


SHORT REPORT

Open Access



# Heterogeneity of post-COVID impairment: interim analysis of a prospective study from Czechia

Mikulas Skala<sup>1,2</sup>, Michal Svoboda<sup>3</sup>, Michal Kopecky<sup>1,2</sup>, Eva Kocova<sup>2,4</sup>, Martin HyrsI<sup>4</sup>, Michal Homolac<sup>5</sup>, Viktor Chrobok<sup>2,5</sup>, Pavel Bostik<sup>2,6,7</sup>, Miroslav Fajfr<sup>6</sup>, Petr Prasil<sup>2,8</sup>, Stanislav Plisek<sup>2,8</sup>, Radek Sleha<sup>7</sup> and Vladimir Koblizek<sup>1,2\*</sup> 

## Abstract

We stratified post-COVID patients into four newly established clinical groups based on the presence or absence of at least one subjective respiratory symptom and at least one objective sign of pulmonary involvement. Nearly half of outpatients and one third of hospitalized post-COVID patients had objective signs of pulmonary involvement without accompanying subjective respiratory symptoms three months after diagnosis.

**Keywords:** Post-COVID, Symptom, Lung function, 6-min Walk Test, Computer tomography

By 29nd January 2021, 100 million cases and 2.1 million deaths due to COVID-19 occurred globally [1]. Similar to after the SARS epidemic, a small proportion of patients who recovered from COVID-19 experience sequelae of various severity [2, 3]. Considering the global spread of the disease and the chronic health impact it not seldom imposes, it is meaningful to develop a simple and practicable tool to stratify post-COVID-19 patients.

In spring and summer 2020, the incidence of COVID-19 in the Czech Republic was significantly lower than in some other European countries. The Hradec Kralove District (551.000 inhabitants) had just 182 SARS-CoV-2 PCR-positive patients, of which 24 were hospitalized and three died. All survivors above 18 years of age were offered participation in our one-year prospective observational study. A total of 102 patients were included in the present analysis (i.e. 57% of all positive cases in our district). Of these, 15 were hospitalized (71% of all

hospitalized) and 87 treated as outpatients (55% of all outpatients). The first follow-up took place 3 months after the COVID-19 diagnosis. In winter 2020–2021, we continued our prospective data collection to elucidate the real trajectory of patients who recovered from acute COVID-19. Currently, more than 400 patients are followed. We are writing this letter to present the first preliminary results and to introduce a proposal for a novel simple stratification of post-COVID patients to navigate their follow-up care.

We use patients' demographics and personal history as documented in hospital records. Subjective respiratory and extra-pulmonary symptoms were assessed with a structured physician–patient interview using validated questionnaires assessing respiratory symptoms, anxiety, depression and posttraumatic syndrome. Functional pulmonary examination, 6-min Walk Test (6-MWT) and chest high resolution computer tomography (HRCT) is used to assess objective signs of pulmonary involvement (PI) in all patients. Laboratory results including antibodies against SARS-CoV-2, cellular immunity parameters, C-reactive protein (CRP), and D-dimers are also recorded. HRCTs are assessed by a multidisciplinary

\*Correspondence: vladimir.koblizek@fnhk.cz

<sup>1</sup> Department of Pneumology, University Hospital Hradec Kralove, Hradec Kralove, Czechia

Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

committee. Only the HRCT findings that cannot be explained with patient personal history and have not been seen in a control cohort (patients examined with chest HRCT following admission to our hospital Emergency department for suspected pulmonary embolization) are considered as pathological. The control cohort is comparable to the study group with respect to gender, age, BMI, any respiratory comorbidities and nicotine exposure.

