Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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Proteome-wide Association Study Identifies Plasma Protein Signatures for Incident Acute Myocardial Infarction across eGFR Strata in the UK Biobank

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Objectives : To identify plasma proteins associated with incident AMI across eGFR strata using a proteome-wide association study (PWAS), and to evaluate whether proteomic features improve AMI prediction in individuals with reduced eGFR.
Methods : Among 31,436 UK Biobank participants with 2,923 plasma proteins (Olink Explore), Cox models were applied in three strata: overall cohort, reduced eGFR subgroup (eGFR <60; N=744), and sensitivity cohort (eGFR <75; N=3,719), adjusting for age, sex, BMI, eGFR, diabetes, hypertension, SBP, cholesterol, CRP, and smoking. FDR $q<0.05$ was applied overall; nominal $p<0.05$ in reduced eGFR strata. Pathway enrichment used clusterProfiler. Machine learning compared clinical-only (Model A) versus clinical plus LASSO-selected proteins (Model B).
Results : Over 13.15 years median follow-up, 1,649 AMI events occurred. After full adjustment, 362 proteins were associated with AMI (FDR $q<0.05$), with cytokine-cytokine receptor interaction as the top KEGG pathway (59 genes, $q=1.9\times10^{-9}$). Sixteen proteins were significant across all eGFR strata, including EDA2R (HR 3.59), MMP12 (HR 1.87), IGFBP4 (HR 2.22), and EGFR (HR 0.22). Two dose-response patterns emerged: monotonically increasing HRs with declining eGFR (e.g., RBFOX3: HR 1.21 to 4.51 from eGFR ≥90 to 30–44), and non-monotonic trajectories peaking at eGFR 60–89. PLA2G7–AMI association was markedly attenuated at eGFR <60 (interaction HR 0.035, $p=0.0009$). Proteomic features improved AUC by 13.5% (0.691 to 0.783; validation AUC 0.798–0.835).
Conclusions : This PWAS identifies 362 AMI-associated proteins and 16 cross-strata consensus biomarkers driven by cytokine signaling. eGFR-dependent dose-response patterns and PLA2G7 interaction offer mechanistic insights into cardiorenal risk. Proteomic profiling substantially improves AMI prediction beyond clinical variables in individuals with reduced kidney function.

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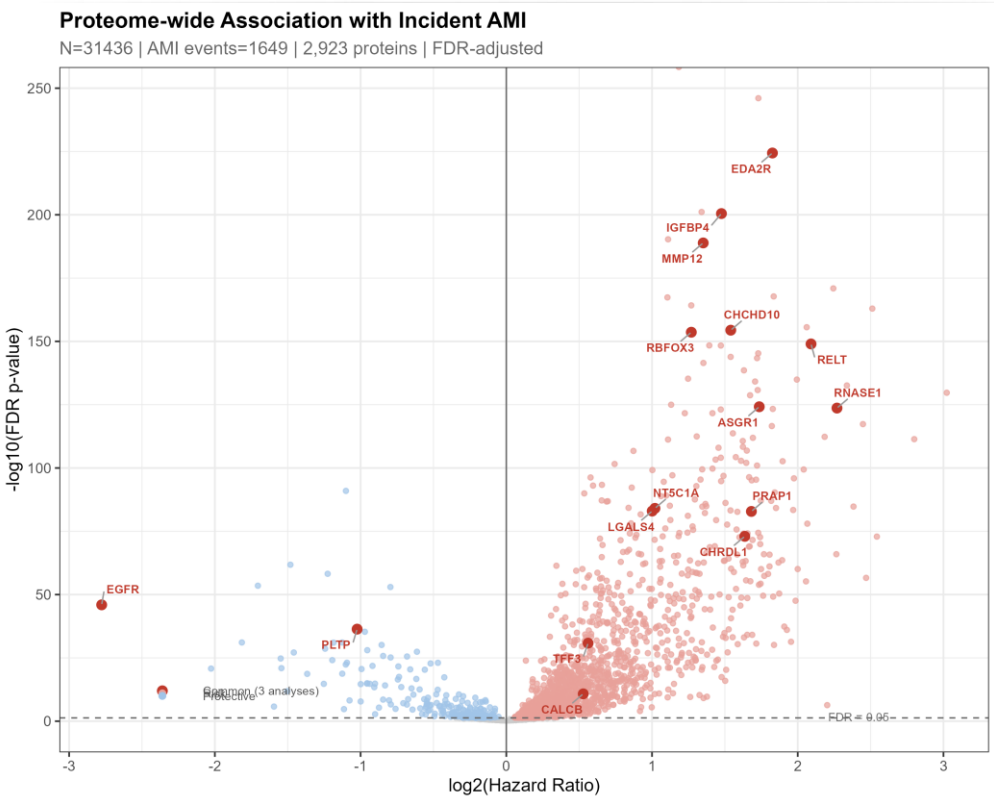

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