Footprint of Long-Term Pulmonary Sequelae of Covid 19 on Post Pandemic Pulmonary Status-An Prospective Observational Study

Prof. Dr. Shanmugananth E[1], Prof. Dr Yu Chye Wah[2], Kshtrashal Singh[3], Susmitha Govind[4]

shankutty1981@gmail.com[1], chyewah@aimst.edu.my[2], kshtrashal@aimst.edu.my[3], Susmitha@aimst.edu.my[4]*

[1]School of Physiotherapy, Sree Balaji Vidyapeeth, Deemed to be University, India,

[2, 3]School of Physiotherapy, Faculty of Allied Health Professions, AIMST University, Malaysia,

[4]School of Physiotherapy, Faculty of Allied Health Professions, AIMST University, Malaysia and Ph.D Scholar, School of Physiotherapy, Sree Balaji Vidyapeeth, Deemed to be University, India

Corresponding Author: susmitha@aimst.edu.my*

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ABSTRACT:

The progression to acute respiratory distress syndrome (ARDS) with more severe symptoms, significant hypoxemia, and the need for hospitalization, including respiratory support. Interstitial lung disease is a known long-term pulmonary sequelae of ARDS and reported in over 60%2 of severe acute COVID-19 ARDS survivors. Recovery from post-COVID-19 interstitial lung disease may be seen over months but has also been reported to be persistent and, in a minority, progressive. Individuals with milder presentations may still suffer from longer-term complications including persistent pulmonary inflammation and fibrosis. Objectives: To study the Impact of Long-Term Pulmonary Sequelae of Covid 19 on Post Pandemic Pulmonary Status. Secondary: To compare the Demographic and clinical variables of Long Covid on post-pandemic Pandemic Pulmonary Status. Methodology: A systematically search from the mentioned databases would be done from inception to June 2024. The reference lists of all the included studies and related reviews for potentially eligible studies will be screened. The keywords proposed to be used includes "post-COVID-19syndrome", "long haulers," "long hauling," and "chronic COVID syndrome." The data collected would be analysed using appropriate statistical methods to determine if there were significant differences between the experimental groups in terms of the outcomes measured. Outcome measurement: systematically search from the many databases would be done. Expected outcomes: Covid 19causes significant difference in the total lung capacity and diffused capacity of the lungs for carbon monoxide on Post Pandemic Pulmonary

Status. Significance of output from the research project: The findings of the study will be submitted to AIMST University, Malaysia with the intention to implement the study results in public interest and welfare...

Keywords: Long-Term Pulmonary Sequelae, COVID-19, Post-Pandemic Respiratory Health.

Background:

Severe acute respiratory syndrome coronavirus, the infectious agent that causes coronavirus disease 2019 (COVID-19), can infect multiple organ systems triggering an inflammatory response resulting in abnormalities in cellular and organ function. This can result in multiple symptoms and associated functional limitations. Respiratory symptoms in acute COVID-19 and in post-acute sequelae of COVID-19 are common and can range from mild and intermittent to severe and persistent, correlating with functional limitations. Although the long-term pulmonary sequelae of COVID-19 infection and PASC are not known, a considered rehabilitative approach is recommended to yield optimal functional outcomes with a return to pre-morbid functional, avocational, and vocational status. The primary site of entry to the human body of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is through the upper and lower respiratory tracts. The angiotensin-converting enzyme receptor is the best-characterized entry receptor for SARS-CoV-2 and is highly expressed in the lung tissue. Infection of respiratory epithelial cells with SARS-CoV-2 generates a pro-inflammatory immune response including complement activation, the severity of which appears to correlate with the severity of acute COVID-19 lung disease. It is likely that variation in gene expression dictate complement hyperactivity1 and disease severity, accounting for the significant variability in the severity of respiratory disease seen with COVID-19. Mild respiratory symptoms including cough, mild breathing difficulty, and chest discomfort on respiration are very common in acute COVID-19 and are typically self-limiting, resolving over days to weeks. Individuals who are unvaccinated, with pre-existing lung conditions and multiple medical comorbidities are at higher risk of more severe respiratory involvement and prolonged respiratory symptoms. Hypoxemia as evidenced by peripheral pulse oximetry of less than 92% is a marker of more severe disease. Pneumonitis, acute COVID-19 pneumonia, and superimposed bacterial infections are less common. Rarely but most concerning is the progression to acute respiratory distress syndrome (ARDS) with more severe symptoms, significant hypoxemia, and the need for hospitalization including respiratory support. Interstitial lung disease is known long-term pulmonary sequelae of ARDS and reported in over 60%2 of severe acute COVID-19 ARDS survivors. Recovery from post-COVID-19 interstitial lung disease may be seen over months but has also been reported to be persistent and, in a minority, progressive. Patients with acute COVID-19 present with variable clinical symptoms, ranging from a mild upper respiratory tract illness—viral bronchitis—to a severe disease with life-threatening complications exemplified by COVID-19 viral pneumonia, ARDS with acute hypoxic respiratory failure, and susceptibility to secondary bacterial pneumonia. Individuals with milder presentations may still suffer from longer-term complications including persistent pulmonary inflammation and fibrosis. Many individuals with mild acute COVID-19 have mild but persistent and significant symptoms of shortness of breath at rest, dyspnoea on exertion, cough, and chest discomfort despite a negative exam and investigations.

