

INVITED EDITORIAL COMMENTARY

Hematoma Expansion in ICH: Targeting Epidemiology or Biology?



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Hematomas expand, and this is often bad for our patients. In fact, hematoma expansion is probably the rule and not the exception, even in patients without coagulopathy. While it is often stated that hematoma expansion occurs 38% of the time, this derives from a seminal publication over two decades ago in which the threshold of 33% enlargement over baseline was used to define hematoma expansion [1]. However, when the placebo group from the phase II factor VIIa study was assessed, any hematoma expansion occurred in 73% of patients. It may be that all patients experience some degree of hematoma expansion if considered from the initial bleeding ictus, even if this expansion occurs prior to initial in-hospital neuroimaging. Intracerebral hemorrhage (ICH) is a dynamic disease, and prevention of hematoma expansion is a compelling target. Unfortunately, finding a treatment that lessens hematoma expansion and improves patient outcome has been elusive [2]. Triangulating between patient selection, a biologically highly active intervention, and an outcome measure that detects meaningful effects seems mandatory.

We have gotten used to the spot sign in ICH. There is something intuitive about seeing contrast extravasation and then subsequently finding hematoma expansion. Even though we do not fully understand whether a spot sign represents continuing bleeding from a hole in a small artery, leakage from an impaired blood–brain barrier, or something else, it feels like we are seeing into the biology of the disease of ICH. However, the problem with

the spot sign is that it requires contrast and an image beyond an initial non-contrast computed tomography (CT). Enter the Hematoma Expansion Prediction (HEP) Score as perhaps the most recent entry into an increasingly crowded field of signs and scores intended to predict hematoma expansion from findings on the initial non-contrast CT scan in ICH patients, without the need for contrast administration. The HEP Score is an ordinal scale comprised of six factors, only one of which relates to findings on the CT scan itself (subarachnoid hemorrhage on baseline CT). The rest of its components relate to the timing of the CT scan in relation to symptom onset and patient characteristics including Glasgow Coma Scale score at presentation and current dementia, smoking, or antiplatelet use. The HEP Score is epidemiology in action. In this recent study, Yogendrakumar and colleagues leverage the dataset from the PREDICT study of spot sign validation in order to assess whether the HEP Score is equivalent in accuracy to the spot sign for predicting hematoma expansion [3]. Their answer is yes and no. A HEP Score of 4 or more has essentially the same sensitivity, specificity, and positive and negative predictive values for significant hematoma expansion (an increase of 33% over baseline volume or an absolute increase of at least 6 ml) as the presence of the spot sign. However, when assessing the occurrence of any hematoma expansion, the spot sign was significantly associated while the HEP Score was not.

This is a key point that cannot be overlooked when considering any of the many hematoma expansion imaging signs and scores now published. A pragmatic argument can be made that a sufficient threshold of hematoma expansion is what matters and being able to predict this using a simple score that is dependent on findings other than those from the CT scan or without contrast administration is highly desirable. However, if the sign or score used to predict hematoma expansion is dependent on the

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threshold used to define that expansion, then we better have the correct threshold. Furthermore, it may be that smaller amounts of hematoma expansion are clinically meaningful to patients even if they do not result in a major change on a relatively blunt outcome measure such as the Modified Rankin Scale (mRS). Thus, a score or sign that can only predict a major biological change is potentially backward engineered starting from limitations in outcome assessment. This brings forth a fundamental question as we seek effective treatments for ICH and other challenging neurocritical care conditions: do only large effects matter or should we accept smaller effects as potentially important to some patients and as building blocks toward bigger things down the road?

Interestingly, there are many ways to a HEP Score of 4 and just having a diagnosis of dementia meets these criteria. While only 5.5% of the patients in the HEP Score spot sign validation study had dementia, it is likely that this would occur frequently in clinical practice. Targeting a treatment for hematoma expansion to all ICH patients with a specific demographic characteristic such as dementia may turn out to be correct, but it seems far from the biology of the active disease process in question.

It is nice to know that the HEP Score is probably equivalent to the spot sign in predicting significant hematoma expansion of $\geq 33\%$ over baseline or ≥ 6 ml. Clinicians and clinical researchers designing interventional studies in 2019 can consider whether they want to use the HEP Score, the blend sign, any hypodensity, time from onset to non-contrast CT Score, the baseline ICH volume, recurrent ICH, anticoagulation with warfarin at onset, intraventricular extension, number of hours from baseline CT to onset Score, the swirl sign, the blend sign, the island sign or stick with the spot sign. But I am jealous of

the transformation in treatment of large vessel ischemic stroke in the past 5 years. An imaging biomarker indicative of the disease biology (perfusion imaging) was coupled with a highly active intervention (new generation embolectomy devices), and the outcome measure used (the mRS) had sufficient discrimination to detect the clinical effect. I can't help but think that the answer in ICH lies in the biology of the disease and that the future should encourage identification of biomarkers that help us select patients based on this biology in real time and not primarily on demographic characteristics. I also think that we should be willing to consider other outcome measurement tools that might detect smaller effects that are clinically valuable to patients and which might occur across the range of hematoma expansion. We shall see.

Conflicts of interest

The authors declare that they have no conflict of interest.

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References

1. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28(1):1–5.
2. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358(20):2127–37.
3. Yogendrakumar V, Ramsay T, Demchuk AM, et al. Independent validation of the Hematoma Expansion Prediction (HEP) Score: a non-contrast score equivalent in accuracy to the spot sign. *Neurocrit Care*. 2019.