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Review Article

Subphenotypes of Acute Respiratory Distress Syndrome: From Biological Heterogeneity to Precision Medicine

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Abstract

Despite the 2012 Berlin definition standardizing acute respiratory distress syndrome (ARDS) diagnosis, pharmacological therapies have consistently failed in phase 3 trials, partly reflecting the syndrome's profound biological heterogeneity. We synthesize evidence on ARDS subphenotyping to evaluate prospects for precision medicine. This narrative review was informed by targeted searches of PubMed/MEDLINE, Embase, and Web of Science from database inception through February 2026, supplemented by an updated PubMed/MEDLINE search through September 2026. Representative clinical trials, multicenter cohorts, mechanistic studies, and methodological reports were selected to support a critical synthesis of ARDS subphenotyping, its therapeutic implications, and barriers to clinical translation. Hyperinflammatory and hypoinflammatory subphenotypes—originally identified using plasma biomarkers (IL-6, IL-8, and soluble tumor necrosis factor receptor 1) in the ARMA and ALVEOLI cohorts—demonstrate reproducible differences in mortality, with worse outcomes in the hyperinflammatory subphenotype, and have shown potential treatment-effect heterogeneity in secondary analyses. Approximately 30%–35% of patients exhibit the hyperinflammatory profile, characterized by greater vasopressor requirements and organ failure. Radiological phenotypes (focal versus non-focal) on computed tomography imaging have been associated with differences in lung recruitability and physiological responses to ventilatory interventions, although the LIVE trial did not demonstrate an overall survival benefit from morphology-guided ventilation. Recent multi-omics studies (transcriptomic, proteomic, and metabolomic) reveal distinct endotypes involving dysregulated innate immunity, endothelial activation, and aberrant coagulation. Machine learning algorithms, particularly unsupervised clustering and deep learning-based computed tomography radiomics, have been investigated for more rapid phenotyping, but reported performance varies by task, cohort, and validation design. However, prospective, phenotype-guided randomized trials remain limited. Subphenotype stratification offers a mechanistically grounded framework for re-evaluating therapies that were ineffective in unselected populations and for investigating phenotype-informed ventilatory strategies. Clinical implementation requires standardized, bedside-compatible biomarker panels and definitive trials demonstrating that phenotype-specific interventions improve patient-centered outcomes.

Introduction

Acute respiratory distress syndrome (ARDS) is a severe, diffuse inflammatory lung injury characterized by alveolar epithelial disruption and refractory hypoxemia.[1,2] Despite refinements in supportive care—namely lung-protective ventilation, prone positioning, and restrictive fluid management—mortality remains substantial (34.9%–46.1%), and effective pharmacotherapies remain elusive.[3,4] A fundamental obstacle to therapeutic progress lies in the syndrome's marked biological heterogeneity: patients meeting Berlin criteria (2012) exhibit divergent etiologies, inflammatory intensities, and mechanical phenotypes that likely obscure treatment signals in traditional trial designs.[5]

The limitations of syndrome-based definitions have become increasingly apparent following successive negative phase 3 trials (e.g., rosuvastatin, ketoconazole), as well as phase 2 trials such as simvastatin and aspirin.[6-9] These failures suggest that aggregating patients by hypoxemia severity and chest radiographic appearance—while clinically practical—may conflate distinct patho-

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physiological entities. Consequently, attention has shifted toward identifying subphenotypes: relatively homogeneous subgroups characterized by differential biomarker profiles and clinical trajectories, with some studies suggesting potential treatment-effect heterogeneity.

Latent class analysis (LCA) of plasma biomarkers in the ARMA and ALVEOLI cohorts first identified the hyperinflammatory and hypoinflammatory subphenotypes, demonstrating that approximately one-third of patients exhibit a systemic inflammatory profile associated with higher mortality and suggesting potential differential responses to positive end-expiratory pressure (PEEP) and fluid-management strategies in secondary analyses.[10-12] Subsequent integration of transcriptomic, proteomic, and radiomic data has further delineated mechanistically distinct endotypes, moving beyond descriptive classification toward mechanistic understanding.[13,14]

Figure 1 summarizes the clinical, radiological, and biological approaches to ARDS subphenotyping discussed in this review and their potential integration with artificial intelligence (AI). Green, yellow, and red indicate clinically available or routinely measurable, investigational, and aspirational elements, respectively. The proposed pathway is conceptual and has not been prospectively validated for treatment selection.

