OPEN ACCESS

Saudi Journal of Medicine

Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

"Role of Spirometry in Lung Function Assessment in Post COVID-19 Pneumonia Cases: Correlation with CT Severity, Duration of Illness, Oxygen Saturation and Ventilatory Support in Critical Care Setting in Tertiary Care Setting in India."

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DOI: 10.36348/sjm.2021.v06i12.008 | **Received:** 13.11.2021 | **Accepted:** 21.12.2021 | **Published:** 26.12.2021

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Abstract

Background: Although Lung is the primary target organ involvement in corona virus disease-19 (COVID-19), post-covid lung pathology and its impact on lung functions is still uncertain. ***Material and methods:*** Prospective multicentric study conducted during May 2020 to September 2021, to find pulmonary function assessment in post-COVID-19 recovered pneumonia cases irrespective of their symptoms, included 600 cases in symptomatic and asymptomatic group and subjected to inclusion and exclusion criteria. All cases were subjected to Spirometry analysis. Statistical analysis was done by using chi-test. ***Results:*** In Spirometry assessment of post-COVID-19 pneumonia cases at 12 weeks post discharge form hospital, abnormal lung function in 77.5% post covid-19 pneumonia cases; restrictive pattern was predominant type and documented in 43.33% cases, normal lung functions were documented in 22.5% cases. In age and gender assessment in normal and abnormal lung functions assessment, statistically significant association in males 90/150 versus females 45/315 [p<0.00001]; and in age of population in study cases as below 50 years 110/300 versus above 50 years 25/165 [p<0.0001]. CT severity score has shown negative impact on lung function after recovery at 12 weeks post-discharge; cases with score <8, 8-15 and >15 documented normal and abnormal lung functions as in 36/54, 60/80 and 39/331 respectively of total 600 study cases [p<0.00001]. Duration of illness has associated negative impact on lung function; <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal lung functions in 108/132, 22/168 and 5/165 cases respectively [p<0.00001]. Low oxygen saturation at entry point has negative impact on overall outcome on lung function; cases with oxygen saturation <75%, 75-90% and >90% observed as normal and abnormal lung functions in 92/18, 35/135 and 6/314 cases respectively [p<0.00001]. Timing of BIPAP/NIV has significant association in attaining normal lung functions after post-COVID19 pneumonia recovery; cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of hospitalization were documented normal and abnormal lung functions in 30/150, 40/35 and 5/50 cases respectively [p<0.00001]. ***Conclusions:*** Pulmonary functions abnormality in post-COVID-19 pneumonia cases has been documented and should be assessed cautiously to have successful treatment outcome. Restrictive lung disease is the predominant lung function impairment in post-COVID 19 recovered lung pneumonia cases. Age above 50 years, male gender, Diabetes, High CT severity, longer duration of illness, proper timing of initiation of BIPAP/NIV therapy, has documented significant impact on post covid lung functions at 12 weeks assessment.

Keywords: Pulmonary functions, spirometry, post-COVID-19, Restrictive pattern.

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic, with approximately 20% of patients infected requiring hospitalization and 6% in critical care and needing invasive ventilatory assistance [1]. Early epidemiological reports showed that 8.2% of total cases presented with rapid and progressive respiratory failure, similar to acute respiratory distress syndrome (ARDS) [2].

COVID-19 is a heterogeneous disease with most patients experiencing mild illness and spontaneous recoveries, but a relevant subgroup of individuals requires hospitalization for pneumonia and other complications. In the initial reports from Wuhan, China, up to one third of patients developed severe pneumonia with acute respiratory distress syndrome (ARDS) [3].

Previous coronavirus infections include severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Similar to COVID-19, SARS and MERS typically begin with an acute illness from which most patients recover after two weeks. However, up to one third of SARS patients developed severe pulmonary complications and ARDS [4]. A subgroup of SARS survivors developed persistent lung parenchymal abnormalities, including pulmonary fibrosis [5, 6]. The appearance of pulmonary fibrosis correlated with severity and duration of the acute illness [7, 8] and radiological features of fibrosis persisted in approximately 30% of patients after three and six months [9, 10]. Older age, and male sex were identified as risk factors for poor outcomes and development of lung fibrosis [9, 11]. With the anticipation of potential long-term sequelae after COVID-19, follow-up strategies have been proposed by several groups from the US, Great Britain, China, and India [12-15].

