# The Future of ARDS Biomarkers: Where Are the Gaps in Implementation of Precision Medicine?

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## 7.1 Introduction

The acute respiratory distress syndrome (ARDS) is a severe form of acute inflammatory lung injury associated with high mortality rates ranging between 27 and 45% depending on severity [1]. Recent literature reported that ARDS is a common clinical syndrome in the intensive care unit (ICU), representing 10.4% of all ICU admissions and 23.4% of patients requiring mechanical ventilation [2]. However, only 51.3–78.5% of ARDS cases are recognized by clinicians, suggesting that clinicians often underdiagnose ARDS when treating patients [2]. As a result, only a fraction of the patients receive treatment interventions for ARDS, such as low tidal volume ventilation, high positive end-expiratory pressure (PEEP), neuromuscular blockade and prone positioning [2]. One of the main challenges in ARDS diagnosis and management is the lack of a simple diagnostic test, resulting in reliance on a consensus definition that tries to encompass a complex syndrome with marked clinical and pathophysiologic heterogeneity [3]. In order to address this problem,

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numerous studies have focused on identifying biomarkers that can aid in the management of ARDS. Biomarkers can provide clues about the pathophysiologic mechanisms involved in ARDS and, when combined with other clinical data, can help in the diagnosis, risk stratification, and treatment of ARDS [4]. However, studies have tested a wide range of biomarkers using a variety of different methods, and are often retrospective studies with small sample sizes. As a result, the optimal way to utilize the biomarkers for clinical management of ARDS is still unclear. In this chapter, we review the current evidence for biomarkers in several aspects of ARDS management and to identify the gaps that need to be addressed before they are routinely applied in clinical medicine.

## 7.2 Current State of Biomarkers in ARDS

### 7.2.1 Biomarkers for Diagnosis of ARDS

A number of biomarkers have been studied to aid in the diagnosis of ARDS, with various levels of correlation with ARDS diagnosis. One of the biomarkers that has been shown to associate strongly with ARDS diagnosis is soluble receptor for advanced glycation end-products (sRAGE), which is the extracellular domain of a multiligand receptor expressed on alveolar type 1 cells and is a marker of lung epithelial injury [5]. In a study by Jabaudon et al., plasma sRAGE levels were found to be elevated in patients with acute lung injury or ARDS, and correlated with clinical and radiographic severity of disease [5]. Another study by Fremont et al. also found that plasma levels of sRAGE, along with several other biomarkers, were significantly elevated in trauma patients who developed acute lung injury/ARDS compared to controls [6]. A recent meta-analysis evaluating the strength of association of several biomarkers with ARDS diagnosis and mortality also found that sRAGE had a high odds ratio for ARDS diagnosis [4].

Another biomarker that has been studied in the diagnosis of ARDS is angiopoietin-2 (Ang-2), a molecule that leads to impairment of lung endothelial barrier function and serves as a marker of lung endothelial injury [7]. In one study, elevated plasma level of Ang-2 in critically ill patients receiving mechanical ventilation was shown to be predictive of acute lung injury/ARDS and to correlate with severity of disease [7]. Another study found that elevated Ang-2 levels were strongly associated with increased development of acute lung injury in critically ill patients [8]. The same study also found that the combination of elevated Ang-2 level and the Lung Injury Prediction Score (LIPS), a clinical prediction score for acute lung injury, had improved performance for identifying patients who developed acute lung injury compared to either component alone [8]. The aforementioned study by Fremont et al. in a trauma ICU population also found that Ang-2 levels were significantly elevated in acute lung injury/ARDS patients compared to controls [6].

Surfactant protein-D (SP-D) is another marker of lung epithelial injury that has been studied in ARDS diagnosis. SP-D is one of the surfactant-associated proteins that are mainly synthesized in alveolar type 2 cells and is thought to be a marker of lung epithelial injury and inflammation [9]. One study found that plasma levels of SP-D were

higher in patients with ARDS compared to matched controls without ARDS [9]. Another study found that SP-D had the highest area under the receiver operating characteristic curve (AUC) among a panel of biomarkers tested for ARDS diagnosis [10].

