Lung function at three months after hospitalization due to COVID-19 pneumonia: Comparison of alpha, delta and omicron variant predominance periods

VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1,2], SOTIRIA MAKRODIMITRI[1], AIKATERINI GKOUFA[1], EIRINI APOSTOLIDI[2], SOTIRIOS PROVATAS[3], PETROS PAPALEXIS[4,5], DEMETRIOS A. SPANDIDOS[6], IOANNIS G. LEMPESIS[2], MARIA N. GAMALETSOU[2] and NIKOLAOS V. SIPSAS[1,2]

[1]Department of Infectious Diseases and COVID-19 Unit, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens; [2]Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens; [3]ENT Department and [4]Unit of Endocrinology, First Department of Propedeutic and Internal Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, 11527 Athens; [5]Department of Biomedical Sciences, University of West Attica, 12243 Athens; [6]Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Greece

Received July 27, 2023; Accepted December 22, 2023

DOI: 10.3892/etm.2024.12372

Abstract. The coronavirus disease (COVID-19) pandemic has already affected millions of individuals, with increasing numbers of survivors. These data suggest that the pulmonary sequelae of the infection may have an effect on a wide range of individuals. The aim of the present study was to evaluate pulmonary function in patients hospitalized due to COVID-19 three months after hospital discharge. A total of 116 patients, 34 females and 82 males, with a mean age of 57.77±11.45 years, who were hospitalized due to COVID-19, underwent pulmonary function testing three months after their hospital discharge. Of these, 83 (71.6%) patients were hospitalized in the period of alpha variant predominance, 16 (13.8%) in the period of delta variant predominance and 17 (14.6%) in the omicron variant predominance period. The mean value of diffusion capacity for carbon monoxide (DLCO)% predicted (pred) was statistically higher in patients affected by the omicron variant (P=0.028). Abnormal values (<80% pred) of DLCO and total lung capacity (TLC) were observed in 28.4 and 20.7% of the patients, respectively. Active smoking was an independent predictor of abnormal values of forced expiratory volume in 1 sec % pred and TLC% pred [P=0.038; odds ratio (OR): 8.574, confidence interval (CI) 1.124-65.424 and P=0.004, OR: 14.733, CI 2.323-93.429, respectively], age was an independent predictor of abnormal values of forced vital capacity % pred and DLCO% pred (P=0.027, OR: 1.124, CI 1.014-1.246 and P=0.011, OR:1.054, CI 1.012-1.098, respectively); and female sex was an independent predictor of abnormal values of DLCO% pred (P=0.009, OR: 1.124, CI 1.014-1.246). A significant percentage of hospitalized patients due to COVID-19 pneumonia will develop abnormal pulmonary function, regardless of the SARS-CoV-2 variant.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Infectious Diseases and COVID-19 Unit, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: vaso_georgakopoulou@hotmail.com

Key words: long COVID-19, lung function, diffusion capacity for carbon monoxide, spirometry, total lung capacity

Introduction

Over 700 million individuals have been affected by the coronavirus disease 2019 (COVID-19), which has already resulted in over 6.5 million deaths (1). The majority of COVID-19 patients have no or minor symptoms, while ~20% of them experience significant symptoms that necessitate hospitalization (2). The most frequent effects of COVID-19 include abnormalities of the respiratory system, although other organs may also be affected (3-7). The host's features, viral dynamics during acute infection and the host immune response have all been reported to correlate with disease severity (8,9). A severe COVID-19 course and greater mortality have been linked to older age, a high body mass index and a variety of comorbidities, including cardiovascular illnesses, diabetes, or types of cancer (10-13).

'Long-COVID' refers to some of the recovered patients who have experienced persistent impairments (14-16). In a retrospective analysis involving 193,113 participants, it was discovered that there is an elevated risk for several clinical outcomes, such as respiratory impairment, after COVID-19 disease (17). Another study found that >20% of COVID-19 survivors had pulmonary function impairment after 6 months. In addition, it has been reported that there had been no significant change in lung function impairment after 2 years in one of the largest research projects, with 349 and 230 subjects who had pulmonary function testing, respectively, 6 months and 2 years after discharge (18,19).

In the present study, compared with their counterparts who were matched for age, sex and chronic pulmonary disease after two years, survivors with a critical illness had a greater risk of diffusion capacity for carbon monoxide (DLCO) impairment, lower residual volume (RV) and lower total lung capacity (TLC) (18).

The most prevalent manifestation, DLCO, has been related to critical courses during acute illness in a number of studies (20-22). The variability of study designs and settings across studies, however, makes it challenging to reach definitive conclusions. Moreover, most of the studies refer to the first waves of the pandemic (23,24).

Several studies have reported a significantly reduced risk of hospitalization, admission to the intensive care unit, requirement for oxygenation and mortality rate in omicron-infected patients compared with those infected with other variants (25-27).

In addition, it has been reported that there is a reduction in the risk of developing the long COVID-19 syndrome with the omicron variant compared with the delta variant (28). However, knowledge about lung function after hospitalization during the omicron variant predominance period is still scarce. The purpose of the present study was to describe the pulmonary function at three months after hospitalization due to COVID-19 pneumonia and to make a comparison of alpha, delta and omicron variant predominance periods.

Materials and methods

Study population and data collection. This retrospective study included consecutive, ambulatory patients who visited the post-COVID-19 Outpatient Clinic of Laiko General Hospital (Athens, Greece) for respiratory function evaluation 3 months after their hospitalization for COVID-19 pneumonia. The period of their hospitalization was between February 15, 2021 and May 15, 2022, covering all the periods of predominance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Inclusion criteria were: i) The ability to perform pulmonary function tests (PFTs) satisfactorily; and ii) a stable clinical and physical condition (vital signs, such as their heart rate, blood pressure and body temperature, were steady and within normal limits. Also, the patients were conscious (aware) and comfortable for at least 4 weeks before evaluation. Exclusion criteria were: i) History of congestive heart failure; ii) primary lung disease such as asthma, chronic obstructive pulmonary disease (COPD), or lung fibrosis; iii) neuromuscular diseases; iv) collagen vascular diseases; and v) occupational exposure that could probably affect lung function. In addition, none of the patients had reported a lung infection 2 weeks before the evaluation.

