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EDITORIAL

Neurological Deterioration in Intracerebral Hemorrhage: Can We Predict It, and What Would We Do If We Could?

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Intracerebral hemorrhage (ICH) is the most fatal and disabling form of stroke, and early treatment is thought to be critical for improving outcomes.[1] Patients with ICH are typically monitored quite closely in the acute setting, with many current treatments aimed at preventing the initial injury from worsening in order to optimize outcome.

See Article by He et al.

Worsening injury often presents as neurological deterioration (ND), commonly defined as a ≥4-point increase on the National Institutes of Health Stroke Scale (NIHSS) or ≥2-point decrease on the Glasgow Coma Scale (GCS).[2,3] This event occurs in ≈30% of patients and is associated with increased risk of functional dependency and death.[4] The time course of ND has been investigated in several studies, and has been classified as early versus delayed, although there is no clear definition for when this time cutoff occurs. In a post hoc analysis of the TICH-2 (Tranexamic Acid in IntraCerebral Hemorrhage-2) trial, delayed ND was defined as that occurring between 48 hours and 7 days after onset.[4] Among 735 (31.7%) participants with ND, 590 (80.3%) had early ND versus 145 (19.7%) with delayed ND. In another post hoc analysis of INTERACT-2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2), 450 (17.3%) had ND within 7 days, and those who had ND between 24 hours and 7 days were considered as having delayed ND.[3]

Which patients will develop ND, and when? Several groups have examined this topic. In one study of 376 patients, investigators found that 176 (47%) patients developed ND within 15 days.[2] They further noted that larger ICH volume, presence of intraventricular hemorrhage (IVH), and hematoma expansion were specifically associated with early ND. In contrast, cerebral edema, fever, and infection were associated with delayed ND. It makes sense that hematoma expansion would be associated with early ND: it is probably the most common, and most feared, reason for early ND, and contributes substantially to mortality.[2] Other groups have found that lobar ICH, larger ICH volume, IVH, and higher systolic blood pressure are similarly associated with early ND.[3–5] Similarly, it makes sense that perihematomal edema contributes to delayed ND, as edema develops more slowly and later in the ICH course than does ICH expansion.[6,7]

Overall, ND is not a diagnosis. Rather, it marks, for clinicians, an underlying process that they otherwise cannot see (without sending the patient for serial neuroimaging). In the acute phase, it can highlight those with ongoing bleeding and ICH expansion and, in the

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later phase, those with edema or medical complications. The presence of ND alerts us to an underlying process that may be preventable, diagnosable, and treatable. Therefore, the ability to predict ND may well help us understand which patients we need to more closely monitor. Who should go to an intensive care unit versus a regular floor? Who should be targeted for treatments aimed at reducing ICH expansion or perihematomal edema? Who needs frequent neurologic checks, costing valuable clinician time and preventing patients from sleeping? Who can safely be managed in a lower-acuity setting and allowed to sleep (reducing risk of in-hospital delirium)[8]?

To answer these questions, clinicians need tools to risk-stratify which patients will develop ND. While there are many ICH clinical prediction scores, most focus on clinical outcome rather than ND, eg, the ICH score,[9] the ICH grading scale (ICH-GS),[10] and the Emergency Department Intracerebral Hemorrhage Scale (EDICH).[11] The 6-point ICH score is the most commonly used, and incorporates age, GCS, presence of IVH, ICH volume, and infratentorial location.[9] The ICH-GS, an attempt to improve the ICH score, showed higher sensitivity and specificity in one study in predicting mortality and favorable functional status at 30 days.[10] The EDICH score incorporates both clinical and laboratory findings in the emergency department in order to predict mortality in the hyperacute phase, and incorporates baseline GCS score, maximum ICH diameter hematoma, international normalized ratio, IVH, and supratentorial location.[11] It is notable that multiple factors contribute to poor outcome, and none of these scores necessarily direct providers to which specific factors to target. What would they do differently for patients with worse scores?

In this issue of the *Journal of the American Heart Association* (*JAHA*), He and colleagues[12] developed a novel tool to predict which patients will develop ND. Tools such as this, if validated, could ideally guide us towards directing more intensive care, more frequent neurologic checks, or therapy targeted at the causes of ND. To establish the SIGNALS (site, size, gender, NIHSS, age, leukocyte, sugar) prediction score, 1542 patients with ICH were allocated into a derivation cohort and validation cohort. In multivariate logistic regression analysis, age ≥70 years, male sex, NIHSS score >10 points, infratentorial location, baseline hematoma volume, fasting blood glucose >7.0 mmol/L, and white blood cell count >9.0×10^9/L were identified as independent predictors of ND and were included in the development of the SIGNALS score. The authors found that this score successfully predicted ND, with a C statistic of 0.848 and area under the curve of 0.827 in the validation cohort. When dichotomized (0–4 versus 5–8), ND occurred in 9% of the low-risk patients and 44% of the high-risk patients. The positive predictive value of a high score for ND was only 0.44, but the negative predictive value of a low score was 0.91.

The SIGNALS score incorporates a range of data, including demographic, clinical, imaging, and biochemical. When compared with other scores designed to predict outcome (rather than ND), the SIGNALS score showed the highest area under the curve of 0.827, suggesting that there is value in using scores specific to the outcomes in question.

Overall, while not perfect, these data are quite promising. They highlight that, using data readily available in practice, clinicians could potentially predict which of their patients will develop ND. The authors are to be commended for their work. If validated in future studies, the SIGNALS score would be a valuable tool in the acute phase.

This leads to the question, of course, of what we would do if we knew our patient would deteriorate? Many clinical trials of acute therapies in ICH have failed to demonstrate improved outcome, perhaps because of failure to effectively stratify which patients will benefit from treatment. Perhaps with better scoring tools, such as SIGNALS, providers could then study targeted interventions. For example, treatments such as intensive blood pressure lowering or procoagulant or antiedema therapy could be targeted to those at highest risk of ND. Alternatively, hospitals could focus the most intensive resources on those at highest risk, while safely admitting the low-risk patients to lower-acuity settings. Even better, lower-risk patients may be able to be safely managed in lower-acuity hospitals closer to their homes, reserving interfacility transport for the patients at highest risk of needing advanced surgical or interventional procedures. Such questions are best asked, and answered, in a world where we have the tools to appropriately mark high- versus low-risk patients.

The SIGNALS study alone is likely not enough to base treatment on at this time. First of all, external validation is the best next step to evaluate its performance in other settings. Second, an increasing number of biomarkers have been reported to be associated with poor outcome in patients with ICH, and it is not yet clear that the 2 involved in SIGNALS are the only ones to add predictive value for this purpose. Finally, some well-established predictors of ND were not analyzed in this study, such as hematoma expansion[5] and perihematomal edema,[6,7] and it would be critical to understand what exactly is being predicted and causing ND in these patients.

In summary, the SIGNALS score appears to be a practical and easy-to-use predictive score for ND in patients with ICH. This study also serves as a call to action, for ICH researchers to develop the tools needed not only to predict long-term outcome but also the short-term clinical course that acute care providers face when these patients arrive. Future rating scales with artificial

intelligence technology may further refine our ability to predict ND, clinical course, and outcome. Once we have optimized prediction tools, we can open the door to best individualize and optimize treatment, providing the best possible outcomes for our patients with ICH.

ARTICLE INFORMATION

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