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Clinical and Functional Outcomes of COVID-19 Survivors After Hospitalization

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Abstract

Coronavirus disease 2019 (COVID-19) causes various clinical manifestations during acute infection and at the post-acute phase with persistent symptoms called long COVID. It occurs in mild and moderate to severe cases which require hospitalization. In patients needing hospitalization, especially intensive care unit admission, the risk of long COVID increases. Many hospitalized patients exhibited more symptoms in 60 days after the illness than non-hospitalized patients. This review aimed to identify the clinical and functional outcomes in COVID-19 survivors after hospitalization. The articles in the PubMed database published in 2019-2021 were reviewed and found 20 be eligible. The clinical outcomes were the appearance or persistence of general and multi-organ symptoms, nutritional disorders, and decreased lung function. The functional outcomes found were decreased muscle strength, physical, psychological, and cognitive functions, increased disability and dependencies, as well as decreased vocational status and quality of life. The incidence of each outcome could not be determined due to the variety of methods used to examine and present outcomes. To conclude, COVID-19 causes long-term clinical and functional outcomes that need to be identified to prevent and manage long-term physical and functional disorders.

Keywords: COVID-19, hospitalization, post-acute COVID-19 syndrome, quality of life, survivor

Introduction

Coronavirus disease 2019 (COVID-19) causes various clinical manifestations. The World Health Organization classifies the severity of this disease into mild, moderate, severe, and critical.¹ The severity of the disease increases the need for hospitalization, intensive care unit (ICU) admission, and even mortality.² People with a comorbid for COVID-19 have a higher risk for more severe disease.³ In addition to causing various symptoms during acute infection, COVID-19 has long-term effects on survivors. This condition is called post-acute sequelae of COVID-19 or long COVID-19 (LC). The LC is a patient with signs and symptoms that persist for about 4-12 weeks or appear after the acute phase (≥ 12 weeks).⁴ Clinical outcomes (CO) and functional outcomes (FO) of COVID-19 survivors can be affected. A review by Hayes, *et al.*,⁵ found over 100 persistent symptoms after COVID-19 infection. Reported symptoms include cardiovascular, pulmonary, respiratory, fatigue, pain-related symptoms, generalized infection symptoms, psychological disorders, cognitive impairment, sensory disturbances, skin problems, and impaired function.⁵

A previous study have shown that LC not only occurs in patients with moderate to severe cases which require hospitalization but also in mild cases.⁶ However, the risk of post-intensive care syndrome (PICS) was increased in patients needing hospitalization, especially ICU admission.⁷ One systematic review found that a large proportion of hospitalized patients exhibited one or more symptoms of LC at 60 days after the illness compared to non-hospitalized patients.⁸ Thus, this review study aimed to identify the CO and FO in COVID-19 survivors after hospitalization to give the knowledge or to develop a rehabilitation program for COVID-19 survivors.

Method

Articles were searched in the PubMed database with keywords ('functional' OR 'clinical') AND ('status' OR 'outcome') AND ('severe' OR 'critical') AND ('COVID-19') AND ('survivor') for the period from September 2021 to October 2021. The article type was an original article published from December 2019 to October 2021. Inclusion criteria were original articles with the study subjects of COVID-19 survivors after being discharged from the hospital, written in English, and freely accessi-

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ble in pdf or HTML format.

The identical articles were identified first, then reviewed based on title, abstract, and keywords. Data taken were the author(s), study design, total subject, outcome assessment period, CO, and FO. Data were synthesized narratively and displayed as a table and text. The CO synthesized was based on symptoms, physical examination, laboratory, and imaging findings, while FO was determined based on functional impairment, disability, and quality of life.

Results

A total of 1,053 articles based on keywords searched and 40 articles matched with eligibility criteria. After reading the full text, 27 articles explaining both CO and FO were found. The study types were a prospective cohort (n = 20), a retrospective cohort (n = 5), an ambidirectional cohort (n = 1), and a cross-sectional (n = 1) study. Twenty prospective cohort studies were analyzed as a final result. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for a systemic review (Figure 1) was used to

explain the results. The result summary is presented in Table 1.

Discussion

Most studies were conducted in the first few months of 2020. During this period, COVID-19 was known to be caused by the original variant of severe acute respiratory system coronavirus 2 (SARS-CoV-2) with various clinical and functional outcomes.

