Biomarkers hint at who recovers motor function after stroke

Written by The Life Science Feed Editorial Team · Published 10 August 2026 · Edited by Mara Voss

Stroke remains a leading cause of long-term disability, with significant variability in functional recovery that clinicians struggle to predict. Understanding the biological underpinnings of this variability could refine prognostication and guide targeted rehabilitation strategies. The PRACTISE trial, a larger investigation into post-stroke recovery, included an exploratory substudy examining longitudinal changes in biomarkers and their association with upper-extremity motor recovery.1

This substudy, published in Clinical Neurology and Neurosurgery, sought to identify specific biological markers that could explain why some patients regain substantial motor function while others do not.1

KEY TAKEAWAYS

- The Pivot: Specific biomarkers, including brain-derived neurotrophic factor (BDNF) and C-reactive protein (CRP), correlate with upper-extremity motor recovery after stroke.
- The Data: Higher baseline BDNF levels correlated with greater motor improvement (r=0.45; P=.001), while elevated CRP at 3 months post-stroke predicted poorer recovery (r=-0.38; P=.004).
- The Action: While not yet ready for routine clinical use, these findings suggest a future where biomarker panels could inform personalized rehabilitation plans for stroke survivors.

Stroke survivors face a challenging and often unpredictable path to recovery, particularly concerning motor function. The extent of upper-extremity motor recovery, which is essential for daily activities, varies widely among individuals, making accurate prognostication difficult. This variability shows a significant unmet need for objective measures that can predict recovery trajectories and potentially guide more effective, individualized rehabilitation interventions. The current clinical assessments, while valuable, often lack the biological granularity to fully explain these differences.1

The PRACTISE trial (NCT05355831) was designed to investigate various aspects of post-stroke rehabilitation. This particular exploratory substudy focused on a cohort of 85 patients who had experienced an ischemic stroke and were undergoing inpatient rehabilitation. The patients, with a mean age of 68.2 years (SD 11.5), were enrolled within 14 days of stroke onset and followed for 6 months. Researchers collected blood samples at baseline (within 7 days of admission), 3 months, and 6 months post-stroke. The primary outcome for this substudy was upper-extremity motor recovery, measured using the Fugl-Meyer Assessment Upper Extremity (FMA-UE) scale, a widely accepted and validated clinical tool. The study was conducted by a team led by M. Kolmos, N.V. Sørensen, and K.L. Gandrup at institutions across Denmark.1

What the trial actually measured

Investigators measured a panel of biomarkers chosen for their potential roles in neuroplasticity, inflammation, and vascular integrity. These included brain-derived neurotrophic factor (BDNF), a key mediator of neuronal survival and plasticity; matrix metalloproteinase-9 (MMP-9), involved in extracellular matrix remodeling and blood-brain barrier integrity; C-reactive protein (CRP), a general marker of systemic inflammation; and vascular endothelial growth factor (VEGF), important for angiogenesis and neuroprotection. The rationale was that changes in these biological pathways could directly influence the brain's capacity for repair and reorganization after injury.1

The FMA-UE score, ranging from 0 to 66, provided a quantitative measure of motor impairment and recovery. A higher score indicates better motor function. Patients underwent standardized rehabilitation protocols, and their FMA-UE scores were assessed at baseline, 3 months, and 6 months. The researchers then performed correlation analyses to determine the relationships between baseline biomarker levels, longitudinal changes in biomarker levels, and the extent of FMA-UE improvement over the 6-month period. This comprehensive approach aimed to capture both static predictive values and dynamic changes that might reflect ongoing recovery processes.1

The numbers

The substudy identified several key associations between biomarkers and upper-extremity motor recovery. Higher baseline levels of BDNF correlated positively with greater FMA-UE improvement from baseline to 6 months (r=0.45; P=.001). This suggests that patients with a stronger neuroplastic potential early after stroke may achieve better motor outcomes. BDNF is known to promote neuronal growth and synaptic plasticity, mechanisms critical for functional recovery.1

Conversely, elevated levels of CRP at 3 months post-stroke showed a negative correlation with FMA-UE improvement (r=-0.38; P=.004). This indicates that persistent systemic inflammation during the subacute phase of recovery may impede motor gains. Inflammation, while initially part of the healing process, can become detrimental if prolonged or excessive, contributing to secondary brain injury and hindering neuroplasticity.1

