ORIGINAL ARTICLE

Relations of established aging biomarkers (IL-6, D-dimer, s-VCAM) to glomerular filtration rate and mortality in community-dwelling elderly adults

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Abstract

Background: Biomarkers improving risk prediction for elderly populations with chronic kidney disease (CKD), an independent predictor of mortality, could be particularly useful. We previously observed that interleukin-6 (IL-6), D-dimer and soluble vascular adhesion molecule (s-VCAM) were independent biomarkers of mortality in elderly individuals. Therefore, we investigated whether these established biomarkers were independently associated with both estimated glomerular filtration rate (eGFR) and mortality.

Methods: The Established Populations for Epidemiologic Studies of the Elderly (EPESE) is a longitudinal cohort of community-dwelling elderly individuals. We investigated the association among eGFR, the biomarkers (IL-6, D-dimer and s-VCAM) and 4-year all-cause mortality using restricted cubic splines within Cox proportional hazards models.

Results: Among 1907 participants in EPESE, 1342 had available creatinine and biomarker measures. Incidence of all-cause mortality was 21.6%. eGFR was associated with all-cause mortality ($P < 0.01$); individuals at the lowest ($<30 \text{ mL/min/1.73 m}^2$) levels had the highest mortality rates. D-dimer and s-VCAM were associated ($P < 0.01$) with mortality, and after adjustment for IL-6, D-dimer and s-VCAM, the mortality risk varied by eGFR level.

Conclusions: In community-dwelling elderly individuals, we observed an association among eGFR, 4-year mortality and IL-6, D-dimer and s-VCAM. eGFR was independently associated with mortality, and the relation between eGFR and mortality was modified by IL-6, D-dimer and s-VCAM, which was most notable in individuals with severely reduced eGFR. These findings suggest that IL-6, D-dimer and s-VCAM may be useful biomarkers for improving risk prediction, but further studies are needed examining the role of these biomarkers in elderly individuals with CKD.

Introduction

In elderly populations, chronic kidney disease (CKD) is highly prevalent [1–4]. It is most commonly manifested as reduced estimated glomerular filtration rate (eGFR) [3, 4]. For elderly individuals, in addition to being an independent risk factor for cardiovascular mortality, reduced eGFR is associated with lower functional status, poorer quality of life and cognitive decline [5–7]. However, despite the increased morbidity and mortality associated with reduced eGFR, traditional Framingham risk factors are poorly predictive in CKD populations. Further, interventions mitigating the risks associated with reduced eGFR have been limited [8–10].

Not only are elderly individuals at increased cardiovascular risk, but as a manifestation of loss of nephron mass, eGFR declines with age [11]. Differentiating these age-related changes from pathologic changes, which portend future morbidity and mortality, is particularly challenging [11]. In order to improve risk prediction and identify potentially modifiable pathways for individuals with CKD, identifying biomarkers related to eGFR and mortality would be especially useful [12, 13].

The Established Populations for Epidemiologic Studies of the Elderly (EPESE) is a longitudinal epidemiology assessment of community-dwelling elderly adults established in 1986. Based on previous work by us and others [14–18], we hypothesized that in this population the biomarkers interleukin-6 (IL-6), D-dimer and soluble vascular adhesion molecule (s-VCAM) would be independently associated with both eGFR and mortality. These three biomarkers of inflammatory, coagulation and endothelial dyshomeostasis associate with mortality in elderly populations [14–16] and are known to be elevated in individuals with CKD [17, 18]. However, their role in elderly individuals with CKD is unclear, especially as they pertain to mortality risk.

Materials and methods

Population and measures

We have previously reported participant criteria and assessments performed as part of the EPESE Study–Duke [14, 19–21]. Briefly, demographics, including age, sex, race and education, were collected at enrollment. The current analyses focused on biomarkers and measures of kidney function from blood obtained at the third in-person interview, which occurred in 1996. Concurrent measures included anthropometrics, physical functional status, cognitive status, depression, self-rated health, self-reported sleep problems, smoking, alcohol use (≥ 2 drinks per week) and self-reported diagnoses of cancer, heart attack, stroke, diabetes and hypertension [22–27].

Biomarker analyses

IL-6, D-dimer and s-VCAM plasma concentrations were determined using enzyme-linked immunoassays (Quantikine, R&D Systems, Minneapolis, MN, USA; Dimertest Tripwell EIA kit, American Diagnostic Corp., Greenwich, CT, USA). We have previously reported the detailed methods of determining IL-6, D-dimer and s-VCAM plasma concentrations [14, 20, 21].

