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EDITORIAL

In Search of Balance—Rethinking the Definition and Subphenotypes of Acute Respiratory Distress Syndrome

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More than half a century after its first description, acute respiratory distress syndrome (ARDS) remains a clinical enigma for both clinicians and researchers. Two key reasons for this scenario are the absence of a gold standard laboratory test for diagnosis and the changing definition of ARDS. The primary objective of any syndromic definition is to identify a relatively homogeneous cohort of patients, thereby enabling their inclusion in research on epidemiology and therapeutics. ARDS is not a disease per se, but a clinical "construct". As suggested before, the definition of a clinical gestalt such as ARDS should consider the interplay within a three-step framework of reliability, feasibility, and validity.[1] Inter- or intra-observer reliability, a measure of "homogeneity" is an important criterion for the research and inter-study comparison. Feasibility, as it suggests, is the practicability in diverse patient populations and clinical settings. Finally, validity involves identifying patients similar to those in the original construct. This is challenging because of the lack of a reference standard or agreement on the conceptual model.[2] Notably, all the successive definitions of ARDS, from the American-European Consensus Conference definition in 1994 to the recent global definition in 2023, have had limitations (Table 1) and contributed to increasing heterogeneity and possible failure of many clinical trials.[3] The research in the last decade focused on the heterogeneity of treatment effect, with the identification of ARDS subphenotypes. It started a debate among the scientific community, while striking a balance between achieving homogeneity through ARDS definitions and approaching heterogeneity through subphenotypes.

Historical perspectives – Temporal evolution of ARDS definitions

In 1967, Petty and Ashbaugh observed that 12 out of 272 patients on mechanical ventilation had contrasting clinical and pathological features characterized by the marked and sudden onset of tachypnea, refractory hypoxia not responding to oxygen therapy, poor lung compliance, and diffuse alveolar infiltrates on the chest radiograph.[4] The cause of such findings could not be ascertained to a single etiology. A key feature recognized was the improvement of hypoxemia with the addition of positive end-expiratory pressure

(PEEP). More importantly, the presence of hyaline membranes was demonstrated in the lung specimens during autopsy. Subsequently, this constellation of clinical, radiological, and histological findings was described as ARDS.[5] Although a formal definition of the syndrome was not established, their work laid the foundation of the conceptual framework of ARDS. This also started a debate between lumpers and splitters on the need to define ARDS.[6]

The latter group came up with a Lung Injury score to classify ARDS. (Figure 1) The score integrates four components—extent of chest-radiograph infiltrates, PaO_2/FiO_2 ratio, applied PEEP, and respiratory system compliance—each graded and averaged (0–4). ARDS was defined as a lung injury score of more than 2.5. The disease severity and response to therapy can be monitored using the individual domains or the composite score.[7] The main challenges were the measurement of static lung compliance and the limited predictive ability for outcomes.

