Original paper • 10.2478/pneum-2024-0012 • 72 • 2023 • 79-84

Pneumologia

The use of simple pulmonary function tests in the post-COVID-19 pulmonary improvement prediction: lessons from a single-center study

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Abstract

English:

Introduction: *Despite the evolving knowledge about COVID-19 convalescents, there is still not enough data to validate simple methods of identifying the non-improvers. Our objective: to look for bad prognostic factors in long-COVID.*
Methods: *We conducted a prospective observational study among previously hospitalized patients with COVID-19. Individual characteristics were gathered and pulmonary function tests - spirometry and lung transfer for carbon monoxide (TL,CO) – were performed twice, approximately one and three months after hospitalization from COVID-19. Control radiological examinations were repeated and compared at the time of the study.*
Results: *After dividing the study group (30 patients) according to improvement in forced vital capacity (FVC) and/or TL,CO we observed that the forced expiratory volume in the first second (FEV1) acquired from spirometry accurately indicates clinical improvement with the area under the curve (AUC) of 0.892 (95% CI 0.73 – 1). Notable differences were found in estimated total lung capacity (eTLC) and radiological score as well.*
Conclusions: *Our findings suggest that simple spirometry with FEV1 assessment performed in the post-COVID period helps select individuals with impaired recovery that should presumably be referred to a respiratory specialist and pulmonary rehabilitation.*

Keywords

COVID-19 • Long COVID • Post-COVID Conditions • Respiratory Function Tests • Oxygen Inhalation Therapy

Utilizarea testelor simple ale funcției pulmonare în predicția îmbunătățirii pulmonare post-COVID-19: lecții dintr-un studiu intr-un singur centru

Rezumat

Romanian:

Introducere: *În ciuda cunoștințelor în continuă avansare în legătură cu pacienții convalescenți post COVID-19, încă nu există suficiente date pentru a valida metode simple de identificare a pacienților care nu prezintă ameliorare. Obiectivul acestui studiu a fost de a căuta factori prognostici nefavorabili în cazul long-COVID-19.*
Metode: *Am realizat un studiu observațional prospectiv printre pacienții anterior spitalizați cu COVID-19. Caracteristicile individuale au fost colectate, iar teste funcționale pulmonare - spirometrie și TRANSFER PRIN MEMBRANA ALVEOLO-CAPILARĂ A MONOXIDULUI DE CARBON (TLCO) – au fost efectuate de două ori, aproximativ la una și trei luni după spitalizarea din cauza COVID-19. Examinările radiologice de control au fost reluate și comparate în momentul studiului.*
Rezultate: *După împărțirea grupului de studiu (30 de pacienți) în funcție de ameliorarea capacității vitale forțate (FVC) și/sau TLCO am observat că volumul expirator forțat în prima secundă (FEV1) obținut din spirometrie indică în mod precis îmbunătățirea clinică, cu o AUC de 0,892 (95% CI 0,73 – 1). S-au găsit diferențe semnificative și în capacitatea pulmonară totală estimată (eTLC) și scorul radiologic.*

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Concluzii: *Descoperirile noastre sugerează că spirometria simplă cu evaluarea FEV1 efectuată în perioada post-COVID ajută la identificarea persoanelor cu recuperare deficitară, care ar trebui, probabil, să fie trimise la un specialist în boli respiratorii și la reabilitare pulmonară.*

Cuvinte-cheie

COVID-19 • long-COVID-19 • Condiții post-COVID • Teste funcționale respiratorii • Terapie cu inhalare de oxigen

Introduction

Despite the oncoming of viral subtypes associated with milder COVID-19 severity, such as Omicron, the world is still facing SARS-CoV-2 global pandemic. Every disease wave produces thousands of patients, some of whom suffer from persistent symptoms and ventilatory insufficiency. The knowledge about predictive factors is gradually evolving [1] disability, and rehabilitation referral rates after coronavirus disease 2019 (COVID-19) and our study sought to indicate factors describing the adverse prognosis of lower respiratory tract involvement and to establish a simple method of patient evaluation for everyday practice. These factors could aid the decision of selecting individual patients for a respiratory specialist referral.

Methods

This study is a prospective study performed in the Outpatient Pneumology Clinic of The Medical University of Lodz. Thirty patients were recruited between December 2020 and May 2021 and everyone was previously discharged from a COVID-related hospitalization. There were two clinical assessments; two to six weeks and three months after the hospitalization. Pulmonary function tests (PFTs) such as (forced) spirometry and TL,CO (single breath method) were performed according to ERS recommendations. The Global Lung Function Initiative 2012 (GLI-2012) reference values were used [2]. All test results were collected with the same type of spirometer with lung transfer for carbon monoxide measurement modality (Lungtest 1000 SB, developed by MES Company). Initial radiological imaging from the time of hospital stay was obtained and control radiological studies were performed. Finally, both scans of every patient were assessed by two individual pneumologists with a minimum of 3-years' experience in lung tomography. The extent of interstitial changes was graduated into the 0-to-4-point scale (0 – no involvement; 1 – less than 25% of lung fields overall; 2 – 25% to 50%; 3 – 50% to 75%; 4 more than 75% involvement.

