Annals of Intensive Care 16 (2026) 100057

Contents lists available at ScienceDirect

Annals of Intensive Care

journal homepage: www.elsevier.com/locate/aicoj

Review

Beyond the PaO_2/FiO_2 ratio: Rethinking ARDS severity through the Lens of physiology

Lou'i Al-Husinat[a], Raghad Khamis[b], Saif Azzam[c], Mohammad Trdeh[b], Basil Jouryyeh[b], Sarah Al Sharie[d], Mudhaffer Touqan[e], Ala' Alomari[f], Prashant Nasa[g,h], Marcus J. Schultz[i,j,k,l], Patricia RM Rocco[m,*,1], Denise Battaglini[n,o,*,1]

[a] Department of General Surgery and Anesthesia, Faculty of Medicine, Yarmouk University, Irbid, Jordan
[b] Department of Internal Medicine, Ministry of Health, Amman, Jordan
[c] Faculty of Medicine, Yarmouk University, Irbid, Jordan
[d] Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States
[e] Department of Emergency, Azraq Refugee Camp Hospital, International Medical Corps, Amman 11185, Jordan
[f] Department of Internal Medicine, Faculty of Medicine, Yarmouk University, Irbid, Jordan
[g] Department of Critical Care Medicine and Anesthesia, New Cross Hospital, the Royal Wolverhampton NHS Trust, Wolverhampton, UK
[h] Department of Intensive Care, Amsterdam University Medical Centers, Amsterdam, Netherlands
[i] Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand
[j] Nuffield Department of Medicine, University of Oxford, Oxford, UK
[k] Department of Anesthesia, General Intensive Care and Pain Management, Division of Cardiothoracic and Vascular Anaesthesia & Critical Care Medicine, Medical University Wien, Vienna, Austria
[l] Department of Anaesthesiology, Rescue–and Pain Medicine, Cantonal Hospital St. Gallen, HOCH Health Ostschweiz, St. Gallen, Switzerland
[m] Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[n] Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genova, Italy
[o] Anesthesia and Intensive Care, IRCCS Azienda Ospedaliera Metropolitana, Genova, Italy

ARTICLE INFO

Keywords:
Acute Respiratory Distress Syndrome
PaO_2/FiO_2ratio
ROX index
mechanical ventilation
personalized mechanical ventilation

ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a heterogeneous clinical syndrome encompassing distinct physiological and biological patterns of lung injury. Despite this heterogeneity, the ratio of arterial oxygen partial pressure to inspired oxygen fraction (PaO_2/FiO_2) remains the cornerstone of ARDS definitions, severity classification, and clinical decision-making. While its simplicity has facilitated widespread use, the PaO_2/FiO_2 ratio incompletely reflects the underlying physiological mechanisms of hypoxemia and should not be interpreted as a stand-alone marker of disease severity. The PaO_2/FiO_2 ratio is highly sensitive to ventilator settings, particularly positive end-expiratory pressure (PEEP), exhibits nonlinear behavior at high inspired oxygen fractions, and provides only a static assessment of gas-exchange. Consequently, it fails to capture key dimensions of ARDS pathophysiology, including lung recruitability, mechanical heterogeneity, and the temporal evolution of injury and response to therapy. These limitations are increasingly relevant in contemporary intensive care, where ventilatory strategies and adjunctive therapies actively modify oxygenation independent of structural lung injury. In this narrative review, we critically re-examine the physiological assumptions underlying the PaO_2/FiO_2 ratio and evaluate its role in current ARDS practice. We synthesize evidence supporting alternative and complementary oxygenation metrics, such as PEEP-adjusted indices, the oxygenation index, and composite measures including the ROX index (SpO_2/FiO_2 adjusted for

Abbreviations: ABG, arterial blood gas; ARDS, Acute Respiratory Distress Syndrome; ATS, American Thoracic Society; COVID-19, Coronavirus Disease 2019; CT, computed tomography; DISC, Department of Surgical Sciences and Integrated Diagnostics; ECMO, extracorporeal membrane oxygenation; ESICM, European Society of Intensive Care Medicine; FiO_2, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; ICU, intensive care unit; MORU, Mahidol-Oxford Tropical Medicine Research Unit; NHS, National Health Service; NIV, non-invasive ventilation; OI, oxygenation index; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; PaO_2/FiO_2 ratio, arterial oxygen partial pressure to fraction of inspired oxygen ratio; P/FP, PaO_2 / (FiO_2 × PEEP); PROSEVA, Proning Severe ARDS trial; ROX index, (SpO_2/FiO_2)/respiratory rate; SOFA, Sepsis-related Organ Failure Assessment; SpO_2, peripheral oxygen saturation; stP/F, standardized PaO_2/FiO_2 ratio; V'/Q', ventilation–perfusion.

* Corresponding authors.
E-mail addresses: prmrocco@biof.ufrj.br (P.R. Rocco), denise.battaglini@unige.it (D. Battaglini).
[1] P.R.M. Rocco and D. Battaglini are co-last authors who contributed equally to the writing of the manuscript.

https://dx.doi.org/10.1016/j.aicoj.2026.100057
; Received in revised form 13 March 2026
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respiratory rate), emphasizing their physiological rationale, clinical interpretability, and practical limitations at the bedside. These metrics are discussed not as replacements, but as tools that may refine the contextual interpretation of hypoxemia. Beyond static oxygenation measures, we explore emerging paradigms that conceptualize ARDS severity as a dynamic, multidimensional construct, integrating longitudinal oxygenation trajectories with respiratory mechanics, imaging-based assessment of lung aeration, and biomarker-informed biological subphenotypes. Repositioning the PaO_2/FiO_2 ratio within this integrated physiological and biological framework may improve patient stratification, enhance the coherence of therapeutic decision-making, in line with the translational goals of modern intensive care.

