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Identification of high-risk patient clusters based on extracellular matrix turnover

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Introduction: Renal fibrosis is a major underlying pathological feature in patients with chronic kidney disease (CKD) and strongly predicts disease progression. We hypothesised that non-invasive assessment of the development and remodelling of fibrosis may have utility for linking dynamic in situ pathology with clinical outcomes. We utilised principal component analysis (PCA) followed by unsupervised cluster analysis for extracellular matrix (ECM) turnover to stratify patients for risk of disease progression and mortality.

Methods: We measured biomarkers of integral components of the renal ECM, including collagen (COL) type III (COL III) formation (PRO-C3) and degradation (C3M), COL VI formation (PRO-C6), versican degradation (VCANM), and laminin degradation (LG1M) in a prospective, observational cohort of patients (N=411) with moderate to advanced CKD (pre-dialysis). Heterogeneity and clustering dimensions were assessed using PCA; based on the PCA results for each patient, unsupervised clustering with Ward method and Euclidian distance was made. One-year disease progression was defined as a decline in eGFR >30% or commencing renal replacement therapy within 12 months. Results were adjusted for potential confounders (age, gender, eGFR, and urinary albumin:creatinine ratio (ACR)). Median follow-up was 46 months (range 0–72).

Results: Three clusters were identified. Cluster demographics and ECM biomarker values are listed in Table 1. In respect to COL III turnover, Cluster 1 and 2 had lower levels of formation biomarkers and Cluster 2 had higher level of degradation biomarkers compared to Cluster 3 (Table 1). A markedly increased level of the COL VI formation biomarker PRO-C6 was seen in Cluster 3 ($p<0.0001$). After adjustment for potential confounders, Cluster 3 was independently associated with an increased risk of both one-year disease progression (OR [95% CI]; 4.03 [1.38-13.79], $p=0.02$) and mortality (HR [95% CI]; 1.89 [1.02-3.49], $p=0.04$).

Conclusion: We have found a cluster of CKD patients with an ECM turnover profile associated with an increased risk of adverse outcomes of one-year disease progression and mortality. The high-risk cluster was generally characterised by higher ECM formation, suggesting that a highly fibrogenic phenotype is associated with faster disease progression.