Problem statement:

With the COVID-19 pandemic having lasted more than 3 years, there are prolonged symptoms and respiratory complications traced in COVID-19 survivors, collectively termed Post–COVID-19 Condition (PCC). Up to 50% of patients have residual symptoms and physiologic impairment, particularly dyspnoea and reduced diffusion capacity. Patients hospitalized during the 1styear of the pandemic exhibit radiologic abnormalities, such as ground-glass opacity, reticular opacity, bronchial dilatation, and air trapping, when imaged more than 1 year after infection. Histologic patterns in post–COVID-19 lung disease include fibrosis, organizing pneumonia, and vascular abnormality, indicating that different pathologic mechanisms may contribute to PCC. These findings suggest that there may be underlying lung damage in patients with persistent respiratory symptoms despite normal chest CT results. Understanding the various histologic patterns of post-COVID-19 lung disease can help guide treatment and management strategies for patients experiencing prolonged respiratory symptoms. This research aims to investigate the Long-Term Pulmonary Sequelae of COVID-19 in terms of total lung capacity (TLC) and diffused capacity of the lungs for carbonmonoxide (DLCO).

Hypothesis

Null Hypothesis (H0):

Covid 19 doesn't cause any significant difference in the total lung capacity and diffused capacity of the lungs for carbon monoxideon Post Pandemic Pulmonary Status.

Research Hypothesis (H1):

Covid 19 causes significant difference in the total lung capacity and diffused capacity of the lungs for carbon monoxide on Post Pandemic Pulmonary Status.

Research Questions

- To study the Long-Term Pulmonary Sequelae of Covid 19 on Post Pandemic Pulmonary Status in terms of total lung capacity (TLC)and diffused capacity of the lungs for carbon monoxide (DLCO).
- To study the Demographic variables of Long Covid on Post Pandemic Pulmonary Status.

Objectives of the Research:

Primary:

To study the Impact of Long-Term Pulmonary Sequelae of Covid 19 on Post Pandemic Pulmonary Status.

Secondary:

To compare the Demographic and clinical variables of Long Covid on Post Pandemic Pulmonary Status

Review Documents:

1. M. Lalwani et al: Cureus, 2023- After one year, a sizable percentage of COVID-19 survivors still have persistent symptoms affecting different bodily systems. Evidence suggests that the lungs are the most affected organs by COVID-19. It may also cause corollary and other medical issues. The literature on preceding COVID-19 infections reviews that patients may also experience chronic impairment in breathing characteristics.

2. Long et al: Frontiers in Medicine,2021-A research done on total of 4,478 COVID-19 patients from 16 cohort studies indicates that patients recovering from COVID-19 manifest long-term, multi-system symptoms, and the adverse effects on psychosocial health and lung functions were the most extensive and persistent ones.

3. X Han et al.:2021•pubs.rsna.org- Six-month follow-up chest CT findings after severe COVID-19 pneumonia showed fibrotic-like changes in the lung in more than one-third of patients who survived severe coronavirus disease 2019 pneumonia. These changes were associated with an older age, acute respiratory distress syndrome, longer hospital stays, and

tachycardia, non-invasive mechanical ventilation, and higher initial chest CT score.

4. JP Kanne et al.: Radiology, 2022•pubs.rsna.org- In the 3rd year of the SARS-CoV-2 pandemic, much has been learned about the long-term effects of COVID-19 pneumonia on the lungs. Approximately one-third of patients with moderate-to-severe pneumonia, especially those requiring intensive care therapy or mechanical ventilation, have residual abnormalities at chest CT 1

year after presentation. Abnormalities range from parenchymal bands to bronchial dilation to frank fibrosis. Less is known about the long-term pulmonary vascular sequelae, but there appears to be a persistent, increased risk of venothromboembolic events in a small cohort of patients. Finally, the associated histologic abnormalities resulting from SARS-CoV-2 infection are similar to those seen in patients with other causes of acute lung injury.

