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# COVID-19-Related Complications

**Bolutife Fawole, MD[1*], Kadae Phimia, MD[2], Ede Omosumwen, MD[3], Folake Adeleye, MD[4], Bolaji Elutilo, MD[5], Oluwatoyin Oluwatuyi, MD[6] and Ogechi Okeke, MD[7]**

[1]All Saints University, School of Medicine Dominica, Roseau, Dominica
[2]Peoples' Friendship University of Russia, Faculty of Medicine, Moscow, Russia
[3]Richmond Gabriel University, St. Vincent and the Grenadines
[4]Obafemi Awolowo University, College of Health Sciences, Ile-Ife, Nigeria
[5]Richmond Gabriel University, St. Vincent and the Grenadines
[6]Oba Okunade Sijuwade College of Health Sciences, Igbinedion University, Edo State, Nigeria
[7]University of Nigeria Nsukka, Enugu State, Nigeria

E-mail: fawolebg@gmail.com; kadaephimia@gmail.com; omosumwen.ede@gmail.com; adeleyefolake@gmail.com; elutilobolaji@yahoo.com; toyin.oluwatuyi2000@gmail.com; ogechiokeke486@yahoo.com

*Corresponding author details: Bolutife Fawole, MD.; fawolebg@gmail.com

## ABSTRACT

The COVID-19 Pandemic has affected millions of people worldwide. In its aftermath some individuals have been left with a sequela. This article aims to describe the symptoms and clinical findings reported among patients with Long-COVID and discuss treatment options. Authors collected, analyzed, and presented information on pulmonary, cardiovascular, endocrinological and neurological complications of COVID-19. Literature review was done across multiple journals from January 2020 till July 2022 using key words, such as COVID-19, long-COVID, cardiovascular, pulmonary, endocrinological and neurological complications. These words were used as Mesh terms, in order to cover other relevant possible words missing. Similar works found in the references of the studies identified were also reviewed. Long-COVID patients reported a number of findings including dyspnea, pneumonia, myocarditis, thyroiditis, increased complications of diabetes mellitus and neurological complications. Clinical findings indicate the likelihood of compromised health in some individuals with long-COVID. Treatment modalities recommend an interdisciplinary approach to ensure an all-encompassing perspective to rehabilitation and enhanced surveillance in individuals with predisposed risks factors.

***Keywords:*** COVID-19; long COVID; COVID-19 complications; cardiovascular complications; pulmonary complications; endocrinologic complications; neurologic complications

## INTRODUCTION

The COVID-19 pandemic has resulted in over 520 million confirmed cases worldwide [1]. The majority of individuals experience resolution of symptoms within two to three weeks [2]. In certain patients, Covid-19 infection has left lasting symptoms. These symptoms have led to the description of a post-COVID syndrome also referred to as long-COVID. A syndrome involving an extended course of various physical and neuropsychiatric symptoms persisting for more than 4-12 weeks without an alternative explanation leading to a depreciation in the quality of life. [2,3]

The National Institute for Health and Care Excellence (NICE) has suggested the following terminology; "Acute COVID-19", for signs and symptoms of COVID-19 lasting up to four weeks, "Ongoing symptomatic COVID-19", for signs and symptoms of COVID-19 lasting 4–12 weeks, "Post-COVID-19 syndrome", for symptoms that develop during or after COVID-19 infection and persist for more than 12 weeks; Ongoing symptomatic and Post-COVID-19 syndrome may be both included in the term "Long COVID-19". [4,5]

## METHODS

Authors collected, analyzed, and presented information on pulmonary and cardiovascular complications of COVID-19. English language literature was searched across multiple journals until May 2022 using combinations of relevant terms, such as COVID-19, long-COVID, cardiovascular, pulmonary, endocrinologic, and neurologic complications. These words were used as MeSH terms, in order to cover other relevant possible words missing. Similar works found in the references of the studies identified were also reviewed.

## PREVALENCE OF LONG COVID

According to Betty Rahman et al [6], the prevalence of long covid varies across and within many countries including UK 1.6-71%, China 49-76%, India 22%, and the USA 16-53% [6].

Several studies have estimated overall prevalence as much as 30- 90 days, six months, and up to one year as well as the characteristics of symptoms commonly reported.

In an ongoing community-based survey by the Office of National Statistics of the prevalence of long COVID, an estimated total of two million people living in private households have self-reported experiencing symptoms of long COVID [defined as symptoms continuing for greater than four weeks post initial suspected acute infection] with 71% reporting symptoms adversely affecting their day-to-day activities significantly. Fatigue 55%, shortness of breath 32%, cough 23%, and muscle ache 23% are the top four most commonly reported symptoms [7].

