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# Puzzling persisting symptoms after COVID-19

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There is an increasingly evident discrepancy between experienced symptoms and underlying pulmonary injury, thus motivating further research to identify the underlying mechanisms of persistent pulmonary symptoms after #COVID19 <https://bit.ly/33nyUxI>

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The coronavirus disease 2019 (COVID-19) pandemic has held the world in its grip for the past 2 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 are 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 a World Health Organization consensus definition concerning symptoms present 3 months beyond the onset of COVID-19, persisting for  $\geq 2$  months, that may fluctuate and relapse over time, and cannot be explained by an alternative diagnosis [2]. The most frequent post-COVID-19 symptoms reported include fatigue, shortness of breath, muscle problems and cognitive dysfunction [3, 4].

In this issue of *ERJ Open Research*, JUTANT *et al.* [5] present a follow-up analysis of the COMEBAC study [6]. They reported on the 4-month outcomes of patients after acute COVID-19 infection and focus on persistent respiratory symptoms. This is a relevant focus considering that it is one of the most prevalent persistent symptoms after COVID-19.

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

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

The primary analysis revealed considerable residual complaints in patients who were interviewed: at least half of the patients still experienced one or more residual symptom, most often fatigue (31%), cognitive dysfunction (21%) and persisting dyspnoea (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 hospitalisation due to COVID-19 on longer-term everyday functioning.

The current follow-up study aims of JUTANT *et al.* [5] 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 finally, 3) assess the relationships between the respiratory symptoms after hospitalisation for COVID-19.



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

Fibrotic lesions were more frequent in older patients, in patients who had been admitted to the ICU, in patients that had acute pulmonary embolism, and in patients that 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 dyspnoea score and 6-min walk distance between patients with and without fibrotic lesions.

Overall, the vast majority (51 out of 78) of the patients with new-onset dyspnoea had no diffusion impairment or fibrotic lesions on chest HRCT. The combination of dyspnoea, diffusion impairment and fibrotic lesions was rare, all in all, indicating the lack of a relationship. The authors conclude that the aetiology of the persisting respiratory complaints remains unclear, and speculate that the dyspnoea 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 hospitalisation for COVID-19. Persisting pulmonary symptoms are a large problem: at 7 months after discharge, (exertional) dyspnoea was reported by 55% of the patients and this exhibited limitations on daily living activities [7]. It was hypothesised that the residual abnormalities on the lungs may be the cause of these complaints, as residual lung abnormalities were present in almost 50% of the patients 3 months after discharge in a meta-analysis [8].

With more recent studies and longer-term follow-up data, however, it becomes increasingly clear that although pulmonary function impairment is common after hospitalisation for COVID-19, this gradually recovers towards normal values up to 1 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 by JUTANT *et al.* [5] further supports 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 cardiopulmonary 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 showed that longitudinal improvement in CMR and CPET parameters did not associate with improvement in cardiopulmonary symptoms, and no correlation between symptoms and pulmonary function was seen [13]. Thus, the pathophysiological basis for persistent pulmonary symptoms remains unclear and alternative mechanisms for ongoing symptoms should be considered.

We are now 2 years into the pandemic and know what does not cause the dyspnoea; it is time to find out what does. As the usual suspects have been excluded, this includes looking for answers outside the chest. Brain imaging studies have found clues in areas with hypometabolism in relation to patients' symptoms [14]; a completely different hypothesis regarding the persistent pulmonary symptoms is thus the possibility of persistent, low-grade brainstem dysfunction affecting the respiratory neurone circuits [15]. In addition, post-viral, ongoing immunological aberrations could be the cause of long-term complaints [16]. More in-depth 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 those causes are known.

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