REVIEW ARTICLES

Biomarkers in acute lung injury

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Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) result in high permeability pulmonary edema causing hypoxic respiratory failure with high morbidity and mortality. As the population ages, the incidence of ALI is expected to rise. Over the last decade, several studies have identified biomarkers in plasma and bronchoalveolar lavage fluid providing important insights into the mechanisms involved in the pathophysiology of ALI. Several biomarkers have been validated in subjects from the large, multicenter ARDS clinical trials network. Despite these studies, no single or group of biomarkers has made it into routine clinical practice. New high throughput "omics" techniques promise improved understanding of the biologic processes in the pathogenesis in ALI and possibly new biomarkers that predict disease and outcomes. In this article, we review the current knowledge on biomarkers in ALI. (Translational Research 2012;159:205–217)

Abbreviations: ARDS = acute respiratory distress syndrome; ALI = acute lung injury; ROC = receiver-operating characteristic; AUROCC = area under the ROC curve; BALF = bronchoalveolar lavage fluid; IL = interleukin; TNF = tumor necrosis factor; sTNFR-I and II = soluble TNF receptors I and II; HMGB = high mobility group box nuclear protein 1; LBP = lipopolysaccharide binding protein; NO = nitric oxide; SP = surfactant proteins; RAGE = receptor for advanced glycation end products; CCSP = clara cell secretory protein; vWF = vonWillebrand factor; s, sICAM-1 = soluble intercellular adhesion molecule-1; Ang-1 and -2 = angiopoietin-1 and -2; PAI-1 = plasminogen activator inhibitor-1; KGF = keratinocyte growth factor; HGF = hepatocyte growth factor; FGF = fibroblast growth factor; VEGF = vascular endothelial growth factor; N-PCP-III = N-terminal procollagen peptide-III; LIPS = lung injury prediction score; LC-MS/MS = liquid chromatography combined with mass spectrometry; IGFBP- = insulin like growth factor binding protein-3; NMR = nuclear magnetic resonance; NFKB = nuclear factor kappa beta

Acute respiratory distress in adults was first described by Ashbaugh and Petty in 1967[1] in a case series of 12 subjects with acute onset of tachypnea, hypoxia, and loss of compliance after a variety of stimuli. Subsequent research has increased our understanding of this disease's pathophysiology,[2] epidemiology,[3] treatment options,[4-11] and outcomes.[3,12] A uniform definition of this syndrome has been adopted for research, epidemiology, and clinical care based on a report of the American-European consensus conference on acute respiratory distress syndrome (ARDS).[13] The incidence of ARDS, and its less severe

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form, acute lung injury (ALI), is believed to be 58.7 and 78.9 cases per 100,000 person-years, respectively,[3] with an estimated 74,500 deaths and 2.2 million ICU days annually. As the US population ages, it is expected that ALI will become an even greater health problem.[14]

Over the last 2 decades, biologic markers have revealed novel information about the pathophysiology of lung injury/repair and identified cells and putative mediators involved in ALI. However, despite this new knowledge biomarkers in ALI remain primarily a research tool. The focus of this review is to outline the current state of biomarkers in ALI and ARDS.

BIOMARKERS

Biomarkers are broadly defined as markers of a biologic process or state. A commonly used definition of a biomarker is "*a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic processes, or pharmacologic responses to a therapeutic intervention*".[15] Thus clinical parameters such as vital signs, physiologic measurements, biochemical, or molecular markers could be used as biomarkers to determine its relationship with an endpoint.

ENDPOINTS IN BIOMARKER RESEARCH IN ACUTE LUNG INJURY

Several clinical endpoints for biomarker research have been investigated in critically ill patients with hypoxic respiratory failure from ALI. These end points have focused on the ability to diagnose ALI in high-risk patients or discriminate patients with hydrostatic from high permeability pulmonary edema. Also of interest are identifying subgroups of patients with different outcomes or response to treatment in patients at risk of or with established ALI. As these are surrogate endpoints, the most clinically relevant outcome is mortality and therefore biomarker research has concentrated on prediction of short- and long-term mortality in ALI. Besides a potential utility in the clinical arena for diagnosis, stratification, and prediction of mortality, biomarkers in ALI could also be used in clinical trials for selection of homogenous patients and as end points.

STATISTICAL BASIS FOR USE OF BIOMARKERS

The rationale of when to measure laboratory parameters, which marker may be useful, and how to interpret the results are not well defined. It is vital that validation and confirmation of candidate biomarkers by robust statistical methods are performed during biomarker discovery. Sensitivity and specificity are common quality parameters for biomarkers. Sensitivity describes the probability of a positive test in cases and specificity describes probability of negative test in controls. An association between sensitivity and specificity is represented in the receiver-operating characteristic (ROC) by graphing sensitivity vs 100-specificity. Area under the ROC curve (AUROCC) is a measure of performance of a marker. There is no absolute cutoff value of AUROCC for robustness of a marker though a minimum of 0.7 is required and values greater than 0.8 are good particularly in a heterogeneous patient population seen with critical illnesses.[16]

An ideal biomarker in ALI should have a clear relationship between the biomarker and the pathophysiologic events. The markers would need to be reliable and reproducible, relatively inexpensive, measure changes in response to interventions, have little or no diurnal variation, be sensitive, disease specific with high positive and negative predictive values, and be sampled by simple methods. Exhaled breath condensate,[17,18] urine,[19,20] undiluted pulmonary edema fluid,[21-23] bronchoalveolar lavage fluid (BALF), and plasma/serum have been studied for biomarker discovery in ALI.

BIOMARKERS OF ARDS/ALI STAGES

The pathologic states of ARDS consist of 3 discrete stages that overlap both temporally and spatially (Fig).[24] Histologically, the initial exudative phase is characterized by diffuse alveolar damage. In this early phase, the epithelial and endothelial cells release factors reacting to injury and death. The loss of cellular integrity results in flooding of the alveolus with a proteinaceous exudate that results in the impairment of gas exchange. The subsequent dilution of surfactant proteins leads to alveolar collapse and decreased lung compliance. Over the ensuing days, the pulmonary edema fluid is cleared and a proliferative stage develops. Histologically, this is marked by proliferation and phenotypic changes in type II alveolar cells and fibroblasts. In the absence of recovery, some patients progress to a fibrotic stage that is characterized by diffuse fibrosis and the obliteration of normal lung architecture. Various observational and clinical studies identify biomarkers that correlate with these stages, some of which have been associated with clinical outcomes. To put the biomarkers in the context of the physiologic stages of ALI, we have segregated them to correspond to the exudative (Table I) and proliferative phase (Table II) of ALI.

EXUDATIVE PHASE

A hallmark of ARDS is diffuse alveolar damage consisting of widespread epithelial and endothelial injury and death accompanied by a proteinaceous exudate. With this histologic finding in mind many investigators have sought to determine if specific cellular proteins