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Phenotypes in ARDS: Moving Towards Precision Medicine

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Abstract

Purpose of Review: To provide an overview of the current research in identifying homogeneous subgroups and phenotypes in ARDS.

Recent Findings: In recent years, investigations have used either physiology, clinical data, biomarkers or a combination of these to stratify patients with ARDS into distinct subgroups with divergent clinical outcomes. In some studies, there has been also been evidence of differential treatment response within subgroups. Physiologic approaches include stratification based on P/F ratio and ventilatory parameters; stratification based on P/F ratio is already being employed in clinical trials. Clinical approaches include stratification based on ARDS risk factor or direct vs indirect ARDS. Combined clinical and biological data has been used to identify two phenotypes across 5 cohorts of ARDS, termed hyperinflammatory and hypoinflammatory. These phenotypes have widely divergent clinical outcomes and differential response to mechanical ventilation, fluid therapy, and simvastatin in secondary analysis of completed trials. Next steps in the field include prospective validation of inflammatory phenotypes and integration of high-dimensional "omics" data into our understanding of ARDS heterogeneity.

Summary: Identification of distinct subgroups or phenotypes in ARDS may impact future conduct of clinical trials and can enhance our understanding of the disorder, with potential future clinical implications.

Keywords

ARDS; phenotypes; heterogeneity; latent class analysis

Introduction

According to the Berlin Definition, acute respiratory distress syndrome (ARDS) is defined as a PaO_2:FiO_2<300 mmHg with bilateral opacities on chest radiograph devoid of a primary cardiac aetiology.[1] In critically-ill patients undergoing mechanical ventilation, these findings are commonplace. Consequently, a wide variety of aetiologies and pathologies are

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coalesced in this diagnosis, leading to complex clinical and biological heterogeneity. Heterogeneity is increasingly being recognized as a central factor contributing to failure of randomized controlled trials (RCTs).[2]

The breadth of the consensus definitions of ARDS, both Berlin and its predecessor the American-European Consensus Conference [3], has permitted efficient recruitment in clinical trials and allowed testing of interventions in a consistent, albeit diverse, phenotype of critical illness. This approach has led to some success; most notably, the NHLBI ARDS Network's low tidal volume trial showed a survival benefit using low-tidal volume ventilation [4], now considered the standard of ventilatory care in ARDS. Beyond this trial, however, in all-comers with ARDS, the literature is notable for the absence of positive RCTs.[2]

Enrollment into RCTs using the current definition raises a second, less frequently addressed, concern- are we approaching the ceiling of detectable benefit in ARDS? For example, the two most recently published NHLBI ARDSnet trials, FACTT (fluid and catheter treatment trial) and SAILS (statins for acutely injured lung from sepsis), had a mortality rate of approximately 26%.[5, 6] To detect a 5% reduction in mortality in these populations would require recruiting over 2200 patients, limiting the feasibility of such trials.

In observational studies, where there are no restrictions in patient selection, the mortality rates in ARDS remain persistently high.[7] High mortality rates coupled with the multitude of failed clinical trials have led researchers to explore novel approaches to combat heterogeneity, and increasingly, subgroups or phenotypes are being sought in ARDS. When identifying such subsets, one of the central questions researchers are attempting to address is whether the correct population or the correct biology are being targeted during RCTs. Identification of homogeneous subgroups or phenotypes within ARDS may have two key implications for RCTs. First, an identified subset may have greater likelihood of encountering an adverse outcome of interest and therefore increase the power to detect a benefit with an intervention. This approach is known as prognostic enrichment.[8] Second, a subset that is biologically homogeneous may be more likely to respond to an intervention that target a specific biologic mechanism, thereby amplifying the effect size and enabling hypothesis testing in a smaller sample. This approach is known as predictive enrichment.[8] Theoretically, both strategies can result in more efficient RCTs and increase the likelihood of detecting an effect with an intervention should one exist. The emerging science of subgroup/phenotype identification in ARDS has potential to inform how clinical trials are conducted in the future. Moreover, these lines of investigations are also yielding novel insights into our understanding of ARDS.

