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**Longitudinal Impact of Serum Chloride-to-Sodium Ratio on the Risks of eGFR
Decline and Mortality in CKD Patients with the Pre-HFpEF Phenotype:
Application of the Parametric G-Formula**

Ara Ko¹, Hyunman Sim³, Dong Ki Kim¹, Woojoo Lee³, Jung Pyo Lee²

¹Department of Internal Medicine, Seoul National University Hospital, Korea, Republic of

²Department of Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, Korea, Republic of

³Department of Internal Medicine, Seoul National University Boramae Medical Center, Korea, Republic of

Objectives : Chloride is a key determinant of diuretic resistance in heart failure, shifting volume assessment paradigms. In chronic kidney disease (CKD) patients with the pre-heart failure with preserved ejection fraction (HFpEF) phenotype achieving euvoemia through delicate dietary and pharmacological titration is highly demanding. Consequently, the serum chloride-to-sodium (Cl/Na) ratio has been introduced as a physiological index to differentiate true chloride depletion from dilutional fluid overload, but its longitudinal impact in this population remains undefined.

Methods : We analyzed a retrospective cohort of 4,470 CKD patients who presented with both preserved EF ($\geq 50\%$) and baseline DD. DD was identified via echocardiographic indices (e.g., E/E', PASP, and LAVI), natriuretic peptides, or diagnostic codes. We assessed the longitudinal Cl/Na ratio status over 5 years, categorized by a literature-derived target-in-range (TIR; 0.72–0.79). Using the parametric g-formula to account for treatment-confounder feedback, we estimated risks associated with hypothetical TIR maintenance, adjusting for dynamic DD status, serum creatinine, serum bicarbonate, and prescriptions (RAAS blockade, SGLT2 inhibitors, and diuretics). Primary and secondary outcomes were $\geq 40\%$ eGFR decline and all-cause mortality.

Results : Over a median follow-up of 24 months, maintaining the Cl/Na ratio within TIR for 5 years was associated with lower risks of eGFR decline (RR 0.89; 95% CI 0.82–0.95) and mortality (RR 0.74; 95% CI 0.61–0.94) versus never achieving TIR. Notably, a Cl/Na ratio persistently below 0.72 was associated with higher risks of eGFR decline (RR 1.09; 95% CI 1.04–1.15) and mortality (RR 1.38; 95% CI 1.14–1.65) relative to remaining in TIR.

Conclusions : In CKD patients with the pre-HFpEF phenotype, maintaining the Cl/Na ratio between 0.72 and 0.79 is associated with reduced renal and mortality risks. Adverse outcomes below 0.72 highlight the physiological burden of chloride depletion, often seen during aggressive decongestion. This objective signal suggests that beyond relying solely on conventional diuresis, exploring alternative therapeutic mechanisms warrants consideration to safely manage cardiorenal risks.