The patients were subjected to the recording of their age, sex, medical history, smoking history, height, weight and body mass index (BMI). The patients were classified into four groups according to the levels of oxygen required during hospitalization: Group A, no oxygen requirement; group B, delivery of oxygen ≤60%; group C, need for delivery of oxygen 60-100% or high flow nasal cannula or non-invasive mechanical ventilation; group D, need for mechanical ventilation.

The retrospective design of the present study could lead to bias from missing data and this was addressed by obtaining only complete data.

The Institutional Review Board of Laiko General Hospital in Athens, Greece, approved the present study (protocol number 765/12-2021). The present study was in accordance with the Declaration of Helsinki of 1995 (as revised in Edinburgh, 2000). All subjects gave written informed consent for enrollment in the present study.

Assessment of lung function. PFTs included spirometry, body plethysmography and the measurement of DLCO. The Powercube Body+, a new generation body box (GANSHORN Medizin Electronic GmbH), was used to perform PFTs. For spirometry, maximal expiratory flow volume estimation was conducted while participants were seated and wearing nose clips. An automated spirometer connected to the body box was used for the measurement of forced expiratory volume in 1 sec (FEV1) and the measurement of forced vital capacity (FVC). Up to three trials were performed and the average of two technically acceptable tests was recorded. The predicted values were those of the European Respiratory Society (29).

DLCO is the volume of CO that diffuses across the alveolo-capillary membrane in one unit of time (1 min) with a certain pressure gradient (1 mmHg) (30). The DLCO was measured with the single breath holding technique using CH_4 and CO as tracer gases. Corrections were made for the arterial hemoglobin concentration. Up to four trials were performed and the average of two technically acceptable trials was recorded. The predicted values were those of the European Respiratory Society (31).

TLC is the volume of air in the lungs upon the maximum effort of inspiration (30). The measurement of TLC was performed using the body plethysmography technique. Breathing at rest and the shutter maneuver, which uses transient occlusion to purposefully block the airflow, come first in the estimation of lung function by body plethysmography. After the opening of the shutter, an expiratory reserve volume (ERV) effort and an inspiratory vital capacity (IVC) effort were performed, allowing the computation of TLC. During measurement, the box is closed with an airtight seal, with the exception of a small, controlled used for the stabilization of the internal pressure. One pressure transducer measures the pressure inside the body box relative to ambient pressure, while another is placed close to the mouth for monitoring mouth pressure during the shutter maneuver. Up to three trials were performed and the average (mean) of two technically acceptable measurements was recorded. The predicted values were those of the European Respiratory Society (29). Abnormal values of FEV1, FVC, DLCO and TLC were considered values <80% of the predicted (29). A summary of the present study scheme is illustrated in Fig. 1.

Statistical analysis. The assessment of the normal distribution of variables was performed with the Kolmogorov-Smirnov test. The mean ± standard deviation (normally distributed) is used to present continuous variables. Categorical variables are displayed as frequencies or percentages. Comparisons of

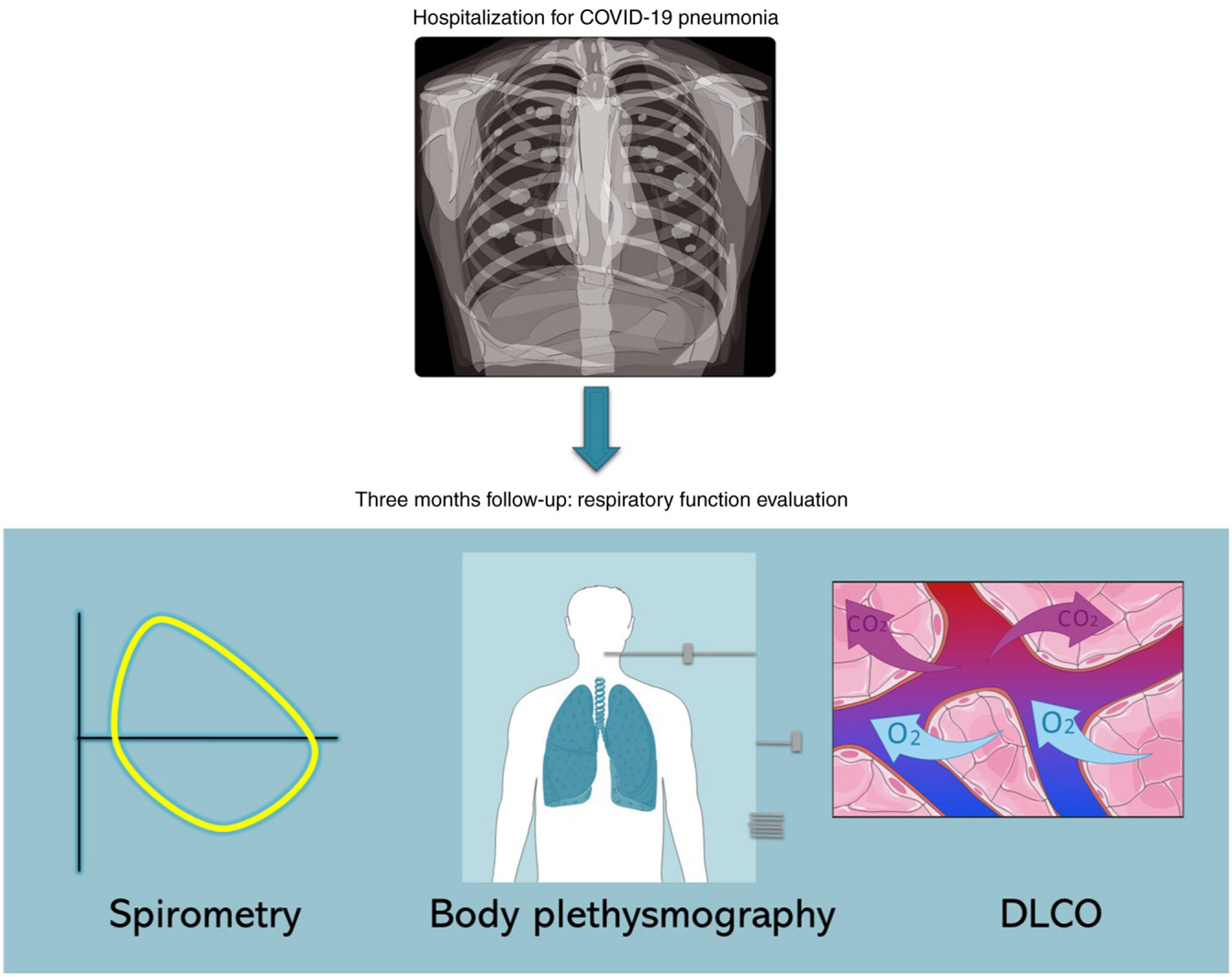

Figure 1. Summary of the study scheme. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). DLCO, diffusion capacity for carbon monoxide.