Clinical Outcomes of COVID-19

The Appearance or Persistence of General Symptoms

The most common symptoms reported by COVID-19 survivors after one month to one year after being discharged from the hospital were shortness of breath and fatigue. The presence of persistent symptoms in COVID-19 survivors is caused by several mechanisms, including the presence of SARS-CoV-2 and a persistent inflammatory response in various tissues, reactivation of neurotrophic pathogens when immune dysregulation occurs, interactions of viruses with the microbiome or virome of the host cell, blood coagulation problems,

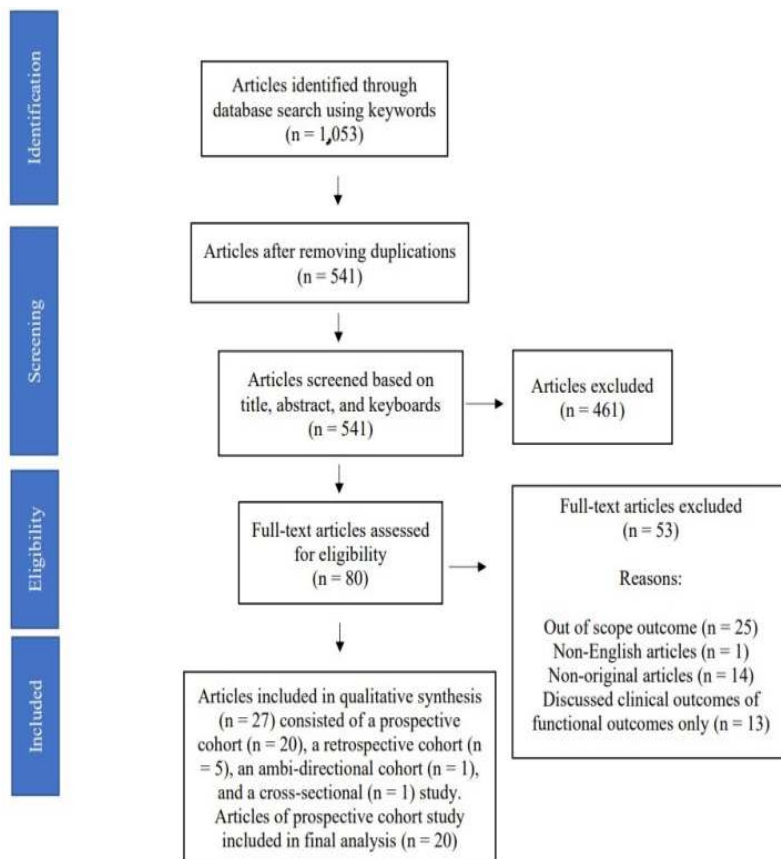


Figure 1. PRISMA Flowchart for the Systematic Review

Table 1a. Summary of Clinical and Functional Outcomes of COVID-19 Survivors After Hospitalization

Author (s)	Total Subject	Result	
		Clinical Outcome	Functional Outcome
Martillo, <i>et al.</i> ⁹	45	Fatigue	<ul style="list-style-type: none"> • PICS • Upper and lower extremity function abnormalities • Minimal, mild, moderate, moderate-severe, severe depression, PTSD, insomnia, anxiety • Cognitive impairment • Disability • HRQoL: mobility, pain/discomfort, self-care, usual activities
Hall, <i>et al.</i> ¹⁰	200	<ul style="list-style-type: none"> • Dyspnea • Impaired ventilation (FVC and DLCO) 	<ul style="list-style-type: none"> • Increase exertional desaturation during 6MWT • Depression, anxiety
D'Cruz, <i>et al.</i> ¹¹	119	<ul style="list-style-type: none"> • Fatigue, dyspnea with persistent cough and burdensome pain, especially in the shoulder, chest, lower extremity, and back, and sleep disturbance 	<ul style="list-style-type: none"> • Decreased four-minute gait speed • Decreased lower body muscular strength and endurance • Increase exertional desaturation by ≥4% and to SpO2 ≤88% during sit-to-stand test • Depression, anxiety, PTSD • Cognitive impairment • 6MWT: decreased exertional capacity • HRQoL: impaired domains of the physical or emotional role and social function
Cao, <i>et al.</i> ¹²	62 at 1 month; 61 at 3 months	<ul style="list-style-type: none"> • Cough, dyspnea, fatigue • Impaired ventilation (FEV1, FVC, MVV under predicted value) 	<ul style="list-style-type: none"> • Psychological disorders: anxiety and depression, PTSD, and insomnia. • Overall HRQoL showed no difficulty in mobility, self-care, usual activities, and anxiety/depression. Moderate pain/discomfort by 41%. • More than half of patients who were previously employed did not return to their work.
Monti, <i>et al.</i> ¹³	39	<ul style="list-style-type: none"> • Alteration in taste or smell, dyspnea at exertion • Malnutrition, at risk for malnutrition 	<ul style="list-style-type: none"> • Cognitive impairment • 6MWT: decreased exertional capacity, increase exertional desaturation • Decrease HRQoL score in all domains
Strumiliene, <i>et al.</i> ¹⁴	51	<ul style="list-style-type: none"> • Fatigue, decreased physical activity, dyspnea at exertion, asthenia, cough, arthralgia, hair loss, headache, insomnia • Decrease pulmonary function test parameters (FVC, FEV1, TLC, VC, DLCO) 	<ul style="list-style-type: none"> • Impairment in all domains of HRQoL • Decreased exertional capacity • Returned to full-time work • Decreased exertional capacity • Decreased HRQoL • Muscle weakness, ICU-AW • Anxiety and depression • Cognitive impairment • HRQoL: decreased • 6MWT: decreased exertional capacity • Psychological disorder: anxiety and depression
Schandl, <i>et al.</i> ¹⁵	113	<ul style="list-style-type: none"> • Psychological disorder: PTSD, anxiety, depression • Decrease TLC and DLCO 	<ul style="list-style-type: none"> • Anxiety/depression • Impairment in all domains of HRQoL • Anxiety, insomnia, PTSD • Decreased HRQoL • Decrease of peripheral muscle strength • Poor sleep quality, PTSD • Cognitive impairment • Dependency • Did not return to their previous level of activity
Van Gassel, <i>et al.</i> ¹⁶	46	<ul style="list-style-type: none"> • Fatigue • Decreased DLCO 	
González, <i>et al.</i> ¹⁷	62	<ul style="list-style-type: none"> • Dyspnea, muscle fatigue, cough • Decreased DLCO and TLC 	
Todt, <i>et al.</i> ¹⁸	251	Dyspnea	
De Lorenzo, <i>et al.</i> ¹⁹	251	Tachypnea, dyspnea	
Rousseau, <i>et al.</i> ²⁰	32	Abnormal estimated glomerular filtration rate	

