Research Square

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Higher serum sodium-to-chloride ratio identifies near-term mortality risk in adults with confirmed chronic kidney disease: a retrospective landmark cohort study

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Research Article

Keywords: chloride, sodium-to-chloride ratio, chronic kidney disease, mortality, electronic health records, electrolyte phenotype

Posted Date: September 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10902236/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Serum chloride is closely coupled to sodium, acid-base balance, volume regulation, and diuretic response, but the prognostic meaning of their ratio has rarely been examined in non-dialysis chronic kidney disease (CKD).

Objective

To evaluate the association between the serum sodium-to-chloride (Na/Cl) ratio at CKD confirmation and subsequent all-cause mortality.

Methods

This retrospective cohort study used de-identified electronic health records from Wuhan Central Hospital. Adults were required to have two creatinine-based estimated glomerular filtration rate (eGFR) values below 60 mL/min/1.73 m2 separated by 90–365 days. The second qualifying measurement defined the index date. Patients with recorded kidney replacement therapy before index were excluded. The exposure was the same-day serum Na/Cl ratio. Cox models adjusted for age, sex, eGFR, total carbon dioxide, albumin, haemoglobin, potassium, diabetes, hypertension, heart failure, coronary disease, and stroke. Proportional-hazards diagnostics prompted prespecified phase-specific analyses.

Results

The complete-case cohort included 2,746 adults (median age, 74.9 years; 45.6% female), with 526 deaths over a median follow-up of 338 days. Each 1-SD higher Na/Cl ratio (SD, 0.048) was associated with higher mortality in the fully adjusted model (hazard ratio [HR], 1.65; 95% confidence interval [CI], 1.52–1.79; P < 0.001). The association was approximately linear (P for nonlinearity = 0.586) and persisted after excluding deaths within 30 days (HR, 1.52; 95% CI, 1.36–1.69) and among patients with sodium and chloride within conventional reference ranges (HR, 1.36; 95% CI, 1.20–1.55). The proportional-hazards assumption was not fully satisfied. The association was stronger during the first 180 days (HR, 1.89; 95% CI, 1.72–2.07) and was not clear among 180-day survivors (HR, 1.14; 95% CI, 0.96–1.35). A model including sodium and chloride separately fit slightly better than the ratio model, indicating that the ratio should be interpreted as an integrated electrolyte phenotype rather than an independent biomarker.

Conclusions

A higher serum Na/Cl ratio at confirmed CKD was associated with near-term mortality in this single-centre EHR cohort. The time-varying association and dependence on its component electrolytes limit causal and incremental-prediction claims. External validation with standardized volume, medication, and acid-base data is required.

Introduction

Chronic kidney disease is defined by persistent abnormalities of kidney structure or function and carries substantial cardiovascular, metabolic, and mortality risk across the continuum of reduced glomerular filtration [1]. Routine electrolyte panels are obtained repeatedly during CKD care, yet their interpretation often centres on potassium and bicarbonate while chloride is treated as a passive companion to sodium. This convention overlooks chloride's contribution to electroneutrality, strong-ion balance, tubuloglomerular signalling, neurohormonal activation, and diuretic response.

Population and hospital-based studies have reported that chloride abnormalities are associated with mortality, often with a U-shaped concentration-response pattern [2, 3]. The Na/Cl ratio may capture relative chloride depletion, dilutional physiology, or mixed acid-base and volume states that are not apparent from either analyte alone. Direct evidence is nevertheless concentrated in selected populations. A multicentre peritoneal-dialysis cohort reported an association between the Na/Cl ratio and mortality [4], while acute heart failure cohorts observed adverse outcomes at higher or extreme ratios [5, 6]. Recent critical-care studies have also renewed interest in chloride concentration and the sodium-chloride difference in acute kidney injury and mixed intensive-care populations [7, 8]. These settings involve dialysis, aggressive fluid administration, or acute decongestion and cannot be assumed to represent non-dialysis CKD.

The prognostic interpretation of the Na/Cl ratio in routinely treated CKD therefore remains uncertain. A clinically useful analysis must distinguish chronic kidney impairment from a single low eGFR, establish the electrolyte measurement before follow-up, account for acid-base and nutritional correlates, and test whether any association is stable over time. This study evaluated the association between the Na/Cl ratio measured on the date of confirmed CKD and subsequent all-cause mortality. We hypothesized that a higher ratio would identify a higher-risk electrolyte phenotype, while recognizing that the ratio might primarily summarize its sodium and chloride components rather than provide independent predictive information.

