e3–e19. [Published erratum appears in *Am J Respir Crit Care Med* 192:644.]
5. Walsh SLF, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, *et al*. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. *Lancet Respir Med* 2016;4:557–565.
6. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, *et al*. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010;35:1322–1328.

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. ■

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

Souvik Maitra, M.D., D.N.B., E.D.I.C.*
All India Institute of Medical Sciences
New Delhi, India

Sulagna Bhattacharjee, M.D., D.N.B., D.M.
Institute of Liver and Biliary Sciences
New Delhi, India

ORCID ID: 0000-0002-2328-9201 (S.M.).

*Corresponding author (e-mail: souvikmaitra@live.com).

References

1. Bhavani SV, Carey KA, Gilbert ER, Afshar M, Verhoef PA, Churpek MM. Identifying novel sepsis subphenotypes using temperature trajectories. *Am J Respir Crit Care Med* 2019;200:327–335.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–810.
3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al*.; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
4. Wu CP, Chen YW, Reddy V, Hafiz A, Wang MJ. Decreasing trend of in-hospital mortality for sepsis, severe sepsis, and septic shock: a U.S. nationwide in-patient database analysis from 2007-2011 [abstract]. *Am J Respir Crit Care Med* 2016;193:A7824.
5. Maitra S, Som A, Bhattacharjee S. Accuracy of quick sequential organ failure assessment (qSOFA) score and systemic inflammatory response syndrome (SIRS) criteria for predicting mortality in hospitalized patients with suspected infection: a meta-analysis of observational studies. *Clin Microbiol Infect* 2018;24:1123–1129.

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

Originally Published in Press as DOI: 10.1164/rccm.201908-1525LE on September 13, 2019

Originally Published in Press as DOI: 10.1164/rccm.201908-1619LE on September 13, 2019

definition; *2*) the definition of sepsis will likely continue to evolve, and we developed the temperature trajectory subphenotypes to be generalizable to past and future definitions; and *3*) temperature trajectories derived only from patients with organ dysfunction on presentation would exclude patients with infection who later developed sepsis during hospitalization; because the development of organ dysfunction due to infection is likely in part related to the immune response, we did not want to exclude these patients from our analysis.

On the suggestion of Dr. Maitra and Dr. Bhattacharjee, we tested the association between temperature trajectory membership and mortality adjusting for the Sequential Organ Failure Assessment (SOFA) score instead of the quick SOFA score. In logistic regression, when we controlled for age, comorbidities, SOFA, and time to antibiotics, membership in the "hyperthermic, fast resolvers" group remained associated with decreased mortality risk (odds ratio, 0.55; 95% confidence interval, 0.42–0.72; $P < 0.001$) compared with the "normothermic" group. Membership in the "hypothermic" group was associated with increased mortality risk (odds ratio, 1.56, 95% confidence interval, 1.30–1.88; $P < 0.001$). These results are similar to those we obtained in the primary analyses presented in our paper.

Although the metric used to determine the accuracy of sepsis definitions is often risk of mortality, definitions developed based on that outcome may not capture the heterogeneity of the sepsis syndrome (2, 3). Developing a trajectory model based on body temperature (a biologically relevant clinical measurement) allowed us to establish subphenotypes that were disentangled from but still predictive of the outcome. Further studies are required to establish the precise biological significance of the temperature trajectory subphenotypes. ■

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

Sivasubramanium V. Bhavani, M.D.*
University of Chicago
Chicago, Illinois

Philip A. Verhoef, M.D., Ph.D.
Kaiser Permanente
Honolulu, Hawaii

Matthew M. Churpek, M.D., M.P.H., Ph.D.
University of Wisconsin
Madison, Wisconsin

ORCID IDs: 0000-0002-9640-6720 (S.V.B.); 0000-0002-1502-5468 (P.A.V.).

*Corresponding author (e-mail: sivasubramanium.bhavani@uchospitals.edu).

References

1. Bhavani SV, Carey KA, Gilbert ER, Afshar M, Verhoef PA, Churpek MM. Identifying novel sepsis subphenotypes using temperature trajectories. *Am J Respir Crit Care Med* 2019;200:327–335.
2. Churpek MM, Snyder A, Sokol S, Pettit NN, Edelson DP. Investigating the impact of different suspicion of infection criteria on the accuracy of quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores. *Crit Care Med* 2017; 45:1805–1812.
3. McLymont N, Glover GW. Scoring systems for the characterization of sepsis and associated outcomes. *Ann Transl Med* 2016;4:527.

Role of Transbronchial Cryobiopsy in Interstitial Lung Diseases: An Ongoing Tale

To the Editor:

We read with great interest the study by Romagnoli and colleagues addressing the histological diagnosis of interstitial lung diseases (ILD) (1). Although transbronchial lung cryobiopsy (TBLC) has been suggested as an initial procedure to obtain tissue from patients with ILD, there is much debate regarding its diagnostic yield, and it is not supported by current guidelines (2). This is the first study to prospectively compare the results of TBLC with the "gold standard" surgical lung biopsy (SLB) in the same patients, and as such, it has been highly anticipated.

However, we have some concerns regarding the interpretation of the results, which led the researchers to conclude that "there is no role for TBLC in the vast majority of patients where histopathology is required for definitive diagnosis of diffuse ILD" (1). As implied by the authors, a distinction should be made between the pathological diagnosis *per se* and the "final diagnosis" as decided by a multidisciplinary assessment (MDA).

In fact, previous studies that compared the results of SLB with final diagnoses made in explanted lungs showed a poor correlation with a pathological diagnosis of usual interstitial pneumonia (3, 4).

Moreover, previously reported interobserver agreement levels for a histopathological diagnosis of ILD by SLB were not high, even in centers with extensive experience (5). The degree of interobserver agreement (i.e., concordance) between the blinded pathological review and the routine pathological reports from SLB are not reported in the current manuscript, although they are mentioned in the Methods section (1). Therefore, we used the data from Tables 2 and E1 in Reference 1 to calculate it. We found an agreement level of 57.1%, with a κ-concordance coefficient of only 0.44 (0.215–0.66). Arguably, this relatively low level of agreement between two pathologists may make one question how "golden" the SLB gold standard is.

Therefore, given that the interobserver agreement level is only 57.1%, it is no wonder that the agreement between SLB and TBLC is also poor, as the article's title suggests. Furthermore, the authors' statement that "patients who are able to undergo SLB should be recommended to do so" is not entirely supported by their data and does not take into account the morbidity and mortality risks of the procedure.

Originally Published in Press as DOI: 10.1164/rccm.201908-1559LE on September 19, 2019