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Applied nutritional investigation

Serum albumin is incrementally associated with increased mortality across varying levels of kidney function

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ABSTRACT

Objectives: Serum albumin (sAlb) may be a strong predictor of longevity in the general population and in chronic kidney disease. This study aimed to determine the relationship between sAlb concentrations and mortality risk independent of kidney function.
Methods: This was a retrospective cohort study of 31 274 adults from the 1999−2010 National Health and Nutrition Examination Survey. The estimated glomerular filtration rate (eGFR) was examined as both a confounder and modifier of the association of sAlb with mortality risk. We examined the association of sAlb (categorized as <3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, 4.6 to <4.8, and ≥4.8 g/dL) with mortality using Cox models. Subsequently, we conducted spline analyses to estimate the association of sAlb with all-cause mortality across varying eGFR levels.
Results: In unadjusted analyses, participants with incrementally lower sAlb concentrations of <4.6 g/dL had an increasingly higher mortality risk compared with those with sAlb levels ranging from 4.6 to <4.8 g/dL (reference), whereas those with higher sAlb levels of ≥4.8 g/dL had a lower mortality risk (hazard ratios [95% confidence interval]: 3.88 [3.26−4.62], 3.59 [3.01−4.27], 2.79 [2.37−3.29], 2.10 [1.79−2.48], 1.72 [1.45−2.03], and 0.71 [0.55−0.92] for sAlb concentrations of <3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, and ≥4.8 g/dL, respectively). Adjusted analyses showed similar findings, although the association of higher sAlb levels of ≥4.8 g/dL with better survival was attenuated to the null. Spline analyses showed that participants with sAlb levels of <4.6 g/dL had higher mortality across all concentrations of eGFR, ranging from 30 to 120 mL/min/1.73 m^2 (reference: sAlb ≥ 4.6 g/dL).
Conclusions: Among a nationally representative U.S. cohort, a graded association was observed between lower sAlb concentrations and higher death risk, which was robust across varying levels of kidney function.

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Introduction

Serum albumin (sAlb), a globular protein consisting of 585 amino acids and a molecular weight of 66.5 kilodaltons, is the most abundant protein in the blood and accounts for at least 75% of oncotic pressure due to its large molecular weight and negative charge. Albumin is synthesized in the liver, and released at a rate of 10 to 15 g/d into the bloodstream. sAlb is measured routinely as a core component of most metabolic panels, and provides insight into patients' nutritional, inflammatory, and overall health status.

The normal reference concentrations for sAlb typically span across a wide range of 3.5 to 5.2 g/dL, and lower concentrations of

sAlb (<3.5 g/dL) have been associated with a higher mortality risk in the general population, as well as those with a chronic disease status. Given that protein-energy wasting is a major contributor to death in patients with chronic kidney disease (CKD), low sAlb levels have been recognized as a marker of poor nutritional status and a potent predictor of death in this population.[1,2] However, the impact of sAlb within so-called normal ranges (>3.5 g/dL) on the health and survival of the general population as well as those with CKD has not been well studied, as prior studies are limited by a lack of granular examination of sAlb concentrations and nonconsideration of kidney function as a potential confounder [1,2]. Furthermore, no studies have examined the relationship between sAlb and mortality risk across varying levels of estimated glomerular filtration rates (eGFRs).

Hence, to address this knowledge gap, we sought to test the hypothesis that lower sAlb concentrations, even within purportedly normal ranges of >3.5 g/dL, are associated with a higher mortality risk independent of kidney function. Using data from the 1999−2010 continuous National Health and Nutrition Examination Survey (NHANES), we examined the granular concentrations of sAlb with survival in the overall cohort, as well as across varying levels of kidney function.