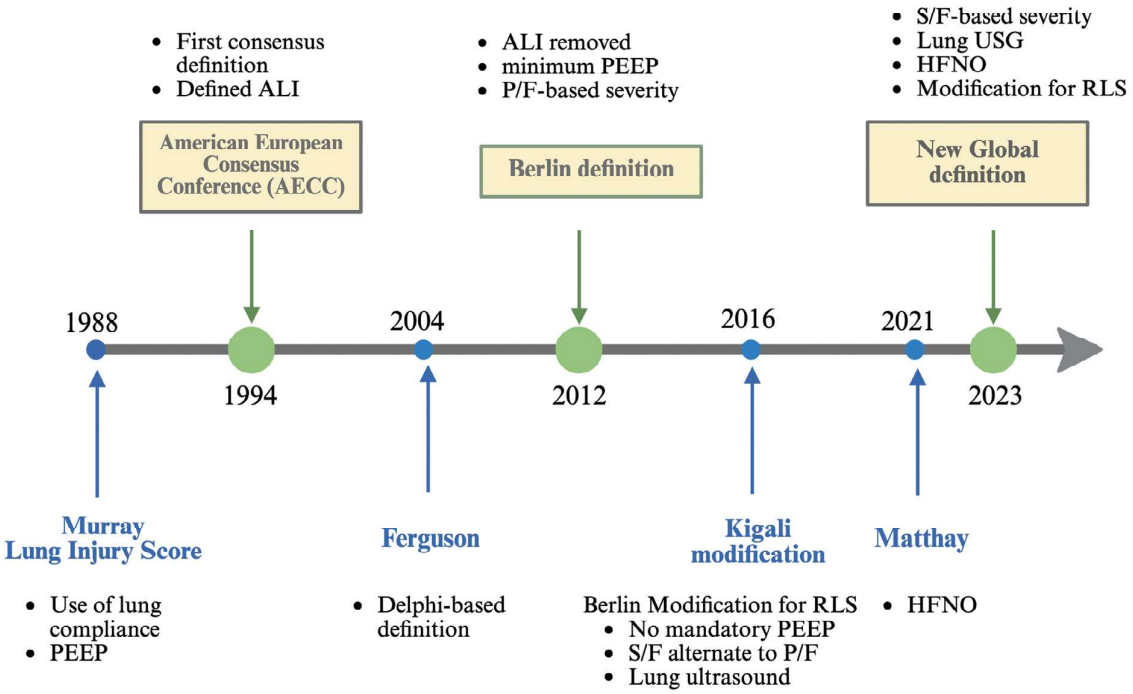

Figure 1: Historical evolution and key changes in the definition of ARDS

AECC: The American European Consensus Conference, ALI: Acute Lung Injury, ARDS: Acute Respiratory Distress Syndrome, RLS: Resource-limited Setting, S/F: SaO_2/FiO_2 ratio, P/F: PaO_2/FiO_2 ratio, HFNO: High Flow Nasal Oxygen, USG: Ultrasonography, PEEP: Positive End-expiratory Pressure

The first consensus conference–the American-European Consensus Conference (AECC), coined ARDS as an acute onset of illness, with a PaO_2/FiO_2 ratio less than 200 mmHg, pulmonary artery wedge pressure less than 18 mmHg when measured or no clinical evidence of left atrial hypertension, and bilateral infiltrates on a frontal chest radiograph.[8] They also introduced the term 'acute lung injury' (ALI), defined by similar features but with a PaO_2/FiO_2 ratio less than 300 mmHg. Notably, the PaO_2/FiO_2 ratio cut-offs for ALI and ARDS were arbitrary. Interestingly, PEEP was omitted, stating that its effects on the pulmonary shunt fraction were inconsistent and time-dependent. The measurement of pulmonary artery wedge pressure, although not considered essential for diagnosis in all cases, was perceived as an important constraint. The absence of a clear definition for acute onset and the poor interobserver reliability in chest radiographs interpretation were also recognized as notable limitations.

To address the limitations of the AECC definition, the Berlin consensus definition was introduced in 2012 utilizing the Delphi methodology. The onset of new or worsening respiratory symptoms within one week of known clinical insult, bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules) on chest imaging (chest radiograph or computed tomography scan), respiratory failure not fully explained by cardiac failure or fluid overload, and a PaO_2/FiO_2 ratio of less than or equal to 300 mmHg with a minimal PEEP of more than or equal to 5 cm H_2O were the key features of this definition. ARDS was stratified into mild, moderate and severe categories based on the severity of hypoxemia, i.e., the PaO_2/FiO_2 ratio. A key strength was that the definition was validated for performance through the statistical analysis of empirical data from ARDS research. The Berlin definition performed marginally better than the AECC definition with an AUROC of 0.577 (95%CI 0.561-0.593).[9] The ventilation with decreasing ratio. However, incorporating the minimal PEEP along with PaO_2/FiO_2 ratio into the definition restricted its applicability among patients managed with arbitrary PaO_2/FiO_2 thresholds were also associated with an increase in the mortality and median duration of mechanical

