

TO THE EDITOR:

Graft-versus-host disease may cause pulmonary restriction, but not all restriction is graft-versus-host disease

Ajay Sheshadri,¹ Howard J. Huang,² Lara Bashoura,¹ Amin M. Alousi,³ Mansour Alkhunaizi,⁴ Husham Sharifi,⁵ and Joe L. Hsu⁵

¹Department of Pulmonary Medicine, MD Anderson Cancer Center, The University of Texas, Houston, TX; ²Division of Pulmonary, Critical Care and Sleep Medicine, Houston Methodist Hospital, Houston, TX; ³Department of Stem Cell Transplantation, MD Anderson Cancer Center, The University of Texas, Houston, TX; ⁴Department of Medicine, Baylor College of Medicine, Houston, TX; and ⁵Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA

Pang et al¹ suggest that the 2019 International Society for Heart and Lung Transplantation (ISHLT) criteria to diagnose chronic lung allograft disease (CLAD)² could be adapted to pulmonary chronic graft-versus-host disease (pcGVHD) after hematopoietic cell transplantation (HCT). Their work shows the deleterious impact of pulmonary impairment on mortality, whether it is due to airflow obstruction or to restriction. However, the implications of considering any noninfectious pulmonary function impairment to represent pcGVHD may unintentionally impede our efforts to better understand bronchiolitis obliterans syndrome (BOS), the predominant form of pcGVHD.

First, we interrogated the underlying assumption that CLAD and pcGVHD are similar enough that we can broadly adapt the same criteria to these disparate populations. BOS is well-known to be the primary manifestation of CLAD after lung transplantation,³ whereas restrictive allograft syndrome (RAS) occurs in 30% of patients with CLAD and was formally recognized as a CLAD subtype in 2014 ISHLT guidelines.⁴ RAS is fundamentally different from BOS beyond patterns of pulmonary impairment.⁵ First, RAS typically manifests earlier and tends to be inexorably progressive, whereas BOS after lung transplantation often exhibits periods of transient stability. Second, RAS is typically associated with higher mortality than BOS. Finally, the main radiologic and histologic patterns in RAS are parenchymal and pleural fibrosis, usually with constrictive bronchiolitis,⁶ whereas BOS is characterized by constrictive bronchiolitis without parenchymal or pleural fibrosis.⁷

Noninfectious pulmonary complications (NIPCs), including BOS, occur in about 20% of HCT recipients and are well known to increase mortality, but these do not necessarily constitute pcGVHD.⁸ Pleuroparenchymal fibroelastosis (PPFE), a hallmark of RAS, is extremely rare after HCT.⁹ PPFE may represent cGVHD, but other NIPCs may not. For example, idiopathic pneumonia syndrome, occurring in 1% to 3% of HCT recipients, often occurs before cGVHD manifests and is often unresponsive to immunosuppressive therapy.¹⁰ Cryptogenic organizing pneumonia, occurring in 1% to 2% of HCT recipients, may occur in the absence of cGVHD and is generally responsive to corticosteroid therapy, unlike severe cGVHD syndromes.¹¹ Histopathologic studies of NIPCs occasionally show nonspecific bronchiolar pathologies,¹² but constrictive bronchiolitis is seen in most patients with RAS.⁶ This implies that post-HCT restrictive lung disorders cannot be definitively linked to cGVHD in the same way that RAS is linked to CLAD. Therefore, assuming that post-HCT pulmonary restriction constitutes cGVHD may hinder the understanding of post-HCT BOS by conflating dissimilar disease processes.

Second, Pang et al¹ found that 13% of patients had mixed obstruction and restriction, although these patients also featured a diverse array of radiologic abnormalities in the lung. Combined with the 3% incidence of pure airflow obstruction, this combined 16% is similar to the results of a previous study which estimated that 14% of patients with extrapulmonary cGVHD also developed BOS.¹³ However, it is not clear how to interpret the ~11% of patients who had undefined phenotype, most of whom had airflow obstruction with less air trapping than patients with the obstructed phenotype, and they developed impairment later in their post-HCT course. The disease in these patients may also represent BOS,

Submitted 26 May 2022; accepted 16 June 2022; prepublished online on *Blood Advances* First Edition 24 June 2022; final version published online 29 August 2022. DOI 10.1182/bloodadvances.2022008201.