Statistical analyses

Baseline data were summarized by counts and percentages, means and standard deviation (SD), or medians and interquartile ranges (IQR). We estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation [28]. We investigated the association between eGFR and 4-year all-cause mortality using restricted cubic splines within Cox proportional hazards models; proportionality assumptions were tested and met for each. Analyses were controlled for age, sex, race, education, body mass index (BMI), functional status (Rosow–Breslau), cognitive status, sleep difficulties, current smoking, alcohol use, depression, self-rated health and self-reported history of cancer, heart attack, stroke, diabetes or hypertension. In the fully-adjusted model, we also controlled for the following biomarkers: IL-6, D-dimer and s-VCAM. Biomarker variables (s-VCAM, IL-6 and D-dimer) were log-transformed to approximate a normal distribution prior to modeling. Interactions of eGFR with age, sex, race and BMI were tested in restricted cubic spline models. Statistical significance was assessed using an omnibus goodness-of-fit test. To assess the potential impact of baseline medications, we conducted a sensitivity analysis including drug class in the fully-adjusted model, and we examined for a significant difference in overall effect using maximum likelihood estimates and a Wald test. Drug classes included in the model were antihypertensive medications, nonsteroidal anti-inflammatory drugs, cholesterol-lowering medications, antiplatelet medications and diabetes medications.

We used SAS PROC PHREG for all models analyses and SAS PROC CORR for the correlation analyses between the biomarkers s-VCAM, IL-6 and D-dimer, and eGFR. For missing data, we excluded individuals without available creatinine. We imputed the mode for categorical variables, the median for ordinal variables and the mean for continuous variables. The maximum number of missing values for a single variable in this group was 52 for baseline function assessed using the Nagi scale.

Results

Baseline characteristics

Among the 1907 participants enrolled and followed in the EPESE Study between the years 1992 and 1996, 1551 had biomarker measurements, 1342 (86.5%) of whom also had serum creatinine available to estimate GFR (Table 1). The mean age was 77.9 years (SD 5.3), and the majority (63%) were women. The functional status of the study population was poor overall (mean Katz score 0.3, Rosow–Breslau score 1.0 and Nagi score 1.3). Self-reported comorbidities were common, especially coronary disease (22.6%), diabetes (24.0%) and hypertension (72.1%). Median eGFR was 48.2 mL/min/1.73 m^2 (IQR 16.6). In all, 75 (5.6%) participants had an eGFR <30 mL/min/1.73 m^2, 1009 (75.5%) had an eGFR 30–59 mL/min/1.73 m^2, 251 (18.7%) had an eGFR 60–89 mL/min/1.73 m^2 and 7 (0.05%) participants had an eGFR ≥ 90 mL/min/1.73 m^2.

For each covariate, we compared those included in our analyses with participants in the EPESE Study excluded due to missing creatinine. Our study sample had significantly more women (84% versus 63%; P < 0.01), participants who were less likely to self-report stroke (6% versus 13%; P < 0.01) or hypertension (64% versus 72%; P = 0.01) and participants with lower mean s-VCAM levels (12.9% versus 13.1%; P = 0.01). We observed no significant

