITU admission and had encephalopathy during the initial infection.[22]

Cognitive impairment was common even among non-severe COVID-19 patients. A study by Davis *et al.* reported brain fog and cognitive impairments in 85% of participants and the most commonly reported symptoms were lack of concentration (75%) and difficulty in thinking (65%), suggesting more severe neurological issues affecting both the central and peripheral nervous systems. Cognitive dysfunction was present in all age groups and increased over the first three months.[7]

Predicting factors of post COVID-19 condition

One study assessed the predicting factors as their preliminary objective,[21] and a few of the included studies[12,14,15,24,25,23] reported associations between persistent symptoms and certain factors. The studies reported severity in the acute phase, greater body mass index, and being female as the strongest predictors for persistent symptoms. However, according to Moreno-Perez *et al.*, no baseline clinical aspects of patients or features of the initial infection behaved as independent predictors of post COVID-19 condition development.[26]

Age and gender

A study by Sudre *et al.* based on self-reported symptoms found increasing age as the strongest predictor of developing long covid, significantly associating with age, rising from 9.9% in patients between 18-49 years to 21.9% in those over 70 or more. In the same study, a higher proportion of post COVID-19 symptoms was observed in females compared with males.[21]

In line with these results, Lorenzo *et al.* found that older age was a strong predictive factor of post COVID-19 condition of both with and without severe COVID-19.[25] Tenford *et al.* found that 35% had not returned to their normal state of health and the proportion differed across age groups, 26%, 32% respectively in among those 18-34 years, 35-49 years, and 47% of individuals aged $\geq$ 50 years.[23]

Initial symptoms

Sudre *et al.* disclosed that patients with more than five symptoms in the first week particularly fatigue, headache, dyspnea, hoarseness of voice, and myalgia had an elevated risk of developing post covid condition. It was found to be the strongest predictor leading to post COVID-19 condition in all age groups in both males and females. While the loss of smell was the most predictive symptom of long COVID in elderly patients aged over 70.[21] Similar results were reported in a study by Augustine *et al.*, where prevalent symptoms beyond 4 to 7 months post initial infection were associated with lower serum lgG titers, anosmia, and diarrhea at disease onset.[14]

Comorbidities and severity of acute COVID-19

Sudre *et al.* suggested that comorbidities could be predictive in developing post COVID-19 condition in adults more than 70 years of age. Particularly asthmatic individuals had a heightened risk of experiencing post COVID-19 symptoms.[21] Tenforde *et al.* reported that individuals with three or more comorbidities including obesity and psychiatric conditions were associated with delayed return to the baseline health status.[23]

Halpin *et al*, reported that patients managed in ICU during the acute phase had a greater prevalence of symptoms in almost all reported symptom categories despite being a younger and less comorbid group. Notably, levels of PTSD symptomatology were found to be twice as high in ICU managed patients compared to ward patients.[12] Huang *et al.* disclosed that the risk of having at least one symptom among severely ill patients was higher than those without severe symptoms and more issues in mobility, pain or discomfort, and anxiety or depression than with non-severely ill patients.[3]

However, Garrigues *et al.* reported no statistically significant variation between severe and non-severe patients in terms of reported symptoms.[27]

DISCUSSION

Available data indicates a significant proportion of patients' experience persisting symptoms following recovery of acute COVID-19. Large variation in prevalence estimates and symptoms can be observed. Variability may be due to the differences in methods of recruiting participants, the range of symptoms investigated across studies, and the use of different measurement techniques and case definitions of symptoms. A direct comparison is therefore not possible. Most of the

surveys lacked controls, so it is not certain how much of the symptoms are COVID-19 specific or more broadly related to a period of illness. Most of the included studies mainly focused on the frequency of symptoms.

Pathophysiological mechanisms related to post COVID-19 condition are still to be identified and there is no exclusive evidence as to what causes post COVID-19 condition. A potential mechanism that may be responsible for reported prevalent respiratory symptoms is persisting inflammation in the lungs. Inflammatory response in lungs and extrapulmonary sites has been detected using [18F]FDG PET/CT in patients following recovery from COVID-19 suggesting persistent inflammation in lungs due to the infection.[28] Endothelial damages, signs of fibrosis, and microangiopathy have also been observed at autopsy which could be another possible cause for common prevalent respiratory symptoms.[29,30] Evidence of olfactory nerve morphological abnormalities at magnetic resonance imaging, suggests the potential damages to olfactory neuronal pathways causing persistent smell impairments.[31] The other possible mechanism that may contribute to these certain persistency of symptoms is brain hypometabolic activity. Brain hypometabolism has been identified in specific cerebral areas in patients with persistent anosmia/ageusia, and fatigue months following acute infection and is likely caused by inflammation.[32]

The findings of studies indicate some factors that affect or certain groups that are differentially affected. Individuals of all ages may experience prolonged symptoms following initial infection. However, not every one of all ages seems to be equally vulnerable. Older age was associated with a greater likelihood of developing post COVID-19 condition,[19] and the presence of post COVID-19 symptoms was more frequently associated with the female gender.[14] Increased risk in older age may be due to physiological changes associated with aging. Higher prevalence rates in females may be attributed to biological sex differences or could also be due to the higher tendency in women reporting their symptoms than men. Disaggregated data on age and gender are rarely reported, making it difficult in understanding the biological factors that may lead to post COVID-19 condition. There is little evidence on the association of ethnicity and post COVID-19 condition. Halpin *et al.* examined the association of ethnicity and found that the Black Asian and Minority Ethnic patients (42.1%) were more likely than White participants (25%) to have dyspnea.[12]

The common limitation of the studies discussed in this review is the use of a relatively small sample size and the use of questionnaires or telephone interviews which could be subjected to recall bias limiting its validity and representability. Most of the surveys were based in higher income western countries, these findings are therefore less likely to be generalizable to other populations. Furthermore, the majority of the studies lacked matched controls, limiting the evaluation of COVID-19 specific impacts.

CONCLUSION

Post COVID-19 symptoms have been identified in a considerable proportion of patients. Future studies should be carried out to have a better understanding and in treating the condition. This would help enable earlier diagnosis and better treatment and rehabilitation for those who have been affected.

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