Editorial

Red cell distribution width: the crystal ball in the hands of intensivists?

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Critically ill patients admitted to intensive care unit (ICU) are at a high risk of morbidity and mortality (1), with significantly increased medical costs. In the meanwhile, intensive care resources are limited, especially in developing countries such as China (2). As a result, rational allocation of limited intensive care resources to those patients who are more likely to benefit from intensive care may depend upon the accurate assessment of clinical prognosis. Therefore, many investigators have developed different prognostic tools, in the form of single parameter, composite indices, and even complicated scores (3-5), in order to assess the severity of illness, predict prognosis, or benchmarking different ICUs. Despite all these efforts, ideal prognostic tools are still lacking, so that investigators are trying to explore new prognostic indices that prove to be accurate, cheap, and readily available.

As a quantitative measurement of variability of red cells or red blood cell volume, red cell distribution width (RDW) has been traditionally considered useful in the differential diagnosis of anemia (6). Elevated RDW has been shown to exert prognostic value in healthy adults 45 years or older (7-9), and chronic conditions (such as coronary heart disease, heart failure, cancer, chronic lower respiratory tract disease, and inflammatory bowel disease) (9-13). During recent years, increased RDW has also been found associated with mortality in acute illness, including acute kidney injury, community-acquired pneumonia, and acute heart failure (14-16). To make the issue more complicated, RDW may be affected by genetic factors, thyroid diseases, renal or hepatic dysfunction, inflammatory disease, nutritional deficiency, and medications (17).

In a recent issue of the *Journal of Thoracic Disease*, Zhang *et al.* (18) reported that, in a retrospective study involving 1,539 critically ill patients admitted to a general ICU during 38-month study period, elevated RDW was associated with risk-adjusted hospital mortality, with odds ratio of 1.11 (95% confidence interval 1.04 to 1.18, P=0.001). However, the prognostic performance of RDW was rather poor [area under the receiver operating characteristic curve (AU-ROC) 0.6202], followed by albumin (AU-ROC 0.6134), C-reactive protein (CRP) (AU-ROC 0.6093), and Charlson index (AU-ROC 0.5980). In addition, RDW changes up to 20 days after ICU admission did not correlate with hospital mortality.

Why does RDW correlate with clinical prognosis in critically ill patients? One possible explanation is that such a correlation might indicate cause and effect relationship. However, current data suggest that this hypothesis is unlikely to be true. More importantly, even if increased RDW might be the direct cause of hospital mortality in ICU patients, we still lack the definitive intervention(s) to reduce RDW. Another possibility is that RDW merely represents a surrogate marker of severity of illness in the early phase of acute illness, and therefore correlates with clinical prognosis. In other words, increased RDW and high mortality are two apples on the same tree, which may be inflammation, poor nutrition, or oxidative stress (9,11,19).

The question remains that why do we need more prognostic indices (such as RDW), acknowledging that we already have a bunch of them, such as acute physiology and chronic health evaluation (APACHE), sequential organ failure assessment (SOFA), serum albumin level, platelet count, and others. Clinical evidence suggests that the old ones exert good, if not excellent, calibration. Calibration measures how much the prognostic estimation of a

predictive model matches the real outcome probability (i.e., the observed proportion of the event), and can be measured by Hosmoer-Lemeshow's χ^2-statistic. Likewise, Zhang *et al.* reported a fair calibration for RDW, as suggested by a Hosmer-Lemeshow's χ^2 of 11.17 (P=0.19) (18). However, most prognostic tools often exhibit poor discrimination. By definition, discrimination reflects the ability of a given prognostic index to distinguish a status (died/survived, event/non-event), and can be measured by AU-ROC. Zhang *et al.* reported a poor AU-ROC for RDW, with 0.6202 for RDW alone, and 0.6618 for composite prognostic indices including RDW, CRP, albumin, and Charlson index (18). One major limitation of the research by Zhang *et al.* is that no comparison of RDW and APACHE has been made. As a result, it still remains unclear whether RDW shows superior prognostic performance than APACHE, the most commonly used and validated prognostic model. Moreover, we do not know whether addition of RDW in the previous prognostic model (such as APACHE) may improve prognostic accuracy. All these questions might be answered by further investigation.

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