

## Long-Covid Syndrome: A Multi-Organ Disorder

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### Abstract

Long-COVID Syndrome, a multi-organ disorder, that persists beyond 12 weeks post-acute SARS-CoV-2 Infection COVID-19. Here we provide a definition for this syndrome and discuss the organs that are involved. The involvement of multiple organs is due to that fact that angiotensin converting enzyme-2 receptors (the entry points for the virus), inflammation and oxidative stress (the immediate effects of the virus) effect all systems of the body. We suggest that this is then perpetuated by a resulting autonomic dysfunction. Since the autonomic dysfunction also effects all systems of the body, the initial infection is compounded and perpetuated by the resulting autonomic dysfunction underlying the Long-COVID Syndrome. We discuss the symptoms and suggest therapies that target the underlying autonomic dysfunction to relieve the symptoms, rather than merely treating symptoms. In addition to treating the autonomic dysfunction, the therapy also treats chronic inflammation and oxidative stress. To fully document the autonomic dysfunction, a full assessment of the autonomic nervous system is recommended, including Cardio-Respiratory Monitoring. Specific measurements of Parasympathetic and Sympathetic activity, both at rest and in response to challenges, connects all symptoms of Long-COVID to the documented autonomic dysfunction(s).

**Keywords:** Long-COVID, Multi-Organ Disorder, Autonomic Dysfunction, Inflammation, Oxidative Stress, Symptoms, Treatment, Quality of Life

### Introduction

SARS-CoV-2 Infection COVID-19 is a major pandemic that is worldwide and causing significant mortality and morbidity. About 80% have mild to moderate disease. However, among the 20% with severe disease, 5% develop a critical illness. There is a subset of patients, however, who will have lingering, persistent or prolonged symptoms for weeks or month afterwards, which we termed "Post-Acute Sequelae of SARS-CoV-2 infection" syndrome or simply the "Post-Acute COVID-19 Syndrome" or "Long COVID-19" or just "Long COVID" or "Long Haulers COVID-19" or simply "Long Haulers" or "Post-Covid Syndrome." This has extended the significant worldwide morbidity from this pandemic. It is estimated that about 10% of patients who tested positive for SARS-COVID-19 will remain ill beyond three weeks and a smaller proportion for months. This is a subset that constitutes the Long-COVID syndrome. Globally, there are estimated over 200 million confirmed cases of COVID-19. Although the majority of infected individuals recover, we still do not know the exact percentage that will continue to experience symptoms or complications after the acute phase of the illness is over.

This prolonged phase with morbidity and ongoing symptoms creates significant burden to the patient and burden to the health-care system and is not completely understood. To complicate matters, not only do the long-term effects of those infected by the virus remain largely unknown, there are reports highlighting that sustained transmission and emergent variants continue to cause challenges to healthcare providers throughout the world, and therefore we do not know when the pandemic will cease. While it is estimated that 10% will develop a chronic syndrome, or symptoms that are persistent, this statistic may actually increase. Since this is a new illness, we do not know the cause or characteristics of the long-term sequelae of someone who has recovered from acute COVID, not just the quality of life, including mental health, but the employment and productivity issues become paramount when the acute phase of COVID, the subacute, and the chronic phases occur. In our experience, approximately 20% of people will exhibit symptoms for more than five weeks and 10% will have symptoms for more than 12 weeks.

## History

COVID-19 was reported in Wuhan, China in December 2019. It is caused by a small novel coronavirus. The acute phase of COVID-19 infected patients has been well described and may have varying number of symptoms and intensity. The majority of patients have fever, sore throat, cough, shortness of breath, and chest pain. Although, multiorgan involvement may become extensive. COVID symptoms may be identified in six clusters [1]. These include:

1. Flu-like with no fever, which consist of headache, loss of smell or taste, cough, muscle pains, sore throat, chest pains.
2. Flu-like with fever, which consists of headache, loss of smell or taste, cough, sore throat, hoarseness, fever, loss of appetite.
3. Gastrointestinal, which consists of headache, loss of smell or taste, loss of appetite, diarrhea, sore throat, chest pain, but no cough.
4. Severe level one, fatigue with headache, loss of smell or taste, cough, fever, hoarseness, chest pain.
5. Severe level two, which consists of confusion with headache, loss of smell, loss of appetite, cough and fever, hoarseness, sore throat, chest pain, fatigue, and muscle pain.
6. Severe level three, which is abdominal and respiratory dysfunction with headache, loss of smell or taste, loss of appetite, cough, fever, hoarseness, chest pain, fatigue, sore throat, confusion, muscle pain, diarrhea, shortness of breath and abdominal pain.

The recovery from COVID-19 usually occurs at seven to ten days after the onset of symptoms in mild disease, but could take up to six weeks in severe or critical illness. It is for this reason that mild cases are usually quarantined for between 7-10 days, and severe illnesses are for a more extended period of time. However, it is believed that even when one is ill for 3-6 weeks, they are probably not actively contagious. Some studies have shown that active coughing is indicative of continuing contagiousness. This has not been clarified. Studies have shown that household cases support the highest incidences of contagiousness and that rational for masks appears to be most beneficial with close contacts for prevention.

The most common feature of acute illness is interstitial pneumonia, which may in some cases be complicated by the serious acute respiratory distress syndrome where individuals require high doses of oxygen. This has a high mortality particularly in elderly people who have comorbidities. The cough is usually dry. Laboratory abnormalities may be present and include low lymphocyte counts, elevated inflammatory markers, such as Sed Rate, C-reactive protein, Ferritin, Interleukin 1 and 6, and Tumor Necrosis Factor abnormalities, and others, which will be discussed later. Coagulation system abnormalities may occur (to be discussed later). Clots may form in the acute phase as well as in the subacute phase, especially if there is a history of clots.

