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Review Article

ภาวะ Long COVID และภาวะแทรกซ้อนระยะยาวทางระบบการหายใจจากโรคโควิด 19

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บทคัดย่อ

บทนำ: ผู้ป่วยที่หายจากโรคโควิด 19 จำนวนมาก มีอาการหลงเหลือหรือเกิดอาการขึ้นใหม่ อาการที่เกิดขึ้นพบได้หลากหลายเกิดขึ้นได้ในระบบการทำงานต่าง ๆ ของร่างกาย รวมทั้งความผิดปกติด้านปริชานและอารมณ์ ผู้ป่วยสามารถมีได้หลายอาการ เรียกอาการเหล่านี้ว่า ภาวะ Long COVID ซึ่งทำให้ผู้ป่วยมีความทุกข์ทรมานบั่นทอนคุณภาพชีวิต ไม่สามารถใช้ชีวิตหรือทำงานได้ตามเดิม ผู้ป่วยโรคโควิด 19 ที่มีอาการรุนแรงมีโอกาสพบภาวะแทรกซ้อนในระบบการหายใจในระยะยาวของโรคโควิด 19 ได้แก่ โรคลิ่มเลือดอุดกั้นในปอด และปอดเป็นพังผืด ภาวะ Long COVID และภาวะแทรกซ้อนระยะยาวทางระบบการหายใจจากโรคโควิด 19 คาดว่าจะมีความสำคัญในทางสาธารณสุขมากขึ้น เนื่องจากมีจำนวนผู้ป่วยโควิด 19 ในประเทศไทยเป็นจำนวนมาก ความรู้ความเข้าใจในธรรมชาติของโรค และการดูแลรักษาผู้ป่วยที่มีภาวะ Long COVID อย่างเป็นองค์รวมจึงเป็นสิ่งสำคัญอย่างยิ่ง

วัตถุประสงค์: เพื่อเป็นการทบทวนความรู้ที่มีในปัจจุบันของภาวะ Long COVID และภาวะแทรกซ้อนระยะยาวทางระบบการหายใจ ในด้านระบาดวิทยา พยาธิวิทยา การดูแลรักษา เพื่อเป็นแนวทางสำหรับการดูแลรักษาผู้ป่วยที่มีภาวะ Long COVID และภาวะแทรกซ้อนระยะยาวทางระบบการหายใจ

วิธีการดำเนินการศึกษา: ทบทวนวรรณกรรม

ผลการศึกษา: ภาวะ Long COVID เป็นกลุ่มอาการที่เกิดขึ้นภายหลังจากหายจากโรคโควิด19 พบระยะเวลาที่เกิดอาการตั้งแต่ 1 ถึง 3 เดือนหลังจากการติดเชื้อ อุบัติการณ์ตั้งแต่ร้อยละ 11-93 แตกต่างกันไปตามนิยาม และระยะเวลาของแต่ละการศึกษา อาการที่เกิดขึ้นแตกต่างกันไปในผู้ป่วยแต่ละราย อาจมีอาการได้มากกว่า 1 อาการ ที่พบบ่อย ได้แก่ อ่อนเพลีย เหนื่อยง่าย ไอ เวียนศีรษะ ปริชานบกพร่อง วิตกกังวล นอนไม่หลับ โดยอาจเป็นอาการที่เกิดขึ้นใหม่ หรืออาการที่หลงเหลือหลังหายจากโรคโควิด19 ปัจจัยเสี่ยงของการเกิดภาวะ Long COVID ได้แก่ เพศหญิง การมีโรคประจำตัวเดิม โดยเฉพาะโรคความดันโลหิตสูง โรคอ้วน ภาวะภูมิคุ้มกันบกพร่อง

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บทคัดย่อ (ต่อ)