Table 1. Baseline characteristics

| Variable | Overall (n = 1342) | eGFR (mL/min/1.73 m^2) | | | | | |
		<15 (n = 10)	15–29 (n = 65)	30–44 (n = 418)	45–59 (n = 591)	60–89 (n = 252)	≥90 (n = 6)
Age, years (mean, SD)	77.9 (5.3)	76.4 (3.2)	81.3 (5.4)	79.5 (5.6)	77.2 (5.0)	76.3 (4.6)	77.2 (2.4)
Gender (% women)	63.0	90.0	78.5	78.9	58.5	42.1	66.7
Race (% Caucasian)	46.7	20.0	46.1	53.8	41.4	49.6	0.0
Education—highest grade completed (mean, SD)	8.9 (4.1)	6.7 (4.8)	8.7 (4.1)	8.9 (3.8)	8.9 (4.1)	8.9 (4.3)	8.8 (4.4)
Katz mean score (SD)	0.3 (0.9)	−1.3 (4.3)	0.1 (3.6)	0.6 (4.9)	−0.2 (4.1)	−0.1 (5.2)	−1.3 (5.5)
Rosow–Breslau mean score (SD)	1.0 (1.1)	2.2 (0.9)	1.6 (1.1)	1.3 (1.2)	0.8 (1.1)	0.8 (1.1)	0.8 (1.2)
Cognitive status—SPMSQ mean score (SD)	1.7 (1.8)	2.1 (1.3)	2.0 (1.5)	1.8 (1.9)	1.7 (1.8)	1.4 (1.5)	2.3 (2.0)
CES-D depression mean score (SD)	2.8 (3.4)	3.8 (4.5)	3.4 (4.1)	3.2 (3.6)	2.6 (3.2)	2.3 (3.3)	3.2 (4.9)
Self-reported comorbidities (%)							
Cancer	17.9	0.0	23.1	20.8	17.8	13.1	0.0
Stroke	13.0	50.0	10.8	16.0	11.6	10.3	16.7
Diabetes	24.0	60.0	27.7	29.1	22.3	16.7	33.3
Hypertension	72.1	90.0	90.8	78.5	70.6	59.9	50.0
Alcohol use (% endorsing ≥2 drinks per week)	24.4	0.0	24.6	16.5	25.5	37.7	0.0
Current smoker	12.0	40.0	7.7	6.5	13.5	15.5	0.0
Biomarkers							
s-VCAM-1 (ng/dL)	14.4 (2.6)	19.6 (4.6)	16.2 (2.2)	14.8 (2.6)	14.2 (2.6)	13.8 (2.5)	15.0 (3.1)
IL-6 (pg/mL)	0.67 (0.6)	0.82 (0.5)	0.9 (0.8)	0.7 (0.6)	0.6 (0.7)	0.6 (0.5)	0.7 (0.5)
D-dimer (μg/L)	3.9 (1.5)	5.3 (2.5)	4.8 (1.9)	4.2 (1.6)	3.8 (1.4)	3.8 (1.3)	4.0 (1.5)

CES-D, Center for Epidemiologic Studies–Depression Scale (modified version); SPMSQ, Short Portable Mental Status Questionnaire.

Table 2. Model-predicted hazard ratios for 4-year all-cause mortality (n = 1342)

	Crude HR (Model 1)	Adjusted HR[a] (Model 2)	Fully-adjusted HR[b] (Model 3)
Biomarkers			
s-VCAM, pg/mL (log)	–	–	1.18
D-dimer, μg/L (log)	–	–	1.23
IL-6, pg/mL (log)	–	–	1.07
eGFR (mL/min/1.73 m^2)			
90	1.71	1.94	2.33
70	1.17	1.08	1.20
60	1.01	0.86	0.92
45	Ref	Ref	Ref
30	1.60	1.43	1.26
15	4.03	2.74	2.11

[a]Adjusted for age, sex, race, education, BMI, Rosow–Breslau, cognitive function, depression, self-rating of health, cancer, heart attack, stroke, diabetes, hypertension, sleeping difficulties, smoking and alcohol use.
[b]Adjusted for all covariates from Model 2 plus all three biomarkers (IL-6, D-dimer and s-VCAM).

difference in age, functional status, cognitive status, mean D-dimer or mean IL-6 plasma concentrations (P > 0.05 for all). Controlling for the covariates in our Cox model, the mortality hazard in those with missing eGFR measurements did not differ from those with eGFR measurements included in our analyses.

Association between biomarkers and 4-year mortality

Baseline measures of s-VCAM and D-dimer were independently associated with incident 4-year mortality in adjusted models (Table 2). Across the study population, a 1 SD increase in log-s-VCAM concentrations was associated with an 18% increase in mortality [hazard ratio (HR) 1.18, 95% confidence interval (CI) 1.01–1.39], and a 1 SD increase in log D-dimer concentrations increased the risk of mortality by 23% (HR 1.23, 95% CI 1.09–1.40). Although a 1 SD increase in log IL-6 concentrations was not significantly related to mortality in our study population (HR 1.07, 95% CI 0.95–1.19), this relationship was stronger and significant (HR 1.13, 95% CI 1.03–1.25) in a sensitivity analysis including all individuals with and without serum creatinine (n = 1551).

Association between eGFR and 4-year mortality

Over a 4-year period, the incidence of all-cause mortality was 21.6%. Individuals with an eGFR of 60–89 mL/min/1.73 m^2 experienced the lowest death rate (17.9%), while individuals with severely reduced eGFR (<15 mL/min/1.73 m^2) experienced the greatest mortality (70.2%) (Table 3). In unadjusted (Model 1) and adjusted (Model 2) Cox proportional hazard models, eGFR was independently associated with mortality at 4-years follow-up (P < 0.01 for both) (Table 2). The relationship between eGFR and 4-years mortality was nonlinear, with the mortality risk being the greatest at lowest and greatest eGFRs (Figure 1). The association was most significant at eGFR levels ≤30 mL/min/1.73 m^2 and ≥70 mL/min/1.73 m^2. In the adjusted model (Model 2), participants with a baseline eGFR of 15 mL/min/1.73 m^2 had a 174% increased mortality risk (HR 2.74). Similarly, participants with a baseline eGFR 90 mL/min/1.73 m^2 had a 94% increased mortality risk (HR 1.94) (Figure 1). Sensitivity analyses demonstrated no significant difference in the association between eGFR and mortality when baseline medications were included in the model (P = 0.21).

