



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Commentary

Long COVID-19—it's not over until?

Dana Yelin^{1,2,*}, Ili Margalit^{1,2}, Dafna Yahav^{1,2}, Michael Runold³, Judith Bruchfeld^{4,5}¹ Infectious Diseases Unit, Rabin Medical Centre, Beilinson Hospital, Petah-Tikva, Israel² Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel³ Department of Respiratory Medicine and Allergy Karolinska University Hospital, Stockholm, Sweden⁴ Department of Infectious Diseases, Karolinska University Hospital, Stockholm Sweden⁵ Division of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Article history:

Received 20 October 2020

Received in revised form

29 November 2020

Accepted 1 December 2020

Available online 11 December 2020

Editor: L. Leibovici

Keywords:

Coronavirus disease 2019 survivors

Long COVID-19

Recovery

Severe acute respiratory syndrome

coronavirus 2

Coronavirus disease-2019 (COVID-19) has swept through the world causing profound morbidity and mortality. Health organizations and governments are overwhelmed with the treatment and prevention of the acute disease. Meanwhile, evidence is gathering that surviving the acute disease is not the whole story, and many COVID-19 survivors experience ongoing symptoms and debilitation [1–4].

Recovered individuals continue to complain of a multitude of symptoms for months. Most of the patients will experience at least one symptom during their convalescent period [3–6]. The most prevalent ongoing symptoms are fatigue, dyspnoea, chest pain, joint pain, palpitations, anosmia and dysgeusia, hair loss, cognitive symptoms (memory and attention deficits) and psychosocial distress (loneliness, anxiety, depression and sleep disorders) [1–4] (see Table 1).

In some of the recovered patients, slow recovery is to be expected. Severe COVID-19 necessitates a prolonged intensive care

unit (ICU) stay, and symptoms of 'post-ICU syndrome' are not unique to COVID-19 [7,8]. However, a retrospective study by Carvalho-Schneider *et al.* shows that individuals who have recovered from mild and moderate COVID-19 are also experiencing post-COVID-19 symptoms, sometimes with disabling features and inability to return to their normal life [4]. Similar persistent symptoms have been described following severe acute respiratory syndrome and Middle Eastern respiratory syndrome illnesses, although for the latter it was described in patients who had severe disease [9].

In their study, Carvalho-Schneider *et al.* examined the effects of COVID-19 on a cohort of 150 recovering patients following mostly mild to moderate episodes who were treated as outpatients [4]. Patients were contacted at 30 and 60 days after symptom onset and asked to answer a simple questionnaire regarding their symptoms and general well-being. The study shows that two-thirds of patients reported at least one symptom on both day 30 and day 60, and one-third of patients were feeling as bad or worse on day 60 as they had felt during the acute episode. The most prevalent symptoms were anosmia or ageusia (27.8% on day 30, 22% on day 60), followed by flu-like symptoms (36% on day 30, 21% on day 60). Ongoing symptoms on day 30 were associated with markers of more severe disease such as hospitalization, oxygen therapy and dyspnoea on presentation. Interestingly, the age group associated with ongoing symptoms was 40–60 years. Ongoing symptoms on day 60 retained significance only for hospitalization and the 40–49 years age group. The finding with the most impact was that about 1 in 9 (11%) were still on sick leave at day 60, a significant red flag for ongoing morbidity and disability following non-critical disease. It is important to note that half (75/150) of the cohort were health-care workers. This may be skewing the results either way as health-care workers tend to be (as a group) younger and healthier on the one hand, and more attuned to medical symptoms on the other.

Xiong *et al.* [1] present a similar picture in their study of recovered hospitalized patients from Wuhan. The authors followed patients for a longer period, almost 4 months after symptom onset (median of 97 days following discharge, combined with median length of stay of approximately 2 weeks), showing that up to 50% of

* Corresponding author: Dana Yelin, Infectious Diseases Unit, Rabin Medical Centre, Beilinson Hospital, 39 Jabotinsky Road, Petah-Tikva, 49100, Israel.