In this narrative review, we critically synthesize developments in ARDS subphenotyping across clinical, physiological, radiological, hemodynamic, biological, and artificial intelligence–assisted domains. We examine the stability and conceptual validity of proposed classifications, the methodological rigor and reproducibility of phenotyping approaches, and the barriers that currently limit bedside implementation. Our objective is to provide a clinically pragmatic roadmap for research and trial design rather than to propose practice-changing phenotype-directed treatment recommendations.

Targeted searches of PubMed/MEDLINE, Embase, and Web of Science were conducted from database inception through February 2026 using combinations of terms related to ARDS subphenotypes, endotypes, latent class analysis, biomarkers, hemodynamics, artificial intelligence, and precision medicine. PubMed/MEDLINE was additionally searched through September 2026 to identify recently published prospective and multi-omic studies. We prioritized landmark clinical trials and their secondary analyses, multicenter cohort studies, external validation studies, mechanistic investigations, and relevant methodological reviews. The selected literature was critically synthesized to evaluate the reproducibility, therapeutic implications, and translational limitations of proposed ARDS subphenotypes. Given the narrative and interpretive scope of this review, no formal systematic-review protocol, risk-of-bias assessment, or meta-analysis was undertaken.

ARDS heterogeneity: The rationale for subphenotyping

Biological and clinical heterogeneity in ARDS manifests across multiple dimensions even among patients fulfilling the Berlin criteria.[15] Etiological drivers range from direct pulmonary insults (pneumonia, aspiration, inhalation injury) to indirect systemic insults (sepsis, trauma, pancreatitis), each engendering distinct inflammatory intensities, lung mechanics, and histopathological patterns.[16,17] This variability underlies the significant differences in mortality rates among different phenotypes—for example, hyperinflammatory patients exhibit an approximately twofold higher 90-day mortality than hypoinflammatory patients (61.6% versus 30.3%)—and may obscure treatment effects in undifferentiated populations, reducing power to detect beneficial interventions in traditional trial designs.[5,18]

Clinical trajectories underscore this heterogeneity: direct pulmonary ARDS typically exhibits alveolar consolidation with protein-rich edema, whereas indirect injury often presents with diffuse interstitial inflammation and relatively preserved aeration.[16] Chest computed tomography (CT) captures these anatomical differences—gravity-dependent lobar consolidations versus homogeneous ground-glass opacification across lung fields—patterns that correlate with lung recruitability and response to mechanical ventilation.[16,19] Biologically, plasma biomarker variability (e.g., interleukin-6 ranging from <50 to >20,000 pg/mL) and divergent gene expression profiles (innate immune activation versus fibroproliferative signatures) suggest biological heterogeneity despite similar bedside severity scores.[18,20,21] Recognition of such heterogeneity constitutes a prerequisite for moving beyond uniform therapeutic approaches toward mechanism-based stratification.

Clinical and physiological subphenotypes

Clinical heterogeneity in ARDS has traditionally been categorized through etiological, mechanical, and temporal lenses, though these frameworks offer only partial pathophysiological resolution. Direct (pulmonary) ARDS arises from parenchymal insults—bacterial pneumonia, aspiration of gastric contents, or inhalational injury—whereas indirect (extrapulmonary) ARDS stems from systemic inflammatory processes such as abdominal sepsis or severe pancreatitis.[16] These categories exhibit divergent respiratory mechanics: pulmonary ARDS typically demonstrates reduced lung compliance with consolidated dependent zones, while extrapulmonary forms often present with relatively preserved aeration but impaired chest wall compliance, altering the transpulmonary pressure dynamics critical for ventilator management.[16,22]

Mechanical stratification based on lung recruitability has gained particular traction following the recognition that static compliance poorly predicts alveolar reopening. Patients with a higher percentage of potentially recruitable lung (>9% of total lung weight, assessed via CT morphometry) may exhibit greater physiological recruitment with higher positive end-expiratory pressure and recruitment maneuvers, whereas the same strategies may expose patients with low recruitability to barotrauma and hemodynamic compromise.[23] This physiological dichotomy, originally characterized by Gattinoni and colleagues, challenges the universal application of standardized ventilator protocols.

Early in the COVID-19 pandemic, the L/H framework was proposed to distinguish Type L, characterized by low elastance, relatively preserved compliance, low lung weight, and limited recruitability, from Type H, characterized by high elastance, reduced compliance, greater lung weight, and greater recruitability.[24] However, analyses of pre-COVID-19 ARDS found compliance to vary continuously without a reproducible threshold, while longitudinal studies of COVID-19 ARDS did not identify stable baseline clusters.[25,26] These findings caution against using the L/H framework for treatment selection without prospective validation.