## Defining Long-Covid

What exactly is Long-COVID Syndrome? There are many definitions that have been offered. Basically, there are individuals who do not completely recover over a period of weeks, usually 2-3 weeks. Since COVID-19 is a novel disease, there is still no consensus of the definition of Long-COVID-19 symptoms. In a study by Salamanna and coworkers, 20% of the reports of long-term COVID symptoms involved abnormal lung function, 24% involved neurological complaints and olfactory dysfunction, and 55% on specific widespread symptoms, mainly chronic fatigue and pain [2]. The World Health Organization (WHO) developed

a clinical case definition of Long-COVID-19 by Delphi methodology that included 12 domains. However, the understanding of this definition has been going through changes as new evidence emerges and we are gaining a better understanding of the consequences of COVID-19 and its mutations. Usually, three or more months past the acute COVID-19 infection, symptoms that last for at least two months and cannot be explained by alternate diagnoses, may fit this definition. These symptoms include fatigue, shortness of breath, cognitive dysfunction, and symptoms that affect the functional capacity of individuals with daily living. Symptoms may fluctuate, flare up or relapse over time.

Long-COVID or Post-COVID-19 is an umbrella term that refers to symptoms persisting past the initial phase. In addition, Long-COVID-19 may adversely affect multiple organ systems, which include the kidneys, lungs, pancreas and heart. Unfortunately, the lack of a standardized definition for Long-COVID Syndrome presents obstacles for researchers in studying the condition with controlled studies and arriving at a precise diagnosis, algorithms and treatment algorithms. In addition, many patients with Long Covid Syndrome require rehospitalization especially those with comorbidities, such as cardiovascular disease, Diabetes Mellitus, obesity, cancer and kidney disease. There is data to suggest that the evolution of Long-COVID Syndrome is driven by chemicals produced in the body from inflammation called cytokines. Research is ongoing regarding pathogenesis that will be discussed later in this communication. Post-infection olfactory dysfunction occurs in over 60% of those with acute SARS-CoV-2 infection, even in asymptomatic infection, and this represents an important frequent symptom of Long-COVID-Syndrome. Also, loss of taste has been seen. Many patients are not diagnosed with Long-COVID-Syndrome, when in reality their taste or smelling remains impaired as the only symptom.

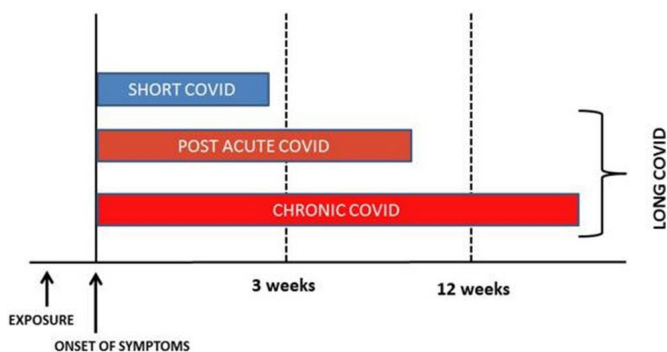
Meta-analysis has shown the prevalence of Long-COVID manifestations. Fatigue and muscle weakness are by far the major symptoms followed by dyspnea and then pain and discomfort. Then there is anxiety and depression and impaired concentration. Insomnia and sleep disorders present with lower frequency. Interestingly, Alopecia has been described as occurring. Chronic cough may persist and arthralgias and myalgias may be present. Chest pain, cognitive impairment, dizziness and headache are also symptoms but less common than the ones above. Persistent sore throat, palpitations, lack of smell, diarrhea, vomiting, fever, blurry vision, lack of taste, nasal congestion, anorexia, nausea, ringing in the ears and rash may be present but at a much lower prevalence. Interestingly, autonomic clusters in the Long-COVID-Syndrome (by COMPASS 31, which is a questionnaire for autonomic symptoms) have identified two clusters. Impaired visual activity and blurry vision were more frequently registered during the acute phase in patients, while depression, chills, weakness, diarrhea, musculoskeletal, palpitations, tachycardia, dryness, cognitive dysfunction, headache, dizziness and tinnitus were more frequently observed in the Long-COVID second cluster. Levels of antibodies to the SARS virus were not different between two clusters. This has given us some insight into one of the main mechanisms of Long COVID Syndrome, mainly autonomic dysfunction, which is an imbalance between the Parasympathetic and Sympathetic nervous systems. It is believed that a chronic inflammatory process, or autoimmune, or even a hormonal imbalance as a consequence of alterations in the hypothalamus-pituitary- adrenal axis may also be operative in conjunction with this acquired autonomic dysfunction with constitutional symptoms as described above.

The term Long-COVID syndrome was first used by Perego and social media to describe symptoms weeks or months after the initial SARS-CoV2 infection [3]. The term "long haulers" was used by Watson and by Yong [3-5]. There may be persistence of one or more symptoms of acute COVID or appearance of new symptoms and they may be relapsing and remitting; therefore, showing the variable presentation of Long-COVID-Syndrome. Interestingly, the majority of people with Long-COVID-Syndrome are PCR negative including any microbiological recovery. It is interesting how many people continue to see infectious disease doctors and seek out other alternative infection diagnoses when serology is continuously negative. Long-COVID-Syndrome or Long-COVID has been defined as the time lag between the microbiologic recovery and clinical recovery [6].