In another study of incident cases recruiting 4182 participants who self-reported symptoms using a study app after post-acute symptoms, 558 (13.3%) experienced long COVID greater than or equal to four weeks, 189 (4.5%) greater than or equal to eight weeks and 95 (2.3%) greater than or equal to 12 weeks

Long COVID has been reported in higher prevalence among people who required hospitalization [8, 9] versus those who did not require hospital care. Indicating that the increased severity of acute infection and use of invasive management protocols such as intubation and mechanical ventilation, presence of preexisting comorbidities (asthma, hypertension and obesity been the most commonly reported) [54, 55] are important determinants of long covid prevalence as well as ages 35-69 years [7].

In China a study enrolling 1733 participants, median age 57 years and who were discharged from the hospital and followed for a period of 6 months include fatigue or muscle weakness in 1038 of 1655 (63%), sleep difficulties in 437 of 1655 (26%) and anxiety and depression in 367 or 1617 (23%) [8].

Other factors that affect prevalence estimates include disparities in vaccinations, Covid-19 variants, study sample size and the use of varying non-covid control groups, source of enrollment, variability of the methodology used, psychodynamic factors and timing of assessment [6].

**RISK FACTORS**

In comparison to men, long covid symptoms were more commonly seen in women, other risk factors included; patients with preexisting respiratory diseases, intensive care unit patients, especially patients who had prolonged hospital admissions [10]. It was also linked to having type 2 diabetes, Epstein Barr Virus, autoantibodies, low cortisol levels, and genetics places an individual at risk of developing long covid symptoms [11].

**PULMONARY COMPLICATIONS**

A range of pulmonary symptoms may occur; dyspnea on exertion, restrictive pulmonary conditions, diminished diffusing capacity for carbon monoxide (DLCO) as well as fibrotic lesions on high resolution computed tomography (HRCT) all associated to the intensity of acute COVID-19 infection [4].

The Swiss Observational COVID-19 study grouped participants into mild/moderate and severe/critical clinical signs. Mild/moderate with clinical signs of pneumonia and peripheral oxygen saturation ($SpO_2$) ≥90%. Severe disease with pneumonia and $S_pO_2$<90% > 30 breaths/min or critical disease i.e. acute respiratory distress syndrome (ARDS), sepsis, septic shock, and multi-organ failure (severe/critical) [12].

Results revealed normal lung function after mild to moderate COVID-19 Infection. Patients with more severe COVID-19 had lower lung volumes which fell within the normal range.

They did however have reduced DLCO, 6-minute walk distance (6MWD), and oxygenation. Patients recorded normal spirometry at follow-up, and those with abnormal pulmonary function tests (PFT) exhibited a restrictive pattern on evaluation of total lung capacity (TLC) or both TLC and forced vital capacity (FVC). [8,12].

Another study following up on 57 patients 30 days after discharge for acute COVID-19 also reported a decrease in DLCO in 52.6% of participants and in addition a decrease in respiratory muscle strength in 49.1% of participants. [13]. A study by Zhao et al following up on COVID-19 survivors three months after recovery revealed lung function abnormalities in 14 patients. DLCO anomalies were the most prevalent symptom. Results also indicated that higher levels of D-dimer at admission were associated with DLCO% predicted < 80% indicating that D-dimer might be a potential biomarker for the prediction of DLCO decline in patients with COVID-19. [2,14]

**IMAGING FINDINGS**

Huang et al. revealed on follow up computer tomography (CT) scan after 30 days revealed 54.4% of patients had residual abnormalities. The majority of abnormalities were patchy ground glass opacities in the peripheral regions. Four patients from the severe group had evidence of pulmonary fibrosis and severe patients tended to have significantly higher CT scores [13].

Zhao et al revealed one to three lung segments to be involved in 54.55% of patients. 23.64% showed bilateral involvement on chest HRCT scans. Features such as ground glass opacities, interstitial thickening, and crazy paving were the most common findings [14].

**MANAGEMENT OF PULMONARY SEQUELAE**

A study of individualized multidisciplinary rehabilitation in 23 patients of which 87% had pulmonary function impairment resulted in significant improvement of lung function, patients experienced improved forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC). However, a significant amount of patients still had limited DLCO. (37) Rehabilitation has been deemed successful in select cases of long-COVID 19. During rehabilitation, patients are advised to a light aerobic exercise paced as tolerated. Breathing exercises are also incorporated into rehabilitation plans. Reviews recommend rehabilitation plans be personalized to patients as needed [38].