variables between groups were performed using the unpaired t-test or one-way ANOVA for continuous variables and the Chi-squared test or Fischer's exact test for categorical variables. The Bonferroni test for multiple comparisons was also used after one-way ANOVA for continuous variables. Statistical analysis was conducted using IBM SPSS-Statistics version 29.0 (IBM Corp.). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline characteristics. A total of 116 (82 male and 34 female) patients with a mean age of 57.77±11.45 years (range 19-84) were finally included in the present study. A total of 83 (71.6%) patients were hospitalized in the period of alpha variant predominance, 16 (13.8%) in the period of delta variant predominance and 17 (14.6%) in the omicron variant predominance period. Of note, the majority of the patients were unvaccinated (103 patients, 88.8%). Abnormal values of FEV1% predicted (pred) were observed in 9 (7.8%) patients, abnormal values of FVC% pred were observed in 8 (6.9%) patients, abnormal values of DLCO% pred were observed in 33 patients (28.4%) and abnormal values of TLC% pred were observed in 24 (20.7%) patients. Baseline characteristics of the present study populations are displayed in Table I.

Characteristics of the study population in relation to the variant. In the cohort of the present study, there was no statistically significant difference in age, BMI, smoking status, sex, or need for oxygen during hospitalization among the patients infected with SARS-CoV-2 in different variant periods. However, there was a statistically significant difference in vaccination status, with the largest percentage of unvaccinated patients observed during the period of alpha variant predominance (P=0.001) (Table II).

PFTs results in the different categories of variants, smoking status, vaccination status, sex and need for oxygen during hospitalization. In addition, the mean values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred were compared in the different categories of variants, smoking status, vaccination status, sex and need for oxygen during hospitalization. A statistically significant difference was observed in the mean

Table I. Characteristics of the study population.

Variable	Frequency	%
Variant		
Omicron	17	14.6
Alpha	83	71.6
Delta	16	13.8
Sex		
Male	82	70.7
Female	34	29.3
Vaccination with at least two doses		
No	103	88.8
Yes	13	11.2
FEV1 <80% pred		
No	107	92.2
Yes	9	7.8
FVC <80% pred		
No	108	93.1
Yes	8	6.9
DLCO <80% pred		
No	83	71.6
Yes	33	28.4
TLC <80% pred		
No	92	79.3
Yes	24	20.7
Need for oxygen during hospitalization		
Group A	8	6.9
Group B	70	60.4
Group C	33	28.4
Group D	5	4.3
Smoking status		
No	59	50.9
Yes	9	7.8
Ex	48	41.3
	Mean	Standard deviation
Age (years)	57.77	11.45
BMI (k/m^2)	29.01	5.76

BMI, body mass index; pred, predicted.

value of DLCO% pred among the patients infected with different variants, with higher values of DLCO% pred observed in patients infected during the omicron variant predominance period (P=0.028). In addition, there was a statistically significant difference in the mean values of FVC% pred, DLCO% pred and TLC% pred among the patients with different needs for oxygen during their hospitalization, with higher values observed in patients of groups A and B (P=0.001, P=0.007 and P=0.001, respectively). Moreover, there was a statistically significant difference in the mean values of DLCO% pred and TLC% pred between vaccinated and unvaccinated patients, with greater values observed among vaccinated patients (P=0.029 and P=0.034, respectively; Table III; Fig. 2).

Regarding the abnormal values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred, higher rates of impaired values of FEV1% pred were observed among the active smokers compared with ex-smokers and to non-smokers (P=0.011), among older patients compared with younger ones (P=0.032) and among patients with higher needs for oxygen during hospitalization compared with those with lower needs (P=0.038). Higher rates of impaired values of FVC% pred were also observed among the patients infected during the delta variant predominance period compared with patients infected during the alpha and delta variant predominance periods (P=0.008), among older patients compared with younger ones (P=0.019) and among patients with higher needs for oxygen during hospitalization compared with those with lower needs (P=0.012). There were also higher rates of abnormal values of DLCO% pred among females compared with males (P=0.004) and among older patients compared with younger ones (P=0.006). Finally, there were higher rates of impaired values of TLC% pred among the active smokers compared with ex-smokers and to non-smokers (P=0.029) and among patients with higher needs for oxygen during hospitalization compared with those with lower needs (P=0.001; Table IV).

Multivariate logistic regression analysis for abnormal values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred. According to binary logistic regression analysis, active smoking is an independent predictor of abnormal values of FEV1% pred and TLC% pred (P=0.038, OR: 8.574, CI 1.124-65.424 and P=0.004, OR: 14.733, CI 2.323-93.429, respectively), age is an independent predictor of impaired values of FVC% pred and DLCO% pred (P=0.027, OR: 1.124, CI 1.014-1.246 and P=0.011, OR: 1.054, CI 1.012-1.098, respectively) and female sex is an independent predictor of impaired values of DLCO% pred (P=0.009, OR: 1.124, CI 1.014-1.246; Table V). Fig. 3 summarizes the main findings of the present study.

Discussion

In the cohort of the present study, abnormal values of FVC% pred was observed in 8 (6.9%) patients of DLCO% pred in 33 patients (28.4%) and of TLC% pred in 24 (20.7%) patients. These findings agree with reports from the existing literature (23,32,33).

The role of age in the development of long COVID-19 syndrome has been contentious, with some researchers finding age to be a remarkable predictor of the syndrome and other studies finding decreased risk with age or no relation (34). Age has been described as an independent factor associated with impaired lung function after hospitalization due to COVID-19 pneumonia in other cohorts from the first pandemic waves (35). Age was an independent factor predicting abnormal lung function in the cohort of the present study, which consisted of patients from different periods of the pandemic.

The intricate process of lung aging arises from the cumulative alteration of lung cellular systems caused by damage

Table II. Characteristics of the study population in relation to the variant.

