ESC European Society of Cardiology
European Heart Journal (2022) **43**, 1138–1140
https://doi.org/10.1093/eurheartj/ehac057

EDITORIAL

Post-COVID-19 illness trajectory in community patients: mostly reassuring results

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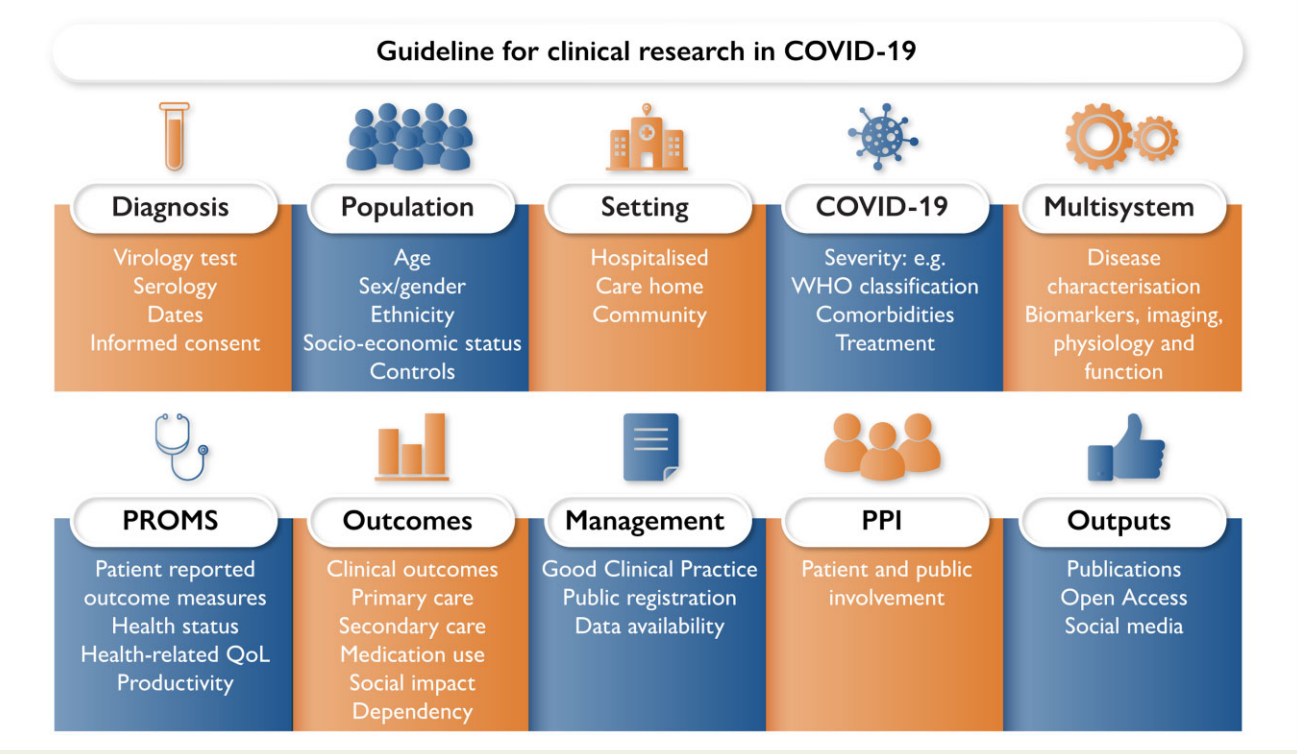
Online publish-ahead-of-print 15 February 2022

This editorial refers to 'Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme', by E.L. Petersen *et al.*, https://doi.org/10.1093/eurheartj/ehab914.



Graphical Abstract Ten standards for clinical research in COVID-19.

The coronavirus disease 2019 (COVID-19) pandemic has imposed widespread illness and tragic loss of life. As a new disease, the lack of medical knowledge about illness trajectory post-COVID-19 has compounded the impact of this pandemic on public health and society, promulgating fear and uncertainty. Currently, the COVID-19 pandemic seems unrelenting as the world encounters a fourth

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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wave of infections driven by transmission of the new B.1.1.529 (Omicron) variant.[1]

