



Early View

Editorial

Jutant *et al.* “Respiratory symptoms and radiologic findings in post-acute COVID-19 syndrome” For ERJ Open 12-2021

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Editorial accompanying

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For ERJ Open 12-2021

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Puzzling persisting pulmonary symptoms after COVID-19 infection

The COVID-19 pandemic has held the world in its grip for the past two years, and with the appearance of new variants demonstrating increasing immune-evasion the end of this pandemic seems currently not in sight. Apart from the ongoing pandemic of acute COVID-19, data is mounting regarding the *subsequent* pandemic of persisting signs and symptoms post-acute COVID-19 infection (1). These sequelae are currently termed post-COVID-19 condition, by WHO consensus definition concerning symptoms present 3 months beyond the onset of COVID-19, persisting for at least 2 months, that may fluctuate and relapse over time and cannot be explained by an alternative diagnosis (2). The most frequent post-COVID symptoms reported include fatigue, shortness of breath, muscle problems and cognitive dysfunction (3, 4).

In this issue of ERJ Open, a follow-up analysis of the COMEBAC study was published (5, 6). They report on the 4-month outcomes of patients after acute COVID-19 infection and zoom in onto persistent respiratory symptoms. A relevant topic; considering this being one of the most prevalent persistent symptoms after COVID-19.

The COMEBAC study was a study on 478 COVID-19 survivors after hospitalization that were followed-up by telephone interview initially and of whom 177 (out of 294 eligible patients) consecutively underwent comprehensive out-patient clinic evaluation when they either still experienced symptoms or had been admitted to the intensive care unit during hospitalization.

The comprehensive evaluation consisted of history, physical examination, a number of patient reported outcomes (on quality of life, fatigue, dyspnea, anxiety/depression and more), pulmonary function tests, high resolution chest computed tomography (HR-CT) and echocardiography in case of cardiac symptoms.

The primary analysis revealed considerable residual complaints in patients that were interviewed: at least half of the patients still experience one or more residual symptom, most often fatigue (31%), cognitive dysfunction (21%) and persisting dyspnea (16%). In the smaller more extensively assessed group after ICU admission or with persistent complaints, these numbers were inherently even larger. Importantly: quality of life was reduced, particularly in the domain physical role functioning (related to performing daily activities and tasks) thus indicating the significant effects of the hospitalization due to COVID-19 on longer term everyday functioning.

The current follow-up study aims were to 1. Determine the prevalence of persistent respiratory symptoms and describe the characteristics and pulmonary function of patients with persisting respiratory symptoms, 2. Determine the prevalence of fibrotic lung lesions and describe the characteristics and pulmonary function of patients with fibrotic lung lesions and to finally 3. Assess the relationships between the respiratory symptoms after hospitalization for COVID-19.

The respiratory symptoms were present in 44% of the selection of patients that underwent comprehensive evaluation. New onset dyspnea was associated with new-onset cough. Interestingly, there were no large differences in pulmonary function tests between patients in patients with and without dyspnea. Whereas 19% of the patients had fibrotic lesions on chest HR-CT, this was not different for patients with and without new-onset dyspnea. Quite a significant number of these patients were considered to have complaints of “functional respiratory complaints” based on a high score (>22) on the Nijmegen questionnaire.

Fibrotic lesions were more frequent in older patients, in patients that had been admitted to the ICU, had had acute pulmonary embolism and had longer duration of mechanical ventilation (in unadjusted analyses). Fibrotic lesions were associated with reduction in pulmonary volumes and diffusion capacity, but no difference was found in new-onset dyspnea score and six-minute walk distance between patients with and without fibrotic lesions.

Overall, the vast majority (51/78) of the patients with new-onset dyspnea had no diffusion impairment or fibrotic lesions on chest HR-CT. The combination of dyspnea, diffusion impairment and fibrotic lesions was rare, all in all indicating the lack of a relationship. The authors conclude that the etiology of the persisting respiratory complaints remains unclear, and speculate that the dyspnea may be multifactorial, including lung sequelae, vascular sequelae after pulmonary embolism, dysfunctional breathing, muscular deconditioning and unknown causes.

The current study adds to the increasing body of literature on mid- and longer term outcomes after hospitalization for COVID-19. Persisting pulmonary symptoms are a large problem: at seven months after discharge (exertional) dyspnea was reported by 55% of the patients and this exhibited limitations on daily living activities (7). It was hypothesized that residual abnormalities on the lungs may be debited to these complaints, as residual lung abnormalities were present in almost 50% of the patients at 3 months after discharge in a meta-analysis (8).