	Variable		
	Age (years)		P-value
Variant	Mean	Standard deviation	0.421
Omicron	60.94	10.44	
Alpha	56.99	11.11	
Delta	58.44	14.09	
	BMI (k/m^2)		
Variant	Mean	Standard deviation	0.123
Omicron	26.97	4.61	
Alpha	29.69	6.06	
Delta	27.64	4.65	
	Sex (no. of patients)		
Variant	Males	Females	0.267
Omicron	11	6	
Alpha	57	26	
Delta	14	2	

	Smoking status (no. of patients)			
Variant	No	Yes	Ex	0.221
Omicron	8	1	8	
Alpha	41	5	37	
Delta	10	3	3	

	Vaccination status (no. of patients)		
Variant	No	Yes	**0.001**
Omicron	7	10	
Alpha	82	1	
Delta	14	2	

	Need for oxygen during hospitalization (no. of patients)				
Variant	Group A	Group B	Group C	Group D	0.543
Omicron	2	11	4	0	
Alpha	5	49	26	3	
Delta	1	10	3	2	

P-values in bold indicate significant difference. BMI, body mass index.

and restoration. The incapacity of lung cells to maintain baseline homeostasis is a result of age-related alterations in intrinsic processes that support cell regeneration and repair, such as telomere shortening, increased oxidative stress, mitochondrial dysfunction and depletion of adult stem cell reserves. A number of anatomical and functional changes in the respiratory tract are linked to normal lung aging. Several of these changes worsen lung function, modify pulmonary

Table III. Mean values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred in the different categories of variants, smoking status, vaccination status, sex and need for oxygen during hospitalization.

	Variable		
	FEV1% pred		P-value
Variant	Mean	SD	0.354
Omicron	103.06	20.52	
Alpha	105.84	15.51	
Delta	99.44	19.26	
	FVC% pred		
Variant	Mean	SD	0.202
Omicron	104.12	20.19	
Alpha	105.63	16.16	
Delta	97.06	20.50	
	DLCO% pred		
Variant	Mean	SD	**0.028**
Omicron	97.11	21.08	
Alpha	85.31	15.35	
Delta	82.02	25.08	
	TLC% pred		
Variant	Mean	SD	0.226
Omicron	98.87	15.44	
Alpha	92.38	14.94	
Delta	89.33	19.67	
	FEV1% pred		
Smoking status	Mean	SD	0.125
No	106.64	17.75	
Yes	94.44	18.09	
Ex	103.96	15.20	
	FVC% pred		
Smoking status	Mean	SD	0.234
No	105.40	18.89	
Yes	94.67	18.40	
Ex	104.40	15.42	
	DLCO% pred		
Smoking status	Mean	SD	0.314
No	87.25	19.91	
Yes	77.55	14.67	
Ex	87.23	16.63	

Table III. Continued.

	TLC% pred		
Smoking status	Mean	SD	0.158
No	94.45	17.92	
Yes	82.29	16.20	
Ex	92.49	12.38	
	FEV1% pred		
Need for oxygen during hospitalization	Mean	SD	0.116
Group A	109.00	19.50	
Group B	106.67	16.00	
Group C	100.82	17.29	
Group D	92.40	16.24	
	FVC% pred		
Need for oxygen during hospitalization	Mean	SD	**0.001**
Group A	108.50	20.20	
Group B	108.80	15.52	
Group C	96.21	17.10	
Group D	87.00	17.21	
	DLCO% pred		
Need for oxygen during hospitalization	Mean	SD	**0.007**
Group A	86.87	18.37	
Group B	90.49	14.91	
Group C	81.18	19.05	
Group D	67.20	35.35	
	TLC% pred		
Need for oxygen during hospitalization	Mean	SD	**0.001**
Group A	95.50	17.13	
Group B	98.32	12.80	
Group C	83.94	14.86	
Group D	70.00	17.26	
	FEV1% pred		
Vaccination status	Mean	SD	0.947
No	104.51	15.94	
Yes	104.85	23.66	
	FVC% pred		
Vaccination status	Mean	SD	0.638
No	103.94	16.66	
Yes	106.38	23.92	

Table III. Continued.

	DLCO% pred		
Vaccination status	Mean	SD	**0.029**
No	85.45	16.99	
Yes	95.61	25.13	
	TLC% pred		
Vaccination status	Mean	SD	**0.034**
No	91.93	15.24	
Yes	101.09	18.84	
	FEV1% pred		
Sex	Mean	SD	0.340
Male	103.59	17.35	
Female	106.88	15.56	
	FVC% pred		
Sex	Mean	SD	0.057
Male	102.12	17.70	
Female	109.21	16.25	
	DLCO% pred		
Sex	Mean	SD	0.052
Male	89.06	18.22	
Female	80.61	17.08	
	TLC% pred		
Sex	Mean	SD	0.418
Male	92.08	16.28	
Female	94.81	14.55	

P-values in bold indicate significant difference. FEV1, forced vital capacity in 1 sec; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; pred, predicted; SD, standard deviation.

remodeling, reduce regeneration and increase vulnerability to pulmonary illness. The lung has developed a variety of innate and adaptive defense mechanisms to maintain homeostasis and react to external stimuli. Oxygen free radicals and proinflammatory cytokines are produced in greater amounts during immunosenescence (36,37). Innate and adaptive immune responses in the lung have been linked to aging-related alterations in prognosis and recovery in pulmonary inflammatory disorders (38).

According to several studies, females face a greater risk of suffering from long term symptoms following SARS-CoV-2 infection (39-41). Autoimmune-related illnesses have been discovered to affect female patients much more frequently than males and autoimmunity has been proposed as a possible mechanism of long COVID-19 syndrome (42). According to some scientists, higher Toll-like receptor 7 (TLR7) expression results in higher IFN signaling in acute COVID-19 and improved viral clearance in females, but continued IFN signaling may result in excessive immune activation and persistent inflammation, predisposing females to a higher risk of autoimmunity and long-term consequences (43,44). The present study also found that female sex was an independent factor associated with impaired values of DLCO% pred, which indicate lung epithelial damage, or interstitial or pulmonary vascular abnormalities (45,46).

Overall, research indicates that females are more likely than males to have lung disorders and that their degrees of severity, rate of exacerbations, hospitalizations and death are all higher in females than in males. These include pulmonary hypertension, asthma, COPD and certain forms of lung cancer, including adenocarcinoma. Moreover, women almost always have certain uncommon and poorly known lung diseases, such as lymphangioleiomyomatosis (47).