'Long-COVID' is defined as the persistence of signs and symptoms that develop during or after an infection consistent with COVID-19 and continue from 4 to 12 weeks (ongoing symptomatic COVID-19) or >12 weeks (post-COVID-19 syndrome) and are not explained by an alternative diagnosis.[2] Post-COVID-19 syndromes are affecting thousands, if not millions, of individuals worldwide, compounding the impact of this pandemic on public health and society. Knowledge gaps on the pathogenesis of post-COVID-19 syndromes undermine healthcare planning and the responses of clinicians for the prevention and treatment of this abstruse condition. Furthermore, the adequacy of clinical research studies is a key consideration for accurate and unbiased interpretation of the data. To date, many research studies have lacked a prospective evaluation of disease pathogenesis and/or health status, and selectively recalled patients, introducing selection bias. Few prospective studies have included multisystem imaging with clinical outcomes. Pre-existing disease complicates attribution of causal inferences in COVID-19. Crucially, many studies have lacked control groups and, of those that have included controls, they may have been historical and selected. Accordingly, the pathophysiology and clinical significance of post-COVID-19 syndromes remain under active investigation in hospitalized[3–5] and non-hospitalized[6] individuals.

In this issue of the *European Heart Journal*, Petersen and colleagues present the results of the Hamburg City Health Study COVID programme.[7] In this cross-sectional, controlled study, 443 individuals aged 45–74 years living in the metropolitan area of Hamburg were examined after a first polymerase chain reaction (PCR)-positive SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) test obtained between 1 March and 31 December 2020 at least 4 months (median 9.6 months) prior to study enrolment. They were statistically matched for age, sex, and education with 1328 population-based controls from the pre-existing Hamburg City Health Study. Based on the protocol for that study, the investigators assessed pulmonary, cardiac, vascular, renal, and neurological status, as well as patient-reported outcome measures (PROMS) of health-related quality of life, anxiety, depression, and cognition. Their study is highly informative particularly in relation to community-based, non-hospitalized individuals.

Using body plethysmography, the investigators documented mildly lower total lung volume (regression coefficient −3.24, adjusted $P = 0.014$) and higher specific airway resistance (regression coefficient 8.11, adjusted $P = 0.001$) after SARS-CoV-2 infection compared with the control group. Using echocardiography and cardiac magnetic resonance imaging, they found slight differences in left and right ventricular function in systole and diastole, and slightly higher circulating concentrations of cardiac biomarkers [factor 1.14 for high-sensitivity troponin I, 1.41 for N-terminal pro-brain natriuretic peptide (NT-proBNP), adjusted $P \leq 0.01$] in post-SARS-CoV-2 patients compared with matched controls, but no other significant differences. Sonographically non-compressible femoral veins, suggesting deep vein thrombosis, were more frequent after SARS-CoV-2 infection (odds ratio 2.68, adjusted $P <$ 0.001), and glomerular filtration rate was slightly lower in post-SARS-CoV-2 cases. Importantly, relative brain volume, prevalence of cerebral microbleeds, and infarct residuals were similar, while mean cortical thickness was higher in post-SARS-CoV-2 cases. There were no between-group differences in health-related quality of life, anxiety, depression, or cognition. The authors concluded that community-dwelling mostly non-hospitalized individuals who have apparently recovered from SARS-CoV-2 infection show subtle signs of subclinical multiorgans being affected related to pulmonary, cardiac, thrombotic, and renal function without signs of structural brain damage, cognition, or quality of life impairment. They suggest that screening may be helpful.

The investigators have exploited the opportunity presented by the Hamburg City Health Study and they are to be congratulated for the scale and quality of their work. This study has strengths and some limitations. The strengths include the requirement for positive SARS-CoV-2 virology results as an inclusion criterion. Case ascertainment is important because a large, population-based cohort study in France disclosed that persistent physical symptoms after COVID-19 infection may be associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection.[8] A second attribute is the comprehensive multisystem evaluations that were enabled by the pre-existing framework of the Hamburg City Health Study. A further strength is the scale of the study, including a comparatively large number of individuals post-COVID-19 (93% of whom were not hospitalized) and an even larger number of controls who had been enrolled before the onset of the COVID-19 pandemic. The prioritized focus on non-hospitalized individuals provides an important community context. This is relevant because the illness trajectory of COVID-19 differs markedly for hospitalized vs. non-hospitalized patients.[6] When considering the COVID literature, clarity on the time point and population type are crucial for interpretation of the data. This study population was enrolled mainly during the chronic phase, beyond convalescence.