โรคทางจิตเวช มีอาการแสดงจากอวัยวะตั้งแต่ 5 อวัยวะขึ้นไปในช่วงเป็นโควิด19 และการนอนโรงพยาบาลช่วงเป็นโควิด 19 ปัจจุบันเชื่อว่า พยาธิวิทยาของภาวะ Long COVID เกิดจากการบาดเจ็บของอวัยวะจากการรุกล้ำของไวรัสโควิด 19 โดยตรง และการอักเสบของอวัยวะจากภาวะภูมิคุ้มกันถูกกระตุ้นจากการติดเชื้อโควิด 19 ระยะเวลาการดำเนินโรคของภาวะ Long COVID ปัจจุบันยังไม่ทราบชัดเจน การดูแลรักษา Long COVID ประกอบด้วย การวินิจฉัยแยก Long COVID จากโรคอื่น ๆ ที่มีอาการคล้ายกันที่ต้องการการรักษาเฉพาะ การใช้ยารักษาตามอาการที่ปรากฏ เช่น อาการปวด นอนไม่หลับ การทำกายภาพบำบัด การให้คำปรึกษาและการรักษาทางจิตเวช สำหรับผู้ป่วยปอดอักเสบจากโควิด19 ควรได้รับการติดตามอาการ และเอกซเรย์ปอดที่ 12 สัปดาห์หลังออกจากโรงพยาบาล ควรได้รับการตรวจสมรรถภาพปอดในรายที่มีอาการเหนื่อย หรือเอกซเรย์ปอดผิดปกติ รวมทั้งการทำเอกซเรย์คอมพิวเตอร์ปอดในรายที่สงสัยโรคลิ่มเลือดอุดกั้นในปอดหรือปอดเป็นพังผืด ควรติดตามอาการ Long COVID ในผู้ป่วยทุกครั้งที่พบแพทย์ ส่วนภาวะแทรกซ้อนในระยะยาวทางระบบการหายใจของโรคโควิด 19 ได้แก่ โรคปอดเป็นพังผืด และโรคลิ่มเลือดอุดกั้นในปอด พบในผู้ป่วยโควิด 19 ที่มีอาการปอดอักเสบรุนแรงมากกว่าผู้ป่วยที่อาการไม่รุนแรง ประโยชน์ของยาต่อต้านการเกิดพังผืดในปอดที่ใช้รักษาโรคปอดเป็นพังผืดไม่ทราบสาเหตุในการรักษาโรคปอดเป็นพังผืดจากโควิด19 ยังต้องรอผลจากการศึกษาที่กำลังดำเนินอยู่ ข้อมูลที่แสดงถึงประโยชน์ของการให้ยาต้านการแข็งตัวของเลือดแก่ผู้ป่วยโควิด 19 หลังออกจากโรงพยาบาลยังมีไม่มาก แต่สามารถลดการเกิดลิ่มเลือดอุดกั้นในปอดในผู้ป่วยบางรายที่มีความเสี่ยงสูงต่อการเกิดลิ่มเลือดอุดกั้นในหลอดเลือดดำได้

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บทคัดย่อ (ต่อ)

สรุป: ในภาวการณ์การระบาดของโรคโควิด 19 ทำให้คาดการณ์ได้ว่า ภาวะ Long COVID จะเป็นปัญหาสำหรับผู้ป่วยที่ถูกบั่นทอนคุณภาพชีวิต และเป็นปัญหาสำคัญในทางสาธารณสุข งานวิจัยที่ค้นหาองค์ความรู้เกี่ยวกับภาวะ Long COVID มีความสำคัญอย่างมากในด้านพยาธิกำเนิดโรค การดำเนินโรค อุบัติการณ์ที่แม่นยำ การจัดแบ่งกลุ่มอาการ การรักษาด้วยยาและการรักษาที่ไม่ใช้ยา รวมถึงผลจากการกลายพันธุ์ของไวรัสโควิด 19 ต่อภาวะ Long COVID การพัฒนาระบบการดูแลรักษา Long COVID ที่มุ่งเน้นสหสาขาวิชาชีพเพื่อการดูแลผู้ป่วยอย่างเป็นองค์รวมและต่อเนื่องเป็นสิ่งสำคัญและท้าทาย

คำสำคัญ: ลองโควิด กลุ่มอาการที่พบหลังโรคโควิด 19 ภาวะแทรกซ้อนระยะยาวทางระบบการหายใจจากโรคโควิด 19 ปอดเป็นพังผืดจากโรคโควิด 19 โรคลิ่มเลือดอุดกั้นในปอดจากโรคโควิด 19