The results were analyzed using the R software for macOS (R Core Team [2016]. R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Continuous data were presented as the mean with SD or median with IQR, depending on the distribution of data. Variables were compared using the unpaired Student's t-test, Welch t-test or the Wilcoxon rank-sum test with continuity correction, depending on data normality and homogeneity of variance. The AUC-ROC was presented as the result and 95% CI. An AUC greater than 0.9 was considered excellent; 0.8 to 0.9, very good; 0.7 to 0.8, good; 0.6 to 0.7, average; and below 0.6, poor.

All study procedures were consistent with the tenets of the Declaration of Helsinki. All patients provided written informed consent for participation in the study. The study procedures were approved by the Bioethical Committee of the Medical University of Lodz [approval No. RNN/58/21/KE].

Results

The mean age was 55 ± 11 years and 76% were men (23/30). Most of the participants were overweight with a mean BMI of 28.85 ± 5.12 and with a median cigarette consumption of 15 [8-30] packyears in the past. 28/30 required oxygen administration, 9/30 high flow nasal oxygen cannula (HFNOT) and 4/30 non-invasive positive airway pressure support (NIV). Regarding pharmacotherapy 29/30 was administered with an antibiotic, 9/30 remdesivir, 5/30 tocilizumab and 5/30 convalescent plasma. Initial lung involvement was 3 [2-4] on a four-point scale. None of the patients required mechanical ventilation and neither of them was treated in the ICU. Previous disease burdens were: 14/30 hypertension, 10/30 obesity, 4/30 heart failure, 4/30 diabetes mellitus, 5/30 asthma and 2/30 atrial fibrillation.

Because TL,CO and FVC emerged as important prognostic factors from previous research [3], our study group was divided into improvement and non-improvement subgroups with the improvement criterium of either ≥10% rise in FVC or ≥15% rise in TL,CO. Subsequently, we searched for statistically important deviations between improvers and non-improvers. The results show that selected subgroups differ in the values of measured FEV_1 and TLC (estimated from TL,CO test). FEV_1 presented with great accuracy according to clinical improvement prediction with AUC 0.892 (95% CI 0.73 – 1; Figure 1). Statistically significant results are shown in Table 1.

Furthermore, patients with no clinical improvement in the study were previously hospitalized longer with a mean time of 29.9 [15-48] days compared to 12.4 [7-14] days in the improvement group (p=0.008). The extent of initial computed tomography changes on a 0-4 scale was higher with a median of 4 [3-4] in the non-improvement and 2 [1-3] in the improvement group (p=0.008); control studies after approximately 3 months did not change significantly in the non-improvement group reaching 4 [3-4] vs 1 point [1-2] (p=0.00002), respectively. The necessity of high-flow nasal oxygen therapy during hospitalization is undoubtedly associated with a deteriorated recovery (p=0.03).

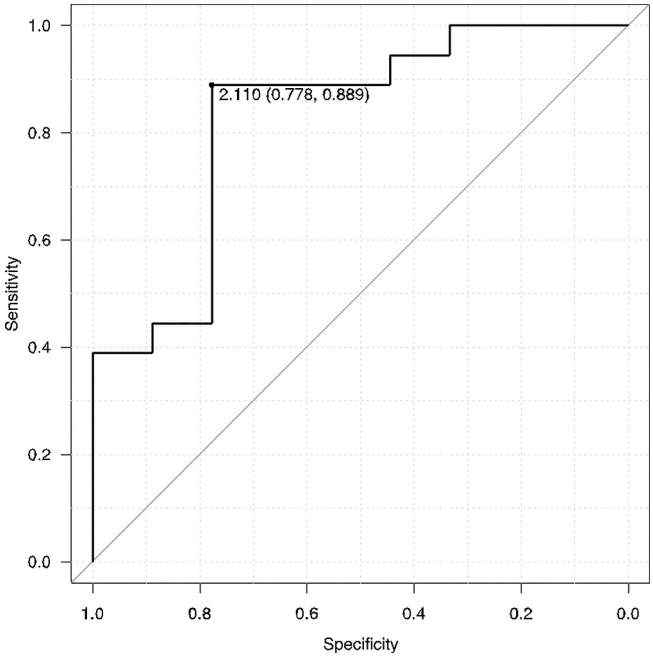

Figure 1. A receiver operating characteristic (ROC) curve for forced expiratory volume in the first second (FEV1) is expressed as the percent of the reference value.