The limitations include the cross-sectional design and the fact that the data appear to be based on a single visit ∼10 months after the initial infection. In the absence of data on the participants' health before COVID-19 or at the time of the initial illness, no firm conclusions can be drawn on causality, or even illness trajectory. The lack of information from the time of the initial infection means that the investigators are reliant on the participants' recall of self-reported symptoms, and objective characterization of the initial illness is lacking. Since 93% of the individuals were not hospitalized, it is reasonable to accept their reports of experiencing either 'mild' or 'moderate' symptoms. Surprisingly, the investigators have not assimilated their findings from discrete organs into a multisystem evaluation. The age limits are focused on mid-life adults, hence individuals <45 years and >74 years are not included. The changes observed in respiratory physiology are mild and diffusion capacity (i.e. transfer factor of the lung for carbon monoxide, TLCO) was not measured, which may have aided assessment of any persistent parenchymal changes (fibrotic or inflammatory) in combination with the measured total lung capacity. Physical capacity was not assessed. Finally, employment status is described, but not ethnicity or socioeconomic status.

How might these mostly subclinical findings translate into population health? The investigators found in mostly non-hospitalized

post-COVID-19 patients that there were no differences in PROMS compared with controls, nor were there associations between objective measures of disease and PROMS. The observed differences in organ function could mostly be considered not clinically significant, although some findings such as possible deep vein thrombosis are of concern. The results are likely to be reliable given the large samples of patients and controls and the rigorous methodology. Overall, the results are important. They should give reassurance that on the question of whether 'any' infection with COVID-19 might be expected to impact on health-related quality of life in the longer term, this appears not to be the case. This is relevant at a population level since most SARS-CoV-2 infections, notably from the Omicron B.1.1.529 variant, are asymptomatic or mild, i.e. not leading to hospital admission.[1]

We propose that clinical research studies in COVID-19 should include a minimum dataset of core elements. These would include information on the diagnosis, population, setting, COVID-19 disease severity, multisystem involvement, PROMS, clinical outcomes, study management, patient and public involvement, and scientific outputs (*Graphical Abstract*). These 10 core elements will help to maintain the standard of clinical research in COVID-19 and facilitate information transfer.

Future population studies should include descriptions of ethnicity and social deprivation. Ideally, the protocols should include objective measures of multisystem disease, functional tests such as cardiopulmonary exercise testing, and PROMS that are validated measures of psychological and physical function. Of note, the Duke Activity Status Index has predictive value for peak oxygen utilization.

Major research initiatives are underway to develop care pathways and interventions to prevent and treat long COVID. Encouraging recent developments for community treatment include the effectiveness of oral molnupiravir, an antiviral drug, for the prevention of death or hospitalization in unvaccinated, community individuals with at least one risk factor for severe COVID-19 illness if treated within 5 days of symptom onset.[9] Further, inhaled corticosteroids[10] but not high-dose zinc and ascorbic acid supplements,[11] may be helpful. Our group is leading the CISCO-21 randomized controlled trial of resistance exercise for the prevention and treatment of post-COVID-19 syndromes.[12]

As highlighted by the World Health Organization, all variants of COVID-19 can cause severe disease or death, in particular for the most vulnerable people, and thus prevention is always key.[1] From a practical perspective, screening of individuals with pre-existing health conditions who have survived COVID-19 may be warranted, especially if symptoms persist or recur. This could be undertaken as part of their standard care. Guidance has recently been provided on managing the long-term effects of COVID-19.[2,13]

In preparing this article, the author's (C.B.) views were brought into sharp focus with the onset of symptomatic COVID-19 confirmed by a PCR-positive result for SARS-CoV-2 followed by a 10-day isolation period. A personalized physical exercise plan and a positive psychological response have been self-prescribed.

Acknowledgements

We acknowledge research support from the British Heart Foundation (RE/18/6134217) and the Chief Scientist Office COVID-19 Rapid Research Response. We thank Dr Andrew Morrow for his help with the central illustration.

Conflict of interest: C.B. and H.K.B. are lead investigators in the CISCO-19 (NCT04403607) and CISCO-21 (NCT04900961) studies. C.B. is employed by the University of Glasgow which holds consultancy and/or research agreements with companies that have commercial interests in the diagnosis and treatment of ischaemic heart disease and/or COVID-19. The companies include Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, HeartFlow, Menarini Farmaceutica, Neovasc, Siemens Healthcare, SomaLogic, and Valo Health. H.K.B. has no further disclosures.

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