

Long COVID-19 syndrome: What we learn from the past?

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Many millions people worldwide has been suffering from an emerging highly contagious viral disease, COVID-19, in the Year 2019. Not only the acute phase or "early phase" can cause mortalities, but also the stage IV or "Long COVID phase" can cause morbidities in these groups of patients. To date, COVID-19 infected patients presented with "Long COVID phase" are rising all the time. At "Long COVID phase" (stage IV), various complications of the bodies' systems are involved, such as pulmonary, cardiovascular, renal, neuropsychiatric, and gastrointestinal systems, etc. The mechanisms underlying these complications are not well established. However, recent reports demonstrated that the symptoms of the stage IV might be resulted from the abnormal immunities after the infection, especially the adaptive immune response. Thus, this prompted us to review the pathophysiology, risk factors, symptomatology and complications, including diagnosis and treatment of "Long COVID phase".


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INTRODUCTION

After the first case of COVID-19 in China in the Year 2019, there are over 180 million cases infected around the world since then. In natural history of this disease, 4 phases of COVID-19 are reported. "Phase I" is called "early stage" with predominant viral replication. This stage is typically asymptomatic and highly contagious. "Phase II" is called "pulmonary phase" characterized by lung viral replication with radiological findings. "Phase 3" is called "hyperinflammatory phase" with the cytokine storm, and "phase 4" is named "long COVID" with acute or subacute to chronic conditions and multiorgan involvement. Usually, the average recovery time of

COVID-19 acute illness is about 2-3 weeks [1]. However, over 70% of infected cases are suffered from some organs impairment within 4 months after diagnosis. As reported, these involve pulmonary complications, such as impaired exercise capacity, and chronic cough; cardiovascular complications, such as hypotension, and tachycardia; gastrointestinal complications, persistent hyperlipidemia, renal impairment, post traumatic stress disorder, hematologic abnormalities and coagulopathy, etc [2]. All these illness "Long COVID" symptoms are so-called as "chronic COVID syndrome", or "long-haul COVID-19", or "post-COVID-19 syndrome", or "long COVID-19 syndrome" [3]. These disease features can affect at all COVID-19 severity, even at mild disease. Nowadays, many descriptions of "Long COVID" have already been proposed, whereas the symptoms lasting over 3 months after the first onset are the most commonly used [4]. Despite of its high prevalence, the specific knowledge and treatment of "Long COVID" are still unelucidated. Thus, in this literature review, we will summarize the areas in the fields of pathophysiology,

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risk factors, symptoms, and complications, including recent management of long COVID-19 syndrome.

Nomenclature

From the year 2020, there is no consensus definite name for "Long COVID", the name as known in public media. At that time, National Institute for Health and Care Excellence (NICE), defined the "Long COVID-19 syndrome" as "signs and symptoms that develop during/after the COVID-19 infection persisting for more than 4 weeks and cannot be explained by any other diagnosis". This means that NICE defines "Long COVID" into two categories, i.e., "Ongoing symptomatic COVID-19", which indicates the symptoms lasting for 4–12 weeks; and the other is "Post- COVID-19 syndrome", which means symptom persistence beyond 12 weeks, in the absence of an alternative diagnosis. Notably, NICE diagnosis is based on "by exclusion" diagnostic criteria [5]. Meanwhile, several terms of "Long COVID" have also been used, such as "Chronic COVID syndrome", "Long Haulers", "Post-infectious COVID-19". The difference of these definitions depends on the organ-based staging of the illness and also the duration of symptoms from the initial onset. For example, the term "Post-infectious COVID-19" is named for those who continued with symptoms beyond 3 weeks after the onset of the disease [6]. Post- Acute COVID-19 syndrome is defined as the persistence of COVID-19 symptoms for >3–4 weeks [7]. Importantly, it must be emphasized that the virus is not found in respiratory secretions in these "Long COVID" cases. Possibly, these symptoms could be called in the scope of "Post viral syndromes".

Pathophysiology of "Long COVID"

There are some mechanisms that have been proposed to cause "Long COVID" (or phase IV COVID-19), as followed [8].

1. The sequelae of organ damage, including the varying extent of organ injury and also the time required to recover of each organ system.
2. Persistent chronic inflammation (convalescent phase) or immune response/auto antibody generation.
3. Rare persistent of virus in the body in people with altered immunity, re-infection, or relapse.
4. Nonspecific effect of hospitalization. Post intensive care syndrome and complications related to corona infection or complications related to comorbidities or adverse effects of medications used.

