



# Nefer, Sinuhe and clinical research assessing post COVID-19 condition

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**Clinical research studies reporting on post COVID-19 condition should follow some basic recommendations** <http://bit.ly/3h4OE1a>

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*“...For this reason I will tell you my name, which is Nefernefernefer. My eyes are as green as Nile water in the heat of summer. I am judged so beautiful that no one, after having said my name three times, can avoid forgetting me.”*

Sinuhe, The Egyptian, by Mika Waltari (1945)

In the immortal classical novel by Finnish writer Mika Waltari (1908–1979) (figure 1), Nefer, a beautiful and cunning Egyptian courtesan, seduces and befools Sinuhe, the pharaoh's physician. Sinuhe is bewitched by her charms and sacrifices everything for her – even his parents' house and grave – only to be cruelly rejected when Nefer tires of playing with him.

The current pandemic of coronavirus disease 2019 (COVID-19) has literally changed our lives and those of our patients. One year after onset, more than 100 million infections have been reported, resulting in an excess of 2.1 million deaths worldwide [1], and counting. In other respiratory virus infections, like influenza, we would expect recovery to pre-infection quality of life and functionality. However, while many COVID-19 patients recover and return to normal health, a yet uncertain proportion of COVID-19 survivors persist with lingering, recurrent symptoms for months after recovering from the acute condition. These long-term outcomes vary from mild symptoms to severe conditions, and sometimes nearly-life threatening episodes. Accordingly, many have not returned to their baseline health after weeks, which also affects productivity and emotional status. The burden and clinical features of the variously named post COVID-19 condition, long COVID, or COVID-19 sequelae, need to be unravelled. After intensive care unit (ICU) treatment, the frequency of post-intensive care syndrome (PICS) is at least 50% [2]. At ICU discharge, as a result of the impact of the acute illness and the hazards of bed rest and hospitalisation, nearly all survivors of critical illness experience impairments in one or more PICS domains. At 3 and 12 months, 64% and 56% of survivors experience one or more new post-intensive care problems, respectively, and co-occurrence is common.

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FIGURE 1 Sinuhe, The Egyptian, by Mika Waltari (1945).

However, post COVID-19 condition is not a hallmark of critically ill patients, but also represents a significant proportion of those that presented with only mild to moderate symptoms after the acute infection. One of the first reports (from 9 July 2020) on this topic, including 143 patients from Italy followed up 2 months after discharge, identified that 87% had at least one persistent symptom, most commonly fatigue and dyspnoea; and decreased quality of life was observed in 44% of the patients in that study [3]. Two more recent reports produced similar findings: a recent telephone survey conducted by the Centers for Disease Control and Prevention in April to June 2020 at 14 US academic healthcare systems in 13 states reported that 35% of COVID-19 patients did not return back to their usual health; [4] and in a Dutch Primary Care series of 126 patients stratified by COVID-19 initial severity, at 3 months follow-up even the 27 mild, and the 51 moderate patients had symptoms and signs to a similar degree observed in the severe and critical ones [5]. In contrast with HIV or hepatitis viruses, other coronaviruses usually produce self-limited infections, while persistent replication of COVID-19 has only been identified in severely immunocompromised patients [6]. However, we know that there are significant chronic health effects in survivors of community-acquired bacterial pneumonia, including an increased risk of heart attack, heart failure, stroke and cognitive impairment [7]. As an analogy with post-viral pneumonia, in a clinical series of 369 severe acute respiratory syndrome (SARS) survivors from Hong Kong, 42.5% had active psychiatric illnesses and 40.3% reported a chronic fatigue problem 4 years after SARS [8].

In this issue of the *European Respiratory Journal*, three European groups report their findings on post COVID-19 condition in independently collected, prospective, observational cohorts of hospitalised COVID-19 patients, who were assessed up to 3 months past infection (table 1). Namely, LERUM *et al.* [9] report on symptoms, quality of life, pulmonary function and chest computed tomography (CT) findings 3 months following hospital admission for COVID-19 in 103 patients from six Norwegian hospitals; SONNWEBER *et al.* [10] report on similar tests performed in 145 patients from five Austrian centres; and finally, GULER *et al.* [11] report on 113 patients from 13 Swiss centres. Across the three studies, COVID-19 survivors are identified from mild to severe cases based on symptoms/events during hospital admission/stay including ICU need, and post COVID-19 condition is characterised depending on case severity. Although symptoms improve significantly over time, about half of these patients presented respiratory-related concerns even 4 months after discharge, most often dyspnoea and impaired lung function. Not surprisingly, the more severe patients, such as those admitted to an ICU while hospitalised, presented with more CT lung abnormalities/pathologies, and reported more trouble in daily-life activities.