Temporal phenotyping distinguishes exudative (early) from fibroproliferative (late) stages, typically demarcated by day 7 of

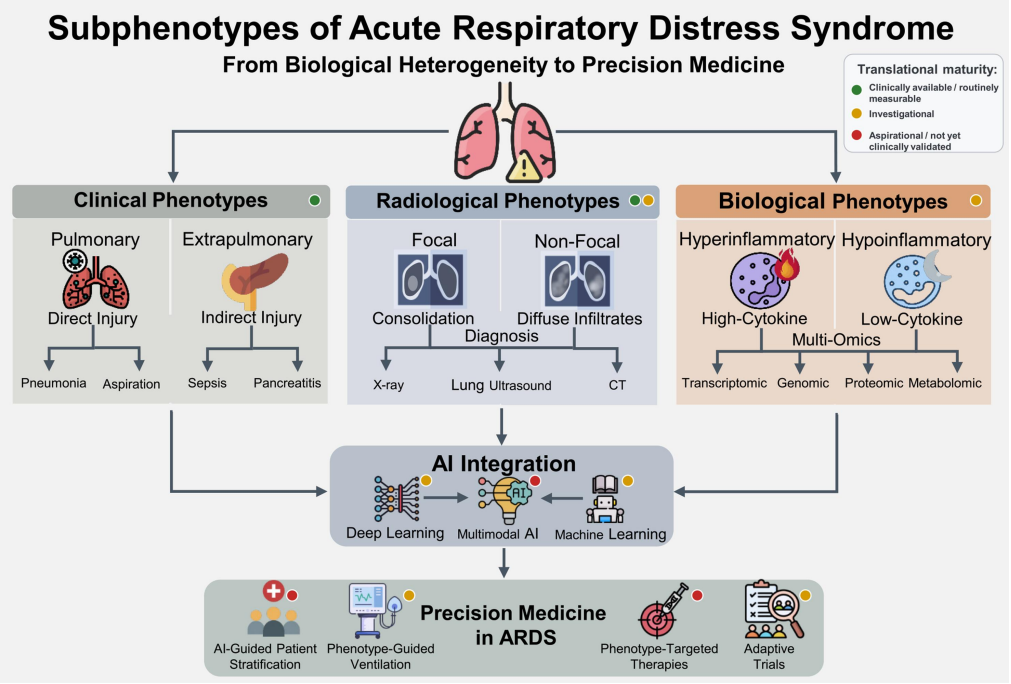


Fig. 1. Conceptual framework linking ARDS subphenotyping to precision medicine. The schematic summarizes clinical, radiological, and biological phenotypes and their potential integration with artificial intelligence (AI). Clinical phenotypes can be identified in routine practice, whereas radiological phenotyping combines clinically available imaging modalities with investigational phenotype-based interpretation. Biological phenotyping, deep learning, machine learning, phenotype-guided ventilation, and adaptive trials remain investigational and require further prospective validation. Multimodal AI, AI-guided patient stratification, and phenotype-targeted therapies remain aspirational and have not been validated for routine clinical use. The green, yellow, and red indicators represent different levels of translational maturity. Green indicates approaches that are clinically available or routinely measurable, yellow indicates investigational approaches, and red indicates approaches that remain aspirational or have not been clinically validated. These colors do not represent evidence quality or strength of recommendation. The proposed framework should not be interpreted as a validated clinical workflow or a treatment algorithm ready for clinical implementation. The schematic was created by the authors using Microsoft PowerPoint. Icons were sourced from Flaticon and are credited to their respective creators: Vitaly Gorbachev, Magnific, Reddie, Gracicon, Iconjam, Flat Icons, justicon, Dewi Sari, and Becris. The icons are used under Flaticon's free license with attribution. No AI tools were used to generate or modify the schematic. ARDS, acute respiratory distress syndrome; CT, computed tomography.

illness.[27] Early ARDS features protein-rich edema, hyaline membrane formation, and exuberant neutrophilic infiltration, whereas later phases involve myofibroblast accumulation, collagen deposition, and aberrant repair signaling.[27,28] These stages raise hypotheses regarding time-dependent therapeutic susceptibility; anti-inflammatory interventions may be more relevant during early injury, whereas antifibrotic approaches could be investigated during later fibroproliferative phases.

While clinically intuitive, these physiological taxonomies inadequately capture biological heterogeneity within each stratum—patients with identical recruitability or temporal stage may harbor divergent inflammatory endotypes. This limitation has propelled the shift toward molecular subphenotyping.