E-mail address: dana.yelin@gmail.com (D. Yelin).

Table 1
Long COVID-19: proportions of main symptoms as reported in different cohorts

	Xiong <i>et al.</i> [1]	Carfi <i>et al.</i> [2]	Townsend <i>et al.</i> [3]	Carvalho-Schneider <i>et al.</i> [4]	Dennis <i>et al.</i> [6]
No. of recovered individuals	538	143	128	130	201
Median time of follow up (days)	97 (IQR 95–102) from discharge	60 (SD 14) from COVID-19 onset	72 (IQR: 62–87) from discharge (or from 14 days following the diagnosis for outpatients)	All individuals were evaluated at day 60 from COVID-19 onset	140 (IQR 105–160) from COVID-19 onset
Fatigue	28.3%	53.1%	52.3%	NA	98.0%
Dyspnoea	26.0%	43.4%	NA	7.7%	87.1%
Chest pain	12.3%	21.7%	NA	13.1%	73.1%
Joint pain	7.6%	27.3%	NA	16.3%	78.1%
Palpitations	11.2%	NA	NA	10.9%	NA
Anosmia and disgeusia	NA	NA	NA	22.7%	NA
Hair loss	28.6%	NA	NA	NA	NA
Cognitive symptoms	NA	NA	NA	NA	NA
Psychosocial distress	22.7%	NA	NA	NA	NA

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; NA, not available; SD, standard deviation.

patients still had symptoms at that time period. The most frequent symptoms in this cohort were fatigue and dyspnoea. Another important feature of this study is the use of a control group from the general population under extreme lockdown in Wuhan. This helps to eliminate the psychological effects of the long and mandatory isolation period experienced by people with COVID-19, causing deconditioning, anxiety and depression. The study shows a significant difference between the two groups, and very few, if any, symptoms in the control group in general.

These studies, and several others published so far, have focused on ascertaining that long COVID-19 exists and describing its early subjective features. It should be stated that less than a year has passed since the onset of the pandemic, and data regarding long-COVID pathogenesis, duration and treatments are still limited. The time has now come to shift the focus of ongoing research to several questions [10].

One of the most important questions we need to answer is for how long will the symptoms last? It is clear that there is a spectrum, i.e. some patients will return to their former life sooner than others. However, even 4 months from symptom onset, a substantial proportion of the patients are still suffering, and we still do not have a maximal cap. Will some patients never completely recover? And if so – who? And what will their natural history look like?

Which patients need follow up? Risk factors for long COVID-19 are still pending. Carvalho-Schneider *et al.* have identified some risk factors for having symptoms in general, such as severity of the acute disease and being in the age group of 40–59 years. However, the relatively small cohort size was underpowered for risk factor assessment of the different symptoms. Treating the ‘mixed bag’ of symptoms as a single entity dilutes our ability to discern risk factors for their accrual, as they probably have different mechanisms and aetiologies. Gender, body mass index, co-morbidities, functional status and physical activity before the disease are good candidates for risk factors and need to be explored. In any case, long COVID-19 in individuals with co-morbidities might stem from exacerbation of the co-morbidity itself. Therefore, these patients need close scrutiny. In addition, the findings of Xiong *et al.* raise a point in favour of long-term follow up of recovered patients who are asymptomatic [1]. The incidence of new-onset diabetes [11] or hypertension [1] is still anecdotal and needs to be explored but considering their long-term effects, it is imperative to identify and screen susceptible patients. Additional specific populations of interest for long-term follow up might be elderly patients, immunocompromised patients, and those living in developing countries.