In present study, we have evaluated lung function assessment at 12 weeks post-discharge in treated cases of covid-19 pneumonia, and correlated with CT severity at entry point, oxygenation status at entry point, total duration of illness at hospitalization, and use of BIPAP/NIV during course of hospitalization.

MATERIALS AND METHODS

Prospective multicentric observational study conducted in Venkatesh chest hospital, and Pulmonary Medicine, MIMSR medical college Latur during May 2020 to June 2021, to find out lung function assessment of post-COVID-19 recovered pneumonia cases after 12 weeks of discharge from hospital. Total 600 cases were enrolled in study after IRB approval and written informed consent of patient.

Inclusion criteria

1. All treated and recovered cases of COVID-19 pneumonia cases above 18-year age, admitted in indoor unit has been enrolled in study
2. Recovered cases of COVID-19 pneumonia irrespective of CT severity were enrolled in study
3. Recovered cases of COVID-19 pneumonia irrespective oxygen saturation was enrolled in study
4. Recovered cases of COVID-19 pneumonia with comorbidity like Diabetes Mellitus, IHD, CVD, CKD, COPD were enrolled in study
5. Recovered cases of COVID-19 pneumonia cases willing to undergo spirometry test were enrolled in study

Exclusion criteria

1. Recovered cases of COVID-19 pneumonia cases not willing to undergo spirometry test
2. Recovered cases of COVID-19 pneumonia cases not able to perform spirometry test
3. Recovered cases of COVID-19 pneumonia cases with neurological issues like hemiparesis or hearing difficulty and having co-ordination problem during spirometry
4. Recovered cases of COVID-19 pneumonia cases with tachypnea or tachycardia and cases with oxygen supplementation at rest were excluded from study
5. Recovered cases of COVID-19 pneumonia below 18 years of age
6. Recovered cases of COVID-19 pneumonia in pregnant females (any trimester was excluded)

All study cases were undergone following assessment before enrolling in study

1. Clinical assessment as- vital parameters like heart rate, respiratory rate, blood pressure and documentation of respiratory adventitious sounds
2. Laboratory parameters- hemoglobin, renal functions, blood sugar level, kidney functions, ECG
3. Spirometry

METHODOLOGY OF SPIROMETRY

Subsequently spirometry evaluation was done by a portable spirometer, SPIROLAB II (manufactured by Medical International Research, Italy); and meets American Thoracic Society and European Respiratory Society standards (ATS & ERS), before and fifteen minutes after administration of 400 microgram salbutamol using pressurized metered-dose inhaler (pMDI) with small-volume spacer device. All patients were instructed not to use any bronchodilator on the preceding night and on day of procedure. Spirometry procedure was carried out as per ATS/ERS task force recommendation for standardization of lung function testing [17]. Subjects who were found to have post-bronchodilator FEV1 (Forced Expiratory Volume in first second)/FVC (Forced Vital Capacity) <0.7 were taken up for final analysis as this value indicates the cut-off for diagnosis of obstructive airway disease according to GOLD guideline. Bronchodilator Reversibility (BDR) was defined as an improvement in FEV1 by at least 12% and 200 ml over pre-bronchodilator value. FEV1/FVC ≥0.7 were excluded as those patients had either a normal spirometry or a purely restrictive ventilatory abnormality. Also, the individuals who failed to fulfil acceptability and reproducibility criteria of spirometry were excluded. FVC, FEV1, and FEV1/FVC ratio values for case patients were compared with gender-specific and race-specific adult predicted normative population values and the control group [16, 20].

The British Thoracic Society (BTS) guidelines recommends the evaluation of PFTs at three months' post-discharge, especially at follow-up with patients suspected of having an interstitial disease [20].