Background

Acute Respiratory Distress Syndrome (ARDS) remains a life-threatening condition in critically ill patients, associated with significant morbidity and mortality worldwide [1]. Since its first description in 1967 [2], ARDS has been defined by the acute onset of hypoxemic respiratory failure with bilateral pulmonary infiltrates and non-cardiogenic pulmonary edema [3]. Despite advances in supportive care and lung-protective ventilatory strategies, improvements in outcomes have been modest, underscoring the marked clinical heterogeneity and biological complexity of this syndrome [4].

Efforts to standardize ARDS diagnosis and severity assessment have evolved over decades, with the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) serving as the cornerstone of successive definitions [5]. The Berlin Definition introduced severity categories under standardized ventilatory conditions to improve prognostic discrimination [3]. More recently, the 2023 Global Definition extended applicability to non-intubated patients and endorsed validated oxygenation surrogates, such as the SpO_2/FiO_2 ratio, to facilitate assessment across diverse care settings [6]. This approach was further supported by the 2025 Delphi consensus, which identified the PaO_2/FiO_2 ratio as a core variable for characterizing ARDS in both clinical practice and research [7].

In addition, environmental factors such as altitude influence baseline PaO_2 and pulmonary hemodynamics. At elevations above 1500 m, the application of standard Berlin criteria may delay ARDS recognition, and both oxygenation indices and responses to PEEP require specific contextual interpretation [8]. These considerations are increasingly relevant with the recognition of high-altitude ARDS (HA-ARDS).

The widespread reliance on the PaO_2/FiO_2 ratio reflects its simplicity, availability, and consistent association with clinically relevant outcomes, including mortality and duration of mechanical ventilation [1]. Accordingly, it remains central to clinical trial eligibility and continues to inform key therapeutic decisions, such as prone positioning and escalation to extracorporeal membrane oxygenation (ECMO) [4,9]. However, the PaO_2/FiO_2 ratio has well-recognized physiological limitations. It is strongly influenced by ventilator settings, particularly positive end-expiratory pressure (PEEP) and FiO_2, exhibits nonlinear behavior at high FiO_2, and provides a static assessment of gas-exchange. As such, it offers limited insight into lung mechanics, recruitability, ventilation–perfusion heterogeneity, or the temporal disease evolution of lung injury and response to therapy. These limitations may lead to overlap between severity categories, potentially obscuring clinically meaningful differences among patients with similar degrees of hypoxemia.

Recent consensus documents have acknowledged these constraints while maintaining the central role of oxygenation indices. The 2023 Global Definition sought to enhance contextual interpretation rather than replace the PaO_2/FiO_2 ratio, aligning diagnostic criteria with contemporary respiratory support practices [6]. Similarly, American Thoracic Society guidelines continue to endorse severity-based decision-making grounded in oxygenation, while emphasizing the need for physiological judgment when escalating therapy [10]. Despite these refinements, there remains no widely accepted framework for integrating oxygenation indices with complementary physiological and biological markers in routine practice or clinical trial design.

Emerging evidence increasingly supports a multidimensional view of ARDS severity. Physiological variables such as respiratory system compliance, driving pressure, mechanical power, and dead space fraction, together with imaging-based assessment and molecular biomarkers, refine risk stratification and align more closely with distinct biological subphenotypes of lung injury [7]. This evolving perspective highlights that ARDS severity is best understood as a dynamic construct, rather than a fixed threshold defined by a single oxygenation ratio.

Against this background, the aim of this narrative review is to critically re-examine the conceptual foundations, clinical utility, and limitations of the PaO_2/FiO_2 ratio in contemporary ARDS care. By synthesizing evidence from evolving definitions, physiological studies, and emerging phenotyping approaches, we aim to reposition oxygenation assessment within an integrated framework that links bedside physiology with underlying biological mechanisms. This perspective intends to support more coherent clinical decision-making, improve patient stratification for interventional studies, and guide individualized management strategies in ARDS.

Why the PaO_2/FiO_2 ratio continues to matter in ARDS management

The PaO_2/FiO_2 ratio remains a cornerstone of ARDS management not because it captures the full biological and physiological complexity of the syndrome, but because it provides a practical, reproducible, and widely accessible measure of gas exchange impairment. Based on routinely available arterial blood gas analysis and the inspired oxygen fraction, it can be applied across diverse clinical settings, ranging from resource-limited environments to highly specialized intensive care units [3,11]. Its simplicity allows early severity assessment and supports timely bedside decision-making [12].

Beyond its feasibility, the PaO_2/FiO_2 ratio provides a standardized framework for communication, research, and protocol-driven care. Its incorporation into the Berlin Definition established a common language for ARDS diagnosis and severity stratification, enabling consistent trial enrollment and meaningful comparisons across studies [3]. Major interventional trials evaluating prone positioning and extracorporeal membrane oxygenation (ECMO) [13,14] have relied on PaO_2/FiO_2–based thresholds to identify patients most likely to benefit from advanced therapies. In this context, the PaO_2/FiO_2 ratio serves as an operational link between impaired oxygenation and therapeutic escalation.

The clinical relevance of the PaO_2/FiO_2 ratio is also supported by its prognostic value. Observational studies and meta-analyses consistently show that more severe hypoxemia, reflected by lower PaO_2/FiO_2 values, is associated with higher mortality, fewer ventilator-free days, and longer intensive care unit stays [1]. Although these severity categories do not represent discrete biological states, they provide clinically meaningful risk stratification and are

incorporated into widely used organ dysfunction scoring systems [15].