Methods

Source cohort

We conducted a retrospective cohort study to examine data from the 1999−2010 continuous NHANES population. The purpose of NHANES is to assess the nutritional status, health behaviors, and health status of U.S. noninstitutionalized civilians [3]. Data from participants enrolled in the continuous NHANES cohort were released in 2-y cycles. From 1999 to 2006, oversampled populations included elderly, adolescent, Mexican-American, non-Hispanic Black, and low-income persons. From 2007 to 2010, oversampled populations included those of elderly, Hispanic, and low-income backgrounds [3].

To select a study cohort representative of the U.S. noninstitutionalized civilian population, a complex, multistage probability design was used. Within each 2-y cycle, approximately 12 000 persons were asked to participate. Potential households were sent letters in the mail as notification of selection into the study. Initial interviews were conducted at the participants' home. The first interview served as a screening tool to determine whether any or all household members were eligible to continue participation. If household members were approved for participation, three additional interviews were conducted, including family, sample participant, and relationship questionnaires. After the home-based interviews, participants were requested to undergo clinical laboratory tests, physical examinations, and nutrition-related interviews located at mobile examination centers [3].

Patients were included provided they were age ≥18 y, had available sAlb data, and did not have missing mortality data. Patients with underlying liver disease and nutritional disorders were retained in the cohort to preserve generalizability.

Exposure ascertainment

We examined the association of sAlb with all-cause mortality in the overall cohort, as well as across varying levels of kidney function. Our primary exposure of interest was sAlb concentration. Within the continuous NHANES cohort, sAlb concentration was measured using the DcX800 method with Bromcresol Purple reagent [3]. We first examined baseline sAlb concentrations

categorized as <3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, 4.6 to <4.8, and ≥4.8 g/dL. Subsequently, we examined continuous sAlb concentrations using restricted cubic spline analyses.

We also examined eGFR as both a key confounder and modifier of the association of sAlb concentrations with mortality risk. The concentration of serum creatinine was established using the Jaffe rate method (kinetic alkaline picrate) [3]. To adjust for errors in the 1999−2000 cohort creatinine measurements, Deming regression was used as follows: Standard creatinine (Y) = 1.013 × NHANES creatinine (X) + 0.147 (r = 0.984) [3]. In the 2005−2006 cohort creatinine measurements, the following equation was used to adjust for errors: Standard creatinine (mg/dL) = −0.016 + 0.978 × (NHANES 05-06 uncalibrated serum creatinine, mg/dL) [3]. The Chronic Kidney Disease Epidemiology Collaboration equation was used for eGFR [4].

Outcome ascertainment

All-cause mortality was the primary outcome of interest. Mortality data were obtained through the National Center for Health Statistics Public-Use Linked Mortality Files [5]. Mortality data were collected from the date of NHANES participation through December 31, 2011. Participant at-risk time began the day after sAlb measurement and ended at death or the end of the follow-up period.

Statistical analyses

Participants' baseline characteristics were summarized using means ± standard deviations (SDs) and proportions according to sAlb category (<4.2, 4.2 to <4.6, and ≥4.6 g/dL) and eGFR (<60, 60 to <90, and ≥90 mL/min/1.73 m^2). Kaplan-Meier plots and log-rank testing were first conducted to ascertain unadjusted associations between sAlb concentrations and mortality. Participants were defined to be at risk of death from the day after sAlb measurement until death or the end of the follow-up period. sAlb concentrations were divided into seven categories (<3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, 4.6 to <4.8, and ≥4.8 g/dL) to evaluate the association between sAlb concentrations and all-cause mortality using 4.6 to <4.8 g/dL as the reference group. Associations of sAlb concentrations with all-cause mortality risk were examined using the following levels of adjustment [6]: Unadjusted model (including sAlb concentration); case-mix adjusted model (including covariates in the unadjusted model, as well as age, sex, race/ethnicity, level of education, diabetes, smoking status, systolic blood pressure, and serum total cholesterol level); and case-mix + eGFR adjusted model (including covariates in the case-mix model, as well as eGFR).

