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Assessment of Medium-Term Impact of Sars-Cov2 Infection on Pulmonary Function in Albanian Young Adults without Previous History of Respiratory Disease

Etleva Qirko Loloci[1], Anxhela Gurakuqi Qirko[2], Eralda Lekli[2], Elizana Petrela[3], Nertila Beqo[1], Albana Gjeli[1], Mehmet Hoxha[1]*

[1]Department of Internal Medicine, Faculty of Medicine, University of Medicine, Tirana, Albania; [2]Department of Biomedical and Experimental Sciences, Faculty of Medicine, University of Medicine, Tirana, Albania; [3]Department of Public Health, Biostatistic sector, Faculty of Medicine, University of Medicine, Tirana, Albania

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***Correspondence:** Mehmet Hoxha, Department of Internal Medicine, Faculty of Medicine, University of Medicine, Tirana, Albania.
E-mail: mehmethoxha@ymail.com
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Abstract

BACKGROUND: No study has been conducted to allow the evaluation of pulmonary dysfunction in Albanian population after medium-severe COVID-19 disease.

AIM: We aimed through this project to overview the spirometry data and correlation to other inflammatory markers in post COVID-19 young adults.

METHODS: A cross-sectional study was performed to access spirometry as pulmonary function test 3–6 months after COVID-19 in young adults ≤45 years old, hospitalized for COVID-19, and presented no known history for previous pulmonary disease.

RESULTS: Among 61 patients, 41 (67.2%) females; mean age 30.6 ± 8.63 years, have undergone a spirometry test 3–6 months after COVID-19. Spirometry data for pulmonary function resulted: 4 patients (6.56%) with pulmonary dysfunction, among them 1 patient (1.64%) Forced expiratory volume in 1 s (FEV1)/Forced vital capacity (FVC) <75%, with generalized bronchial obstruction and 3 patients (4.92%) with small airway obstruction (brochiolo-obstruction), FEF 25–75 <60%. According to criteria classification for disease, severity (SpO_2 <94% and/or pulmonary infiltrates >50%) 22 (36.06%) had severe COVID-19. Among two groups of COVID severity, resulted statistically significant ($p < 0.05$), the difference for visual analogue scale (VAS) for dyspnea perception reported during 1st month post-COVID-19 after 6 min moderate physical activity and FEV1/FVC (Tiffeneau Index value) resulted no statistically significant changes between groups for inflammatory markers such as C reactive protein level, absolute lymphocyte count, FEF 25–75 or body mass index. D-dimer value had statistically significant change between two groups of COVID-19 severity. In two groups where present VAS dyspnea perception (≤5) and (>5), no significant correlation was found regarding FEV1/FVC and FEF 25–75 values among groups.

CONCLUSION: The results show that there are few patients that show obstructive pulmonary dysfunction evaluated by spirometry. As investigated by other published studies probably the effects in pulmonary function are improved after few months and bronchial hyper-reactivity post- COVID-19 needs further investigation.

Introduction

The COVID-19 pandemic has an increased attention to evaluate the acute, subacute, and long-term consequences in respiratory system. Immediately after COVID-19 breakout, several cohort studies were conducted to evaluate mostly pulmonary parenchyma damage and fibrosis in severe COVID-19. There are reported controversial findings for the association between asthma and severity of COVID-19, whereas allergic rhinitis has a protective effect against severe COVID-19. The inconsistent findings between asthma and the severity of COVID-19 may be due to the different scale of the study in case series, criteria for hospitalization of COVID-19 patients, racial disparities, patient age, severity of asthma, and the condition of asthma control in the patients [1].

Available scientific data support the low expression of ACE2 receptors in airways, due to TH2 inflammation in respiratory tract of allergic subjects, playing a probable protective role toward severe form of COVID-19. Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19, but not clearly with risk of being hospitalized with COVID-19 [2]. On the other side, the real consequences of immune mediation in SARS-COV-2 infection and its role as interchange trigger due to the overstimulation of T cell-mediated immune response in most individuals with highly symptomatic disease, it is largely unknown. It was reported that almost half of adults admitted to hospital due to COVID-19 reported persistent symptoms 6–8 months after discharge. Fatigue and respiratory symptoms were most common, and female sex was associated with persistent symptoms [3]. Risk factors for COVID-19 persistent

symptoms, especially fatigue, were not associated with initial severity [4].

In children, history of allergic respiratory diseases was a risk factor (2.66, 1.04–6.47) for post-COVID-19 condition after 12 months [5]. Although in children and young adults was rarely reported a post-infectious, hyper-inflammatory response following SARS-CoV2 infection [6].

