Reply: BAL lymphocyte percentage is as good as the company it keeps

Reply to O. Moran-Mendoza and M. Khalil:

We thank O. Moran-Mendoza and M. Khalil for their interest in our work. In their correspondence, they highlight differences between our findings and others, suggesting a re-analysis of our data after excluding studies that used bronchoalveolar lavage (BAL) lymphocyte % as part of the diagnostic criteria for fibrotic hypersensitivity pneumonitis (HP), in an effort to reduce incorporation bias. Given the absence of studies meeting these criteria, we find this suggestion unfeasible.

As outlined in both our manuscript [1] and the recent American Thoracic Society/Japanese Respiratory Society/Asociación Latinoamericana del Tórax guidelines for HP [2], there are no randomised controlled trials or controlled observational studies evaluating BAL lymphocyte % as a diagnostic test for fibrotic HP. Both systematic reviews and meta-analyses included only observational studies reporting on BAL lymphocyte % in patients with fibrotic HP [3]. A subset of the 42 studies included in our meta-analysis explicitly stated inclusion of BAL lymphocyte % in the diagnostic criteria for HP (n=22), 10 studies did not state inclusion of BAL in diagnostic criteria, and 10 studies reported unclear case definitions. However, given that BAL lymphocyte % were reported in each parent study, it is prudent to assume that BAL was undertaken for clinical purposes and informed the HP diagnoses; otherwise it would not have been performed or reported. Erroneously assuming that BAL lymphocyte % was not incorporated into the diagnostic evaluation in these circumstances would introduce serious bias. Notably, the HP guideline committee performed a sensitivity analysis removing studies that explicitly stated incorporation of BAL lymphocyte % as part of their diagnostic criteria for HP [3]. Results were unchanged, so those papers were ultimately kept in their final analysis. In their discussion, they comment that inclusion bias cannot be excluded because BAL findings may have influenced the final diagnosis of HP, even if it was not described. That two large robustly conducted systematic reviews did not identify a single study that definitively addressed the research question of interest should confirm that no such studies currently exist to inform the additive discriminative value of BAL lymphocyte % in the diagnosis of fibrotic HP.

The conference abstract by Yang *et al.* [4] reports on pooled findings from seven studies, with an estimated mean±SD BAL lymphocyte % of 32±18%, lower than our reported estimate. The authors acknowledge that they found "no proper studies assessing the diagnostic accuracy of the BAL lymphocyte count in chronic HP, compared to IPF". We cannot speculate further why differences exist between this abstract and our study given the abstract's lack of detail on search strategy, parent studies, case definitions, or statistical methodology. However, our protocol was publicly registered, with details of our case definitions, parent studies, and statistical methodology presented transparently in the manuscript and its supplementary material.

We expect numerical differences between our findings and those from the HP guideline, given different search strategies, parent study inclusion criteria, and case definitions for "fibrotic" HP. Despite this, there are more consistencies than differences. Both report that BAL lymphocyte % is higher in fibrotic HP compared to IPF, while identifying high heterogeneity between studies. The pooled mean BAL lymphocyte % difference between fibrotic HP and IPF was 21% with a 95% confidence interval of 14–27%. This means that the true difference likely lies somewhere between those upper and lower bounds. In our meta-analysis, BAL lymphocytes were 43% for chronic HP (95% CI 38–48%) and 10% for IPF (95% CI 7–13%). Had we pooled the mean differences between chronic HP and IPF from our parent studies, the estimate would

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No single value of BAL lymphocyte % in fibrotic hypersensitivity pneumonitis will be diagnostic for all, and it must be considered in the context of other clinical, radiological and histopathological features https://bit.ly/3qSwUDo

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likely fall within the range presented in the guideline. However, the mean difference is less clinically relevant that the performance characteristics of the test, a point highlighted in the editorial accompanying the guideline's systematic review [5]. Despite these seemingly impressive and statistically significant differences between fibrotic HP and IPF, the area under the receiver operating characteristic curve was dismal at 0.54, based on data from the same studies used to calculate the mean difference. In our analysis of individual patient data, the optimally performing threshold for BAL lymphocyte % was 20%, providing sensitivity and specificity of only 68% of 65%, respectively, and predictive values that are suboptimal for a diagnostic test. These estimates are similar to those from the international guideline. While BAL lymphocyte % appears higher in fibrotic HP compared to IPF and some other forms of interstitial lung disease, the performance characteristics suggest that it must be considered as one of many data points when arriving at the HP diagnosis. There is unlikely a single value that will establish diagnoses with sufficient confidence in a majority of clinical cases. As outlined in the HP guideline, exposure status, high-resolution computed tomography pattern, and BAL with/without histopathology reviewed in the multidisciplinary discussion remains the diagnostic gold standard for this enigmatic lung disease [2].

A re-analysis of data that insufficiently addresses incorporation or inclusion bias will not further advance the field. Future work should aim to define the additive discriminative value of BAL in patients with fibrotic HP [6], and better characterise the BAL lymphocyte % relationship with antigenic exposures and patient-specific factors [7].

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References

1 Adderley N, Humphreys CJ, Barnes H, *et al.* Bronchoalveolar lavage fluid lymphocytosis in chronic hypersensitivity pneumonitis: a systematic review and meta-analysis. *Eur Respir J* 2020; 56: 2000206.
2 Raghu G, Remy-Jardin M, Ryerson CJ, *et al.* Diagnosis of hypersensitivity pneumonitis in adults. an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.
3 Patolia S, Tamae Kakazu M, Chami HA, *et al.* Bronchoalveolar lavage lymphocytes in the diagnosis of hypersensitivity pneumonitis among patients with interstitial lung disease. *Ann Am Thorac Soc* 2020; 17: 1455–1467.
4 Yang R, Scott J, Moran-Mendoza O. Bronchoalveolar lavage differential in chronic hypersensitivity pneumonitis: a meta-analysis. Am J Respir Crit Care Med 2017; 195: A1592.
5 Ryerson CJ. Making sense of bronchoalveolar lavage lymphocytosis in fibrotic interstitial lung disease. *Ann Am Thorac Soc* 2020; 17: 1382–1383.
6 Johannson KA, Elicker BM, Vittinghoff E, *et al.* A diagnostic model for chronic hypersensitivity pneumonitis. *Thorax* 2016; 71: 951–954.
7 Bonella F, Costabel U. The perpetual enigma of bronchoalveolar lavage fluid lymphocytosis in chronic hypersensitivity pneumonitis: is it of diagnostic value? *Eur Respir J* 2020; 56: 2001534.

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