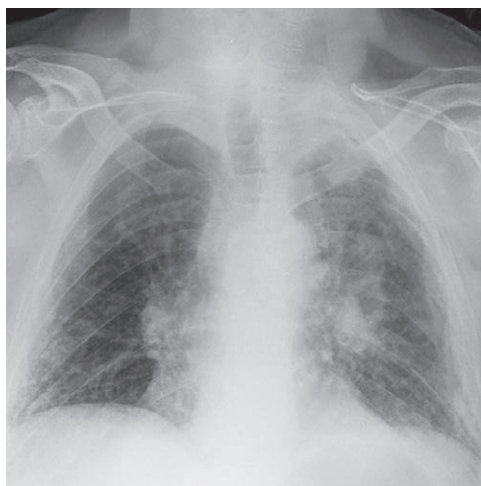


# Heterogeneity in Intensive Care

## Low Severity Does Not Mean Low Risk!

Romain Pirracchio, M.D., Ph.D., Michael A. Gropper, M.D., Ph.D.

Intensivists often treat syndromes rather than diseases. Syndromes are defined as sets of medical signs and symptoms that are correlated with each other and, often, with a particular disease. Therefore, syndromes are heterogeneous entities that may be related to variety of underlying causes. Among the most frequent conditions leading to intensive care unit admission are shock, acute kidney injury, and acute lung injury, all of which are syndromes with diverse causation. In practice, this heterogeneity translates into a wide range of severity and broad potential for evolution and has great implications for research and therapeutics. Acute respiratory distress syndrome (ARDS) is a typical example of a very heterogeneous critical syndrome. Similar to the Acute Kidney Injury Network's definition for acute kidney injury,<sup>1</sup> the recent Berlin definition<sup>2</sup> for



**“...[M]ild for a medical condition [like ARDS] severe enough to require intensive care unit admission may already signify severe in terms of outcome...”**

ARDS was adopted to provide clinicians and researchers with a more specific definition for this entity. Besides refining the diagnostic criterion, the Berlin task force created three severity grades of ARDS (mild, moderate, and severe) based on the  $\text{PaO}_2/\text{FiO}_2$  ratio. Within each of these subgroups, the patients are supposed to be more similar, *i.e.*, less heterogeneous.<sup>1,2</sup> The article by Pham *et al.* in this issue of ANESTHESIOLOGY eloquently shows that mild ARDS is substantially under appreciated.<sup>3</sup>

Although the idea of creating comparable subgroups based on severity—and thus on the potential for unfavorable outcome—is generally desirable, a major drawback relates to defining a mild severity subgroup. This

subgroup, because of its supposed mildness, may gain less attention from clinicians in terms of monitoring and level of care and less attention from the investigators. However, mild for a medical condition severe enough to require intensive care unit admission may already signify severe in terms of outcome, especially when considering long-term and functional outcomes.<sup>4</sup> Such a phenomenon has been well described for traumatic brain injury and acute kidney injury.<sup>5,6</sup> Indeed, both mild traumatic brain injury and mild acute kidney injury are associated with significant adverse outcomes, while, at the same time, are still very underrepresented in clinical studies.

The study by Pham *et al.* uses the data from the largest multicenter observational study on ARDS patients after the publication of the Berlin criteria (nearly 13,000 patients were included in 459 intensive care units from 50 countries), and produced by the Large observational study to UNDERstand the Global impact of Severe Acute respiratory Failure (LUNG-SAFE) consortium, led by two anesthesiologists (John Laffey, M.D., M.A., of Ireland; and Giacomo Bellani, M.D., Ph.D., of Italy).<sup>3</sup> The creation of such a large-scale multinational network has to be celebrated because it provides a unique opportunity to examine ARDS in its entire diversity of presentation and outcome. The ancillary study performed by Pham *et al.* is extremely important because it focuses on mild forms of ARDS as defined by the Berlin definition. They demonstrate that hospital mortality is as high as 30% in this subgroup, supporting the need for a

Image: J. P. Rathmell.

Corresponding article on page 263.

Accepted for publication November 4, 2018. From the Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California.

Copyright © 2018, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2019; 130:190–1

specific clinical and research focus on this group. As previously demonstrated for traumatic brain injury or acute kidney injury, mild forms of ARDS are generally excluded from clinical studies. Even more important, Pham *et al.* clearly show that baseline classification may fail to discriminate between patients with favorable and poor outcomes. Indeed, initial response to treatment, as evaluated using the evolution of the  $\text{PaO}_2/\text{FiO}_2$  ratio over the first few intensive care unit days, is helpful in identifying subgroups of patients with very different hospital mortality rates, ranging from 9.9 to 37.4%.

Although the authors<sup>3</sup> were not able to identify clear modifiable factors associated with disease progression or hospital mortality, their results are still very relevant to clinicians and clinical researchers. Indeed, they invite intensivists to pay greater attention to mild ARDS (as pointed out by the authors, only half of these patients were considered as genuine ARDS by the clinicians). The data also prompt operating room anesthesiologists to seek early identification of patients from this population and accordingly adjust intraoperative monitoring and resuscitation, including protective mechanical ventilation and fluid and transfusion restriction. In the future, the identification of early markers (including biomarkers) may help the clinician to better predict the potential for evolution to ARDS. Until then, the results by Pham *et al.* underline the importance of reassessing ARDS severity after 24 to 48 h after the onset of acute lung injury. This may be particularly important in trauma patients and when the respiratory failure is related to pneumonia. Last but not least, for the researchers, these results suggest that high-quality research is needed on this specific subgroup of ARDS, where current guidelines may not apply and, at least, may need to be adapted. Further studies are also needed to evaluate the effect of mild ARDS on long-term outcomes, including markers of functional status such as exercise tolerance, post-traumatic stress disorders, and ability to return to work. Examining such patient-centered outcomes might add even more urgency to the need to better understand and accurately treat this subgroup of patients. This study constitutes a critically important first step in demonstrating the effect of mild ARDS on mortality and, thus, highlights the fact that even mild forms of ARDS should be considered critical care urgencies. Indeed, in critically ill patients, low severity never means low risk.

## Competing Interests

The authors are neither supported by nor maintain any financial interest in any commercial activity that may be associated with the topic of this article.

## Correspondence

Address correspondence to Dr. Gropper: michael.gropper@ucsf.edu

## References

1. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network: Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11:R31
2. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–33
3. Pham T, Serpa Neto AS, Pelosi P, Laffey JG, De Haro C, Lorente JA, Bellani G, Fan E, Brochard LJ, Pesenti A, Schultz MJ, Artigas A; LUNG SAFE Investigators, European Society of Intensive Care Medicine Trials Group: Outcomes of patients presenting with mild acute respiratory distress syndrome: Insights from the LUNG SAFE study. *ANESTHESIOLOGY* 2019; 130:263–83
4. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Shanholtz C, Husain N, Dennison CR, Herridge MS, Pronovost PJ, Needham DM. Depressive symptoms and impaired physical function after acute lung injury: A 2-year longitudinal study. *Am J Respir Crit Care Med*. 2012; 185:517–24
5. McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, Beers SR, Gordon WA, Valadka AB, Manley GT, Okonkwo DO; TRACK-TBI Investigators: Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. *J Neurotrauma* 2014; 31:26–33
6. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG: Acute kidney injury in critically ill patients classified by AKIN *versus* RIFLE using the SAPS 3 database. *Intensive Care Med* 2009; 35:1692–702