participants moving from relatively low-risk to high-risk subgroups of future diseases, such as chronic obstructive pulmonary disease. As highlighted by Guo and colleagues, and also discussed elsewhere (5), this highlights the importance of taking the heterogeneity of processes that can lead to chronic airway obstruction into account (e.g., bronchopulmonary dysplasia after preterm birth as one specific example) (6). Whether the growth failure group will experience the same (or different) lung aging process as the persistently low group needs to be explored in future studies (7). As pointed out in an accompanying editorial by Custovic and Fontanella (8), the potential respiratory consequences of moving from a higher to a normal group will also have to be explored.

Finally, we agree with Guo and colleagues that different trajectory models and predictive scores should be evaluated in different studies and populations to define normal versus abnormal trajectories for clinical use, thus allowing for interventions in those at risk of lung function growth failure and/or accelerated decline. We believe that a life-course approach incorporating genetics with both early and adult life events are, to date, the best alternative to better understand the pathogenesis of chronic respiratory disease through the lifetime (9). ■

References

1. Wang G, Hallberg J, Faner R, Koefoed H-J, Kebede Merid S, Klevebro S, et al. Plasticity of individual lung function states from childhood to adulthood. Am J Respir Crit Care Med 2023;207:406–415.
2. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–338.
3. Wang G, Hallberg J, Charalampopoulos D, Sanahuja MC, Breyer-Kohansal R, Langhammer A, et al. Spirometric phenotypes from early childhood to young adulthood: a Chronic Airway Disease Early Stratification study. ERJ Open Res 2021;7:00457-2021.
4. Stanojevic S, Filipow N, Ratjen F. Paediatric reproducibility limits for the forced expiratory volume in 1 s. Thorax 2020;75:891–896.
5. Celli B, Fabbri L, Criner G, Martinez FJ, Mannino D, Vogelmeier C, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. Am J Respir Crit Care Med 2022;206: 1317–1325.
6. Um-Bergström P, Pourbazargan M, Brundin B, Ström M, Ezerskyte M, Gao J, et al. Increased cytotoxic T-cells in the airways of adults with former bronchopulmonary dysplasia. Eur Respir J 2022;60: 2102531.
7. Olvera N, Casas S, Vonk JM, Garcia T, Boezen HM, van den Berge M, et al. Circulating biomarkers in young individuals with low peak FEV$_1$. Am J Respir Crit Care Med 2023;207:354–358.
8. Custovic A, Fontanella S. Evolution of lung function within individuals: clinical insights and data-driven methods. Am J Respir Crit Care Med 2023;207: 379–381.
9. Agustí A, Melén E, DeMeo DL, Breyer-Kohansal R, Faner R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. Lancet Respir Med 2022;10:512–524.

Novel Insight into Pulmonary Fibrosis and Long COVID

Jan C. Kamp[1,2]*, Christopher Werlein[2,3]*, Edith K. J. Plucinski[2,3], Lavinia Neubert[2,3], Tobias Welte[1,2], Peter D. Lee[4], Paul Tafforeau[5], Claire Walsh[6], Mark P. Kuehnel[2,3], Detlef Schuppan[7,8], Marius M. Hoeper[1,2], Danny D. Jonigk[2,9‡], and Maximilian Ackermann[10,11‡]

[1]Department of Respiratory Medicine and [3]Institute of Pathology, Hannover Medical School, Hannover, Germany; [2]Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), German Center of Lung Research (DZL), Hannover, Germany; [4]Department of Mechanical Engineering and [6]Centre for Advanced Biomedical Imaging, University College London, London, United Kingdom; [5]European Synchrotron Radiation Facility, Grenoble, France; [7]Institute of Translational Immunology and Research Center for Immune Therapy, University Medical Center, Johannes Gutenberg University, Mainz, Germany; [8]Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [9]Institute of Pathology, RWTH Aachen Medical University, Aachen, Germany; [10]Institute of Pathology and Molecular Pathology, Helios University Clinic, University of Witten/Herdecke, Wuppertal, Germany; and [11]Institute of Functional and Clinical Anatomy, University Medical Center, Johannes Gutenberg University of Mainz, Mainz, Germany

ORCID IDs: 0000-0002-5002-409X (J.C.K.); 0000-0001-9086-2293 (M.M.H.); 0000-0001-9996-2477 (M.A.).