From a physiological standpoint, hypoxemia reflects the combined effects of intrapulmonary shunt, ventilation–perfusion mismatch, and diffusion impairment. The PaO_2/FiO_2 ratio therefore acts as a global indicator of gas exchange failure, even though it cannot distinguish among the underlying mechanisms [16]. When interpreted with appropriate attention to ventilator settings and inspired oxygen concentration, it remains a useful starting point for patient assessment.

At the same time, the features that make the PaO_2/FiO_2 ratio attractive, simplicity and standardization, also define its limitations [11,17]. Its dependence on PEEP and FiO_2, nonlinear behavior at high oxygen fractions, and inability to reflect lung mechanics or recruitability limit its interpretability when used in isolation. Recognizing these constraints is essential to place oxygenation within a broader physiological context, and to guide more individualized approaches to ARDS management.

When the PaO_2/FiO_2 ratio is reduced

Despite its established role, the PaO_2/FiO_2 ratio provides only a partial assessment of ARDS severity and may be misleading in certain clinical contexts [12]. Oxygenation is highly sensitive to ventilatory conditions, particularly PEEP, and to changes in inspired oxygen fraction along nonlinear regions of the oxygen dissociation curve. As a result, improvements in the PaO_2/FiO_2 ratio may occur in the absence of meaningful changes in alveolar recruitment, lung overdistension, or patient-centered outcomes. This dissociation is evident in trials of higher PEEP strategies, in which gains in oxygenation did not consistently translate into improved survival [18].

Hemodynamic factors can also influence the PaO_2/FiO_2 ratio independent of lung injury. Changes in cardiac output and pulmonary perfusion may substantially alter arterial oxygenation, leading to apparent improvements in the PaO_2/FiO_2 ratio that primarily reflect circulatory redistribution rather than true alveolar recruitment. Classic physiological studies have demonstrated that PEEP-induced increases in PaO_2 are frequently accompanied by proportional reductions in cardiac output, resulting in shunt reduction without meaningful improvement in ventilation–perfusion matching and, in some cases, in global oxygen transport. Experimental and clinical studies have shown that reduced pulmonary perfusion, whether due to hypovolemia or right ventricular dysfunction, can worsen oxygenation indices despite relatively preserved lung mechanics [19,20].

Additional limitations arise from the nonlinear relationship between PaO_2 and FiO_2. Identical PaO_2/FiO_2 ratios obtained at different FiO_2 levels may correspond to distinct physiological states, reducing comparability across patients and over time. This issue becomes particularly relevant when oxygenation is estimated using SpO_2/FiO_2 ratio, for which accuracy declines at higher saturation ranges despite validated correction methods [21,22].

Importantly, the PaO_2/FiO_2 ratio does not capture several key dimensions of ARDS pathophysiology, including respiratory system compliance, dead space ventilation, ventilation–perfusion heterogeneity, or the mechanical forces imposed by ventilatory support [23,24]. In spontaneously breathing patients receiving high-flow nasal oxygen or noninvasive ventilation, variable and imprecise FiO_2 delivery further reduces the reliability of oxygenation-based indices [6]. Moreover, ARDS is a dynamic condition [25], and single time-point measurements fail to reflect evolving trajectories that carry prognostic and therapeutic significance [26].

While the PaO_2/FiO_2 ratio provides useful risk stratification, it is limited by its sensitivity to ventilatory settings and patient-specific factors, and does not capture underlying lung mechanics, recruitability, or biological heterogeneity. Consequently, identical PaO_2/FiO_2 values may represent substantially different physiological states, which can affect both prognostic assessment and therapeutic decision-making [27].

Standardization of ventilatory conditions has been proposed to improve comparability of PaO_2/FiO_2 measurements. Villar et al. suggested that both FiO_2 and PEEP should be standardized when using PaO_2/FiO_2 for ARDS severity assessment, enhancing the reliability of risk stratification across patients and studies [28].

Interpretation of PaO_2/FiO_2 ratios may also require adjustment in patients residing at high altitude. Altered baseline PaO_2 and pulmonary hemodynamics above 1500 m can influence both oxygenation and PEEP response, potentially delaying ARDS diagnosis and affecting clinical management [29].

Together, these limitations preserve the clinical relevance of the PaO_2/FiO_2 ratio while clearly defining the risks associated with its use in isolation. Rather than serving as a definitive marker of disease severity, the PaO_2/FiO_2 ratio should be viewed as an initial descriptor whose clinical meaning emerges only when integrated with complementary physiological, imaging, and biological information. Such an approach more accurately reflects the multidimensional and evolving nature of ARDS and supports more informed clinical decision-making (Table 1).

What else should we measure? Refining oxygenation beyond the PaO_2/FiO_2 ratio

Recognition of the physiological and interpretative limitations of the PaO_2/FiO_2 ratio has stimulated the development of complementary oxygenation metrics designed to preserve bedside feasibility while improving clinical context. These measures can be broadly categorized as pressure-adjusted, ventilation-adjusted, effort-sensitive, and resource-adapted measures, each addressing specific factors that systematically confound interpretation of conventional oxygenation indices in ARDS.

Importantly, large-scale observational data indicate that variables reflecting respiratory mechanics and ventilatory intensity may provide stronger prognostic information than oxygenation alone. In a secondary analysis of the LUNG SAFE cohort, normalized elastance, driving pressure, and the composite variable $4\Delta P$ plus respiratory rate, measured on day 1 of controlled mechanical ventilation, were the strongest predictors of ICU mortality, outperforming both PaO_2/FiO_2 and mechanical power. These findings reinforce the concept that oxygenation severity, when interpreted in isolation, incompletely reflects the biological and mechanical burden of lung injury, and that integration of respiratory mechanics and ventilation intensity provides a more physiologically grounded framework for risk stratification [30].

