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REVIEW

Research Progress on Phenotypic Classification of Acute Respiratory Distress Syndrome: A Narrative Review

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Abstract: Acute respiratory distress syndrome (ARDS) is a clinical syndrome that is characterized by an acute onset and refractory hypoxemia. It remains an important contributor to high mortality in critically ill patients, and the majority of clinical randomized controlled trials on ARDS provide underwhelming findings, which is attributed in large part to its pathophysiological and clinical heterogeneity, among other aspects. It is now widely accepted that ARDS is highly heterogeneous, growing evidences support this. ARDS phenotypic and subphenotypic studies aim to further differentiate and identify ARDS heterogeneity in the hope that clinicians can benefit from it, then can diagnose ARDS faster and more accurately and provide targeted treatments. This review collates and evaluates the major phenotype-related research advances of recent years, with a specific focus on ARDS biomarkers and clinical factors.

Keywords: acute respiratory distress syndrome, ARDS, phenotypic classification, biomarker, clinical variable

Plain Language Summary

ARDS has been a hot topic of research in critical care medicine. Unfortunately, the clinical interventions available for ARDS have mostly been negative. It is now widely accepted that ARDS is highly heterogeneous, growing evidences support this. On the other hand phenotypic studies seem to provide researchers with a new way of recognizing ARDS. Considering the clinical applicability, we reviewed the studies on ARDS phenotypes in biomarkers and clinical variables. The results were pleasantly surprising. They showed through secondary analysis of the source data that ARDS patients can be further classified according to certain specific biomarkers or clinical variables, and this classification may be more representative of ARDS patients than the traditional classification based on etiology or severity of oxygenation index, etc., which provides a great contribution to achieve precise treatment of ARDS.

Introduction

In 1967, Ashbaugh et al described 12 cases of respiratory distress syndrome and proposed the concept of acute respiratory distress syndrome (ARDS) for the first time.[1] As this syndrome is explored further, the definition and diagnostic criteria for ARDS are continuously updated and iterated. Until 2012, the Berlin standard was proposed.[2] After more than 50 years of exploration, research on ARDS has made progress in lung-protective ventilation,[3] prone position ventilation,[4] carbon dioxide clearance in vitro, and neuromuscular block,[5,6] but the morbidity and mortality of ARDS have not substantially decreased.[7] A multicenter retrospective analysis conducted in mainland China revealed that ARDS continues to be a major problem in central intensive care units (ICUs) and that its in-hospital mortality rate has still not decreased significantly.[8] Additionally, the majority of ARDS survivors experience sequelae, such as mental and cognitive abnormalities, muscle atrophy, and nervous system diseases, which significantly reduce their quality of life.[9–11] Numerous randomized controlled studies on ARDS have been conducted in the past 50 years and have demonstrated unfavorable findings.[12] It is now widely acknowledged that the primary cause of these unfavorable findings is ARDS

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heterogeneity. This heterogeneity is illustrated by differences in etiology, pathological changes, and clinical manifestations between affected patients.[13] Existing secondary analysis studies have shown that the addition of phenotypic analysis to some ARDS trials can lead to surprisingly positive test results. In this review, we delve into some of the ARDS phenotypic findings to improve the understanding of ARDS and to provide ideas for future ARDS study designs.

Phenotype and Subphenotype

Phenotypes are defined as having similar characteristics that can be observed or detected as a result of the interaction of genes and the environment.[14] For instance, individuals who demonstrate traits of intractable hypoxemia belong to the same phenotype. Subphenotypes are subtypes that can be further divided into groups based on shared risk factors, developmental pathways, marker expression, mortality risk, and other distinctive biological or clinical characteristics or responses to treatment with the same phenotype.[15] According to the oxygenation index, ARDS subphenotypes can be divided into mild, moderate, and severe categories.[2] According to lung imaging, they can also be divided into localized and diffuse categories.[16] The above classification approach gives us a certain knowledge of the pathophysiology of ARDS, but still does not address the clinical treatment well, and numbers of randomized controlled trials on clinical interventions have shown negative results. Therefore, scholars have attempted other aspects in order to reclassify the ARDS phenotype. Fields already included different proteomic expression patterns,[17–19] particular gene expression loci,[20–22] various transcriptome features,[23] and metabolomics[24–26] can all be used as criteria for classification (Figure 1). However, the results mainly concentrated on clinical factors and biomarkers.