Post-viral bronchial hyper-reactivity syndrome is common after respiratory tract viral infections; however, its prevalence after COVID-19 is unclear. One recent study investigated bronchial hyper-responsiveness in patients with normal baseline lung function but persisting respiratory symptoms. In that study, they are reported only 3.9% of patients who had bronchial hyper-responsiveness after COVID-19, suggesting that as a complication of COVID-19 and indicating a minor role of prior postulated post-viral bronchial hyper reactivity [7] Another study revealed that 43% of patients with a history of COVID-19 had a positive BCT, but uninfected patients had a significantly higher number (56%) of positive BCT ($p = 0.02$). The cause of dyspnea in patients with a history of COVID-19 was not associated with bronchial hyper-reactivity. They concluded bronchial hyper-responsiveness in infected people is likely to be caused by an underlying allergy, which may be exacerbated by the disease [8].

Our present study is the first ongoing study in Albanian population to asses pulmonary function effects in moderate-severe post-COVID-19 condition in young adults.

Aim

To evaluate the prevalence of compromised pulmonary function in the period 3–6 months post COVID-19 in Albania, in patients under 45 years, without previously known respiratory disease and to correlate any findings with dyspnea perception, clinical and radiological features, including comparison to literature.

Methods

This was a prospective cross-sectional study. Patients hospitalized in main tertiary hospital center in Albania, were contacted after hospital discharge to enter in the study. Before initiation Medical Ethical Commission approval and individual informed patient consent was taken. The study has a comparative character for the medium-term prevalence of pulmonary function test changes post-COVID-19. Results have been interpreted both conceptual and critical, to compare and evaluate a series of perspectives on the consequences and factors affection post-COVID-19 pulmonary function among young people in Albania.

Statistical analysis

SPSS 25.0 was used to analyze data. Student's t-test and Mann–Whitney test are used to compare results between groups. A $p < 5\%$ was considered statistically significant. Dyspnea was evaluated by visual analog scale (VAS) ranged 0 (none) – 10 (severe dyspnea perception).

Time period

The study has been carried out from October 2021 to October 2022, at least in 1 time slot for each patient at 3–6 months after acute SARS-COV2 infection. The visit included spirometry, anamnestic data, and VAS questionnaire for dyspnea.

Inclusion criteria

Post-COVID-19 patients diagnosed by PCR/or serology and CT infiltrations and hospitalized in COVID hospitals in Albania. Age criteria: 18–45 years old.

Exclusion criteria

Known respiratory diseases or any concomitant disease that can compromise pulmonary function (e.g. known systemic autoimmune disease), important mental/neurological diseases, active infectious diseases, coronary artery disease/cardiac insufficiency, and active smokers were excluded from the study.

Study limitations

We lacked the equipment to perform the body plethysmography to asses more pulmonary function parameters, like TLC (specifically for evaluating the pulmonary restriction), neither bronchial provocation test for bronchial hyper-reactivity, nor the diffusion capacity of the lungs for carbon monoxide (DLCO) for the assessment of the alveolar – blood-barrier thickening and worsening of O_2 and CO_2 gas exchange. Because of strict exclusion criteria, the number of patients was limited. COVID-19 vaccination and population immunity limited the number of new patients 3–6 months after the study initiation.

Results

In the study, 61 patients were included, who fulfilled all criteria, 41 (67.2%) females and 20 (32.8%)

Table 1: Visual analogue scale for dyspnea perception and spirometry data among groups of COVID-19 disease severity

Variables	SpO_2 during hospitalisation ≤94% in air	SpO_2 during hospitalisation >94% in air	p
Patients (n = 61)	n = 22	n = 39	NA
Symptoms perception VAS			
Persistent-dyspnea reported during 1st month post-COVID-19	2.41 ± 2.71	3.43 ± 2.78	0.08
Dyspnea reported during 1st month post-COVID-19 after 6 min moderate physical activity	3.54 ± 2.97	5.5 ± 3.12	0.007
Persistent dyspnea reported during 3rd–6th month post-COVID-19	1.38 ± 1.95	1.55 ± 1.92	0.38
Dyspnea reported during 3rd–6th month post-COVID-19 after 6 min moderate physical activity	2.62 ± 2.7	3.18 ± 2.54	0.22
Spirometry			
FEV_1/FVC	1 ± 0.01	1.05 ± 0.09	0.039
FEF25%–75% of predicted	114.79 ± 30.71	113.45 ± 32.8	0.551

*Mann–Whitney test. FVC, FEV_1, Tiffeneau index, FEV_1/FVC: The forced mid-expiratory flow (FEF25–75%). FVC: Forced vital capacity, VAS: Visual analogue scale, FEV1: Forced expiratory volume in 1 s, FEF: Forced mid-expiratory flow.

males; mean age 30.6 ± 8.63 years. All included participants had performed chest computerized tomography during COVID-19 and had typical infiltrations of pulmonary parenchyma. PCR test for SARS COV-2 was positive in 49 (80.3%) during hospitalization.