Methods

Study design and data source

A retrospective cohort was reconstructed from the original de-identified electronic health record source files of Wuhan Central Hospital. No previously cleaned cohort, project cache, derived table, or model object was used. The source files contained patient demographics, raw laboratory measurements,

diagnoses, and recorded clinical events. The available laboratory period extended from May 2013 through November 2022; qualifying index dates in the final cohort ranged from July 2020 through November 2022. Reporting was aligned with the STROBE recommendations [10].

Study population and index date

Adults aged 18 years or older were eligible when they had two serum-creatinine measurements yielding eGFR below 60 mL/min/1.73 m2 separated by 90–365 days. eGFR was calculated using the 2021 CKD-EPI creatinine equation without race [9]. For each patient, the first second measurement that completed a qualifying pair defined the index date. Same-day serum sodium, chloride, and total carbon dioxide were required. Patients were excluded if dialysis, kidney failure, or kidney transplantation had been recorded on or before index, or if no positive follow-up time was available. This chronicity rule reduced misclassification from an isolated acute creatinine elevation but did not eliminate residual acute illness at the index measurement.

Exposure assessment

Raw laboratory names were mapped to standardized sodium, chloride, creatinine, total carbon dioxide, potassium, calcium, phosphate, glucose, albumin, and haemoglobin concepts. Values were converted to numeric form, units were restricted to those specified in the analysis script, and physiologically implausible observations were removed using rules declared before cohort assembly. Multiple measurements of the same analyte on one date were summarized by their median. The primary exposure was serum sodium divided by serum chloride on the index date. It was analysed per cohort-specific SD and in quartiles. Serum sodium minus chloride was examined as an alternative exposure. Restricted cubic modelling was approximated with a natural spline with three degrees of freedom.

Outcome and covariates

Outcome and covariates

The outcome was all-cause death recorded after index and on or before 9 November 2022. Patients without recorded death were administratively censored on that date. Covariates were selected a priori and included age, sex, index eGFR, total carbon dioxide, albumin, haemoglobin, potassium, and pre-index recorded diabetes, hypertension, heart failure, coronary disease, and stroke. Diagnoses were identified from raw diagnostic codes and names dated on or before index. Albumin was missing in 12.2% and haemoglobin in 10.1% of the otherwise eligible cohort; other model variables had negligible or no missingness. The primary analysis used complete cases, and the resulting selection was quantified in the cohort flow.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges and categorical variables as counts and percentages. Cox proportional-hazards models were fitted sequentially: an unadjusted model; a demographic-kidney model adjusted for age, sex, and eGFR; and a fully adjusted model containing all prespecified covariates. Hazard ratios are reported with 95% CIs. Quartiles were compared with the lowest quartile. A likelihood-ratio test compared the spline model with a linear exposure model. Schoenfeld-residual tests assessed proportional hazards.

Sensitivity analyses excluded deaths within 30 days, truncated follow-up at one year, replaced the ratio with the sodium-chloride difference, restricted the cohort to eGFR below 45 mL/min/1.73 m2, and restricted sodium and chloride to 135–145 and 98–107 mmol/L, respectively. Component models compared the ratio with standardized sodium, standardized chloride, and a joint sodium-plus-chloride specification. Because the proportional-hazards test for the ratio was significant, associations were also estimated for 0-180 days and among patients surviving beyond a 180-day landmark. Two-sided $P < 0.05$ was considered statistically significant. Analyses were conducted in R version 4.6.0 using data.table and survival.

Bias considerations

The design explicitly addressed temporality, left truncation, and immortal time by fixing exposure at the second CKD-qualifying measurement and starting follow-up on that date. Requiring repeated kidney-function testing and complete same-day electrolytes introduced informed-presence and selection bias. Residual reverse causation remained plausible because the index panel could be obtained during acute illness. The early-death exclusion and phase-specific analyses were therefore treated as central rather than decorative sensitivity analyses. Death outside linked hospital records may have been incompletely captured, and non-death kidney outcomes were not used as primary endpoints because recorded events were sparse.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee of Wuhan Central Hospital (Approval No. WHZXKYL2022-112). The requirement for individual informed consent was waived owing to the retrospective use of de-identified data.