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Long COVID and Long-term Pulmonary Complications of COVID-19

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Abstract

Introduction: Significant numbers of patients recovering from COVID-19 have persistent or new symptoms which can affect more than one organ including mental and psychiatric symptoms. This constellation of symptoms is defined as Long COVID, causing sufferings and detrimental qualities of life to those affected. Potential late pulmonary complications of COVID-19 include lung fibrosis and pulmonary embolism. Long COVID is gaining more public heath importance as many people having been infected. Knowledge in pathogenesis, symptoms, and treatment of Long COVID are essential.

Objective: This article aims to review the current knowledge of Long COVID and long-term pulmonary complications of COVID-19 in epidemiology, pathogenesis, and treatment for caring of patients with Long COVID and long-term pulmonary complications.

Method of study: Literature review

Results: Long COVID is a constellation of symptoms occurring 1-3 months after patients have recovered from acute COVID-19. The incidence of Long COVID was 11% to 93% after the acute infection owing to disparities in definitions of Long COVID, population assessed, accuracy of self-reporting of symptoms, and length of follow-up period among studies. Long COVID can affect single or multiple organs causing different symptoms in each individual patient. The common symptoms are fatigue, dyspnea, cough, headache, dizziness, cognitive impairment, anxiety, depression, and insomnia. These symptoms either happen for the first time or persist after the acute COVID-19. Risk factors for Long COVID include female sex, comorbidities especially hypertension, obesity, immune suppressed, psychiatric conditions, having symptoms from more than 5 organs, and hospitalization during acute COVID-19. Pathogenesis of Long COVID is currently based on direct organs invasion from SARS-CoV-2 and organ inflammation elicited by immune system after infection. The duration of Long COVID is not yet known exactly in the present. The management of Long COVID comprises accurate exclusion from other diseases with symptoms mimicking Long COVID, pharmacological therapies based on

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symptoms of individuals and non-pharmacological approaches such as physical and mental rehabilitation, and counselling with multidisciplinary approach. Patients with COVID-19 pneumonia should be followed with chest radiography at 12 weeks after recovery and symptoms including those of Long COVID. Lung function tests or computed tomography may be required in some patients with persistent chest symptoms or being suspected of pulmonary vascular disease or pulmonary fibrosis. Symptoms of Long COVID should be inquired when following up patients. Long-term pulmonary complications of COVID-19 comprises pulmonary fibrosis and pulmonary embolism which are associated with severe COVID-19. Ongoing clinical trials are investigating antifibrotic drugs used in idiopathic pulmonary fibrosis in patients with recent hospitalization with COVID-19 and persistent lung involvement. Extended use of anticoagulants after discharge from hospital may reduce venous thromboembolism (VTE) and death in selected patients with high risk of VTE.

Conclusion: Given the SARS-CoV-2 pandemic situation, it is believed that Long COVID, and long-term pulmonary complications of COVID-19 will be imminently problematic for patients suffering from symptoms and will be of public health concern. It is important that research continue to explore Long COVID in aspects such as pathogenesis, natural history, precise epidemiology, clinical classification of syndrome, optimal treatments, and impact of the novel variants of the virus. Development of holistic multidisciplinary cares for patients with Long COVID is essential and challenging.

Keywords: Long COVID, Post-COVID-19 syndrome, long-term pulmonary complications of COVID-19, post COVID-19 lung fibrosis, post COVID-19 pulmonary embolism