Radiological and imaging-based subphenotypes

CT characterizes structural heterogeneity in ARDS through quantifiable anatomical distributions, most notably the focal versus non-focal dichotomy. Focal ARDS exhibits segmental or lobar consolidations confined to gravity-dependent regions, with relatively preserved aeration in non-dependent zones; conversely, non-focal ARDS demonstrates diffuse, homogeneous ground-glass opacification and extensive non-aerated tissue across all lung levels.[29,30] This distinction—originally quantified by Gattinoni using CT density histograms—reflects divergent pathophysiology: focal and non-focal patterns may exhibit different physiological responses to prone positioning, recruitment maneuvers, and PEEP; however, whether these differences can reliably guide treatment selection remains uncertain.[29-32] Matched physiological and quantitative CT data also showed that similar degrees of hypoxemia can coexist with different compliance and aeration patterns, reinforcing that oxygenation severity alone does not define the mechanical phenotype.[33]

Lung ultrasound (LUS) offers a radiation-free bedside alternative for monitoring aeration dynamics.[34] Progressive transformation from A-lines to confluent B-lines and subpleural consolidations allows semi-quantitative tracking of lung recruitment or derecruitment during PEEP titration.[35,36] However, LUS-based phenotyping remains operator-dependent and cannot detect lung overinflation, making it inferior to CT in these respects.[37] The ongoing international PEGASUS randomized trial is evaluating LUS-guided morphology-specific ventilation; its pilot phase

reported 88% classification accuracy against expert consensus, supporting multicenter feasibility but not yet clinical efficacy.[38]

While imaging clarifies anatomical heterogeneity, structural patterns incompletely predict biological inflammation intensity—patients with identical CT morphologies may harbor divergent plasma biomarker profiles. This disconnect necessitates integration with molecular phenotyping for precise therapeutic stratification.

Hemodynamic and cardiovascular subphenotypes

ARDS can impose a substantial load on the pulmonary circulation through hypoxic pulmonary vasoconstriction, endothelial injury, microvascular obstruction, and the effects of positive-pressure ventilation. The resulting increase in pulmonary vascular resistance raises right ventricular (RV) afterload; because the thin-walled RV is poorly adapted to an acute pressure load, RV dilatation may progress to systolic impairment, ventricular interdependence, reduced left ventricular filling, and systemic circulatory failure.[39,40] This continuum is not adequately represented by a single binary definition of RV dysfunction, particularly because ARDS-associated circulatory failure may also reflect left ventricular dysfunction or a hyperdynamic, vasoplegic state.

In a retrospective single-center cohort of 801 patients who underwent transthoracic echocardiography within 7 days of ARDS onset, Chotalia *et al.*[41] applied latent class analysis to echocardiographic and hemodynamic variables and identified four candidate cardiovascular subphenotypes: preserved biventricular function (43%), RV dilatation with largely preserved systolic function (24%), RV dilatation with impaired systolic function (13%), and a high-cardiac-output state with hyperdynamic left ventricular function (21%). Ninety-day mortality was 19%, 40%, 78%, and 59%, respectively ($P < 0.0001$). The class characterized by RV dilatation with systolic impairment showed the strongest independent association with 90-day mortality (adjusted odds ratio 6.9, 95% confidence interval 4.0–11.8).[41] These findings suggest that multivariable cardiovascular phenotyping may separate distinct mechanisms and degrees of circulatory failure more effectively than conventional dichotomous RV dysfunction criteria.

These candidate classes generate physiologically plausible but unproven therapeutic hypotheses. For example, the RV pressure-overload phenotypes may identify patients in whom reduction of RV afterload warrants investigation, whereas the high-cardiac-output phenotype may reflect vasoplegia rather than primary pump failure.[40,42] However, the available evidence does not establish phenotype-specific treatment effects. The Chotalia study was retrospective, conducted at a single center, and included only patients who underwent echocardiography, creating a risk of selection bias. In addition, cardiovascular class assignment may be state-dependent and influenced by ventilator settings, fluid and vasoactive therapy, and assessment timing. External prospective validation and evaluation of temporal stability are therefore required before these candidate subphenotypes can be used for treatment selection.