Results

Cohort construction and baseline characteristics

Among 135,072 source persons, 6,006 adults had two eGFR values below 60 mL/min/1.73 m2 separated by 90–365 days. Same-day sodium, chloride, and total carbon dioxide were available for 4,947; 3,331 remained after excluding recorded kidney replacement therapy before index; and 3,328 had positive follow-up. The complete-case primary cohort included 2,746 adults (Fig. 1). Median age was 74.9 years,

1,251 (45.6%) were female, and median eGFR was 43.9 mL/min/1.73 m2. Diabetes was recorded in 50.3%, heart failure in 49.7%, and coronary disease in 68.7%. The median Na/Cl ratio was 1.334 (IQR, 1.304–1.362). Across increasing ratio quartiles, chloride decreased more strongly than sodium changed, while heart failure became more common and total carbon dioxide increased (Table 1).

Table 1
Baseline characteristics by sodium-to-chloride ratio quartile

variable	Overall	Q1	Q2	Q3	Q4
age	74.9 (67.2–83.1)	72.9 (65.8–81.3)	74.0 (66.3–82.1)	76.0 (68.4–83.9)	77.3 (69.5–84.2)
egfr	43.9 (31.9–52.3)	34.1 (21.8–46.8)	45.3 (33.9–52.0)	47.8 (37.1–54.5)	45.7 (35.5–52.9)
sodium	140.3 (137.9-142.3)	139.8 (137.7-141.7)	140.6 (138.5-142.4)	140.8 (138.5-142.7)	139.9 (137.1-142.6)
chloride	105.4 (102.2–108.0)	109.3 (107.4-111.1)	106.6 (105.0-108.2)	104.5 (102.6-105.9)	100.6 (98.0-102.7)
na_cl_ratio	1.334 (1.304–1.362)	1.284 (1.267–1.294)	1.319 (1.312–1.326)	1.347 (1.340–1.354)	1.387 (1.373–1.408)
tco2	23.3 (21.2–25.6)	21.3 (19.3–23.0)	23.0 (21.4–25.0)	24.0 (22.1–26.0)	25.4 (23.0-27.5)
albumin	38.9 (35.0-42.5)	37.0 (32.8–40.7)	39.2 (35.5–42.7)	39.8 (35.8–43.0)	39.4 (35.7–43.2)
hemoglobin	115.0 (99.0-130.0)	102.8 (87.0-120.0)	116.0 (103.0-130.0)	118.0 (104.0-132.0)	121.0 (107.0-135.0)
potassium	4.3 (4.0-4.8)	4.6 (4.2–5.1)	4.4 (4.0-4.8)	4.2 (4.0-4.6)	4.1 (3.8–4.6)
female	1251 (45.6%)	299 (44.5%)	304 (45.0%)	325 (45.6%)	323 (47.2%)
diabetes	1381 (50.3%)	347 (51.6%)	340 (50.3%)	330 (46.3%)	364 (53.1%)
hypertension	2439 (88.8%)	587 (87.4%)	606 (89.6%)	639 (89.6%)	607 (88.6%)
heart_failure	1366 (49.7%)	279 (41.5%)	323 (47.8%)	361 (50.6%)	403 (58.8%)
coronary_disease	1887 (68.7%)	420 (62.5%)	468 (69.2%)	495 (69.4%)	504 (73.6%)
stroke	1654 (60.2%)	373 (55.5%)	405 (59.9%)	448 (62.8%)	428 (62.5%)

Values are median (IQR), n (%), or model estimates as labelled. P values < 0.001 are displayed as < 0.001 in the manuscript narrative.

Association with all-cause mortality

During 2,718 person-years of observation (median follow-up, 338 days; IQR, 156–563), 526 deaths were recorded. Each 1-SD higher Na/Cl ratio was associated with mortality in the unadjusted model (HR, 1.31; 95% CI, 1.21–1.43), the demographic-kidney model (HR, 1.33; 95% CI, 1.23–1.44), and the fully adjusted model (HR, 1.65; 95% CI, 1.52–1.79; P < 0.001). Compared with quartile 1, adjusted HRs were 1.65 (95% CI, 1.26–2.15) for quartile 2, 1.49 (95% CI, 1.12–1.98) for quartile 3, and 3.29 (95% CI, 2.51–4.30) for quartile 4 (Table 2). The spline supported an overall association (P < 0.001) without clear nonlinearity (P = 0.586; Fig. 2).

