**SUPPLEMENTARY APPENDIX**

# Longitudinal FGF23 Trajectories and Mortality in Patients with Chronic Kidney Disease

Tamara Isakova, MD, MMSc,[1,2] Xuan Cai, MS,[2] Jungwha Lee, PhD,[2] Dawei Xie, PhD,[3] Xue Wang, MS,[3] Rupal Mehta, MD,[1,2] Norrina B. Allen, PhD,[2] Julia J. Scialla, MD, MHS[4,5] Michael J. Pencina, PhD,[5] Amanda H. Anderson, PhD, MPH,[3] John Talierco, DO,[6] Jing Chen, MD, MMSc, MSc,[7] Michael J. Fischer, MD, MSPH,[8] Susan P. Steigerwalt, MD,[9] Mary B. Leonard, MD, MSCE,[10] Chi-yuan Hsu, MD, MSc,[11] Ian de Boer, MD, MS,[12] John W. Kusek, PhD,[13] Harold I. Feldman, MD, MSCE,[3] Myles Wolf, MD, MMSc,[4,5] for the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators[†]

Running title: Serial FGF23 & Mortality in CKD

Corresponding author: Myles Wolf, MD, MMSc, 2 Genome Court, Room 2018, Durham, NC 27710; Phone: 919-684-6752; FAX: 919-684-3011; myles.wolf@duke.edu

## Supplemental Tables

**Supplemental Table 1. Sensitivity analyses:** Model 5 from the 5-time point FGF23 trajectory analysis in Table 3 of the main manuscript is the base model used for comparison in the following additional analyses.

| FGF23 trajectory group | Total N | Deaths N | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Model 5 from Table 3** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.49 (3.17–6.35) |
| Rapidly rising | 99 | 67 | 15.23 (8.24–28.14) |
| **Model 5, incorporating 1-year lag to start of follow-up time*** | | | |
| Stable | 639 | 73 | Reference |
| Slowly rising | 430 | 147 | 6.70 (3.86–11.61) |
| Rapidly rising | 103 | 60 | 42.84 (18.08–101.57) |
| **Model 5 plus adjustment for number of anti-hypertensive medications** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.46 (3.15–6.32) |
| Rapidly rising | 99 | 67 | 15.56 (8.44–28.68) |
| **Model 5 plus adjustment for cardiovascular events in preceding year** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.48 (3.17–6.34) |
| Rapidly rising | 99 | 67 | 15.22 (8.15–28.43) |
| **Model 5 plus adjustment for number of hospitalizations in preceding year** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.64 (3.25–6.61) |
| Rapidly rising | 99 | 67 | 15.67 (8.49–28.92) |
| **Model 5 plus adjustment for markers of inflammation at the baseline visit** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.41 (3.11–6.26) |
| Rapidly rising | 99 | 67 | 14.16 (7.62–26.32) |
| **Model 5 plus adjustment for time-updated use of phosphate binders, active vitamin D, calciferols** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.48 (3.17–6.34) |
| Rapidly rising | 99 | 67 | 14.97 (8.11–27.63) |
| **Model 5 plus adjustment for 25D and 1,25D levels at the year 2 visit** | | | |
| Stable | 724 | 102 | Reference |
| Slowly rising | 486 | 221 | 4.29 (2.98–6.17) |
| Rapidly rising | 99 | 67 | 17.67 (9.00–34.73) |

Covariate adjustment is for covariates obtained at the analysis-specific time 0 except for baseline UACR and baseline eGFR, which are obtained at the CRIC Study baseline visit.

Model 5 is stratified by center and adjusted for age, sex, race, ethnicity, eGFR trajectories, baseline UACR, serum albumin, hemoglobin, SBP, BMI, diabetes, smoking, history of coronary artery disease, heart failure, stroke, and peripheral vascular disease, calcium, phosphate, PTH, and lnFGF23.

*For the lag-analysis, we derived the trajectory groups anew including only individuals that survived to year 5 post-baseline.

Abbreviations: FGF23, fibroblast growth factor 23; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; SBP, systolic blood pressure; BMI, body mass index; PTH, parathyroid hormone; lnFGF23, natural log-transformed fibroblast growth factor 23; 25D, 25-hydroxyvitamin D; and 1,25D, 1,25-dihydroxyvitamin D.