Interpretive algorithms were used in determining restrictive or obstructive patterns and spirometry results were analyzed and categorized in four groups as [16-19].

1. Normal- FEV1/FVC ratio of >70% and an FVC of > 80% predicted
2. Obstructive-Airway obstruction was defined as an FEV1/FVC ratio of <70% and an FVC of > 80% predicted
3. Mixed-combined defects were FVC of < 80% predicted and an FEV1/FVC ratio of<70%
4. Restrictive-restrictive defects as an FEV1/FVC ratio of >70% with an FVC of < 80% predicted

The statistical analysis was done using chi-squared test. Significant values of $\chi 2$ were seen from probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

Observation and Analysis

In this study, total 600 post-COVID-19 recovered pneumonia cases were enrolled, between age group 18-95 years of age; age above 50 years were 60% (360/600) and age below 50 were 40% (240/600). In gender distribution in study group, male population was 68.33 % (410/600) and females were 31.66% (190/600). Main symptoms in study group were shortness of breath in 79% cases, cough especially dry in 48% cases, and fatigability in 79% cases, Tachycardia in 72% cases, Tachypnea in 24% cases and oxygen desaturation on 6 min walk in 21% cases.

Table-1: **Spirometry assessment of post-COVID 19 pneumonia cases at 12 weeks of discharge from hospital (n=600)**

	Total cases (n=600)	Percentage (%)
Normal	135	22.5
Obstructive	85	14.16
Mixed	120	20
Restrictive	260	43.33

In Spirometry assessment of post-COVID 19 pneumonia cases at 12 weeks post discharge form hospital, restrictive pattern was predominant type documented in 43.33% cases, normal lung functions were documented in 22.5% cases [Table 1].

Table-2: Age and gender distribution in post-COVID-19 pneumonia cases (n=600) with Lung Function patterns

Age of study population	Normal Lung Functions (135/600)	Abnormal Lung functions (465/600)	P value
<50 years (n=240)	90	150	$\chi 2$= 51.61
>50 years (n=360)	45	315	*P* <0.00001
Gender	Normal Lung Functions (135/600)	Abnormal Lung Functions (465/600)	
Male (n=410)	110	300	$\chi 2$= 13.91
Female (n=190)	25	165	*P* <0.0001

We observed abnormal lung function in 77.5% post covid-19 pneumonia cases, and statistically significant association in males (90/150) versus females (45/315) normal and abnormal lung functions respectively [p<0.00001]; similar observation also documented in age of population in study cases as below 50 years (110/300) versus above 50 years (25/165) [p<0.0001] [Table2].

Table-3: Correlation of CT severity (at entry point) and lung function assessment by spirometry in post-covid-19 pneumonia cases after 12 weeks post discharge from hospital

CT severity	Normal lung functions (n=135)	Abnormal lung functions (n=465/600)	Analysis
<8 score (n=90)	36	54	
9-15 (n=140)	60	80	$\chi 2$=79.42
>15 (n=370)	39	331	*P* <0.00001

CT severity score has shown negative impact on lung function after recovery at 12 weeks post-discharge; cases with score <8, 8-15 and >15 documented normal and abnormal lung functions as in 36/54, 60/80 and 39/331 respectively of total 600 study cases [p<0.00001] [Table3].

Table-4: Duration of illness at entry point during hospitalization and its effect on Lung functions at 12 weeks of discharge in post-COVID-19 pneumonia cases

Duration of illness	Normal lung functions (n=135)	Abnormal lung functions (n=465)	Analysis
<7 days (n=240)	108	132	$\chi 2$ =119.96 *P* <0.00001
8-15 days (n=190)	22	168	
>15 days (n=170)	5	165	

Duration of illness has associated negative impact on lung function; <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal lung functions in 108/132, 22/168 and 5/165 cases respectively [p<0.00001] [Table 4].