Pressure-adjusted indices represent the most direct refinement of the PaO_2/FiO_2 ratio. The P/FP ratio incorporates PEEP into the conventional PaO_2/FiO_2 metric [PaO_2 /(FiO_2 × PEEP)], thereby capturing the contribution of end-expiratory lung volume and ventilatory intensity to arterial oxygenation. In a pooled analysis of seven ARDS Network trials including more than 3400 patients [31], the P/FP ratio demonstrated improved discrimination for hospital mortality compared with the PaO_2/FiO_2 ratio, particularly at higher PEEP levels. These findings suggest that accounting for ventilatory pressure improves prognostic accuracy without departing from familiar diagnostic thresholds [32] (Fig. 1).

Ventilation-adjusted metrics aim to capture abnormalities in gas exchange that are obscured by oxygenation alone. The standardized PaO_2/FiO_2 ratio (stP/F) incorporates $PaCO_2$ as a surrogate of alveolar hypoventilation and respiratory drive, thereby providing a more integrated view of gas-exchange efficiency [(PaO_2 + 1.66 × $PaCO_2$–66.4)/FiO_2] [33]. Observational studies, including prospective cohorts of patients with COVID-19–related acute respiratory failure,

Table 1
Comparative overview of oxygenation indices used in ARDS.

Index (Formula)	Key features and strengths	Principal limitations and challenges
PaO_2/FiO_2 ratio	**Simplicity and standardization:** Requires only PaO_2 and FiO_2; universally available and anchors major ARDS definitions (Berlin, Global) and clinical trial enrollment. **Prognostic relevance:** Lower values are associated with higher mortality at the population level. **Clinical communication:** Provides a common framework to guide escalation strategies (e.g., prone positioning, ECMO).	**Physiological reductionism:** Condenses a heterogeneous syndrome into a single variable; insensitive to lung mechanics, dead space, and V'/Q' heterogeneity. **Ventilator dependence:** Strongly influenced by PEEP and FiO_2; changes may reflect ventilatory adjustments rather than lung recovery. **Static measurement:** Single time-point measurements fail to capture temporal trajectories and perform poorly in spontaneously breathing or unstable patients.
P/FP Ratio ($PaO_2/(FiO_2$ x PEEP))	**Physiological contextualization:** Incorporates PEEP, partially accounting for ventilatory intensity and recruitment. **Improved discrimination:** May enhance prognostic stratification compared with the PaO_2/FiO_2 ratio, particularly at higher PEEP levels.	**Increased complexity:** Requires additional calculation, limiting intuitive bedside use. **Limited generalizability:** Validation is heterogeneous, with inconsistent impact on clinical decision-making across ARDS subphenotypes.
Standardized PaO_2/FiO_2 (stP/F) $(PaO_2 + 1.66 \times PaCO_2 - 66.4)/FiO_2$	**Integrated gas-exchange assessment:** Adjusts for $PaCO_2$, capturing effects of hypoventilation and respiratory drive. **Improved prognostic performance:** Demonstrates improved performance over the conventional PaO_2/FiO_2 ratio in selected cohorts, including COVID-19–related respiratory failure.	**Operational complexity:** Requires full arterial blood gas analysis and calculation, limiting rapid bedside applicability. **Context-dependent validation:** Validation largely confined to specific disease populations.
Oxygenation Index (OI) (FiO_2 x Mean Airway Pressure / PaO_2)	**Ventilatory intensity integration:** Incorporates mean airway pressure, offering a mechanistically richer assessment of oxygenation failure. **Established clinical role:** Widely used in pediatric ARDS and ECMO referral criteria.	**Restricted applicability:** Dependent on invasive ventilation and unavailable in non-intubated patients. **Limited adult adoption:** Less practical for routine use compared with simpler indices.
ROX Index (SpO_2/FiO_2/Respiratory Rate)	**Effort-sensitive assessment:** Integrates oxygenation with respiratory rate, reflecting work of breathing. **Predictive validity:** Well validated for predicting HFNO success or failure. **Bedside feasibility:** Rapid, non-invasive, and intuitive.	**Context specificity:** Designed for HFNO monitoring rather than global ARDS diagnosis or severity grading. **Pulse oximetry limitations:** Influenced by perfusion, dyshemoglobinemia, and skin pigmentation.
S/F Ratio (SpO_2/FiO_2) & Kigali Modification	**Global accessibility:** Enables ARDS identification without arterial blood gases, improving feasibility in resource-limited settings. **Equity-focused innovation:** Incorporated into the 2023 Global ARDS Definition. **Validation:** Kigali criteria (S/F $\leq$ 315 with SpO_2 $\leq$97%) validated across multiple low-income settings.	**Surrogate limitations:** Shares FiO_2 dependence and physiological limitations of the PaO_2/FiO_2 ratio. **Measurement variability:** Susceptible to errors related to perfusion, hemoglobin abnormalities, and oximeter bias.

Summary of commonly used oxygenation indices in acute respiratory failure and ARDS, including their formulas, principal physiological features, clinical strengths, and key limitations. The table contrasts traditional gas-exchange–based metrics with indices that incorporate ventilatory intensity, respiratory effort, or noninvasive surrogates, highlighting their respective applicability across different clinical contexts, levels of respiratory support, and resource settings. Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; HFNO, high-flow nasal oxygen; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; PEEP, positive end-expiratory pressure; SpO_2, peripheral oxygen saturation; V'/Q', ventilation–perfusion.

suggest that this approach may outperform the traditional PaO_2/FiO_2 ratio in predicting clinical deterioration and the need for invasive ventilation, particularly in patients with combined oxygenation and ventilatory impairment [34].