A total of 102 patients were included in the study between June and October 2020 and had their first follow-up examination three months from the COVID-19 diagnosis. The mean age was 46.7 years, there were slightly more women (55 women) and the majority of patients (75%) had no comorbidities. The majority of patients were symptomatic at the time they were PCR-positive ( $n=99$ , i.e. 97%). Three months from the onset of the disease, 56 (55%) patients had persistent subjective symptoms they did not have prior to COVID-19. Respiratory symptoms were reported by 35% of patients (23% dyspnoea, 14% cough, 13% pain/chest discomfort), non-pulmonary symptoms mostly included fatigue (22%) and anosmia (21%) more in Table 1. Pulmonary examination most frequently showed reduced pulmonary diffusion (40%). Desaturation during 6-MWT was seen in 11% of patients. HRCTs showed a pathology with causal association to previous COVID-19 in 47% of patients: air trapping (32%), linear opacity (16%), bronchiectasis (12%), multifocal ground glass opacity (11%), fibrosis (6%), and consolidation (2%). Patients with elevated D-dimers underwent CT angiography; none of them had residual pulmonary emboli. In some patients, laboratory results showed persistent inflammatory response (CRP

elevation in 11%) and increased pro-coagulation activity (D-dimer elevation in 10%).

We stratified post-COVID patients into four groups based on the presence or absence of at least one subjective respiratory symptom and at least one objective sign of PI, i.e. reduction in pulmonary diffusion and/or exertion desaturation of oxygen and/or HRCT pathology with suspected post-COVID aetiology. Group A patients do not have any symptoms or signs of PI. Group B patients have symptoms without objective signs of PI. Group C patients have no symptoms but do have objective signs of PI. Group D patients suffer from symptoms and objective signs of PI. Moreover, to enable a comprehensive evaluation of the data, patients with extra-pulmonary symptoms in each group were additionally marked with letter E. The stratification is detailed in the Fig. 1.

When applied to our study cohort, our post-COVID patient stratification was independent of patient gender, BMI or smoking history, while it correlated with age. In the outpatient cohort ( $n=87$ ) three months post diagnosis, 23% of patients were in group A (no subjective respiratory symptoms and no objective signs of PI), 8% in group B (symptoms with no signs of PI), 46% in group C (no symptoms with signs of PI) and 23% in group D (symptoms and signs of PI). Extra-pulmonary symptoms were reported by 43% of outpatient cohort (added E). In hospitalized patients ( $n=15$ ), the stratification three months after the diagnosis was as follows: A—13%, B—0%, C—33%, D—54% and 67% with added E (Fig. 1).