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world and was declared pandemic by World Health Organization (WHO) in March 2020. Despite vaccination efforts, the virus has infected over 490,000,000 individuals, including 6,181,850 deaths, reported to WHO as of 12 April 2022.[1] With ongoing new waves of novel virus variants, the infection tolls have continued to escalate as the new variants has gain an ability of evading the natural or vaccination-induced immunity and increased transmissibility. As more of the population has been vaccinated, severe COVID-19 has been shifted towards vulnerable populations such elderly people, unvaccinated people, and people with comorbidities. Although COVID-19 severity has been hampered by vaccination and the efficacies of novel antiviral drugs, substantial numbers of the infected individuals have suffered a wide range of symptoms after recovering from acute infection. Some of those symptoms could be defined as a long-term complication such as pulmonary fibrosis after COVID-19 pneumonia or venous thromboembolism or post-critical illness syndrome. Furthermore many of the symptoms cannot be attributed to an alternative diagnosis with people exhibiting structural or functional impairment of multiple organs. These constellation of symptoms after COVID-19 gained widespread attention from academic communities across the world as published literatures continues to describe cases of COVID-19 patients who subsequently develop these symptoms.

National Institute of Health and Care Excellence (NICE) defines Long COVID as symptoms that continue or develop after acute covid infection which cannot be explained by alternative diagnosis. This term includes ongoing symptomatic covid-19, from 4 to 12 weeks post-infection, and post-covid-19 syndrome beyond 12 weeks post-infection.[2] The National Institutes of Health (NIH) describes the condition as sequelae that extend beyond four weeks after initial infection.[3] There are disparities in Long COVID epidemiology reporting, which is owing to no standard definition, patients assessed, length of follow up, symptoms examined and self-reporting accuracy.

Most of data did show an association of severity in acute COVID-19 and frequency of developing manifestation of Long COVID. A report from Italy found that 87% of people discharged from hospitals showed persistence of at least one symptom even at 60 days. Among these, 32% had one or two symptoms, and 55% had three or more.[4] Whereas the prevalence of residual symptoms is about 35% in patients treated for COVID-19 on outpatient base.[5] Recent community-based survey in the UK reported that 3.5% of people were experiencing self-reported persisting symptoms at least 4 weeks after onset of COVID-19.[6] Many patients with mild symptoms also develop Long COVID symptoms. More severe or more involved organs at acute COVID-19 may result in higher incidence or severity of Long COVID symptoms.[7]

Symptoms

Fatigues

Fatigue is more profound than being overtired. It is unrelenting exhaustion that reduces a person's energy, motivation, and concentration. Many cross-sectional and cohort studies have shown that fatigue is the most reported symptoms of Long COVID. There is discordance in prevalence of fatigue in Long COVID among studies owing to the various defined criteria of Long COVID, accuracy of self-reporting, data collection methods, duration of follow up, predominant variants of SARS-CoV-2 observed in each study, characters of patients among studies, and numbers of vaccination taken by individuals in each of the studies.[6,8] Small cross-sectional and cohort studies of persisting symptoms or Long-COVID symptoms in patients seeking medical care done as early as 2020 during the first and second wave of COVID-19 pandemic described persisting fatigue in 16 to 98% of patients at 1 to 6 months after COVID-19 onset.[9] National survey of 4-week period of people living in private households in the UK estimated prevalence of ongoing fatigue after COVID-19 at 69% of people having Long COVID as of 3 September 2022.[6] It is postulated that congestion of lymphatic system and the subsequent toxic accumulation in the CNS system caused by an increased resistance to cerebrospinal fluid drainage through the cribriform plate because of olfactory neuron damage, may contribute to post-covid-19 fatigue. Hypometabolism in the frontal lobe and the cerebellum due to inflammation and cell-mediated immune response, rather than direct viral invasion and damage contribute to fatigue in covid.[10,11] Social isolation with negative psychological impacts associated with the covid-19 pandemic have also been linked to chronic fatigue.[12] Lastly, peripheral factors such as direct SARS-CoV-2 infection of skeletal muscle, resulting in damage, weakness, and inflammation to muscle fibers and neuromuscular junctions may contribute to fatigue.[13,14]