What is the cause of each of the ongoing symptoms? Mechanisms of direct viral invasion, thrombosis, hyperactivation of the immune system and hormonal dysregulation have all been

suggested as causing the acute manifestations of COVID-19, but it is unclear which, if any, plays a part in long COVID-19. Dennis *et al.* have shown multi-organ dysfunction using MRI that is suggestive of an ongoing inflammatory process in recovering patients [6], but its aetiology still needs to be ascertained. Additionally, certain rare syndromes such as Guillain–Barré syndrome [12], myasthenia gravis [13], postural–orthostatic tachycardia syndrome [14] and others may account for some patients' symptoms.

What control group should be used, if any? These are trying times for all of us. Lockdowns, unemployment, anxiety about the disease and the economy, and for many, grief may cause symptoms in the general population and therefore we must ascertain which of the symptoms we see are unique to recovering patients. Special consideration must be set for using and choosing a control group in describing long COVID-19. Xiong *et al.* used people under strict lockdown, but this group may not be available in many areas [1].

And last and most important—how can we help our patients? Reassurance and advice for patience is not enough for some of our patients. These are suffering people who are eager to return to their normal selves. Until we know more regarding the causes and possible treatments for long COVID-19 symptoms, recovering patients should be evaluated at designated multidisciplinary clinics, entered into systematic long-term follow up and linked to programmes aimed at specific physical and cognitive rehabilitation as well as emotional support systems. Further research is necessary to lay the foundations for these interventions aimed at addressing long COVID-19 symptoms. Individuals convalescing from COVID-19 seem to face a new challenge—recovering completely, and it is our duty to assist them in their recovery.

Transparency declaration

All authors report no conflicts of interest relevant to this article. No external funding was received.

Authors' contributions

All authors contributed to the writing of the manuscript and reviewed the final version.

References

- Xiong Q, Xu M, Li J, Liu Y, Zhang J, Dong W, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect* 2021;27:89–95. <https://doi.org/10.1016/j.cmi.2020.09.023>.
- Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–5.

- [3] Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. medRxiv 2020. <https://doi.org/10.1101/2020.07.29.20164293>.
- [4] Carvalho-Schneider C, Laurent E, Lemaigen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with non-critical COVID-19 two months after symptoms' onset. *Clin Microbiol Infect* 2021;27:258–63. <https://doi.org/10.1016/j.cmi.2020.09.052>.
- [5] Mahase E. Covid-19: what do we know about "long covid"? *BMJ* 2020;370:m2815. <https://doi.org/10.1136/bmj.m2815>.
- [6] Dennis A, Wamil M, Kapur S, Alberts J, Badley AD, Decker GA, et al. Multi-organ impairment in low-risk individuals with long COVID. medRxiv 2020. <https://doi.org/10.1101/2020.10.14.20212555>. ePub ahead of print.
- [7] Lee M, Kang J, Jeong YJ. Risk factors for post-intensive care syndrome: a systematic review and meta-analysis. *Aust Crit Care* 2020. <https://doi.org/10.1016/j.aucc.2019.10.004>. ePub ahead of print.
- [8] Jaffri A, Jaffri UA. Post-Intensive care syndrome and COVID-19: crisis after a crisis? *Heart Lung* 2020. <https://doi.org/10.1016/j.hrtlng.2020.06.006>. ePub ahead of print.
- [9] Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. *J Rehabil Med* 2020;52. <https://doi.org/10.2340/16501977-2694>.
- [10] Yelin D, Wirtheim E, Vetter P, Kalil AC, Bruchfeld J, Runold M, et al. Long-term consequences of COVID-19: research needs. *Lancet Infect Dis* 2020;20:1115–7.
- [11] Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-onset diabetes in COVID-19. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMc2018688>. ePub ahead of print.
- [12] Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré syndrome associated with SARS-CoV-2. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMc2009191>. ePub ahead of print.
- [13] Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med* 2020. <https://doi.org/10.7326/120-0845>. ePub ahead of print.
- [14] Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. *Clin Auton Res* 2020:1–3. <https://doi.org/10.1007/s10286-020-00727-9>. 0123456789.