Molecular Predictors of Mortality in Frail Patients with Hip Fractures

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Purpose: Inflammatory burden in hip fracture has been poorly investigated. Cytokines such as C-reactive protein (CRP), interleukin (IL)-10, IL-6, and tumor necrosis factor (TNF)-α have been shown to play a role in predicting complications and mortality. Many studies have only investigated a few different types of inflammatory proteins. We aimed to identify molecular inflammatory predictors of mortality in frail patients who have sustained fragility hip fractures utilizing proteomic analysis. This method allows us to measure 96 target inflammatory proteins with increased specificity through proximity extension assays.

Methods: From the Functioning of Elder Muscle Understanding Recovery (FEMUR) study, 32 patients were studied. These patients were aged >65 years with a clinical frailty score of ≥4 and presented with a fragility hip fracture. Routine audit personnel prospectively completed the Standardised Audit of Hip Fracture of Europe (SAHFE) form including the following outcomes, 30-day and 6-month mortality, and development of at least 1 postoperative complication. Olink Proteome biomarker analysis was undertaken from serum samples obtained at the time of anesthetic prior to surgery. Statistical analysis included Spearmans correlation, Kaplan-Meier survival, and receiver operating characteristic curve analysis.

Results: In patients with hip fracture, 6 proteins were strongly associated with 6-month mortality. Low levels of DNER ($P < 0.001$), interferon gamma ($P < 0.001$), monocyte chemotactic protein (MCP)-2 ($P < 0.001$), and TWEAK ($P < .001$) and higher levels of IL-4 ($P < 0.001$) and IL-13 ($P < 0.001$) were found to correlate with a higher risk of mortality at 6 months. Elevated levels of IL-13 were correlated with time to surgery >36 hours ($P = 0.016$), development of postoperative complications ($P = 0.012$), and 30-day mortality ($P = 0.045$) similar to the Nottingham hip fracture score (NHFS) (IL-13 AUC [area under the curve] 0.815, 95% confidence interval [CI] 0.632-0.999; NHFS AUC 0.88, 95% CI 0.734-1.000).

Conclusion: To our knowledge this is the first study to investigate a range of molecular inflammatory markers using proteomic analysis in patients with fragility hip fractures and their relationship with mortality. We have highlighted several potential biomarkers of mortality that may help guide therapeutic treatments and provide prognostic information. Further work is underway to identify molecular markers of frailty and their correlation with frailty outcomes.