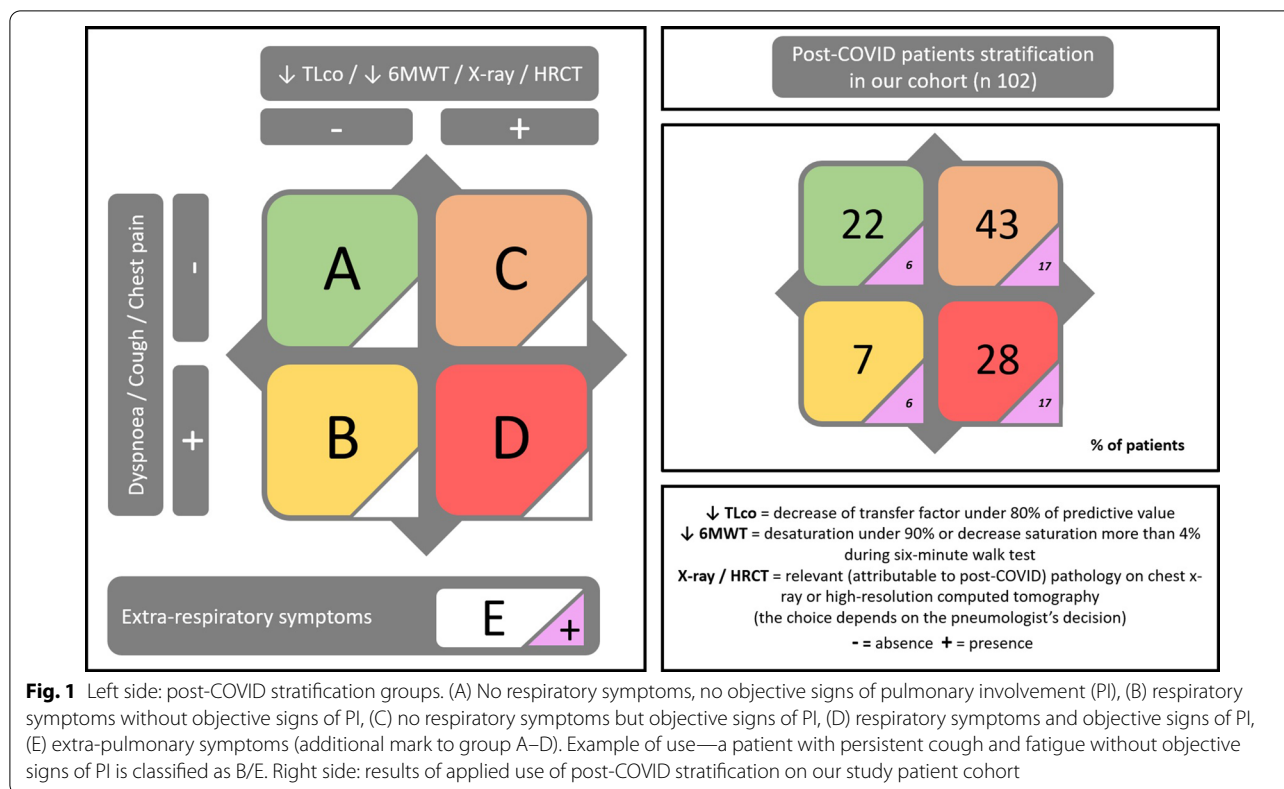
Therefore, the majority of previously hospitalized patients had subjective symptoms and objective signs of PI. Nearly half of outpatients and one third of hospitalized patients had objective signs of PI without accompanying subjective symptoms. Furthermore, in our cohort, there is a statistically significant correlation between the presence of respiratory symptoms (CAT, mMRC; groups B and D) and higher level of anxiety (Beck) and depression (Zung). We have observed a clear trend towards more frequent hyper-inflammatory and hyper-coagulation status in Groups C and D.

With the ongoing pandemic, more data on chronic impact of COVID-19 called post-COVID are available. Even though pulmonary tissue is the predominant system involved during the acute phase of COVID-19 and the available data suggest that, in addition to fatigue, respiratory symptoms are the main post-COVID symptoms, the chronic consequences might involve multiple organs [4–6]. In patients hospitalized for COVID-19, respiratory sequelae are common after four months from discharge [7] and patients with more severe disease course during hospitalization have more severe pulmonary injury [8]. The recently presented data from a large post-COVID cohort from Italy showed fatigue and breathless to be the

**Table 1** Extra-pulmonary symptoms three months after COVID (N = 102)

Extra-pulmonary symptoms	n (%)
Fatigue	22 (21.6%)
Loss of smell	21 (20.6%)
Loss of taste	7 (6.9%)
Cephalgia	6 (5.9%)
Memory impairment	5 (4.9%)
Arthralgia/myalgia	4 (3.9%)
Conjunctivitis	2 (2.0%)
Dyspepsia	2 (2.0%)
Subfebrile	1 (1.0%)
Others	14 (13.7%)
At least one non-pulmonary symptom	47 (46.1%)

Table provides an overview of all extra-pulmonary symptoms of patients three months after the diagnosis of COVID-19. Some patients reported more than one symptom



most common post-COVID symptoms [9]. On the other hand, many patients report physical symptoms without having any lasting physiological injury. [10].

However, other organ systems must not be overlooked and it is likely that other non-pulmonary complications/sequelae of COVID-19 will be seen more frequently. In addition to assessing respiratory symptoms and objective signs of PI, our study will continue to also gather data on extra-pulmonary signs of post-COVID and the extra-pulmonary signs are also included in the proposed stratification.