Studies on the phenotypes and subphenotypes of ARDS are helpful to understand the characteristics of the syndrome and its pathogenic mechanisms, and they are also helpful for advancing the development of personalized therapies. Previous studies have confirmed that some biomarkers play an important role in the pathogenesis and progression of ARDS,[27,28] and targeted therapeutic regimens can be implemented based on patient biomarker characteristics.[29] However, in practical clinical work, patients' basic information, vital signs, and other data are the first-hand information that doctors evaluate after assessing patients. Therefore, further analysis and classification of such data can also help clinical workers to better identify ARDS and provide more timely and effective treatment.

Subphenotypes of Biomarkers in ARDS

Biomarkers are biochemical indicators that can be used to mark structural and functional changes in bodily systems, organs, tissues, and cells, and they play an important role in the study of disease pathogenesis, drug treatment, and prognosis.[30,31] Furthermore, biomarker expression also helps to identify subtypes of highly heterogeneous diseases.[32]

There are numerous negative RCT studies with ARDS. Calfee et al[33] performed a secondary analysis of data from two negative RCT studies on ARDS and surprisingly found two phenotypes that could better distinguish the ARDS population: the hyperinflammatory and the hypoinflammatory phenotypes. Compared with the hypoinflammatory phenotype, the hyperinflammatory phenotype was characterized by higher plasma soluble tumor necrosis factor receptor 1, interleukin-6 (IL-6), IL-8, and plasminogen activator inhibitor-1 (PAI-1) concentrations; a higher heart rate and total minute ventilation; a lower systolic blood pressure; and lower bicarbonate and protein C concentrations. Delucchi et al[17] further validated the above two subphenotypes and showed that the number of patients with both

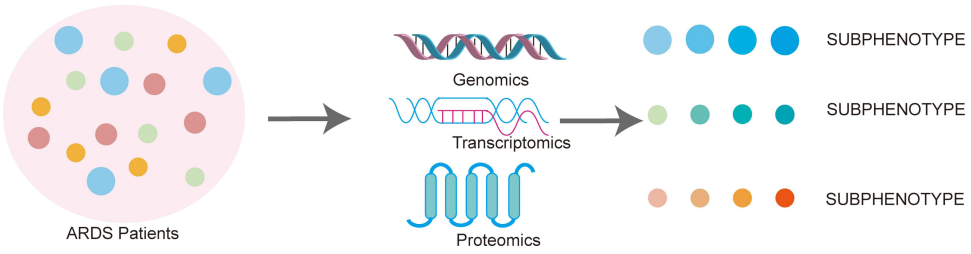

Figure 1 Partial phenotypic and subphenotypic study of ARDS. A phenotype is the sum of patients with homogeneous presentations, such as ARDS. Subphenotypes are refined classifications of patients with homogeneous phenotypes based on certain specific indicators. Current ARDS phenotypic studies include biomarkers, clinical variables, and even extend to genomics, transcriptomics, and proteomics, but they are not as clinically useful as biomarkers and clinical variables.

subphenotypes was well stabilized during the first 3 days. Furthermore, another secondary investigation by Sinha et al[34] discovered two subtypes that can effectively characterize patients with ARDS, and the traits of both subphenotypes were consistent with the results of Calfee et al.[33]

These studies including phenotype establishment, phenotype stability and reproducibility, by Calfee et al, have amply demonstrated the feasibility of phenotypic studies in ARDS. But they were all secondary analyses. Bos et al[35] conducted a prospective study using clustering analysis to identify ARDS subphenotypes. In the prospective study, four biomarkers, including IL-6, interferon-γ, vascular protease ½, and PAI-1, identified two subphenotypes: non-inflammatory and reactive. The reactive phenotype demonstrated similar features to the phenotype described by Calfee et al. The above study revealed that there is some similarity in biomarker-based subphenotypic classification of ARDS, whether in secondary analyses or in prospective studies.