This review outlines some of the strategies that are currently being used to identify subgroups and phenotypes in ARDS and how they may impact clinical trials (Table 1). In addition, the review will also outline future directions and emerging research in the field.

Physiologically-derived Phenotypes in ARDS

A simple approach to finding homogeneous subsets within ARDS is to use physiological variables for stratification. This strategy may provide prognostic enrichment and has been used with some success. Two recent RCTs, ACURASYS (ARDS et Curarisation Systematique; neuromuscular blockade vs placebo) [9] and PROSEVA (prone-positioning vs routine care),[10] leveraged the higher mortality associated with increased ARDS severity [1] to only recruit patients with PaO_2:FiO_2 <150 mmHg. Both studies found a survival benefit compared to the control. Maiolo and colleagues used this threshold of PaO_2:FiO_2 to further dichotomize moderate ARDS in a small population of patients and found the subset with lower PaO_2:FiO_2 were more likely to have greater lung inhomogeneity and increased lung water as judged by CT imaging.[11*]. Amato and colleagues have recently shown driving pressure to be independently associated with increased mortality.[12] In addition, pulmonary dead space [13] and ventilatory ratio,[14*] a bedside marker of impaired ventilation, have also been shown to be independently associated with adverse clinical outcomes in ARDS. Future trials could use these respiratory variables to enrich populations, particularly when testing supportive therapy.

Clinically-derived Phenotypes in ARDS

Numerous clinical features contribute to heterogeneity in ARDS, and the only shared commonality amongst them is their ability to add noise for those studying the disorder. The most obvious source of clinical heterogeneity is the underlying risk factors leading to ARDS. The clinical and pathophysiological features of the major ARDS risk factors and how they are distinct from one another remains poorly charted. Progress has been made, however, when studying risk factors as broader groups. For example, the clinical and biological features of patients with trauma-related ARDS were reported to be significantly different compared to patients with other risk factors, with evidence of less severe endothelial and epithelial injury in the former.[15]

Investigators have also studied differences in risk factors by stratifying patients into direct (pulmonary) and indirect (extra-pulmonary) ARDS. This distinction has been proposed as far back as the original AECC consensus conference definition of ARDS.[4] Several studies have shown distinct physiological and radiological patterns when comparing the two subgroups.[16, 17] Indirect ARDS was associated with increased areas of groundglass opacification and fewer of consolidation on CT imaging and with increased chest wall elastance (stiffer chest wall).[16, 17] Whereas, direct ARDS was associated with more evenly distributed areas of groundglass opacification and consolidation on CT imaging and with increased lung elastance (stiffer lungs).[16, 17] Further, Gattinoni and colleagues also reported that in patients with early-stage ARDS the efficacy of recruiting collapsed areas of the lung with additional PEEP was significantly less in direct ARDS compared to indirect ARDS.[16] In contrast, Thille and colleagues in a retrospective study of 71 patients with late-stage ARDS found no differences in lung recruitability between the two subgroups.[18] Interestingly, the investigators of this study were also unable to classify patients as either direct or indirect ARDS in 37% of the cases, highlighting the challenge of using these subgroups clinically. Key differences in the timing of these two studies make direct

comparisons difficult. Whether optimal ventilatory strategies may differ between these subgroups warrants further investigation.

Biological patterns are also known to differ between these two groups, with lower levels of circulating markers of endothelial injury (e.g. angiopoietin-2) and higher levels of markers of epithelial injury (e.g. surfactant protein D) in direct ARDS.[19] More recently, Luo and colleagues found that clinical predictors of outcome differed between pulmonary and extra-pulmonary ARDS.[20*] In pre-clinical (animal model) studies, the two aetiological subgroups appear to respond differently to recruitment maneuvers in rats [21] and methylprednisolone in a murine model of ARDS.[22] Despite the wealth of available data, adoption of these subgroups of ARDS in the clinical setting or prospectively in clinical trials remains limited.