To the Editor:

With interest, we have read the contribution of Hatabu and colleagues in a recent issue of the *Journal* summarizing the current knowledge on residual radiological and histological pulmonary alterations after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). The authors point out the lack of knowledge regarding the histopathologic manifestations and underlying mechanisms of residual coronavirus disease

*These authors contributed equally as first authors.

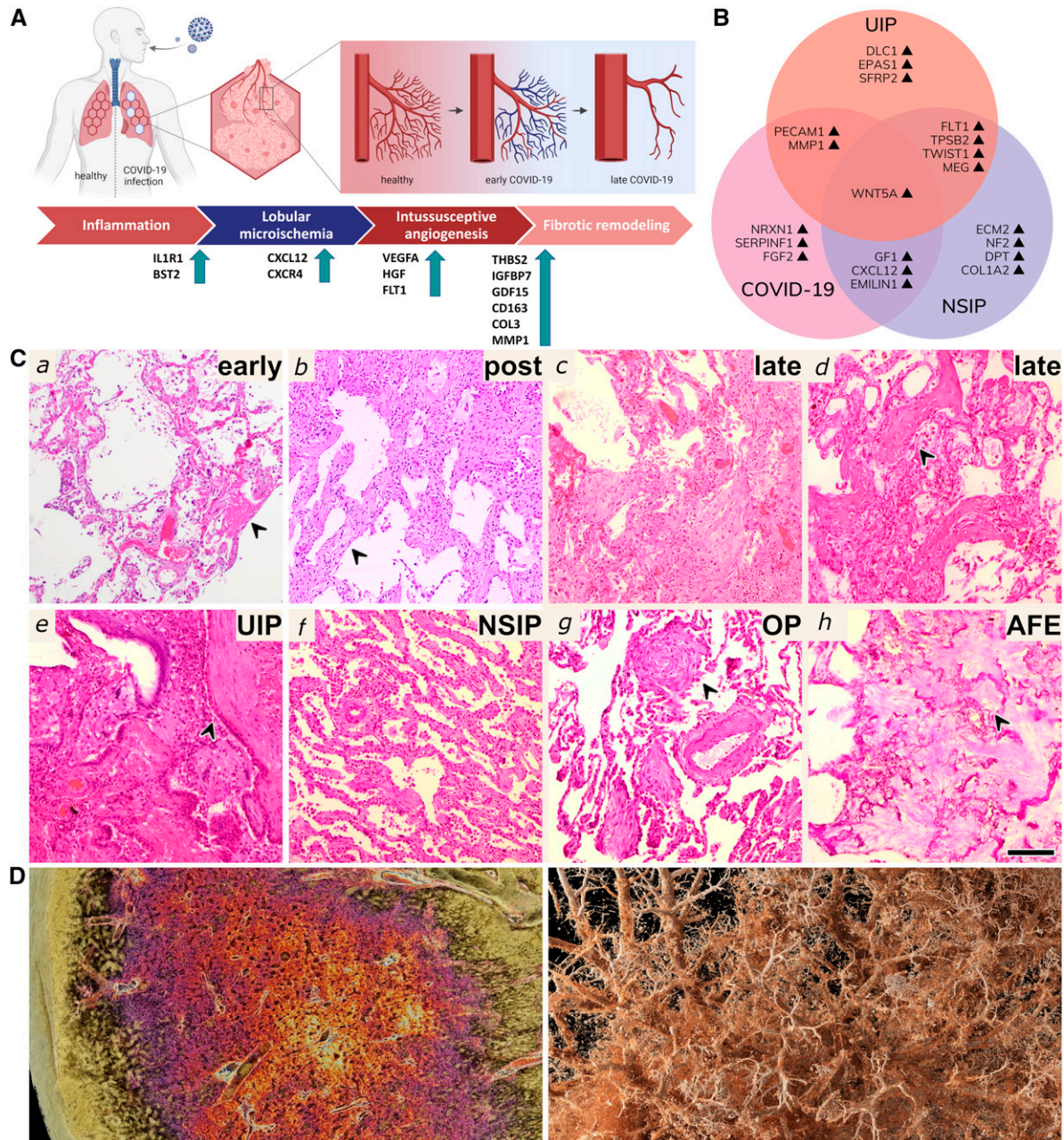‡These authors contributed equally as senior authors.