MMP-9 levels also demonstrated a dynamic relationship with recovery. Patients with higher baseline MMP-9 levels experienced less FMA-UE improvement (r=-0.31; P=.012). But a decrease in MMP-9 levels from baseline to 3 months was associated with better recovery (r=0.29; P=.018). This suggests that while initial high levels of MMP-9 might be detrimental, a subsequent reduction could signify a more favorable environment for recovery, possibly reflecting the resolution of acute injury and blood-brain barrier disruption.1

VEGF levels did not show a statistically significant correlation with motor recovery in this cohort. This was somewhat unexpected, given VEGF's known role in vascular repair and neuroprotection. It is possible that the timing of measurements or the specific patient population did not capture a relevant association for this particular biomarker, or that its impact on motor recovery is less direct than other factors.1

The average FMA-UE score at baseline was 28.7 (SD 10.1), indicating moderate to severe upper-extremity impairment. By 6 months, the mean FMA-UE score improved to 41.2 (SD 12.8), representing a mean improvement of 12.5 points. This level of improvement is clinically meaningful, as a change of 5-10 points on the FMA-UE is often considered to reflect a substantial functional gain. The range of individual improvements was wide, from minimal change to near-complete recovery, reinforcing the need for predictive biomarkers.1

Subgroup analyses, though exploratory due to the sample size, hinted at differential biomarker responses. For instance, patients with more severe baseline motor deficits (FMA-UE 1

Where it falls short

The exploratory nature of this substudy is the obvious caveat. With a sample size of 85 patients, the power to detect subtle associations or to perform extensive subgroup analyses was limited. The findings, while statistically significant for the primary correlations, should be considered hypothesis-generating rather than definitive. The study also focused exclusively on ischemic stroke patients, meaning the generalizability to hemorrhagic stroke or other cerebrovascular events is unknown.1

Another limitation involves the timing and frequency of biomarker measurements. While three time points provided longitudinal data, critical early changes immediately post-stroke or more frequent sampling during peak neuroplasticity might have revealed additional insights. The study also did not account for potential confounding factors such as concomitant medications, comorbidities, or the intensity and type of rehabilitation therapy received, all of which can influence recovery outcomes. The Oxford Handbook of Neurology provides a concise overview of these complex interactions in stroke management.1

The study design did not include a control group receiving no rehabilitation, which is ethically unfeasible in stroke

research but means the observed recovery cannot be solely attributed to the biological factors without considering the impact of therapy. The FMA-UE, while robust, is a clinical assessment and inherently subject to some inter-rater variability, though efforts were made to standardize assessments. The study did not explore genetic polymorphisms that might influence individual biomarker levels or responses to stroke, which could add another layer of complexity to predicting recovery.1

The investigators also acknowledged that the chosen biomarker panel, while relevant, is not exhaustive. Other emerging biomarkers related to neuronal integrity (e.g., neurofilament light chain), glial activation, or epigenetic modifications could offer further insights into the process of stroke recovery. Future research should aim to integrate a broader array of biological markers with advanced imaging techniques to build a more comprehensive predictive model.1

Still, the findings provide a valuable foundation for future research. The identification of BDNF and CRP as potential predictors of motor recovery opens avenues for developing targeted interventions. For instance, therapies aimed at enhancing BDNF signaling or modulating inflammatory responses could theoretically improve outcomes, particularly if guided by individual biomarker profiles. The challenge lies in translating these correlative findings into actionable clinical strategies.1

CLINICAL IMPLICATIONS

These biomarker findings from the PRACTISE substudy offer a tantalizing glimpse into a future where stroke prognostication moves beyond clinical scales alone. The clear correlation between baseline BDNF and recovery, alongside the detrimental effect of sustained inflammation (CRP), suggests that we are beginning to understand the biological drivers of functional return. This is not yet a diagnostic panel for routine use, but it points to a more personalized approach to rehabilitation.

For clinicians, the data reinforces the importance of managing systemic inflammation in the subacute phase of stroke recovery. While CRP is a non-specific marker, its association with poorer outcomes at 3 months suggests that aggressive management of infections or other inflammatory conditions during this critical window could indirectly support motor recovery. It also highlights the potential for future therapies that might directly modulate neuroplasticity, perhaps by enhancing BDNF pathways.

The industry should take note. The variability in stroke recovery represents a significant market for prognostic tools and targeted interventions. Developing assays that can reliably measure these biomarkers, and then designing trials for therapies that modulate them, could lead to substantial improvements in patient outcomes. The next step is to validate these markers in larger, prospective studies and to determine if interventions based on these profiles can genuinely alter recovery trajectories.

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