Editorial

Serum total bilirubin, an indicator for the impact of hemoglobin catabolism on outcome of patients with the acute respiratory distress syndrome

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Evaluation of disease severity and prognostication of long- and short-time outcome are essential for therapeutic decision-making and resource allocation in Critical Care Medicine. On the Intensive Care Unit (ICU), multiple outcome prediction tools exist such as various scoring systems combining several clinical, physiologic, and biochemical measurements to quantify collective organ dysfunction and therewith grade disease severity. Because organ dysfunction in critically ill patients changes dynamically over time, recent scoring models incorporate sequentially measured biomarkers. However, so far the classical and best-known prediction score models use biomarkers measured on ICU admission. Ideal prognostic biomarkers have a high sensitivity and specificity for the degree of organ dysfunction and are easy to measure and implantable into routine care.

The acute respiratory distress syndrome (ARDS) is a frequent disease among patients on the ICU and associated with a considerable mortality. Realizing the frequent organ-interactions in systemic life-threatening diseases, classic biomarkers that are usually used to monitor organ functions of organs other than the lung came into focus in ICU patients with ARDS (1). In this issue of the Journal, Zheng *et al.* present results of their analyses of the Medical Information Mart for Intensive Care IV (MIMIC-IV) database on the association of Serum Total Bilirubin (TBIL) with 30-day mortality in ICU patients with an ARDS (2). TBIL is frequently measured in critically ill patients as a routine examination biomarker for liver dysfunction. With two thirds of the selected ARDS patients from the MIMIC-IV database having TBIL levels measured within 24 hours after ICU admission, Zheng *et al.* could demonstrate a dose-dependent association between TBIL serum levels and 30-day as well as hospital mortality (2).

Despite the single-center, retrospective, small sample size, and only hypothesis-generating nature of the study, the results contribute to the understanding of ARDS pathophysiology. TBIL is an end product of hemoglobin catabolism with the ubiquitous enzyme heme oxygenase-1 driving the degradation of heme into iron, carbon monoxide and biliverdin. Biliverdin is processed via unconjugated bilirubin to water-soluble conjugated bilirubin in the liver with TBIL describing a combination of unconjugated and conjugated bilirubin.

In the latest understanding of ARDS and sepsis pathophysiology, hemoglobin and heme catabolism are noted to play a relevant role. Increased plasma concentrations of cell-free hemoglobin appear associated

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with increased mortality in patients with sepsis (3). Recently, increased plasma concentrations of cell-free hemoglobin were shown to correlate with acute kidney injury in patients with ARDS and treatment with veno-venous extracorporeal membrane oxidation (4). Because increased plasma concentrations of the endogenous hemoglobin-scavenger haptoglobin were associated with protection from renal injury in the same patient cohort, one might speculate, that increased plasma levels of cell-free hemoglobin might not only serve as a marker for disease severity but might also contribute to pathophysiology and ARDS-associated complications (4). For free heme, the central role in the pathogenesis of severe sepsis has been already demonstrated (5). Furthermore, the heme break-down by the heme-catabolizing heme oxygenase-1 was found to be protective (5). With TBIL being the end product of heme catabolism by heme oxygenase-1, the findings of Zheng and colleagues underline the importance of hemolysis and hemoglobin breakdown in disease conditions such as ARDS and sepsis. Increased levels of TBIL on admission to ICU might not only be an indicator of disease severity with a focus on hepatic dysfunction but might also reflect the contribution of hemoglobin catabolism and hemolysis to ARDS pathophysiology and disease severity. The results presented here underline the importance to study hemoglobin pathophysiology in the context of ARDS and sepsis. Identifying hemoglobin catabolism as a contributor in ARDS pathophysiology might open the door for translational researchers to hunt for novel treatment approaches that target hemoglobin breakdown products in critically ill patients.

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