Strengths of these studies include novelty, tackling an iron-hot medical crisis, quality integration of many sites, and use of both routinely/actively collected medical data for research purposes, in a situation borderline with near collapse. They have implications for clinical research, unravelling the late sequelae, clinical management, public health surveillance and health service planning. However, some limitations deserve discussion. 1) Limited sample size and duration: ranging from 25 to 38 person-years of experience in each of these studies, they add up to a maximum of barely 100 person-years altogether; we will need

TABLE 1 Characteristics of each prospective cohort of clinical cases, analysis and main findings on post-COVID-19 respiratory outcomes

	Population	Follow-up	Analysis	Main findings
<b>LERUM <i>et al.</i> [9]</b>	103 patients across 6 medical centres in Norway	3 months (~90 days) after admission	Descriptive analysis of patients based on ICU admission. Univariate logistic model for severity indices and respiratory outcomes. Multivariate logistic model for respiratory outcomes related to ICU stay.	Approximately 50% patients presented persistent dyspnoea on exertion, and 25% reduced $D_{LCO}$ . Participants admitted to ICU during hospitalisation presented more CT abnormalities and reported more problems in daily-life activities, but similar lung function and self-reported dyspnoea to those not admitted to ICU.
<b>SONNWEBER <i>et al.</i> [10]</b>	145 patients across 4 medical centres in Austria	60 and 100 days after admission	Overall and subgroup descriptive analyses for time-related differences. Secondary analyses using adjusted generalised linear models to account for time-series.	Major improvement of symptoms over time, however, 41% patients presented symptoms after 100 days: most frequently dyspnoea (36%) and impaired lung function (21%). Small proportion of patients with cardiac impairment or pulmonary hypertension. Frequent finding in CT scans of lung pathologies (63%) without fibrosis.
<b>GULER <i>et al.</i> [11]</b>	113 patients across 9 medical centres in Switzerland	4 months (~120 days) after discharge	Descriptive analysis of patient's outcomes stratified into mild and severe cases. Adjusted logistic models for radiological features related to disease severity.	$D_{LCO}$ percent of predicted identified as the single most important factor associated with severe/critical COVID-19, translated to reduced walking distance and oxygen desaturation on exercise. Presence of mosaic hypoattenuation on chest CT at follow-up was significantly associated with previous severe/critical COVID-19.

COVID-19: coronavirus disease 2019; ICU: intensive care unit;  $D_{LCO}$ : diffusion capacity of the lung for carbon monoxide; CT: computed tomography.

many thousands (millions) of person-years' experience in COVID-19 survivors to grasp its full scope, and by subgroups, of its associated sequelae. 2) Limited statistics: all these studies (except SONNWEBER *et al.* [10] with three time points) use a pre-post study design, so a continuous assessment with generalised linear model or other might be also applied. 3) Restricted scope: these studies address mostly pulmonary function, again with the exception of the report by SONNWEBER *et al.* [10], which also collected markers of cardiac function; however, there are increasing reports of chronic cardiac [12] and neurological ill-health [13], among others, in COVID-19 hospitalised survivors, which will certainly contribute to long-term symptoms and functional outcomes. 4) Bias: the first assessments of any new disease often include selected samples carrying common biases such as lead time (information bias), apparent increased survival (selection bias) and unmeasured residual confounding, among other biases; true representativity will come from population studies from non-elite centres, non-hospitalised subjects, and including patients from low-and-middle-income countries. 5) Baseline assessments: understandably, urgency precluded many baseline assessments prior to COVID-19, such as the effect of previous smoking exposure or previous lung conditions, which have previously resulted in somewhat erroneous interpretations [14]. 6) Applicability of findings: finally, all have insufficient follow-up to know if the observed defects are permanent or will resolve; the effects of potential re-infection remain to be seen, along with any eventual immunological effects of different COVID-19 vaccines. In addition, no cardiopulmonary exercise testing with oxygen consumption assessment was performed to identify muscular impairment.

Interestingly, these three studies confirm that in a large proportion of post-COVID-19 patients, dyspnoea and fatigue are not justified by cardiopulmonary tests, as often identified in clinical practice. In spite of being hospitalised requiring supplemental oxygen, only a small proportion of patients with lung fibrosis, cardiac impairment or pulmonary hypertension were indeed identified. Therefore, these findings suggest that symptoms alone should not guide the management of long-term COVID-19 patients. Moreover, these observations highlight the need to differentiate lung or pulmonary vascular (associated with silent micro-thrombosis) injury [15], from (steroid) myopathy or the development of a systemic exertion intolerance disease, formerly known as chronic fatigue syndrome (SEID/CFS) or myalgic encephalitis. That syndrome was characterised by fatigue for longer than 6 months, post-exertional malaise, unrefreshing sleep plus orthostatic intolerance or cognitive impairment; pathogenesis might be *via* the immune

disbalance associated with SARS-CoV-2 infection, inducing an activation in the expression of endogenous viruses or epigenetic changes increasing cellular metabolism.