We defined the case-mix adjusted model a priori as our primary model, which included potential confounders of the sAlb-mortality association. We designated the case-mix + eGFR adjusted model as an exploratory model because eGFR may be interpreted as a potential confounder versus intermediate of the sAlb-mortality relationship (i.e., in terms of the former, kidney dysfunction may influence appetite and thereby influence nutritional/protein intake; in terms of the latter, higher protein intake may lead to kidney function deterioration in the context of CKD). sAlb is also a marker of inflammation (i.e., negative acute phase reactant); thus, we also implemented sensitivity analyses in which we incrementally adjusted for C-reactive protein (CRP) using case-mix + eGFR + CRP adjusted models.

Subgroup analyses were conducted to explore associations of lower (<4.6 g/dL) versus higher sAlb concentrations (≥4.6 g/dL) with all-cause mortality across strata of selected subgroups including age (<46 versus ≥46 y), sex (male versus female), race/

ethnicity (non-Hispanic White versus non-Hispanic Black versus Hispanic), self-reported diabetes status (diabetic versus borderline diabetic versus nondiabetic, in response to the question "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"), smoking status (nonsmoking versus every day versus some days), systolic blood pressure (<120 versus ≥120 mm Hg), total cholesterol level (<200 versus ≥200 mg/dL), and eGFR (<60 versus 60 to <90 versus ≥90 mL/min/1.73 m^2).

We also examined the differential association of high (≥ 4.6 mg/dL) versus low (<4.6 g/dL) sAlb concentration with all-cause mortality across varying eGFR levels examined as a continuous variable. Three restricted cubic spline functions were created for eGFR with four knots at the 5th, 35th, 65th, and 95th percentiles. Subsequently, we included the dichotomized sAlb variable, spline functions of eGFR, and their interaction terms in the Cox model along with the aforementioned covariates. Hazard ratios (HRs) of high versus low sAlb at a given eGFR level were estimated as follows: HR of high serum albumin = $\beta_{alb} + \beta_1 \times SP_1 + \beta_2 \times SP_2 + \beta_3 \times SP_3$, where SP_1, SP_2, and SP_3 are values of spline functions at a given eGFR, respectively; β_{alb} is the coefficient of the dichotomized sAlb concentration; and β_1, β_2, and β_3 are the coefficients of the interaction terms of SP_1, SP_2, and SP_3 with the dichotomized sAlb concentration, respectively.

Imputation by means was used to account for missing data. Total cholesterol had <0.01% (n = 3) missing values, whereas systolic blood pressure had 54.7% (n = 17 122) missing values. All other covariates had complete data. Spline analyses were conducted using Stata, version 13.1 (Stata Corp., College Station, TX). All other analyses were carried out using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Study population

After applying eligibility criteria, the final study cohort was composed of 31 274 participants (Fig. 1), among whom 11 384 participants had sAlb concentrations of <4.2 g/dL, 13 834 participants had sAlb concentrations of 4.2 to 4.6 g/dL, and 6056 participants had sAlb concentrations of >4.6 g/dL. The mean ± SD and median

sAlb concentrations of the overall cohort were 4.2 ± 0.4 g/dL and 4.3 g/dL, respectively. Baseline characteristics stratified by sAlb category are shown in Table 1.

Compared with participants with lower sAlb concentrations (<4.2 g/dL), those with higher sAlb concentrations (≥4.6 g/dL) tended to be younger and male, had a higher prevalence of being non-Hispanic White and Hispanic and a lower prevalence of being non-Hispanic Black, were more likely to be college graduates, were more likely to be nondiabetic and less likely to be nonsmokers, had lower systolic blood pressure values, and had lower total cholesterol and higher eGFR levels. Baseline characteristics stratified by eGFR category are shown in Table 2.

Predictors of serum albumin concentration

In adjusted logistic regression analyses, significant predictors of lower sAlb concentrations (<4.6 g/dL) included older age, female sex, non-Hispanic Black race/ethnicity, and presence of diabetes (Table 3). In contrast, significant predictors of higher sAlb concentrations (≥4.6 g/dL) included Hispanic race/ethnicity and having completed a college degree.

