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Editorial

Nefer, Sinuhe and clinical research assessing post-COVID-19 syndrome

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Title: Nefer, Sinuhe and clinical research assessing post-COVID-19 syndrome

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Text:

-"…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**), 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 the ones of our patients. One year after onset, 61+ million infections have been reported resulting in an excess of 1.4 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, also affecting productivity and emotional status. The burden and clinical features of the now called post-COVID-19 syndrome, long-term COVID-19, or COVID-19 sequelae, need to be unraveled. After ICU, the frequency of post-intensive care syndrome (PICS) is at the least 50%.[2] At ICU discharge, as a result of the impact of the acute illness and the hazards of bed rest and hospitalization, 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.

However, post-COVID-19 syndrome 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 (July 9, 2020) on this topic, including 143 patients from Italy followed up two months after discharge, identified that 87% had at least one persistent symptom, most commonly fatigue and dyspnea; and decreased quality of life was observed in 44.1% of the patients in that study.[3] Two more recent reports produced similar findings: A recent CDC Telephone survey conducted April to June 2020 at 14 U.S. academic health care 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 three months follow-up even the 27 mild and 51 moderate patients had symptoms and signs in a similar degree than 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 SARS survivors from Hong Kong, 42.5% had active psychiatric illnesses and 40.3% reported a chronic fatigue problem four years after SARS.[8]

In this issue of the Journal, three European groups report their findings on post-COVID-19 syndrome in independently collected, prospective, observational cohorts of hospitalized COVID-19 patients, who were assessed up to three months past infection (**Table 1**). Namely: Vigeland TV, *et al*.[9] report on symptoms, quality of life, pulmonary function, and chest CT findings three months following hospital admission for COVID-19 in 103 patients from six Norwegian hospitals. Sonnweber T, *et al*.,[10] report on similar tests performed in 145 patients from five Austrian centres. And finally, Guler SA, *et al.*, [11] report on 113 patients from 13 Swiss centers. In the three studies, COVID-19 survivors are identified as mild or severe cases based on symptoms/events during hospital admission/stay including ICU need, and post-COVID-19 syndrome is characterized depending on case severity. Albeit symptoms improve significantly over time, about half of these patients present respiratory-related concerns even 4-months after discharge, most often dyspnea and impaired lung function. Not surprisingly, the more severe patients such as those admitted to an ICU while hospitalized, presented the 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 services planning. However, some limitations deserve discussion, including: Limited sample size and duration: ranging from 25 to 38 person-year experience in each of these studies, they add up to a maximum of barely 100

person-year altogether; we will need many thousands (millions) of person-year experience in COVID-19 survivors to grasp its full scope, and by subgroups, of its associated sequalae. Limited statistics: all these studies (but Sonnweber T, *et al*.,[10] with two time points) use a pre-post study design, so a continuous assessment with generalized linear model (GLM) or other might be also applied. Restricted scope: these studies address mostly pulmonary function, yet again Sonnweber T, *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 other in COVID-19 hospitalized survivors, that will certainly contribute to long-term symptoms and functional outcomes. Bias: first assessments of any new disease often included 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 centers, non-hospitalized subjects and including patients from low-and-middle-income countries. Baseline assessments: understandably, urgency precluded many baseline assessments prior to COVID-19, such as the effect of previous smoking exposure or previous lung conditions, that have previously resulted in somewhat erroneous interpretations.[14] Applicability of findings: finally, all have insufficient follow-up to know if the observed defects are permanent or will resolve; it remains to be seen effects of potential re-infection, and 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 patients dyspnea and fatigue are not justified by cardiopulmonary tests, as often identified in clinical practice. In spite of being hospitalized 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 (steroids) myopathy or the development of a systemic exertion intolerance disease, formerly known as chronic fatigue syndrome (SEID/CFS) or myalgic encephalitis. That syndrome was characterized 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.

With all likelihood, many more reports pooling patients from either single centers 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 syndrome (**Table 2**). Some of them have already been implemented in the encompassing three ERJ papers, but the definition itself of what post-COVID-19 syndrome 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 (i.e.: 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: 1) 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 antibodies serologic test does not mean recovery neither. The definition should include duration, but also severity and fluctuation of symptoms, plus functional status and quality of life. It is needed to track people for six-months at the least and set up local registers. Second, it is needed to differentiate organ sequelae from SEID/CFS. Third, it is needed to identify a biomarker or laboratory test (like we have for acute infection or post-acute hyperinflammatory illness). Lastly, it is needed to identify determinants on who is more likely to experience prolonged disease following SARS-CoV-2 infection.