5. The sequelae of critical illness, including the social and financial impact of COVID-19, and psychological ones.
6. Deconditioning, psychological issues like post-traumatic stress.

However, in "Long COVID", the multiple mechanisms may contribute to the onset of this condition. One of the pathogeneses of "Long COVID" was suggested to be the outcomes of "the oxidative stress and inflammation that leads to weak immunologic response and incomplete viral eradication" [9]. Moreover, T-cells dysfunction and thyroid dysfunction may also promote "Long COVID" pathogenesis, similarly in an autoimmune disease [10]. Multisystem inflammatory syndrome (MIS) results in the elevation of systemic pro-inflammatory markers, such as CRP, IL-6, ferritin, and D-dimer. It is proposed to involve in dysregulated adaptive immune system and autoantibodies in these cases [11]. Thus, the potential mechanisms of "Long COVID" can be summarized into 3 major mechanisms [7]:

1. Virus-specific pathophysiology in organ system
2. Immunologic aberrations and inflammatory damage responding to the stage I-III of COVID-19
3. The sequelae of post-critical illness

Of note, the molecular mechanisms involving in pathogenesis of COVID-19 have 3 physiological systems, i.e., (1) the kinin-kallicrein system; (2) the renin-system angiotensin; (3) the coagulation system coexpressed with hACE2-R in alveolar cell [12].

Risk factors for developing "Long COVID"

The risk factors for those infected with COVID-19 highly associated with "Long COVID" are noted. Women are twice commonly found than men. Increasing age is also found "Long COVID" commonly than those in younger one. Presentation of COVID-19 with over 5 symptoms in the first week of the acute stage increases risk of "Long COVID". Developing of "Long COVID" can also increase with those who have co-morbidities [13]. As reported, the elevation of blood urea nitrogen (BUN) and D-dimer levels are the risk factors of pulmonary dysfunction, especially in three-month survivors of COVID-19 [14]. Though the changes of D-dimer, CRP, and lymphopenia may serve as potential biomarkers of "Long COVID", these inflammatory markers are known to fluctuate in concordance with disease severity and patient characteristics [4].

Symptomatology and complications of "Long COVID"

From previous report, "Long COVID" patients usually manifest with a wide range of physical and

psychological symptoms, which can be categorized into 2 clusters symptoms [1]:

1. Those with only symptoms of fatigue, headache, and upper respiratory complaints.
2. Those with multi-system complaints including fever and gastrointestinal complaints.

Generalized symptoms

Fatigue is the most common generalized symptoms found in "Long COVID" at 55% using the Fatigue Severity Scale. Some reports showed that after ten weeks follow-up post SAR-CoV-2 infection, 50% of patients developed fatigue. No correlation is demonstrated between COVID-19 severity, fatigue, and the inflammatory level. Moreover, female sex shows high correlation with fatigue and depression. Other generalized symptoms include headache, myalgia, sore throat, skin rashes, alopecia, and unrefreshing sleep [13].

Respiratory sequelae

In "Long COVID", dyspnea is the most common persistent symptoms found in this disease, ranging from 42-66%, and prevalence at 60-100 days follow-up. It is most likely that those patients who suffered from dyspnea are in old age group. The pulmonary function test, such as diffusion capacity for carbon monoxide, and total lung capacity, may take time to recover from the onset of disease. The possible mechanisms of dyspnea include pre-existing lung abnormalities, fibrotic changes inducing cytokines releasing, pulmonary vascular damage, and thromboembolism [7,15].

Cardiovascular sequelae

The most common symptom in cardiovascular system is postural orthostatic hypotension (or tachycardia syndrome), resulting in palpitation, dizziness, headache, etc. Other cardiovascular symptoms that may be presented are myocardial infarction, myocarditis, pericarditis, arrhythmias, chest pain, and cardiac failure, including venous thromboembolism. Increasing of major adverse cardiac events 3 times higher at the median of 5 months post discharge has been reported. The possible mechanisms underlying these symptoms include autonomic dysfunction, hypovolemia, hyperadrenergic stimulation, dysautonomia, and psychological stress. However, the etiology of some events requires further study [8,16,17].