A few other examples of biomarkers that have been shown to correlate with ARDS diagnosis in some studies include von Willebrand factor (vWF), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-8 [4, 6, 8, 11] (Table 7.1).

**Table 7.1** Selected biomarkers and their studied use in the acute respiratory distress syndrome (ARDS)

| Biomarker | Mechanism | Studied uses | References |
|---|---|---|---|
| Soluble receptor for advanced glycation end-products (sRAGE) | Extracellular domain of multiligand receptor expressed on alveolar type 1 cells; involved in propagating inflammatory response; elevated plasma levels can indicate lung epithelial injury | Correlation with:<br>– ARDS diagnosis<br>– ARDS severity<br>– ARDS mortality and outcomes | [4–6, 18, 19] |
| Angiopoietin-2 (Ang-2) | Binds Tie2 receptors on lung endothelial cells; impairs endothelial barrier function and increases adhesion of inflammatory cells; elevated plasma levels can indicate lung endothelial injury | Correlation with:<br>– ARDS diagnosis<br>– ARDS severity<br>– ARDS mortality<br>Distinguishing ARDS phenotype | [6–8, 19] |
| Surfactant protein-D (SP-D) | Synthesized in alveolar type 2 cells and non-ciliated bronchiolar epithelium; contributes to regulation of lung inflammation; elevated plasma levels can indicate lung epithelial injury | Correlation with:<br>– ARDS diagnosis<br>– ARDS mortality and outcomes<br>Distinguishing ARDS phenotype | [9, 10, 15–17, 19] |
| von Willebrand factor (vWF) | Glycoprotein involved with hemostasis; released by endothelial cells into systemic circulation in endothelial activation or injury | Correlation with:<br>– ARDS diagnosis<br>– ARDS mortality<br>Distinguishing ARDS phenotype | [4, 6, 8, 11, 19] |
| Interleukin-6 (IL-6) | Nonspecific pro-inflammatory cytokine | Correlation with:<br>– ARDS diagnosis<br>– ARDS mortality<br>Distinguishing ARDS phenotype | [4, 6, 19] |
| Interleukin-8 (IL-8) | Nonspecific pro-inflammatory cytokine | Correlation with:<br>– ARDS diagnosis<br>– ARDS mortality<br>Distinguishing ARDS phenotype | [4, 6, 8, 19] |
| Tumor necrosis factor-α (TNF-α) | Nonspecific pro-inflammatory cytokine | Correlation with:<br>– ARDS diagnosis<br>– ARDS mortality | [4, 6] |
| Fas, Fas ligand | TNF family of cytokine and receptor, expressed in many cell types including lung epithelial cells; high concentrations in BALF can indicate pro-apoptotic activity and lung epithelial injury | Correlation with:<br>– ARDS diagnosis<br>– Overall severity of illness in ARDS patients | [13] |

*BALF* bronchoalveolar lavage fluid

Given the wide array of biomarkers that have shown promising results for ARDS diagnosis, some studies have examined the utility of combining several biomarkers into a panel for ARDS diagnosis. One study found that a panel of biomarkers consisting of sRAGE, procollagen peptide III, brain natriuretic peptide, Ang-2, IL-8, IL-10 and TNF-α had high diagnostic accuracy for ARDS diagnosis [6]. The same group of investigators also studied a different set of biomarkers consisting of SP-D, sRAGE, IL-6, IL-8 and club cell secretory protein, and found that the panel had higher AUC for ARDS diagnosis compared to any one of the biomarkers by itself [10]. However, partially due to the wide variability in the biomarkers that have been tested and included in the panels, there is currently no consensus about which biomarker or a panel of biomarkers is the best for ARDS diagnosis.

