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Plasma Biomarkers in Acute Respiratory Distress Syndrome: A Work in Progress

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In this issue of *Critical Care Medicine*, Terpstra et al (1) review the current status of plasma biomarkers as they relate to the diagnosis and prognosis of the acute respiratory distress syndrome (ARDS). ARDS is a common syndrome in the critically ill and is associated with significant morbidity and mortality (2, 3). The underdiagnosis of ARDS (4), underutilization of potentially life-saving therapies (5), and high morbidity and mortality have driven research aimed at discovering diagnostic and prognostic tools that are more objective and accurate than our current bedside assessments (6). Given the changing face of ARDS with a modified definition (7) and evidence of decreasing associated mortality (8), this is an opportune time to summarize the current knowledge of plasma biomarkers in the diagnosis and prognosis of ARDS.

Terpstra et al conducted a systematic, quantitative, and comparative review of the utility of plasma biomarkers for diagnosis and prognosis of ARDS. An extensive search of the literature yielded a total of 762 studies; after excluding the majority of these studies for reasons including lack of relevance to ARDS, use of healthy rather than critically ill controls, and biomarkers with only a single published study, 54 studies with a total of 3753 patients were included in the final meta-analysis. Of these, 20 diagnostic studies compared ARDS patients to non-ARDS patients, and 19 prognostic studies compared ARDS survivors to ARDS non-survivors. For each biomarker, an odds ratio (OR) for the outcome of interest (diagnosis of ARDS or mortality) was calculated by pooling data from all studies on each biomarker, while also including heterogeneity analyses.

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Competing Interests Statement
The authors declare that they have no financial or non-financial competing interests.

Authors' Contributions
DRJ and LBW both prepared and participated in the drafting and subsequent revisions of the manuscript.

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In regards to the diagnosis of ARDS in an at-risk patient population, Krebs von den Lungen-6 (KL-6) had the strongest association with the diagnosis of ARDS, followed by lactate dehydrogenase, soluble receptor for advanced glycation end products (RAGE), von Willebrand factor (vWF), and interleukin-8 (IL-8). Among patient with ARDS, plasma interleukin-4 (IL-4), interleukin-2, angiopoietin-2, KL-6, and interleukin-1 beta had the strongest associations with subsequent mortality.

The authors should be commended on their extensive, quantitative review of the literature and attempts at providing a comparative analysis of a number of plasma biomarkers and how they may relate to the diagnosis and prognosis of this complex clinical syndrome. However, caution is warranted in interpreting these data for several reasons. First, although the tables are organized in a hierarchical fashion by decreasing ORs which may suggest that one biomarker is more predictive of a diagnosis or outcome, it is important to emphasize that unlike positive or negative predictive values, ORs are not predictive, but rather describe the strength of the association of a variable with an outcome. From the current study we can conclude that KL-6 has a strong association with the diagnosis of ARDS in an at-risk patient population. However, without knowing the false positive and false negative rates we remain unsure as to how well KL-6 would perform at the bedside in predicting the diagnosis of ARDS. Second, ORs can be inflated in studies with small sample sizes and frequent outcomes (9), such as the two studies (10, 11) included in the IL-4 and mortality analysis that included only 54 patients and had mortality rates as high as 86%. This point is further supported in both tables by the general pattern of lower ORs and narrower confidence intervals in biomarker analyses that included a larger number of patients. Third, there is substantial heterogeneity in the patient populations studied. For example, one study that contributed a large number of patients to the diagnostic biomarker evaluation (12) included only trauma patients, a subgroup of patients known to have different clinical features and biomarker profiles (13) compared to patients with ARDS related to other risk factors. Fourth, the timing of biomarker measurement was not uniform and in some cases may have not been clinically meaningful. For example, in the KL-6 study by Sato et al (14) that was included in the diagnostic biomarker analysis, KL-6 was measured a median of 6.5 days *after* the onset of ARDS. Finally, very few of the biomarkers were compared head-to-head in the same patients, which adds to the difficulty of assessing the relative value of a given biomarker. In summary, the meta-analysis highlights the current shortcomings in the field of ARDS biomarkers. Definitive validation of candidate biomarkers that can be used clinically for diagnosis and prognosis of ARDS will require large, prospective studies that measure multiple biomarkers in well phenotyped patients at uniform intervals.

In addition to summarizing the available data with regards to biomarkers for prognosis and diagnosis of ARDS, the meta-analysis also provides important insight into the pathogenesis of this syndrome. Taking the strength of associations with the diagnosis of ARDS into account, the diagnosis of ARDS is associated most strongly with plasma biomarkers of epithelial (KL-6, RAGE) and endothelial (vWF) dysfunction. Conversely, plasma biomarkers of inflammation had stronger associations with mortality in ARDS patients, with weaker associations seen among markers of epithelial and endothelial function. These conclusions are limited by the fact that not all the biomarkers were studied in both

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diagnostic and prognostic capacities; however this meta-analysis may provide further support for past studies (10, 11) which have shown that elevated and persistent inflammation, rather than endothelial and epithelial dysfunction, may play a role in poor clinical outcomes. However, this observation may be confounded by the implementation of lung-protective ventilation, a known anti-inflammatory intervention (15), during the period of this review. Indeed, the predictive value of all biomarkers for diagnosis and prognosis in ARDS needs to be re-evaluated in patients treated in the era of protective mechanical ventilation, further underscoring the need for well designed, prospective studies.

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Abbreviations

ARDS	acute respiratory distress syndrome
KL-6	Krebs von den Lungen-6
RAGE	soluble receptor for advanced glycation end products
vWF	von Willebrand factor
IL-8	interleukin-8
IL-4	interleukin-4
OR	odds ratio

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