Studies have also shown that patients with severe illnesses are not recommended to begin early rehabilitation and should only be initiated after ruling out contraindications [39]. Further supported by other studies revealing a significant amount of patients experienced relapses, primarily triggered by exercise, physical or mental activity, and stress [40]. It is also of importance that patients with comorbidities be managed to prevent further deterioration.

Other studies have also revealed patients with mild to moderate or on-off symptoms and those who were never hospitalized should be considered candidates for rehabilitation and a failure to do so may see a significant population of long-COVID patients ignored by healthcare systems [41].

**CARDIOVASCULAR COMPLICATIONS**

One study followed 26 college athletes none of whom required hospitalization or antiviral treatment from day 11 to 53 after acute COVID-19 infection. No ST/T wave changes were recorded on electrocardiogram, and ventricular volumes and functions were all normal on trans-thoracic echocardiogram (ECG) and cardiac magnetic resonance imaging (CMR).

Patients recorded normal cardiac enzymes. Four athletes had CMR findings consistent with myocarditis and 2 of these had evidence of pericardial effusion and shortness of breath while the other 2 were symptomatic. Another 12 athletes had late gadolinium enhancement (LGE) [(15].

Another study followed patients from the US Department of Veteran Affairs national database who survived beyond 30 days comparing them to controls without evidence of COVID-19 infection. Results revealed an increased incidence of cardiovascular diseases in all subgroups of patients, non-hospitalized, hospitalized, or admitted to the intensive care unit (ICU) in comparison to the control group [16]. Common conditions included atrial fibrillation, ischemic heart disease, myocarditis, heart failure, and thromboembolic disease. Risks were deemed to be evident regardless of age, race, or sex, and were evident in patients without prior cardiovascular disease prior to COVID-19 [16,17].

**MANAGEMENT OF CARDIOVASCULAR SEQUELAE**

Approaches proposed by experts involved screening of high-risk individuals for cardiac complications and those presenting with symptoms during the acute phase. Screening includes history, blood test panel (C-reactive protein, troponin, B-type natriuretic peptide/NT-proBNP, glycated hemoglobin, lipids), ECG, and transthoracic echocardiography at least eight to 12 weeks from infection. Patients with clinically significant abnormalities after the screening, are recommended to undergo further testing. Non-invasive tests such as CMR, stress single positron emission computed tomography, Holter monitoring, and coronary tomography angiography (CTA) can be considered following screening investigations; invasive coronary angiography or EMB may be indicated for high-risk individuals. Further guidelines have been suggested in the case of athletes and a graded return to exercise is suggested. Management of post-COVID-19 acute coronary symptoms should be in line with the European Society of Cardiology (ESC) and the American Heart Association (AHA) [36].

Management of post-COVID-19 tends to be mainly supportive and may require multidisciplinary care with monitoring of patient symptoms as well as mental health and social service support. Management of pre-existing conditions should be ensured. Calorie restriction and diet, tailored graded exercise, stress reduction, and good sleep hygiene should be emphasized owing to the association between long-COVID and obesity [36].

**ENDOCRINOLOGIC COMPLICATIONS**

- THYROID GLAND

Studies have shown that some patients with COVID-19 have also presented with subacute thyroiditis [18,19,20,21]. This may be due to the direct interaction between the SARS-COV2 with the ACE receptors on the thyroid gland [22,23,24,25]. It may also be due to euthyroid sick syndrome which is seen in critically-ill patients [26].

- DIABETES MELLITUS

Diabetes mellitus is associated with an increased risk of complications in patients with COVID-19 [27,28,29]. Studies conducted in Italy and Germany have shown an increased occurrence and severity of DKA in youth and children with new-onset type 1 diabetes mellitus during the time of COVID-19 with no change in its incidence in the general population [30,31,32].

A case report on a 19-year old male from Germany who presented with DKA and insulin-dependent DM five to seven weeks after asymptomatic COVID-19 infection indicated that he did not have the typical autoantibodies associated with DM 1 [33]. This raises the question as to the pathogenesis of DM 1 in this patient. The authors suggest that since the beta pancreatic cells express the ACE2 receptors which the SARS-COV2 binds to, the direct destruction of the beta pancreatic cells by the virus leads to the lack of the diabetic auto bodies typically seen in DM 1 [33]. Patients with COVID-19 who present with DKA require higher doses of insulin to achieve better control [34].