While the biomarkers discussed thus far are measured from plasma samples, bronchoalveolar lavage fluid (BALF) has been studied as another potential source for biomarkers. Since BALF is obtained from the distal airspaces that are close to the site of lung injury, it is thought to better reflect the local lung environment [12]. One study found that Fas and Fas ligand, which are signal molecules involved in the apoptosis pathway, were found in higher concentrations in the pulmonary edema fluid from patients with ARDS than in that from control patients with hydrostatic edema [13]. This study also found higher Fas and Fas ligand concentrations in the pulmonary edema fluid of the ARDS patients than in simultaneously collected plasma samples, supporting the potential utility of BALF as a source of biomarkers. The counterargument is that ARDS can be a patchy process occurring as a result of both pulmonary and extrapulmonary causes, and systemic compartment sampling such as serum or plasma may be more suitable for monitoring the processes related to ARDS [14]. Additional limitations in using BALF for measuring biomarkers is that sampling requires an invasive procedure and the variable dilution of BALF samples could make quantitative assessments of biomarkers more difficult [12].

### 7.2.2 Biomarkers for Prognostication in ARDS

The use of biomarkers has also been studied for prognostication or risk stratification to predict several outcome measures in patients with ARDS. One study showed a smaller increase in SP-D level in ARDS patients ventilated with lung-protective strategy compared to those ventilated with the conventional strategy, indicating that SP-D may serve as a marker of ventilator-induced lung injury (VILI) in ARDS [15]. The same study also found a correlation between higher SP-D levels in ARDS patients and mortality, number of days on the ventilator, and length of stay in the hospital, supporting its value in prognostication of ARDS. Eisner et al. found a similar association between higher SP-D levels in ARDS and greater risk of death, fewer ventilator-free days, and fewer organ failure-free days [16], and Jensen et al. reported that higher levels of SP-D at the time of ICU admission were not only predictive of ARDS but were also associated with low likelihood of successfully weaning from the ventilator at 28 days [17]. Similarly, Calfee et al. reported that higher

sRAGE levels were associated with increased severity of acute lung injury, increased mortality, and fewer ventilator-free and organ failure-free days [18]. Several other biomarkers, including sRAGE, Ang-2, IL-6 and IL-8, were shown to be elevated in non-survivors from ARDS and associated with higher mortality [12, 19], and the meta-analysis discussed previously reported that IL-4, IL-2, Ang-2 and Krebs von den Lungen-6 had the highest odds ratios for ARDS mortality [4]. Although procalcitonin (PCT) has not been extensively studied in ARDS overall, a study by Tseng et al. found that higher levels of plasma PCT were associated with increased mortality from ARDS caused by severe community-acquired pneumonia [20].

Because of this potential utility in predicting ARDS outcomes, biomarkers have also been studied in conjunction with existing clinical prediction models to enhance their performance. As discussed previously, the combination of Ang-2 level and LIPS had higher AUC for acute lung injury development than either component alone [8], and similar results were found for combining Ang-2 and LIPS in another study in a Han Chinese patient population [21]. SP-D and IL-8 have also been used in combination with the Acute Physiology and Chronic Health Evaluation (APACHE)-III score to develop a mortality prediction model for ARDS, which was validated using the patients from several prior ARDS trials [22]. These results suggest that biomarkers may have utility in prognostication and risk stratification of ARDS patients, both alone and in combination with currently available clinical prediction models for ARDS.