Table 1. Pulmonary function tests with their mean values in the improvement and non-improvement groups.

Parameter	Non-improvement	Improvement	p-value
FEV_1 I, L, median [IQR]	2.04 [1.53-2.06]	3.11 [2.34-4.06]	p=0.007
FEV_1 I, %, median [IQR]	59.89 [46-74]	87.28 [76.25-97.25]	p=0.0003
FEV_1 II, L, median [IQR]	2.3 [1.94-2.51]	3.26 [2.58-3.96]	p=0.004
FEV_1 II, %, median [IQR]	69.1 [56.75-79]	90.22 [85-99]	p=0.0002
FEV_1 Area under the curve	0.89 [95% CI 0.73 – 1]		
FVC I, L, median [IQR]	2.44 [1.88-2.44]	3.82 [2.8-4.9]	p=0.008
FVC I, %, median [IQR]	56.11 [39-73]	84.44 [75.25-92]	p=0.0003
FVC II, L, median [IQR]	2.69 [2.23-2.93]	4.05 [3.13-4.85]	p=0.002
FVC II, %, median [IQR]	62.7 [52-71]	88.11 [79.75-98.75]	P=0.00001
FVC Area under the curve	0.85 (95% CI 0.68 – 1)		
TLC I, L, median [IQR]	4.33 [3.44-4.96]	5.7 [4.61-6.86]	p=0.02
TLC I, %, median [IQR]	60.78 [52-74]	89.56 [77.5-98]	p=0.003
TLC II, L, median [IQR]	4.43 [3.89-5.28]	5.77 [4.78-7.01]	p=0.02
TLC II, %, median [IQR]	75.6 [62.5-81.75]	93 [81-103]	p=0.008
TL,CO I, mL/min/mm Hg, median [IQR]	4.71 [3.08-5.37]	6.96 [5.68-9.34]	p=0.05
TL,CO I, %, median [IQR]	57.38 [44.75-57.25]	80.11 [68.5-96]	p=0.005
TL,CO II, mL/min/mm Hg, median [IQR]	5.66 [3.89-6.43]	8.01 [5.97-10.31]	p=0.03
TL,CO II, %, median [IQR]	68.9 [53-73.5]	90% [76-99.75]	p=0.03
TL,CO, Area under the curve	0.74 (95% CI 0.49 - 0.98)		

TLC – estimated total lung capacity, FEV_1 – forced expiratory volume in the first second, FVC – forced vital capacity, TL,CO - lung transfer for carbon monoxide.

Discussion

Our results suggest that FEV1 measured two to six weeks after hospital discharge from the acute COVID 19 is efficient and specific for pulmonary improvement prediction defined as 15% TL,CO or 10% FVC rise during a further 2-month observation time. It is especially important as FEV1 is acquired from a simply forced spirometry maneuver which is widely performed in general practitioners' offices in many countries.

Unfortunately, it is difficult to compare our original results with existing research data. Most studies concerning pulmonary function testing performed only singular measurements, without association with future individual outcomes. Many authors did not deliver precise spirometry results and they divided abnormalities into obstructive and restrictive patterns, the second of which is most likely associated with symmetrically decreased FEV1 and FVC. Accordingly, the proper timing of pulmonary testing is not known; most data come from pulmonary function tests executed 3 months after COVID 19. "After" is a key matter as part of the studies start to count the time from the onset of symptoms or the positive test for SARS-CoV-2, while others perform it from the end of hospitalization or isolation. European Respiratory Society declared that "the long-term sequelae are not fully understood" and "few data are available on predictors of long-term consequences of COVID-19" in a recently published 2022 long COVID follow-up statement [5]. Clinical recommendations remain descriptive, where published results are confronted with expert opinion; there is no evidence grading up to this day.