In EPESE, eGFR was negatively correlated with all three biomarkers: s-VCAM (R = −0.18; P < 0.01), IL-6 (R = −0.12; P < 0.01) and D-dimer (R = 0.16; P < 0.01). When we included all three biomarkers, s-VCAM, IL-6 and D-dimer, in the fully-adjusted Cox model (Model 3), eGFR remained independently associated with mortality (P = 0.02). However, the change in the mortality risk varied by level of eGFR: at lower levels of eGFR the mortality risk was reduced and at greater levels of eGFR the mortality risk was

Table 3. Absolute incidence for 4-year mortality, by level of eGFR

	Events (n)	Incidence (%)
eGFR (mL/min/1.73 m^2)		
≥90	2	2/6 (33.3)
60–89	45	45/252 (17.9)
45–59	111	111/591 (18.8)
30–44	94	94/418 (22.5)
15–29	31	31/65 (47.7)
<15	7	7/10 (70.0)
Overall	290	290/1342 (21.6)
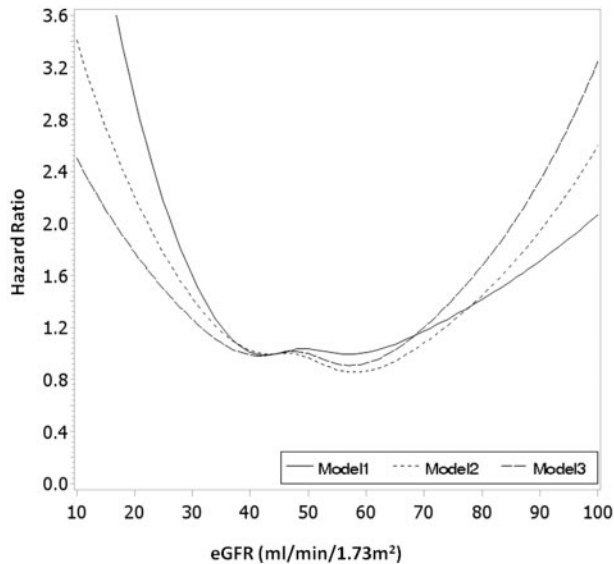
Fig. 1. Cox models demonstrating the unadjusted (Model 1), adjusted (Model 2) and fully-adjusted (Model 3) hazards ratio for the association between eGFR and 4-year all-cause mortality. Hazard ratios are relative to baseline eGFR of 45 mL/min/1.73 m^2. Model 2 includes the following covariates: age, sex, race, education, BMI, Rosow–Breslau, cognitive function, depression, self-rating of health, cancer, heart attack, stroke, diabetes, hypertension, sleeping difficulties, smoking and alcohol use. Model 3 includes all covariates from Model 2 plus all three biomarkers (IL-6, D-dimer and s-VCAM)

increased (Figure 1). At an eGFR of 30 and 15 mL/min/1.73 m^2, the HR for eGFR and mortality was reduced by 12% (HR 1.26) and 23% (HR 2.11), respectively (Table 2). On the other hand, we observed an increased mortality risk at greater levels of eGFR. At an eGFR of 70 mL/min/1.73 m^2, the HR was increased by 10% (HR 1.20), and at an eGFR of 90 mL/min/1.73 m^2 the risk was increased by 17% (HR 2.33) (Figure 1).

Discussion

Among community-based elderly adults, the biomarkers IL-6, D-dimer and s-VCAM were all negatively correlated with eGFR. In linear models, the biomarkers D-dimer and s-VCAM were independently associated with mortality. Further, the relation between eGFR and mortality was modified by the biomarkers IL-6, D-dimer and s-VCAM, and similar to other studies, both reduced and elevated levels of eGFR were associated with mortality in this elderly population [29–31]; however, our study extends these findings by demonstrating that eGFR was associated with mortality independent of IL-6, D-dimer and s-VCAM—biomarkers, which themselves have been shown to be
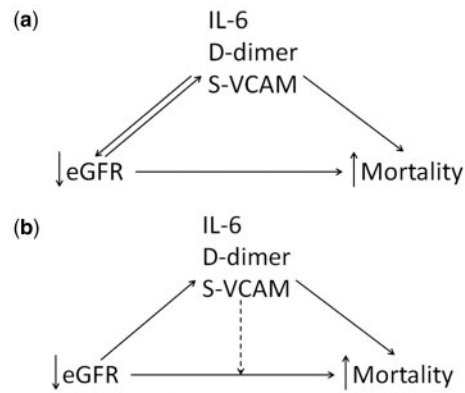