Another major source of clinical heterogeneity is the timing of onset of ARDS. The Berlin Definition is time-bound to within one week of onset.[1] Within the constraints of this time-frame, difference in outcomes are known to exist between early and late stage ARDS.[23] In a recent observational study, Zhang and colleagues found that late onset ARDS (> 48 hours post-ICU admission) was associated with shorter survival time and increased risk of mortality, confirming the findings of previous investigators.[24*, 25] Using latent class analysis, Reilly and colleagues identified two temporal-based phenotypes in trauma-associated ARDS.[26] The first phenotype was associated with early-onset (Day 1 and 2) and the second phenotype with late-onset (Days 3 and 4) ARDS. The early-onset phenotype was associated with higher thoracic Injury Severity Score, increased incidence of shock and red blood cell transfusion requirements.[26] Additionally, early-onset patients had higher plasma levels of soluble receptor for glycation end-products (sRAGE) and angiopoietin-2, suggesting greater disruption of the alveolar-epithelial barrier and more endothelial injury. Using strategies such as risk-factor or time of onset represents a simple and attainable method of identifying meaningful subgroups nested within ARDS that may have differing biological pathways and outcomes.[27]

Biology-derived Phenotypes in ARDS

Numerous disease-altering pharmacotherapies have been tested in large multicenter trials and have ubiquitously failed to show a benefit in ARDS.[2] In retrospect, given the broad nature of ARDS definitions, it may be unlikely that a single biological process could be effectively targeted in this population, thereby consigning disease-altering therapies to failure. Consequently, significant uncertainty remains as to whether the trial failure was a feature of therapy ineffectiveness or merely a failure of trial design. In this setting, research seeking biologically-derived phenotypes in ARDS is emerging.

Increasingly, biomarkers are being proposed as measures to identify subphenotypes in ARDS. Numerous plasma biomarkers have been implicated as predictors of poor outcome in ARDS. These include pro-inflammatory markers (IL-6, IL-8, and soluble tumor necrosis factor receptor-1),[28–31] markers of endothelial injury (angiopoietin-2, intercellular adhesion molecule-1),[31–33] markers of epithelial injury (surfactant protein-D, sRAGE), [34, 35*] and markers of impaired coagulation (plasminogen activator inhibitor-1, protein

C).[31, 36] A comprehensive summary of biomarkers in ARDS can be found in an excellent review by Binnie and colleagues.[37] Beyond prognostication, another benefit of biomarker-based phenotypes is that they can be informative of the underlying pathogenic pathways contributing to lung injury.

In the recent literature, sRAGE has been studied most extensively and may have potential to identify subpopulations in ARDS. Jabaudon and colleagues conducted a meta-analysis of 8 prospective RCTs and observational studies.[35] They found baseline plasma sRAGE level was an independent predictor of 90-day mortality in ARDS. This finding builds on the previous work of the same investigators that found that elevated levels of sRAGE were associated with impaired alveolar fluid clearance in ARDS.[38] Further, in a prospective study of 119 patients with ARDS, Mrozek and colleagues found that plasma sRAGE and PAI-1 levels were significantly higher in patients with non-focal changes on CT scanning compared to those with focal changes.[39**] Non-focal ARDS was also associated with increased mortality. These findings suggest that sRAGE could be useful in identifying phenotypes of ARDS that are not only prognostically informative but also have distinct radiological and/or pathological abnormalities.

Many specialties outside critical care have successfully used biologically-driven phenotypes in broad clinical problems with the explicit aim of predictive enrichment and testing biology-specific therapies. For instance, in oncology, biomarkers are increasingly being used to identify patients for clinical trials. Successful examples include the use of cetuximab therapy in K-ras positive colorectal tumours,[40] vemurafenib in BRAF V600E mutation positive metastatic melanoma,[41] and trastuzumab in her-2 positive breast cancer.[42] Similarly, asthma, like ARDS, has long been recognized as a complex clinical syndrome with considerable underlying heterogeneity.[43] Using complex biomarker-based modelling, researchers have successfully identified relatively homogeneous phenotypes within asthma that have allowed phenotype-specific therapies for patients.[44] For example, in the eosinophilic-asthma phenotype, two recent RCTs testing monoclonal antibodies targeting IL-5 activity, thereby reducing eosinophil activation, found that these therapies led to fewer exacerbations in otherwise poorly controlled asthmatics.[45–47]