In terms of interventions, several secondary analyses showed surprising results. Previously, The National Heart, Lung, and Blood Institute conducted two large randomized controlled trials (RCTs) to examine the response of patients with ARDS to low tidal volume ventilation (referred to here as AMAR)[3] and different positive end-expiratory pressure (PEEP) settings (referred to here as ALVEOLI).[36] Calfee et al[33] re-analyzed the two trials and found that patients with the hypoinflammatory phenotype were more suitable for the high PEEP strategy to reduce mortality. In another secondary analysis of a randomized controlled trial investigating fluid management strategies (referred to here as FACTT),[37] the ARDS subtypes identified by Famous et al[38] were similar to those of Calfee et al. The response of both subtypes to randomized fluid management strategies showed that the overall prognosis was better with the conservative fluid strategy than with the liberal fluid strategy in patients with the hyperinflammatory phenotype, while patients with the hypoinflammatory phenotype were more suitable for the liberal fluid strategy. In terms of pharmacological treatment, Calfee et al[18] performed a secondary analysis of ARDS treatment with simvastatin (HARP-2 trial).[39] First, they obtained two subtypes similar to their previous study: hyperinflammatory and hypoinflammatory. Second, the 28-day survival rate was significantly higher in patients treated with simvastatin in the hyperinflammatory group than in the placebo-treated group, whereas there was no significant difference in 28-day mortality between patients treated with simvastatin and those administered placebo in the hypoinflammatory group, which is distinct from the results of the original trial. This means that biomarker-based phenotypic classification of ARDS holds the potential to realize individualized treatment for patients.

However, some scholars have proposed a different view, suggesting that plasma biomarkers respond to the degree of systemic inflammation, but expression in the alveolar region is unclear. Thus, Heijnen et al[40] performed a secondary analysis of the BASIC study,[41] which was a prospective observational study examining the relationship between the pulmonary microbiota and the prognosis of critically ill patients. They showed that the biological subphenotypes driven by plasma markers did not show profound differences in selected key features of alveolar inflammatory mediators and the pulmonary microbiota. Hashem et al[42] also showed that after grouping patients with ARDS on the basis of high and low inflammation criteria, there was no significant difference in 6-month or 9-month survival between the two groups. They also suggested that the existing staging may only be a short-term response to ARDS.

The above findings suggest that plasma biomarkers can be used to achieve subphenotypic classification of ARDS, and the subgroups show positive results in terms of clinical interventions. However, the stability and sensitivity of the phenotypes still need to be studied. Further research into the mechanisms of action of biomarkers may identify new therapeutic targets. However, the above studies still have limitations. First, these studies are mostly secondary analyses, and prospective studies are lacking. Second, the primary source of these biomarkers is the plasma, but changes in pulmonary microorganisms and inflammatory mediators are also closely associated with the occurrence and mortality of ARDS.[43,44] Thus, only using plasma biomarkers to indicate ARDS subphenotypes may reduce the classification accuracy. Third, in addition to the above biomarkers, other biomarkers, such as the receptor for advanced glycation end products, surfactant protein D, and lactate dehydrogenase, are strongly associated with ARDS development and prognosis.[31,45] Thus, studies incorporating more biomarkers for analysis to obtain more homogeneous ARDS subphenotypes need to be performed. In clinical practice, most of the biomarkers are difficult to measure at the bedside or in the in-hospital setting, so the clinical use of biomarkers is limited. Thus, convenient and accurate clinical testing methods still need to be developed.

Subphenotypes of Clinical Variables in ARDS

Clinical factors, including blood pressure, body temperature, heart rate, and partial pressure of oxygen (PaO_2), are easier to measure in clinical practice than biomarkers.[46] These variables reflect changes in different aspects of the patient's underlying physical condition, ventilatory response, and inflammatory response, and are the most direct and easily monitored indicators for clinical workers. Thus, due to the limitations of measuring biomarkers, some researchers have begun subphenotypic studies of ARDS that focus on clinical factors.

