RESPONSE

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TO THE EDITOR:

A starting point for the phenotypic classification of pulmonary chronic graft-versus-host disease

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We appreciate the commentary by Sheshadri et al[1] regarding our manuscript entitled "The ISHLT chronic lung allograft dysfunction consensus criteria are applicable to pulmonary chronic graft-versus-host disease." We concur with Sheshadri et al and highlighted in the limitations portion of our manuscript that the concept of pulmonary chronic graft-versus-host disease (pcGVHD) cannot be broadened to include all the pulmonary complications that might occur after hematopoietic stem cell transplantation (HSCT), especially restrictive lung diseases, before a clear causative and clinical relationship is successfully established between cGVHD and the respective pulmonary disease after HSCT. The goal of our research was to propose a tool for further deciphering lung abnormalities in patients with cGVHD. We anticipated that the study would increase the awareness of pulmonary complications in HSCT recipients and trigger further investigation into the pathophysiology, diagnosis, risk stratification, prevention, and treatment of different forms of lung disease in patients with cGVHD.

As highlighted by Sheshadri et al and as summarized in our study limitations, our study did not aim to establish the causality between cGVHD and the proposed pcGVHD phenotypes, time of onset, phenotypical distribution, and post-pcGVHD survival. In our study, 75% of the cohort had severe cGVHD according to a National Institutes of Health global score, and 80% of the cohort did not have pre-HSCT or longitudinal pulmonary function data. Furthermore, we lacked a non-cGVHD control group. Therefore, large-scale, multicenter longitudinal studies that enroll HSCT recipients with or without cGVHD who undergo frequent pulmonary function testing are needed to validate the results of our study and shed more light on the clinical manifestation, time of onset, phenotype distribution, and pathophysiology of the pulmonary complications we observed in patients with cGVHD. Such information is important for validating the utility of the tool proposed in our study.

Various biomarkers for cGVHD have been proposed and studied, including donor/recipient gene polymorphisms, immune cell profiles, and secretory cytokines; however, the utility of any biomarker for diagnosing cGVHD earlier than is possible with clinical manifestations or diagnosing organ-specific injury from cGVHD needs to be validated.[2-5] In the absence of biomarkers, early and accurate diagnosis of cGVHD is a challenge.[6] It is plausible that a valid cGVHD biomarker would help distinguish noninfectious pulmonary complications that are not caused by cGVHD from those that are caused by cGVHD. We concur with Sheshadri et al that there is a dire need for cGVHD biomarkers and that the subject merits rigorous exploration.

Nonetheless, application of the proposed Adapted Criteria requires meticulous attention from multiple disciplines. Recognition of other phenotypes of pcGVHD does not conflict with the research in bronchiolitis obliterans. The recognition of restrictive allograft syndrome as a distinct entity of chronic lung allograft disease (CLAD) in lung transplant recipients has greatly broadened the landscape of CLAD research. Similarly, we hope our research facilitates the recognition of other lung disease phenotypes in cGVHD and improves global pcGVHD research efforts. Furthermore, we anticipate that our research will facilitate

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crosstalk between those who perform HSCT and lung transplantations to improve the outcomes of transplant recipients in both fields.

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