In accordance, investigators have sought to identify biologically-derived phenotypes in ARDS using latent class analysis (LCA), a type of mixture modelling that seeks to identify unidentified subgroups in heterogeneous population.[48] First, using a composite of clinical, demographic, biomarker data as class-defining variables, LCA was applied to two NHLBI ARDS Network trials, ARMA and ALVEOLI.[4, 49] In both cohorts, a two-class model best fit the population. The first class was termed ‘hypoinflammatory’ and the second class was termed ‘hyperinflammatory’. The hyperinflammatory phenotype constituted approximately 30% of the population and was characterized by amplified inflammatory signals, as evidenced by elevated plasma levels of IL-6, IL-8, sTNFR-1, increased prevalence of shock, and increased prevalence of non-pulmonary sepsis (Figure 1). The hyperinflammatory phenotype was also associated with significantly higher mortality and fewer ventilator-free days (Table 2). Further, the assigned phenotypes, their characteristics, and respective clinical outcomes were similar at Day 0 and at Day 3 in both cohorts.[50*] In the FACTT study comparing fluid conservative to fluid liberal management in ARDS,[5] the same

investigators found two phenotypes with remarkably similar characteristics to their prior findings.[51*] Perhaps of greatest interest in the analyses was the observed differential treatment response in the phenotypes to randomized interventions, namely PEEP and fluid-management strategies, in the ALVEOLI and FACTT trials respectively.

LCA has also been applied to data from the HARP-2 trial,[52] a UK and Ireland intensive care research group's RCT that tested the efficacy of simvastatin in ARDS. Despite using a limited set of class-defining variables, the two-phenotype model once again best described the population.[53**] In the hyperinflammatory phenotype, treatment with simvastatin was associated with significantly higher survival rates compared to placebo. No difference in survival was observed in the hypo-inflammatory phenotype or the original trial (Figure 2). Interestingly, there was no treatment response in subgroups when patients were stratified by either APACHE II score or severity of ARDS, suggesting the observed enrichment goes beyond mere severity of illness.

Most recently, LCA was applied to data from a fourth NHLBI-funded trial that tested the efficacy of rosuvastatin in ARDS (SAILS).[6] In this more contemporaneous and sepsis-specific cohort of ARDS, once again the two phenotypes were identified.[54*] Unlike HARP-2, however, there was no treatment benefit associated with rosuvastatin in either phenotype. This discrepancy may, in part, be due to the type of statin used (i.e. hydrophilic vs lipophilic) in the SAILS trial. Given these studies are all retrospective, their findings must be treated with caution, and prospective validation of these approaches will be mandatory. Nonetheless, they represent a potential avenue for prognostic and perhaps predictive enrichment.

Other investigators have also sought to identify biologically driven subgroups in ARDS. Bos and colleagues used a panel of biomarkers to perform cluster analysis in an observational cohort.[55*] They also identified two clusters: 'uninflamed' and 'reactive'; with the latter associated with enhanced inflammation and increased mortality. Compared to the hyperinflammatory phenotype identified using LCA, the 'reactive' phenotype constituted a much greater proportion of the population (58%). Nonetheless, these findings substantiate the notion that the ARDS population can be stratified by severity of inflammation and may represent a pathway for potential therapies.

The primary barrier to identifying biologically-driven ARDS phenotypes in the clinical and trial settings is the inability to quantify biomarkers rapidly and at the bedside. Most biomarkers rely on research methods rather than clinical laboratories for quantification. Biomarker quantification using point-of-care testing is the next step in the evolution of phenotype research. A second impediment to the clinical identification of the hyperinflammatory and hypoinflammatory phenotypes is the complexity of the latent class models. To circumnavigate this issue, biomarker-dependent parsimonious models comprising of 3 variables, have been shown to classify these phenotypes with high accuracy.[48, 51, 56] Prior to use in the trial or clinical setting, the efficacy of such models will require prospective evaluation.