In fact, the majority of those with Long Covid Syndromes have biochemical and radiological recovery. It has been postulated that there are two stages of Long-COVID-Syndrome:

- 1) symptoms that extend beyond three weeks, but less than 12 weeks, which is more of a subacute phase; and
- 2) chronic COVID symptoms that extend beyond 12 months. An interesting diagram and timeline have been postulated, which shows that Short-COVID will generally last less than three weeks from onset of symptoms [7].

Post-acute COVID, or subacute COVID will last from onset of symptoms approximately up to 10-12 weeks and chronic COVID will last from onset of symptoms beyond 12 weeks. See Figure. It would make sense to group the Post-Acute or Subacute COVID, which lasts from up to 10-12 weeks, and then chronic COVID, which lasts more than 12 weeks as Long COVID Syndromes. In this review, however, we are more concerned with those symptoms that last more than 12 weeks, the true long- or prolonged-COVID Syndrome.



**Figure :** Classification of long COVID [7].

Sometimes individuals are fairly asymptomatic, and by the time they develop Long-COVID symptoms, we do not know when the initial infection occurred nor are we certain. They did not undergo any test to confirm SARS-CoV2. When these individuals develop multiple symptoms consistent with a Long-COVID Syndrome, we oftentimes consider them as probable, or possible Long COVID Syndrome, since we cannot confirm that they indeed did have COVID exposure since they were asymptomatic. With individuals who were symptomatic but not tested it is more likely that this is a Long-COVID-Syndrome. The problem is not only in those who have persistent symptoms who have never tested positive for COVID, but similarly in individuals who had upper respiratory tract infections and had a negative COVID test and then developed long prolonged symptoms. The question must be asked, "Did they have a false-negative test performed

too early or too late in the disease course?" Antibodies are unreliable as up to 1/5 patients do not seroconvert, and antibody levels decrease over time and by three months oftentimes are not measurable. Not only is the morbidly important with Long-COVID-Syndrome, but the economic cost to society, as 1/3 people in one survey did not return to their job for up to three weeks after being COVID-positive. Further, this is more common in older people. Not returning to work is often associated with obesity and psychiatric disease. In addition, given the similarity between Long-COVID Syndrome and Autonomic Dysfunction, and the ability of psychosocial stress to trigger symptoms of Autonomic Dysfunction further blurs the distinction between Long-COVID and Autonomic Dysfunction.

Of all the risk factors for individuals that develop the Long Covid Syndrome, it is noted that the risk of COVID is twice as common in women as it is in men. Increasing age is also a risk factor for development of Long-Covid Syndrome. Studies show that individuals who develop Long Covid Syndrome are four years older than those who did not [8]. Patients with five or more symptoms in the acute phase of illness, have a higher likelihood of developing a Long Covid Syndrome. We have empirically found that obesity and increased body mass index is an extremely important risk factor as is female gender. Symptoms that various studies report to be predictors of Long-COVID-Syndrome include diarrhea, anosmia, dyspnea, pleurisy, skin sensitivity, and A blood type [9]. One study showed that a lower SARS-CoV2 IgG titer at the beginning of the observation period was associated with a higher frequency of Long-COVID-Syndrome [10]. Also, the severity of acute COVID-19 suggests that the recovering critically ill patient commonly experiences long-lasting mental health issues that include depression, anxiety, post-traumatic stress, memory disorders, attention deficit disorders, and ongoing brain fog. This is controversial as others have shown that acute disease was not associated with Long-COVID-Syndrome. All of this negativity speaks to a heterogeneous presentation of Long-COVID-Syndrome with risk factors including its time-line.

Even if the virus is cleared, there were high neutralized antibody titers that suggest that the immune system could continue to be overactive and induce this syndrome. Therefore, the question of autoimmunity is raised. This is especially true since viral shedding has shown that persistent fragments of viral genes and body secretions may cause hyperimmune responses, and this may explain some of the persistent symptoms in Long-COVID-Syndrome. Although, lingering Autonomic Dysfunction also presents with auto-immune-like symptoms. Meta-analysis of prolonged COVID-19 looking at age, gender, comorbidities, ethnicity and severity of acute disease confirm that female gender and Long-COVID risk are associated. In addition, increasing age, minority/ethnicity was also associated with Long Covid Syndrome. However, some of these results have been inconsistent [11]. Studies have shown that Long-Covid Syndrome effects with previously hospitalized and non-hospitalized patients are similar. Perhaps, the best-known study from the Office for National Statistics (ONS) study including controlled participants reports that the most common symptoms persisting for 12 or more weeks include fatigue (8.3%), headaches (7.2%), cough (7%, myalgias (5.6%), [12].

A lack of case-controlled studies presents a direct attribution of symptoms that are solely related to COVID-19; however, larger perspective studies with match-controlled groups are needed. Similarly, many of the studies and statistics on Long Covid Syn-

drome are based on Long-COVID cohorts produced in Western Europe on patients recently discharged from the hospital. As a result, there was not enough information on Long-COVID-19 patients in low-to middle income countries and people who were not hospitalized. Also, there are no large studies that focus on children, specifically. This is despite the fact that young children are affected and may be affected by Long-COVID.

### Multiple Organ Systems Involved

The Long-COVID-Syndrome is a complex condition with prolonged heterogeneous symptoms that are related to multiple organ involvement. Long-COVID-Syndrome involves hyperinflammatory and hypercoagulable states that affect all organ systems. It reflects a maladaptation of the Angiotensin Converting Enzyme 2 (ACE 2) pathway. ACE-receptors are present in virtually every organ system. Therefore, it is understandable that many organ systems are susceptible to involvement from direct viral infection and inflammation. As previously mentioned, depending on duration of symptoms, Long-COVID Syndrome may be divided into two stages post-acute COVID, or symptoms extending beyond three weeks but less than 12 weeks, and chronic or Long-COVID where symptoms extend beyond the 12 weeks [13].