With more recent studies and longer-term follow-up data it however becomes increasingly clear that although pulmonary function impairment is common after hospitalization for COVID-19, this gradually recovers towards normal values over time up to one year after discharge (9, 10). Likewise, radiological abnormalities gradually improve over time and are rarely severe (11). Despite the improvement in pulmonary function over time, more and more studies indicate that patient-reported symptoms do not improve (3, 12).

The current study of Jutant et. al further support the increasingly evident discrepancy between experienced symptoms and underlying pulmonary injury, thus motivating further research to identify the underlying mechanisms of persistent pulmonary symptoms.

Several studies using cardio pulmonary exercise testing (CPET) have been performed in this light. A recent study is of particular interest: using serial CPET, cardiac magnetic resonance imaging (CMR), pulmonary function and symptoms found that longitudinal improvement in CMR and CPET parameters did not associate with improvement in cardiopulmonary symptoms and no correlation

between symptoms and pulmonary function (13). Thus, the pathophysiological basis for persistent pulmonary symptoms remains unclear and alternative mechanisms for ongoing symptoms should be considered.

We are now two years into the pandemic and know what not causes the dyspnea, it is time to find to answer to what is. As the usual suspects have been excluded, this includes looking for answers outside of the chest. Brain imaging studies have found clues of areas with hypometabolism in relation to patients' symptoms (14). A completely different theory regarding the persistent pulmonary symptoms thus is the possibility of persistent low-grade brainstem dysfunction affecting the brain's respiratory neuron circuits (15). Also, post-viral ongoing immunologic aberrations could be debit to long-term complaints (16). More in dept research in such fields is desirable, as the jury is still out on the causes of persistent pulmonary symptoms after COVID-19 infection, and a solution is most likely to be found when the causes are known.

Conflicts of interest

All authors declare no conflicts of interest.

References

1. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ*. 2021:n1648.
2. WHO. [Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1]
3. Bek LM, Berentschot JC, Heijnenbroek-Kal MH, Huijts S, Van Genderen ME, Vlake JH, et al. Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *MedRxiv*, Preprint, version posted 13-12-2021, accessed 21-12-2021, DOI: <https://doi.org/10.1101/2021.12.11.21267652>
4. Ayoubkhani D. Statistical bulletin Office for National Statistics Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 Estimates of the prevalence of self-reported "long COVID", and the duration of ongoing symptoms following confirmed coronavirus infection, using UK Coronavirus (COVID-19) Infection Survey April 2021 [Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021>]
5. Jutant et al. Je. Respiratory Symptoms and Radiologic Findings in Post-Acute COVID-19 Syndrome. *ERJ Open Research*. 2021.
6. Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, et al. Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. *JAMA*. 2021;325(15):1525.
7. Fernández-De-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Palacios-Ceña M, Rodríguez-Jiménez J, De-La-Llave-Rincón AI, et al. Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. *Respiration*. 2021:1-10.
8. So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. *BMC Pulmonary Medicine*. 2021;21(1).
9. Hellemons ME, Huijts S, Bek L, Berentschot J, Nakshbandi G, Schurink CAM, et al. Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc*. 2021.
10. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *The Lancet Respiratory Medicine*. 2021;9(7):747-54.
11. Pan F, Yang L, Liang B, Ye T, Li L, Li L, et al. Chest CT Patterns from Diagnosis to 1 Year of Follow-up in COVID-19. *Radiology*. 2021.
12. Shah AS, Ryu MH, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, et al. Changes in pulmonary function and patient-reported outcomes during COVID-19 recovery: a longitudinal, prospective cohort study. *ERJ Open Research*. 2021;7(3):00243-2021.
13. Cassar MP, Tunnicliffe EM, Petousi N, Lewandowski AJ, Xie C, Mahmood M, et al. Symptom Persistence Despite Improvement in Cardiopulmonary Health – Insights from longitudinal CMR, CPET and lung function testing post-COVID-19. *EClinicalMedicine*. 2021;41:101159.
14. Rudroff T, Workman CD, Ponto LLB. 18F-FDG-PET Imaging for Post-COVID-19 Brain and Skeletal Muscle Alterations. *Viruses*. 2021;13(11):2283.
15. Yong SJ. Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. *ACS Chemical Neuroscience*. 2021;12(4):573-80.
16. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nature Medicine*. 2021;27(4):601-15.