

## Response to “Noninvasive determinants of pulmonary hypertension (PH) in interstitial lung disease (ILD)” by Joseph et al.

To the Editor

We read with great interest the recently published paper “Noninvasive determinants of pulmonary hypertension (PH) in interstitial lung disease (ILD)” by Joseph et al.<sup>1</sup> In this paper, the authors assessed gas exchange parameters obtained during submaximal exercise testing as a non-invasive measure to detect PH in ILD patients. Based on their results, they suggest utilizing a combination of estimated right ventricular systolic pressure (eRVSP) by echocardiogram, the ratio of the forced vital capacity (FVC) to diffusing capacity for carbon monoxide (DLCO), and  $GX_{CAP}$ , a gas-exchanged derived estimate of pulmonary vascular capacitance, to predict concomitant PH in ILD patients.

While we commend the authors on their excellent and novel work, we would raise the following questions in regard to their investigation.  $GX_{CAP}$  assessed during submaximal exercise testing, while a novel measurement to detect PH in ILD patients, has been shown to have a similar predictive role in heart failure with preserved ejection fraction (HFpEF) patients.<sup>2</sup> HFpEF patients were not specifically excluded from this present study since practically speaking, invasive hemodynamics alone (i.e., pulmonary artery wedge pressure less than 15 mmHg) is neither sensitive nor specific for ruling out HFpEF. As a result, could HFpEF had played a confounding role in the outcomes of the patients in the PH-ILD group? Perhaps incorporating other determinants of diastolic heart disease such as left atrium volume index and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity on echocardiogram would have provided additional information. Likewise, in the prior study by the same authors, an optimal cut-off of 394 was utilized to signal an abnormal  $GX_{CAP}$  but in the present study, a cut-off of 416 was used, signaling some degree of inconsistency with this novel variable.<sup>2</sup>

A closer look at the data and the methodology to apply decision tree analysis via CART to choose predictive variables for PH-ILD is interesting. Unfortunately, the

reliability of the individual components used is suspect.<sup>3</sup> As the authors point out, relying on eRVSP in ILD patients has several challenges. Moreover, ILD patients frequently undergo echocardiogram as part of routine ILD monitoring. Therefore, utilizing variables that are commonly assessed in ILD patients to develop a tool for early detection in PH may be more practical.<sup>4,5</sup> On the other hand, FVC/DLCO ratio has previously been utilized in multi-component scoring tools to improve the overall accuracy of predicting PH in ILD patients and pulmonary function testing is routinely performed in this patient population.<sup>6</sup>

In conclusion, we commend Joseph et al. for excellent work in attempting to identify noninvasive determinants of PH in ILD patients. In particular, the utilization of exercise variables to determine the concomitant presence of PH is novel and unique. However, we would caution that the use of  $GX_{CAP}$ , without a well-established abnormal cut-off point, and the potential confounder of HFpEF in this study requires further investigation and validation. We would also suggest that routine testing in ILD patients, such as pulmonary function tests and chest imaging, plays a more significant role in the early detection of PH rather than use of inconsistent variables such as an eRVSP by echocardiogram.<sup>4,5</sup> That said, we share in their overarching message and also emphasize and encourage the need to detect PH early in ILD patients so as to potentially treat these patients with inhaled pulmonary vasodilator therapy and/or refer for lung transplant evaluation.

### AUTHOR CONTRIBUTIONS

**Raj Parikh:** Conceptualization; data curation; investigation; methodology; validation; writing-original draft; writing-review and editing; guarantor. **Harrison W. Farber:** Conceptualization; investigation; methodology; validation; writing-original draft; writing-review and editing.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Pulmonary Circulation* published by John Wiley & Sons Ltd on behalf of Pulmonary Vascular Research Institute.


## DATA AVAILABILITY STATEMENT

The data can be made available.

## ETHICS STATEMENT

Informed consent from IRB was not required for this study.

Raj Parikh<sup>1</sup> 

Harrison W. Farber<sup>2</sup> 

<sup>1</sup>*Division of Pulmonary, Critical Care and Sleep Medicine, Hartford Hospital, Hartford, Connecticut, USA*

<sup>2</sup>*Division of Pulmonary, Sleep and Critical Care Medicine, Tufts Medical Center, Boston, Massachusetts, USA*

## Correspondence

Raj Parikh, Division of Pulmonary, Critical Care, and Sleep 85 Seymour St. #923 Hartford, CT 06106, USA.

Email: [Raj.parikh210@gmail.com](mailto:Raj.parikh210@gmail.com)

## ORCID

Raj Parikh  <http://orcid.org/0000-0003-3063-6002>

Harrison W. Farber  <http://orcid.org/0000-0002-0297-7902>

## REFERENCES

1. Joseph P, Savarimuthu S, Zhao J, Yan X, Oakland HT, Cullinan M, Heerdt PM, Singh I. Noninvasive determinants of pulmonary hypertension in interstitial lung disease. *Pulm Circ.* 2023;13(1):e12197.
2. Oakland HT, Joseph P, Elassal A, Cullinan M, Heerdt PM, Singh I. Diagnostic utility of sub-maximum cardiopulmonary exercise testing in the ambulatory setting for heart failure with preserved ejection fraction. *Pulm Circ.* 2020;10(4):1–10.
3. Keir GJ, Wort SJ, Kokosi M, George PM, Walsh SLF, Jacob J, Price L, Bax S, Renzoni EA, Maher TM, MacDonald P, Hansell DM, Wells AU. Pulmonary hypertension in interstitial lung disease: limitations of echocardiography compared to cardiac catheterization. *Respirology.* 2018;23:687–94.
4. Parikh R, Konstantinidis I, O'Sullivan DM, Farber HW. Pulmonary hypertension in patients with interstitial lung disease: a tool for early detection. *Pulm Circ.* 2022; 12(4):e12141.
5. Rahaghi FF, Kolaitis NA, Adegunsoye A, de Andrade JA, Flaherty KR, Lancaster LH, Lee JS, Levine DJ, Preston IR, Safdar Z, Saggat R, Sahay S, Scholand MB, Shlobin OA, Zisman DA, Nathan SD. Screening strategies for pulmonary hypertension in patients with interstitial lung disease. *Chest.* 2022;162(1):145–55.
6. Sonti R, Gersten RA, Barnett S, Brown AW, Nathan SD. Multimodal noninvasive prediction of pulmonary hypertension in IPF. *Clini Respir J.* 2019;13(9):567–73.