Figure 1. (*A*) The trajectory of severe and fatal pulmonary coronavirus disease (COVID-19) is driven by a time-dependent evolution of different pathomechanisms. Initially, there is high inflammatory activity promoting microthrombosis with consecutive lobular microischemia and tissue hypoxia. This, in turn, leads to a rapid and aberrant expansion of the vascular plexus by progressive intussusceptive neoangiogenesis, which appears to drive fibrotic tissue remodeling and to contribute to the long-term physical impairment known as long COVID syndrome. This cascade-like pathophysiology is based on the sequential expression of distinct markers. (*B*) Venn diagram of selected differentially expressed genes compared with control samples (adjusted $P \leq 0.05$). Comparative analysis demonstrated an overlap between usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and COVID-19. (*C*) Histologic comparison of COVID-19 and different interstitial lung diseases (ILDs). (*a*) Early COVID-19 with diffuse alveolar damage showing hyaline membranes (indicated by an arrowhead). (*b*) Post-COVID chronic interstitial fibrosis in explanted lungs with an NSIP-like pattern. (*c* and *d*) Late COVID-19 (>7 days of hospitalization before death)–associated changes with rather unspecific interstitial thickening of alveolar septae (c) and organizing pneumonia (OP)-like changes (d, arrowhead). (*e*–*h*) These patterns were compared with different ILD patterns of (*e*) UIP with foci of activated fibroblasts (arrowhead), (*f*) NSIP with homogeneous thickened alveolar septae, (*g*) OP with intraalveolar mesenchymal proliferations (arrowhead), and (*h*) AFE with collagen-filled alveolar spaces and hyperelastosis of the remodeled alveolar septae (arrowhead). (*D*) Cinematic rendering of a hierarchical phase-contrast tomography scan from a 74-year-old male patient who succumbed to COVID-19 depicts the mosaic-like affection of lung parenchyma (left) as well as the spatial heterogeneity of affected airways in COVID-19 (right). AFE = alveolar fibroelastosis.

(COVID-19)–associated lung abnormalities. However, the leading mechanisms contributing to pulmonary fibrogenesis in severe COVID-19—and, therefore, presumably to long COVID—have recently been explored.

In the early phase of the pandemic, we analyzed the time-dependent molecular motifs of pulmonary COVID-19 using transcriptome profiling of autopsy lungs from patients who succumbed to severe COVID-19 either within the first 7 days of hospitalization or later (2). Here, we could demonstrate an early shift from proinflammatory to profibrotic gene expression patterns and further identify several signaling pathways involved in the initiation of pulmonary fibrogenesis in severe COVID-19. In a subsequent follow-up study (3), serum markers and lung tissue from patients with COVID-19 at different hospitalization times were analyzed using comprehensive 3D imaging and multi-omics analysis and compared with those from healthy controls, patients with influenza A pneumonia, and patients with different interstitial lung diseases (ILDs; usual interstitial pneumonia [UIP], nonspecific interstitial pneumonia [NSIP], and alveolar fibroelastosis [AFE]). Our morphomolecular findings provide evidence of widespread microvascular occlusions due to capillary micro-thrombosis of pulmonary and bronchial vessels with concomitant secondary lobular ischemia as a mechanistic correlate to the observed mosaic-like appearance of COVID-19 in conventional radiologic imaging. In addition, we could demonstrate an increasing prevalence of intussusceptive neoangiogenesis and consecutive fibrotic remodeling over the course of hospitalization. On the molecular level, these alterations were associated with enhanced proangiogenic and profibrotic signaling and massive matricellular gene expression, as detected by holistic transcriptome, metabolome, and proteome profiling. Moreover, we identified liquid biomarkers predicting a severe course of disease (and, possibly, also long-lasting sequelae) in COVID-19. ILD lungs with UIP, NSIP, and AFE injury patterns were similarly analyzed and compared with COVID-19 lungs. We previously reported differences between the angiogenetic patterns of different ILDs (4). While NSIP and AFE, two clinically rapid progressing fibrosis patterns, display increased intussusceptive neoangiogenesis, UIP is characterized by a rather sprouting angiogenesis-driven pattern. It is interesting that, although intussusceptive neoangiogenesis was prevalent in the lungs of patients with COVID-19 who showed signs of fibrosis and required longer hospitalization, these showed a separate distinct gene expression pattern, only in part overlapping with those of other ILDs (3). Analysis by light microscopy revealed early (<7 days hospitalization) COVID-19 pneumonia to be characterized by diffuse alveolar damage, as previously described (5). In lungs from patients who had been hospitalized for >7 days, we found variable interstitial changes, ranging from a rather unspecific, peribronchial-accentuated thickening of alveolar septae with distorted alveolar spaces to organizing pneumonia with occasional remnants of hyaline membranes. In lung explants of patients who received transplants because of irreversible lung fibrosis after COVID-19, we saw prominent interstitial fibrosis with multiple facets, including NSIP-like alterations. Compared with chronic ILD, the histologic patterns of post-COVID alterations showed distinct fibrotic