Serum albumin concentration and mortality

In the overall cohort, a total of 2803 all-cause deaths were observed. The median follow-up time was 73 months (interquartile range, 39−112 months). In the unadjusted analyses, we observed that incrementally lower sAlb concentrations of <4.6 g/dL were associated with a higher death risk (reference: 4.6 to <4.8 g/dL), whereas higher sAlb concentrations of ≥4.8 g/dL were associated with a lower death risk (HR [95% confidence interval]: 3.88 [3.26−4.62]; 3.59 [3.01−4.27], 2.79 [2.37−3.29], 2.10 [1.79−2.48], 1.72 [1.45−2.03], and 0.71 [0.55−0.92] for sAlb concentrations of <3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, and ≥4.6 g/dL, respectively; Fig. 2A and Table 4).

After adjustment for case-mix covariates, we again observed that sAlb concentrations of <4.6 g/dL were associated with a higher death risk; however, associations of higher sAlb concentrations (≥4.8 g/dL) with lower mortality were attenuated to the null (adjusted HR [95% confidence interval]: 3.53 [2.04−4.23], 1.90
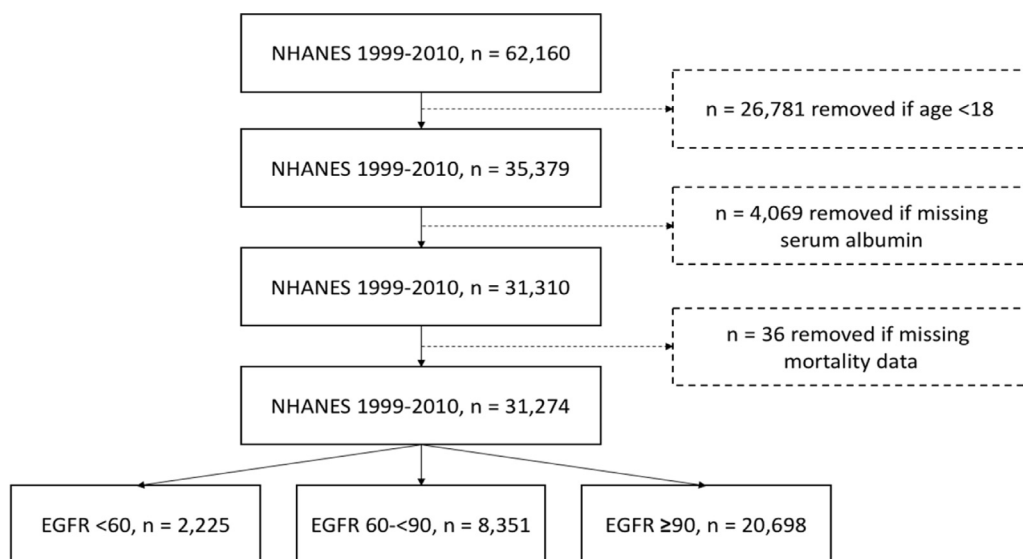

Fig. 1. Study flow chart

Table 1
Baseline characteristics of National Health and Nutrition Examination Survey participants (N = 31 274) according to serum albumin categories