**Supplemental Table 2. eGFR trajectories and risk of death.**

| eGFR trajectory group | N Total | N events | Unadjusted | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|---|---|---|
| **Up to 5 annual time points, median duration of subsequent follow-up time 3.4 years in 1309 total participants at risk** | | | | | | | |
| Stable | 267 | 26 | Reference | Reference | Reference | Reference | Reference |
| Slowly declining | 510 | 146 | 3.63 (2.34–5.64) | 2.61 (1.65–4.12) | 2.24 (1.39–3.60) | 2.21 (1.36–3.58) | 1.92 (1.10–3.37) |
| Rapidly declining | 532 | 218 | 6.22 (4.04–9.57) | 4.35 (2.74–6.91) | 3.05 (1.83–5.07) | 2.90 (1.73–4.87) | 2.06 (0.97–4.39) |
| **Up to 4 annual time points, median duration of subsequent follow-up time 4.3 years in 1376 total participants at risk** | | | | | | | |
| Stable | 259 | 29 | Reference | Reference | Reference | Reference | Reference |
| Slowly declining | 569 | 184 | 3.67 (2.42–5.55) | 2.71 (1.75–4.19) | 2.16 (1.37–3.40) | 2.03 (1.28–3.22) | 1.47 (0.85–2.54) |
| Rapidly declining | 548 | 242 | 5.83 (3.87–8.79) | 4.06 (2.58–6.37) | 2.68 (1.62–4.44) | 2.54 (1.52–4.24) | 1.32 (0.61–2.84) |
| **Up to 3 annual time points, median duration of subsequent follow-up time 5.1 years in 1412 total participants at risk** | | | | | | | |
| Stable | 255 | 33 | Reference | Reference | Reference | Reference | Reference |
| Slowly declining | 627 | 207 | 3.20 (2.17–4.72) | 2.45 (1.63–3.67) | 1.98 (1.32–2.99) | 1.92 (1.26–2.93) | 1.54 (0.85–2.79) |
| Rapidly declining | 530 | 250 | 5.35 (3.63–7.88) | 3.76 (2.47–5.72) | 2.38 (1.51–3.75) | 2.39 (1.50–3.81) | 1.29 (0.59–2.80) |

Covariate adjustment is for covariates obtained at the analysis-specific time 0 except for baseline UACR and baseline eGFR, which are obtained at the CRIC Study baseline visit.

Model 1: stratified by center, adjusted for age, sex, race, and ethnicity

Model 2: Model 1 plus baseline UACR, serum albumin and hemoglobin

Model 3: Model 2 plus diabetes, smoking, SBP, BMI, history of coronary artery disease, history of heart failure, history of stroke, and history of peripheral vascular disease

Model 4: Model 3 plus calcium, phosphate, PTH, lnFGF23, and baseline eGFR

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; SBP, systolic blood pressure; BMI, body mass index; PTH, parathyroid hormone; lnFGF23, natural log-transformed fibroblast growth factor 23.