Omics-derived Phenotypes in ARDS and Future Directions

Precision medicine is defined as implementation of prevention or treatment strategies that takes into account differences in peoples' genes, lifestyle, and environment.[57] Broadly speaking, the initiative moves practice away from the 'average' patient and focuses instead on individuals. Putatively, these ambitions align perfectly with critical care practice. Given the immeasurable variance observed in patient demographics, pathologies, and disease severity, without formally assigning it as such, critical care physicians have long managed their patients as individuals. Yet, scanning the recent critical care literature, one finds precision medicine jarringly juxtaposed with protocolized care that has been in the ascendancy over the last 20 years.[58–60]

As such, precision medicine remains aspirational in critical care. The advent of big data analytics and access to high-throughput 'omics' data can, in theory, offer unbiased approaches to phenotype identification and may enable precision-based care in ARDS. With a series of studies, Meyer and colleagues have elegantly demonstrated how genomic data may be used to inform future trials. First, using a discovery approach, they identified a coding variant for interleukin-1 receptor antagonist (IL1RA) gene that was protective against developing ARDS.[61] These patients also had elevated levels of plasma IL1RA and it was postulated that this conferred a protective anti-inflammatory effect towards developing ARDS. In a follow-up secondary retrospective analysis of a clinical trials testing the efficacy of recombinant IL1RA in septic shock, Meyers and colleagues found significant heterogeneity in treatment effect dependent on baseline plasma IL1RA levels.[62*] Counterintuitively, higher IL1RA levels at baseline were associated with a survival benefit with recombinant IL1RA therapy, demonstrating how challenging it is to study biological interventions in critical illness.

In both adults and children, transcriptomic data has been successfully used to identify biology-specific subgroups in sepsis.[63–65] In a secondary analysis of observational pediatric sepsis data, a phenotype-specific treatment benefit was observed with corticosteroid therapy, suggesting a route to predictive enrichment.[66**] In ARDS, transcriptomic studies remain largely under-utilised. Likewise, metabolomics [67] and miRNA [68] have been used in discovery analyses in small populations, but like transcriptomics, these technologies remain in their infancy in ARDS research.

Conclusion

Over the last decade, there has been increased awareness of heterogeneity in ARDS, and several novel methods have emerged to identify meaningful subgroups. These studies have enhanced understating of the underlying pathophysiology in ARDS and in some cases have challenged conventional wisdom. Biomarker-based phenotypes and clinical subgroups have been identified that may provide improved prognostication and may identify subgroups in ARDS that respond to therapies targeting specific biological pathways. Prospective validation of these approaches along with development of methods to identify biological phenotypes in real time will be important next steps in achieving the promise of precision critical care for ARDS.

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Key Points

- Heterogeneity in ARDS is a central factor that has led to multiple failed clinical trials.
- Burgeoning field of science has emerged in identifying subsets within ARDS.
- These subsets can be potentially used for prognostic and predictive enrichment in trials.
- Prospective studies are needed to confirm evidence of differential treatment response in biologically-defined phenotypes, prior to incorporation into clinical practice.