Fig. 2. The biomarkers may be mediators or confounders or the relation between eGFR and mortality (a) or they may be mediators and/or effect modifiers of the relation between eGFR and mortality (b).

independently associated with mortality in this population [14]. Nonetheless, these three biomarkers appear to modify the relation between eGFR and mortality in this elderly population: mortality risk was decreased by up to 23% among those with the most renal impairment when all three biomarkers were included in the models.

Previous studies among CKD populations have demonstrated that aggressive lipid-lowering therapies and targeting of other traditional risk factors only partially mitigate mortality risk [32, 33]. Individuals with reduced eGFR have several potential reasons for increased mortality including malnutrition, chronic inflammation, increased oxidative stress and vascular and endothelial dysfunction related to uremia and calcium-phosphorus dysregulation [34, 35]. Our findings further suggest that these nontraditional pathways may also be important for elderly populations with CKD. The risk reduction observed among those with severe kidney impairment in the presence of IL-6, D-dimer and s-VCAM—all markers of these nontraditional risk pathways—suggests that they may be important mediators of CKD and mortality.

Furthermore, CKD is associated with lower functional status, poorer quality of life and cognitive decline in the elderly [5–7]. Chronic inflammation, increased oxidative stress and vascular and endothelial dysfunction may also play roles in these associations [6, 7]. IL-6, D-dimer and s-VCAM all are associated with functional disabilities in elderly populations [15, 16, 20, 36]. Our findings suggest these biomarkers, which were negatively correlated with eGFR, may be downstream mediators of CKD in the elderly, and further investigation into the roles of IL-6, D-dimer and s-VCAM as mediators of functional decline among elderly individuals with CKD are needed.

Although we had *a priori* assumptions about the relation among the three biomarkers, eGFR and mortality, our analyses are limited in the ability to differentiate whether the biomarkers are confounders rather than mediators of the relation between eGFR and mortality (Figure 2a). Across the range of eGFR, we observed a difference in the effect of these biomarkers on the relation between eGFR and mortality. At low levels of eGFR, the biomarkers weakened the relation between eGFR and mortality while at high levels they strengthened the relation. It is plausible that IL-6, D-dimer and s-VCAM are both effect modifiers and mediators of the relation between eGFR and mortality in elderly populations (Figure 2b).

We noted a few additional limitations of our study. Due to loss of follow-up or lack of biomarker or kidney function

assessments, not all participants enrolled in EPESE were included for analysis. To reduce any possible selection bias caused by this potential differential missingness, we examined differences between participants included in our analyses and those who were excluded due to missing assessment of kidney function; we failed to observe a difference in the mortality hazard between those with and without eGFR measurements. Nonetheless, residual selection bias must still be considered. Also, caution must be used when inferring causal associations. Although there is *a priori* reason to consider that IL-6, D-dimer and s-VCAM are downstream factors related to CKD, it is plausible that in elderly individuals they are upstream factors related to CKD. Furthermore, the role of these biomarkers at very low (<15 mL/min/1.73 m^2) or high levels of eGFR (≥90 mL/min/1.73 m^2) should be interpreted with caution due to the small number of participants in our study. Finally, residual confounding by unmeasured variables remains a possibility. In particular, we did not have baseline proteinuria data available, which as a known independent risk factor for eGFR decline and cardiovascular mortality may represent an important source of confounding, and additional investigations into the causal pathways between CKD and mortality in elderly individuals are needed.

In conclusion, in a population of community-based elderly adults, we observed an association among eGFR, 4-year mortality and IL-6, D-dimer and s-VCAM. eGFR was independently associated with mortality, which was most pronounced at the low and high ends of the eGFR range. This relation between eGFR and mortality in this elderly population was modified by the biomarkers IL-6, D-dimer and s-VCAM, especially in individuals with severely reduced eGFR. These findings suggest that IL-6, D-dimer and s-VCAM may be useful biomarkers for improving risk prediction when considering kidney function as mortality risk; however, further studies examining the role of these biomarkers in elderly individuals with CKD are needed.

Funding

Conflict of interest statement

None declared.

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