Unlike for Sinuhe, no need to repeating 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 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, Mika Waltari (1945)

Figure. Sinuhe, The Egyptian, by Mika Waltari (1945)

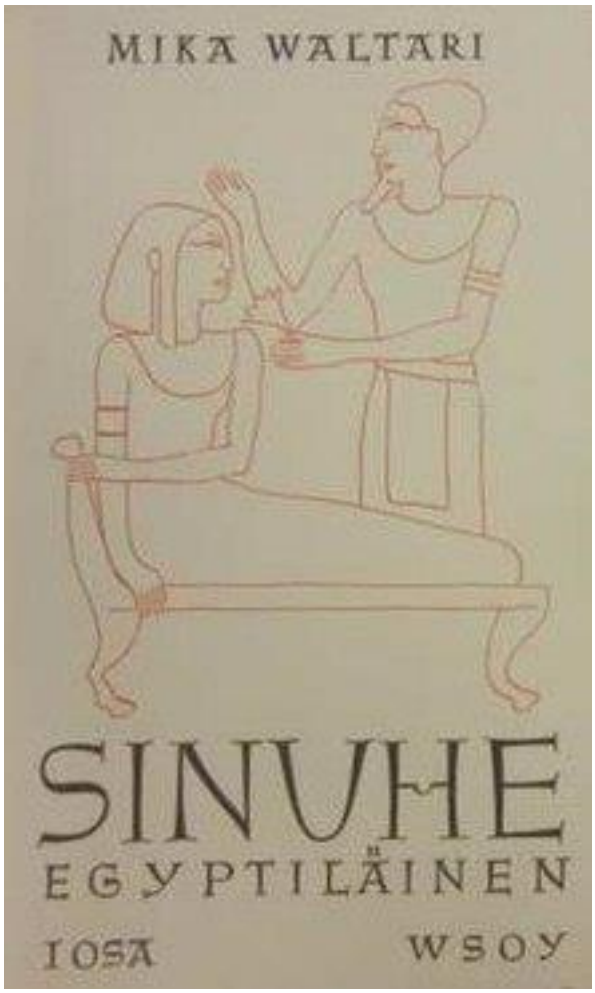

Table 1. Characteristics of each prospective cohort of clinical cases, analysis and main findings on post-COVID-19 respiratory outcomes

	Population	**Follow up**	**Analysis**	**Main findings**
Vigeland TV, *et al*. [9]	103 patients across 6 medical centers 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 diffusion lung capacity for carbon monoxide (DLCO). Participants admitted to ICU during hospitalization 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.
Sonnweber T, *et al*. [10]	145 patients across 4 medical centers in Austria.	60, and 100 days after admission	Overall and subgroup descriptive analyses for time-related differences. Secondary analyses using adjusted generalized 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
Guler SA, *et al*. [11]	113 patients across 9 medical centers 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	DLCO-percent 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

Table 2. Recommendations for future clinical observational studies on post-COVID-19 syndrome

1. Reports should follow all/most STROBE recommendations for observational research, and attach their checklist [24]
2. Minimal follow-up of six months
3. Early, active identification of subjects at risk of severe sequelae
4. Use reference groups (i.e.: hospital controls via electronic health records; or population-based controls; or else)
5. Tests, questionnaires and tools to assess patient outcomes should be pre-specified as per a protocol
6. A minimum dataset to merge variables/values/patients in a standard dictionary should be implemented
7. Characterize risk factors known for persistence of symptoms: high blood pressure, overweight/obesity, smoking, mental health conditions, other comorbidities and their treatment, …
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 of patients (and their carers) objectively
11. Identify early potential pharmacological (e.g. steroids) and non-pharmacological (IMV and NIMV, …) adverse events
12. Report at the least three sets of serial measurements over time, to fully assess recovery
13. Use objective techniques, like cardiopulmonary exercise test, to assess the 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 to characterize the post-COVID-19 syndrome
17- Assess correlation between symptoms and abnormal peak oxygen consumption

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