Table-5: Oxygen saturation at entry point and its effect on lung function at 12 weeks of discharge in post-COVID-19 pneumonia cases

Oxygen saturation	Normal lung functions (n=135)	Abnormal lung functions (n=465)	Analysis
<75% (n=110)	92	18	$\chi 2$ =317.52 *P* < 0.00001
75-90% (n=170)	35	135	
>90% (n=320)	6	314	

Low oxygen saturation at entry point has negative impact on overall outcome on lung function; cases with oxygen saturation <75%, 75-90% and >90% observed as normal and abnormal lung functions in 92/18, 35/135 and 6/314 cases respectively [p<0.00001] [Table5].

Table-6: BIPAP/NIV initiation time at entry point and its effect on lung function at 12 weeks of discharge in post-COVID-19 pneumonia cases (n=310)

BIPAP used (n=310) with duration of illness	Normal lung functions	Abnormal lung functions	Analysis
Entry point < 1days (n=180)	30	150	
3- 7 days (n=75)	40	35	$\chi 2$ =47.12 *P* < 0.00001
After 7 days (n=55)	5	50	

Timing of BIPAP/NIV has significant association in attaining normal lung functions after post-COVID19 pneumonia recovery; cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of hospitalization were documented normal and abnormal lung functions in 30/150, 40/35 and 5/50 cases respectively [p<0.00001] [Table 6].

DISCUSSION

1. Pattern of Spirometry analysis in study cases:

In present study, spirometry assessment of post-COVID 19 pneumonia cases at 12 weeks post discharge form hospital, restrictive pattern was predominant type documented in 43.33% cases, normal lung functions were documented in 22.5% cases. Guler SA *et al*. [21] demonstrated lower lung volumes (TLC, FVC, and FEV1) in patients after severe/critical COVID-19, the higher FEV1/FVC ratio in the severe/critical subgroup suggests a tendency toward a restrictive physiology, and the lack of difference in respiratory muscle strength suggest a lung parenchymal rather than a respiratory muscle issue. Mo *et al*. [23] reported an impairment of diffusion capacity followed by restrictive ventilatory defects, which are both associated with the severity of the disease. You J *et al*. [24] published first reports on lung function related to COVID-19 indicated that patients have a restrictive defect and a small airways dysfunction that can be persistent and not related to the disease severity.

Seven studies Frija-Masson *et al*. [25], Huang *et al*. [29], Li *et al*. [27], Liu *et al*. [26], Mo *et al*. [23] You *et al*., [24] Zhao *et al*. [28] reported the spirometry test in post-covid cases and documented reported variable prevalence of restrictive pattern in severe COVID-19 infection that ranges from (10.53%) to (50%). All studies showed forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio. Liu *et al*. [26] did not report patterns of PFT abnormality; six studies [23-25, 27-29] found a prevalent restrictive pattern in 59% and obstructive pattern in 16% post-covid pneumonia cases. Similarly, in our study, we have documented restrictive pattern in 43.33% and obstructive pattern in 14.16% cases.

R. Torres-Castro *et al*. [30] done systematic review and meta-analysis of Respiratory function in post-COVID-19 cases and observed altered diffusion capacity, restrictive pattern and obstructive pattern were found in 39%, 15% and 7% of patients, respectively. Salem *et al*. [31] in their study documented finding of restrictive lung impairment in about 50% of post-COVID-19 pneumonia survivors is in line with several

previous studies. A recent study done by Fumagalli *et al.* [32] found a significant incidence of a restrictive pattern in 10 (76%) out of 13 patients after 6 weeks from recovery in covid pneumonia cases. These variations in the prevalence of restrictive lung defect among COVID-19 pneumonia survivors could be explained by the differences in the time of assessment which range from close to discharge to three months after discharge. These studies suggest that patients affected by COVID-19 pneumonia are at increased risk of developing restrictive pulmonary diseases after recovery from the acute illness.

Timing of spirometry analysis was important in follow-up post-covid cases, as ongoing inflammation till one month of duration of illness has negative impact on real time lung function assessment by spirometry. We have followed BTS recommendations [20] as for 3 months' post discharge in all post-covid cases. All above mentioned studies [23-29] have performed spirometry analysis in one-month post discharge.