Multiple organ sequelae and abnormalities of COVID-19 that may go beyond the acute phase of infection are increasingly being noted as data are being collected. Assessment of key clinical, serological, and imaging features are important to understand the natural history of this disease as it progresses beyond the acute viral infection phase. Workup consisting of pulmonary function tests, chest X-rays, six-minute walk tests, pulmonary embolism workups (when needed), echocardiograms (even serially), and (at times) high resolution CT scans (to assess for fibrosis) should also be considered. These will be discussed under the Pulmonary section. Hematological assessment may lead to extending thromboprophylaxis against clots and high-risk survivors. A neuropsychiatric screening for anxiety, posttraumatic stress, sleep disorders, depression, cognitive impairment, memory abnormalities and other factors associated with brain fog is important. A neuropsychiatric screening should include a full autonomic dysfunction test, especially in patients with orthostatic intolerance symptoms and chronic fatigue syndromes. Amnesia, sore throat, hoarseness, runny nose, hair loss, hearing loss and tremors have been reported at low incidences in Long-COVID Syndrome [14]. If there are renal function abnormalities, Nephrology follow-up and creatinine clearance determination with urinalysis evaluation may be needed. These may be performed in person or on virtual clinical visits. Next is a discussion of some of the various organ systems and how they are affected.

### Pulmonary System

The pulmonary system is the most commonly involved. Chronic complications, such as chronic cough, fibrotic lung changes also known as Long-COVID fibrosis or post-ARDS fibrosis, bronchiectasis and pulmonary vascular disease may occur [15]. Even if a person is asymptomatic, they may have CT scan abnormalities that are seen many months after infection has resolved. If COVID-19 leads to pulmonary fibrosis it may result in shortness of breath and the need for supplemental oxygen. In a post-acute COVID-19 Chinese study approximately 50% of 349 patients who underwent high resolution computer tomography of the chest at six months had at least one abnormality pattern [16]. These changes involved the appearance of ground-glass opacities. There are also long-term risks of pulmonary embolisms and chronic pulmonary hypertension, but at this point it is unknown

and further research is being conducted. It is thought that patients with a greater severity of acute COVID, especially those on high-flow nasal cannula and noninvasive or invasive ventilation are at the highest risk for long-term severe pulmonary complications that include even pulmonary function test abnormalities such as persistent diffusion impairment. Pulmonary vascular micro-clotting or micro thrombosis has been observed in 20% to 30% of patients with COVID-19 [17,18].

Persistent lung symptoms are to be expected in many patients with Long-COVID Syndrome because the lungs appear to be one of the main organs affected by the virus. This may result in (1) diffuse damage to the alveoli, the lining of the small sacs in the lungs, (2) desquamation of alveolar epithelial type 2 cells, (3) pulmonary fibrosis, (4) Hyaline membranes, (5) scattered interstitial inflammation, and (6) monocytes and macrophages [19].

Up to six months after hospitalization, pulmonary function abnormalities or structural changes may occur. In severe COVID-19 patients, up to 35% of patients at six months may show fibrotic-like changes after infection [20]. Abnormal airway function may occur up to 11 months in severe COVID-19 infections [21]. Persistent diffusion lung carbon monoxide impairment also described the noncritical COVID patients who present with shortness of breath may occur up to four months after infection [22]. Other abnormalities include abnormalities in total lung capacity, poor expiratory Vol at 1 second (FEV1), forced vital capacity (FVC), FEV1 to FVC ratio, and small airway function abnormalities [23]. Mild cases usually have persistent chronic cough, which may be due to fibrosis, bronchiectasis and pulmonary vascular disease. Individuals also have oxygen desaturation during exertion compared to individuals who have no symptoms of shortness of breath post-COVID [24].

### Cardiac Involvement

Common cardiac problems may occur with labile heart rate and blood pressure response to activity. Myocarditis and pericarditis may occur chronically. In the acute stages, myocardial infarction, cardiac failure, life-threatening arrhythmias and sudden cardiac death have been described. The incidents of arrhythmias in Long-COVID-Syndrome is unknown, but many individuals have palpitations and studies using ambulatory monitoring need to be further conducted. Sequelae from acute COVID may occur, such as coronary artery aneurysm, aortic aneurysm, atherosclerosis, venous and arterial thrombotic disease including life-threatening pulmonary embolism [25]. These structural abnormalities may manifest itself in Long-COVID Syndrome long after recovery of acute illness and predispose to arrhythmias, breathlessness, and acute coronary events, such as heart attacks and chest pain syndromes.

Myocardial injury is the most common abnormality detected with acute COVID infection. It is usually detected even when patients are asymptomatic with no cardiac symptoms with elevated cardiac troponin levels, which may be evident in a high percentage of patients with COVID-19 [26]. Further research is ongoing as to whether this myocardial injury pattern, even when subclinical, may lead to increased arrhythmias and heart failure in the long-term. Echocardiographic studies have shown abnormalities with COVID, including right ventricular dysfunction 26.3%, left ventricular dysfunction 18.4%, diastolic dysfunction

13.2% and pericardial perfusion 7.2%. To what extent this is reversible in patients who go on to Long-COVID-Syndrome is not known [27]. In addition, sleep abnormalities and difficulties that reduce quality of life have been noted in Long-COVID-19 Syndrome patients. These may also adversely affect cardiac function, provoke arrhythmias, elevate blood pressure and exacerbate or cause hypertensive states.