5. M Ferioli et al.:-2021•Eur Respiratory Soc- The role of 6MWT in Covid-19 follow up- Worldwide there is an imbalance between the number of patients discharged after Covid-19 and the availability of healthcare resources to follow them after acute illness. Six-minute walking test (6MWT) is a valid and inexpensive measure of exercise capacity for people with chronic lung disease. We used 6MWT during follow-up of patients discharged after Covid-19 to verify if it can be a reliable measure of the disease recovery .During 6MWT we reported walking distance in meters (6MWD), lowest SpO2 when breathing air (SpO2 nadir), desaturation and distance–saturation product (DSP), defined as the product of 6MWD and SpO2 nadir (Table). Data from the first 100 subjects show that 6MWD and DSP at 6 months correlates positively with percent predicted DLCO ($p=0.0001$) and inversely with HRCT severity score at six months ($p<0.05$). In addition, patients with PaO2/FiO2 during hospitalization (P/F nadir) <200 mmHg performed statistically significant lower 6MWD, SpO2 nadir and DSP and a larger desaturation during 6MWT at 2 months and a lower SpO2nadir and a larger desaturation at 6 months compared to patients with a P/F nadir >200 mmHg during hospitalization. In conclusion, 6MWT is a useful test in post-Covid-19 follow-up as it correlates with the severity of acute disease and with functional/radiological impairment in the chronic phase of Covid-19. Furthermore, it shows the progressive improvement in exercise capacity.

6. MS Durstenfeld et al.:- JAMA network.2022 - Use of cardiopulmonary exercise testing to evaluate long COVID-19 symptoms in adults: a systematic review and meta-analysis- Reduced exercise capacity is commonly reported among individuals with COVID-19 symptoms more than 3 months after SARS-CoV-2 infection (long COVID-19 [LC]).Cardiopulmonary exercise testing (CPET) is the criterion standard to measure exercise capacity and identify patterns of exertional intolerance.

7. Persistent post–COVID-19 interstitial lung disease. An observational study of corticosteroid treatment-KJ Myall et al.:.Annals of the American Thoracic Society, 2021- Following SARS-CoV-2 pneumonitis, a cohort of patients is left with both radiological inflammatory lung disease and persistent physiological and functional deficit. Early treatment with corticosteroids was well tolerated and associated with rapid and significant improvement. These preliminary data should inform further study into the natural history and potential treatment for patients with persistent inflammatory ILD following SARS-CoV-2 infection.

8. S Ehrmann et al.: The Lancet Respiratory Medicine, 2021- Awake prone positioning for COVID-19 acute hypoxemic respiratory failure: a randomized, controlled, multinational, open-label meta-trial Awake prone positioning of patients with hypoxemic respiratory failure due to COVID-19 reduces the incidence of treatment failure and the need for intubation without any signal of harm. These results support routine awake prone positioning of

patients with COVID-19 who require support with high-flow nasal cannula.

9. R Gloeckl et al.: Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study -ERJ open research, 2021- Our study shows that pulmonary rehabilitation is a feasible, safe and effective therapeutic option in COVID-19 patients independent of disease severity.

10. J Herrmann et al.: Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia -Nature communications, 2020- Early stages of the novel coronavirus disease (COVID-19) are associated with silent hypoxia and poor oxygenation despite relatively minor parenchymal involvement. Although speculated that such paradoxical findings may be explained by impaired hypoxic pulmonary vasoconstriction in infected lung regions, no studies have determined whether such extreme degrees of perfusion redistribution are physiologically plausible, and increasing attention is directed towards thrombotic micro embolism as the underlying cause of hypoxemia. Herein, a mathematical model demonstrates that the large amount of pulmonary venous admixture observed in patients with early COVID-19 can be reasonably explained by a combination of pulmonary embolism, ventilation-perfusion mismatching in the non-injured lung, and normal perfusion of the relatively small fraction of injured lung. Although underlying perfusion heterogeneity exacerbates existing shunt and ventilation-perfusion mismatch in the model, the reported hypoxemia severity in early COVID-19 patients is not replicated without either extensive perfusion defects, severe ventilation-perfusion mismatch, or hyper perfusion of non - oxygenated regions.

11. S Nopp et al.: Outpatient pulmonary rehabilitation in patients with long COVID improves exercise capacity, functional status ,dyspnea, fatigue, and quality of life, 2022- In patients with long COVID, exercise capacity, functional status, dyspnea, fatigue, and quality of life improved after 6 weeks of personalized interdisciplinary pulmonary rehabilitation. Future studies are needed to establish the optimal protocol, duration, and long-term benefits as well as cost-effectiveness of rehabilitation.

12. M Spielmanns et al.: Effects of a comprehensive pulmonary rehabilitation in severe post-COVID-19 patients-International journal of environmental research and public health, 2021- Comprehensive PR in PG is very effective according to the results in FIM, 6-MWT and FT. Therefore, we recommend PR following severe post-COVID-19 infections.