Biological and multi-omics subphenotypes

LCA of plasma biomarkers in the ARMA and ALVEOLI cohorts identified, and subsequent analyses in HARP-2 and FACTT reproduced, the hyperinflammatory (HYP) and hypoinflammatory (HYPO) subphenotypes that transcend etiological and radiological categories.[10-12] The HYP subphenotype—comprising approximately 30%–35% of patients—exhibits elevated interleukin-6 (IL-6) levels (median 348 pg/mL; interquartile range 133–1355), IL-8, soluble tumor necrosis factor receptor-1 (sTNFR-1), and angiopoietin-2, alongside greater vasopressor requirements and organ failure burden.[11,12] Secondary analyses suggested potential treatment-effect heterogeneity: the hyperinflammatory subphenotype was associated with more favorable outcomes under higher-PEEP and conservative fluid-management strategies, whereas corresponding benefits were not observed in the hypoinflammatory subphenotype.[10,12] Crucially, Delucchi *et al.*[43] showed that the subphenotypes were largely stable over the first 3 days, although a minority of patients changed classification.

In COVID-19 ARDS, an initial prospective cohort suggested a lower prevalence of the hyperinflammatory phenotype than in historical ARDS, while a larger single-center LCA identified two classes overlapping established inflammatory subphenotypes and an observational corticosteroid-by-class interaction.[44,45] Unsupervised whole-blood transcriptomics identified interferon-dominant and immune-checkpoint-dominant clusters, and longitudinal host-response profiling showed that classification may vary with sampling time and the level of respiratory support.[46,47]

Transcriptomic and genomic analyses reveal distinct gene expression signatures underlying these inflammatory dichotomies. Sarma and colleagues found that hyperinflammatory ARDS was characterized by increased interferon and T-cell receptor signaling, coupled with activation of the integrated stress response and inflammasome.[48] Morrell *et al.*[49] further showed that proinflammatory alveolar macrophage programs were enriched early and subsequently downregulated in patients alive and extubated by day 28, whereas they progressively increased in those who died or remained mechanically ventilated. Zhang *et al.*[50] further delineated two distinct differentiation branches of type II alveolar epithelial cells : one leading to fibrosis and the other to epithelial repair. Pediatric ARDS studies extend this evidence chain: unsupervised whole-blood transcriptomics identified three candidate CHOP ARDS Transcriptomic Subtypes (CATS 1–3) with distinct biological profiles and outcomes, although the single-center study included only 96 children and lacked external validation.[51] Biomarker-based LCA subsequently identified hypo- and hyperinflammatory classes across pediatric cohorts, while paired pulmonary and blood multi-omics demonstrated interferon-dominant immune dysregulation in severe pediatric ARDS.[52-54]

Proteomic and metabolomic layers add mechanistic granularity beyond transcriptional snapshots. Protein signatures implicate dysregulated coagulation (decreased protein C), endothelial injury and activation (elevated von Willebrand factor antigen and Angiopoietin-2), and impaired lipoprotein metabolism.[55,56] Metabolomic analyses have implicated glycolytic reprogramming in inflammatory ARDS phenotypes and identified differences in arginine metabolism between COVID-19-associated and bacterial sepsis-associated ARDS.[57,58]

Integrative multi-omics approaches—combining transcriptomic, proteomic, and metabolomic data—promise superior endotype resolution but face methodological constraints: batch effects across platforms, high dimensionality relative to sample sizes, and

limited external validation.[14,59] Current machine learning implementations (e.g., similarity network fusion) remain largely confined to exploratory analyses pending prospective clinical trial integration.[59]

Artificial intelligence-driven ARDS subphenotyping

Machine learning algorithms, particularly unsupervised clustering methods (LCA, K-means, Gaussian mixture models), have been reported to reproduce and refine ARDS phenotypes across independent cohorts with good discriminative performance in selected studies.[60-62] Supervised approaches, including gradient boosting machines and random forests, now predict phenotype membership using parsimonious clinical variables (bicarbonate, vasopressor use, and creatinine) with performance approaching that of full biomarker panels, offering potential for bedside implementation without specialized laboratory infrastructure.[63]

Deep learning methods have also been explored for lung imaging tasks, including multi-class lung disease classification using chest X-ray and CT images, cross-volume CT image-to-image translation, and real-time segmentation of lung ultrasound artifacts.[64-66] In ARDS-related imaging research, deep learning has been evaluated for detecting ARDS on chest radiographs with external validation, while CT-based radiomics has been investigated for predicting subsequent ARDS in patients with chest trauma.[67,68] These studies illustrate the potential of AI for image-based disease detection, image processing, and risk prediction. However, the application of deep learning to focal and non-focal ARDS classification remains insufficiently established. Further research is needed to assess the generalizability of these approaches across different clinical settings.

