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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Urinary proteome profiling reveals complement cascade as a progressor of type 2 diabetic kidney disease

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Objectives : Diabetic kidney disease (DKD) has emerged as the primary cause of chronic kidney disease. Herein, we conducted urinary proteomics on patients with biopsy-proven type 2 DKD to identify potential therapeutic biomarkers associated with kidney progression.
Methods : We conducted quantitative proteomics on urine samples collected at the time of kidney biopsy. 64 patients were diagnosed with biopsy-confirmed DKD in the context of type 2 diabetes. Kidney progression was defined as either doubling of serum creatinine, ≥50% decrease in estimated glomerular filtration rates, or the development of end-stage kidney disease. After unsupervised clustering and differential expression analysis, we identified urinary biomarkers linked to kidney progression and calculated their hazard ratios using a Cox regression model adjusted for various factors.
Results : A total of 2,313 proteins were quantified from patients with an estimated glomerular rate of 55.4 ml/min/1.73 m^2 (interquartile range, 43.9–74.9) and a random urine protein-to-creatinine ratio of 3.1 g/g (1.7–7.0). Over a median follow-up period of 2.3 years, 39 patients experienced kidney progression. The urinary proteins were clustered into two groups, and kidney progression was primarily observed in one group. This group exhibiting kidney progression had an elevated complement cascade as a proteomic set (adjusted HR, 4.6 [1.9–11.5]). Analyses of differentially expressed markers and pathways revealed upregulation of proteins involved in the complement cascade in the kidney progression group. After calculating complement scores derived from complement intensities, patients with high scores exhibited advanced glomerular sclerosis and arteriolar hyalinosis, intensified interstitial fibrosis and tubular atrophy, and had an increased risk of kidney progression compared to those with low scores (adjusted HR, 2.4 [1.0–5.5]).
Conclusions : Urinary proteome profiling confirms the involvement of the complement cascade in the progression of type 2 DKD. The findings will serve as the basis for studies aimed at manipulating relevant complements for the treatment of patients with type 2 DKD.

Figure 1.png

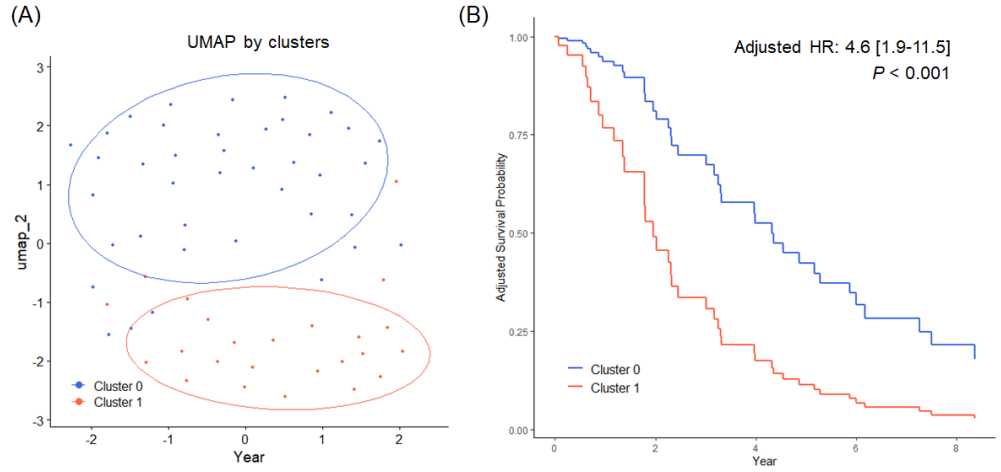
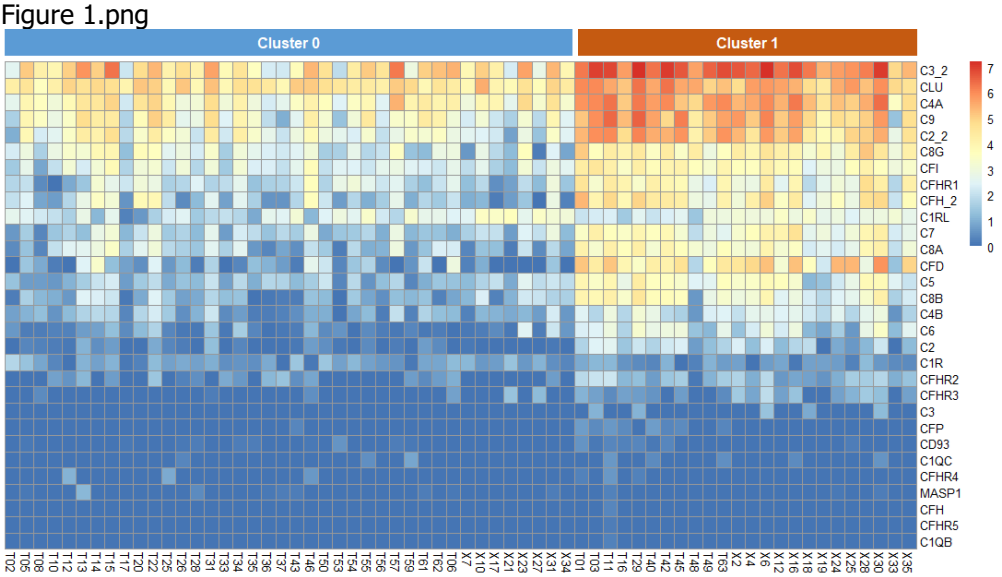

(A)
UMAP by clusters
umap_2
Year
Cluster 0
Cluster 1
(B)
Adjusted HR: 4.6 [1.9-11.5]
P < 0.001
Adjusted Survival Probability
Year
Cluster 0
Cluster 1

Figure 1.png


Cluster 0
Cluster 1
C3_2
CLU
C4A
C9
C2_2
C8G
CFI
CFHR1
CFH_2
C1RL
C7
C8A
CFD
C5
C8B
C4B
C6
C2
C1R
CFHR2
CFHR3
C3
CFP
CD93
C1QC
CFHR4
MASP1
CFH
CFHR5
C1QB