The family history for COVID-19 was negative in 9 (14.8%), same severity or more severe in 35 (57.4%).

Spirometry data for pulmonary function resulted: 4 patients (6.56%) with pulmonary dysfunction, among them 1 patient (1.64%) Forced expiratory volume in 1 s (FEV1)/Forced vital capacity (FVC) <75%, with generalized bronchial obstruction and 3 patients (4.92%) with small airway obstruction (bronchial-obstruction), FEF 25–75 <60% (Table 1).

According to criteria classification for disease severity (SpO_2 <94% and/or pulmonary infiltrates >50%) 22 (36.06%) had severe COVID-19 (Table 2). Among two groups of COVID severity, resulted statistically significant ($p < 0.05$), the difference for VAS for dyspnea perception reported during 1st month post-COVID-19 after 6 min moderate physical activity and FEV1/FVC (Tiffeneau Index value). The differences were not significant for persistent dyspnea reported during 3rd–6th month post-COVID-19 in rest and after 6 min of physical activity.

Table 2: Inflammatory markers data among groups of COVID-19 disease severity

Variables	SpO_2 during hospitalisation ≤94% in air	SpO_2 during hospitalisation >94% in air	p
Patients, n = 61	n = 22	n = 39	NA
D-dimer	495 ± 655.91	600.3 ± 651.46	0.006
CRP	10.08 ± 10.2	9.54 ± 6.33	0.757
LYMF	1.92 ± 1.08	2.07 ± 1.8	0.683

*Mann–Whitney test. CPR: C Reactive protein, LYMF: Absolute number of lymphocytes, LYMF: Let your mind float.

It resulted no statistically significant changes between groups for inflammatory markers such as C-reactive protein level, absolute lymphocyte count, and FEF 25–75 or body mass index (BMI). There was a statistically significant change for D-Dimer values. In two groups where present VAS dyspnea perception (≤5) and (>5), no significant correlation was found regarding FEV1/FVC and FEF 25–75 values among groups.

No statistically significant changes were found regarding BMI and spirometry results (Table 3).

Table 3: Body mass index correlation with spirometry data

Variables	Normal spirometry	Bronkiolo-obstruction	p
BMI	25.97 ± 4.2	24.74 ± 3.95	0.590

BMI: Body mass index.

Discussion

In our investigation in PubMed, Google scholar, and Scopus, few studies have included mainly children and young adults [5] and none of reviewed had strict exclusion criteria for conditions that would affect pulmonary function (comorbidities, smoking, etc).

Published data indicate that spirometric indices appear to be generally well preserved but that a defect in diffusing capacity (DLco) is a prevalent abnormality identified on follow-up lung function; present in 20–30% of those with mild-to-moderate disease; and 60% in those with severe disease [3]. Because of equipment lack, it was impossible to evaluate DLco in our study population.

Studies performed to patients who had COVID in early pandemic during 2020, reported evidence of pulmonary function affection, which is generally improved after 6–12 months, supported by literature review in Table 4 [9], [10].

Our study included patients that had COVID-19 after March 2021 and aligned to many studies conducted 2021–2022 [11], [12] show no significant pulmonary function changes in spirometry data among these patients. The results may be related to less aggressive virus genotype or better treatment approach after 1st year of pandemic.

In two groups where present VAS dyspnea perception (≤5) and (>5), no significant correlation was found regarding FEV1/FVC and FEF 25–75 values among groups supposing that dyspnea perception is not related with pulmonary dysfunction in spirometry 3–6 months after COVID-19.

Among two groups of COVID severity resulted statistically significant, the difference for VAS dyspnea perception reported during 1st month post-COVID-19 after 6 min moderate physical activity and FEV1/FVC (Tiffeneau Index value), but not significant 3–6 months after COVID-19. This result may indicate an

