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Biomarkers for ARDS What is New?

Despite several biomarkers having been studied for diagnosis and/or prognosis of acute respiratory distress syndrome (ARDS), their extensive use has not been established. Better knowledge of the pathophysiology of ARDS and acute lung injury (ALI) may help develop new biomarkers.

Acute respiratory distress syndrome (ARDS) is characterised by non-cardiogenic pulmonary oedema and respiratory failure (Matthay et al. 2019) and is diagnosed by clinical parameters defined in the last Berlin definition (Ranieri et al. 2012). The presence of an acute insult, bilateral opacities in thoracic images, hypoxaemia despite receiving a positive end-expiratory pressure or continuous positive airway pressure higher or equal to 5 mmHg, and the absence of a cardiogenic cause are required for ARDS diagnosis (Bernard and Artigas 2016). Different insults or causes have been described as associated with ARDS (Bos and Ware 2022). ARDS is not always developed despite the presence of these conditions and also can vary according to the aetiology. While only 30% of severe pneumococcal pneumonia develop ARDS (Cilloniz et al. 2018), almost all patients admitted to ICU with COVID-19 developed ARDS (Ceccato et al. 2022). Different virulence factors, inflammatory responses, and their interaction may explain this.

Epithelial and endothelial barrier disruption and damage may be variable in ARDS and could be impaired with mechanical stretch (Matthay et al. 2012; Ware and Matthay 2000). These phenomes activate the inflammatory and coagulation pathways leading to the first phase of ARDS named exudative. A second phase is named proliferative where resolutions of ARDS are started. A third fibrotic phase is variable and is not always developed. It is related to the duration of mechanical ventilation (Ware and Matthay 2000).

Calfee et al. (2014) have described two sub-phenotypes of ARDS. Unbiased latent class analysis of clinical and biomarker characteristics of ARDS patients demonstrated hypo-inflammatory and hyper-inflammatory groups. These have different clinical and biological features and different responses to therapy. In the hyper-inflammatory group, there is a higher level of inflammatory biomarkers, higher vasopressor use, lower serum bicarbonate, higher prevalence of sepsis, higher mortality, and fewer ventilator and organ failure-free days, compared to the hypo-inflammatory group. Bos et al. (2017) identified two phenotypes in the MARS cohort as well. Levels of inflammatory, coagulation and endothelial activation proteins expression were higher in the reactive cohort, instead uninflamed have lower levels of markers. Currently, the PHIND study (NCT04009330) aims to evaluate a point-of-care assay to prospectively identify phenotypes at the bedside.

The identification of an accurate diagnostic, a predictive or prognostic marker for ARDS would significantly improve our understanding of this heterogeneous disease. Recent progress in several areas of biomarkers research, including advances in the development of point-of-care testing technologies, has the potential to transform the application of biomarkers at the bedside for diagnosis, risk stratification, molecular phenotyping, and monitoring therapeutic response (Bernard and Artigas 2016; Ware and Calfee 2016). Nevertheless, the heterogeneity in features, underlying causes, different phases, and phenotypes makes it hard the identification of biomarkers to predict clinical outcomes or personalise treatment. Several studies have looked into markers of epithelial and endothelial injury,

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coagulation, and inflammation and have shown a combination of clinical predictors with biomarkers that were better at predicting mortality compared to either clinical or biomarkers alone (Ware et al. 2010; Fremont et al. 2010; Calfee et al. 2011).

Systemic and Local Biomarkers

A combination of seven biomarkers including the receptor for advanced glycation end-products (RAGE), procollagen peptide III (PCP III), brain natriuretic peptide (BNP), angiopoeitin-2 (Ang-2), interleukin-8 (IL-8), tumour necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) were superior to clinical diagnosis for the diagnosis of ARDS in severe trauma with an area under the curve ROC (AUCROC) of 0.86 (Fremont et al. 2010). The combination of markers for lung epithelial injury, collagen deposition, cardiac dysfunction, endothelial activation/injury, and inflammation allows an accurate diagnosis of acute lung injury (ALI) in these selected populations.

In a posthoc analysis of two clinical trials in patients with ARDS, measures of intercellular adhesion molecule-1 (ICAM-1), von Willebrand factor, IL-8, soluble tumour necrosis factor receptor-1, and surfactant Protein-D (SP-D) improved the prognosis of risk of death at the moment of enrolment to the study (Calfee et al. 2011).

In septic patients, a panel including inflammatory and epithelial injury markers (RAGE, SP-D, Club Cell Protein-16[CC-16], IL-8, and IL-6) were useful for the diagnosis of ARDS in a case-control study. The combination of markers showed higher AUC than each marker, indicating the potential value of combining lung epithelial and inflammatory markers for the diagnosis of ARDS (Ware et al. 2013).