However, lesions of COVID-19 are more likely to impact bilateral pulmonary and multiple lobs than those of SARS. Previous studies have been reported that SARS have long-term effects on lung function, chest CT scans, and related physiological characteristics in part of survivors, even at one year after discharge [9, 33-35].

2. Age and gender distribution with lung function patterns in post-COVID-19 pneumonia cases

We observed abnormal lung function in 77.5% post covid-19 pneumonia cases, and statistically significant association in males (90/150) versus females (45/315) normal and abnormal lung functions respectively [p<0.00001]; similar observation also documented in age of population in study cases as below 50 years (110/300) versus above 50 years (25/165) [p<0.0001] AM Salem *et al*. [31] observed that the female sex was an independent predictor for impaired lung diffusion using multivariable logistic regression (P = 0.024), and No significant predictor for the restrictive pattern was detected. Seven studies [23-29] documented most affected age groups as Frija-Masson *et al*. as 54 years (46-62 years), Huang *et al.* as 46.7± 13.7 years, Li *et al*. doesn't documented age group affection in their study, Liu *et al.* as 69.1±7.8 years, Mo et al as 49.1±14.0, You *et al*. as 50.7 ± 12.1 years, Zhao *et al*. as 47.7 ±15.5 years reported in their study.

3. Is there any correlation between CT severity (at entry point) and lung function assessment by spirometry in post-covid-19 pneumonia cases after 12 weeks post discharge from hospital?

In present study, CT severity score has shown negative impact on lung function after recovery at 12 weeks post-discharge; cases with score <8, 8-15 and >15 documented normal and abnormal lung functions as in 36/54, 60/80 and 39/331 respectively of total 600 study cases [p<0.00001].

This is the first study included large number of post-covid cases and documenting the effect of CT Severity illness score when patient was hospitalized to indoor unit and its impact on overall pulmonary functions outcome at 12 weeks of discharge from hospital.

Lewis *et al*. [40] in their study included mild and moderate disease with 20% of patients being severe or critical disease. Based on the small numbers of critically ill patients, a trend towards worsening lung function, there is likely a component of lung fibrosis and destruction of alveoli causing reduced PFT values.

4. Does duration of illness at entry point during hospitalization and its effect on Lung functions at 12 weeks of discharge in post-COVID-19 pneumonia cases?

In present study, duration of illness has negative impact on lung function at 12 weeks of discharge; as duration <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal lung functions in 108/132, 22/168 and 5/165 cases respectively [p<0.00001].

This is the first study included large number of post-covid cases and documenting the effect of duration of illness when patient was hospitalized to indoor unit and its impact on overall pulmonary functions outcome at 12 weeks of discharge from hospital.

5. Oxygen saturation at entry point and its effect on lung function at 12 weeks of discharge in post-COVID-19 pneumonia cases

In present study, Low oxygen saturation at entry point has negative impact on overall outcome on lung function; and cases with oxygen saturation <75%, 75-90% and >90% observed as normal and abnormal lung functions in 92/18, 35/135 and 6/314 cases respectively [p<0.00001].

This is the first study included large number of post-covid cases and documenting the effect of hypoxia (oxygen saturation at entry point) during hospitalization in indoor unit and its impact on overall pulmonary functions outcome at 12 weeks of discharge from hospital.

6. Does BIPAP/NIV initiation time at entry point has any effect on lung function at 12 weeks of discharge in post-COVID-19 pneumonia cases (n=310)?

In present study, timing of BIPAP/NIV has significant association in attaining normal lung functions after post-COVID19 pneumonia recovery. Covid-19 pneumonia cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of

hospitalization were documented normal and abnormal lung functions in 30/150, 40/35 and 5/50 cases respectively [p<0.00001] Guler SA *et al.* [21] documented negative correlation between the duration of mechanical ventilation during the acute disease and pulmonary function at 4-month follow-up. This might be due to a prolonged impairment after very severe COVID-19 or related to more severe disease course in susceptible patients. Alternatively, Herridge MS *et al.* [22] proposed ventilator induced lung-injury is a well-described challenge post-ARDS, which can impact on pulmonary function after recovery from the acute illness. Faverio P [39] *et al.* documented radiological abnormalities and abnormal lung functions in up to 58% of patients with COVID-19, which was present as pulmonary sequelae, although of mild entity in the majority of cases, at 6-month follow-up, the need for invasive ventilatory support during hospitalization is a risk factor for detection of radiological abnormalities, but not for DLCO impairment, at follow-up.