Smoking is an established risk factor for lung function decline (48). It has also been linked to long term consequences after SARS-CoV-2 infection (38,49). In the cohort of the present study, smoking, except for the abnormal values of FEV1% pred, was associated with abnormal values of TLC which indicate a restrictive pattern of pulmonary dysfunction (50). These data suggested that expanding the promotion of tobacco cessation strategies are new priorities in this pandemic era.

The present study demonstrated some important attributes that should be presented. It is one of a handful of studies that include patients from a long period of the pandemic. Although the mean values of DLCO% pred were higher in patients infected during the period of omicron variant predominance, the percentage of patients with abnormal values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred did not differ among patients infected with the three different variants of SARS-CoV-2, suggesting that a significant proportion of patients who are hospitalized due to COVID-19 pneumonia will develop abnormal lung function regardless of the SARS-CoV-2 variant.

In addition, considering that the majority of the cohort of the present study was unvaccinated against SARS-CoV-2, the present study provided indirect evidence that vaccination against SARS-CoV-2 is not only crucial for preventing severe acute illness but also to limit post-acute sequelae of this infection. The findings of the present study indicated that it is important to build vaccine confidence in the general population and this can potentially reduce lung impairment rates after hospitalization, visits to outpatient clinics for abnormal lung function and overall health costs.

There are several limitations in the present study. First, the lack of pre-SARS-CoV-2 infection PFTs makes it difficult to tell to which extent the infection affected the lung function. Second, this is a single center study on hospitalized COVID-19 patients. Moreover, a low representation of patients with ICU admission in the cohort of the present

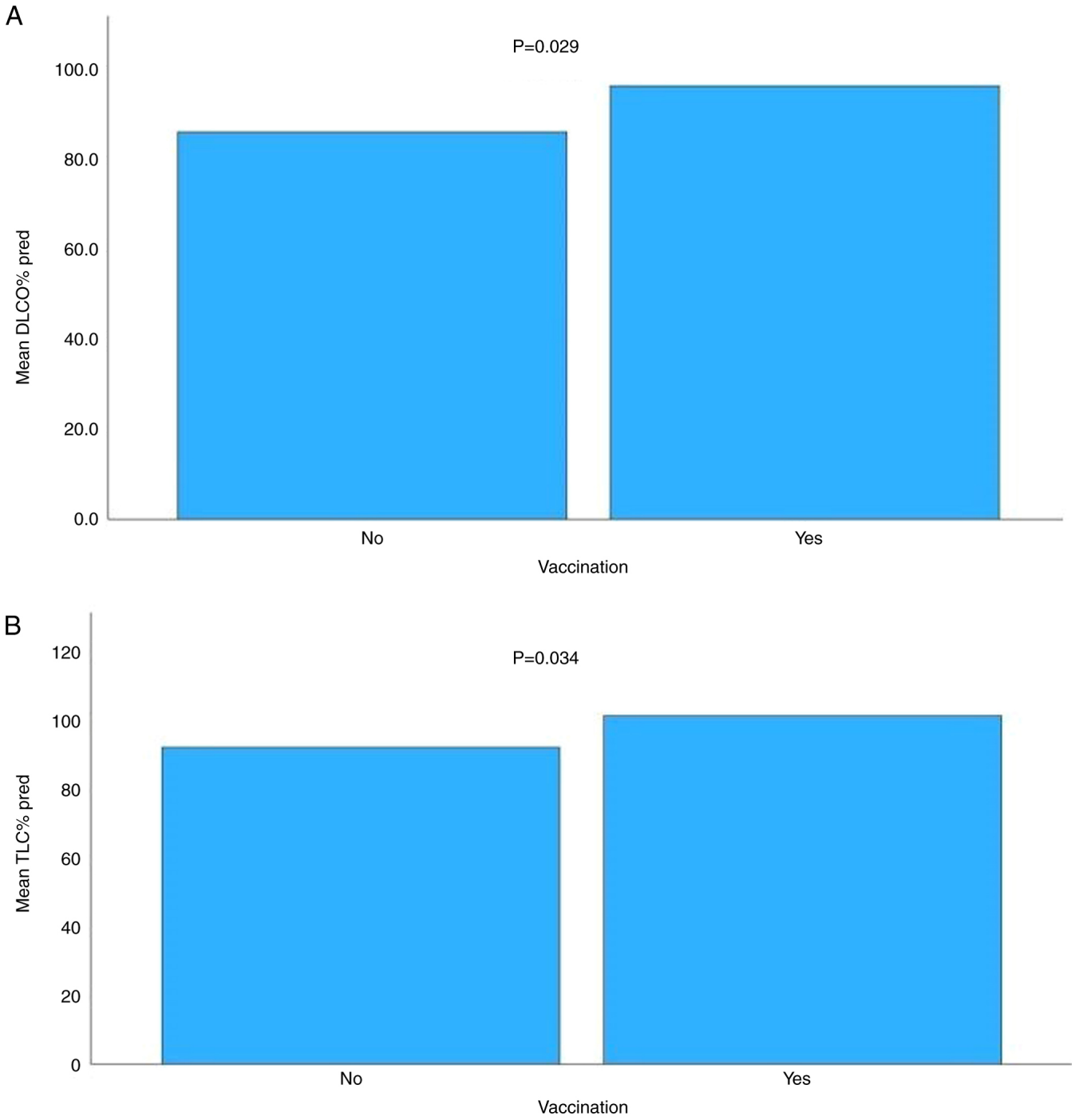

Figure 2. Statistically significant difference in the mean values of (A) DLCO% pred and (B) TLC% pred between vaccinated and unvaccinated patients, with greater values observed among vaccinated patients (P=0.029 and P=0.034, respectively). DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity.

study does not permit the generalizability of the present study findings to this specific population. In addition, the specific viral variations of patients were not identified. The prevalent variant at the time the patient was identified as having SARS-CoV2 infection served as the basis for the variant assignment.

In conclusion, the present study in a predominantly unvaccinated cohort of patients hospitalized for COVID-19 pneumonia revealed independent associations between age, female sex, smoking and abnormal lung function three months post-acute infection. These findings underscore the importance of considering these factors in the post-acute care of COVID-19 survivors. While the percentage of patients developing abnormal lung function did not vary significantly across different variant predominance periods, future research should explore these associations in more diverse cohorts. These insights contribute to our evolving understanding of the long-term consequences of COVID-19 and offer valuable considerations for clinical practice and future investigations.