Integrative multimodal AI—combining electronic health record trajectories, imaging features, and molecular biomarkers through multi-layer perceptrons or attention mechanisms—aims to capture patient-specific dynamic endotypes evolving over days 1–7 in the intensive care unit. Nevertheless, such approaches face profound validation barriers: sample sizes rarely exceed 5,000 patients (potentially limiting complex deep learning models), interpretability remains limited ("black box" criticism), and prospective clinical utility—demonstrating that real-time phenotype updates alter clinician behavior and improve outcomes—remains unproven.[69,70]

Potential therapeutic implications

Traditional ARDS management has largely applied uniform ventilatory and pharmacological strategies to heterogeneous populations. Subphenotyping may support enrichment of prospectively defined groups and re-evaluation of interventions that were neutral overall but showed possible treatment-effect heterogeneity in secondary analyses.[5,71] Table 1 summarizes the defining features and potential therapeutic implications of the major ARDS subphenotypes.[10-12,16,17,22,29,31,39-42,62,72,73]

Secondary analyses of ARDS trials suggested that hyperinflammatory and hypoinflammatory subphenotypes may respond differently to higher PEEP, conservative fluid management, and simvastatin, while an observational COVID-19 ARDS analysis suggested differential associations with corticosteroids.[10-12,45] However, inflammatory classification does not directly measure lung recruitability or cardiovascular tolerance of PEEP; corticosteroid exposure in the COVID-19 analysis was not randomized, and these interactions remain vulnerable to limited power, model-dependent assignment, and multiple testing.[45,74] They should therefore be considered hypothesis-generating rather than sufficient for treatment selection.

Radiological phenotypes may likewise show different physiological responses to ventilation. Focal ARDS has been associated with improved oxygenation after prone positioning, whereas non-focal, more recruitable patterns may show greater improvements in oxygenation and compliance after recruitment maneuvers and PEEP titration.[31,72] Conversely, aggressive recruitment in focal morphology may cause hemodynamic compromise without corresponding recruitment benefit.[31] These observations do not establish that morphology should currently determine ventilatory management.

Barriers to clinical translation

Despite their reproducibility in observational cohorts and secondary analyses, ARDS subphenotypes have not yet become validated treatment-selection tools. A mortality-associated subgroup provides prognostic enrichment, whereas predictive enrichment requires evidence that the causal effect of a treatment differs across subgroups. Most reported treatment–subphenotype interactions have been derived retrospectively from trials designed for unselected populations and remain vulnerable to model-dependent classification, limited statistical power, and multiple testing. These findings should therefore be considered hypothesis-generating rather than sufficient evidence for routine treatment selection.[75]

The LIVE trial illustrates the risks of acting on an imperfectly assigned phenotype. Ventilation tailored to focal or non-focal lung morphology did not reduce 90-day mortality in the intention-to-treat analysis, and lung morphology was misclassified in 21% of patients.[73] Although a per-protocol analysis excluding misclassified patients suggested possible benefits, it no longer preserved the protection afforded by randomization. The trial therefore neither established nor definitively excluded benefit from morphology-guided ventilation; instead, it demonstrated that inaccurate phenotype assignment may expose patients to a discordant strategy and obscure any true treatment effect.[73]

Biological classifiers face related methodological and operational limitations. Latent class analysis produces probabilistic, model-dependent groups whose assignment varies with the selected variables, study population, assay characteristics, missing-data handling, and sampling time; despite the overall stability reported by Delucchi *et al.*,[43] a minority of patients may change class over time.[75] Classification thresholds have not been standardized across assay platforms, and differences in analytical performance and calibration may lead to inconsistent phenotype assignment.[74,75] Severity-related confounding is another important concern: patients with greater illness severity are more likely to receive intensive interventions and to experience adverse outcomes, potentially generating or exaggerating apparent treatment–subphenotype interactions in secondary analyses.[75] Moreover, classifier performance in retrospective datasets does not guarantee equivalent performance during prospective bedside use.[62,74] Until prospectively specified phenotype-stratified trials demonstrate improved patient outcomes, ARDS subphenotypes should not be

Table 1. Major ARDS subphenotypes: Identification criteria and evidence for potential therapeutic relevance