7. Other important observations in present study

A). Inhaled corticosteroids (ICS) given to post-covid patients at the time of discharge were having symptomatic improvement in terms of dyspnea index, although head-to-head comparison of lung functions assessment before and after ICS were not available as we have performed spirometry after 12 weeks of discharge and initial spirometry assessment was not available.

B). Inhaled Ciclesonide doesn't show any symptomatic benefit as compared to inhaled budesonide or fluticasone at any point during course of covid pneumonia from evolution to resolution.

C) Although Higher CT severity scores were associated with higher proportion of lung parenchymal abnormalities, Lung function assessment (spirometry) shows mixed pattern (mixed obstructive-restrictive) in 20 % study cases, and we assume rational for these observations may be 'mosaic type' with 'parenchymal fibrosis' i.e. heterogeneous lung involvement; and majority of these cases shown slowly resolving over 12 weeks. In these categories of mixed spirometry function abnormality (20 % cases), significant symptomatic improvement was documented with inhaled budesonide and formoterol and we repeated after 3 months of therapy and documented near complete resolution of lung functions after prompt evaluation and targeted these patients with conventional lung anti-fibrotics, pirfenidone and Nintedanib over 12 weeks with inhaled bronchodilators with inhaled corticosteroids. The exact mechanism of the injury of the lungs by COVID-19 is still a new subject that is under debate. Studies [36-38] that included autopsies of COVID-19 patients described an acute lung injury with diffuse alveolar damage associated with fibrotic changes and microthrombi in the pulmonary vasculature.

D) Limitations of study- DLCO assessment were not available at our center and it was not done in study cases. DLCO assessment in post covid cases will help in documenting micro-thrombosis and macro-thrombosis in pulmonary vasculature in post covid setting, also it will help in predicting response to anticoagulants and antiplatelets and need for same in follow up settings. We have used D-dimer assessment, and resting plus exertional heart rate (heart rate after 6 min walk) as alternative option to DLCO in predicting need of anticoagulation, while antiplatelets we continued for 12 weeks in all cases and recommended to use for one year in co-morbid cases, especially in presence of DM, HTN, recent stroke, obesity, malignancy and COPD.

CONCLUSIONS

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Spirometry is cost effective, non-invasive, easily available, sensitive tool for assessment lung function in post covid care setting and it will help management of these cases by assessing response to treatment. Pulmonary functions abnormality in post-COVID-19 pneumonia cases has been documented and should be assessed cautiously to have successful treatment outcome. Restrictive lung disease is the predominant lung function impairment in post-COVID 19 recovered lung pneumonia cases. Age above 50 years, male gender, Diabetes mellitus, High CT severity, longer duration of illness, proper timing of initiation of BIPAP/NIV therapy, has documented significant impact on post covid lung functions at 12 weeks assessment. All post covid cases needs lung functions assessment by spirometry to predict course of underlying lung pathology and targeting interventions accordingly.

REFERENCE

1. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*, *395*(10223), 497-506.
2. Cypel, M., & Keshavjee, S. (2020). When to consider lung transplantation for COVID-19. *The Lancet Respiratory Medicine*, *8*(10), 944-946.
3. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*, *395*(10223), 497-506.
4. Tsui, P. T., Kwok, M. L., Yuen, H., & Lai, S. T. (2003). Severe acute respiratory syndrome: clinical outcome and prognostic correlates. *Emerging infectious diseases*, *9*(9), 1064.
5. Cheung, O. Y., Chan, J. W. M., Ng, C. K., & Koo, C. K. (2004). The spectrum of pathological changes in severe acute respiratory syndrome (SARS). *Histopathology*, *45*(2), 119-124.