In non-intubated patients, indices that incorporate respiratory effort are particularly informative. The ROX index, which combines SpO_2/FiO_2 with respiratory rate, has been consistently validated as a predictor of high-flow nasal oxygen success. By integrating oxygenation with respiratory workload, the ROX index addresses a critical limitation of the PaO_2/FiO_2 ratio: its inability to reflect the physiological cost of maintaining oxygenation. Its simplicity and reproducibility have facilitated widespread adoption in clinical practice, especially during the COVID-19 pandemic [35]. Prospective data indicate that ROX performs at least as well as more complex composite scores in this setting [30,31].

For invasively ventilated patients, the oxygenation index (OI), which incorporates mean airway pressure [(FiO_2 $\times$ mean airway pressure)/PaO_2], provides a more physiologically grounded assessment of hypoxemia severity by explicitly accounting for the intensity of ventilatory support. Long established in pediatric ARDS and ECMO decision-making [36], OI offers valuable insight into oxygenation failure that is not captured by PaO_2/FiO_2 alone, although the need for additional ventilatory variables has limited its routine use in adult practice [32].

More recently, composite indices linking oxygenation to mechanical stress have been proposed. The Oxygenation Stretch Index (OSI), which integrates PaO_2/FiO_2 and driving pressure, was shown to be independently associated with 60-day mortality in patients with COVID-19–associated ARDS [37]. By explicitly coupling oxygenation impairment with the magnitude of cyclic lung stress, OSI conceptually bridges gas exchange and ventilator-induced lung injury risk, reinforcing the principle that severity assessment should reflect not only how well the lung oxygenates, but also the mechanical cost at which oxygenation is achieved. Although current evidence remains limited to selected populations, this approach exemplifies the shift toward physiologically integrated severity metrics (Fig. 2).

In settings where arterial blood gas analysis is unavailable, SpO_2/FiO_2-based approaches, including the Kigali modification, offer pragmatic alternatives [17]. These strategies have expanded ARDS recognition in low-resource environments and are now incorporated into the 2023 Global Definition. However, their performance remains influenced by FiO_2 variability, peripheral perfusion, and the inherent limitations of pulse oximetry, particularly at higher saturation levels [36,37].

Despite these developments, no alternative oxygenation metric has consistently demonstrated superiority over the PaO_2/FiO_2 ratio across diverse ARDS populations or led to clear changes in therapeutic decision-making [11]. Constraints related to computational complexity, parameter availability, and context-specific applicability continue to limit widespread adoption. As a result, the PaO_2/FiO_2 ratio remains the anchor of oxygenation assessment, while complementary indices provide physiological nuance and situational specificity. Together, these tools reflect a shift from reliance on a single static measure toward a more informed, context-aware evaluation of hypoxemia in ARDS.

Emerging insights: trajectories, subphenotypes, and multidimensional assessment

Although refined oxygenation indices improve contextual interpretation, they remain constrained by a shared reliance on isolated measurements of gas exchange. Increasing evidence indicates that

	PaO_2/FiO_2	SpO_2/FiO_2	ROX	OI	P/FP	stP/F
Conventional O_2	🔴	🟡	🔴	🔴	🔴	🔴
HFOT	🔴	🟡	🟢	🔴	🔴	🔴
NIV	🟡	🟡	🟡	🔴	🔴	🔴
Invasive MV	🟢	🟡	🔴	🟢	🟢	🟡
ECMO	🟡	🔴	🔴	🟡	🟡	🟡

🟢 = Valid / preferred
🟡 = Context dependent
🔴 = Limited reliability

Fig. 1. Context-dependent validity of commonly used oxygenation indices across respiratory support modalities.
This schematic summarizes the physiological appropriateness and known limitations of widely used oxygenation indices—PaO_2/FiO_2, SpO_2/FiO_2, ROX index, oxygenation index (OI), PaO_2/FiO_2 adjusted for mean airway pressure (P/FP), and standardized PaO_2/FiO_2 (stP/F)—across different levels of respiratory support, including conventional oxygen therapy, high-flow oxygen therapy (HFOT), noninvasive ventilation (NIV), invasive mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). Color coding reflects conceptual interpretation based on underlying physiology: green indicates indices that are physiologically appropriate and commonly informative in a given context; yellow denotes indices whose interpretation requires careful consideration of ventilatory settings, support modality, and clinical context; red indicates substantial limitations or reduced interpretability due to decoupling between measured oxygenation and effective lung stress, ventilatory support, or gas exchange mechanisms. This figure represents a conceptual synthesis of physiological principles and methodological constraints and is not intended as a guideline, performance ranking, or outcome prediction tool.

