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Reply to Kobayashi *et al.*

From the Authors:

We thank Dr. Kobayashi and colleagues for their interest and insightful comments regarding our recent randomized trial (1). We agree that imbalances in some baseline factors could be a limitation of this study.

As described in our article, a *post hoc* baseline adjustment analysis in separate models was conducted, and it was confirmed that there was no change in the conclusion regarding survival. It is well known that *post hoc* analysis using multiple factors can have issues involving multiplicity and credibility, and may lead to contradictory conclusions simply owing to the play of chance (2). Therefore, the adjusted treatment differences from the *post hoc* analysis were not shown in our article.

Regarding the concurrent use of corticosteroids, as indicated by Dr. Kobayashi and colleagues, corticosteroids could possibly downregulate the expression of anticoagulant factors and cell-surface receptors that mediate the antiinflammatory activity of thrombomodulin alfa.

On the other hand, the use of corticosteroids for patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is weakly recommended in the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement (3) and is considered a standard treatment in Japan, although clinical evidence has not been established through controlled studies. Indeed, corticosteroid therapy is used for most patients with AE-IPF in Japan. In addition, in all of the previous clinical studies that suggested the efficacy of thrombomodulin alfa in patients with AE-IPF and provided theoretical support for the implementation of our trial, thrombomodulin alfa was used concomitantly with corticosteroids (4–6). Given these circumstances, and taking ethical issues and the generalizability of the study results into consideration, all of the subjects in our trial were treated with corticosteroids concomitantly.

It should be noted that patients with AE-IPF were included in this study, and that the results of the study do not provide evidence regarding the usefulness of thrombomodulin alfa in patients with stable IPF. ■

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Ultrasound-guided Transthoracic Needle Aspiration to Diagnose Invasive Pulmonary Aspergillosis

To the Editor:

We read with interest the recent American Thoracic Society guideline regarding microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice (1). According to this guideline, if the results of serum and BAL galactomannan testing are both negative but invasive pulmonary aspergillosis (IPA) is still suspected, biopsy with histopathology and culture is suggested. Given the invasive nature of biopsy and the necessity of transportation for computed tomography–guided procedures, ultrasound-guided transthoracic needle aspiration (TTNA) may be a feasible alternative choice for making a definite mycologic diagnosis, especially in the ICU setting. Herein, we report a patient with IPA whose diagnosis was established only after ultrasound-guided TTNA.

A 79-year-old man with underlying diseases of old stroke with dementia, chronic kidney disease, and newly diagnosed systemic lupus erythematosus was admitted to the ICU after intubation for presumed community-acquired pneumonia with acute respiratory failure. Computed tomography of the chest showed consolidation in the left upper lobe with abscess formation (Figure 1A). Cultures of blood, tracheal aspirate, and BAL fluid revealed no evidence of bacteria, fungus, or *Mycobacterium* infection. The galactomannan level in serum and BAL fluid was 0.13 and 0.51, respectively. A bedside lung ultrasound showed areas of tissue-like consolidation with linear air bronchograms (Figure 1B), and ultrasound-guided TTNA was performed. The culture of lung aspirate yielded *Aspergillus* and *Cladosporium* species 5 days later and intravenous voriconazole was administered for the diagnosis of proven invasive fungal pneumonia. He was extubated on postintubation Day 10 and discharged 1 1/2 months later to a long-term care facility with dependence on noninvasive ventilation.

Microbiological laboratory testing has been proposed as an aid in the diagnosis of IPA (1), but the lack of culture evidence and the category of "probable" disease are the main diagnostic limitations. Although semiquantitative *Aspergillus*-positive culture of BAL fluid were included in a clinical algorithm of "putative" IPA (2), the sensitivity is only 20–50%, as in the depicted case (3). Ultrasound-guided transthoracic procedures have less frequent iatrogenic complications than computed tomography–guided procedures, probably as a result of real-time visualization of vasculatures and air bronchograms, and can be performed by interventional pulmonologists in ICUs without the need for patient transportation (4). Ultrasound-guided TTNA has been shown to have a high microbiological yield and low complication rates for the diagnosis of pneumonia in both adults and children (4). To our knowledge, this is the first study to report the use of ultrasound-guided TTNA to diagnose IPA in a patient under mechanical ventilation in the ICU setting. The major limitation of ultrasound-guided TTNA is the need to ensure contact of the pulmonary lesion with the pleural surface to make the "ultrasound window" amenable to intervention. Fortunately, the most common abnormal radiological features of IPA in critically ill patients are infiltrates and consolidation (2), which may have a higher probability to be pleural based than traditional features such as the halo sign or air crescent sign in severely immunocompromised patients. Ultrasound-guided TTNA may be a feasible and safe alternative diagnostic method to establish a "proven" diagnosis of IPA and/or other invasive fungal pneumonia from a sterile pulmonary aspirate. ■

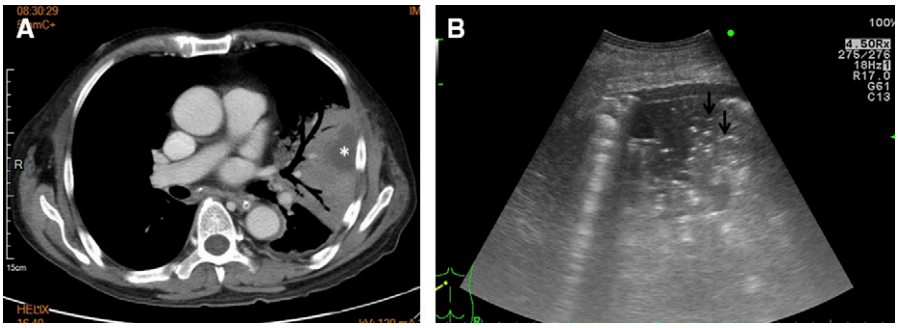

Figure 1. (*A*) Computed tomography of the chest showing consolidation in the left upper lobe with abscess formation (asterisk). (*B*) Bedside lung ultrasound showing areas of tissue-like consolidation with linear air bronchograms (arrows).

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