Notes: 6MWT = Six-minute Walk Test, DLCO = Diffusing Lung Capacity for Carbon Monoxide, FEV1 = Forced Expiratory Volume at 1 s, FVC = Forced Vital Capacity, HRQoL = Health-Related Quality of Life, ICU-AW = Intensive Care Unit-Acquired Weakness, MVV = Maximal Voluntary Ventilation, PICS = Post-intensive Care Syndrome, PTSD = Post-traumatic Stress Disorder, TLC = Total Lung Capacity, VA = Alveolar Volume, VC = Vital Capacity.

dysfunction of vagal nerve signaling, abnormal cell metabolism, the presence of primitive immune cell activity, and molecular mimicry leading to autoimmunity between pathogens and host cells.²⁹⁻³⁰

The Appearance or Persistence of Multi-organ Symptoms
 Angiotensin-converting enzyme 2 (ACE2), employed by SARS-CoV-2 as a receptor to enter human cells, is abundant in lung epithelial cells, especially in the alveoli. However, ACE2 is also widespread in various organs,

Table 1b. Summary of Clinical and Functional Outcomes of COVID-19 Survivors After Hospitalization

Author (s)	Total Subject	Result	
		Clinical Outcome	Functional Outcome
Sigfrid, et al. ²¹	327	Fatigue, dyspnea, sleeping problems, headache, limb weakness, myalgia, arthralgia or swelling, dizziness/lightheadedness, balance problems, swollen ankle, palpitations, seeing problems, constipation, stomach pain, diarrhea, persistent cough, chest pains, pain on breathing, anosmia, persistent fever, ageusia, nausea/vomiting, swallowing problems, skin rash, passing urine problems, hemiplegia/paresthesia, toe lesions, weight loss	<ul style="list-style-type: none"> • Anxiety/depression • Disability in walking or mobility, memory, and concentration • Decreased overall domains of HRQoL
Latronico, et al. ²²	114 evaluated at least once; 69 at least twice; 43 three times	<ul style="list-style-type: none"> • Fatigue, ICU-AW • At risk of malnutrition or being malnourished • Decreased DLCO 	<ul style="list-style-type: none"> • 6MWT: abnormal • Decreased handgrip strength at 3 months, abnormal global muscle strength at 3, 6, and 12 months • Anxiety, depression, PTSD at 3 months • Cognitive impairment • Dependency at 3 and 6 months, and independency at 12 months • Return to work at 3, 6, and 12 months, reduced effectiveness at work at 3 and 6 months, not return to work at 3, 6, and 12 months
Boari, et al. ²⁵	94	<ul style="list-style-type: none"> • Lamented fatigue, effort dyspnea, anorexia, dysgeusia or anosmia, insomnia • Alteration in DLCO 	<ul style="list-style-type: none"> • Anxiety
Bellan, et al. ²⁴	238	<ul style="list-style-type: none"> • Dyspnea, ageusia, anosmia, arthralgia, myalgia, cough, diarrhea, chest pain • Decreased DLCO 	<ul style="list-style-type: none"> • 2-minute walk test: 40.5% outside reference ranges of expected • Mild, moderate, severe PTSD • Mobility: limited
Guler, et al. ²⁵	66	<ul style="list-style-type: none"> • Exertional dyspnea • Had generally lower lung volumes, decreased DLCO 	6MWT: decreased exertional capacity, increase exertional desaturation
Veenendaal, et al. ²⁶	50	<ul style="list-style-type: none"> • Fatigue, weakened condition, polyneuropathy, dyspnea, muscle weakness/stiffness, shoulder pain, restriction of extremities, difficulty sleeping, walking, impaired hand function • Weight loss • Impaired ventilation (FEV1, FVC under predicted value), decreased DLCO under predictive value 	<ul style="list-style-type: none"> • Cognitive impairment • 10% no change in work, 13% reduced work rate, 10% occupation change, 13% re-integration, and 43% too ill to work