Table 2
Association between sodium-to-chloride ratio and all-cause mortality

model	n	events	HR	CI_low	CI_high	p
Unadjusted	2,746	526	1.31	1.21	1.43	< 0.001
Demographic_kidney	2,746	526	1.33	1.23	1.44	< 0.001
Fully_adjusted	2,746	526	1.65	1.52	1.79	< 0.001

Values are median (IQR), n (%), or model estimates as labelled. P values < 0.001 are displayed as < 0.001 in the manuscript narrative.

Robustness, component models, and time dependence

The association persisted after excluding deaths within 30 days (HR, 1.52; 95% CI, 1.36–1.69), at a one-year horizon (HR, 1.74; 95% CI, 1.60–1.89), with the sodium-chloride difference (HR, 1.62; 95% CI, 1.47–1.78), among patients with eGFR below 45 mL/min/1.73 m2 (HR, 1.66; 95% CI, 1.50–1.85), and when both component electrolytes were within conventional reference ranges (HR, 1.36; 95% CI, 1.20–1.55; Table 3 and Fig. 3).

Table 3
Sensitivity and restriction analyses

analysis	n	events	HR	CI_low	CI_high	p
Exclude deaths within 30 days	2,616	396	1.52	1.36	1.69	< 0.001
One-year horizon	2,746	441	1.74	1.60	1.89	< 0.001
Additional serum sodium and chloride adjustment	2,746	526	1.76	0.75	4.16	0.196
Exposure as sodium-chloride difference	2,746	526	1.62	1.47	1.78	< 0.001

Values are median (IQR), n (%), or model estimates as labelled. P values < 0.001 are displayed as < 0.001 in the manuscript narrative.

The ratio model had slightly lower AIC than the chloride-only model (7437.0 vs 7449.6) and slightly higher concordance (0.776 vs 0.772). A joint sodium-plus-chloride model fit slightly better than the ratio

model (AIC, 7433.6; concordance, 0.777). When the ratio and both component concentrations were entered together, the ratio estimate was imprecise (HR, 1.76; 95% CI, 0.75–4.16; P = 0.196), consistent with mathematical collinearity and limited independent information.

The proportional-hazards test was significant for the ratio (P = 0.014) and globally (P < 0.001). In phase-specific analyses, the adjusted association was strongest during the first 180 days (HR, 1.89; 95% CI, 1.72–2.07). Among 1,959 patients alive at 180 days, the association with later mortality was not clear (HR, 1.14; 95% CI, 0.96–1.35; P = 0.144). These findings narrowed the interpretation to near-term risk rather than a constant long-term effect.

Discussion

In adults with CKD confirmed by repeated low eGFR measurements, a higher same-day serum Na/Cl ratio was associated with recorded all-cause mortality after adjustment for kidney function, acid-base status, nutritional and haematologic markers, and major cardiovascular comorbidity. The association remained evident within conventional sodium and chloride ranges and after excluding deaths during the first 30 days. However, it was concentrated in the first 180 days, and a model using sodium and chloride separately fit slightly better. The ratio therefore appears to identify a near-term electrolyte and illness phenotype; these data do not establish an independent biological effect, causal pathway, or treatment target.

The direction of association is consistent with evidence linking lower chloride or higher sodium-relative-to-chloride patterns to adverse outcomes. A recent multicentre peritoneal-dialysis cohort directly associated the Na/Cl ratio with mortality [4], and heart-failure cohorts have reported adverse outcomes across higher or extreme ratio categories [5, 6]. Community and hospital-survivor cohorts have also linked chloride abnormalities to mortality [2, 3]. Related associations have been reported in acute kidney injury, mixed critical illness, cirrhosis, and fluid-therapy cohorts [7, 8, 11, 12], with additional sepsis studies emphasizing dose-response and longitudinal chloride trajectories [13, 14]. Meta-analyses in acute and chronic heart failure likewise support hypochloremia as a risk marker, although thresholds, timing, and covariate handling differ substantially [15, 16]. The current study adds a non-dialysis CKD population defined by laboratory chronicity rather than a single diagnostic code or isolated creatinine value.