Table IV. Abnormal values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred in the different categories of variants, smoking status, sex, vaccination status and need for oxygen during hospitalization.

	Parameter			
Variable	Alpha	Delta	Omicron	P-value
FEV1 <80% pred				
No	79	13	15	0.130
Yes	4	3	2	
FVC <80% pred				
No	80	12	16	**0.008**
Yes	3	4	1	
DLCO <80% pred				
No	61	9	13	0.333
Yes	22	7	4	
TLC <80% pred				
No	66	10	15	0.163
Yes	16	6	2	
	Smoking status			
	No	Yes	Ex	
FEV1 <80% pred				
No	54	6	46	**0.011**
Yes	4	3	2	
FVC <80% pred				
No	54	7	46	0.148
Yes	4	2	2	
DLCO <80% pred				
No	44	4	34	0.152
Yes	14	5	14	
TLC <80% pred				
No	48	4	38	**0.029**
Yes	10	5	9	
	Sex			
	Male	Female		
FEV1 <80% pred				
No	74	33		0.212
Yes	8	1		
FVC <80% pred				
No	75	33		0.279
Yes	7	1		
DLCO <80% pred				
No	65	18		**0.004**
Yes	17	16		
TLC <80% pred				
No	63	28		0.390
Yes	18	6		

Table IV. Continued.

	Vaccination status		
	No	Yes	
FEV1 <80% pred			
No	96	11	0.275
Yes	7	2	
FVC <80% pred			
No	97	11	0.200
Yes	6	2	
DLCO <80% pred			
No	74	9	0.844
Yes	29	4	
TLC <80% pred			
No	81	10	0.835
Yes	21	3	

	Age (years)		
	Mean	SD	
FEV1 <80% pred			
No	57.20	11.53	**0.032**
Yes	64.56	8.11	
FVC <80% pred			
No	57.09	11.49	**0.019**
Yes	66.88	5.81	
DLCO <80% pred			
No	55.94	11.18	**0.006**
Yes	62.36	10.95	
TLC <80% pred			
No	57.19	11.44	0.534
Yes	58.79	10.29	

	Need for oxygen during hospitalization				
	Group A	Group B	Group C	Group D	
FEV1 <80% pred					
No	8	66	30	3	**0.038**
Yes	0	4	3	2	
FVC <80% pred					
No	7	68	30	3	**0.012**
Yes	1	2	3	2	
DLCO <80% pred					
No	6	55	20	2	0.106
Yes	2	15	13	3	
TLC <80% pred					
No	6	65	18	2	**0.001**
Yes	2	5	14	3	

P-values in bold indicate significant difference. FEV1, forced vital capacity in 1 sec; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; pred, predicted.

Table V. Multivariate logistic regression analysis for abnormal values of FEV1% pred, FVC% pred, DLCO% pred and TLC% pred.

Logistic regression analysis for FEV1 <80% pred				
			95% CI for OR	
Variable	P-value	OR	Lower	Upper
Group A	Ref	Ref	Ref	Ref
Group B	0.999	42.479	0.000	NC
Group C	0.999	77.603	0.000	NC
Group D	0.999	45.972	0.000	NC
Non-smoker	Ref	Ref	Ref	Ref
Active smoker	**0.038**	8.574	1.124	65.424
Ex-smoker	0.259	0.339	0.052	2.221
Age per year	0.060	1.086	0.997	1.182
Logistic regression analysis for FVC <80% pred				
			95% CI for OR	
Variable	P-value	OR	Lower	Upper
Group A	Ref	Ref	Ref	Ref
Group B	0.077	0.050	0.002	1.386
Group C	0.360	0.230	0.010	5.341
Group D	0.849	1.394	0.046	42.213
Age per year	**0.027**	1.124	1.014	1.246
Omicron variant	Ref	Ref	Ref	Ref
Alpha variant	0.573	0.478	0.037	6.237
Delta variant	0.247	4.574	0.350	59.849
Logistic regression analysis for DLCO <80% pred				
			95% CI for OR	
Variable	P-value	OR	Lower	Upper
Age per year	**0.011**	1.054	1.012	1.098
Female sex	**0.009**	3.291	1.352	8.009
Logistic regression analysis for TLC <80% pred				
			95% CI for OR	
Variable	P-value	OR	Lower	Upper
Group A	Ref	Ref	Ref	Ref
Group B	0.138	0.205	0.025	1.665
Group C	0.231	3.355	0.463	24.302
Group D	0.227	5.121	0.362	72.442
Non-smoker	Ref	Ref	Ref	Ref
Active smoker	**0.004**	14.733	2.323	93.429
Ex-smoker	0.859	0.901	0.286	2.839

P-values in bold indicate significant difference. FEV1, forced vital capacity in 1 sec; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide; TLC, total lung capacity; pred, predicted; CI, confidence interval; OR, odds ratio.