Lombardo, et al. ²⁷	189	Fatigue and weakness, myalgia and arthralgia, sleep disorders, respiratory disorders, sensory alterations, gastrointestinal symptoms, movement impairments	Neurocognitive impairments
Bertolucci, et al. ²⁸	39	Dysphagia, peripheral nervous system impairment	<ul style="list-style-type: none"> • Delirium • Total Dependency • Cannot walk

Notes: 6MWT = Six-minute Walk Test, DLCO = Diffusing Lung Capacity for Carbon Monoxide, FEV1 = Forced Expiratory Volume at 1 s, FVC = Forced Vital Capacity, HRQoL = Health-Related Quality of Life, ICU-AW = Intensive Care Unit-Acquired Weakness, MVV = Maximal Voluntary Ventilation, PICS = Post-intensive Care Syndrome, PTSD = Post-traumatic Stress Disorder, TLC = Total Lung Capacity, VA = Alveolar Volume, VC = Vital Capacity.

such as the heart, intestines, and kidneys.³¹ Therefore, the virus can persist and damage various organs, resulting in other manifestations, both during the acute phase and after the patient recovers. Autoimmunity is also known to cause inflammation and damage in various organs.²⁹ One study found an abnormal estimated glomerular filtration rate.²⁰ Acute kidney failure is one of the complications due to COVID-19, which has a prevalence of 17%, of which 77% have severe COVID-19, and 5% of the total patients require renal replacement therapy.³² In addition to the kidneys, abnormal results were found in cardiovascular organs, gastrointestinal, and neurological tissue.³²

Decreased Lung Function

Various studies carried out pulmonary function tests on COVID-19 survivors. They found that ventilation was impaired through a decrease in forced vital capacity and forced expiratory volume in one second, a decrease in total lung capacity, and a decrease in diffusion capacity.^{10,12,14-17,22-26} COVID-19 survivors needed a long period to recover due to lung fibrosis and other morphological changes fully. The recovery rate is affected by the severity level, which is affected in turn by gender, obesity, and the presence of comorbidities.¹⁴ Predominant impairment of lung function is a restrictive pattern with

a reduction of diffusing capacity for carbon monoxide (DLCO) value.¹⁴

Nutritional Disorders

Nutrition-related problems that arise in COVID-19 survivors, especially severe degrees of disease, are caused by other related manifestations.³³ Difficulty of swallowing and weakness can make it difficult for the patient to eat. This condition is exacerbated by reduced appetite, resulting in muscle wasting.³³ In the end, survivors reported a weight loss of >5% of their pre-illness body weight.³⁴ In other survivors, the diagnosis of malnutrition was established. Moderate to severe malnutrition is the most common diagnosis.³⁵

Functional Outcomes of COVID-19

Decreased Muscle Strength

Decreased muscle strength may occur due to chronic skeletal muscle damage by SARS-CoV-2.³⁶ In addition, muscle weakness can be the result of immobility that occurs during hospitalization.³⁷ Prolonged ICU stay or mechanical ventilation used increased the occurrence of ICU-related muscle weakness.^{20,22}

Decreased Physical Performance

The 6MWT was the most frequently used method to determine decreased exercise capacity and increased exertional desaturation post-COVID-19.^{10,12,14-17,22,25} Wong, *et al.*, described that in patients who had exertional desaturation or hypoxemia (reduced SpO₂ \geq 4%), 45% had walking distance less than the lower limit of normal on the 6-minute walking distance, and 100% had DLCO less than the lower limit of normal.³⁸ These results suggest that desaturation during exercise is associated with pulmonary vascularity.³⁸

