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Factors associated with small airway obstruction in COVID-19 survivors: A cross-sectional study among health-care providers

Minarni ES. Aritonang[1*], Pandiaman Pandia[2], Andika Pradana[2] and Taufik Ashar[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [2]Division of Asthma and COPD, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [3]Department of Environmental Health, Universitas Sumatera Utara, Medan, Indonesia

*Corresponding author: sespiany93@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) has been identified for more than two years, yet studies assessing post-infection lung function are limited. Reports on lung function in COVID-19 patients indicate that patients have restrictive defects and small airway dysfunction that can persist and are not necessarily related to the severity of the disease. The aim of this study was to assess the incidence of small airway obstruction and its incidence-associated factors among COVID-19 survivors to better describe the long-term effects of COVID-19. A cross-sectional study was conducted among COVID-19 survivors who less than 50 years at Medan Adventist Hospital between 2020–2022. The data were collected through interview, direct assessment and respiratory examination. A total of 89 COVID-19 survivors were recruited of which the majority of them were female with a mean age of 32.6-year-old with the largest group was 19–30 years. The comorbidities found among the survivors were heart and thyroid disorders, with the most common symptom of post-COVID-19 was fatigue. Most of them had mild COVID-19. The mean forced mid-expiratory flow ($FEF_{25-75\%}$) was 96.3±20.22, with an incidence rate of small airway obstruction was 19.1%. Univariate and multivariate analyses indicated no significant association between age, gender, comorbidities, history of oxygenation during COVID-19 treatment, COVID-19 severity and the type of post COVID-19 syndrome symptoms with the incidence of small airway obstruction. In conclusion, among COVID-19 survivors who were less than 50 years old, those studied variables seems have less association with the incidence of small airway obstruction. Nevertheless, a further study with a bigger sample size is important to be conducted.

Keywords: Long COVID, COVID-19 survivor, pulmonary function test, small airway obstruction, risk factor

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus disease that was first identified in Wuhan, Hubei Province, China, in December 2019 [1]. COVID-19 has an average incubation period of 5–6 days but can extend up to 14 days. As of the end of 2022, a total of 6.6 million deaths out of 50 million COVID-19 cases have been reported worldwide [2]. In Indonesia, the overall incidence of COVID-19 was 2,050 per 100,000 populations, with a mortality rate of 55 per 100,000 populations [3].

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Due to the extensive lung injury caused by COVID-19, there are concerns about persistent lung damage in COVID-19 survivors. Studies on other coronavirus-related pneumonia diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have shown that persistent lung function and exercise capacity impairments could last for months or even years [4,5]. COVID-19 survivors may also experience post-acute COVID-19 (long COVID), which is the persistence of symptoms for over four weeks from disease onset, with symptoms including cough, dyspnea, and neuropsychological disorders [6]. Furthermore, pulmonary functional tests have shown reduced diffusion capacity and features of obstructive pattern in patients with long COVID [6]. Although not established, literature have shown that SARS-CoV-2 causes disruption of diffusion capacity which leads to obstructive patterns in the small airway [7].

Initial reports on lung function related to COVID-19 indicate that patients have restrictive defects and small airway dysfunction that can persist and are not necessarily related to the severity of the disease [8,9]. Additionally, Mo *et al.* reported a decrease in diffusion capacity followed by restrictive ventilation defects, both of which are associated with disease severity [10]. A cohort study of 277 recovered patients found that 141 of them experienced post-COVID-19 syndrome, with 9.3% of them showing changes in lung function with the most dominant feature observed was a restrictive lung pattern [8]. Another study in 2021 stated that air trapping occurs in patients with post-acute COVID-19 symptoms and is not dependent on the severity of the initial infection, indicating obstruction in the small airways [11]. In contrast, another study showed that even among patients with severe COVID-19 infection, distal bronchial inflammation in the small airways did not appear until three to six months after COVID-19, and there were no long-term impairments in small airway function [12]. Furthermore, among subjects with post-COVID dyspnea, 40% had lacked pulmonary reserve and abnormal dead space response to exercise [13]. The study also showed a mean forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) of 80.2 and reduced forced mid-expiratory flow ($FEF_{25-75\%}$), indicating small airway disease occurring in 70% of cases [13].

Considering the variety of study results regarding COVID-19 survivors, there can be potential challenges for COVID-19 survivors despite confirmed negative. Since, post-COVID-19 syndrome in survivors will affect the quality of life and work performance, this study was conducted to determine factors associated with small airway obstruction among healthcare workers with post-COVID-19 syndrome.