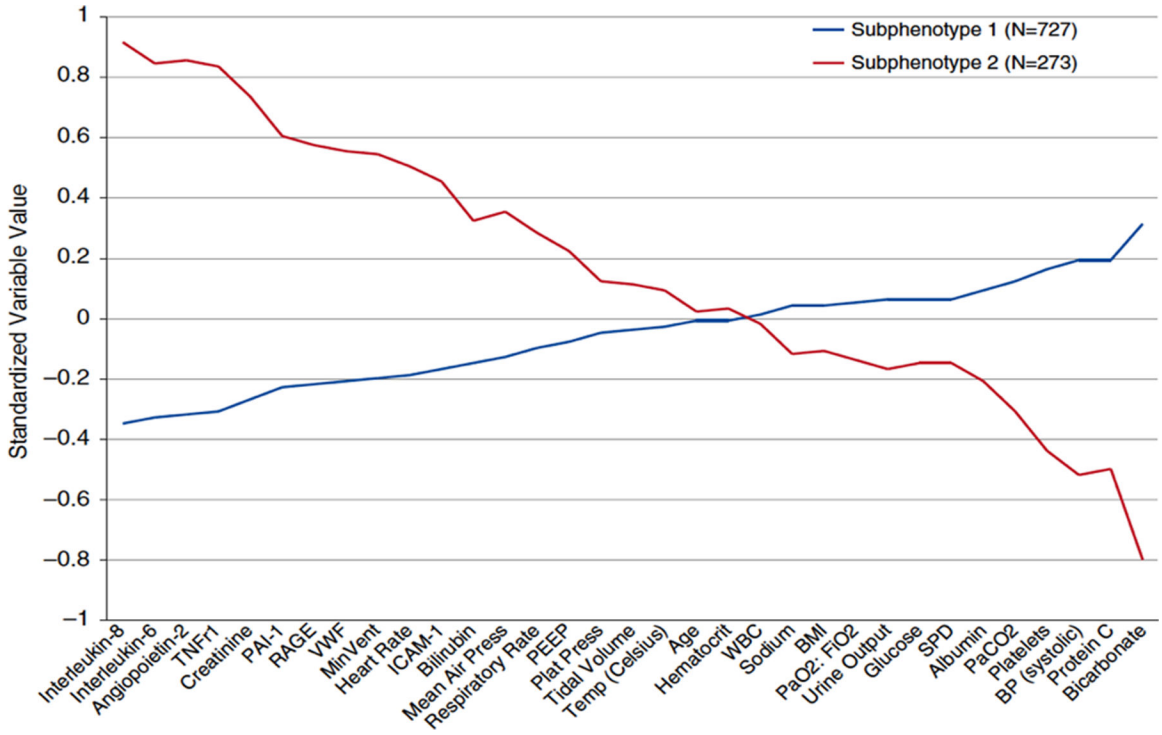

Figure 1.

Standardized values for continuous class-predicting variables in FACTT. The variables are sorted from left to right in descending order for the difference in values between the hypo-inflammatory subphenotype (1) and hyper-inflammatory subphenotype (2). Values were standardized using z-scale. BMI = body mass index, ICAM-1 = intercellular adhesion molecule-1, PAI-1 plasminogen activator inhibitor-1, PEEP positive end-expiratory pressure, TNFr1 = tumor necrosis factor receptor-1, SPD = Surfactant protein D, RAGE = receptor for advanced glycation end-products, Min Vent = minute ventilation. This figure has been previously published (Famous et al, Am J Respir Crit Care Med. 2017;195(3):331–8).[50]