The National Institute for Health and Care Excellence defines post-COVID syndrome as a group of signs and symptoms that continue for 12 weeks or longer from the disease onset [6]. According to another definition, the post-COVID-19 patients report „lasting effects of the infection “ or they have usual symptoms persisting significantly longer than expected [6, 7, 11]. Various tools to detect post-COVID sequelae are being developed based on patient-reported, subjective, symptoms, e.g. the Post-COVID Functional Status (PCFS) scale [12]. Structural post-COVID PI is seen mainly in hospitalized patients [13]. Some authors newly suggest that the phenomenon of symptomatic post-COVID may not be directly attributable to the post-viral impairment and, instead, these may be biopsychosocial effects of COVID-19 [14].

Our data mainly advert to the patients who have no respiratory symptoms three months post-COVID-19 diagnosis but have objective signs of PI (not explained through their personal history). Therefore, these patients (Group C patients in the proposed stratification) may not fulfil the aforementioned post-COVID definitions focusing on the presence of subjective symptoms. This group can frequently be seen among COVID-19 outpatients.

The small single-centre patient sample size certainly needs to be recognized as a limitation of the present data. It should, nevertheless, be acknowledged that the cohort included more than 50% of all post-COVID patients from the first wave of pandemic in spring 2020. We are also aware that the proposed stratification tool might be more suitable for healthcare systems with wide availability of pulmonary diffusion measurement in the care of post-COVID patients. Our data are also limited by the lack of baseline pre-COVID HRCTs in outpatients with mild course of the disease. Moreover, in the absence of sufficient data, it is uncertain, whether the PI we observed can be considered as a COVID-19-specific viral pneumonia in terms of long-term radiological changes and their clinical relevance [15]. Further follow-up in these patients is required to determine whether the observed changes are reversible.

The clinical relevance of our proposed post-COVID patient clinical stratification tool must, understandably, be validated and possibly corrected using data from other centres. This correspondence is an invitation to such a joint activity.

## Conclusion

Considering the continuation of the global COVID-19 pandemic and the growing data on its chronic impact, there is a clear need for a simple clinical tool to triage post-COVID patients and organize follow-up medical care. We established a new tool for rapid stratification of post-COVID patients based on a targeted search for respiratory and extra-pulmonary symptoms and assessment of objective signs of pulmonary involvement. When applied to our patient cohort comprising 57% of all positive „spring 2020 cases“, this stratification identified a high-risk group of patients with post-COVID syndrome and objective pulmonary involvement (group D), a group with post-COVID syndrome but without objective pathology (group B) and, importantly, an asymptomatic group with pulmonary involvement (group C). In our opinion, this group (C) warrants increased attention. Even though at present, these patients have no respiratory symptoms, the exertional respiratory insufficiency and/or reduced pulmonary diffusion and/or some of the CT/X-ray findings have a potential to develop into symptomatic progression and permanent damage. This is supported by the clear trend towards more frequent hyper-inflammatory and hyper-coagulation status we observed in these patients (similarly to group D). However, since this group is not meeting the current criteria for post-COVID syndrome based on symptoms only, it might be slipping the attention of health care providers. In addition, our stratification identifies patients requiring care of medical specialities other than pneumologists (the added E group).

## Abbreviations

6-MWT: 6-Min Walk Test; CAT: COPD Assessment Test; CRP: C-reactive protein; HRCT: High resolution computer tomography; mMRC: Modified Medical Research Dyspnoea Scale; PCFS: Post-COVID functional status; PI: Pulmonary involvement; TLco: Transfer factor for carbon monoxide or diffusing capacity for carbon monoxide.

## Acknowledgements

The authors would like to acknowledge the contribution of a medical writer, Dita Engova, MPharm, PhD for editing this manuscript.

## Authors' contributions

MS, MH, MK, EK, MH2, PP collected the data; MF and RS performed the laboratory assessment of blood samples; VK, MS, MS2, VK, VCH, PB, SP performed data analyses and prepared the manuscript. MS, VK, and MK interpreted the

patient data and were a major contributors in writing of the manuscript. All authors read and approved the final manuscript.

## Funding

Supported by MH-CZ DRO (UHHK, 00179906).