Elevated levels of interleukin-18 (IL-18), a cytokine activated by inflammasomes, were observed elevated in patients with ARDS (traumatic or sepsis ARDS) and correlated with the severity and mortality of patients (Dolinay et al. 2012).

Direct lung injury mainly caused by pneumonia and aspiration is characterised by more severe lung epithelial and less severe endothelial injury and inflammation with a higher level of SP-D and RAGE and a lower Ang-2 compared with indirect ARDS (Calfee et al. 2015). Indirect ARDS is characterised by higher severity scores and a high number of organ failures compared with direct ARDS, even though mortality is similar (Luo et al. 2017). Ang-2 levels showed better accuracy than other endothelial dysfunction biomarkers in patients with ALI and sepsis, and the highest levels were found in patients with non-pulmonary sepsis. Ang-2 also may predict the onset of ALI before clinical signs and identify patients with a high risk to develop ARDS (Agrawal et al. 2013). On the other hand, a greater plasma level of RAGE, a marker of injury of alveolar cell type I, was correlated with a high lung injury score and lower compliance and was associated with poor outcomes in patients who did not receive protective mechanical ventilation parameters. Also, the levels of the soluble form of RAGE inversely correlate with alveolar fluid clearance, and a decrease in the measures was observed after the resolution of lung injury and alveolar fluid clearance was restored in an in vivo model (Calfee et al. 2008; Jabaudon et al. 2015). Serum sRAGE concentrations are elevated in COVID-19 patients and may predict independently of other variables the need for invasive mechanical ventilation (Lim et al. 2021). Endothelial injury and dysfunction have great interest in other areas such as cardiovascular diseases or oncology. Further studies should evaluate the impact of other endothelial markers studied in other conditions (Balistreri 2022).

SP-D levels are correlated with pulmonary oedema measured by radiographic assessment of lung oedema (RALE) or lung ultrasound score (LUS) irrespective of the cause of ARDS. sRAGE and Ang2 were associated with pulmonary oedema as well but were not associated when subgroups were analysed separately.

Eight plasma biomarkers were included to differentiate between the two subphenotypes described by Calfee et al. (2014): SP-D, von Willebrant factor antigen, soluble intracellular adhesion molecule 1 (sICAM-1), IL-6 and Il-8, soluble tumour necrosis factor receptor (TNFR1), plasminogen activator inhibitor-1 (PAI-1) and protein C. Bos et al. (2017) included a selection of 4 biomarkers IL-6, interferon-gamma, Ang ½, and PAI-1 to clustered ARDS into biological phenotypes (reactive and uninflamed) with different mortality rates. The stability of ARDS phenotypes has been shown over the first three days of enrolment in two clinical trials (Delucchi et al. 2018), and they respond differently to fluid management strategies (Famous et al. 2017). These findings have the potential to transform the way we approach patients with ARDS, selecting patients who may benefit from specific therapeutic strategies and tailoring the treatment for every single patient.

There is a difference between the systemic reaction indicated by biological phenotypes and the local alveolar reaction emphasising the importance of phenotyping the alveolar compartment in future research. Recently, a study showed that phenotypes according to plasma or bronchoalveolar levels had minimal overlap (Sathe et al. 2023). Moreover, Heijnen et al. (2021) observed a non-difference in levels of biomarkers between subphenotypes reactive or uninflamed/hypo-inflammatory or

hyper-inflammatory. In other critically ill conditions such as VAP, the difference in biomarkers were observed in bronchoalveolar lavage fluid (BALF) but not in serum (Morris et al. 2010). A theory that may explain this phenomenon is the compartmentalised immune response (Morris et al. 2022). This theory may change the way of measuring biomarkers for pulmonary conditions.

Exhaled Breath Markers

Markers of endothelial, epithelial injury, protein-rich pulmonary oedema, and systemic or alveolar host response could be measured through a heat moisture exchange filter (Bastarache et al. 2021; McNeil et al. 2018). Nevertheless, this technique still requires validation.

Measures of samples from exhaled breath analysing volatile organic compounds using gas-chromatography and mass spectrometry could be a non-invasive, real-time approach to diagnosing changes in lung inflammation, or bacterial overgrowth. Through gas chromatography and mass spectrometry, metabolites can be detected in exhaled air of patients. In a study including more than 100 patients, octane, acetaldehyde, and 3-methyl heptane were identified as biomarkers of ARDS (Bos et al. 2014; Bos 2018) and showed a moderate-good accuracy (AUC ROC 0,78-0,80) for the diagnosis of ARDS compared to cardiopulmonary oedema or pneumonia.