In 2020, Zhang et al[47] conducted a secondary analysis of a randomized controlled trial, which studied the treatment efficacy of rosuvastatin in patients with ARDS (referred to here as SAILS).[48] The analytes included several clinical variables, such as age, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score, creatinine, systolic blood pressure, diastolic blood pressure, PaO_2, and partial pressure of carbon dioxide, among others, and the k-means clustering analysis was performed to obtain the best four classification models. The phenotype 3 population, which was characterized by a relatively high platelet count ($390.05 \pm 79.43 \times 10^9$/L) and a low creatinine concentration (1.42 ± 1.08 mg/dL), had significantly lower 28-day, 60-day, and 90-day mortality rates in the treatment group than in the placebo group, suggesting that such patients could benefit from rosuvastatin. In the other three populations, there was little difference in benefit between the treatment and placebo groups. Even there was a much higher mortality rate in the treatment group than in the placebo group in phenotype 4, which was characterized by a high APACHE III score (110.18 ± 24.35) and a high serum glucose concentration (484.35 ± 154.83 mg/dL).

Liu et al[46] screened patients with ARDS who met the inclusion criteria from a multicenter ICU database and included 21 clinical variables (covering basic vital signs, electrolyte profile, inflammatory indicators, ventilation indicators, and renal function, among others). They obtained three different subphenotypes using the k-means clustering analysis and the specific classification indicators included white blood cell count, body temperature, heart rate, respiratory rate, systolic blood pressure, age, serum creatinine, urea nitrogen, and serum bicarbonate. Patients who followed this subtyping had different responses to fluid management, PEEP, and rosuvastatin therapy. Notably, the authors also analyzed the relationship between the three subtypes and the subtypes classified on the basis of the severity of the oxygenation index, as defined by the Berlin criteria.[2] Patients with mild, moderate, and severe ARDS were included in each subtype. This indicates that the prior classification of patients with ARDS based on the oxygenation index may have some limitations and that patients can be classed using multidimensional and more suitable markers. Nevertheless, further analysis of the characteristics of the three subphenotypes revealed that although the clinical characteristics of the three phenotypes differed significantly, their specific values did not differ significantly; thus, the clinical definition remains difficult.

Duggal et al[49] expanded the study volume to six randomized controlled trials. They used common clinical data, and after data screening and analysis, they finally concluded that nine clinical variables, namely arterial pH, PaO_2, creatinine, bilirubin, bicarbonate, mean arterial pressure, heart rate, respiratory rate, and FiO2, were able to better distinguish the two different ARDS subtypes. The 28-day, 60-day, and 90-day mortality rates and the number of days without ventilator use were significantly different between the two groups. Additionally, their study included patients with different clinical and biological characteristics, while considering temporal and geographic differences.

The above studies suggest that patients with ARDS can be further distinguished by analyzing the characteristics of clinical variables and that early analysis of these clinical variables may enable the use of targeted therapeutic interventions. However, based on the results of previous studies using clinical variables to distinguish subphenotypes, it appears that the accuracy of ARDS classification models needs to be improved. Moreover, studies on the stability of existing subphenotypes are lacking, and most secondary studies have included data from the same randomized controlled trials, resulting in a relatively narrow population. Thus, future prospective studies should include as many highly heterogeneous ARDS patients as possible. In terms of statistical methods, there were differences in the methods used to handle data, such as missing values and abnormal values, between studies, which led to differences in the final indicators used to identify ARDS subphenotypes. Moreover, the reproducibility and stability of the phenotypic categories derived in previous studies and the optimal number of classification models need to be studied. As such, further prospective randomized controlled studies are essential.