### 7.2.3 Biomarkers for Distinguishing Phenotypes of ARDS

ARDS has been recognized as a clinically and biologically heterogeneous syndrome, with different underlying etiologies of ARDS resulting in different mechanisms of lung injury and various clinical phenotypes [3, 19]. A better mechanistic understanding of ARDS may enable further improvements in classification and management of this complex and heterogeneous syndrome, and there has been a growing interest in addressing ARDS heterogeneity using biomarkers [14]. For example, an early study reported that SP-D and SP-A levels were highest in patients with pneumonia as the ARDS risk factor and lowest in those with trauma as the ARDS risk factor [16]. The same study also found that higher SP-D levels had the strongest association with the risk of death in patients with sepsis and pneumonia, but higher SP-D levels were related to a lower risk of death in patients with trauma. Another study by Ware et al. found that the level of vWF, a marker of endothelial injury, was lower in patients with ARDS from trauma compared to other causes, and lower in patients with indirect lung injury compared to direct lung injury [11]. Calfee et al. subsequently compared the levels of several biomarkers between patients with ARDS from direct versus indirect lung injury [19]. They found that patients with ARDS from direct lung injury had higher levels of SP-D, a marker of epithelial injury, and lower levels of Ang-2, a marker of endothelial injury. In the same study, the investigators also performed a secondary analysis of a multicenter trial and found that patients with ARDS from direct lung

injury had lower levels of vWF, IL-6, and IL-8 than those with indirect ARDS. Although the result regarding vWF in this study differs from that of the study by Ware et al. [11], these findings nonetheless suggest that different risk factors or phenotypes of ARDS result in different profiles of biomarkers. As such, biomarkers may be helpful for distinguishing different phenotypes of ARDS and potentially identifying various pathophysiologic mechanisms involved in ARDS that can be targeted for future therapies.

## 7.3 Gaps in Implementation of Biomarkers in ARDS

### 7.3.1 Barriers to the Clinical Application of Biomarkers in ARDS

While the above studies have demonstrated the potential utility of biomarkers in ARDS diagnosis, classification, and prognostication, currently there are significant limitations in their application and implementation in the clinical management of ARDS. Numerous biomarkers for ARDS have been studied in various contexts, but there is no single biomarker that reliably predicts ARDS diagnosis or an outcome of interest [12]. Many of the studies discussed in this review have wide variations in the patient populations recruited, biomarkers that were tested, timing and methods of biomarker measurement, and the endpoints or outcomes of interest. Many studies were also limited by the retrospective nature of the study and/or small sample sizes. These factors make it difficult to determine the optimal way to utilize biomarkers in the clinical management of ARDS.

There are also practical aspects of biomarker testing in ARDS that need to be addressed in future studies. An ideal biomarker should have high sensitivity and specificity, and be cost effective and easy to measure in a time-sensitive manner to be useful in the management of ARDS, given the acuity of this syndrome [3, 12]. Even if a biomarker or a panel of biomarkers is found to be predictive for the diagnosis or for an outcome measure of ARDS, it must be feasible to use in real time in clinical practice with the above characteristics. There is also some debate about which body compartment may be the best to sample for ARDS-related biomarkers. As discussed previously, BALF is thought to better reflect the local lung environment during lung injury and can capture biomarkers that may not be present in extrapulmonary sites, but requires an invasive procedure for sampling [14]. Plasma samples, on the other hand, are much easier to collect and may be better suited for analyzing systemic processes that are also involved in ARDS pathogenesis [14]. Exhaled breath and exhaled breath condensate have also been examined as a noninvasive source of volatile organic compounds that can serve as ARDS biomarkers [23, 24], but their utility in ARDS management and the methods for measuring these compounds need to be further assessed. All in all, more studies are needed to determine which biomarker (or panel of biomarkers) will have the best utility for predicting the diagnosis of or outcome from ARDS with reasonable accuracy, as well as the cost effectiveness and ease of measurement to be useful in a clinical setting.

### 7.3.2 Gaps in Identifying Additional Uses of Biomarkers in ARDS

Although prior studies have examined the use of biomarkers in various aspects of ARDS management, a majority of studies appears to focus on diagnosis and/or prognostication in ARDS. Studies examining the role of biomarkers in other aspects of ARDS management are relatively lacking, and more studies are needed to investigate additional applications of biomarkers. For example, the use of biomarkers to monitor progression of ARDS or response to treatment interventions needs more investigation. Some studies showed that ARDS patients who were ventilated with a lung-protective strategy with lower tidal volumes had a smaller increase in plasma SP-D levels over time [15, 16]. These findings suggest that measuring biomarkers over time may have a role in monitoring the severity of lung injury and the response to treatment interventions in ARDS.