Dyspnea

Dyspnea is common in Long COVID ranging from 30-90% at 6 month.[15] This symptomatology can be attributed to multiple mechanisms. Pulmonary function test in Long COVID can be obstructive and restrictive physiologic defects and impaired lung diffusion capacity.[16,17,18,19,20] Hospitalized covid patients were found to have reduced exercise capacity assessed by 6-minute walk distance or dyspnea score and impaired lung functions measured at 12 weeks after symptoms onset, however, exercise capacity and physiologic impairment improve over time.[21] Studies of cardiopulmonary exercise test (CPET) of Long COVID suggest deconditioning as predominant cause of dyspnea irrespective of imaging sequelae, lung function tests.[22] Most individuals who develop long-term breathing difficulties post-covid-19 have no signs of permanent or long-lasting lung damage.[23,24]

Cardiovascular

Chest pain and palpitation was found in as many as 21% and 9% in 60 days and 6 months accordingly after discharge from hospital.[4,25] A routine cardiac magnetic resonance imaging (CMR) follow up study of COVID-19 patients at median day of 71 found 60% of patients have ongoing cardiac inflammation suggesting that

cardiac effects of SARS-CoV-2 can be prolonged.[26] Abundant ACE2 receptors in the heart provide a direct route of the viral entry into cardiomyocyte. Pathological response is myocarditis provoked by inflammatory immune cells. Prolonged inflammation and cellular damage prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis which can be arrthymogenic. Afferent autonomic nerve dysfunction caused by viral injury to myocyte causes complications such as postural orthostatic tachycardia (POTS),[9] which is increasingly found after COVID-19. POTS has not yet been known much about its exact pathophysiology.

Cognition and Mental health

Neurological and mental impairment in Long COVID are diverse in symptoms domain such as encephalopathy, delirium, psychiatric illness, cerebrovascular disease. All of which could be resulted from non-immunological effects from critical illness such as hypoxia, hypotension, prolong mechanical ventilation support and aberrant immunological process induced by SARS-CoV-2 infection such as dysfunctional pro-inflammatory microglial cells and self-perpetuating neurotoxicity of the neurons.[9] Cognitive impairment, so called 'brain fog', can be with or without fluctuation and may manifest as difficulties in concentration, memory, language, and executive dysfunction.[27] Stroke and headache are prevalent in those recovered from acute covid-19, with estimated 5 week prevalence of headache at 10.1% of all covid-19 survivors.[10] Hypercoagulability and cardiac embolism also increase incidence of stroke following covid-19 infection.[28,29] Guillain-Barre syndrome and Alzheimer's disease have been associated with covid-19.[30,31] Mental illness such as post-traumatic stress disorder (PTSD), anxiety, depression, and obsessive-compulsive symptoms could be the sequelae of acute covid-19. All of which are caused by physical and social avoidance imposed by the pandemic or exacerbation of underlying psychiatric disorders.[9]

Olfactory and gustatory dysfunction

Olfactory and gustatory dysfunction was found in 7.9% and 8.2% of patients who had covid-19 assessed at 5 weeks after acute infection.[32] The possible mechanism of olfactory dysfunction is explained by viral entry into olfactory support cell, stem cell and perivascular cell via ACE2 receptor and inflammation which impair cell function. ACE2 receptors are also expressed in the mucous membrane of the mouth, especially on the tongue. Gustatory dysfunction could be resulted from the same way of mechanism as olfactory dysfunction.[33,34]

Kidney dysfunction

Specific mechanism of kidney dysfunction after acute COVID-19 has not been fully elucidated. One study reported kidney dysfunction in 35% of patients recovered from acute COVID-19 infection at 6 months.[25] 30% of patients who required inpatient dialysis continued to require dialysis after discharge.[35] The mechanism is now thought to be associated with sepsis and hemodynamic derangement and hypoxemia from lung injury which result in acute tubular necrosis as the most common histopathology.[36]

Endocrine sequelae

COVID-19 has been associated with new-onset hyperglycemia and worsening of pre-existing diabetes mellitus including hyperglycemia and diabetic ketoacidosis that can persist into post-acute COVID-19 period.[37] Hyperglycemic complications of COVID-19 may be resulted from insulin secretory deficit by direct viral injury, indirect immunological and inflammatory damage, peripheral insulin resistance by inflammatory state, or iatrogenic cause by corticosteroid therapy.[38]