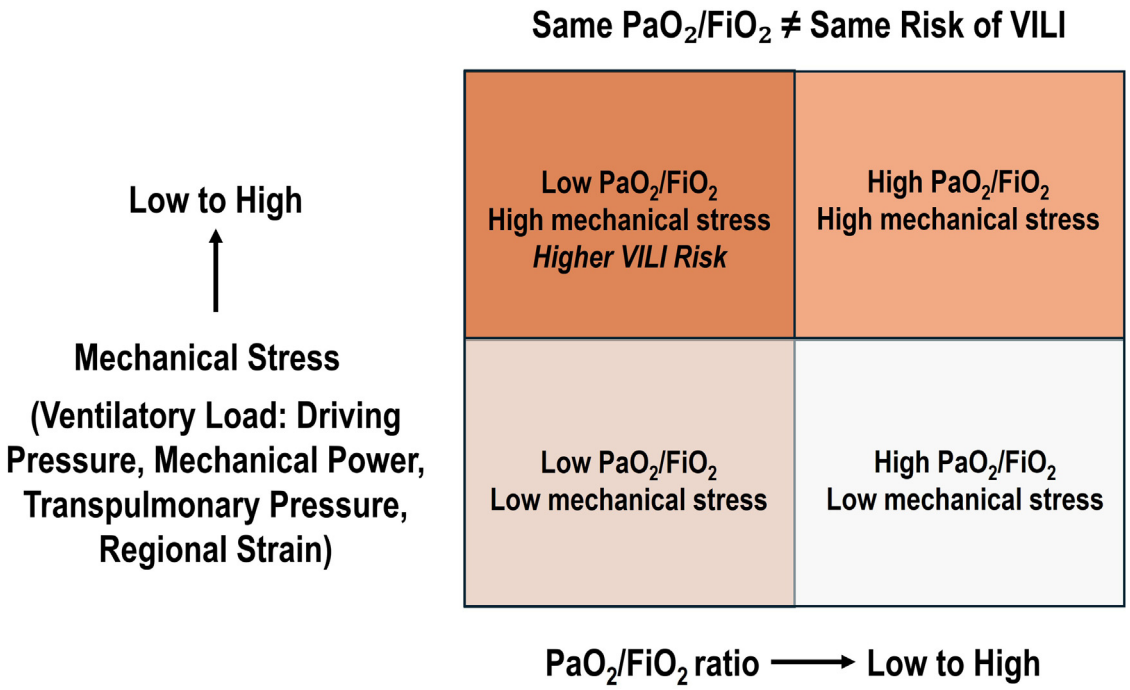

Fig. 2. Similar oxygenation does not imply similar risk of ventilator-induced lung injury (VILI).
Conceptual matrix illustrating that patients with comparable PaO_2/FiO_2 may be exposed to substantially different risks of VILI depending on the level of mechanical stress imposed by ventilation. Mechanical stress denotes the ventilatory load applied to the lung (e.g., driving pressure, mechanical power, transpulmonary pressure, or regional strain) and is not intended to represent disease severity. High mechanical stress is associated with increased VILI risk regardless of PaO_2/FiO_2, whereas low mechanical stress may limit lung injury even in the presence of impaired oxygenation. Shading reflects conceptual differences in relative risk rather than quantitative or validated risk categories. This framework emphasizes the limitations of oxygenation-based assessment alone and supports integrating ventilatory mechanics into lung-protective decision-making.

ARDS severity is more accurately characterized by temporal trajectories of physiological variables and by underlying biological heterogeneity than by static oxygenation thresholds alone. This concept is consistent with large observational cohorts, such as LUNG SAFE [1], in which early respiratory mechanics and ventilatory intensity outperformed oxygenation alone in outcome prediction.

Large multicenter analyses demonstrate that the evolution of oxygenation over the first 24–48 h provide substantially greater prognostic information than baseline PaO_2/FiO_2 ratio categories [38]. Patients with persistent or worsening hypoxemia during this early period experience markedly higher mortality than those with early improvement, even when initial oxygenation severity is comparable

[39]. Reassessment of oxygenation after initial stabilization and under standardized ventilatory conditions improves risk stratification and may better identify patients most likely to benefit from escalation strategies such as prone positioning or extracorporeal support [40]. These findings highlight the limitations of single time-point classifications and reinforce the dynamic nature of ARDS progression.

Beyond physiological trajectories, molecular subphenotyping has revealed biologically distinct ARDS subsets that are not captured by oxygenation metrics. Hyperinflammatory phenotypes, characterized by elevated circulating cytokines, markers of endothelial injury, and soluble tumor necrosis factor receptors, are consistently associated with worse outcomes despite similar PaO_2/FiO_2 values at presentation [41]. Importantly, these subphenotypes show differential responses to therapies, including corticosteroids, fluid management strategies, and immunomodulatory interventions [42]. These observations support a framework in which oxygenation severity is interpreted alongside systemic inflammatory status to guide therapeutic decisions and trial design.

Advanced imaging further exposes the limitations of oxygenation-based classification. Patients with similar PaO_2/FiO_2 ratios may differ substantially in lung recruitability, regional aeration, and ventilation–perfusion matching. Computed tomography–based analyses have shown that a meaningful proportion of patients classified as mild or moderate ARDS have highly recruitable lungs [43], whereas others with severe hypoxemia demonstrate limited recruitability and greater susceptibility to ventilator-induced lung injury [44,45]. Such heterogeneity has direct implications for ventilatory strategy selection and risk mitigation.

Collectively, these insights support a multidimensional framework for ARDS assessment (Fig. 3), integrating four complementary domains: gas exchange, lung mechanics, structural and functional imaging, and biological phenotype. Within this framework, the PaO_2/FiO_2 ratio retains value as an initial screening and communication tool but is insufficient as a stand-alone marker of disease severity. Emerging computational approaches may facilitate integration of these data streams, although their clinical utility will depend on rigorous validation, interpretability, and feasibility at the bedside [6,46].