Table 1. Components of ARDS definition and their limitations

Definition	Components of the definition	Limitations of the definition
American European Consensus Conference (AECC) criteria	Acute onset PaO_2/FiO_2 ratio ≤ 300 mmHg for acute lung injury and ≤ 200 mm Hg for ARDS (regardless of PEEP level) Bilateral infiltrates on frontal chest radiography PAWP ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension	The duration of onset was not mentioned Risk factors for ARDS were not formally defined PaO_2/FiO_2 ratio cut-off was arbitrary No minimal PEEP Poor interobserver reliability in chest radiography interpretation
Berlin definition	Onset of new or worsening respiratory symptoms within one week of known clinical insult Bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules) on chest imaging Respiratory failure not fully explained by cardiac failure or fluid overload A PaO_2/FiO_2 ratio ≤ 300 mmHg for with PEEP ≥ 5 cm H_2O Severity can be classified on basis of PaO_2/FiO_2 ratio: *Mild ARDS*= 201–300 mmHg *Moderate ARDS:* = 101–200 mmHg *Severe ARDS:* ≤ 100 mmHg	Chest radiograph or computed tomography scan may not be available in low-resource settings. Arterial blood gas analysis may not be available in resource-constrained settings With the requirement of PEEP ≥ 5 cm H_2O, diagnosis of ARDS among patients on HFNO or NIV is not possible
New Global Definition	Onset of new or worsening respiratory symptoms within one week of known risk factor Bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules) on chest imaging (chest radiograph or computed tomography scan or lung ultrasound) Pulmonary edema is not exclusively or primarily attributable to cardiogenic pulmonary edema/ fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. *Nonintubated ARDS* – PaO_2/FiO_2 ratio ≤ 300 mm Hg or SpO_2/FiO_2 ratio ≤ 315 (If SpO2 is ≤ 97%) on HFNO with flow of ≥ 30 L/min or NIV/CPAP with at least 5 cm H_2O end expiratory pressure *Intubated ARDS* – Severity can be classified on basis of PaO_2/FiO_2 (similar to Berlin definition) or SpO_2/FiO_2 ratio (If SpO_2 is ≤ 97%) with PEEP ≥ 5 cm H_2O Mild ARDS= 236–315 Moderate ARDS= 149–235 Severe ARDS= ≤ 148 *ARDS in resource-limited settings* – SpO_2/FiO_2 ratio ≤ 315 (If SpO_2 is ≤ 97%) with no mandatory PEEP or minimum flow rate of oxygen	Heterogeneity of the diagnosed populated with different subtypes such as resource-limited settings and nonintubated ARDS Subphenotypes such as hyperinflammatory versus hypoinflammatory were not integrated into the definition

ARDS - Acute Respiratory Distress Syndrome, CPAP - Continuous Positive Airway Pressure, HFNO - High Flow Nasal Oxygenation, NIV - Non-Invasive Ventilation, PAWP - Pulmonary Artery Wedge Pressure, PEEP - Positive End Expiratory Pressure

ventilation with decreasing ratio. However, incorporating the minimal PEEP along with PaO_2/FiO_2 ratio into the definition restricted its applicability among patients managed with high-flow nasal oxygen (HFNO) therapy. Moreover, the limited availability of arterial blood gas led to the search for alternative oxygenation metrics in resource-limited settings.

In 2016, Riviello et al., proposed modifying the Berlin criteria (Kigali modification) to address the challenges of ARDS diagnosis in resource-limited settings. The adaptations included the omission of mandatory PEEP, the adoption of an SpO_2/FiO_2 ratio ≤ 315 (if SpO_2 is ≤ 97%) in place of the PaO_2/FiO_2 ratio, and the incorporation of lung ultrasound with chest x-ray for detecting bilateral pulmonary opacities. In a small single-center study from Rwanda, the Kigali modification led to the identification of an additional 42 (4%) patients, with nearly one-third requiring ICU admission and a 50% mortality rate.[10] Subsequently, many studies evaluated its use in both high-income countries and resource-limited settings and reported concerns with potentially identifying patients without acute long injury and lesser severity.[11,12] A recent meta-analysis on the incidence and outcomes of ARDS in Sub-Saharan Africa noted a high variability and challenges of validation due to the use of different definitions (including Kigali modification), study design (retrospective), lack of inter-study comparison, and accuracy of SpO_2/FiO_2 ratio, especially in dark-skinned individuals and with SpO_2 >97%.[13] Although, Kigali modification is a considerable advancement towards feasibility, there are concerns related to the validity and reliability of the criteria, with potential for over-inclusive, diagnosing heterogenous pathologies and impact of interventions on the patients diagnosed with an extended definition (heterogeneity of treatment effect).

The New Global Definition of ARDS

In light of evolving evidence and advancements in clinical management, a new definition of ARDS was introduced in 2023.[14] The salient features of this new definition were:

1. the presence of confounding conditions such as atelectasis or pulmonary oedema secondary to cardiac failure or fluid overload, does not preclude the diagnosis of ARDS, as long as a known precipitating risk factor for ARDS exists.
2. accepting the use of lung ultrasound for chest imaging to diagnose bilateral opacities (infiltrates).
3. patients on high-flow nasal oxygen (HFNO) with a flow of ≥ 30 L/min could be included.
4. allowing the SpO_2/FiO_2 ratio as an alternative to PaO_2/FiO_2 ratio to assess oxygenation and severity of ARDS.
5. incorporation of Kigali modification as a criterion for resource-limited settings–no need for minimal PEEP and the use of alternative tools such as SpO_2/FiO_2 ratio and lung ultrasound, wherever feasible.

Similar to previous definitions and the Kigali modification, the New Global Definition is a forward step in the terms of feasibility; however, in the absence of an assessment of the reliability and validity, the widespread use of the definition will be challenging. The evidence from early takers is not encouraging,[15] particularly with the use of SpO_2/FiO_2 ratio,[16–18] and HFNO.[19,20]

Is the New Global Definition Truly Helpful in Low- and Middle-Income Countries?

