Acute lung injury and predictors of mortality

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THE REPORT FROM Prabhakaran et al., one of the current articles in focus, also a Translational Physiology article (Ref. 5, see p. L20 in this issue), presents a study about the fibrinolytic protease inhibitor, plasminogen activator inhibitor-1 (PAI-1), in 26 patients with acute lung injury (ALI) (5). Patients with hydrostatic edema (HE; n = 25) served as a comparison group. The investigators had two hypotheses: 1) that plasma and edema fluid levels of PAI-1 would be higher in patients with ALI than in patients with HE, and 2) that the magnitude of elevation in PAI-1 levels would be an important predictor of prognosis among the ALI patients.

Since (as the authors themselves note) previous studies have shown that PAI-1 levels are elevated in the bronchoalveolar lavage fluid of ALI patients, the likelihood that they would be elevated in undiluted pulmonary edema fluid, obviously, was quite high. Thus this first hypothesis was straightforward. And indeed, Prabhakaran et al. (5) show that mean PAI-1 levels were approximately fourfold higher in the edema fluid of ALI patients than in the HE patients.

The second hypothesis is more interesting. In this case, the authors report that PAI-1 levels were higher in the subset of ALI patients who died (n = 18) than in those who lived (n = 8). Likewise, 100% of patients with PAI-1 levels that were >2 SD above the mean value of those who survived (even though the lung samples were obtained within just 12 h of intubation) went on to die. Thus the authors conclude that PAI-1 levels “identify those with ALI that have a poor prognosis,” and furthermore, that “these data clearly demonstrate the significance of [high PAI-1 levels] with respect to both the etiology and prognosis of clinical ALI.”

Since there is no reason to doubt the veracity of the measurements, the data seem to speak for themselves: high PAI-1 levels indicate that the fibrinolytic system is disturbed in ALI; among patients with ALI, high levels predict a high risk for death. The natural conclusion: a severely disturbed fibrinolytic system must be contributing to excess mortality in patients with ALI. Since a recent clinical trial also demonstrated that administration of the anticoagulant, activated protein C, improves mortality (2), it isn’t unreasonable to think that a malfunctioning fibrinolytic system might, somehow, increase mortality.

So, how fair are these conclusions? To judge, we should review them in the context of steps proposed for evaluating new predictors of intensive care unit (ICU) outcome (3, 7). The process might be summarized as follows: 1) select an outcome of interest (in this case, mortality and duration of unassisted ventilation), 2) select a patient population to be studied (here, ALI patients), 3) select a predictor (PAI-1 levels in this case), 4) collect the data, 5) develop a prediction model, 6) validate the model, 7) evaluate the model’s impact, and finally, eventually, 8) update the model when new data become available.

So, we can ask, how does the study by Prabhakaran et al. (5) measure up against these criteria?

Prabhakaran et al. (5) chose two outcomes to evaluate: mortality and duration of unassisted ventilation. The former is an easily defined binary end point of obvious relevance. However, the choice of hospital mortality instead of ICU mortality is a subtlety that should not be overlooked. ICU mortality is especially relevant when one seeks not only to link the predictor to outcome but also to suggest that there may be an etiological association as well (as seems to be the case here). Hospital mortality is more important when one intends to show societal impact. Prabhakaran et al. do not make clear why they chose to use hospital mortality, how it differed from ICU mortality (if it did), and whether the association with outcome held up with ICU vs. hospital mortality.

The other outcome variable, duration of unassisted ventilation (sometimes referred to as ventilator-free days or VFD), is more controversial. Some advocate VFD as a statistically more powerful surrogate for mortality (6), allowing studies to be designed with smaller numbers of patients. Obviously, this is not a consideration in this case. One might infer that if disturbances in the fibrinolytic system affect the natural history of ALI, and if the duration of respiratory failure affects the duration of ventilator dependence, then measures of the fibrinolytic system might predict VFD. However, Prabhakaran et al. (5) do not explicitly state why they chose to evaluate VFD as an outcome variable.

Patient selection for evaluation is obviously a critical choice. As noted elsewhere, the definition and criteria for identifying patients with ALI (despite the published “standards” of the American European Consensus Conference) have been and continue to be a murky business (8). Equally relevant is whether the patients actually studied are truly representative of the ALI patient population. The authors themselves note in their discussion that only patients who had “aspirable edema fluid” could be entered into this study, and thus they may have had “more severe lung injury and a higher mortality rate than the general population with...
This is not a trivial observation (see below), and it raises an important point. Because the patients studied had ALI doesn’t mean that the results obtained in this study apply to all patients with ALI, unless the patient population studied was representative of the general ALI population. In the current study, 63% of the patients were “septic,” the mean PaO₂/FiO₂ ratio was 75 mmHg, the average tidal volume used in ventilator management was 11.7 ml/kg, and the hospital mortality was 70%. In contrast, in the well-known trial of tidal volume management performed by the National Institutes of Health ARDSNet (1), only 26% of patients were septic in the “traditional” tidal volume group (corresponding to the average tidal volume used in the present study), the mean PaO₂/FiO₂ ratio was 134 mmHg, and mortality was 40%. It is hard to escape the conclusion that the ALI populations in these two studies were substantially different. Whether and/or how these differences might have any impact on the association of mortality with PAI-1 levels, of course, is impossible to discern.

Another critical step in evaluating putative predictors of mortality is to build the statistical model used to demonstrate an association between predictor and outcome. As already noted, Prabhakaran et al. (5) found that PAI-1 levels were higher in the subset of ALI patients who died vs. those who lived and that PAI-1 levels >2 SD had a 100% positive predictive value to predict hospital death. However, many factors, obviously, can affect mortality. To isolate a particular factor as uniquely important, two approaches are generally taken. One is the standard clinical trial, in which an intervention that should affect the putative factor is the only variable (ideally) that is different between treated and untreated groups. The other approach is through regression analysis, in which multiple variables that are known or suspected to affect mortality are sequentially and/or simultaneously evaluated in a statistical model. Prabhakaran et al. noted that a number of demographic and physiological variables did not associate with mortality, but a diagnosis of sepsis and a high SAPS II score (a measure of illness severity) did. It would have been interesting to know whether PAI-1 levels were still predictive of mortality when these other variables were taken into account (the specific objective of a multivariate regression analysis).

Likewise, it is not unreasonable to ask whether PAI-1 levels that are >2 SD above the survivor mean are predictive of death, but this is still an arbitrary cut point. One could legitimately also wonder how predictive PAI-1 levels were across the full spectrum of measured values. Were they linearly related, or did they demonstrate a threshold phenomenon? Each finding suggests a different biological mechanism.

These considerations lead one finally to the often repeated truism that no one study is ever “definitive.” For studies such as the one by Prabhakaran et al. (5), replication is the key to validation. The simplest next step would be to determine that the cut points identified in this study remained predictive of death in a second group of similar patients. Even better would be a study that showed that PAI-1 levels were predictive of death in dissimilar groups of ALI patients; such observations would suggest that PAI-1 levels were not only a powerful predictor of mortality but robust as well.

Ultimately, however, studies such as the one by Prabhakaran et al. (5) cannot demonstrate the significance of the putative predictor “with respect to . . . etiology” as the authors conclude; they can only identify an association and suggest that the predictor is mechanistically connected to outcome. To prove that the predictor is etiologically linked to outcome requires a carefully designed interventional clinical trial. In the meantime, the study by Prabhakaran et al. adds to the long list of factors known to be disturbed in ALI (4). In other words, it is another piece to a very complicated puzzle.

REFERENCES