Other organs

ACE2 receptors are found in various organs which underly the organ dysfunction in post covid-19 infection through direct damage from SARS-CoV-2 or systemic inflammatory process. Pancreatitis was found in patients with mild or severe covid-19, but serum amylase was higher in patients with more severe disease.[39] Postmortem and case studies have described the impact that COVID-19 has on the spleen, including atrophy of lymphoid follicles, a decrease in T and B lymphocytes leading to lymphocytopenia, and thrombotic events such as infarcts.[40,41] Other organs susceptible for viral direct and indirect damage include liver, gastrointestinal tract and muscles.[9]

Risk factors of Long COVID

The risks of Long COVID have not yet been fully elucidated. A cross-sectional study was conducted in non-hospitalized post covid infection patients and found the risks of not returning to their usual health status which included age ≥50-year, female sex, pre-existing medical condition especially hypertension, obesity, an immunosuppressive condition, and psychiatric condition.[5] One study showed that requiring hospital treatment for acute COVID-19 and more than 5 organs involvement at initial covid infection associated with Long COVID symptoms.[24,42] The prevalence of any Long COVID symptoms is higher in women compared with men (23.6% versus 20.7%), while the age group estimated to be most greatly affected by Long COVID symptoms is 35-49 years (26.8%), followed by 50-69 years (26.1%), and the ≥70 years group (18%).[32] However, some evidence from a prospective study showed no relationship between baseline characteristics and development of Long COVID.[43] Long COVID multi-system symptoms can be cyclical in disease natural course, waxing and waning and recurring with fluctuation in intensity.

Treatment of Long COVID

Fatigue, cognitive and neuropsychiatric symptoms

Currently, there are no proved pharmacological therapy for chronic fatigue in Long COVID. The management of these sequelae of covid 19 focuses on providing supported patient self-management which include multidisciplinary rehabilitation, setting realistic goal that can be achievable by patients through the program and providing contacting personnel for sources of advice and support in continuing holistic care. This can be accomplished by providing integrated and coordinated primary care, community, rehabilitation, mental health services, patient organizations, and online support groups. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) for

treatment of chronic fatigue from Long COVID have concerns over potential adverse effects such as post-exertional malaise and small short-lived subjective improvement of fatigue.[44] Sleep disturbances, anxiety, depression, PTSD, and OCD can be managed according to the relevant guidelines.[9] Self-management including stopping smoking, avoiding extreme exercise and pollutants, can help mitigate exacerbation of breathlessness. Multidisciplinary approach to therapeutic intervention is also recommended such as pulmonary rehabilitation, breathing exercise and health advice.[45,46] Opioid can be used to treat dyspnea in patient with Long COVID.[47]

Cardiovascular

Currently, patients who suffered from cardiovascular symptoms after COVID-19 should be evaluated for responsible cardiovascular diseases and should be followed as established specific disease guidelines as non-COVID-19 patients. Beta-blockers are recommended by NICE guideline to treat arrhythmia and angina. Myocarditis maybe improved by supportive treatment and immunomodulators.[45]

Other organs

Close follow-up of patients with Long COVID and adequate investigative procedures should be done to promptly diagnose and treat organ specific symptoms such as ongoing renal dysfunction, opportunistic infection resulting from immunosuppressive drugs treating post-covid organ inflammation or from altered gut microbiome, and covid-19 associated destructive thyroiditis.

Long-term pulmonary complication and treatment

Pulmonary fibrosis

Patients who experience acute respiratory distress syndrome during acute SARS-CoV-2 infection have longer duration of oxygen supplement, have older age, have pre-existing pulmonary dysfunction, and are at high risk of subsequent pulmonary fibrosis.[48,49] The development of fibrotic lung in patients with ongoing dyspnea is believed to be caused by cytokines such as interleukin 6, TGF-β, and TNF-α.[50] In the alveoli of the lung, inflammation results in production of proinflammatory cytokines and reactive oxygen species (ROS) in surrounding tissue and blood stream. Endothelial damage triggers the activation of fibroblasts, which deposit collagen and fibronectin resulting in fibrotic changes, and sustains hyperinflammatory state through compliments activation disrupting the normal coagulation pathways, increasing the risk of thrombosis. SARS-CoV-2 nucleocapsid protein is believed to promote pulmonary fibrosis through Angiotensin-converting enzyme-2 (ACE2) downregulation which enhances TGF-β signaling. Lastly, mechanical power derived from mechanical ventilation could result in ventilator-induced lung injury and subsequent pulmonary fibrosis.[51] Cohort studies of mild to moderate acute covid cases demonstrate fibrotic change on HRCT consisting primarily of reticulation and traction bronchiectasis observed after 3 months of hospital discharge in 25-75% of patients.[23,24] In large Chinese cohort of patients who needed oxygen supplement during acute covid infection with one-fourth of them needed HFNC,

