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Reply to Vijayakumar and Shah

From the Authors:

We thank Vijayakumar and Shah for their letter regarding our report on the high prevalence of pulmonary sequelae at 3 months in mechanically ventilated survivors of coronavirus disease (COVID-19) assessed by pulmonary function testing and high-resolution computed tomography (HRCT) (1). They raise some important points that are discussed below.

Vijayakumar and Shah rightfully point out that the definition of fibrosis used is relevant for interpretation of our data. Almost all patients had parenchymal bands with a pattern of fibrous residual changes at the 3-month follow-up, and in approximately half, these were accompanied with other signs of fibrosis on chest CT such as parenchymal distortion, volume loss, and/or bronchiolectasis. The evolution of the fibrous bands over time is interesting but not yet systematically screened for. Currently, around one-fifth of our cohort has had a repeated chest CT after the 3-month follow-up in which the fibrous bands were still unchanged.

Pulmonary embolism was diagnosed in 14 out of 22 participants in whom a CT angiogram was performed during admission. As noted, there was no systematic screening for pulmonary embolism during the initial wave, which limits any judgments about relations. Both macro- and microthrombosis with hypoperfusion are common during COVID-19 admission, but their role in long-term pulmonary dysfunction and responsiveness to anticoagulants is unclear (2). Perfusion defects are difficult to assess on HRCT, which was the standard modality in our follow-up. Follow-up data with dual-energy contrast-enhanced CT would potentially be of added value in this regard.

New low-attenuation areas with pattern of emphysematous destruction or cavitation were present in a quarter of the survivors, which we agree with Vijayakumar and Shah is very interesting. To elucidate its pathophysiology, we aimed to compare the follow-up scan with any available CT scan performed during the admission. Although these data need to be interpreted with caution, they suggest that these lesions evolve either from affected areas showing a vacuole sign or from unaffected areas without infiltration or destruction. Thus, we agree that these new lesions may not be COVID-19 specific but rather a consequence of acute respiratory distress syndrome severity and/or ventilator-induced injury.

The etiology of ground-glass opacifications, either inflammatory or fibrotic, may indeed be of relevance for therapeutic intervention and further recovery. Radiological follow-up to assess their evolution over time will be key to address this issue.

The 6-minute-walk test (6MWT) represents an integrated measure of both cardiopulmonary and skeletal muscle function (3), the latter likely being an equally significant contributor to impaired 6MWT results. The four patients in our cohort with significant (>4%) desaturation during the 6MWT were similarly affected in terms of pulmonary function test, HRCT results, and self-reported shortness of breath.

Small airway disease was indirectly assessed by the presence of air trapping on the expiration HRCT scan (4). Although many patients showed some air trapping, defined as more than 2–3 secondary lobules per lobe, the extent of air trapping was limited. Furthermore, we had no previous expiration CT scans in this study cohort, so we were not able to judge this finding as new. In contrast to its prevalence, the extent of air trapping was limited. This is in agreement with the absence of reversibility in pulmonary function test: no significant effect of bronchodilation on either FEV_1 or FVC (median change 1.0 [−1.0 to 4.0] and 0.0 [−2.0 to 2.0] % of predicted, respectively). In addition, none of the patients met the criteria for bronchodilator reversibility (change in FEV_1 and/or FVC >12% and >200 ml), demonstrating that restriction, not obstruction, was the dominant spirometry feature seen in the survivors of COVID-19.

We appreciate the remarks of Vijayakumar and Shah, which in our view highlight two key challenges that remain to be addressed in future work: *1*) the long-term follow-up of these respiratory sequelae and their evolution/persistence over time and *2*) unraveling the role of (micro)thrombosis in the respiratory sequelae as observed in survivors of COVID-19. ■

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The Visible and Invisible Faces of the Iceberg of Type 2 Asthma

To the Editor:

We read with great interest the review article by Dr. Wenzel (1). The author has well illustrated the importance of the asthma phenotype and endotype, and biomarkers and the role of advances in this area in biologically targeted therapies, especially in type 2 (T2)-high severe asthma. In this report, the author stated that integrated approaches, including clinical and molecular phenotyping, regarding responses to biological therapy significantly improved our understanding of phenotypes and even endotypes of severe asthma (1). We would like to thank Dr. Wenzel for her contribution to the literature with such a valuable review. We also would like to share our opinions on this report.

In clinical practice, inexpensive and easily accessible biomarkers and observable clinical conditions are used for the T2 asthma phenotype, which can reflect the T2 asthma endotype. We can think of it as the visible side of an iceberg. The Global Initiative for Asthma main report defined the T2 asthma phenotype by one or more of the following features: skin prick test against aeroallergens and/or specific IgE positivity, blood eosinophilia, sputum eosinophilia, fractionated exhaled nitric oxide elevation, and oral corticosteroid dependence (2).

The association of phenotypes of asthma, which is quite heterogeneous, with cellular, molecular, immunological, and pathophysiological mechanisms is called endotype (3, 4). We can think of it as the invisible side of an iceberg. T-helper cell type 2 (Th2) and IgE, and innate lymphoid cell 2 (ILC2) and IL-5–IL-13 pathways, play a role in the T2 asthma endotype (5, 6). In the Th2 and IgE-dominant subendotype of the T2 asthma endotype, in the presence of coactivators such as alarmins (TSLP, IL-33, and IL-25) released from the epithelium, Th2 cells of the adaptive immune response are stimulated by dendritic cells, and as a result, they produce IL-4, IL-5, and IL-13 (5, 7). IL-5 is an essential cytokine for the proliferation, survival, maturation, and activity of eosinophils. Both IL-4 and IL-13 induce IgE switching and IgE synthesis by B cells activated by $CD4^+$ T cells. The allergen-specific IgEs lead to mast cell activation by binding to the FcεR1 receptors on mast cells, thus revealing early- and late-phase allergic inflammation. In addition, these cytokines contribute to the migration of inflammatory cells to the airway, bronchial hyperreactivity, and airway remodeling (5, 7). In the ILC2-dominant subendotype of the T2 asthma endotype, epithelial-derived alarmins released after epithelial damage caused by toxins (especially Staphylococcal enterotoxins), irritants, aeroallergens, and microorganisms activate ILC2. IL-5 and IL-13 are produced in response to prostaglandin D2 by PGD2 receptors expressed on ILC2 (5). The underlying inflammatory pathways (endotype and subendotypes), observable features (phenotypes), and biological markers reflecting T2 inflammation are shown in Figure 1.

As a result, studies on asthma phenotypes and endotypes have gained momentum in recent years. There are no more simple distinctions in asthma such as intrinsic and extrinsic asthma. Understanding asthma phenotypes, endotypes, and biomarkers that reflect them has become even more important as many biologic treatments have begun to offer a targeted approach aimed at treating underlying inflammation in asthma. ■

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