Chest pain and palpitations are status post-acute phase of COVID. In a Chinese study, palpitations were reported in 9% and chest pain in 5% of patients six months after follow-up [16]. To track heart inflammation, one of the most effective and sensitive tests is cardiac magnetic resonance imaging (MRI). Inflammation rates may be as high as 60% more than two months after a diagnosis of COVID, although this is a very difficult test to obtain in many centers that do not have it readily available [28]. Long-COVID Syndrome patients may be present with chest pain in 17% of patients, palpitations in 20% of patients, and dyspnea on exertion 30% of patients [27]. The question of myocarditis is always raised especially in children, but adults are also known to have myocarditis and this may be smoldering. One study showed that in healthy college athletes the mild symptoms were asymptomatic up to 15%, and they have evidence of MRI findings consistent with myocarditis on a screening study [29]. More importantly, many of the chest pains and palpitations, which appear to be cardiology in etiology, are actually due to autonomic dysfunction, including the postural orthostatic tachycardia state. Therefore, the importance of not only doing cardiac imaging, ambulatory monitoring, stress testing, six-minute walk test, echocardiography and other noninvasive cardiac workup, but also autonomic testing, such as cardio-respiratory monitoring, HRV interval testing, beat-to-beat blood pressure with tilt testing and sudomotor testing may be useful in diagnosing autonomic nervous dysfunction. Arrhythmias are noted Long-COVID but attention to the use of anti-arrhythmic drugs, Amiodarone for example, must be used carefully in patients who have fibrotic pulmonary changes after COVID-19 [30].

### Neurological

Encephalitis, seizures, and other conditions including prolonged brain fog may occur for several months after acute COVID infection [31]. Three months after follow-up MRI, abnormalities may be demonstrated [32]. Neuropsychiatric sequelae are often common and reported with many post-viral symptoms, such as chronic tiredness, myalgias, depressive symptoms, non-restorative sleep [33]. Migraine headaches, often refractory to treatment, and late-onset headaches have been presumed to be due to high cytokine levels [34]. In a follow up study of 100 patients, 38% had ongoing headaches after six weeks [35]. Loss of taste and smell may also persist for up to six months and longer on follow-up of patients. Brain fog, cognitive impairment, concentration, memory difficulties, receptive language, executive function abnormalities may also persist over a long period of time. This may be related to autonomic dysfunction and other factors [36,37]. Psychiatric manifestations are also common in COVID-19 survivors of more than one month. In an Italian study, approximately 15% have at least some evidence of depression and post-traumatic stress, anxiety, insomnia and obsessive-compulsive behavior [38]. Some studies have shown up to 30-40% of patients with COVID-19 have depression and anxiety for prolonged periods of time [39].

After ischemic or hemorrhagic strokes, hypoxic and endemic damage, may lead to reversible encephalopathy syndrome and acute disseminated myelitis. These and other neurological de-

fects may require extensive rehabilitation and their sequelae may linger. Also, acute critical illness, myopathy and neuropathies resulting during acute COVID-19 may leave residual symptoms weeks to months later [40]. Again, Long-COVID often involves brain fog. This may involve mechanisms of cardiac deconditioning, post-traumatic stress or dysautonomia. Long-term cognitive defects may be seen occurring in up to 20% - 40% of patients [41-43]. The association between Long-COVID-Syndrome and brain fog may be the result of the autonomic dysfunction, specifically Sympathetic Withdraw, and the associated decreased cerebral perfusion [44,45].

Autonomic dysfunction has been noted to be significant. Patients with orthostatic tachycardia and inappropriate sinus tachycardia may benefit from heart rate management including beta-blockers and other autonomic therapies [personal observations] [46]. Muscle wasting and fragility are often seen prolonged. This is because COVID-19 when it is severe may cause catabolic muscle weakness and feeding difficulties [47]. Neuropsychiatric manifestations of COVID-19 have been documented in a British study including stroke and altered mental status. Multiple psychiatric symptoms emanating from encephalopathy and encephalitis and primary psychiatric diagnoses were noted in young adults [48]. Prolonged effects on patients who have had prone ventilation and COVID may cause focal and multifocal peripheral nerve damage [49]. Symptoms consistent with orthostatic hypotension syndrome and painful small fiber neuropathy were reported in as short as three weeks and as long as three months [50-53].

The most frequent neurological long-term symptoms in patients were myalgias, arthralgias, sleeping troubles and headaches [54]. Autonomic dysfunction findings resulting from analysis of Compass-31 Questionnaires demonstrates significant symptomatology [55]. Based on autonomic symptoms by Compass-31, two clusters were obtained with differential characteristics. Cluster 2 exhibited high scores of Compass-31. This accounted for 31% of all patients included. Median Compass-31 score of 22 suggesting that one third of patients with PCS may yield higher scores when compared with the general population [56]. Patients with higher scores exhibited more clinical manifestations and depression. These clusters have therapeutic implications and clinicians should be aware of particular manifestations during the follow-up and all psychosocial intervention may reduce the burden of Long-COVID Syndrome [57]. Orthostatic intolerance has been described from a series of patients that had either resting or postural hypotension or tachycardia [50]. Orthostatic intolerance symptoms presented from orthostatic hypotension, vasovagal syncope, and postural orthostatic tachycardia syndrome that all occur and last for a prolonged period of time after COVID viral infection. The Symptoms are often associated with palpitations, breathlessness and chest pain, which are common symptoms seen in Long-COVID patients. It is postulated that high catecholamine levels may lead to paradoxical vasal dilatation and increased activation of the Vagus nerve that may result even in syncope and also sympathetic activity withdraw [58,59].