Methods

Study setting and patients

A cross-sectional study was conducted at Advent Medan Hospital, Medan, Indonesia of which data were collected from January 2020 to May 2022. The study sample consisted of COVID-19 survivors who were employee at Advent Medan Hospital and met the inclusion criteria. The inclusion criteria included being between 18 and 50 years of age, having a confirmed COVID-19 and declared recovered with PCR SARS-CoV-2 negative, at least four weeks post the onset of the first symptom of COVID-19, and employee at Advent Medan Hospital (doctors, nurses, or medical support staffs). Individuals with a history of nebulizer/inhaler usage, having pre-existing lung diseases, aged older than 50 years, obese, having severe chronic obstructive pulmonary disease (COPD) due to smoking, and having communication disorders were excluded from the study.

Data collection

COVID-19 survivors who met the inclusion criteria were contacted for a follow-up examination via telephone. Data collection was conducted through interviews and direct examinations. The collected data included age, body mass index (BMI), comorbidities, oxygenation history during COVID-19 treatment, duration of hospitalization, and severity of COVID-19.

Study variables

Comorbidities included any history of cardiovascular or thyroid diseases and BMI to evaluate obesity; a history of oxygenation included nasal cannula, non-rebreathing mask, high-flow nasal cannula, non-invasive ventilator, and mechanical ventilator. Hospital length of stay was the duration of treatment in the hospital (measured in mean and median); COVID-19 severity was the evaluation result of COVID-19 severity during hospital admission and hospitalization (categorized as mild, moderate, severe). Post COVID-19 syndrome symptoms were also assessed such as insomnia, cough or fatigue.

Spirometry examination was conducted to diagnose small airway obstructive lung disease based on the guideline (Spirostik Complete, Geratherm Respiratory, 8-inch Touch Version). The diagnosis of small airway obstructive lung disease was determined based on a forced mid-expiratory flow ($FEF_{25-75\%}$) ratio. Subjects with $FEF_{25-75\%}$ ratio of <80% were considered to have a small airway obstruction.

Statistical analysis

Chi-squared test was used to determine the association between sex, age, BMI, comorbidities (cardiovascular and thyroid diseases), post COVID-19 syndrome symptoms, hospital length of stay, oxygenation history, and severity of COVID-19 with the incidence of small airway obstruction. Multivariate analysis using multiple logistic regression was used to determine the probability of small airway obstruction in COVID-19 survivors based on significant variables from the univariate analysis. Results were considered statistically significant if $p<0.05$ and the data analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

Results

Subjects' characteristics

A total of 89 COVID-19 survivors were included in this study and their characteristics are presented in **Table 1**. Most subjects were women (71.9%), with a mean age of 32.06 years. In addition, most subjects (73%) had mild COVID-19, with fatigue (11.2%) as the most common symptom of post-COVID-19 syndrome. The mean $FEF_{25-75\%}$ was 96.28±20.22, and 19.1% of subjects had small airway obstruction (**Table 1**).

Table 1. Characteristics of COVID-19 survivors included in the study (n=89)

Characteristics	Frequency (%)
Sex	
Man	25 (28.1)
Woman	64 (71.9)
Age (years), mean (SD)	32.06 (7.33)
19–30	50 (56.2)
31–45	33 (37.1)
46–59	6 (6.7)
BMI (kg/cm²), mean (SD)	24.69 (3.16)
Normal weight	46 (51.7)
Overweight	39 (43.8)
Obesity	4 (4.5)
Cardiovascular disease	
Yes	1 (1.1)
No	88 (98.9)
Thyroid disease	
Yes	2 (2.2)
No	87 (97.8)
Post COVID-19 syndrome symptoms	
Insomnia	1 (1.1)
Cough	2 (2.2)
Fatigue	10 (11.2)
None	76 (85.4)
Oxygenation	
Nasal cannula	3 (3.4)
Non-rebreathing mask	2 (2.2)
None	84 (94.4)
COVID-19 severity	
Mild	65 (73)
Moderate	21 (23.6)
Severe	3 (3.4)
Hospital length of stay (day), mean (SD)	10.88 (4.85)
$FEF_{25-75\%}$, mean (SD)	96.28 (20.22)

Characteristics	Frequency (%)
Small airway obstruction	
Yes ($FEF_{25-75\%}$ <80%)	17 (19.1)
No ($FEF_{25-75\%}$ ≥80%)	72 (80.9)

Factors associated with small airway obstruction incidence

The associations between the studied risk factors and small airway obstruction incidence are presented in **Table 2**. The result showed no statistically significant association between the studied variables with small airway obstruction incidence with all had $p>0.05$.