Category	Phenotype	Identification criteria	Key features	Representative biomarkers	Evidence and potential therapeutic relevance	Key references
Biological	Hyperinflammatory (HYP)	LCA of plasma biomarkers (IL-6, IL-8, sTNFR-1, Ang-2)	30%–35% prevalence; greater vasopressor use, acidosis, and multi-organ dysfunction; consistently higher mortality across cohorts	High IL-6 348 (133–1355) pg/mL; IL-8↑; sTNFR-1↑; Ang-2↑; protein C↓	Prognostic evidence: in LUNG SAFE, 90-day mortality was 57% (414/725) in HYP versus 33% (694/2088) in HYPO patients ($P < 0.0001$). Treatment-effect evidence remains post hoc: phenotype-by-treatment interaction $P = 0.049$ for PEEP strategy and $P = 0.0039$ for fluid strategy in secondary analyses of randomized trials. In HARP-2, 28-day mortality among HYP patients was 32% with simvastatin versus 45% with placebo ($P = 0.008$), although the parent trial was neutral. These findings are hypothesis-generating	Calfee *et al.* (2014),[12] Famous *et al.* (2017),[10] Calfee *et al.* (2018),[11] Maddali *et al.* (2022)[62]
Biological	Hypoinflammatory (HYPO)	LCA cluster with low inflammatory markers	65%–70% prevalence; lower inflammatory burden and organ dysfunction than HYP; lower cohort-level mortality	Low IL-6 79 (35–197) pg/mL; normal protein C	Post hoc analyses suggest different responses to PEEP and fluid strategies than in HYP patients, but do not establish harm or a phenotype-specific treatment recommendation. Prospective biomarker-stratified trials are required	Calfee *et al.* (2014),[12] Famous *et al.* (2017),[10] Calfee *et al.* (2018)[11]
Etiological	Direct (pulmonary)	Direct lung insult (pneumonia, aspiration, inhalation injury)	Predominant alveolar epithelial injury; more localized consolidation and, in early physiological studies, lower recruitability than indirect ARDS	SP-D↑; CC16↑; sRAGE↑	Etiology may be associated with different physiological responses to PEEP and recruitment, but no validated etiology-specific ventilatory strategy has been established	Gattinoni *et al.* (1998),[22] Shaver *et al.* (2014),[16] Calfee *et al.* (2015)[17]
Etiological	Indirect (extrapulmonary)	Systemic insult (sepsis, pancreatitis, trauma)	Predominant endothelial injury; more diffuse loss of aeration and, in early	Ang-2↑; vWF↑; ICAM-1↑	Greater physiological recruitment has been reported in selected studies, but this does not establish clinical benefit from higher PEEP or recruitment maneuvers. No validated etiology-	Gattinoni *et al.* (1998),[22] Shaver *et al.* (2014)[16]

Table 1. Major ARDS subphenotypes: Identification criteria and evidence for potential therapeutic relevance (*continued*)

Category	Phenotype	Identification criteria	Key features	Representative biomarkers	Evidence and potential therapeutic relevance	Key references
			physiological studies, greater recruitability than direct ARDS		specific strategy exists	
Radiological	Focal	CT showing predominantly lobar or segmental loss of aeration, usually in dependent regions; morphology assigned by trained imaging assessment	Low recruitability; "baby lung" physiology; risk of PEEP-induced overdistension in non-dependent zones	Variable (can be HYP or HYPO); often epithelial injury pattern	Physiological studies report oxygenation improvement with prone positioning and limited recruitment with aggressive recruitment maneuvers. In the LIVE trial, morphology-guided ventilation did not reduce 90-day mortality in the intention-to-treat analysis; 21% were misclassified. Not a validated treatment algorithm	Gattinoni *et al.* (2001),[29] Constantin *et al.* (2010),[31] Constantin *et al.* (2019),[73] Yang *et al.* (2025)[72]
Radiological	Non-focal (diffuse)	CT showing diffuse loss of aeration without a predominant focal pattern; morphology assigned by trained imaging assessment	High recruitability; diffuse alveolar damage; potential for alveolar reopening	Variable (can be HYP or HYPO); often endothelial injury pattern	Physiological studies suggest greater recruitment and compliance responses to recruitment maneuvers or PEEP titration. The neutral LIVE intention-to-treat result and clinically important misclassification preclude routine morphology-guided treatment	Gattinoni *et al.* (2001),[29] Constantin *et al.* (2010),[31] Constantin *et al.* (2019)[73]
Hemodynamic/cardiovascular	Four candidate cardiovascular classes	Latent class analysis of echocardiographic and hemodynamic variables obtained within 7 days of ARDS onset	Preserved biventricular function (43%); RV dilatation with preserved systolic function (24%); RV dilatation with systolic impairment (13%); hyperdynamic high-output state (21%)	Echocardiographic and hemodynamic variables rather than a validated circulating biomarker panel	Retrospective single-center evidence: 90-day mortality was 19%, 40%, 78%, and 59% across the four classes ($P < 0.0001$). The class characterized by RV dilatation with systolic impairment showed the strongest independent association with 90-day mortality (adjusted OR 6.9, 95% CI 4.0–11.8). These classes support prognostic and mechanistic stratification, but phenotype-specific management has not been prospectively validated	Ryan *et al.* (2014),[39] Zochios *et al.* (2023),[40] Chotalia *et al.* (2023a, 2023b)[41,42]

