The current trial (1) was the only randomized trial. Three observational studies provided data for survival rate difference on Day 90 (3, 5, 6). Because baseline patient characteristics were not significantly different in any item of these three studies, we believe using raw comparison data is allowed. A random-model meta-analysis on the basis of these three reports with 109 patients yielded Day 90 survival rate difference of 26% in favor of the rhTM arm (95% CI, 13–39%; $P < 0.001$) without heterogeneity ($I^2 = 0\%$; P for heterogeneity = 0.39). Baseline data were different in another observational study with 40 cases (4); however, this study provided adjusted OR for 90-day survival, which made this article eligible for a meta-analysis. Pooled ORs for 90-day survival on the basis of these four studies (3–6) were 3.1 in favor of rhTM-treated patients (95% CI, 1.8–5.3; $P < 0.001$; $I^2 = 0\%$; P for heterogeneity = 0.54). Most of the control subjects in the non-rhTM arm of these four studies were treated with high-dose corticosteroids with a tapering dose. Some of them were also treated with low-molecular-weight heparin, cyclosporine, immunosuppressants, anticoagulants, antiplatelets, and polymyxin. Two studies adopted 0.06 mg/kg/d rhTM, and the other two adopted 380 U/kg/d rhTM on Days 1–6. In short, there was no clear difference of treatment strategy between the current trial (1) and previous observational studies (3–6). Notably, most of the key authors in the four included articles were named in the author list of the recent article by Kondoh and colleagues (1). We suppose many readers would like to know what introduced this large discrepancy between the current trial (1) and previous observations (3–6). Four additional reports that were excluded from our analysis also revealed favorable outcomes for the rhTM arm; three were excluded because they might include the same patients as an included article (3), and one was excluded because of including nonspecific interstitial pneumonia cases.

In any case, we are grateful to Kondoh and colleagues (1) for providing the most up-to-date survival data of AE-IPF cases and alerting us not to use rhTM for AE-IPF. ∎

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Reply to Horita and Takeshi

From the Authors:

We thank Dr. Horita and Dr. Takeshi for their interest and important comments regarding our recent randomized trial (1).

The 90-day survival proportion in the non–thrombomodulin alfa arm was much higher than that in previous reports (2–4), as indicated by Horita and Takeshi. Indeed, as well as the 90-day survival proportion in the placebo group, the 90-day survival proportion in all subjects included in the full analysis set in our study was even higher than assumed. Some possible reasons for this unexpected result were discussed in our article, but no clear reason was found.

We also did not anticipate the discrepancy between the results of our study and those of previous studies. Although some possible reasons for this discrepancy were also considered in our article, the definite reason is still unclear.

As we discussed in our article, acute exacerbation of idiopathic pulmonary fibrosis could have a heterogeneous pathology, meaning there would be factors that remain to be elucidated. Consequently, it may be important to examine the prognostic factors of acute exacerbation to select a more homogeneous population and/or to have a more balanced allocation of cases in future studies. ∎

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In Search of the Ideal Risk Score in Sepsis

To the Editor:

We read with great interest the recent article by Machado and colleagues (1) revealing low sensitivity of the quick Sequential Organ Failure Assessment (qSOFA) score ⩾2 in predicting mortality among emergency department and ward patients with suspected infection or sepsis and that using qSOFA ⩾1 and qSOFA ⩾1 together with lactate improved sensitivity. Being from a middle- to upper-income country comparable with Brazil, we performed an observational retrospective cohort study in a tertiary public university hospital in Turkey to evaluate and compare the predictive roles of qSOFA and SOFA scores, systemic inflammatory response syndrome (SIRS) criteria, and Modified Early Warning Score (MEWS) (2, 3) obtained during the 48 hours before ICU admission for hospital mortality. A total of 120 patients admitted to the medical ICU from the emergency department or wards between January 1 and May 31, 2018, with suspected infection were included. The hospital mortality rate was 33%. Sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) (95% confidence interval) of qSOFA ⩾2 were 72.7% (54.2–86.0), 47.1 (36.4–58.0), and 0.60 (0.49–0.71), respectively. The corresponding values for SOFA ⩾2 were 97.0 (82.4–99.8), 37.2 (22.7–43.1), and 0.65 (0.54–0.75), respectively; for SIRS ⩾2, they were 87.8 (70.8–96.0), 12.6 (6.7–21.9), and 0.50 (0.39–0.62), respectively; and for MEWS ⩾4, they were 84.8 (67.3–94.2), 42.5 (32.1–53.5), and 0.64 (0.53–0.74), respectively. In this study, the sensitivity of qSOFA with the standard cutoff value of 2 was the lowest among all scores; therefore, its use as a screening tool and mortality predictor might not be sufficient.

qSOFA was introduced as a mortality prediction tool on the basis of North American and European cohorts with an area under the curve of 0.81 for patients outside the ICU (4). However, in a large study in patients admitted to the ICU in Australia and New Zealand (5), in which investigators used the scores calculated within the first 24 hours of ICU admission, SOFA had the greatest prognostic accuracy (AUROC, 0.75), with qSOFA and SIRS having AUROCs of 0.61 and 0.59, respectively.

Early warning scores could also be more accurate than qSOFA scores for predicting mortality and ICU transfer. In a recent study by Churpek and colleagues (6), qSOFA was found to be less accurate than early warning scores for predicting in-hospital mortality in non-ICU patients with suspicion of infection. qSOFA score greater than or equal to 2 had a sensitivity of 68.7%, specificity of 63.5%, and AUROC of 0.69 (0.67–0.70), whereas the AUROC was 0.77 (0.76–0.79) for the National Early Warning Score and 0.73 (0.71–0.74) for MEWS.

Though the authors conducted a single-center study, together with the other studies, the accuracy of the qSOFA score as a risk score remains questionable. SOFA and early warning scores seem to be better mortality predictors. ■

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