Hypovolemia may also exacerbate or worsen these symptoms. The relationship between COVID-19 infection and how it affects the autonomic nervous system is not completely understood, but it is believed to be due to inflammatory cytokine release and a cytokine storm, which results from the initial sympathetic activation produced by a pro-inflammatory cytokine release [60]. However, vagal stimulation (i.e., in coordination with the immune response to COVID-19) may also result in anti-inflamma-

tory responses [61]. The COVID-19 relationship to autonomic dysfunction may be by the viral infection itself. Immuno-mediated neurological syndromes have been described [62]. It is well known that some forms of orthostatic hypotension and POTS are associated with autoantibodies perhaps caused by other viruses in the past, and this may also be the case with COVID; for example, antibodies against Alpha and Beta and muscarinic receptors.

Treatment of these autonomic nervous systems disorders involves exercise with both aerobic and resistant elements in a graded fashion that oftentimes begin with recumbent exercises, “low and slow” [63]. Fluid and electrolyte repletion is required. Avoiding exacerbating factors, such as prolonged sitting and warm environments is recommended. Some counter maneuvers and isometric exercises, compression garments especially up to the waist, or abdominal binders are recommended. Pharmacological treatment that may involve many different regimens may be prescribed, such as volume expanders (e.g., Fludrocortisone or Desmopressin) may be used along with vaso activation (e.g., Midodrine or Mestinon). If there are prominent hyperadrenergic symptoms, Propranolol, Clonidine, Methyldopa or other beta-blockers may be considered, especially for a postural orthostatic tachycardia response.

Again, the questionnaire that addresses autonomic symptoms, such as the Composite Autonomic Symptom Scale-31 (Compass-31), may be used to validate dysautonomia symptoms in post COVID patients. In a study of 180 participants (70% males), orthostatic hypotension was found in 13.8% of the subjects [64]. The mean Compass-31 score was 17.6 with the most affected domains being orthostatic intolerance, sudomotor, gastrointestinal, and pupillomotor dysfunction. Higher Compass-31 scores were found in those with neurological symptoms due to more severe orthostatic intolerance symptoms. Interestingly, gastrointestinal, urinary and pupillomotor domains were more represented than non-neurological symptom groups. Therefore, this study concluded that it is important to monitor autonomic nervous system symptoms as a complication of COVID-19 disease that may persist in a post-acute period. Other prominent autonomic dysfunctions in these post-COVID individuals included secretomotor and sweating abnormalities in about half the study population and thermoregulatory alterations.

Another feature of COVID-19 involves the urinary tract and bladder incontinence. Urinary symptoms may occur with inflammation and demyelination of the pudendal nerve. This has been reported in other viral infections [65,66]. Up to a half of Long-COVID Syndrome patients may have urinary dysfunction [64]. It is also suggested that sexual impairment such as erectile dysfunction is possible after COVID infections which may affect both endothelial and autonomic components. However, the psychiatric component due to stress and anxiety cannot be separated [67,68]. Compass-31 scoring highlights gastrointestinal symptoms after COVID. These may occur along with a combination of other symptoms, including abnormal appetite, nausea and diarrhea. This is because in the GI tract there is a significant amount of angiotensin coenzyme ACE-2 receptors present. [69]. Vision disturbances may also occur in Long-COVID syndromes including sore eyes and light sensitivity [70]. In acute conjunctivitis, an abnormal pupil response has been noted [71]. Light sensitivity is often a common complaint. Nearly 50% of study patients complained of ocular abnormalities [64]. Therefore, multiple organ systems may manifest symptoms in Long-COVID syndrome which may be attributed to the autonomic dysfunction, and this need not necessarily just be orthostatic

intolerance symptoms [72]. As noted, GI, ocular, urological, sudomotor, and endocrine organs may be affected.

Dysautonomia, including anosmia, hypogeusia, headaches and hypoxia has been shown to be components of the Long-COVID syndrome [73]. The dysautonomia is hypothesized to occur secondary to COVID-19 infection. The demonstrated dysregulation of heart rate variability (HRV) testing is reflected in abnormal Nociception Level (NOL) index; an index that refers to abnormal parasympathetic-sympathetic balance. The NOL algorithm with a multiparameter, non-linear combination of (1) heart rate, (2) HRV, (3) amplitude of the finger, photoplethysmography, skin conduction level, and (4) time derivatives were obtained using a noninvasive finger probe [73]. Autonomic dysfunction has been reported in up to 63% of patients presenting with specific symptoms having survived a COVID-19 infection between March 2020 and January 2021. Diagnoses were revealed by recording and evaluating beat-to-beat blood pressure and heart rate during head-up tilt [74]. As long as six to eight months after recovery from COVID-19, patients still suffer residual autonomic symptoms and 60% are unable to return to work and only 50% have completely recovered [75].

Chronic fatigue syndrome, also known as post-infective syndrome, has been commonly recognized in the Long-COVID Syndrome. A study of 20 fatigued and 20 non-fatigued Long-COVID patients with a mean age 44.5 (90% female) were followed up for 166 days. A scale known as a Chalder Fatigue Scale was used. They underwent an Ewing autonomic function test battery, including deep breathing, active standing, Valsalva and cold-pressure testing, with continuous electrocardiogram, blood pressure monitoring, and cerebral oxygenation. A 24-hour ambulatory blood pressure monitoring was conducted. Findings included no differences between the fatigued and non-fatigued patients in autonomic testing. There was an that increase in anxiety, strongly associated with Chronic Fatigue Syndrome. This, however, is in contradistinction to other studies which have shown autonomic dysfunction with Long-COVID syndrome and chronic fatigue [76].