Biomarker concentrations are cohort-specific distributions rather than universal diagnostic thresholds. Phenotypes are probabilistic, may overlap across domains, and may change over time. Reported treatment-effect findings are principally post hoc secondary analyses or physiological observations and should not be interpreted as clinical recommendations. ↑, increased; ↓, decreased. Ang-2, angiopoietin-2; ARDS, acute respiratory

distress syndrome; CC16, club cell protein 16; CI, confidence interval; CT, computed tomography; HARP-2, Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction-2 study; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-8, interleukin-8; LCA, latent class analysis; LUNG SAFE, Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure; OR, odds ratio; PEEP, positive end-expiratory pressure; RV, right ventricular; SP-D, surfactant protein D; sRAGE, soluble receptor for advanced glycation end-products; sTNFR-1, soluble tumor necrosis factor receptor-1; vWF, von Willebrand factor.

used for routine treatment selection.[75]

Future directions

The next priority is to develop rapid, parsimonious, and externally validated classifiers and to test them prospectively. Studies should prespecify the classifier, sampling time, treatment assignment, outcome, and treatment-by-subphenotype interaction before enrollment.[75] PHIND used a near-patient assay with an analytical run time of approximately 1 h, while SPARC achieved a median interval of 2.2 h from blood collection to real-time subphenotype assignment, supporting the operational feasibility of rapid classification; both studies were observational and did not test phenotype-directed treatment.[76,77] PANTHER is designed as a phase 2 multiarm adaptive platform trial incorporating baseline inflammatory phenotyping, whereas PEGASUS is testing LUS-guided morphology-specific ventilation.[38,78]

Multimodal approaches may further integrate longitudinal clinical data, physiological waveforms, imaging, and molecular measurements, but they require interoperable data infrastructure, external validation, calibration across healthcare systems, and interpretable outputs.[79,80] Their value should ultimately be judged by whether prospective use changes clinical decisions and improves patient-centered outcomes, rather than by discrimination metrics alone.[63,75]

Limitations

Several limitations affect the interpretation and clinical application of the available evidence. Most associations between ARDS subphenotypes and outcomes are observational and may be affected by confounding. Evidence that treatment effects differ across subphenotypes comes mainly from post hoc analyses of completed trials, which often involve small subgroups, multiple comparisons, and uncertainty in phenotype assignment.[10-12,75] Differences in patient populations, sampling time, assays, and classifier definitions may reduce generalizability, although parsimonious classifiers have performed well in several external trial cohorts.[43,74,75] Misclassification in the LIVE trial further illustrates the difficulty of using research phenotypes to guide bedside treatment.[73] Current evidence supports the biological and prognostic relevance of several subphenotypes, but their clinical utility for treatment selection has not yet been established in prospective trials.[73,75] Because this narrative review used targeted searches without a systematic-review protocol, formal risk-of-bias assessment, or meta-analysis, some relevant studies may have been missed.

Conclusions

ARDS represents a biologically heterogeneous spectrum rather than a uniform entity. Integrating clinical, radiological, and multi-omic stratification with machine learning offers a mechanistically grounded framework to disaggregate this complexity. Realizing precision medicine in ARDS requires prospective validation through phenotype-enriched randomized trials that prospectively test prespecified interventions within validated subgroups, standardized bedside phenotyping tools with turnaround times under 4 h, and interpretable artificial intelligence systems that earn clinician trust through transparent decision logic. The transition from descriptive subphenotypes to therapeutic implementation now constitutes the critical priority for ARDS research.

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The icons used in Figure 1 were sourced from Flaticon and created by Vitaly Gorbachev, Magnific, Reddie, Gracicon, Iconjam, Flat Icons, justicon, Dewi Sari, and Becris. The icons are used under Flaticon's free license with attribution.

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Conflict of interest

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Author contributions

Literature search, data organization, manuscript drafting and revision, reference standardization, and Figure 1 preparation (HL); review framework development, critical manuscript review and

revision, Table 1 preparation, and funding acquisition (XM). Both authors read and approved the final manuscript.

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