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Improving Acute Respiratory Distress Syndrome Diagnosis
Is Lung Ultrasound the Answer?

The acute respiratory distress syndrome (ARDS) is a clinical syndrome that lacks a gold standard diagnostic test. In the absence of a gold standard, the Berlin definition of ARDS attempts to capture the clinical, laboratory, and radiographic features that best represent the underlying conceptual model of ARDS as an acute diffuse lung injury that manifests with alveolar flooding, impaired gas exchange, and acute respiratory failure (1). ARDS is underdiagnosed clinically (2), a problem that has been attributed to poor interobserver reliability in applying the Berlin definition (3). Variability in identification of the fundamental diagnostic criterion of bilateral opacities consistent with pulmonary edema on the chest radiograph is particularly problematic (3). Although chest computed tomography (CT) may be a more reliable imaging modality for diagnosis of ARDS, CT imaging can be difficult to obtain in critically ill patients, has not been rigorously validated for diagnosis of ARDS, and is not available in resource-constrained clinical settings.

Lung ultrasound has been proposed as an alternative imaging modality for ARDS diagnosis. Lung ultrasound can be readily applied at the bedside without the need for patient transport and is frequently available in resource-constrained settings, even when other imaging modalities are not. The use of lung ultrasound to test for bilateral opacities was formally proposed in the Kigali modification of the Berlin definition (4). In that study, several modifications of the Berlin definition were deployed, including substitution of Sp_{O_2}/Fi_{O_2} for Pa_{O_2}/Fi_{O_2}, elimination of the requirement for positive pressure ventilation, and use of lung ultrasound to test for bilateral opacities, defined as the presence of B-lines or consolidation without associated effusion in at least one area on each side of the chest. Using the Kigali definition, the hospital prevalence of ARDS in a large urban hospital in Rwanda was 4% with a mortality of 50%; none of these patients were captured by the Berlin definition. The Kigali definition was externally validated in a large European teaching hospital (5) and found to be overly sensitive compared with the Berlin definition, largely because of the lack of specificity of the ultrasound criteria. However, beyond these studies, there has been minimal large-scale validation of lung ultrasound as a diagnostic tool for ARDS.

In this issue of the *Journal*, Smit and colleagues (pp. 1591–1601) report a multicenter study designed to systematically derive and validate a more quantitative lung ultrasound score for the diagnosis of ARDS (6). The authors are to be congratulated for a thoughtfully designed and implemented study. Consecutive mechanically ventilated patients underwent a 12-region lung ultrasound examination to quantify the presence and severity of B-lines, consolidation, pleural effusions, abnormal pleural lines, and several other features of lung morphology. These findings were then compared with expert ARDS diagnosis using all features of the Berlin definition (clinical history, blood gas analysis, chest CT if available, and chest radiograph). Determination of ARDS status was made by a panel of expert clinicians who applied an ARDS certainty score (7), an approach that has been shown to modestly improve interobserver agreement for the Berlin

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definition. For initial derivation modeling, only patients with expert agreement using this scale (certain ARDS or certain no ARDS) were included, and 31% of the patients with uncertain ARDS status in the derivation cohort were excluded.

The resultant three-component lung ultrasound ARDS score (LUS-ARDS) incorporates scores for left and right lung aeration based on the presence and number of B-lines in each assessed region as well as the number of pleural line abnormalities in anterolateral regions. The area under the receiver operating characteristic curve for the diagnosis of ARDS was 0.90 in the derivation cohort when patients with uncertain expert diagnosis were excluded and 0.83 when those patients were included. In the validation cohort, the area under the receiver operating characteristic curve was 0.85 when patients with uncertain expert diagnosis were excluded and 0.80 when those patients were included. To illustrate how this continuous score might be used clinically, a low cutoff of 8 to maximize sensitivity and a high cutoff of 27 to maximize specificity were shown to perform well for the classification of high and low likelihood of ARDS. However, in the validation cohort, 52% of patients had a LUS-ARDS between 8 and 27; only 48% could be classified as high or low likelihood of ARDS using the LUS-ARDS.

This study has both strengths and limitations. Strengths include the prospective design, enrollment of consecutive patients, inclusion of two study sites, methodologic rigor, and the unbiased data-driven approach for derivation of the LUS-ARDS. However, questions about generalizability arise from both the patient population and the selection of ultrasound operators. In both cohorts, almost all patients had a pulmonary cause of ARDS (93% in derivation, 84% in validation), mostly because of pneumonia. Whether the proposed construct is applicable to nonpulmonary ARDS is unknown. In addition, the study population was predominantly nonobese. Obesity can make ultrasound imaging more difficult, and whether these findings would be applicable in a predominantly obese population such as patients in the United States is an open question. In addition, all the ultrasound assessments for this study were done by only three individuals: two at the Amsterdam study site and one at the Maastricht site. Although attempts were made to quantify intra- and interobserver reliability between ultrasound operators, these were done in only 12 patients by retrospective analysis of static images. Because ultrasound imaging is well known to be operator and training dependent, this type of study needs to be repeated with multiple ultrasound operators across a variety of clinical settings. Finally, the 2.5-fold relative weighting of the left aeration score compared with the right aeration score in the derived LUS-ARDS is puzzling and underscores the need for further validation.

A final limitation is one that is inherent to the field of ARDS diagnosis. The lack of a gold standard for diagnosis of ARDS presents a challenge for diagnostic research, and there is a paucity of guidance for appropriate methodology in this situation (8). In the present study, the LUS-ARDS was compared with the Berlin definition as the best available reference standard. To account for potential inaccuracy of the Berlin definition, an expert panel applied an ARDS certainty score, and a secondary analysis included only those patients who had a chest CT that could be incorporated into the diagnostic algorithm. Although this approach is reasonable, the poor interobserver reliability of the Berlin definition ultimately makes it difficult to reliably estimate the value of this new diagnostic test. This fundamental issue will continue to plague our field as we grapple with efforts both to improve ARDS diagnosis and to update the Berlin definition to reflect recent changes in clinical practice. ■

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