Several mechanisms may explain why the ratio tracks risk without implying that modifying it would improve outcomes. Chloride participates in macula-densa sensing, renin release, extracellular fluid distribution, and acid-base electroneutrality. In heart failure, lower chloride has been associated with diuretic resistance and neurohormonal activation [17–20], prompting a broader cardiorenal chloride framework [21–23]. Experimental and clinical discussions also link chloride-rich fluids, renal vasoconstriction, and acute kidney injury, while emphasizing that concentration, fluid balance, and bicarbonate cannot be separated cleanly [24, 25, 34]. In this cohort, increasing ratio quartiles were characterized by lower chloride, higher total carbon dioxide, and more heart failure. The ratio may thus

integrate volume-contraction, diuretic exposure, alkalosis, nutritional status, and acute disease severity, none of which was measured completely.

CKD itself alters acid excretion and bicarbonate homeostasis. Contemporary reviews describe the pathogenesis and clinical consequences of CKD metabolic acidosis [26, 29, 31, 32]. Meta-analyses and cohort evidence address bicarbonate treatment, dietary alkali, and changes in serum bicarbonate [27, 28, 30, 33]. Our finding should not be interpreted as evidence for chloride supplementation or against bicarbonate therapy. Total carbon dioxide was included as a covariate, but venous or arterial pH, anion gap, urinary chloride, dietary sodium and chloride intake, fluid administration, and time-updated diuretic dosing were unavailable. A high Na/Cl ratio can arise through different physiological routes, and the same numerical value may not represent the same state across patients.

The early concentration of risk is scientifically important. A stable causal exposure would be expected to show a more persistent proportional effect, whereas the loss of a clear association after the 180-day landmark suggests acute or subacute illness, treatment intensity, or incomplete recovery at CKD confirmation. Requiring a second low eGFR reduces single-measurement misclassification but can also select patients undergoing repeated testing during illness. The result is therefore compatible with informed presence and reverse causation. Future studies should anchor exposure in stable outpatient care, include medication and fluid histories, distinguish acid-base phenotypes with pH and urinary electrolytes, and validate the time-varying pattern in an external system.

This study has strengths. The cohort was rebuilt directly from original source RDS files with recorded file checksums and a complete data lineage. CKD chronicity, exposure timing, prior kidney replacement therapy, physiologic ranges, duplicate same-day measurements, and each sample attrition step were encoded in reproducible scripts. Multiple sensitivity analyses tested early events, reference-range restriction, alternative exposure definition, kidney-function severity, component models, and proportional hazards. The analysis also retained a negative incremental-information result rather than presenting the ratio as a novel score.

The limitations are substantial. This was a single-centre retrospective study with index dates concentrated between 2020 and 2022, overlapping the COVID-19 era. Death ascertainment may be incomplete outside linked records, and cause-specific death was unavailable. Complete-case analysis excluded 582 otherwise eligible patients, principally because albumin or haemoglobin was missing. Repeated testing, electrolyte measurement, and survival long enough to confirm CKD created selection and left-truncation concerns. Medication dose, intravenous fluid, oedema, blood pressure, pH, anion gap, dietary intake, and urinary electrolytes were not sufficiently standardized for analysis. Diagnostic comorbidities were code-based. The proportional-hazards assumption was violated, the association was not clear after the 180-day landmark, and the ratio was mathematically dependent on sodium and chloride. Residual confounding and reverse causation are therefore likely.

A higher serum Na/Cl ratio at the date of confirmed CKD was associated with near-term recorded mortality, but it did not behave as a stable independent long-term predictor. The ratio may be a low-cost

signal that prompts clinical review of volume, medications, acid-base status, nutrition, and intercurrent illness. It should not guide electrolyte treatment without prospective validation.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee of Wuhan Central Hospital (Approval No. WHZXKYL2022-112). The requirement for individual informed consent was waived owing to the retrospective use of de-identified data.

Consent for publication

Not applicable.

Data availability

The individual-level hospital data contain protected health information and are not included in the submission package. Access is subject to institutional governance and applicable approvals. Aggregated tables, analysis code, data dictionaries, and source-file checksums are provided in the reproducibility package.

Funding

This work was supported by The Central Hospital of Wuhan under Grant NO.26YJ-AI-04

Competing interests

The authors declare no competing interests.