Psychological Disorder

Anxiety and depression were the most frequently reported psychological disorders in COVID-19 survivors, especially those requiring hospitalization.³⁹ Mental health disorders occur due to direct neuro-invasion by viruses that cause nerve cell damage or due to immune activation that causes an inflammatory response, especially in the brain.³⁹ In addition, having to undergo isolation makes it difficult to meet family and the inability to carry out normal activities, as well as guilt toward those closest to them because they have increased the risk of exposure to disease, all of which become stressors for the emergence of symptoms of anxiety and depression.⁴⁰

Cognitive Impairment

Not all literature describes methods for assessing the presence of cognitive impairment. However, in some

literature that explains this, the Montreal Cognitive Assessment method was found to be the most widely used method to assess cognitive impairment. Similar to psychological disorders, cognitive impairment is also caused by damage to neurological function and the immune system.^{32,39} In addition, patients undergoing treatment in hospitals do not receive stimulation and cognitive reorientation due to limited interactions between humans.⁴⁰ Cognitive symptoms that arise post-COVID-19 include difficulty thinking and concentrating (brain fog), decreased memory, and difficulty carrying out executive functions.³⁷ Any disturbances in physical, mental health, and cognitive functions cause post-intensive care syndrome, seen in individuals who have had treatment in an intensive care unit.⁷

Increased Disability and Dependency

Physical impairments that arise are related to the treatment given in the acute phase.⁴⁰ The more severe the severity of the disease, the more complex the treatment given in the hospital. Severe disease increases the likelihood of mechanical ventilation, sedation, and neuromuscular blockade associated with prolonged immobilization.⁴⁰ Subsequent immobilization causes muscle and joint contractures, making it difficult for the patient to move. These disabilities make survivors dependent on carrying out daily activities. The Short Physical Performance Battery test method can be used to measure mobility ability through walking speed, Functional Ambulatory Category for walking/ambulation ability, and Barthel Index to determine individual dependence in daily activities.⁴⁰

Decreased Vocational Status

COVID-19 infection caused a significant reduction in return to workability.^{13,15,20,22,26} Several studies found that 50% to 87.5% of COVID-19 survivors did not return to their previous work or activity.^{13,15,20} One study found that 43% of COVID-19 survivors felt too ill to work.²⁶ Among survivors who returned to work, many experienced a reduction of work capacity.^{22,26}

Decreased Health-Related Quality of Life

Most studies found that all domains of HRQoL decreased in COVID-19 survivors after hospitalization.^{12-19,21} Short-form 36 items and European Quality of Life 5 Dimension were the most common HRQoL assessment instruments.^{12-16,18,19,21} The decrease in HRQoL was associated with symptoms, especially shortness of breath and fatigue, decreased physical performance, stress in family and work, and social isolation.^{12-14,16} The decrease in physical performance was associated with decreased pulmonary function.¹⁶

Conclusion

The CO identified in several studies is the appearance or persistence of general symptoms, multi-organ symptoms, decreased lung function, and nutritional disorders, while the FO includes decreased muscle strength and physical performance, psychological or cognitive disorders, increased disability or dependency, as well as decreased vocational status and HRQoL. With various methods used to examine the CO and FO of COVID-19 survivors after hospitalization and not all literature being equipped with a percentage of each outcome, the authors could not determine the incidence of each outcome. Further studies need to elucidate the incidence and differential outcomes associated with each variant of SARS-CoV-2 and their specific mechanisms. After knowing these outcomes, medical personnel are expected to be able to assess the CO and FO of COVID-19 patients to be used as a basis for carrying out rehabilitation management. Good cooperation between medical personnel and survivors is needed to improve the HRQoL and prevent persistent anatomical and physiological damage to the body.

Abbreviations

COVID-19: coronavirus disease 2019; ICU: Intensive Care Unit; LC: Long COVID, CO: Clinical Outcomes; FO: Functional Outcomes; PICS: Post-intensive Care Syndrome; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ACE2: Angiotensin-Converting Enzyme 2; DLCO: Diffusing Lung Capacity for Carbon Monoxide; 6MWT: Six-minute Walk Test; HRQoL: Health-Related Quality of Life.

Ethics Approval and Consent to Participate

Not applicable.

Competing Interest

The authors declares that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

Not applicable.

Authors' Contribution

AN, SSSP, and MHB contributed to all conception, analysis, and interpretation of results, as well as writing the manuscripts and revising them. All authors read and agreed to the final version of the submitted manuscript.

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