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Reply to Callahan

From the Authors:

We thank Dr. Callahan for his letter regarding our recent publication on the clinical effectiveness of pirfenidone and nintedanib for patients with idiopathic pulmonary fibrosis (IPF) (1). We appreciate his remarks on our methodology, and agree that controlling for index treatment site (academic vs. community practice) would be a valuable addition to the literature. Unfortunately, as with all retrospective studies, our analysis was limited by the confines of the dataset we used. Although our data allow for subgroup analysis by region, they do not allow for separation by the granular geographic detail necessary to divide the cohort into patients with IPF treated in academic centers and those treated in community practice. Our hope is to analyze the effectiveness of these medications again with a Medicare fee-for-service cohort, which would allow for treatment variation analyses by entities such as "hospital referral regions," a methodology that has allowed for the study of geographic differences and academic medical center practice variation in the past (2, 3).

We also endorse his support for treatment initiation in consultation with disease experts, as well as the importance of multidisciplinary discussions to confirm the diagnosis of "true" IPF—practices that have been corroborated by many of the recent guidelines and literature (4, 5). As acknowledged in our article, the diagnosis of IPF can be clinically challenging, which then makes the use of billing codes in this population quite complex and susceptible to some degree of misidentification. With the local cohort validation, we believe we were able to identify a population largely consisting of patients with "true" IPF, although (as described) miscoding is still possible.

The potential for misidentification is perceptively highlighted by Dr. Callahan in his identification of the proportion of patients in our cohort with rheumatoid arthritis (RA). Although we agree that the patients with concomitant RA in the cohort make alternative diagnoses possible, the number is small enough that it should not affect the overall analysis. In addition, patients with RA and a usual interstitial pneumonia pattern on imaging (as is likely for those in our cohort, given their coded diagnosis of IPF) have been shown to have mortality similar to that observed in those with "true" IPF, which makes it even more unlikely that the outcomes were modified by the less than 9% of individuals in the cohort with RA (6).

Once again, we thank Dr. Callahan for his letter and very much appreciate his discussion about the value of multidisciplinary teams when diagnosing IPF, and his advocacy for an analysis comparing academic medical centers and community practices when determining the effectiveness of pirfenidone and nintedanib. We look forward to further studies evaluating these and other important questions surrounding the antifibrotic medications for patients with IPF. ■

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Adherence to the Prevailing Sepsis Definition Is Quintessential to Subphenotype Identification

To the Editor:

We read the article "Identifying Novel Sepsis Subphenotypes Using Temperature Trajectories" by Bhavani and colleagues (1) with great interest. The authors identified four subphenotypes of patients with sepsis from temperature trajectories and found a significant variability in clinical outcomes and inflammatory markers. However, there are a few concerns that we believe need to be mentioned.

The authors included hospitalized patients with infection according to Rhee's criteria and did not adhere to the current Sepsis-3 definition (2) or the previous American College of Chest Physicians/Society of Critical Care Medicine sepsis definition (3). Sepsis-3 defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection." We believe that this has incurred a significant bias that may be reflected as lower in-hospital mortality rates in both the derivation and validation cohorts. The authors reported an overall in-hospital mortality of 6% in the derivation cohort and 6.1% in the validation cohort. On the other hand, a U.S. nationwide inpatient database analysis revealed that in-hospital mortality declined from 23.7% to 18.4% between 2007 and 2011 (4). In that study, the authors identified sepsis, severe sepsis, and septic shock according to ICD-9 coding. Significant heterogeneity in the mortality rate among patients with septic shock is already known. We believe that the patients included in this study had "suspected infection" rather than sepsis.

As we understand it, the authors used the quick Sequential Organ Failure Assessment (qSOFA) score as an indicator of disease severity; however, qSOFA is known to be inferior to SOFA for predicting in-hospital mortality in patients in both ICU and non-ICU settings (5). Therefore, the role of baseline disease severity as an independent predictor of mortality cannot be ruled out in four temperature trajectory groups when qSOFA is used. ■

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Reply to Maitra and Bhattacharjee

From the Authors:

We thank Dr. Maitra and Dr. Bhattacharjee for their comments on our recent article on using temperature trajectories to identify sepsis subphenotypes (1). We agree that our study cohort was not restricted to patients who met the criteria for sepsis but instead included all hospitalized patients who had been admitted through the emergency department with suspected infection. We included all patients with suspected infection in this study for the following reasons: *1*) dysregulated responses to infection occur on a spectrum, and the biological response to infection is unlikely to change abruptly as soon as a patient meets the current sepsis

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