In all likelihood, many more reports pooling patients, from either single centres or in collaborative national/international efforts [16], will emerge. We have started to collect a list of recommendations for future clinical research studies reporting on post COVID-19 condition (table 2). Some of them have already been implemented in the encompassing three *ERJ* papers, but the definition itself of what post COVID-19 condition is, by consensus of the World Health Organization [17], the European Centre for Disease Prevention and Control [18], the European Respiratory Society [19] and others, or for how long, and which tests to use to assess it, still needs further evidence. Anyway, 4 weeks as breakpoint to identify late sequelae, as proposed by DATTA *et al.* [20], seems utterly insufficient.

Many unknowns remain on what proportion of COVID-19 survivors will require multidisciplinary post-COVID-19 clinics to address both persistent symptoms and potential long-term respiratory and other complications (*e.g.* acute kidney injury, myocarditis, psychiatric outcomes) [21], and on what standard treatments and management strategies should be applied [22], most likely to be periodically revisited whenever new, significant evidence be available. It will be another toll of this pandemic, to add up to the global risks we face in these most uncertain times [23].

These observations have four important clinical implications. The first step is getting universal definitions for recovery. Recovery cannot be stated when someone is testing negative or being discharged from hospital. A negative follow-up PCR or positive antibody serological test does not mean recovery either. The definition should include duration, but also severity and fluctuation of symptoms, plus functional status and quality of life. Tracking people for 6 months is required at the least, as is the set-up of local registries. Second, differentiation of organ sequelae from SEID/CFS is needed. Third, identification of a biomarker or laboratory test is needed, similar to those we have for acute infection or post-acute hyperinflammatory illness. Lastly, identification of determinants of who is more likely to experience prolonged disease following SARS-CoV-2 infection is also needed.

Unlike for Sinuhe, there is no need to repeat three times the name of this disease to remember it, as COVID-19 will not be forgotten by patients, their relatives and caretakers in the foreseeable future.

*“...Sinuhe, my friend, we have been born into strange times. Everything is melting – changing its shape – like clay on a potter’s wheel. Dress is changing, words, customs are changing, and people no*

TABLE 2 Recommendations for future clinical observational studies on post COVID-19 condition

- 1) Reports should follow all/most STROBE recommendations for observational research, and attach their checklist [24]
- 2) Minimum follow-up of 6 months
- 3) Early, active identification of subjects at risk of severe sequelae
- 4) Use reference groups (hospital controls *via* electronic health records, or population-based controls, for example)
- 5) Tests, questionnaires and tools to assess patient outcomes should be pre-specified as per protocol
- 6) A minimum dataset to merge variables/values/patients in a standard dictionary should be implemented
- 7) Characterise risk factors known for persistence of symptoms: high blood pressure, overweight/obesity, smoking, mental health conditions, other comorbidities and their treatment, *etc.*
- 8) Recording of real-time data with apps, remote sensors and e-health
- 9) Assess mental status and post-traumatic stress disorder
- 10) Assess quality of life in patients (and their carers) objectively
- 11) Identify early potential pharmacological (*e.g.* steroids) and non-pharmacological (invasive/noninvasive ventilation, *etc.*) adverse events
- 12) Report at least three sets of serial measurements over time, to fully assess recovery
- 13) Use objective techniques, like cardiopulmonary exercise testing, to assess exercise impairment
- 14) Assess effects of targeted rehabilitation
- 15) Differentiate from systemic exertion intolerance disease, formerly known as chronic fatigue syndrome (SEID/CFS)
- 16) Identify laboratory tests or biomarkers for characterisation of post COVID-19 condition
- 17) Assess correlation between symptoms and abnormal peak oxygen consumption

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COVID-19: coronavirus disease 2019; STROBE: STrengthening the Reporting of OBservational studies in Epidemiology.

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longer believe in the gods – though they may fear them. Sinuhe, my friend, perhaps we were born to see the sunset of the world, for the world is already old, and twelve hundred years have passed since the building of the pyramids. When I think of this, I want to bury my head in my hands and cry like a child.”

Sinuhe, The Egyptian, by Mika Waltari (1945)

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