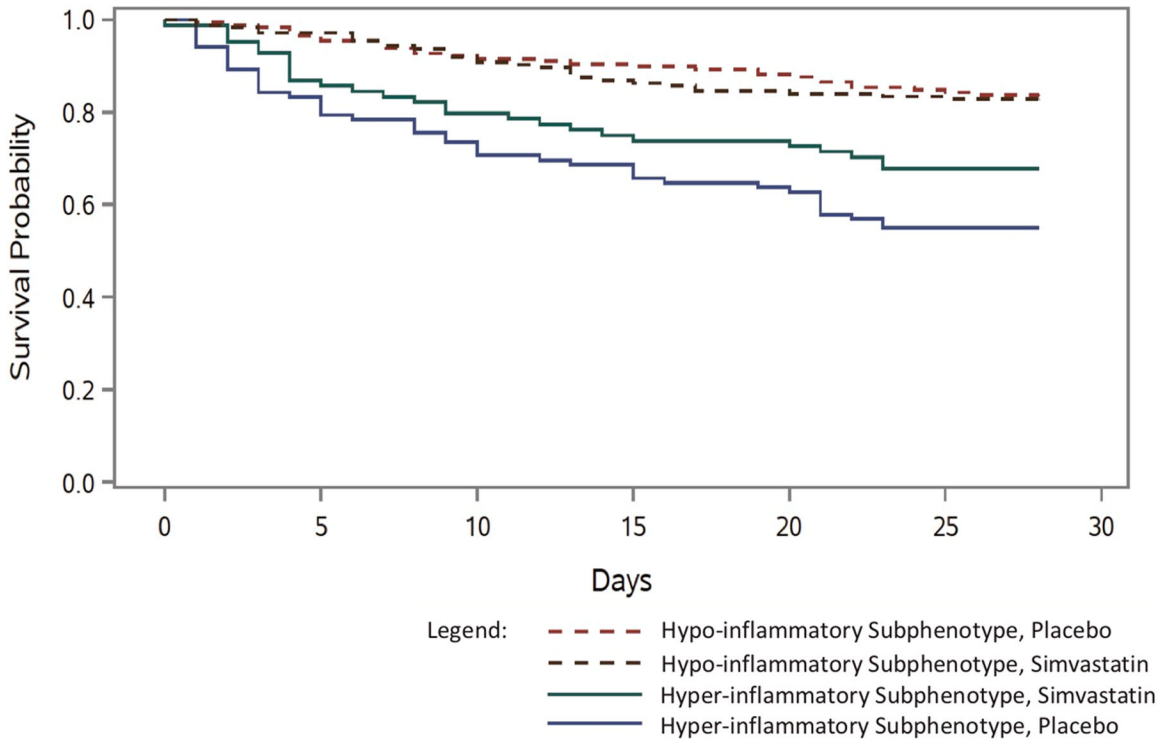

Figure 2.

90-day survival in patients in the HARP-2 trial. Patients were stratified by subphenotype and randomized treatment groups (simvastatin vs placebo). Simvastatin was associated with significantly higher survival rates than placebo (p=0.03). This figure has been previously published (Calfee et al Lancet Respir Med. 2018;6(9):691–8).[51]

Table 1.

Summary of strategies used for identifying subgroups in ARDS. This table is original to the manuscript.

Phenotype Identification	Stratifying Strategy	Utility	Ref
ARDS	Not Applicable (parent phenotype)	Testing Supportive Therapies	(5)
Physiologically Derived	PaO_2/FiO_2	Subset into homogeneous groups according to severity of impairment	(8, 9, 11–13)
	Pulmonary dead space		
	Ventilatory Ratio		
	Driving Pressure		
Clinically Derived	Aetiological: Direct vs Indirect	Subset into patients more likely to have homogeneous natural history and/or biology	(17, 18, 20–24)
	Chronological: Early vs Late		
Biologically Derived	Biomarker-based: Focal vs Non-focal	Identify phenotypes with specific underlying biological pathways.	(33, 36, 37, 46, 49, 51)
	Composite Biological and Clinical: Hypo-inflammatory vs Hyper-inflammatory	Potential for targeted therapies	
Omics Derived	Genome-wide association	Identify novel biologically specific pathways	(58, 59)
	MicroRNA Transcriptomic Analysis	Pathway-specific interventions	

Table 2.

Adverse clinical outcomes in subphenotypes in four NHLBI randomized controlled trial cohorts. Unmarked P-values represent the chi-squared test. *Denotes the Mann-Whitney U test. This table is original to the manuscript.

	Mortality (90-day)			Ventilator Free Days (to 28 days)		
	Hypoinflammatory	**Hyperinflammatory**	**p-value**	**Hypoinflammatory**	**Hyperinflammatory**	**p-value**
ARMA*	23%	44%	0.006	17.8	7.7	< 0.001*
ALVEOLI	19%	51%	< 0.001	18.4	8.3	< 0.001*
FACTT	22%	45%	< 0.001	19	3	< 0.001*
SAILS	21%	38%	< 0.001	23	15	< 0.001*