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.

References

1. Kondoh Y, Azuma A, Inoue Y, Ogura T, Sakamoto S, Tsushima K, et al. Thrombomodulin alfa for acute exacerbation of idiopathic pulmonary fibrosis: a randomized, double-blind placebo-controlled trial. Am J Respir Crit Care Med 2020;201:1110–1119.

2. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, et al.; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636–649.

3. Sakamoto S, Shimizu H, Ishishi T, Sugino K, Kurosaki A, Homma S. Recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: a historically controlled study. Respir Investig 2018;56:136–143.

4. Kataoka K, Taniguchi H, Kondoh Y, Nishiyama O, Kimura T, Matsuda T, et al. Recombinant human thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis. Chest 2015;148:436–443.

5. Hayakawa S, Matsuawa Y, Irie T, Rikikate H, Okada N, Suzuki Y. Efficacy of recombinant human soluble thrombomodulin for the treatment of acute exacerbation of idiopathic pulmonary fibrosis: a single arm, non-randomized prospective clinical trial. Multidiscip Respir Med 2016;11:38.

6. Anai T, Kida H, Ogata Y, Marumo S, Matsuoka H, Gohma I, et al.; Osaka Acute Exacerbation of Interstitial Pneumonia Research Group. Recombinant thrombomodulin for acute exacerbation in idiopathic interstitial pneumonias. Respiriogy 2019;24:658–666.

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Nobuyuki Horita, M.D., Ph.D.*
Kaneko Takeshi, M.D., Ph.D.
Yokohama City University Graduate School of Medicine
Yokohama, Japan

*Corresponding author (e-mail: horitano@yokohama-cu.ac.jp).

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

Yasuhiro Kondoh, M.D., Ph.D.*
Tosei General Hospital
Aichi, Japan

Arata Azuma, M.D., Ph.D.
Nippon Medical School
Tokyo, Japan

Jun Tagawa
Asahi-Kasei Pharma Corporation
Tokyo, Japan

Sakae Homma, M.D., Ph.D.
Toho University
Tokyo, Japan

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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.

References
1. Kondoh Y, Azuma A, Inoue Y, Ogura T, Sakamoto S, Tsushima K, et al. Thrombomodulin alfa for acute exacerbation of idiopathic pulmonary fibrosis: a randomized, double-blind placebo-controlled trial. Am J Respir Crit Care Med 2020;201:1110–1119.
2. Kondoh Y, Cottin V, Brown KK. Recent lessons learned in the management of acute exacerbation of idiopathic pulmonary fibrosis. Eur Respir Rev 2017;26:170050.
3. Kataoka K, Taniguchi H, Kondoh Y, Nishiyama O, Kimura T, Matsuda T, et al. Recombinant human thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis. Chest 2015;148:436–443.
4. Ishiaki T, Sakamoto S, Kinoshita A, Sugino K, Kurosaki A, Homma S. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. Respir Res 2015;18:207–207.

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.

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

Arzu Topeli, M.D., M.Sc.*
Batuhan Baspinar, M.D.
Ebru Ortac Ersoy, M.D.
Hacettepe University
Ankara, Turkey

ORCID ID: 0000-0002-5874-9087 (A.T.).

*Corresponding author (e-mail: atopeli@hacettepe.edu.tr).

References
1. Machado FR, Cavalcanti AB, Monteiro MB, Sousa JL, Bossa A, Bafi AT, et al.; Instituto Latino-Americano de Sepsis network investigators. Predictive accuracy of the quick sepsis-related organ failure assessment score in Brazil: a prospective multicenter study. Am J Respir Crit Care Med 2020;201:789–798.
2. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. QJM 2001;94:521–526.
3. Tanriver MD, Yıldırım G, Kehya E, Erdoğan O, Nacar DK, Ozsik L, et al. Does the implementation of modified early warning scores spare workforce by decreasing the frequency of nurse assessments? Acta Medica (Cordoba) 2014;3:80–83.
4. Seymour CW, Liu VX, Iwashyna TJ, Brunnikhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762–774.
5. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al.; Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE). Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 2017;317:290–300.
6. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, et al. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. Am J Respir Crit Care Med 2017;195:906–911.