The studies analyzed in this review illustrate that there are limitations in classifying patients with ARDS using the Berlin criteria alone. Previous studies on ARDS phenotypes (Table 1) are still primarily retrospective analyses. Thus,

Table 1 Summary of Research

Study	Design	Statistical Methods	Trial	Categorical Indicators	Class Model
Calfee 2014[33]	Retrospective analysis	LCA	ARMA, ALVEOLI	sTNFr1, IL-6, IL-8, PAI-1, heart rate, total minute ventilation, bicarbonate, systolic blood pressure, protein C.	2-subphenotype model
Bos 2017[35]	Prospective studies	Cluster analysis	-	IL-6, IFN–γ, ANG1/2, PAI-1	2-subphenotype model
Sinha 2018[34]	Retrospective analysis	LCA	SAILS	IL-6, IL-8, sTNFr1, ICAM-1, PAI-1, protein C	2-subphenotype model
Famous 2017[38]	Retrospective analysis	LCA	FACTT	IL-8, IL-6, sTNFr1, serum bicarbonate, protein C, Ang-2, RAGE	2-subphenotype model
Calfee 2018[18]	Retrospective analysis	LCA	HARP-2	IL-8, sTNFr1, bicarbonate, vasopressor use	2-subphenotype model
Zhang 2020[47]	Retrospective analysis	K-means cluster analysis	SAILS	Platelet count, creatinine, APACHE III score, Serum glucose	4-subphenotype model
Liu 2021[46]	Retrospective analysis	K-means cluster analysis	eICU collaborative research database, FACTT, ALVEOLI, SAILS	WBC count, temperature, heart rate, respiratory rate, SBP, age, BUN, serum creatinine, serum bicarbonate	3-subphenotype model
Duggal 2022[49]	Retrospective analysis	K-means cluster analysis	ARDSNet, ART	Heart rate, mean arterial, pressure, respiratory rate, bilirubin, bicarbonate, creatinine, PaO2, arterial pH, FiO2	2-subphenotype model

Notes: HARP-2, simvastatin in acute lung injury to reduce pulmonary dysfunction–2 study; ALVEOLI, randomized controlled trials of higher versus lower PEEP; ARDSNet, trials including ARMA, ALVEOLI, FACTT, EDEN, SAILS; ARMA, randomized controlled trials of lower tidal volume ventilation.
Abbreviations: LCA, latent class analysis; sTNFr1, soluble tumor necrosis factor receptor-1; IL-6, interleukin-6; IL-8, interleukin-8; ANG1/2, angiopoetin1/2; PAI-1, Plasminogen activator inhibitor −1; BUN, blood urea nitrogen; SBP, systolic blood pressure; ICAM-1, intercellular adhesion molecule-1; WBC, white blood cell count; APACHE, Acute Physiology and Chronic Health Evaluation; ART, Acute Respiratory Distress Syndrome Trial; FACTT, Fluid and Catheter Treatment Trial; SAILS, rosuvastatin in sepsis-associated acute respiratory distress syndrome; eICU, telehealth intensive care unit.

future prospective studies are needed. It is necessary to conduct more research to see whether other factors, such as biomarkers and clinical characteristics, can be integrated to produce more thorough subphenotypic outcomes. The unsupervised learning methods and the variables included in previous studies are not entirely consistent, which is one of the reasons for the inconsistent ARDS subphenotypes.[50] Furthermore, advanced statistical analysis methods play an important role in ARDS subphenotype identification, and attempts have been made to distinguish ARDS subphenotypes with higher accuracy and easy clinical application using modern machine learning algorithms.[51]

Conclusions

Although researchers have undertaken a great number of phenotypic studies on ARDS, we still have not worked out the best classification model, and there are still many problems in the clinical application. Nevertheless, it is undeniable that ARDS phenotype research has great potential, which can help to discover the beneficiary population of intervention measures. At the same time, the reliable ARDS phenotype classification methods will also help to discover potential therapeutic targets to achieve precise treatment of ARDS. In future studies, we need to optimize experimental design protocols, screen for more reliable phenotypic classification schemes, and pay attention to the conversion of models to clinical applications.

Abbreviations

ARDS, acute respiratory distress syndrome; ICUs, central intensive care units; IL-6, interleukin-6; IL-8, interleukin-8; PAI-1, plasminogen activator inhibitor-1; RCTs, randomized controlled trials; PEEP, positive end-expiratory pressure; PaO2, partial pressure of oxygen; APACHE, Acute Physiology and Chronic Health Evaluation.

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Author Contributions

All authors made a significant contribution to the work reported. Whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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