13. Jason H Maley et al.:-Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC) 2022- Large numbers of individuals who have been infected with SARS-CoV-2, the virus responsible for COVID-19, continue to experience a constellation of symptoms long past the time that they have recovered from the acute stages of their illness. Often referred to as "long COVID," these symptoms, which can include fatigue, shortness of breath, palpitations, cognitive dysfunction ("brain fog"),sleep disorders, fevers, gastrointestinal symptoms, anxiety, depression, and others, can persist for months and can range from mild to incapacitating. Although still being defined, these effects can be collectively referred to as post acute sequelae of SARS-CoV-2 infection (PASC). The magnitude of this problem is not yet known, but given the millions of individuals worldwide who have had, or will have, COVID-19, the societal impacts are likely to be profound and long lasting. It is widely acknowledged that systematic study is needed to develop an evidence-based approach for caring for patients with PASC. At present, there is a dearth of rigorous scientific evidence regarding effective assessment and treatment of PASC that prevents the creation of evidence-based clinical guidelines. However, the US health system is currently seeing an increase in the

number of patients presenting with PASC, and there is an urgent need for clinical guidance in treating these patients. The goal of this, and future statements, is to provide practical guidance to clinicians in the assessment and treatment of patients presenting with PASC.

14. KEJ Philip et al.: An online breathing and wellbeing programme (ENO Breathe) for people with persistent symptoms followingCOVID-19: a parallel-group, single-blind -The Lancet Respiratory Medicine, 2022- Our findings suggest that an online breathing and wellbeing programme can improve the mental component of HR QoL and elements of breathlessness in people with persisting symptoms after COVID-19.

Relevance to Government Policy

There is no policy by government of Malaysia on Long-Term impact of COVID-19 on Post-Pandemic Respiratory Health. Although government of Malaysia has its policy on managing COVID 19 and addressing regulatory issues. This study will help government of Malaysia to shape its national policy on Post Pandemic Covid 19 Impact of respiratory health.

Methodology

Description of Methodology

A systematically search from the mentioned databases would be done from inception to June 2024. The reference lists of all the included studies and related reviews for potentially eligible studies will be screened. The keywords proposed to be used includes "post-COVID-19 syndrome", "long haulers," "long hauling," and "chronic COVID syndrome."

Study design: prospective observational study design utilizing the following internet-based databases:

- PubMed,
- Scopus,
- Cochrane library and
- World Health Organization (WHO) COVID-19 database

Study area and period

- This study will be conducted in AIMST University, Malaysia it is expected to be completed within the timeframe of 3 year.

Sample size & Population

- 385 samples calculated through probability sampling using G power software. This study employs a probability sampling method (simple random), a strategic choice that capitalizes on the accessibility of database. To quantify the extent of the sampling, the research employs the sophisticated Qualtrics Statistical Application (Carrie A. Miller et al., 2020). This tool enables the researchers to calculate an estimated sample size that is statistically significant.

Sampling method

- Probability sampling method

Eligibility criteria: The following study designs would be included in this review:

randomized trials (with randomization at either individual or cluster levels),

- case-controlled studies,
- case reports,
- case series prospective cohorts,
- interrupted time series studies, and
- repeated cross-sectional studies,
- The primary outcomes of interest would be symptoms reported by authors of articles, including persistent or new symptoms in terms of lung functioning (TLC & DLCO)

Data collection and analysis:

study setting (country), Data would be analysed in an prospective observational manner. four-year time frame in terms of:

- Type of study,
- Study participants,
- Outcome measures, and

- Study findings (reported symptoms)

Data entry and analysis

The data analysis will be performed by using SPSS. Descriptive statistic will be used for data analysis which will focus through table and chart. Tabulation and computation of frequencies and percentages will be calculated on selected variables

Results:

Large numbers of articles supported that individuals who have been infected with SARS-CoV-2, the virus responsible for COVID-19, continue to experience a constellation of symptoms long past the time that they have recovered from the acute stages of their illness. Often referred to as "long COVID," these symptoms, which can include fatigue, shortness of breath, palpitations, cognitive dysfunction ("brain fog"), sleep disorders, fevers, gastrointestinal symptoms, anxiety, depression, and others, can persist for months and can range from mild to incapacitating. Although still being defined, these effects can be collectively referred to as post-acute sequelae of SARS-CoV-2 infection (PASC). It is widely acknowledged that there is currently an increase in the number of patients presenting with PASC, and there is an urgent need for clinical guidance in treating these patients.

Discussion:

Individuals with chronic lung diseases including chronic obstructive pulmonary disease (COPD), moderate to severe asthma, bronchiectasis, interstitial lung diseases, cystic fibrosis, and pulmonary hypertension, are at increased risk for more severe acute COVID and acute respiratory consequences, as well as post-acute sequelae of COVID-19 (PASC) and persistent respiratory symptoms and disease.

Conclusion:

Recovery from post-COVID-19 interstitial lung disease may be seen over months but has also been reported to be persistent and, in a minority, progressive.

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