In this evolving landscape, the role of the PaO_2/FiO_2 ratio is being refined rather than replaced. Its greatest value lies in anchoring assessment within a broader, dynamic, and individualized understanding of ARDS pathophysiology—one that acknowledges hetero-

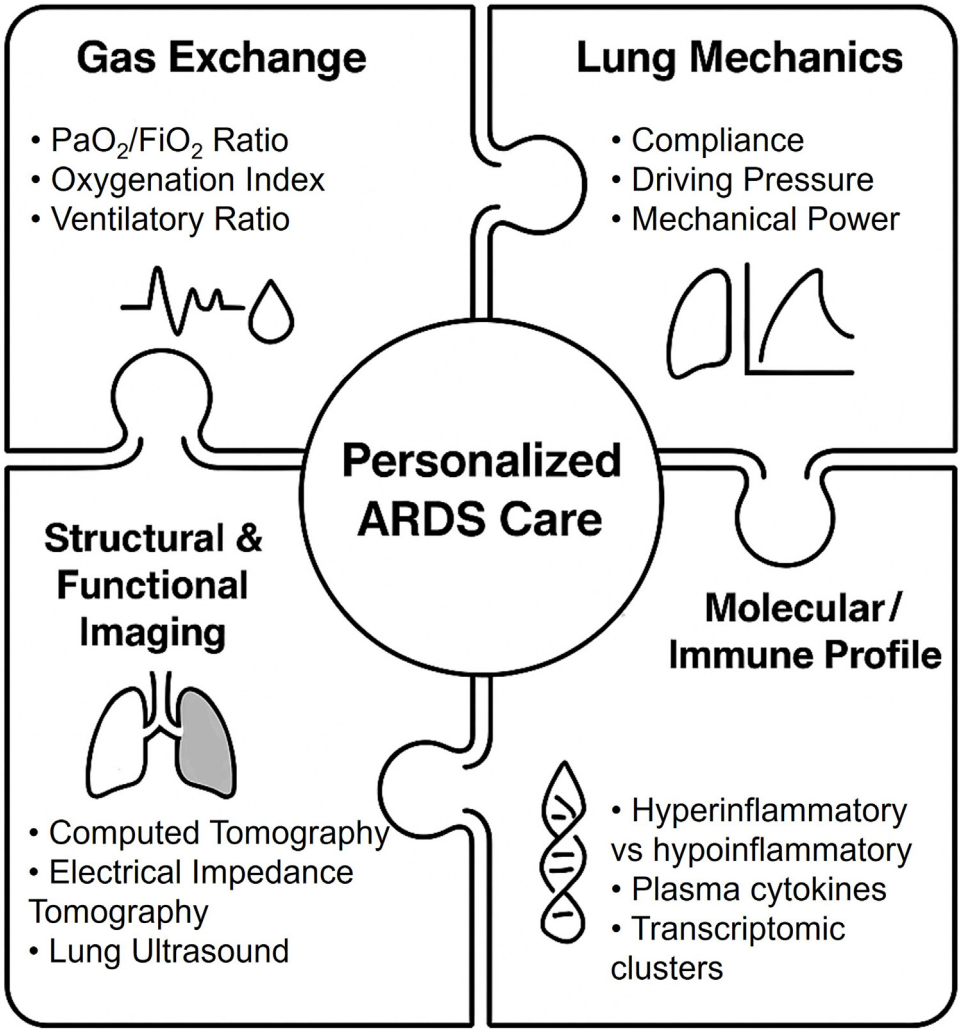

Fig. 3. Multidimensional framework for personalized assessment and management of ARDS.
Schematic representation of a multidimensional approach to ARDS severity assessment, integrating four complementary domains that jointly inform personalized care. Gas exchange reflects global impairment of oxygenation, traditionally assessed by the PaO_2/FiO_2 ratio and related indices. Lung mechanics encompass respiratory system compliance, driving pressure, and mechanical power. Structural and functional imaging [e.g., computed tomography, electrical impedance tomography and lung ultrasound] provides insight into lung aeration, regional heterogeneity, and recruitability. Molecular and immune profiling reflects underlying biological heterogeneity, including inflammatory and endothelial injury pathways. The convergence of these domains supports a dynamic, integrated evaluation of ARDS that moves beyond single static metrics toward individualized, mechanism-informed clinical decision-making.

geneity, tracks disease evolution, and aligns physiological insight with more precise and adaptive critical care strategies [47].

Clinical guidelines and recommendations

Current international guidelines continue to position the PaO_2/FiO_2 ratio as a central component of ARDS diagnosis, severity stratification, and therapeutic decision-making, while explicitly emphasizing that it should not be interpreted in isolation. Recent guidance from major societies, including the American Thoracic Society, the European Society of Intensive Care Medicine, and the Surviving Sepsis Campaign, reaffirms the PaO_2/FiO_2 ratio as a key trigger for evidence-based interventions, particularly prone positioning and ECMO [48].

Prone positioning is strongly recommended for patients with moderate-to-severe ARDS who remain hypoxemic despite optimized lung-protective ventilation, most commonly defined by a PaO_2/FiO_2 ratio below 150 mmHg. This recommendation is supported by high-quality evidence demonstrating a survival benefit in this population, most notably in the PROSEVA trial [14]. Similarly, venovenous ECMO is advised for selected patients with refractory hypoxemia, commonly using PaO_2/FiO_2 thresholds below 80 mmHg after maximal conventional support, consistent with criteria employed in the EOLIA trial and subsequent guideline statements [13]. These thresholds remain essential for aligning escalation pathways, referral practices, and clinical trial eligibility.

At the same time, current guidelines emphasize that oxygenation thresholds must be interpreted within a broader clinical and physiological context. Decision-making should incorporate radiographic confirmation of bilateral lung involvement, assessment of respiratory system mechanics, including compliance, plateau pressure, and driving pressure, hemodynamic stability, and the temporal evolution of oxygenation. This approach recognizes the ventilator dependence and temporal variability of the PaO_2/FiO_2 ratio and reduces the risk of misclassification based on isolated measurements.