Post infectious Myalgic Encephalomyelitis, which is also synonymous with Chronic Fatigue Syndrome, has been recognized along with sleep disturbances, neurocognitive changes, orthostatic intolerance and post-exertional malaise [77,78]. Fatigue at three weeks post symptoms may occur in 13-33% of patients. There are many factors responsible which include sleep disturbances, autonomic dysfunction with sympathetic predominance, endocrine disturbances, abnormalities of the hypothalamic-pituitary-adrenal axis, reactive mood disorders and depression and anxiety. Findings therefore concluded that chronic fatigue post Long-COVID Syndrome is multifactorial. More testing is required to see the association of autonomic disturbances with the emergence of a chronic fatigue syndrome. This has been demonstrated with other viral infections. In fact, in the cohort at our autonomic clinic we have found significant disturbances in Cardiorespiratory and heart rate variability testing in patients with chronic fatigue with Long-COVID-Syndrome with abnormal autonomic responses, including sympathetic withdraw (associated with orthostatic dysfunction) and vagal excess with postural change (associated with pre-syncope symptoms). Both autonomic dysfunctions are associated with poor cerebral and possibly coronary perfusion. These symptoms present regardless of whether they have drops in blood pressure, postural rise in heart rate or none of the above changes.

It has been widely reported that autonomic dysfunction and various viral infections including HIV, Herpes virus, enterovirus 71, flavivirus, Human-T lymphotropic virus, etc. may result in loss of heart rate variability, hypersalivation, photophobia, and dyspnea. Epstein-Barr virus may lead to dysautonomia through alterations of cerebral autoregulation by high nitric oxide release with subsequent autonomic nervous system dysfunction [79]. It has been postulated that the coronavirus shares a common feature of neuroinvasion [80].

SARS-CoV-2 may also reach the autonomic nervous system

1. by employing the retrograde axonal transport by the olfactory nerve [81].
2. via ACE 2 receptors and brain stem pathways [82].
3. via systemic blood circulation [83].
4. by immune injury [84], and
5. neuronal pathways [85].

The virus may also indirectly invade the autonomic nervous system by the enteric nervous system (ENS) and its sympathetic afferent neurons by infecting the GI tract [86,87]. In a study of 50 patients showed that 26% of patients had sweat dysfunction as measured by SUDOSCAN test with motor, sensory and autonomic dysfunction [88]. Abnormalities of heart rate variability is more common in COVID-19 patients who develop fatigue, Long-COVID-19 is found to be associated with persistent symptoms, such as hypoxia and fatigue due to development of dysautonomia [89-91]. It is initially believed that SARS-COVID-19 causes sympathetic nervous system activation with catecholamine excess of activation in a sympathetic storm which activates the renin angiotensin system. Simultaneously, there is inhibition of the parasympathetic nervous system mediated anti-inflammatory effect, that leads to a decrease in neuro-vagal anti-inflammatory response and enhances the cytokine storm. This all leads to cardiopulmonary complications and COVID-19-induced dysautonomia [87]. The Parasympathetic responses reported above are found at rest. There is an abnormal Parasympathetic response to stress that may also occur, exaggerating the dynamic Sympathetic response to stress, thereby amplifying and prolonging the Sympathetically-mediated inflammatory, histaminergic, pain, and anxiety responses in a post-traumatic-like fashion [92].

### **Gastrointestinal Symptoms Associated with Long-Covid Syndrome**

COVID-19 may cause intestinal dysfunction due to changes in intestinal microbes and an increase in inflammatory cytokine. Multiple organ systems may evolve acutely and may even produce septic shock. Increasing diarrhea may be an early manifestation that may continue in the chronic phase. In the chronic phase the Gastrointestinal (GI) sequelae may include persistent anorexia, vomiting, abdominal pain along with diarrhea. It appears gastrointestinal (GI) symptoms are accompanied by inflammation or intestinal damage. Coronavirus has also been found in the stool [93]. Acute hepatocellular injury was also identifying with elevated liver enzymes. Fecal oral transmission of COVID-19 may be suspected because of the presence of COVID-19 RNA in stool samples of COVID-19-positive patients [94]. GI upset may also be due to gastric and intestinal motility dysfunction due to COVID-induced Parasympathetic dysfunction. For example, diarrhea and abdominal pain may be due to excessive Parasympathetic activity causing overly-rapid GI motility.

At least 76% of patients had one of the GI sequelae symptoms 90-days after discharge of COVID-19, persisting to six months after disease onset [95]. Only 13% of patients recorded GI symptoms on admission and 49% during hospitalization. After discharge, GI symptoms were present in 44% of patients. The most common GI sequelae were loss of appetite at 24%, nausea 18%, acid reflux 18%, and diarrhea 15%. Less common symptoms were abdominal distention 14%, belching 10%, vomiting 9%, abdominal pain 7% and bloody stools 2%. Patients who had GI symptoms going beyond 90 days more often had shortness of breath and myalgia as coexisting presenting symptoms in the acute phase. Interestingly, patients with GI sequelae were less frequently severely ill than those without GI sequelae 17% versus 37%. These patients with GI sequelae appeared to have a lower frequency of supplemental needs in the long-term also. Also, patients with GI sequelae at 90 days were treated more often with proton-pump inhibitor and corticosteroids and were less frequently treated with enteral nutrition. This suggests that there are different mechanisms in Long-COVID Syndrome for GI abnormalities versus pulmonary or cardiac. GI symptoms six-months after coronavirus showed that 29% of 220 patients reported GI symptoms six months after COVID-19; 9.6% had diarrhea, 11% had constipation, 9.4% abdominal pain, 7.1% nausea and vomiting and 16% with heartburn [96].