6. Ketai, L., Paul, N. S., & Ka-tak, T. W. (2006). Radiology of severe acute respiratory syndrome (SARS): the emerging pathologic-radiologic correlates of an emerging disease. *Journal of thoracic imaging*, *21*(4), 276-283.
7. Tse, G. M., To, K. F., Chan, P. K., Lo, A. W. I., Ng, K. C., Wu, A., ... & Ng, H. K. (2004). Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). *Journal of clinical pathology*, *57*(3), 260-265.
8. Hwang, D. M., Chamberlain, D. W., Poutanen, S. M., Low, D. E., Asa, S. L., & Butany, J. (2005). Pulmonary pathology of severe acute respiratory syndrome in Toronto. *Modern pathology*, *18*(1), 1-10.
9. Hui, D. S., Wong, K. T., Ko, F. W., Tam, L. S., Chan, D. P., Woo, J., & Sung, J. J. (2005). The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*, *128*(4), 2247-2261.
10. Ngai, J. C., Ko, F. W., Ng, S. S., TO, K. W., Tong, M., & Hui, D. S. (2010). The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*, *15*(3), 543-550.
11. De Wit, E., Van Doremalen, N., Falzarano, D., & Munster, V. J. (2016). SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology*, *14*(8), 523-534.
12. Zheng, Z., Yao, Z., Wu, K., & Zheng, J. (2020). Patient follow-up after discharge after COVID-19 Pneumonia: Considerations for infectious control. *Journal of medical virology*, *92*(11), 2412-2419.
13. Balachandar, V., Mahalaxmi, I., Subramaniam, M., Kaavya, J., Kumar, N. S., Laldinmawii, G., ... & Cho, S. G. (2020). Follow-up studies in COVID-19 recovered patients-is it mandatory?. *Science of the Total Environment*, *729*, 139021.
14. Raghu, G., & Wilson, K. C. (2020). COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. *The Lancet Respiratory Medicine*, *8*(9), 839-842.
15. George, P. M., Barratt, S. L., Condliffe, R., Desai, S. R., Devaraj, A., Forrest, I., ... & Spencer, L. G. (2020). Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*, *75*(11), 1009-1016.
16. Crapo, R. O., Morris, A. H., & Gardner, R. M. (1981). Reference spirometric values using techniques and equipment that meet ATS recommendations. *American Review of Respiratory Disease*, *123*(6), 659-664.
17. Miller, M. R., Hankinson, J. A. T. S., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., ... & Wanger, J. A. T. S. (2005). Standardisation of spirometry. *European respiratory journal*, *26*(2), 319-338.
18. Renzetti Jr, A. D., Bleecker, E. R., Epler, G. R., Jones, R. N., Kanner, R. E., & Repsher, L. H. (1986). Evaluation of impairment/disability secondary to respiratory disorders. *American Review of Respiratory Disease*, *133*(6), 1205-1209.
19. Enright, P. L., & Hyatt, R. E. (1987). *Office spirometry: a practical guide to the selection and use of spirometers*. Philadelphia: Lea & Febiger.
20. British Thoracic Society. (2020). British Thoracic Society guidance on respiratory follow up of patients with a clinico-radiological diagnosis of COVID-19 pneumonia. *Br Thorac Soc*.
21. Guler, S. A., Ebner, L., Aubry-Beigelman, C., Bridevaux, P. O., Brutsche, M., Clarenbach, C., ... & Funke-Chambour, M. (2021). Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *European respiratory journal*, *57*(4).
22. Herridge, M. S., Tansey, C. M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., ... & Cheung, A. M. (2011). Functional disability 5 years after acute respiratory distress syndrome. *New England Journal of Medicine*, *364*(14), 1293-1304.
23. Mo, X., Jian, W., Su, Z., Chen, M., Peng, H., Peng, P., ... & Li, S. (2020). Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *European Respiratory Journal*, *55*(6).
24. You, J., Zhang, L., Zhang, J., Hu, F., Chen, L., Dong, Y., ... & Zhang, S. (2020). Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge. *Journal of Infection*, *81*(2), e150-e152.
25. Frija-Masson, J., Debray, M. P., Gilbert, M., Lescure, F. X., Travert, F., Borie, R., ... & Bancal, C. (2020). Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. *European Respiratory Journal*, *56*(2).
26. Liu, K., Zhang, W., Yang, Y., Zhang, J., Li, Y., & Chen, Y. (2020). Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complementary therapies in clinical practice*, *39*, 101166.
27. Li, X., Wang, C., Kou, S., Luo, P., Zhao, M., & Yu, K. (2020). Lung ventilation function characteristics of survivors from severe COVID-19: a prospective study. *Critical Care*, *24*(1), 1-2.
28. Zhao, Y. M., Shang, Y. M., Song, W. B., Li, Q. Q., Xie, H., Xu, Q. F., ... & Xu, A. G. (2020). Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*, *25*, 100463.
29. Huang, Y., Tan, C., Wu, J., Chen, M., Wang, Z., Luo, L., ... & Liu, J. (2020). Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respiratory research*, *21*(1), 1-10.

