Principal Components Analysis of Biomarkers of Neurodegeneration, Inflammation, and Microvascular Disease Discriminate Between Trajectories of Recovery after Traumatic Brain Injury (TBI).

Ramon Diaz-Arrastia[1], Hannah Radabaugh[2], Sonia Jain[3], Xiaoying Sun[3], Catherine Demos[4], Martin Stengelin[4], Nikhil Padmanabhan[4], Taron Gorham[4], George Sigal[4], Jacob Wohlstadter[4], Kevin Wang[5], Ava Puccio[6], Andrea Schneider[1], Danielle Sandsmark[1], Geoff Manley[2]
[1] University of Pennsylvania, [2] University of California, San Francisco, [3] University of California, San Diego, [4] MesoScale Diagnostics, LLC, [5] Morehouse University, [6] University of Pittsburgh

Objectives: Understanding the molecular mechanism(s) of neurodegeneration after brain injury will be necessary to develop effective disease-modifying therapies.

Methods: Plasma was collected on the day of injury from 394 patients with TBI (200 Glasgow Coma Scale (GCS) score 13-15; 194 GCS 3-12) and again two weeks after from 369 patients in the same cohort. Plasma levels of 45 biomarkers were measured using Meso Scale Diagnostics assays, including proteins related to neurodegeneration, inflammation, and vascular injury. Probabilistic Principal Components Analysis (PPCA) was used to reduce dimensionality and identify collinearity between biomarkers, using the pcaMethods package in R. PCA biplots were generated to visualize sample scores and variable loadings.

Results: Age (SD) was 41.1 (16.4) years for the GCS 13-15 participants, and 37.4 (15.5) years for the GCS 3-12 cases. 33.0% of GCS 13-15 participants had abnormal cranial CT findings, while 90.2% of GCS 3-12 cases had abnormal CTs. Three PCs, accounting for 47% of variance (VAF), were deemed optimal by Scree criterion (PC1 VAF=25%, PC2=14%, PC3=8%). On Day 1 after injury, all PC scores differed significantly across TBI severity groups (3-group ANOVA: GCS 13-15 CT-ve, GCS 13-15 CT+ve, GCS 3-12; PC1 and PC2 $p<0.0001$, $p=0.01$ for PC3). PC1 and PC2 also discriminated between those who made a good recovery (GOSE 7-8) from those with disability (GOSE 1-6) (two-sided t-test; PC1 $p<0.0001$, PC2 $p<0.0006$), while PC3 did not. A subsequent PPCA analysis of biomarker expression 2-weeks after injury revealed three PCs explaining 48% of variance (PC1=31% VAF, PC2=11%, PC3=6%). All 3 PCs discriminated by injury severity (PC1 and PC3 $p<0.0001$, PC2 $p=0.042$) and recovery (PC1 and PC3 $p<0.0001$, PC2 $p=0.0031$).

Conclusion: Protein biomarkers of neurodegeneration, inflammation, and vascular injury measured on the first day and 2 weeks after TBI show promise as tools for differentiating injury severity and predicting functional outcome.