© 2022 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.

despite a slightly lower total lung capacity, but the adapted ISHLT criteria, which must account for the probability of RAS after lung transplantation, unnecessarily incorporate radiologic findings into the post-HCT diagnostic algorithm. Because pre-HCT radiologic abnormalities are common¹⁴ and pre-HCT radiology may not have been evaluated, patients with the undefined phenotype may simply have the obstructed phenotype. Similarly, most patients lacked pre-HCT pulmonary function tests (PFTs), which are imperative for properly adapting ISHLT criteria in the first place; without pre-HCT PFTs, undiagnosed pre-HCT pulmonary impairment may lead to overdiagnosis of cGVHD with the adapted criteria.¹⁵ Because PFTs are a prerequisite for HCT, not including pre-HCT PFTs is a major flaw of the proposed adaptation of the ISHLT criteria. Furthermore, this might misclassify preexisting non-cGVHD airflow obstruction, such as asthma, as a new impairment. In accordance with the 2019 ISHLT statement, we suggest that patients with the undefined phenotype must be characterized in greater detail before being considered as having pcGVHD.

Finally, we challenge the assumption that all restrictive lung disease necessarily denotes pcGVHD. First, Pang et al¹ note that nearly half of pulmonary restriction was a result of truncal sclerosis, a severe cGVHD syndrome. Here, it is expected that a severe cGVHD syndrome will increase mortality,¹⁶ but this does not necessarily imply alloimmune inflammation of the lung. Second, it is not clear how the investigators evaluated infections, particularly in patients evaluated early in the study period. Given the long duration of the study and the evolution of diagnostic algorithms for infection, undiagnosed viral infections may cause pulmonary impairment and increase mortality after HCT, but most patients never develop BOS.¹⁷ Finally, the abnormalities shown on computed tomography (CT) scan, which the authors consider to be consistent with pulmonary restrictive disorders, are nonspecific. For example, pleural abnormalities are common,¹⁸ but these rarely constitute cGVHD.¹⁹ Others, such as ground-glass opacities, are notoriously nonspecific and may reflect injuries that predated the initial study evaluation.²⁰ Given that these imaging abnormalities are not definitively linked to pcGVHD, we would not advocate for nonspecific CT findings to be part of the post-HCT diagnostic criteria.

The work by Pang et al¹ improves our recognition of the impact of post-HCT pulmonary impairment; indeed, the finding that restrictive and undefined phenotypes had higher mortality highlights the importance of monitoring this vulnerable population. However, the finding that obstruction and mixed phenotypes did not increase mortality contradicts earlier pivotal studies²¹ and may be a result of a smaller sample or an artificial split between undefined impairment and other obstruction. Taken as a whole, the notion that this adapted approach to diagnosing pcGVHD would improve our care of post-HCT recipients requires further proof. First, the lack of clarity for what disease processes constitute these patterns of impairment is a weakness; pulmonary function alone can rarely diagnose specific diseases. Second, although mechanistic studies of post-HCT BOS are difficult to conduct and are generally lacking, we argue that this necessitates multicenter collaboration to create well-characterized cohorts with BOS rather than to broaden criteria to include restrictive disorders, which would lead to heterogeneous study populations. Similarly, therapeutic trials for pcGVHD will benefit from more careful patient selection and not broader inclusion criteria; the rewards of careful phenotyping have been reaped in diseases like severe asthma.²² Third, post-HCT restrictive disorders are understudied,

and they clearly harm HCT recipients. These NIPCs should be studied separately from BOS, because efforts to mitigate these disorders may require unique strategies. Finally, the lack of a control group without severe cGVHD limits the generalizability to more typical HCT populations.

Pang et al¹ have shown the value of PFTs to identify patients at high risk for mortality after HCT. We would argue that pulmonary impairment, particularly in the case of lung restriction, is not always cGVHD. The National Institutes of Health criteria may miss certain patients who have pcGVHD,²³ but it would be unwise to conflate patients with myriad non-cGVHD pulmonary diseases to those with BOS simply based upon the presence of any pulmonary impairment. Rather, we would argue that pulmonary function should be a common screening platform for NIPCs and BOS (and rarely PPFE), and that further work is needed to address the dearth of biomarkers to diagnose BOS and other NIPCs early in their course. We would urge the community to focus their efforts on improving diagnostic criteria for individual disease processes rather than advocating for those that are simply easier to apply.