- ADRENAL GLAND

Findings from a case report of a patient in England, indicate that adrenal hemorrhage (AH) is a rare but potential complication of COVID-19 [35]. In this case report, a 53-year-old man who presented with pleuritic chest pain, shortness of breath and fever was investigated with CT pulmonary angiogram which revealed bilateral pulmonary embolism and possible right adrenal hemorrhage which was confirmed with an abdominal CT [35]. A normal adrenal function was confirmed with a Synacthen test and the patient recovered without complications [35]. On the patient's 5 month follow up, CT imaging indicated a near resolution of the adrenal hemorrhage [35].

**NEUROLOGIC COMPLICATIONS**

- ACUTE CEREBROVASCULAR DISEASE

Acute cerebrovascular disease is one of the more serious and common neurological complications of COVID-19 infection [42]. Despite deep venous thromboembolism prophylaxis, studies showed an incidence of ischemic stroke was 5% in patients hospitalized with COVID-19 in China [43], 2.5% in Italy [44], and 3.7% in Netherlands [45]. Younger patients with COVID-19 have also presented with ischemic stroke [46]. Patients with COVID-19 associated ischemic stroke should be managed with intravenous thrombolysis or vascular thrombectomy if necessary [47].

- ENCEPHALITIS AND ENCEPHALOPATHY

Encephalitis is a rare complication of COVID-19 but has been reported in a number of cases [48]. In a 58-year-old woman who presented with altered mental status, cough, and fever, clinical findings and imaging studies were the bases for the diagnoses [48, 49]. Brain MRI showed hemorrhagic rim-enhancing lesions within the medial temporal lobes, subinsular regions, and thalami [48]. Treatment of increased intracranial pressure and supportive care are key in the management of encephalitis in patients with COVID-19 infection [50].

- GUILLAIN-BARRE SYNDROME (GBS)

Guillain-Barre syndrome has been linked to two cases of COVID-19 infection in Wuhan, China and five cases in Italy [51,52,53]. Patients experienced upper respiratory symptoms ranging from five to 14 days before developing symmetric weakness and there were three patients who developed respiratory failure [51,52,53]. Nasopharyngeal polymerase chain reaction (PCR) test was positive in all patients, chest imaging studies were characteristic of COVID-19 infection, however, cerebrospinal fluid (CSF) did not reveal the presence of SARS-CoV-2 (51,52,53). IVIG was administered to all the patients, but poorer outcomes were observed in the patients who had respiratory failure [51,52,53].

**CONCLUSION**

As we move further away from the initial waves of the COVID-19 pandemic, long COVID has emerged as a major health issue.

This review was designed to analyze and enumerate the pulmonary, cardiac, endocrinologic, and neurologic complications of COVID-19. With regards to the broad range of pulmonary complications that occur as an effect of long COVID, the mild/moderate clinical signs were pneumonia and a decreased oxygen saturation ($SpO_2$) ≥ 90%. The severe clinical signs included ARDS, sepsis, and septic shock, often stemming from pneumonia and $S_pO_2$<90% > 30 breaths/min. DLCO anomalies were the prevailing symptoms, therefore indicating that a possible biomarker for DLCO decline in COVID-19 patients is D-dimer. Imaging findings featured ground glass opacities, interstitial thickening as the most common residual abnormalities.

The widespread cardiovascular complications consisted of atrial fibrillation, ischemic heart disease, myocarditis, heart failure and thromboembolic disease. Among athletes, myocarditis and pericardial effusion, and shortness of breath were present. Diagnosis of cardiac complications was done with CMR, stress single positron emission computed tomography, Holter monitoring, and CTA. Higher risk individuals on the other hand received invasive coronary angiography or EMB. Management of pulmonary complications, include rehabilitation with light aerobic exercise as well as breathing exercises.

Endocrinologic complications include subacute thyroiditis, new-onset DM 1 and adrenal hemorrhage. Imaging studies, clinical presentation and laboratory studies were utilized for diagnosis. Management of these complications included supportive treatment and insulin therapy for new-onset DM 1. Neurologic complications consisted of acute cerebrovascular disease, encephalitis, and Guillain-Barre syndrome. Management of these complications included thrombolytic, ICP reduction and IVIG therapy respectively.

**AUTHOR'S CONTRIBUTIONS**

All authors contributed to the conception, design of the manuscript, literature search, writing of the manuscript and final approval of manuscript.

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**DECLARATION OF COMPETING INTEREST**

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