A GI symptom was the most bothersome recurrent symptoms in 83 patients, 11%. Many symptoms resembled Irritable Bowel Syndrome. There were 39% who met criteria for the Rome IV Criteria for Irritable Bowel Syndrome, and women were much more likely to report this than men. These symptoms were not trivial as almost 10% of patients reported this as their most significant symptom [96]. Studies are currently evaluating the long-term consequences of COVID-19 on the GI system, including postinfectious, Irritable Bowel Syndrome, and Dyspepsia.

### **Hematological Sequelae of Long-Covid Syndrome**

Long-COVID venous thromboembolism has been estimated to be less than 5%. A single center report of 163 patient in the United States without post-discharge thrombotic prophylaxis suggested a 2.5% cumulative incidence of thrombosis at 30 days following discharge. This included segmental pulmonary embolism, intracardiac thrombus, thrombosed AV fistulas and ischemic stroke [97]. Late onset hematological complications with Long-COVID-19 has become an emerging medical problem for the hematologists. These include coagulopathy disorders, immune-thrombotic states, and hemorrhagic events. Late onset thrombocytopenia related to immune system dysregulation has also been reported as a rare complication of COVID-19 [98].

### **Kidney Disease**

Patients that are extremely frail and have chronic comorbidities are at an increased risk for kidney disease and progression of kidney failure after infection of SARS-CoV-2. The kidney function gradually declines over time even in the absences of the virus infection [99]. Initially, approximately 28% of patients hospitalized with COVID are diagnosed with acute kidney injury and up to 9% have shown a received kidney replacement therapy. A study of 26 autopsy patients who died from COVID-19 were reported in China. Clusters of coronavirus-like particles were noted in epithelial cells and diffuse proximal tubal injury was demonstrated [100]. Others found that older-aged diabetes, cardiovascular disease, black race, hypertension, and need for ventilation and vasopressor medications are at risk for acute kidney injury in COVID-19 [101].

## Olfactory and Gustatory Abnormalities

Recovery of the Olfactory and Gustatory system may last more than one month after the onset of smell and taste loss [102,103]. Loss of olfactory receptor neurons may be the mechanism in some of these cases. Long-lasting effects on taste and smell are uncommon but have been noted in isolated cases.

## Pathophysiology of Long Covid-19

The mechanism behind the causation of Long-COVID Syndrome may be multifactorial. As mentioned earlier, immune response, antibody generations, direct effects of the virus, complications of the critical illness, psychosocial factors and post-intensive care syndrome, post-traumatic stress and oxidative stress may be operative mechanism. Deconditioning may also be a factor [7]. The mechanism of heart failure as another organ system involved pro-inflammatory cytokines with interleukin 1 and interleukin 6 tumor necrosis factors, and these may cause prolonged effects [104]. Redox imbalance linking COVID-19 and chronic fatigue syndromes and systemic inflammation and neuroinflammation have also been postulated [105]. Oxidative phosphorylation may be operative in a hyperinflammatory state with altered cardiorespiratory function. It is thought that viral infections cause a shift in Mitochondrial energy system contribution from ATP synthesis to innate immune signaling occurs in order to eradicate pathogens, promote inflammation, and eventually restore tissue homeostasis [106]. An increased rate of glycolysis and down-regulation of oxidative phosphorylation is seen [107]. Oxidative stress has been implicated in many acquired myocardial disorders and may lead to significant autonomic dysfunction [108].

## Treatment in Long-Covid Syndrome

For the most part, supportive therapy for Long-COVID symptoms is a keystone and there is treatment for autonomic dysfunction that may be demonstrated objectively in a laboratory. As mentioned earlier, volume expanders and vasodilators in addition to fluids, electrolytes, compression garments, and various exercise techniques have been prescribed for orthostatic intolerance symptoms. Omega-3 fatty acid and dietary supplementation have been investigated [109]. It is believed that Omega-3 may help resolve inflammatory imbalance. L-arginine has also been proposed as a treatment modality [110]. Included in the L-arginine pathway is the production of Nitric Oxide. Nitric Oxide maintains or improves the health and function of endothelial cells and benefits the immune system, especially in chronic fatigue states. Various antioxidants and zinc have also been used empirically, but there are no controlled studies to confirm their utility. All of these therapies also effect proper autonomic function to help relieve Long-COVID symptoms [111]. Vaccination has been suggested as possibly a factor that may ease symptoms of Long-COVID. In one large survey, 57% of responders reported an overall improvement in their symptoms following vaccination and around 19% reported an overall deterioration [112]. Mental health conditions may be treated with various psychological aides, such as cognitive behavioral therapy as well as antidepressants, including tricyclics. Treatment of liver function abnormalities Irritable Bowel Syndrome, dyspepsia and other GI symptoms are very challenging. Renal dysfunction should be followed serially, nephrotoxins avoided and proper hydration maintained. However, from a large study of fully vaccinated people 2.6% were found to contract the virus (labeled as "Breakthrough" patients) [113]. Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing

antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented. Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

## LONG-COVID

Cardiopulmonary testing for unexplained dyspnea post COVID-19 was reported [114]. Patients with symptoms consistent with chronic fatigue had an abnormal pattern of oxygen uptake on cardiopulmonary testing consistent with what is seen with chronic fatigue syndrome. Circulatory impairment, abnormal ventilatory pattern and chronic fatigue syndrome may be common in patients with post-acute sequelae of post-concussive syndrome, and this accounts for the mechanism of dyspnea in many patients who do not have pulmonary disease from Long-COVID. The symptoms of Long-COVID Syndrome may all be associated with autonomic dysfunction as measured with Cardio-Respiratory testing [111] and relieved with appropriate autonomic therapy based on the Cardio-Respiratory test [108].

## Conflicts of Interest:

Only Dr. Colombo has any conflicts of interest, specifically as inventor of P&S Monitoring technology and officer of Physio PS, Inc.

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