One of the comprehensive metanalysis [6] including 15 studies with a follow-up period in a range of 1-6 months showed that abnormal pulmonary function tests (PFTs) were present in 44.3% of the group of 1359 patients; with impaired carbon oxide lung transfer as the most frequently observed finding in 34.8%, and restrictive or obstructive patterns in 16.4% and 7.7%, respectively. Guo et al. [4] managed to collect and categorize studies according to time post-discharge; though they did not acquire FEV1 data. Among 886 participants after spirometry - 10% presented FVC impairment; among 1575 TL,CO -tested participants, 48% presented TL,CO below 80% of the normal range. A smaller systematic review including 7 studies and 380 patients estimated the occurrence of altered lung transfer for CO, restrictive and obstructive patterns to be 39%, 15%, and 7%, respectively [7]. Lorent et al compared PFTs results of 226 hospitalized patients [8]; while 3 months post-discharge there were 10% with spirometric abnormalities, at 12 months' timeline the results of FEV1 improved from 7.1% to 11% and FVC from 4.5% to 7.8%. Studies concerning smaller groups like that from Johnsen et al. [9] emphasize that 68% of patients had reduced lung function based on FEV1 or TL,CO. In the abovementioned studies, the lowered FEV1 criterium was often less than 80% of the predicted value without taking the z-score and percentile into consideration, and many study participants were not hospitalized or did not require oxygen therapy at all; both factors can significantly alter the study results.

A few factors associated with worse PFTs emerge from published research. These are e.g.: the ICU admission [10], mechanical ventilation [11], ARDS diagnosis [12], pO2/FiO2 ratio below 200 during hospitalization [13], number of days on oxygen therapy [14], maximum inspired positive airway pressure [15], maximum inspired FiO2 [15], length of stay [16], female sex [17],[10], asthma [18], COPD [11],[10], chronic kidney disease [10], preexisting immunosuppression [11], SARS-CoV-2 IgG titer at 4 months [11], lower serum lactate dehydrogenase [19], persistent HRCT changes at 12 months [17]. The severity of COVID 19 pneumonia is divided differently by various authors; nevertheless, PFTs among patients with severe/critical pneumonia more often indicate impaired TL,CO [11],[19],[20], sometimes alongside other parameters like FEV1, FVC and TLC affected simultaneously [11]. It brings into consideration the hypothesis of whether FEV1 can be used to select individuals with non-resolving post-COVID interstitial lung disease.

Surprisingly, the symptomatology of the patients does not always follow the results of PFTs. On the one hand, FEV1 and TL,CO values seem to correlate with mMRC scores and health-related quality of life, especially physical functioning domain [20]. There are conflicting and confusing results suggesting no significant difference in PFTs when comparing patients with persisting long COVID-19-related symptoms and asymptomatic ones [11]. While even more than one-fourth of subjects, who recovered from hospitalized COVID-19 may present with exercise ventilatory insufficiency on overall [21], the exercise capacity at 3 months after discharge appears not to be significantly different depending on the initial severity of the disease [22] and it requires further explanation in the research.

As an encore to our results, we show that the requirement of high-flow nasal oxygen therapy (HFNOT) uses in the course of acute disease, worse initial CT score and length of hospital stay are factors that closely correlate with poor pulmonary function improvement. In the ambitious analysis from China, 390 patients were qualified for pulmonary function tests (PFTs) and chest high resolution computed tomography (HRCT) approximately 5 months from discharge [23] and the odds ratio for TL,CO impairment was much higher in patients provided with supplemental oxygen during hospitalization, HFNOT included. The disease severity, initial CT score and oxygen dependence are related to a higher dyspnea score [14] at the 12-week follow-up and the increased total CT score [14],[23] while survivors receiving HFNOT, NIV or both are more likely to have abnormal HRCT at 12 months as well [17]. These data remain consistent with our findings and logic.

Our study has some important limitations, most importantly the group size and its heterogeneity, determining its character as a hypothesis-generating pilot study and should be reproduced in a more powered size sample. Nevertheless, we believe that it might once more point researchers' attention to the importance of widely available spirometry. Our group also managed to perform PFTs twice, while a few observational studies failed to prospectively investigate lung function.

Finally, we are aware that disease progression is a complex process and such a simple parameter as FEV1 is only one of the possible elements in this context. However, we believe our pilot study has the potential to open the discussion and our results can be reproduced in a bigger sample and the broad context of clinical parameters.

To sum up, FEV1 arose in our study group as an important prognostic factor that could help to guide the post-COVID care, while, on the other hand, the extension of lung involvement during hospitalization and oxygen dependency both correlate with persistent CT abnormalities and PFTs alterations in the follow-up [11],[12],[15],[17], [24],[25],[26],[27].

Conclusions

This paper sought to find factors associated with long-term impaired respiratory function among COVID convalescents. When evaluating a post-COVID patient in general practice, it is important to perform spirometry (with FEV1 and FVC) and measure the actual lung transfer for carbon monoxide. Additionally, it is worthwhile to consider the duration of hospitalization, the use of HFNOT and the initial CT score. This data can highlight patients requiring prolonged pneumologist care and those that should obligatorily undergo pneumological rehabilitation.

Funding

None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

All patients provided written informed consent for participation in the study. The study procedures were approved by the Bioethical Committee of the Medical University of Lodz [approval No. RNN/58/21/KE].

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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