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EDITORIAL COMMENTARY

Lung Function After Coronavirus Disease 2019: Some Answers, More Questions

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(See the Major Article by Iversen et al, on pages 1308–16.)

As we embark on the third year of the global coronavirus 2019 (COVID-19) pandemic, it is important to take stock not only of what we have learned, but of what we still do not yet understand about this unprecedented disease. Thus, even as we continue to struggle with the acute burden of another surge in cases fueled by yet another severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, we would be remiss to neglect the growing, second pandemic of "long COVID," the term often used to describe postacute sequelae of SARS-CoV-2 infection.

Although the long-term impacts of COVID-19 can affect multiple organ systems, a growing number of studies indicate that respiratory morbidity after COVID-19, whether measured with lung function, radiologic abnormalities, or symptoms, is quite common [1–4]. Given the extensive interstitial and pulmonary vascular insults that accompany acute COVID-19, studies including lung function measurements have, not surprisingly, identified a range of deficits including obstructive and restrictive patterns and, most commonly, impaired diffusing capacity of carbon monoxide (DLCO). To date, these studies have largely focused on individuals with more severe COVID-19 who required hospitalization, which thankfully represents the minority of infected individuals. However, this leaves a large gap in our understanding of whether the hundreds of millions worldwide who had milder cases will be at risk for long-term pulmonary impairment. In addition, as is often the case with studies of lung function after an acute insult, preinfection lung function measurements were not available for the patients included in these analyses, and so any postinfection impairments in lung function are made in comparison to expected values, rather than to a particular individual's preinfection baseline.

In this issue of *The Journal of Infectious Diseases*, Iverson et al [5] begin to address some of the outstanding gaps in our understanding of pulmonary impairment after COVID-19. They leveraged the Copenhagen General Population Study, an ongoing, population-based prospective cohort study of the Danish population residing in the Copenhagen area. The study, which has been running since 2003, has provided a rich data source for a multitude of analyses across disease conditions. In this case, the authors took advantage of the fact that all participants undergo spirometry testing as part of the baseline cohort assessment to conduct a case-control study of lung function declines associated with COVID-19 infection. They identified 146 individuals with prepandemic baseline spirometry testing who had a positive reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2, 107 of whom were willing and able to complete follow-up spirometry testing, in addition to measurement of lung volumes and the DLCO. Of note, only 12 (11%) of these individuals had severe disease requiring hospitalization (just one of whom required mechanical ventilation)—leaving most of the cohort with mild or asymptomatic disease. Cases were compared to 499 controls matched on age, sex, smoking status, and ethnicity who had 2 prepandemic spirometry test results available.

To assess the impact of COVID-19 on lung function, Iverson et al [5] first performed repeated-measures linear mixed-effects modeling to determine the mean yearly change in lung function between those with and without COVID-19. Of note, the mean time between baseline and follow-up spirometry sessions for cases and controls was 6.4 and 8.4 years, respectively (although the earliest baseline visit was in December 2003, 16 years before the COVID-19 pandemic began). Furthermore, the median time from positive SARS-CoV-2 test to the follow-up spirometry session for cases was 156 days, approximately 5 months after infection. They found a significant interaction between time and SARS-CoV-2 infection, such that those with COVID-19 had a 7.3 mL/year greater decline in the forced expiratory volume in 1 second (FEV_1) and a 22.6 mL/year greater decline in the forced vital capacity (FVC) compared to

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controls. These effects were consistent across sensitivity analyses limited to the 95 patients who did not require hospitalization and those whose follow-up lung function testing was performed more than 6 months after infection. They also used simple linear regression to model the differences in lung function between baseline and follow-up, with adjustment for the time since the baseline spirometry measurements. With this second set of models, they found that COVID-19 was associated with declines of 114 mL (4% predicted) and 301 mL (7% predicted) in the FEV_1 and FVC, respectively. It is interesting to note that, although these values both exceed the minimum clinically important difference for these parameters, respiratory symptoms were largely comparable between cases and controls, both at baseline and follow-up. Reasons for the perceived lack of increased symptoms among those with reduced lung function after COVID-19 infection are not clear but could reflect the relative insensitivity of the limited respiratory symptom assessments performed in this study.

