RESEARCH LETTER

Associations of Serum Amphiregulin Levels With Kidney Failure and Mortality: The Chronic Renal Insufficiency Cohort (CRIC)

To the Editor:

Amphiregulin, a low-affinity ligand for the epidermal growth factor receptor (EGFR), plays a significant role in kidney tissue injury, repair, and inflammation.[1-3] Amphiregulin sustains profibrotic EGFR activation in proximal tubule cells and promotes kidney fibrosis after injury.[1] Given its involvement in kidney fibrogenesis, we hypothesized that plasma amphiregulin is a prognostic biomarker of chronic kidney disease (CKD) progression and adverse outcomes in patients with CKD. In the present study, we investigated whether plasma amphiregulin levels are associated with greater risks of future kidney failure and mortality in a cohort of individuals with CKD.

METHODS

We measured serum amphiregulin levels in 1,250 individuals enrolled in the Chronic Renal Insufficiency Cohort (CRIC), a prospective, observational cohort study of patients with CKD, using immunoassay.[4] Multivariable-adjusted Cox proportional hazards models tested associations between serum amphiregulin levels and the primary outcome of progression to kidney failure, defined as initiation of kidney replacement therapy (dialysis or kidney transplantation), and the secondary outcome of death.[5] Details on the study cohort and statistical analysis are provided in Fig S1 and the Supplemental Methods.

RESULTS

The baseline characteristics of the 1,250 CRIC Study participants by quintiles of serum amphiregulin levels are shown in Table S1. The median (Q1-Q3) serum amphiregulin levels was 5.3 (2.5-37.6) pg/mL. The mean age was 60 ± 11 years, and the mean estimated glomerular filtration rate (eGFR) was 44 ± 17 mL/min/1.73m^2. Participants in the lowest quintile of serum amphiregulin level had a higher eGFR. Serum amphiregulin levels had a negative correlation with eGFR ($r = -0.08$ and $P = 0.003$). The correlation with proteinuria ($r = 0.02$ and $P = 0.38$) did not reach statistical significance (Fig S2). During a median follow-up time of 11.2 and 13.6 years, 373 participants progressed to kidney failure and 514 participants died, respectively. Fig 1 and Table S2 show multivariable-adjusted associations of serum amphiregulin levels with future kidney failure and death. In unadjusted models, individuals in the second to fifth quintiles of serum amphiregulin levels had a higher risk of developing kidney failure than individuals in the first quintile (Table S2). However, these associations were attenuated and no longer statistically significant after further adjustment for clinical characteristics, including eGFR (Fig 1A; Table S2).

In fully adjusted models, individuals with amphiregulin levels in the second to fourth quintiles had a higher risk of death than those in the lowest quintile. However, this increased risk was not observed when comparing individuals in the highest quintile (fifth) with those in the lowest (first) (Table S2). Using restricted cubic splines, we observed that the association between serum amphiregulin levels and the risk of death did not demonstrate a linear relationship or clear threshold effect (Fig 1B).

DISCUSSION

This study investigated the relationship between serum amphiregulin levels and kidney health outcomes in 1,250 participants from the CRIC Study. Our findings suggest that serum amphiregulin levels in the CRIC cohort did not demonstrate a consistent association with future kidney failure and death after multivariable adjustment including kidney function.

Amphiregulin has been recognized for its diverse roles in various biological processes such as development and differentiation as well as tissue repair, inflammation, and fibrosis.[1-3,6-8] Recent studies in rodent models of injury-induced kidney fibrosis have demonstrated amphiregulin's profibrotic effects through amplifying EGF receptor signaling[1] and demonstrated that silencing amphiregulin can ameliorate kidney fibrosis.[3] In the setting of inflammatory kidney diseases, a study in rodent models demonstrated that amphiregulin exacerbates glomerulonephritis by activating myeloid cells.[2] However, its role is not singularly pathogenic; in both murine and human lupus nephritis, amphiregulin has been shown to be overexpressed and activates proinflammatory monocytes/macrophages while simultaneously downregulating pathogenic CD4$^+$ T cell responses, resulting in an overall anti-inflammatory and reno-protective effect in lupus nephritis.[6] Similar to our study, a study of individuals with CKD found that serum amphiregulin levels correlated negatively with eGFR.[9] In the latter study, there was no statistically significant correlation with ΔeGFR after 3 years of follow-up.[9]