Contribution: A.S., H.J.H., L.B., A.M.A., M.A., H.S., and J.L.H. contributed to writing this article.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: A.S., 0000-0002-8091-0180; H.J.H., 0000-0002-3358-6795; L.B., 0000-0003-1126-4039; A.M.A., 0000-0002-2498-8573; H.S., 0000-0002-2331-3961; J.L.H., 0000-0002-7050-6504.

Correspondence: Ajay Sheshadri, Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Unit 1462, Houston, TX 77030; email: asheshadri@mdanderson.org.

References

1. Pang Y, Charya AV, Keller MB, et al. The ISHLT chronic lung allograft dysfunction consensus criteria is applicable to pulmonary chronic graft-versus-host disease. *Blood Adv*. 2022;6(14):4196-4207.
2. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment—a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant*. 2019;38(5):493-503.
3. Cooper JD, Billingham M, Egan T, et al; International Society for Heart and Lung Transplantation. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. *J Heart Lung Transplant*. 1993;12(5):713-716.
4. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2014;33(2):127-133.
5. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2011;30(7):735-742.
6. Ofek E, Sato M, Saito T, et al. Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis. *Mod Pathol*. 2013;26(3):350-356.

7. Byrne D, Nador RG, English JC, et al. Chronic lung allograft dysfunction: review of CT and pathologic findings. *Radiol Cardiothorac Imaging*. 2021;3(1):e200314.
8. Bergeron A, Chevret S, Peffault de Latour R, et al. Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation. *Eur Respir J*. 2018;51(5):1702617.
9. Higo H, Miyahara N, Taniguchi A, Maeda Y, Kiura K. Cause of pleuroparenchymal fibroelastosis following allogeneic hematopoietic stem cell transplantation. *Respir Investig*. 2019; 57(4):321-324.
10. Wenger DS, Triplette M, Crothers K, et al. Incidence, risk factors, and outcomes of idiopathic pneumonia syndrome after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2020;26(2):413-420.
11. Freudenberger TD, Madtes DK, Curtis JR, Cummings P, Storer BE, Hackman RC. Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. *Blood*. 2003; 102(10):3822-3828.
12. Meignin V, Thivolet-Bejui F, Kambouchner M, et al. Lung histopathology of non-infectious pulmonary complications after allogeneic haematopoietic stem cell transplantation. *Histopathology*. 2018;73(5):832-842.
13. Au BK, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17(7): 1072-1078.
14. El Boghdady Z, Oran B, Jiang Y, Rondon G, Champlin R, Kontoyiannis DP. Pretransplant chest computed tomography screening in asymptomatic patients with leukemia and myelodysplastic syndrome. *Bone Marrow Transplant*. 2017;52(3): 476-479.
15. Parimon T, Madtes DK, Au DH, Clark JG, Chien JW. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. *Am J Respir Crit Care Med*. 2005;172(3):384-390.
16. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood*. 2002;100(2):406-414.
17. Sheshadri A, Chemaly RF, Alousi AM, et al. Pulmonary impairment after respiratory viral infections is associated with high mortality in allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2019;25(4):800-809.
18. Modi D, Jang H, Kim S, et al. Incidence, etiology, and outcome of pleural effusions in allogeneic hematopoietic stem cell transplantation. *Am J Hematol*. 2016;91(9):E341-E347.
19. Alousi A, Ghosh S, Rice D, et al. Pleuropericarditis, obliterative bronchiolitis and lymphocytic interstitial pneumonitis after allogeneic haematopoietic stem cell transplantation. *BMJ Case Rep*. 2011; 2011:bcr1120103488.
20. Franquet T, Müller NL, Lee KS, Giménez A, Flint JD. High-resolution CT and pathologic findings of noninfectious pulmonary complications after hematopoietic stem cell transplantation. *AJR Am J Roentgenol*. 2005;184(2):629-637.
21. Cheng GS, Storer B, Chien JW, et al. Lung function trajectory in bronchiolitis obliterans syndrome after allogeneic hematopoietic cell transplant. *Ann Am Thorac Soc*. 2016; 13(11):1932-1939.
22. Ortega HG, Liu MC, Pavord ID, et al; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207.
23. Wolff D, Radojic V, Lafyatis R, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2020 highly morbid forms report. *Transplant Cell Ther*. 2021;27(10):817-835.