Table 4: Literature review

Title of the article	Study	Number of patients involved	Age	Time when conducted	Main criteria of inclusion	Pulmonary affections
Lung function before and after COVID-19 in young adults: A population-based study [11]	Mogensen *et al*.	853	Adults	2020–2021	Patients after COVID-19, who already had a previous spirometry mean 3, 4 years ago	No evidence that COVID-19 results in impaired spirometric lung function in a population-based sample of young, healthy adults with mild-to-moderate disease
Pulmonary function and persistent clinical symptoms in children and their parents 12 months after mild SARS-CoV-2 infection [12]	Bode *et al*.	182	53 children 4–14 years, 34 ado-lescents 14–25 years, 95 adults > 25 years	2022	25% with persistent dyspea, 12 months after COVID-19	Spirometry values did not significantly differ between the particular subgroups of the cohort (adults, adolescents, children; infected and noninfected individuals)
Comparison of pulmonary function test, diffusion capacity, blood gas analysis and CT scan in patients with and without persistent respiratory symptoms following COVID-19 [15]	Lehman *et al*.	135	20–90	2022	Long lasting symptoms mean 85 days after COVID-19	Compared to asymptomatic patients, patients with ongoing symptoms were younger and presented a significant lower FVC, TLC and TLCO SB
Mild-to-moderate COVID-19 impact on the cardiorespiratory fitness in young and middle-aged populations [16]	Back *et al*.	80	18–60	September 2020-March 2021	Patients diagnosed with COVID-19, without severe signs and symptoms, were evaluated 1 month after the infection	Despite not showing signs and symptoms of severe disease during infection, adult survivors had losses of lung function and cardiorespiratory capacity 1 month after recovery from COVID-19
The investigation of pulmonary function changes of COVID-19 patients in 3 months [17]	Ye *et al*.	56	23–79	2020	Patient hospitalized January-March 2020, 3 months after having been discharged	24 of the 56 patients still had pulmonary dysfunction and all of them had small airway dysfunction
Pulmonary function evaluation after hospital discharge of patients with severe COVID-19 [18]	Polesse *et al*.	41	51 ± 14	2021	15–30 days after discharge	Observed a high prevalence of symptoms, in addition to a significant change in lung function and DLCO, in the postdischarge assessment of patients requiring hospitalization after admission for COVID-19
Pulmonary function 3–5 months after hospital discharge for COVID-19: A single centre cohort study [19]	Krueger *et al*.	257	59–75	2020–2021	Survivors February–December 2020, 3–5 months after COVID-19	Many COVID-19 survivors, especially after a critical disease course, showed pulmonary function sequelae, mainly DLCO impairments, 3–5 months after discharge. Implications of the COVID-19 burden
Lung function and radiological findings 1 year after COVID-19: A prospective follow-up [9]	Tarasso *et al*.	284	60.5 ± 11.9	2021	12 months after COVID-19 for patients hospitalized May–June 2020	Our data suggest that a significant percentage of individuals would develop pulmonary sequelae after COVID 19 pneumonia, regardless of severity of the acute process
Lung function sequelae in COVID-19 patients 3 months after hospital discharge [20]	Sibila *et al*.	172	56.1 ± 19.8	2020	Patients hospitalized March–April 2020, spirometry 3 months after discharge	Evidence of altered pulmonary function at 3 months of follow-up, as defined by values of FEV1, FVC and/or DLCO < 80% of reference. The most frequent abnormality was reduced DLCO (98 patients (57%)), followed by low FEV1 (43 patients (25%)) and low FVC (42 patients (24%))
Lung-function trajectories in COVID-19 survivors after discharge: A 2-year longitudinal cohort study [10]	Zhang *et al*.	288	Adults	2020–2022	COVID-19 survivors over 2 years after infection. The changes of PFTs, the mMRC Dyspnea Scale, 6-min walking test HRQoL	Improvement of PFTs parameters from 6 months to 1 year after infection From 1-year to 2-year follow-up, the PFTs parameters generally decreased, which was not observed to be associated with changes of 6MWD and HRQoL

CT: Computed tomography, FVC: Forced vital capacity, TLC: Total lung capacity, TLCO SB, DLCO: Diffusion capacity of carbon monoxide, PFTs: Pulmonary function tests, mMRC: Modified Medical Research Council, HRQoL: Health-related quality of life, 6MWD: 6-minute walking distance, FEV_1: Forced expiratory volume in 1 s.

improvement in pulmonary function after the 1st month of COVID-19 disease.

Impact of inflammation markers

Elevation in serum inflammatory marker CRP may be indicative of COVID-19 infection severity and mortality and suggested that these parameters may predict COVID-19 severity [13]. Our study resulted no significant change between severity groups and CPR level. D-Dimer is known as important predictor for severity and mortality of COVID-19 [14]. In 15% of the patients recovered from COVID-19, persistent D-dimer elevation was observed after a median of 3 months following COVID-19. These patients had experienced a more severe COVID and still presented more frequently a lower mean pO_2 [13]. Our study resulted a significant change among level of D-Dimer and COVID-19 severity characterized by SpO_2 during hospitalization.

Conclusion

The results show that there is minimal change of pulmonary function evaluated by spirometry as pulmonary function test, only in 4 (6.56%) of patients with obstructive patterns in the period of 3–6 months after COVID-19 disease with evidences pulmonary infiltrations in Albanian young adults. Disease severity was significantly correlated with D-Dimer values during hospitalization but not with PCR level, lymphocyte absolute count and BMI, FEV1/FVC (3–6 months) after COVID-19. These patients should undergo further testing evaluate persistence of obstruction and other conditions that may relate COVID-19 disease with bronchial hyper-reactivity in young adults. The possibility of triggered allergic condition after COVID-19 in non-previous allergic patients should be investigated by further studies.

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