Strengths of the study include the availability of routine, prepandemic lung function measurements enabled by the design of the Copenhagen cohort in addition to the focus on nonhospitalized individuals, for whom few data have been published to date. At the same time, there are several limitations to this study that may impact the generalizability and long-term implications of the findings. First, the cohort was ethnically homogeneous and entirely composed of Caucasians. Second, the timing of pulmonary function testing was variable, with most baseline assessments occurring many years before the pandemic and approximately one fourth of follow-up assessments occurring as early as 3 months after infection. Third, and not specific to this study, there continue to be challenges and uncertainty about how best to describe changes in lung function after an acute insult such as COVID-19. In this case, Iverson et al [5] chose to leverage mixed-effects models and report the primary outcome of lung function as a rate of annual decline. However, this approach implies that declines in lung function were consistent between the baseline and follow-up assessments, an assumption that is unlikely in the case of COVID-19. Nevertheless, these individuals suffered an acute infection that likely caused a single, isolated "drop-off" in lung function, as was described with the second set of linear regression models. Finally, although prior COVID-19 infection may impact the subsequent rates of decline in lung function (as has been shown for other pulmonary infections such as tuberculosis [6]), this particular study only has 1 postinfection measurement and, thus, cannot provide information on rates of decline after COVID-19.

Despite compelling evidence from this relatively small study that even mild COVID-19 is associated with clinically significant declines in lung function, there continue to be important gaps in our understanding. In an ideal setting, these findings would be replicated in larger cohorts and with repeated follow-up assessments to determine whether the declines in lung function seen in this analysis represent a single, acute drop-off or whether normal, age-related declines in lung function are subsequently accelerated in COVID-19 survivors. A recently published study from Wuhan, China is somewhat reassuring in this respect, because they found that lung function tended to improve during the first 12 months after infection [3]. The nature of respiratory symptoms following COVID-19 is another area of uncertainty that will require larger longitudinal studies to adequately address. Although respiratory symptoms were not prominent in this cohort of patients with mild disease (albeit with limited assessment, as mentioned previously), data about the prevalence, severity, and duration of post-COVID respiratory symptoms remain mixed [3, 4, 7, 8].

As we continue to wrestle with how best to treat patients with COVID-19, both in the acute phases and in the aftermath, there is a critical need to better understand the pathogenesis and biological drivers of any declines in lung function. For example, a recent study linked persistent immune activation to long-term sequelae after COVID-19 [9]. Ultimately, such understanding may open the door to consideration of host-directed therapies to mitigate lung injury, even for those with mild COVID-19 disease who might not otherwise qualify for disease-directed antiviral or immunosuppressive treatment. In addition, those identified to be at risk for post-COVID impairments in lung function can be linked with appropriate follow-up care. The impact of host-immunity, whether from vaccination or prior infection, on attenuating lung injury in the context of COVID-19 is also not known, nor whether the extent of host lung injury will vary among viral variants. Given that both vaccination and viral variants may impact viral loads during acute infection [10], it is tempting to speculate that they could also influence the extent of pulmonary impairment, but studies will be needed to confirm such suspicions.

It is unfortunate that, even as the growing availability and uptake of vaccines bring with them the promise of an end to the COVID-19 pandemic, we may be forced to confront a second global epidemic of chronic lung disease. Impaired lung function, irrespective of the cause, is associated with excess morbidity and mortality across multiple populations [11–14]. With more than 265 million COVID-19 survivors to date [15], the potential population-level impact of post-COVID-19 lung disease is truly staggering. Thankfully, there are a growing number of calls and consortia focused on the long-term complications of COVID-19 that will hopefully begin to address some of the gaps highlighted above [16].

Notes

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