NIV, or invasive mechanical ventilation, ground-glass opacities was the majority of CT scan abnormalities found at 6 months after hospital discharge.[25] Currently, lack of long-term follow up of pulmonary fibrosis in patients recovering from COVID-19 makes it difficult to forecast the natural course of fibrotic consequences in these patients.

COVID-associated ARDS or acute lung injury and its consequences of pulmonary fibrosis biologically and epidemiologically share the same risk factors as idiopathic pulmonary fibrosis (IPF). There are evidences of immune-mediated lung damage and classical acute lung injury pathway that both exists in covid-19-induced lung injury and IPF. Antifibrotic drugs in connective tissue disease-related interstitial lung disease (CTD-ILD) shows benefit to slow forced vital capacity (FVC) decline.[52,53] Given the similarities of immune mediated fibrotic pathways in CTD-ILD and aberrant immune response in SARS-CoV-2 associated fibrosis, together with direct viral-induced cytotoxicity, antifibrotic drugs that target proinflammatory and profibrotic cytokines may potentially prevent or ameliorate fibrotic consequence following COVID-19 especially in patients with risk factors. There are several proteins which are the targets for novel antifibrotic drugs, many of which play roles in viral-induced lung injury or lung fibrosis, for example, $\alpha_v\beta_6$ integrin-mediated viral internalization which is the mainstream of the pathway leading to TGF-β and IL-1 secretion that are responsible for pulmonary fibrosis and cytokine storm in severe covid, c-Jun N-terminal kinase (JNK) which takes pivotal role in sepsis-induced lung injury and mTOR pathway which indicates rapamycin to be repurposing drugs.[54] Several ongoing clinical trials are evaluating efficacies of nintedanib and pirfenidone, two anti-fibrotic drugs used in IPF, in patients with recent hospitalization with COVID-19 and persistent lung involvement and some degree of functional impairment primarily in lung function declines.[51] An important concern regards the rapidity of onset of action of anti-fibrotic drugs which indicates timing of drug introduction in the course of COVID-19.However, clinical trials have demonstrated benefits of slowing FVC decline as early as 4-6 weeks after initiation of antifibrotic drugs.[52,55] This suggests a quick onset of action in attenuating fibrogenesis that could be achieved in severe COVID-19-associated lung fibrosis.

Pulmonary embolism

Immune-mediated thromboinflammation plays a key role in COVID-19 associated micro and macrovenous and arterial thrombosis. Among VTE, PE is more common than deep vein thrombosis (DVT) in COVID-19 patients. Postmortem lung autopsies of COVID-19 patients found microvascular thrombosis in lung tissue, reflecting in situ thrombosis secondary to severe lung inflammation as an underlying mechanism.[56] High incidence of thromboembolic diseases, especially with VTE, are more frequently associated with moderate and severe COVID-19 patients who need high demanding care (HDU) or intensive care than patients with less severe disease.[57] Observational studies and case series found higher incidence of VTE in COVID-19 ARDS than non-COVID-19 ARDS; most of which are pulmonary embolism.[58] Prompt diagnosis of VTE based on clinical suspicion during hospitalization