Our study did not establish serum amphiregulin levels as an effective biomarker for adverse kidney outcomes. This could be attributed to the dualistic role of amphiregulin in kidney pathology, in which it may exhibit protective effects depending on the specific disease condition. It is possible that the differential expression and role of amphiregulin in urine, as opposed to its serum levels, could offer a more direct insight into kidney-specific processes, potentially providing a better performing biomarker of kidney health and disease progression. In addition, although our study leveraged a large cohort for biomarker measurements, we cannot exclude that unmeasured confounding factors have influenced our results.

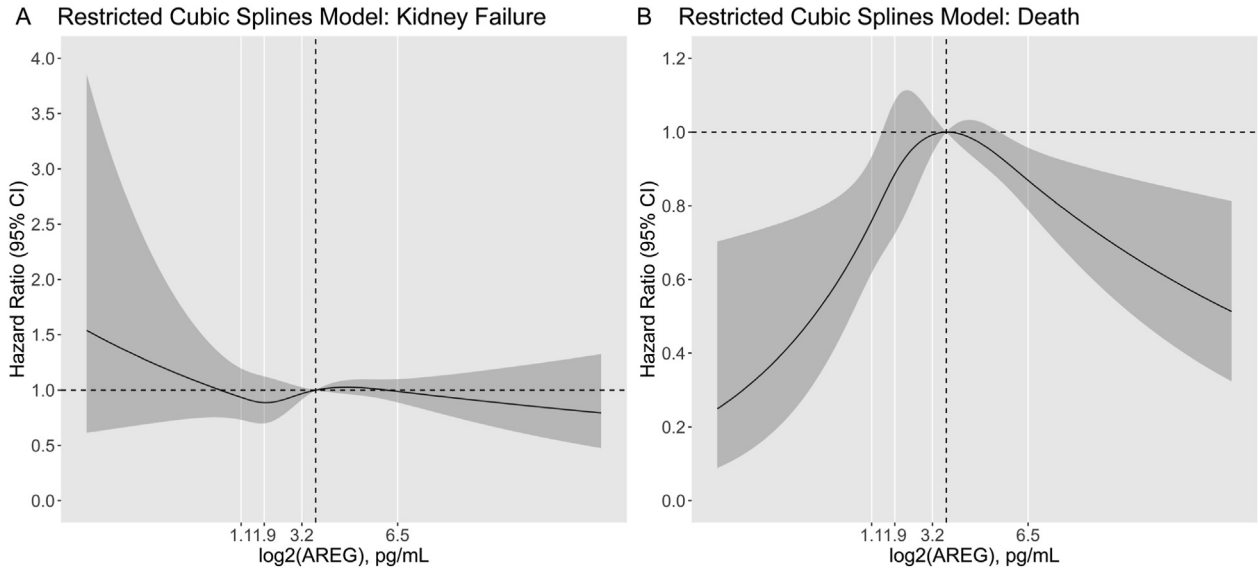

Figure 1. Association of serum amphiregulin levels with kidney failure (A) and death (B) in individuals with CKD. Restricted cubic spline model reflects multivariable-adjusted model for age, sex, Black race, study center, proteinuria, eGFR, diabetes, systolic blood pressure, use of angiotensin converting enzyme inhibitor/angiotensin-II receptor blocker, body mass index, history of cardiovascular disease, and education. Abbreviations: AREG, amphiregulin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Item S1: Supplemental Methods.

Figure S1: Selection of CRIC Study participants.

Figure S2: Spearman correlation coefficients between serum amphiregulin, kidney function, and proteinuria.

Table S1: Baseline Characteristics of CRIC Study Participants by Quintiles of Serum Amphiregulin.

Table S2: Serum Amphiregulin and the Risks of Adverse Clinical Outcomes in the CRIC Study.

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