Biomarkers in Acute Lung Injury—Marking Forward Progress

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• Biomarkers • Clinical predictors • ALI • ARDS

An invited commentary in the *Lancet* in 1997 noted, "despite two decades of intense effort, there is still no means of predicting reliably whether an individual patient will develop the acute respiratory distress syndrome (ARDS)".[1] Shortly thereafter, the National Institutes of Health National Heart, Lung, and Blood Institute ARDS Clinical Network (ARDSNet) trial of lower tidal volume ventilation,[2] with an unprecedented 21% relative risk reduction in mortality, led to renewed optimism in the field of acute lung injury (ALI). In addition to guiding clinical management, this and subsequent ARDSNet studies have served as valuable sources of biologic samples for large-scale validation of multiple biomarkers.[3]

This article reviews the state of the art regarding biomarkers for prediction, diagnosis, prognosis, and surrogate endpoints in ALI, drawing on data from ARDSNet studies as well as other well-characterized patient populations. In addition to candidate biomarker studies, contributions from the omics revolution, with its many subgenres—genomics, proteomics, metabolomics, and others—are discussed. Given the significant progress in the past decade, there is optimism that the next decade will be marked by continued advancements in the ability to apply biomarkers to the diagnosis, treatment, and prognostication in the clinical syndrome of ALI.

BIOMARKER RESEARCH IN ALI: DEFINITIONS AND GOALS

A widely cited definition for a biomarker came from the 1998 National Institutes of Health Biomarker Definitions Working Group: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".[4] This definition

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makes no supposition about the material nature of the characteristic in question. Reflecting this, the World Health Organization suggests that a biomarker is "any substance, structure or process that can be measured in the body or its products and influence or predict the incidence or outcome of disease".[5] More broadly, the World Health Organization proposed that a biomarker is "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The response may be functional and physiological, biochemical at the cellular level, or a molecular interaction."[6] This definition provides a mechanistic framework for conceptualizing biomarkers in ALI and serves as a reminder that clinical signs, such as pulse and blood pressure, can also be biomarkers. The fundamental goal of biomarker research is to determine the relationship between a given biomarker and relevant clinical endpoints.[7]

Several relevant clinical endpoints have been the focus of biomarker research in ALI. The most clinically important outcome is mortality,[8] and prediction of hospital or short-term mortality has been the predominant focus of biomarker research in the past decade.[9] Another clinical endpoint of import is that of diagnosis—can a biomarker that is specific to lung injury facilitate the diagnosis in high-risk patients or distinguish between the high permeability pulmonary edema of ALI and cardiogenic edema? Related to diagnosis is the prediction of ALI in at-risk patients. More accurate identification of patients likely to develop ALI would facilitate trials of novel agents or quality-improvement initiatives for prevention of ALI. Similarly, identification of subgroups of patients either at risk of or with established ALI who may have a differential response to treatment could facilitate enrollment of more homogenous populations into clinical trials and represents an additional clinical endpoint of interest.

A further potential role for biomarkers of ALI is as surrogate endpoints in clinical trials.[7] A biomarker response to treatment might substitute for a hierarchically more important clinical endpoint, such as mortality in early-phase clinical trials, that are not powered for mortality.[10] The use of surrogate endpoints, however, can be problematic in critical care. Improvements in surrogate endpoints, such as oxygenation and organ failures, have not consistently been associated with mortality reductions in sepsis or ALI studies.[2] Conversely, an absence of signal in a surrogate endpoint does not necessarily imply a failure to improve mortality outcomes.[11] In summary, there are many potential roles for biomarkers in clinical ALI and these roles coalesce around predicting progression from the at-risk state, to diagnosis, to response to treatment, to risk stratification and to prognosis.

Biomarkers—Illuminating Biologic Pathways

Another important goal of biomarker research is to shed light on the relative contribution of biologic pathways to ALI pathogenesis. Assays of candidate biomarkers that reflect various aspects of ALI pathogenesis derived from experimental models can provide confirmation that these pathways are important in the pathophysiology of human disease. Furthermore, modeling candidate biomarkers in a head-to-head comparison has emerged as a powerful tool to determine the best performing biomarkers, an approach that can also provide important glimpses into pathogenesis.[12]

The apparent association of cytokines, biologic pathways, and clinical outcomes in ALI must be tempered, however, by the knowledge that biomarkers, such as cytokines, are members of complex cascades and networks. Assessing levels of an individual cytokine dissociated from the levels of its antagonists or natural inhibitors may lead to the erroneous impression that an altered cytokine level reflects derangements in a biologic pathway.[13] In addition, immune-reactive assays that measure the