30. Torres-Castro, R., Vasconcello-Castillo, L., Alsina-Restoy, X., Solis-Navarro, L., Burgos, F., Puppo, H., & Vilaró, J. (2021). Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology*, *27*(4), 328-337.
31. Salem, A. M., Al Khathlan, N., Alharbi, A. F., Alghamdi, T., AlDuilej, S., Alghamdi, M., ... & Sabit, H. (2021). The Long-Term Impact of COVID-19 Pneumonia on the Pulmonary Function of Survivors. *International Journal of General Medicine*, *14*, 3271.
32. Fumagalli, A., Misuraca, C., Bianchi, A., Borsa, N., Limonta, S., Maggiolini, S., ... & Colombo, D. (2021). Pulmonary function in patients surviving to COVID-19 pneumonia. *Infection*, *49*(1), 153-157.
33. Hui, D. S., Joynt, G. M., Wong, K. T., Gomersall, C. D., Li, T. S., Antonio, G., ... & Sung, J. J. Y. (2005). Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax*, *60*(5), 401-409.
34. Xie, L., Liu, Y., Xiao, Y., Tian, Q., Fan, B., Zhao, H., & Chen, W. (2005). Follow-up study on pulmonary function and lung radiographic changes in rehabilitating severe acute respiratory syndrome patients after discharge. *Chest*, *127*(6), 2119-2124.
35. Ong, K. C., Ng, A. W. K., Lee, L. S. U., Kaw, G., Kwek, S. K., Leow, M. K. S., & Earnest, A. (2005). 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. *Chest*, *128*(3), 1393-1400.
36. Damiani, S., Fiorentino, M., De Palma, A., Foschini, M. P., Lazzarotto, T., Gabrielli, L., ... & D'Errico, A. (2021). Pathological post-mortem findings in lungs infected with SARS-CoV-2. *The Journal of pathology*, *253*(1), 31-40.
37. Barton, L. M., Duval, E. J., Stroberg, E., Ghosh, S., & Mukhopadhyay, S. (2020). Covid-19 autopsies, oklahoma, usa. *American journal of clinical pathology*, *153*(6), 725-733.
38. Haft, J. W., Atluri, P., Ailawadi, G., Engelman, D. T., Grant, M. C., Hassan, A., ... & Arora, R. C. (2020). Adult cardiac surgery during the COVID-19 pandemic: a tiered patient triage guidance statement. *The Annals of thoracic surgery*, *110*(2), 697-700.
39. Faverio, P., Luppi, F., Rebora, P., Busnelli, S., Stainer, A., Catalano, M., ... & Pesci, A. (2021). Six-month pulmonary impairment after severe COVID-19: a prospective, multicenter follow-up study. *medRxiv*.
40. Lewis, K. L., Helgeson, S. A., Tatari, M. M., Mallea, J. M., Baig, H. Z., & Patel, N. M. (2021). COVID-19 and the effects on pulmonary function following infection: A retrospective analysis. *EClinicalMedicine*, *39*, 101079.