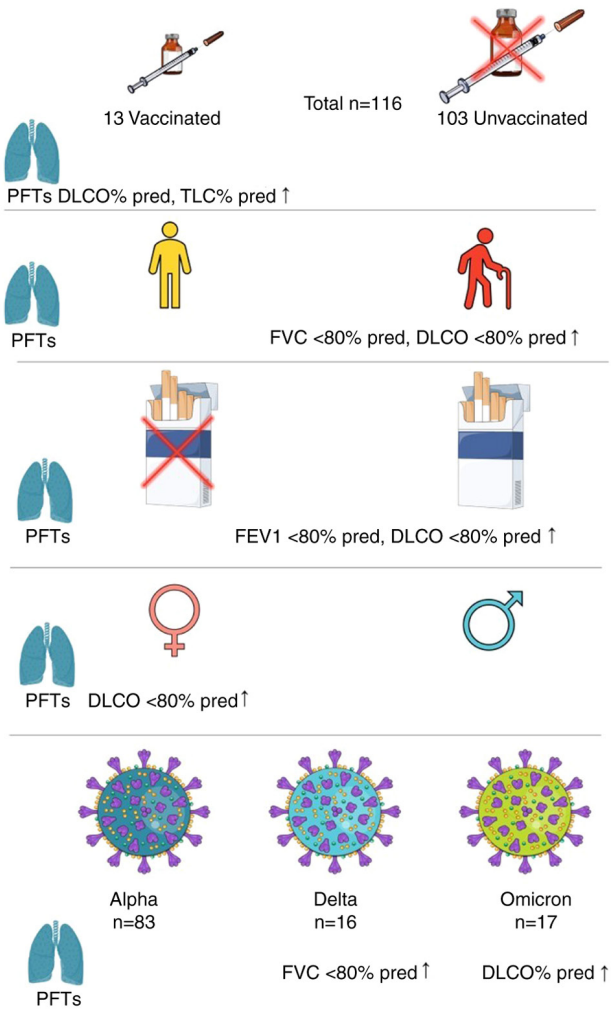

Figure 3. Summary of main novel findings regarding the vaccination status, age, smoking, sex and variant and the PFTs in individuals 3 months post-hospitalization for COVID-19 pneumonia. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). PFTs, pulmonary function tests; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 sec FVC, forced vital capacity; TLC, total lung capacity; pred, predicted.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article. The raw data is available from the corresponding author upon reasonable request.

Authors' contributions

NVS and VEG conceptualized the present study. VEG, AG, SM, DAS, MNG, EA, PP, IGL, SP and NVS made a substantial

contribution to data interpretation and analysis and wrote and prepared the draft of the manuscript. VEG and NVS analyzed the data and provided critical revisions. VEG and NVS confirm the authenticity of all the data. All authors contributed to manuscript revision and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in line with the Declaration of Helsinki and gained approval by the Institutional Review Board of Laiko General Hospital (approval no. 765/12-2021). Written informed consent was obtained from the patients for participation and publication of the data.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

References

1. Cascella M, Rajnik M, Aleem A, Dulebohn SC and Di Napoli R: Features, evaluation, and treatment of coronavirus (COVID-19) [Updated 2023 Aug 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.
2. Sheleme T, Bekele F and Ayela T: Clinical presentation of patients infected with coronavirus disease 19: A systematic review. Infect Dis (Auckl) 13: 1178633720952076, 2020.
3. Siafarikas C, Stafylidis C, Tentolouris A, Samara S, Eliadi I, Makrodimitri S, Spandidos DA, Mathioudakis N, Karamichalos P, Papalexis P, *et al*: Radiologically suspected COVID-19-associated organizing pneumonia responding well to corticosteroids: A report of two cases and a review of the literature. Exp Ther Med 24: 453, 2022.
4. Georgakopoulou VE, Gkoufa A, Damaskos C, Papalexis P, Pierrakou A, Makrodimitri S, Sypsa G, Apostolou A, Asimakopoulou S, Chlapoutakis S, *et al*: COVID-19-associated acute appendicitis in adults. A report of five cases and a review of the literature. Exp Ther Med 24: 482, 2022.
5. Cholongitas E, Bali T, Georgakopoulou VE, Giannakodimos A, Gyftopoulos A, Georgilaki V, Gerogiannis D, Basoulis D, Eliadi I, Karamanakos G, *et al*: Prevalence of abnormal liver biochemistry and its impact on COVID-19 patients' outcomes: A single-center Greek study. Ann Gastroenterol 35: 290-296, 2022.
6. Georgakopoulou VE, Avramopoulos P, Papalexis P, Bitsani A, Damaskos C, Garmpi A, Venetikou MS, Paramythiotis D, Karlafti E, Sklapani P, *et al*: COVID-19 induced hypoparathyroidism: A case report. Exp Ther Med 23: 346, 2022.
7. Georgakopoulou VE, Gkoufa A, Garmpis N, Makrodimitri S, Papageorgiou CV, Barlampa D, Garmpi A, Chiapoutakis S, Sklapani P, Trakas N and Damaskos C: COVID-19 and acute pancreatitis: A systematic review of case reports and case series. Ann Saudi Med 42: 276-287, 2022.
8. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, *et al*: Risk factors associated with Acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180: 934-943, 2020.
9. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J and Ho A: SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: A systematic review and meta-analysis. Lancet Microbe 2: e13-e22, 2021.
10. Georgakopoulou VE, Gkoufa A, Bougea A, Basoulis D, Tsakanikas A, Makrodimitri S, Karamanakos G, Spandidos DA, Angelopoulou E and Sipsas NV: Characteristics and outcomes of elderly patients with Parkinson's disease hospitalized due to COVID-19-associated pneumonia. Med Int (Lond) 3: 34, 2023.
11. Gkoufa A, Maneta E, Ntoumas GN, Georgakopoulou VE, Mantelou A, Kokkoris S and Routsi C: Elderly adults with COVID-19 admitted to intensive care unit: A narrative review. World J Crit Care Med 10: 278-289, 2021.
12. Lempesis IG and Georgakopoulou VE: Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges. World J Clin Cases 11: 2925-2933, 2023.
13. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, *et al*: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 395: 507-513, 2020.
14. Thaweethai T, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, McCorkell L, Nadkarni GN, Parthasarathy S, Singh U, *et al*: Development of a definition of postacute sequelae of SARS-CoV-2 infection. JAMA 329: 1934-1946, 2023.
15. Efstathiou V, Stefanou MI, Demetriou M, Siafakas N, Makris M, Tsivgoulis G, Zoumpourlis V, Kympouropoulos SP, Tsoporis JN, Spandidos DA, *et al*: Long COVID and neuropsychiatric manifestations (review). Exp Ther Med 23: 363, 2022.
16. Efstathiou V, Stefanou MI, Demetriou M, Siafakas N, Katsantoni E, Makris M, Tsivgoulis G, Zoumpourlis V, Kympouropoulos SP, Tsoporis JN, *et al*: New-onset neuropsychiatric sequelae and 'long-COVID' syndrome (Review). Exp Ther Med 24: 705, 2022.
17. Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, Lipsitch M and Cohen K: Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: Retrospective cohort study. BMJ 373: n1098, 2021.
18. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, *et al*: 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397: 220-232, 2021.
19. Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, Liu M, Wang Y, Cui D, Wang Y, *et al*: Health outcomes in people 2 years after surviving hospitalisation with COVID-19: A longitudinal cohort study. Lancet Respir Med 10: 863-876, 2022.
20. E E, R F, Öi E, Im L, M L, S R, E W, C J, M H and A M: Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge. Respir Med 182: 106394, 2021.
21. Riou M, MarcoT C, Oulehri W, Enache I, Pistea C, Chatron E, Labani A, Geny B, Ohana M, De Blay F, *et al*: Respiratory follow-up after hospitalization for COVID-19: Who and when? Eur J Clin Invest 51: e13603, 2021.
22. Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ and Carlsten C: A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax 76: 402-404, 2021.
23. Lee JH, Yim JJ and Park J: Pulmonary function and chest computed tomography abnormalities 6-12 months after recovery from COVID-19: A systematic review and meta-analysis. Respir Res 23: 233, 2022.
24. Liu T, Wu D, Yan W, Wang X, Zhang X, Ma K, Chen H, Zeng Z, Qin Y, Wang H, *et al*: Twelve-month systemic consequences of coronavirus disease 2019 (COVID-19) in patients discharged from hospital: A prospective cohort study in Wuhan, China. Clin Infect Dis 74: 1953-1965, 2022.
25. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND and Xu R: COVID infection rates, clinical outcomes, and racial/ethnic and gender disparities before and after omicron emerged in the US. medRxiv: Feb 22, 2022 (Epub ahead of print).
26. Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, Ramlall R, Spoor S, de Villiers T, Van der Walt Z, *et al*: Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in Tshwane, South Africa. Int J Infect Dis 116: 38-42, 2022.
27. Arabi M, Al-Najjar Y, Mhaimeed N, Salameh MA, Paul P, AlAnni J, Abdelati AA, Laswi I, Khanjar B, Al-Ali D, *et al*: Severity of the omicron SARS-CoV-2 variant compared with the previous lineages: A systematic review. J Cell Mol Med 27: 1443-1464, 2023.
28. Antonelli M, Pujol JC, Spector TD, Ourselin S and Steves CJ: Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. Lancet 399: 2263-2264, 2022.

29. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R and Yernault JC: Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. Eur Respir J Suppl 16: 5-40, 1993.
30. Georgakopoulou VE, Asimakopoulou S and Cholongitas E: Pulmonary function testing in patients with liver cirrhosis (review). Med Int (Lond) 3: 36, 2023.
31. Cotes JE, Chinn DJ, Quanjer PH, Roca J and Yernault JC: Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J 6 (Suppl 16): S41-S52, 1993.
32. Karampitsakos T, Sotiropoulou V, Katsaras M, Tsiri P, Georgakopoulou VE, Papanikolaou IC, Bibaki E, Tomos I, Lambiri I, Papaioannou O, *et al*: Post-COVID-19 interstitial lung disease: Insights from a machine learning radiographic model. Front Med (Lausanne) 9: 1083264, 2023.
33. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, Hu P, Guo L, Liu M, Xu J, *et al*: 1-Year outcomes in hospital survivors with COVID-19: A longitudinal cohort study. Lancet 398: 747-758, 2021.
34. Wang C, Ramasamy A, Verduzco-Gutierrez M, Brode WM and Melamed E: Acute and post-acute sequelae of SARS-CoV-2 infection: A review of risk factors and social determinants. Virol J 20: 124, 2023.
35. Tarraso J, Safont B, Carbonell-Asins JA, Fernandez-Fabrellas E, Sancho-Chust JN, Naval E, Amat B, Herrera S, Ros JA, Soler-Cataluña JJ, *et al*: Lung function and radiological findings 1 year after COVID-19: A prospective follow-up. Respir Res 23: 242, 2022.
36. Schneider JL, Rowe JH, Garcia-de-Alba C, Kim CF, Sharpe AH and Haigis MC: The aging lung: Physiology, disease, and immunity. Cell 184: 1990-2019, 2021.
37. Aghali A, Koloko Ngassie ML, Pabelick CM and Prakash YS: Cellular senescence in aging lungs and diseases. Cells 11: 1781, 2022.
38. Cho SJ and Stout-Delgado HW: Aging and lung disease. Annu Rev Physiol 82: 433-459, 2020.
39. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, Clark A, Ntatsaki E and Vassiliou VS: Risk factors associated with post-COVID-19 condition: A systematic review and meta-analysis. JAMA Intern Med 183: 566-580, 2023.
40. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mulè G, Augello M, Mondatore D, Allegrini M, Cona A, *et al*: Female gender is associated with long COVID syndrome: A prospective cohort study. Clin Microbiol Infect 28: 611.e9-611.e16, 2022.
41. Torjesen I: Covid-19: Middle aged women face greater risk of debilitating long term symptoms. BMJ 372: n829, 2021.
42. Opsteen S, Files JK, Fram T and Erdmann N: The role of immune activation and antigen persistence in acute and long COVID. J Investig Med 71: 545-562, 2023.
43. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, *et al*: Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol 23: 210-216, 2022.
44. Souyris M, Mejía JE, Chaumeil J and Guéry JC: Female predisposition to TLR7-driven autoimmunity: Gene dosage and the escape from X chromosome inactivation. Semin Immunopathol 41: 153-164, 2019.
45. Hanidziar D and Robson SC: Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. Am J Physiol Lung Cell Mol Physiol 320: L12-L16, 2021.
46. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, Ledot S, Morgan C, Passariello M, Price S, *et al*: Pulmonary angiopathy in severe COVID-19: Physiologic, imaging, and hematologic observations. Am J Respir Crit Care Med 202: 690-699, 2020.
47. Silveyra P, Fuentes N and Rodriguez Bauza DE: Sex and gender differences in lung disease. Adv Exp Med Biol 1304: 227-258, 2021.
48. Trakas N, Georgakopoulou VE, Melemeni D, Damaskos C, Mantzouranis K, Garmpis N, Gkoufa A, Papalexis P, Chlapoutakis S, Sklapani P, *et al*: Association between smoking cessation and alterations in forced expiratory volume in one second (FEV1). A follow-up study from a Greek tobacco cessation clinic. Addict Health 14: 87-95, 2022.
49. Barthélémy H, Mougenot E, Duracinsky M, Salmon-Ceron D, Bonini J, Péretz F, Chassany O and Carrieri P: Smoking increases the risk of post-acute COVID-19 syndrome: Results from a French community-based survey. Tob Induc Dis 20: 59, 2022.
50. Martinez-Pitre PJ, Sabbula BR and Cascella M: Restrictive lung disease. In: StatPearls. StatPearls Publishing, Treasure Island, FL, 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560880/.