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on a reasonable request.

## Declarations

### Ethics approval and consent to participate

A multidisciplinary study approved (20th April 2020) by the Ethics Committee of the University Hospital Hradec Kralove, Czechia (reference number—202005 S01P). All patients signed a written consent.

### Consent for publication

Not applicable.

### Competing interest

The authors declare that they have no competing interests.

### Author details

<sup>1</sup> Department of Pneumology, University Hospital Hradec Kralove, Hradec Kralove, Czechia. <sup>2</sup> Faculty of Medicine in Hradec Kralove, Charles University, Prague, Czechia. <sup>3</sup> Masaryk University Institute of Biostatistics and Analyses, Brno, Czechia. <sup>4</sup> Department of Radiology, University Hospital Hradec Kralove, Hradec Kralove, Czechia. <sup>5</sup> Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Hradec Kralove, Hradec Kralove, Czechia. <sup>6</sup> Institute of Medical Microbiology, University Hospital Hradec Kralove, Hradec Kralove, Czechia. <sup>7</sup> Faculty of Military Health Science Hradec Kralove, University of Defense, Brno, Czechia. <sup>8</sup> Department of Infectious Diseases, University Hospital Hradec Kralove, Hradec Kralove, Czechia.

Received: 16 February 2021 Accepted: 5 April 2021

Published online: 12 April 2021

## References

- Weekly epidemiological update—29 January 2021. <https://www.who.int/publications/m/item/>. Last accessed 29 Jan 2021.
- Ngai JC, Ko FW, Ng SS, et al. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15:543–50. <https://doi.org/10.1111/j.1440-1843.2010.01720.x>.
- Alwan NA. A negative COVID-19 test does not mean recovery. *Nature*. 2020;584:170.
- Eapen MS, Lu W, Gaikwad AV, et al. Endotelial to mesenchymal transition: a precursor to post-COVID-19 interstitial pulmonary fibrosis and vasculature obliteration? *Eur Respir J*. 2020;56:2003167. <https://doi.org/10.1183/13993003.03167-2020>.
- Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. 2020. <https://doi.org/10.1136/thoraxjnl-2020-215818>.
- COVID-19 rapid guideline: managing the long-term effects of COVID-19. <https://www.nice.org.uk/guidance/ng188/resources/>. Last accessed December 2020.
- Bellan M, Soddu D, Balbo PE, et al. Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA Netw Open*. 2021;4(1):e2036142. <https://doi.org/10.1001/jamanetworkopen.2020.36142>.
- Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–32. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8).

9. Venturelli S, Benatti S, Casati M, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect.* 2021;149:E32. <https://doi.org/10.1017/S0950268821000145>.
10. D'Cruz RF, Michael D, Waller MD, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res.* 2021;7(1):00655–2020. <https://doi.org/10.1183/23120541.00655-2020>.
11. Mahase E. COVID-19: What do we know about “long COVID”? *BMJ.* 2020;370:m2815. <https://doi.org/10.1136/bmj.m2815>.
12. Klok FA, Boon GJAM, Barco S, et al. The post-COVID-19 functional status scale. A tool to measure functional status over time after COVID-19. *Eur Respir J.* 2020;56:2001494. <https://doi.org/10.1016/j.erspc.2020.01.0494>.
13. Rogliani P, Calzetta L, Coppola A, et al. Are there pulmonary sequelae in patients recovering from COVID-19? *Respir Res.* 2020;21:286. <https://doi.org/10.1186/s12931-020-01550-6>.
14. Sykes DL, Holdsworth L, Jawad N, et al. Post-COVID-19 symptom burden: what is long-COVID and how should we manage it? *Lung.* 2021. <https://doi.org/10.1007/s00408-021-00423-z>.
15. Li P, Zhang JF, Xia XD, et al. Serial evaluation of high-resolution CT findings in patients with pneumonia in novel swine-origin influenza A (H1N1) virus infection. *Br J Radiol.* 2012;85(1014):729–35. <https://doi.org/10.1259/bjr/85580974>.

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