should be implemented given high incidence of VTE in COVID-19 patients especially in those with obesity and preexisting risk factors for VTE. Universal standard prophylactic doses of subcutaneous slow molecular weight heparin (LMWH) or unfractionated heparin (UFH) for hospitalized COVID-19 patients are advocated by authoritative organizations over therapeutic doses of LMWH or UFH due to relatively high rates of VTE found in reports of COVID-19 patients population.[59,60] However, the optimal management of COVID-19 associated thrombosis remains uncertain regarding dose intensity and duration of anticoagulation after hospital discharge. Several observational studies suggests the incidence of VTE after hospital discharge are as low as 0.2-2.5% and routine extended VTE prophylaxis beyond hospitalization is not currently recommended in general COVID-19 patients, but may be reasonable for at least 2 weeks and up to 6 weeks post-hospital discharge in selected patients with high risk of VTE and low risk of bleeding such as advanced age, cardiovascular disease, cancer, ICU admission, past history of VTE, immobilization, thrombophilia, and elevated D-dimer (>2 times upper limit of normal).[60,61,62,63] Rivaroxaban in post-discharge COVID-19 patients with high risk of VTE improved composite outcome of VTE, arterial thromboembolism, and cardiovascular death compared to no extended thromboprophylaxis in a recent clinical trial.[64] There are ongoing randomized controlled trials to evaluate the efficacy and safety of extended post-discharge anticoagulant in COVID-19 patients.

Follow up recommendation for post-COVID-19 infection

Patients with COVID-19 pneumonia, who need care in ICU or are dependent on high oxygen concentration are more likely to have poorer long-term outcomes with persisting abnormal radiography or physiologic impairment than those with mild COVID and do not previously need intensive care as has been reported in previous SARS epidemics. This has rationale in scheduled follow up of patient discharged from hospital. Data from patients infected with coronaviruses informed that approximately two-thirds of these patients have full CXR resolution at 12 weeks.[45,65]

Patient who has high risk features of the long-term complications are suggested to undergo early follow up assessment at 4-6 weeks after discharge. This early follow-up should include holistic assessment of possible immediate and long-term complications such as post-intensive care syndrome (ICU-acquired weakness, cognitive impairment, depression, anxiety and posttraumatic stress disorder),[66] need for oxygen therapy, consideration for rehabilitation, symptoms of Long COVID such as breathlessness, fatigue, and anxiety for instance, and diagnosis of venous thromboembolism. Then patients should undergo CXR at 12 weeks. If CXR has persistent or significant residual abnormalities or patients have ongoing respiratory symptoms, they should undergo full clinical assessment for pulmonary function testing, walk test with an assessment of oxygen saturation, echocardiogram, and sputum sample for microbiological analysis. If the aforementioned clinical assessment has any abnormalities, patients should be considered for

high-resolution CT (HRCT) or CT pulmonary angiogram (CTPA) to assess for interstitial lung disease (ILD) or pulmonary embolism. If there are evidence of ILD or pulmonary vascular diseases, patients should be referred to relevant specialist clinics. If comprehensive clinical and relevant radiological assessment are not responsible for symptoms, patients should be suspected for dysfunctional breathing or fatigue and should be referred for physiotherapy.

Patients with mild or moderate COVID-19 pneumonia, such as those who admitted on ward and do not need high flow oxygen therapy, should have routine follow up of CXR at 12 weeks from hospital discharge. If the CXR has completely resolved or has insignificant changes such as atelectasis, then patients should be discharged from follow up. For patients with significant persistent CXR abnormalities at 12 weeks and are clinically improving, consider repeat CXR after 6 weeks since the first CXR. If patients have persisting respiratory symptoms or the arranged pulmonary function test later show abnormalities, the patients will be required further investigations which may include HRCT or CTPA.[65]

Conclusion

Given the large scale of SARS-CoV-2 pandemic and with many people having been infected, the long-term complications of COVID-19 are of increasing concern. Health care needs for patients suffered Long COVID will continue to increase imminently in the near future. It is important that research continue to explore this enigmatic syndrome in all aspects such as pathogenesis and natural history, precise epidemiology, clinical classification of syndrome, optimal treatments, and impacts of the novel variants of the virus. Though, it may challenge the harnessing of scalable healthcare infrastructure. Multidisciplinary approach for comprehensive care of these patients in the outpatient setting is also essential.

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