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HIGH-THROUGHPUT PROTEOMICS IDENTIFIES ETIOLOGY-SPECIFIC MOLECULAR SIGNATURES OF STROKE RECURRENCE—INSIGHTS FROM THE CRESCENDO CONSORTIUM

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Background and aims: Despite advances in stroke treatment, recurrence risk remains largely unchanged over two decades. In the multicenter CiRculating mEdiators of Stroke reCurrENce anD aetiOlogies (CRESCENDO) consortium, we conducted the first large-scale proteomic analysis of 5,400 targets to characterize post-stroke blood-based proteomic signatures associated with 90-day recurrence.

Methods: CRESCENDO compiled comprehensive prospective cohorts from Hannover (Germany), Barcelona/Seville (Spain), and Zurich/Basel (Switzerland), comprising 4,854 patients sampled within 24 hours of ischemic stroke. A subset of 175 patients (75 recurrent, 100 non-recurrent), balanced for age, sex, NIHSS, was profiled using the Olink Explore HT panel. Protein levels were compared between recurrent and nonrecurrent cases, and their predictive values were evaluated.

Results: Across all etiologies, G kinase anchoring protein-1 (GKAP1) was elevated in recurrent cases (logFC = 0.72, adjusted P = 0.02). Etiology-stratified analyses revealed upregulation of Carboxylesterase 1 (CES1) in patients with atherosclerotic index stroke and recurrence (logFC = 1.19, adjusted P = 0.02), and enrichment of Centromere Protein F (CENPF), Biliverdin Reductase B (BLVRB), and Parkinson disease protein 7 (PARK7) patients with cardioembolic index stroke and recurrence (logFC = 1.13, 0.99, 0.98, adjusted P = 0.02, 0.03, 0.04). Recurrence prediction using clinical data alone had an accuracy of 0.55, which increased to 0.61 when etiology-specific proteins were added.

Conclusions: High-throughput proteomics identified novel, etiology-specific proteins associated with 90-day recurrence. The improvement in predictive accuracy when integrating these markers suggests that etiology-stratified proteomic profiling can uncover distinct biological drivers of recurrence, warranting larger studies to refine targeted secondary prevention.

Conflict of interest: nothing to disclose.