Why do we need a new definition at all? The answer largely depends on the perspective from which the question is asked and on the inherent trade-offs involved.

From a research perspective, the broader feasibility and applicability of a New Global definition across diverse populations may seem advantageous. The Berlin Definition already presented significant diagnostic challenges, the LUNG SAFE study suggested that up to two-thirds of patients were either missed or diagnosed late for ARDS, leading to delays in implementing evidence-based interventions such as lung-protective ventilation and prone positioning.[21] However, this may come at the cost of reliability and validity, leading to a loss of homogeneity that could seriously hinder scientific progress—a potentially high price to pay for including more patients under the diagnosis. In contrast, for clinicians at the bedside, greater feasibility may be beneficial by enabling earlier recognition and timely management. From a patient perspective, reliability and validity may appear less critical, provided that feasibility supports faster and more effective care.

Connecting the dots – defining ARDS and the way forward

In the past decade, a growing body of research has delineated several distinct subphenotypes of ARDS, encompassing physiological, clinical, and biological domains. Although subphenotyping represents a considerable progress in personalized patient management and future research using predictive and prognostic enrichment. Currently, there is lack of prospective research about the feasibility and accuracy of subphenotyping ARDS in precision-based medicine.[22,23]

In the context of shortcomings of the current ARDS definition, an international Delphi expert panel identified the next steps for defining and subphenotypes of ARDS. Moreover, a broader consensus was developed on the conceptual model of ARDS, thereby, providing a foundational framework for the face validity of a future definition. The conceptual model of a patient with ARDS includes an acute onset (within days to weeks), the presence of a risk factor, infiltrates on lung imaging, lung inflammation, increased alveolar-capillary permeability, low pulmonary compliance, and ventilation-perfusion mismatch leading to increased dead space and/or substantial hypoxemia. Moreover, considering the ongoing scholarly discourse on ARDS definition, future attempts may consider contextualizing definitions for clinical care, research, and education.

Bridging the Future: Aligning Knowledge Gaps with Research Priorities

Our understanding of ARDS has advanced considerably over the past two decades; however, substantial lacunae still persist. In this context, aligning our research priorities with the knowledge gaps is the way forward. This aspect was deliberated upon and addressed by the international Delphi expert consensus on ARDS.[22] Several important knowledge gaps warrant attention, including:

1. Pathogenesis: The relative contributions of direct microbial injury, microthrombi formation, and pulmonary as well as endothelial capillary leakage in the development of ARDS.
2. Disease Trajectory: The influence of illness trajectory and response to therapeutic interventions on the diagnosis and classification of ARDS.
3. Severity Assessment: The reliability and validity of categorizing ARDS severity using the SpO_2/FiO_2 ratio as a surrogate for PaO_2/FiO_2.
4. Subphenotype Dynamics: The stability of ARDS subphenotypes across different patient populations, its temporal stages, and the resultant longitudinal disease trajectories.
5. Clinical Translation: The feasibility of translating subphenotype-based classifications into bedside practice to enable personalized patient management.

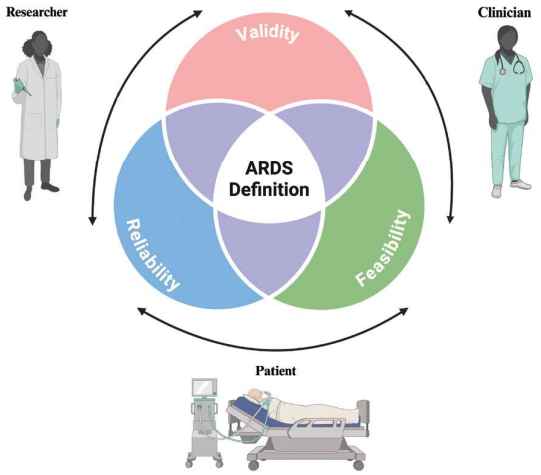

Figure 2: The framework for defining ARDS.

The definition of ARDS should be assessed within the framework of reliability, feasibility, and validity. Defining ARDS for stakeholders, including clinicians, researchers, and patients, requires a careful balance among these three components.

CONCLUSION

Capturing the complexity of ARDS within a single, uniform definition is a formidable task, more so in today's precision-medicine era where individual variability is increasingly recognized. The future definitions of ARDS should be measured not only on the framework of reliability, feasibility and validity, but also considering the trade-offs of the context (catering to clinical care, research and medical education), the dynamic trajectory (capturing the temporal trends of severity variables), and the diversity among patient population (Figure 2).

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