**Supplemental Table 3. Systolic blood pressure trajectories and risk of death.**

| SBP trajectory group | N Total | N events | Unadjusted | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|---|---|---|
| **Up to 5 annual time points, median duration of subsequent follow-up time 3.4 years in 1309 total participants at risk** | | | | | | | |
| Low stable | 484 | 107 | Reference | Reference | Reference | Reference | Reference |
| Moderate stable | 612 | 191 | 1.62 (1.25–2.10) | 1.26 (0.95–1.68) | 1.02 (0.75–1.38) | 1.06 (0.77–1.46) | 1.04 (0.74–1.46) |
| Elevated rising | 213 | 92 | 2.77 (2.02–3.82) | 2.05 (1.44–2.94) | 1.34 (0.91–1.98) | 1.34 (0.88–2.03) | 1.21 (0.77–1.88) |
| **Up to 4 annual time points, median duration of subsequent follow-up time 4.3 years in 1376 total participants at risk** | | | | | | | |
| Low stable | 542 | 139 | Reference | Reference | Reference | Reference | Reference |
| Moderate stable | 602 | 210 | 1.53 (1.21–1.94) | 1.25 (0.97–1.63) | 1.01 (0.77–1.33) | 0.99 (0.74–1.32) | 0.92 (0.68–1.25) |
| Elevated rising | 232 | 106 | 2.46 (1.84–3.30) | 1.83 (1.31–2.55) | 1.19 (0.83–1.70) | 1.18 (0.81–1.71) | 1.09 (0.74–1.62) |
| **Up to 3 annual time points, median duration of subsequent follow-up time 5.1 years in 1412 total participants at risk** | | | | | | | |
| Low stable | 724 | 201 | Reference | Reference | Reference | Reference | Reference |
| Moderate stable | 533 | 210 | 1.69 (1.36–2.10) | 1.41 (1.11–1.78) | 1.11 (0.87–1.42) | 1.11 (0.86–1.43) | 1.15 (0.87–1.52) |
| Elevated rising | 155 | 79 | 2.48 (1.82–3.39) | 1.83 (1.30–2.59) | 1.19 (0.82–1.72) | 1.09 (0.73–1.62) | 0.93 (0.61–1.43) |

Covariate adjustment is for covariates obtained at the analysis-specific time 0 except for baseline UACR and baseline eGFR, which are obtained at the CRIC Study baseline visit.

Model 1: stratified by center, adjusted for age, sex, race, and ethnicity

Model 2: Model 1 plus eGFR, baseline UACR, serum albumin, and hemoglobin

Model 3: Model 2 plus diabetes, smoking, BMI, history of coronary artery disease, history of heart failure, history of stroke, and history of peripheral vascular disease

Model 4: Model 3 plus calcium, phosphate, PTH, lnFGF23, and baseline eGFR

Abbreviations: SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; BMI, body mass index; PTH, parathyroid hormone; lnFGF23, natural log-transformed fibroblast growth factor 23.

**Supplemental Table 4. Serum phosphate trajectories and risk of death.**

| Phosphate trajectory group | N Total | N events | Unadjusted | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|---|---|---|
| **Up to 5 annual time points, median duration of subsequent follow-up time 3.4 years in 1309 total participants at risk** | | | | | | | |
| Stable | 1134 | 320 | Reference | Reference | Reference | Reference | Reference |
| Rising | 175 | 70 | 2.04 (1.51–2.77) | 2.26 (1.52–3.34) | 1.86 (1.24–2.80) | 1.66 (1.07–2.56) | 1.55 (0.98–2.45) |
| **Up to 4 annual time points, median duration of subsequent follow-up time 4.3 years in 1376 total participants at risk** | | | | | | | |
| Stable | 1187 | 370 | Reference | Reference | Reference | Reference | Reference |
| Rising | 189 | 85 | 2.03 (1.54–2.67) | 2.01 (1.42–2.84) | 1.62 (1.14–2.30) | 1.62 (1.10–2.39) | 1.36 (0.90–2.05) |
| **Up to 3 annual time points, median duration of subsequent follow-up time 5.1 years in 1412 total participants at risk** | | | | | | | |
| Stable | 1259 | 416 | Reference | Reference | Reference | Reference | Reference |
| Rising | 153 | 74 | 2.06 (1.52–2.77) | 1.82 (1.25–2.66) | 1.42 (0.96–2.09) | 1.49 (0.98–2.26) | 1.37 (0.86–2.18) |

Covariate adjustment is for covariates obtained at the analysis-specific time 0 except for baseline UACR and baseline eGFR, which are obtained at the CRIC Study baseline visit.

Model 1: stratified by center, adjusted for age, sex, race, and ethnicity

Model 2: Model 1 plus eGFR, baseline UACR, serum albumin, and hemoglobin

Model 3: Model 2 plus diabetes, smoking, SBP, BMI, history of coronary artery disease, history of heart failure, history of stroke, and history of peripheral vascular disease

Model 4: Model 3 plus calcium, PTH, lnFGF23 and baseline eGFR

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; SBP, systolic blood pressure; BMI, body mass index; PTH, parathyroid hormone; lnFGF23, natural log-transformed fibroblast growth factor 23.