Although emerging data indicate that biological subphenotypes, particularly hyperinflammatory profiles characterized by elevated markers such as interleukin-6 or angiopoietin-2, are associated with worse outcomes despite similar PaO_2/FiO_2 ratios [41], current guidelines do not recommend biomarker-guided management in routine practice. Instead, these findings delineate a clear research priority, requiring prospective validation and demonstration of feasibility across diverse clinical settings before integration into formal recommendations.

In summary, within existing guideline frameworks, the PaO_2/FiO_2 ratio remains an indispensable, rapid, and widely applicable triage tool that anchors key therapeutic decisions. Its strength lies not in comprehensive pathophysiological characterization, but in its role as a standardized entry point into a multidimensional assessment that aligns reproducible care pathways with individualized clinical judgment. As ARDS management evolves, future guidelines are likely to build upon, rather than replace, this foundation by incorporating trajectories, physiology, and biological heterogeneity into more nuanced decision frameworks.

The future of ARDS evaluation

The assessment of ARDS is progressively moving beyond static, threshold-based metrics toward dynamic and multidimensional frameworks that more accurately reflect disease heterogeneity and temporal evolution. Increasing evidence demonstrates that longitudinal oxygenation trajectories offer greater prognostic value than isolated PaO_2/FiO_2 ratio measurements, allowing identification of distinct patterns of persistence, improvement, or resolution that are closely associated with clinical outcomes [47,49].

Within this evolving paradigm, computational approaches that integrate serial PaO_2/FiO_2 ratios with additional physiological variables, such as ventilatory parameters, respiratory rate dynamics, and continuous pulse oximetry, are under active investigation. Retrospective and single-center studies suggest that such models may improve early risk stratification and anticipate clinical deterioration before conventional recognition. However, these approaches remain largely exploratory. Their clinical adoption will depend on rigorous external validation, transparency in model development, and demonstration of consistent benefit across diverse patient populations and healthcare systems.

Parallel advances in non-invasive monitoring offer more immediately applicable opportunities to refine ARDS evaluation. Continuous SpO_2/FiO_2 assessment combined with respiratory rate analysis may facilitate earlier identification of evolving hypoxemic respiratory failure outside the ICU, including emergency departments and hospital wards [6]. These strategies are particularly relevant in resource-limited settings, where adaptations such as the Kigali criteria allow ARDS identification without arterial blood gas analysis [17]. Ongoing studies are evaluating whether these strategies can meaningfully shorten time to intervention and improve outcomes in pre-ICU populations [50,51].

One of the most significant conceptual advances has been the development of composite physiological indices that interpret oxygenation within the broader context of lung pathophysiology. Indices incorporating the PaO_2/FiO_2 ratio alongside variables such as PEEP, $PaCO_2$, dead space fraction, respiratory system compliance, and mechanical power have demonstrated improved prognostic performance over oxygenation alone in selected cohorts [33]. These findings suggest that future ARDS definitions and management algorithms may continue to rely on the PaO_2/FiO_2 ratio as a foundational measure, while embedding it within layered indices that better capture ventilatory intensity and the severity of lung injury.

Despite rapid innovation, feasibility, interpretability, and generalizability remain critical considerations. Advanced analytic tools and composite metrics must be evaluated not only for predictive accuracy but also for their impact on clinical decision-making and accessibility across varied care settings. In this context, the enduring strength of the PaO_2/FiO_2 ratio lies in its simplicity and universal availability, supporting its role as an initial screening and triage metric within stepped diagnostic and therapeutic frameworks. More sophisticated physiological and computational tools are likely to complement, rather than replace, the PaO_2/FiO_2 ratio by enabling more refined assessment in patients with severe, atypical, or refractory disease.

Conclusions

The PaO_2/FiO_2 ratio remains a foundational component of ARDS diagnosis and severity stratification, supported by its simplicity, broad availability, and reproducible association with clinically meaningful outcomes. Its continued inclusion in international definitions and practice guidelines reflects its practical value as a rapid and universally applicable indicator of hypoxemia. At the same time, the PaO_2/FiO_2 ratio is inherently constrained by physiological nonlinearity, sensitivity to ventilatory and hemodynamic conditions, and limited ability to reflect the biological heterogeneity and temporal evolution of lung injury.

Accumulating evidence indicates that ARDS severity cannot be adequately characterized by a single, static oxygenation metric. Pressure- and ventilation-adjusted indices, measures incorporating respiratory effort, longitudinal oxygenation trajectories, and biologically informed subphenotypes offer complementary perspectives that more closely link gas exchange abnormalities to underlying

pathophysiology and treatment responsiveness. Integrating oxygenation with respiratory mechanics, ventilatory intensity, and systemic inflammatory profiles improves risk stratification and better reflects the complexity of ARDS encountered at the bedside.

Future frameworks for ARDS assessment should therefore reposition the PaO_2/FiO_2 ratio not as a stand-alone determinant of severity, but as an initial reference point within a dynamic, multidimensional evaluation strategy. Preserving its role as a pragmatic triage and communication tool, while embedding it within physiologically and biologically informed models, provides a coherent path toward more individualized clinical decision-making and more precise trial design. In this context, the enduring value of the PaO_2/FiO_2 ratio lies not in its completeness, but in its ability to anchor a broader and more nuanced understanding of ARDS severity.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

PRMR received personal grants from the Brazilian Council for Scientific and Technological Development (CNPq; grant 0306599/2023-6) and the Rio de Janeiro State Research Foundation (FAPERJ; grant E-26/210.338/2022), none of which supported the present work. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

Data availability

Not applicable.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank Moira Elizabeth Schottler, MBA, Rio de Janeiro, Brazil, for editing assistance.

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