remodeling, which significantly varied inside its own cluster, along with the distinct molecular and 3D-imaging findings on angiogenesis and gene expression. Our postmortem results are in line with a very recent comparative study of radiologic and histopathologic findings in transbronchial cryobiopsies of patients post–COVID infection with residual radiologic abnormalities (6) in which three different histologic phenotypes have been proposed: *1*) "chronic fibrosing," characterized by the progression of interstitial pneumonia; *2*) "acute and/or subacute injury" with variable lung injuries, including organizing pneumonia, NSIP, and diffuse alveolar damage; and *3*) "vascular changes" with increased vascularity, dilatation, and distortion of capillaries and venules. Thereby, post-COVID-19–related fibrosis reveals a distinct morphomolecular pattern.

Taken together, these findings (summarized in Figure 1) provide a sound foundation for better understanding of the underlying pathophysiology of severe COVID-19 and its trajectory toward interstitial fibrosis. Obviously, long COVID is a multisystemic symptom complex, and persistent pulmonary tissue abnormalities might account only for a very minor part of affected patients. However, mechanisms involved in COVID-19–associated pulmonary fibrogenesis (e.g., impaired microcirculation and altered angiogenesis) might also be prevalent in respiratory or skeletal muscles, or even in the nervous system, and therefore persistently compromise the physical and mental capacities that are encouraging for future studies. ∎

Author disclosures are available with the text of this letter at www.atsjournals.org.

Correspondence and requests for reprints should be addressed to Jan C. Kamp, M.D., Department of Respiratory Medicine, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Email: kamp.jan-christopher@mh-hannover.de.

References

1. Hatabu H, Kaye KM, Christiani DC. Viral infection, pulmonary fibrosis, and long Covid. *Am J Respir Crit Care Med* 2023;207:647–648.
2. Kamp JC, Neubert L, Ackermann M, Stark H, Werlein C, Fuge J, *et al.* Time-dependent molecular motifs of pulmonary fibrogenesis in COVID-19. *Int J Mol Sci* 2022;23:1583.
3. Ackermann M, Kamp JC, Werlein C, Walsh CL, Stark H, Prade V, *et al.* The fatal trajectory of pulmonary COVID-19 is driven by lobular ischemia and fibrotic remodelling. *EBioMedicine* 2022;85: 104296.
4. Ackermann M, Stark H, Neubert L, Schubert S, Borchert P, Linz F, *et al.* Morphomolecular motifs of pulmonary neoangiogenesis in interstitial lung diseases. *Eur Respir J* 2020;55:1900933.
5. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–128.
6. Ravaglia C, Doglioni C, Chilosi M, Piciucchi S, Dubini A, Rossi G, *et al.* Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection. *Eur Respir J* 2022;60: 2102411.