To the Editor:

We read with great interest the work of Adegunsoye and colleagues showing a significant association between enlarged mediastinal lymph nodes (MLNs) on chest computed tomography and survival in patients with interstitial lung diseases (ILDs) (1). They report a 66% prevalence of enlarged MLNs according to the type of ILD, with various potential causes of development as previously pointed out. The authors raise the hypothesis that enlarged MLNs may be reflective of underlying immunologic phenomena in lung tissue, which in turn contribute to the pathophysiology of disease progression in pulmonary fibrosis. However, we suggest that the potential involvement of environmental exposures in ILDs, particularly anthracosis, should be discussed. Anthracosis caused by coal dust and other environmental factors such as air pollution, biomass fuels used extensively for cooking (“hut lung”), and cigarette smoking is also known to be a source of damage in pulmonary alveolar proteinosis does not necessarily imply idiopathic disease. Lancet Respir Med 2018;6:448.

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### Prognostic Impact of Mediastinal Lymph Nodes in Interstitial Lung Diseases: Is Environmental Exposure the Offender?

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**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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By D. Gern

Reply to Lescoat et al. and to Khamis et al.

From the Authors:

We welcome the interest shown by Lescoat and colleagues and Khamis and colleagues in our publication (1), and thank the authors for their letters. Although the clinical value of plasma biomarkers is well established in many chronic disease states, we recognize that limitations exist regarding their use in prognostication of outcomes. As alluded to by Lescoat and colleagues, the magnitude of the prognostic effect for individual plasma biomarkers will likely vary across diverse forms of interstitial lung disease (ILD) and at different thresholds. Indeed, circulating plasma biomarker levels may be lower relative to biomarker concentrations within specific organs that are directly involved in tissue repair and homeostasis. Also, the extent of disease activity that typically occurs across multiple extrapulmonary organs, such as those affected in connective tissue disease associated with ILD, may accentuate this variation.

With regard to IL-6, it has been suggested that this cytokine has a bidirectional role in the pathogenesis of lung fibrosis. Whereas IL-6 blockade at an early inflammatory stage can accelerate lung fibrosis, blockade at an early fibrotic stage may ameliorate subsequent fibrogenesis (2). These factors could conceivably account for the potentially favorable results that are observed when IL-6 is therapeutically targeted in scleroderma-associated ILD (3). We did find that mean plasma IL-6 levels were nonsignificantly decreased in subjects with enlarged mediastinal lymph nodes (MLNs) in our study, but chose to report median plasma cytokine values in our comparative analyses because these values are less subject to the influence of outliers (1). In both our primary and replication cohorts, the median plasma IL-6 levels did not differ by MLN size (Figure 1) and did not predict mortality risk. We therefore reiterate that we cannot conclude from the data presented in our study that IL-6 might be protective in fibrotic ILD, and agree with Lescoat and colleagues that further study of the blockade of IL-6 in clinical trials is warranted (1).

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Figure 1. (A) Box plots depicting IL-6 (pg/ml) levels stratified by MLN size (mm) in patients with ILD within the UCHICAGO (n = 116) and UCDAVIS (n = 118) cohorts. Comparison of cytokine concentrations in patients with MLN < 10 mm and MLN ≥ 10 mm, using the Wilcoxon signed-rank test for matched nonparametric data in 10,000 bootstrap replications to improve precision at the 95% confidence interval level. (B) Box plots depicting NT-proBNP (pg/ml) levels stratified by MLN size (mm) in patients with ILD within the UCHICAGO cohort (n = 628). For clarity, NT-proBNP data points for two subjects (16.116 and 22.812 pg/ml) are not depicted. Group comparisons for unmatched nonparametric data were conducted using the Pearson chi-squared test for equality of the medians between patients with MLN ≥ 10 mm (purple) and MLN < 10 mm (gray). ILD = interstitial lung disease; MLN = mediastinal lymph node; NT-proBNP = N-terminal pro–B-type natriuretic peptide; UCDAVIS = University of California, Davis; UCHICAGO = University of Chicago.

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