Neuropsychiatric sequelae

"Long COVID" has been associated with major depressive disorder, anxiety disorder, and insomnia. Manifestation of malaise, headache, vertigo, tremor, and

myalgia has also been found. Some studies reported symptoms of anosmia, and ageusia, without rhinorrhea or nasal congestion [18]. The possible mechanisms involving these symptoms are direct viral infection, neuroinflammation, microvascular thrombosis and neurodegeneration [7].

Hematologic sequelae

Thromboembolic events, such as venous thromboembolism, pulmonary embolism, intracardiac thrombus, and ischemic stroke, are reported in "Long COVID". Notably, thrombosis is found more common than bleeding. The mechanisms of these events are due to hyperinflammatory and hypercoagulable state [19].

Endocrine sequelae

Diabetic ketoacidosis has been found after the resolution of COVID-19, though no history of diabetes mellitus. Subacute thyroiditis and thyrotoxicosis has also been reported. Diagnosis of Hashimoto thyroiditis or Graves' disease has been recognized. The possible mechanisms of endocrine sequelae are direct viral injury, immunological and inflammatory damage [7].

Renal sequelae

Acute kidney injury can occur in 5-30% of COVID-19 cases depending on varying degree of severity. Approximately 35% of patients at 6 months show decreasing in estimated glomerular filtration rate (eGFR). The possible mechanism may be thrombi in the renal microcirculation that potentially contribute to the renal injury [7].

Gastrointestinal sequelae

Significant symptoms in gastrointestinal and hepatobiliary systems have been reported, such as post-infectious irritable bowel syndrome and dyspepsia. The changes in gut microbiota have also been recognized. Specifically, *Faecalibacterium prausnitzii*, which is a butyrate-producing anaerobe associated with normal health, has been found to inversely correlate with disease severity [7,20].

DIAGNOSIS

To diagnose "Long COVID", the risk factors and clinical manifestation are approached. All risk factors that lead to "Long COVID" should be identified, for example, the old age group, a severity of acute phase COVID-19, obesity, female sex, and comorbidities. However, "Long COVID" is not always related to severity of acute illness. Nowadays, diagnosis of "Long COVID" is presented when

patients do not have other medical explanations (diagnosis by exclusion) [21]. This is a process of taking history and physical examination, including investigations, as usual, such as duration of current symptoms, timing, and pre-existing diseases. Investigations that should be carried out include; complete blood count, renal and liver function tests, CRP, ferritin, thyroid function test, and chest XR. Other specific diagnostic tools might be also necessary.

TREATMENT

The guidelines for taking care of "Long COVID" patients have three major principles of care, i.e., personalized care, multidisciplinary support, and rehabilitation. In order to cope with personalized care, self-management of the symptoms with the appropriate support is led by medical doctor who has relevant skills and experience. A multidisciplinary support team includes psychological and psychiatric aspects of management. Healthcare professionals should also be involved in this team, such as expert in treating fatigue, and other symptoms. Physiotherapist, including speech and language therapists should support the rehabilitation team. Minor symptoms, such as cough, pain, and myalgia, can be supportive and symptomatic treatment. To date, three pathways for treating of "Long COVID" and hospitalization, depending on the severity of acute COVID-19, have been proposed [8]:

1. **Those who had never admitted with acute illness:** In this case, the general practitioner can conduct the holistic assessment and care.
2. **Those who needed hospitalization with acute illness:** In this case, patients should undergo a 12-week post discharge assessment, which include chest XR. If chest XR is normal, and no more symptoms, patients can be discharged. Follow up and evaluation are needed to be done before 12 weeks. Because the symptoms can usually be resolved by 12 weeks.
3. **Those with acute illness who was in Intensive Care Unit (ICU):** In this case, patients should undergo a post multidisciplinary clinic assessment at 4-6 weeks post discharge. If better, follow up as the other hospitalized ones is recommended. However, the frequency and duration of follow up is not exactly defined at this time.

CONCLUSION AND FUTURE PERSPECTIVE

After the acute illness of COVID-19, the multiorgan manifestations are detected, named as "Long COVID". The symptoms involve in various systems, such as pulmonary, cardiovascular, neuropsychiatric, renal,

gastrointestinal, and endocrine systems. Though some mechanisms of these symptoms from "Long COVID" have been proposed, however, many mechanisms still cannot be elucidated. It is the challenge for the healthcare team to integrate all the knowledge and discipline for the improvement of taking care of patients in this group in the future.

Conflicts of Interest: Declare of no conflict of interest

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