MicroRNA

MicroRNA (miRNA) can be easily measured and hence are potential diagnostic and therapeutic targets in ARDS (Cardinal-Fernández et al. 2016). Plasma levels of miRNA-146a and miRNA-155 significantly increased in sepsis and sepsis-induced ALI. Pro Inflammatory related miRNAs miR-34a, miR-132, miR-155, miR-15a, miR-21, miR-27b, and miR-146a were described in LPS induced ALI. Some of them stimulate the NF-ϰB signalling pathway. Also, several miRNAs may be associated with endothelial injury such as miR-887-3p, miR-34a-5p, or miR-1246. In at-risk ARDS patients, Zhu et al. (2017) demonstrated that miRNA-181a, miRNA-92a, and miRNA-424 were protective biomarkers, and in addition to Lung Injury Pulmonary Score can improve the risk estimate of ARDS. During the COVID-19 pandemic a signature based on 2miRNA, miR-192-5p, and miR-323a-3p, may predict the survival probability with an AUCROC of 0.80 (de Gonzalo-Calvo et al. 2021).

“the rapidly developing field of study of extracellular vesicles could make them valuable biomarkers of injury and targets or vehicles for new therapies”

Extracellular Vesicles

The rapidly developing field of study of extracellular vesicles (EVs) and their natural features such as their high biocompatibility and low immunogenicity, the increased specificity to target cells or tissues, the ability to cross biological barriers, the use of endogenous cellular machinery of loading and their capacity to mirror the composition and the metabolic status of their source cells, could make EVs valuable biomarkers of injury, and targets or vehicles for new therapies.

When lung cells are subjected to external stimuli, such as hypoxia, inflammatory factors, or pathogens, they may alter the amount and the composition of the EVs they secrete, and this is crucial for ARDS progression and development (Ye et al. 2020). These changes that can be detected in the blood and bronchoalveolar lavage fluid (BALF) of ARDS patients, may provide new strategies for the aetiological diagnosis of ARDS and also predict the progression of this syndrome.

On the one hand, it has been demonstrated that serum/plasma EVs of patients with ARDS have a strong potential to guide clinical decisions on early intervention measures to block the development of lung inflammation leading to ARDS since they reflect contributions from most systemic tissues (Hu et al. 2022). A study carried out in patients with severe pneumonia revealed that the combined expression of exosomal miR-126, miR-27a, miR-146a, and miR-155 in plasma, predicted the development of ARDS with an AUCROC of 0.909 (95 % CI 0.815 –1) (Wu et al. 2019). In addition, Sun et al. (2012) demonstrated that EVs containing nitrated sphingosine-1-phosphate receptor-3 (S1PR3) shed into the circulation during inflammatory lung states represented a novel ALI biomarker linked to disease severity and outcome. The high heterogeneity that characterises serum EVs, also spurs new diagnosis opportunities, as in the case of a study performed in 2022, where the monitoring of the dynamics of serum EVs subsets (classified by size, concentration, and surface marker profile) distribution in the plasma of COVID-19 patients highlighted their predictive value and their correlation with the immune responses during COVID-19 progression (Yim et al. 2022).

On the other hand, changes in specific EVs markers in BALF samples may also be used as diagnostic tools in lung injury, particularly when it is due to external stimuli, such as respiratory pathogens (Hu et al. 2022). It has been demonstrated that the EVs from BALF of patients with pulmonary infection had a higher expression of miR–17–5p and miR–193a–5p in contrast with control patients, turning them into a new biomarker for pneumonia. Similarly, Letsiou et al. (2021) revealed that EVs carrying mitochondrial serve as diagnostic biomarkers of lung injury associated with microbial infection and Mahida et al. (2022) observed that the presence of CD14+/CD81+ BALF EVs is enriched in patients with sepsis-induced ARDS and an elevated count of this marker is associated with increased mortality in these patients as well as the presence of EVs containing the mRNA of phospholipase-IIA A2 (sPLA2-IIA) which is, not only a marker of early-phase ARDS but also a tracer of spatiotemporal events characterising the propagation and exacerbation of the syndrome (Kitsiouli et al. 2021).

A more exhaustive study of differentially expressed markers and the validation

of specific transcripts of EVs present in both, plasma and BALF of ARDS patients, is necessary to implement them in the clinic as definitive biomarkers for a more efficient stratification of ARDS aetiologies and thus, offering a more precise and early intervention.

Conclusion

Despite several biomarkers having been studied for diagnosis and/or prognosis of ARDS, their extensive use have not been established. Despite the fact that it could be useful to identify phenotypes, it is still unknown how biomarker measures may change in clinical practice. Further studies are warranted to determine if biomarkers may be used to identify differential diagnoses, aetiologies, prognosis, phenotypes, development of VILI, and therapeutic targets. Meanwhile, better knowledge of the pathophysiology of ARDS and ALI may help us to develop new biomarkers.

Conflict of Interest

None. ■

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