Author contributions

X.L. and F.Z. contributed equally to this work. X.L. conceived and designed the study, performed the statistical analyses, interpreted the data, and drafted the original manuscript. F.Z. curated the electronic health records, established the analytical dataset, conducted the data quality control and integrity verification, and designed the visualization strategy for all figures and tables. N.Z. critically revised the manuscript for important intellectual content, contributed to the interpretation of the results, and provided input on the Discussion section. X.Z. supervised the project, provided clinical expertise, verified

the clinical interpretation, and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version and agree to be accountable for all aspects of the work.

Acknowledgements

The authors gratefully acknowledge the clinical and administrative staff of Wuhan Central Hospital for their assistance with patient care and data management. We also thank the patients who contributed their medical data to this research. This work was supported by The Central Hospital of Wuhan under Grant NO.26YJ-AI-04, and the funders had no role in the study conduct or reporting.

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Figures

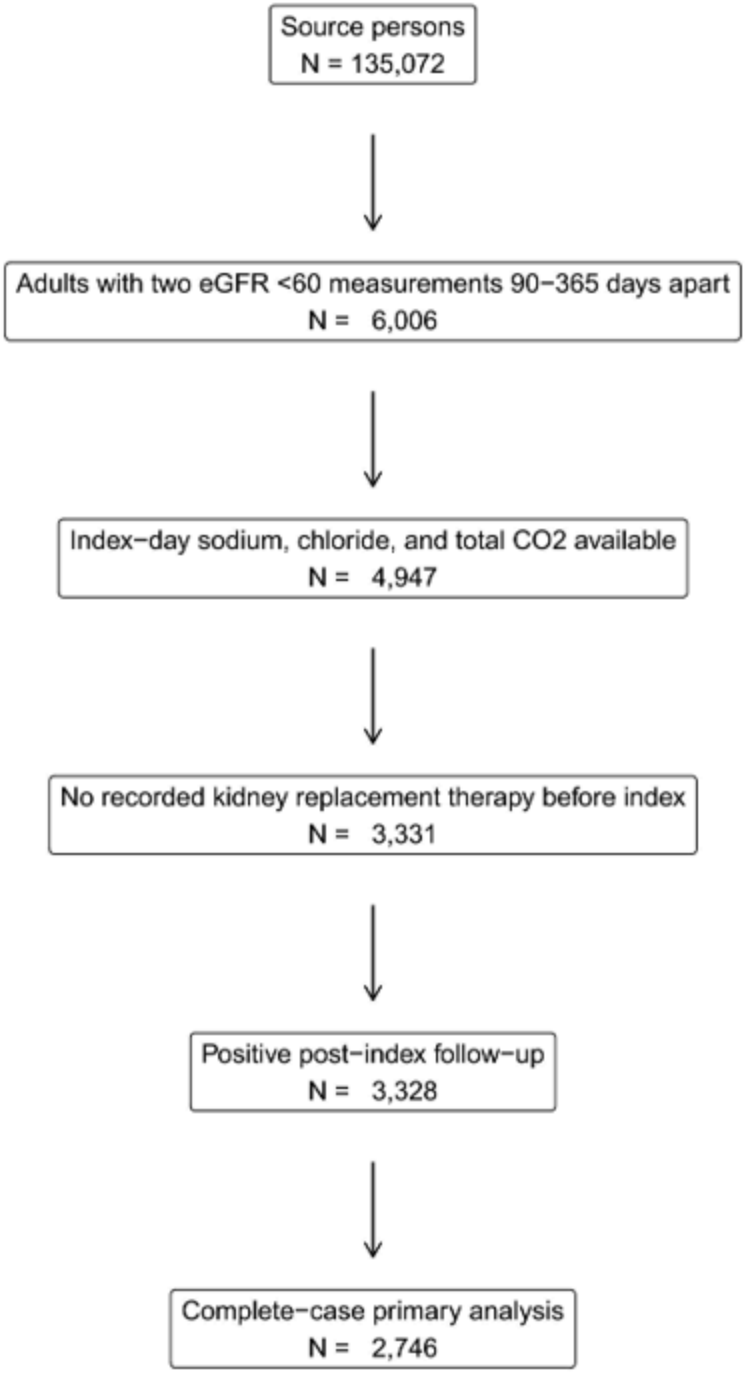


Figure 1

Cohort selection flowchart

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