Further studies are also needed for application of biomarkers in differentiating the phenotypes of ARDS and aiding in the development of future therapies for ARDS. The clinical and pathophysiologic heterogeneity in ARDS is thought to have contributed to many failures in developing therapies for ARDS, and elevation of specific biomarkers may help identify biologic or molecular pathways that can be targeted in future therapies [3]. For example, ARDS from direct lung injury appears to be characterized by lung epithelial injury, and studies evaluating therapies targeting the epithelium (e.g., keratinocyte growth factor) may preferentially enroll these patients [19]. Elevation of sRAGE level has also been implicated in identifying the subgroup of ARDS patients who have epithelial injury and may benefit from tailored therapy [5, 25], though the exact molecular target in this pathway for potential therapy still remains to be elucidated. On the other hand, ARDS from indirect lung injury appears to be characterized by endothelial injury, and these patients may benefit from future therapies targeting the endothelium and the pathways for protecting the endothelial barrier function (e.g., recombinant Ang-1) [7, 19]. Biomarkers can potentially help improve the mechanistic understanding of different ARDS phenotypes and develop a classification system, which may then help select patients who are most likely to benefit from new therapies targeting specific biologic or molecular pathways [3, 14]. Such advancements can be an important step in the application of precision medicine in ARDS management.

### 7.3.3 Additional Tools for ARDS Biomarker Discovery

In addition to the protein biomarkers, a relatively new scientific method that may be helpful in tackling these challenges of ARDS diagnosis and management is metabolomics. Metabolomics is an emerging field of "-omics" that simultaneously analyzes a large number of metabolites and biological compounds in an untargeted approach to identify clinically relevant biomarkers and potential therapeutic targets [26]. Because metabolites represent a level downstream of genomics and proteomics, it is thought to be closer to the phenotype of disease and more reflective of the biological perturbations in a disease process [14]. Metabolomics has been

applied in defining the phenotypes of other heterogeneous pulmonary diseases, such as asthma and chronic obstructive pulmonary disease, and has started to be used in studies of ARDS as well [14]. A pilot study by Stringer et al. using nuclear magnetic resonance (NMR) spectroscopy of plasma samples found higher levels of total glutathione, adenosine, and phosphatidylserine, and lower levels of sphingomyelin in patients with sepsis-induced acute lung injury compared to healthy volunteers [26]. Another study by Viswan et al. used NMR spectroscopy of mini-BALF from ARDS patients and identified 29 metabolites [27]. Among these, six metabolites (proline, lysine, arginine, taurine, threonine, glutamate) were used to construct a predictive model for distinguishing mild versus moderate/severe ARDS. A handful of other studies have also applied metabolomic approaches to ARDS and identified biological profiles of deranged energy metabolism, increased fibrosis and inflammation, and disturbed cellular turnover in ARDS [14]. However, many of these studies have mainly focused on deriving a distinct metabolic signature of ARDS compared to control subjects, and also suffer from variability in the study populations and the methods by which the samples are measured and analyzed. Thus, more studies are needed to determine the utility of metabolomics in ARDS, with standardization of patient recruitment and sample collection, preparation, and analysis [14].

## 7.4 Conclusion

Numerous biomarkers have been studied for diagnosis, classification, and prognostication of ARDS. While several biomarkers have shown promising results in helping to better understand, diagnose, classify, and manage ARDS, their application to clinical settings is currently limited due to the large number of biomarkers being tested and the wide variability in the method and the timing of measurement. Further studies are needed in order to determine which biomarkers will be sufficiently accurate for predicting the diagnosis of or outcome from ARDS, and also be practical and cost effective to be useful in clinical settings. More studies are also needed in order to standardize the methods of measuring the biomarkers and to prospectively validate their utility in clinical management of ARDS. Through these steps, biomarkers can help better characterize and phenotype ARDS patients, identify potential biological and molecular targets for treatment, and allow for a more precise and tailored approach to treating this complex clinical syndrome.

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