The results of multivariate analysis are presented in **Table 3**. The variables included in the multivariate analysis were all variables that had a $p<0.25$ from the univariate analysis. The eligible independent variables were gender ($p=0.135$), age ($p=0.061$), BMI ($p=0.105$), heart disease ($p=0.191$), and insomnia ($p=0.191$). Among all the examined risk factors, no significant factors were found to have association with the incidence of small airway obstruction.

Table 2. Univariate analysis showing the associations between studied variables and small airway obstruction incidence (n=89)

Variable	Small airway obstruction		*p*-value
	Yes (n=17)	No (n=71)	
Gender			
Woman	15 (23.4)	49 (76.6)	0.135[a]
Man	2 (8.0)	23 (92.0)	
Age, year			
18–30 years	13 (26.0)	37 (74.0)	0.061[a]
31–59 years	4 (10.3)	35 (89.7)	
BMI			
Normal weight	11 (23.9)	35 (76.1)	0.232[b]
Overweight and obesity	6 (14.0)	37 (86.0)	
Cardiovascular disease			
Yes	1 (100.0)	0	0.191[a]
No	16 (18.2)	72 (81.8)	
Thyroid disease			
Yes	0	2 (100.0)	1.000[a]
No	17 (19.5)	70 (80.5)	
Insomnia			
Yes	1 (100.0)	0	0.191[a]
No	16 (18.2)	72 (81.8)	
Cough			
Yes	1 (50.0)	1 (50.0)	0.347[a]
No	16 (18.4)	71 (81.6)	
Fatigue			
Yes	2 (20.0)	8 (80.0)	1.000[a]
No	15 (19.0)	64 (81.0)	
Oxygenation			
Yes	1 (20.0)	4 (80.0)	1.000[a]
No	16 (19.0)	68 (81.0)	
Severity			
Moderate-severe	6 (25.0)	18 (75.0)	0.381[a]
Mild	11 (16.9)	54 (83.1)	
Hospital length of stay, days			
Mean (SD)	9.94 (2.3)	11.1 (5.26)	0.324[c]
Median (Min-max)	10 (7–14)	10 (6–44)	

[a] Analyzed Fisher's exact test
[b] Analyzed using Chi-squared test
[c] Analyzed using Mann-Whitney U test

Table 3. Multivariate analysis showing the associations between studied variables and small airway obstruction incidence (n=89)

Variable	Odds ratio (OR)	95%CI	*p*-value
Gender	2.604	0.528–12.852	0.240
Age	2.110	0.592–7.521	0.250
BMI	2.034	0.635–6.516	0.232
Cardiovascular disease	3175508891.361	0.000	1.000
Insomnia	6460344148.265	0.000	1.000

Discussion

COVID-19 is a disease that may cause extensive lung injury, and persistent lung damage has been reported among survivors. Symptoms including cough, dyspnea and neuropsychological disorders have also been reported among the survivors, which persist for several weeks following resolution of acute COVID-19. Furthermore, small airway obstruction has been reported to occur as a long-term complication [4-6]. In this study, we found that more than half of survivors (56.2%) in the age group of 19–30 years. Previous studies indicated a decline of lung function assessed through spirometry in COVID-19 survivors in particular those aged >50 years, as lung function decreases with increasing patient age, as evidenced by decreased lung tissue elasticity, function, and muscle strength [14-16]. Our results did not show a significant association between age and the incidence of small airway obstruction, which contrasts with previous studies [14-16]. This probably because we only included survivors aged between 18 and 50 years-old.

The majority of subjects in this study were females, accounting for 64 subjects (71.9%). This might be due to the fact that females typically have more frequent contact with people in their surroundings [17]. However, another study in males have shown that the higher incidence in males could be attributed to higher rates of smoking and alcohol consumption [17]. Based on the study location, there were more female employees than males, leading to a higher number of females affected by COVID-19 than males.

In this study, the highest number of subjects with BMI issues were overweight (43.8%), but our analysis did not show a significant association. The proposed pathogenic mechanism assumes that the early damage caused by COVID-19 is similar to that caused by SARS [18,19]. This is caused by microvascular injury with early interstitial thickening and radiologically clear lungs, followed by severe hypoxemia and subsequent development of alveolar damage, leading to gradual loss of alveolar space [18,19]. Decreased alveolar volume can result in temporary changes in the mechanical properties of the chest wall and respiratory muscles after critical illness and is believed to contribute to long-term lung parenchymal dysfunction post-COVID-19 [18-21]. Obesity is a detrimental risk factor in SARS-CoV-2 patients [22]. Above an BMI of 23 kg/m^2, there is a linear increase in the risk of severe COVID-19 leading to hospitalization [23]. The endocrine role of adipose tissue is believed to influence the release of inflammatory mediators in COVID-19. Additionally, the direct effect of fat accumulation in the chest and abdomen can decrease lung volume, causing airway inflation and increasing respiratory resistance [24]. Another potential mechanism that may influence the severity of COVID-19 is airway remodeling or increased thickness of the respiratory airway walls, possibly associated with adipose tissue accumulation in the airways, which can affect lung function [25-28].

Individuals with comorbidities are at a higher risk of increased mortality and severity of COVID-19. In a retrospective multi-center cohort study of 80 hospitalized patients in the United States, the most commonly found comorbidities were systemic hypertension (47.5%), asthma (36.3%), chronic obstructive pulmonary disease (30.0%), and chronic kidney disease (12.5%) [29]. Patients with comorbidities experienced a six-fold increase in the risk of hospitalization and a twelve-fold increase in mortality compared to patients without comorbidities [30,31]. Additionally, patients with interstitial lung disease were more likely to experience a decline in lung function in their pulmonary function test [29]. However, in this present study, there was no significant association found between having comorbidities and small airway obstruction. In our study, we excluded some diseases (pre-existing lung diseases and COPD due to smoking) to avoid bias, and only a few samples had specific comorbidities, which may explain why the findings differ from previous studies.

In this study, 16.9% of survivors with a history of mild severity and 25% with a history of moderate severity experienced small airway obstruction (p=0.381). During the early rehabilitation phase, the overall severity score of the lungs did not have a significant association with lung function, which is inconsistent with previous research on SARS survivors [32]. Impaired lung function may not necessarily be related to the severity of the disease. We speculate that this might be because many severe patients received glucocorticoids during hospitalization, suggesting that corticosteroids may improve the prognosis of patients with COVID-19.

The mean value of $FEF_{25-75\%}$ was 96.28%, with the lowest value being 60.66% and the highest 160.33%. Based on the categorization of $FEF_{25-75\%}$ values, there were 17 subjects (19.1%) with small airway obstruction. The initial reports on lung function related to COVID-19 indicate that patients have restrictive abnormalities and small airway dysfunction that can persist and are not necessarily related to the severity of the disease [8,9]. Changes in diffusion capacity, restrictive disorders, and obstructive disorders were found in 39%, 15%, and 7% of patients, respectively. A significant confounding factor in our analysis of obstructive patterns was the presence of chronic respiratory disease as a comorbidity [16].

The low proportion and severity of small airway dysfunction in this present study also suggest that COVID-19 is more likely associated with diffuse lung epithelial damage and small airway impairment. Pathological findings indicate that mucus plugs were found in the small airways of some severe COVID-19 patients, which may explain the decline in ventilation function to some extent. Besides acute lung injury, neuromuscular weakness can also lead to decreased lung function [10,33].

This study has limitations due to the lack of initial pulmonary function test results before illness, making it difficult to compare lung function before and after illness. Only a small number of patients had chronic respiratory diseases. Additionally, the relationship between CT images and lung function parameters was not analyzed in this study. Finally, this cross-sectional analysis only provided a brief follow-up, so the long-term dynamic variation of lung function after discharge from the hospital still requires further investigation. Another limitation is that a small number of critically ill patients were included in this study, which hindered effective analysis. Many of these patients did not survive, making the pulmonary function test could not be obtained.

Conclusion

Our study suggested that the incidence rate of small airway obstruction in COVID-19 survivors was 19.1%, with a mean $FEF_{25-75\%}$ rate of 96.3±20.22. There was no significant association between age, gender, comorbidities, history of oxygenation during COVID-19 treatment, COVID-19 severity and the type of post COVID-19 syndrome symptoms with small airway obstruction in COVID-19 survivors. However, since the study sample in this study was relatively small, further studies are warrant to confirm the results of this study.

Ethics approval

This study has received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, with the number of 1153/KEPK/USU/2022.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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