	Serum albumin (g/dL)				
	Total	<4.2	4.2−4.6	≥4.6	P
n (%)	31 274	11 384 (36.4)	13 834 (44.2)	6056 (19.4)	
Age, y (mean + SD)	48 ± 20	51 ± 20	48 ± 19	39 ± 18	< 0.001
Female sex (%)	52	68	48	29	< 0.001
Race (%)	48	45	49	50	< 0.001
Non-Hispanic White	20	26	18	12	
Non-Hispanic Black	28	26	28	33	
Hispanic	4	4	4	5	
Other					
Education (%)	13	14	13	11	< 0.001
<9th grade	19	19	18	19	
9−11th grade	24	24	24	26	
High school/GED	26	27	26	25	
Some college	18	16	18	19	
College graduate	< 0.1	< 0.1	< 0.1	< 0.1	
Refused	< 0.1	< 0.1	< 0.1	< 0.1	
Unknown					
Smoking status (%)	17	17	17	17	< 0.001
Every day	3	3	3	5	
Some days	24	25	25	19	
Not at all					
Diabetes (%)	10	14	9	6	< 0.001
Systolic BP, mm Hg (mean ± SD)	124 ± 21	126 ± 23	125 ± 21	121 ± 17	< 0.001
Total cholesterol, mg/dL (mean ± SD)	197 ± 43	197 ± 45	198 ± 42	194 ± 43	0.005
eGFR, mL/min/1.73 m^2 (mean ± SD)	97 ± 26	95 ± 29	96 ± 24	105 ± 23	< 0.001

BP, blood pressure; eGFR, estimated glomerular filtration rate; GED, general education development; SD, standard deviation

Table 2
Baseline characteristics of National Health and Nutrition Examination Survey participants (N = 31 274) according to baseline eGFR category

	eGFR mL/min/1.73 m^2				
	Total	< 60	60 - <90	≥ 90	P-value
n (%)	31 274	2681 (8.6)	8923 (28.5)	19670 (62.9)	
Age, y (mean + SD)	48 ± 20	74 ± 10	61 ± 15	38 ± 15	< 0.001
Female sex (%)	52	53	47	54	< 0.001
Race (%)					< 0.001
Hispanic	28	13	19	35	
Non-Hispanic White	48	67	62	39	
Non-Hispanic Black	20	17	15	22	
Other	4	3	4	5	
Education (%)					0.38
<9th grade	13	20	14	12	
9−11th grade	19	17	14	21	
High school/GED	24	25	24	24	
Some college	26	21	26	27	
College graduate	18	16	22	16	
Refused	0.05	0.22	0.04	0.03	
Unknown	0.11	0.19	0.17	0.07	
Smoking status (%)					< 0.001
Every day	17	8	14	19	
Some days	3	1	2	4	
Not at all	24	41	34	17	
Diabetes (%)	10	26	13	6	< 0.001
Systolic BP, mmHG (mean ± SD)	124 ± 21	141 ± 26	132 ± 22	119 ± 17	< 0.001
Total cholesterol, mg/dL (mean ± SD)	197 ± 43	195 ± 46	203 ± 42	194 ± 43	< 0.001
Serum albumin concentration, g/dL (mean ± SD)	4.24 ± 0.38	4.09 ± 0.36	4.23 ± 0.31	4.27 ± 0.40	< 0.001
Proportion with albumin <4.2 g/dL	36	53	38	33	
Proportion with albumin ≥4.6 g/dL	19	7	14	23	

BP, blood pressure; eGFR, estimated glomerular filtration rate; GED, General Education Development; SD, standard deviation

[1.59−2.27], 1.55 [1.31−1.83], 1.33 [1.12−1.56], 1.27 [1.07−1.51], and 1.19 [0.93−1.54] for sAlb concentrations of <3.8, 3.8 to <4.0, 4.0 to <4.2, 4.2 to <4.4, 4.4 to <4.6, and ≥4.6 g/dL, respectively; Fig. 2B and Table 4). A similar pattern of findings was observed in case-mix + eGFR and case-mix + eGFR + CRP adjusted analyses (Fig. 2C and Table 4).

Subgroup analyses

In the unadjusted analyses, we observed that sAlb concentrations of <4.6 g/dL were associated with a higher mortality risk across all subgroups, except for nonsmokers (reference: sAlb ≥ 4.6 g/dL; Fig. 3A and Table 5).

Table 3
Logistic regression analyses of predictors of serum albumin concentrations of <4.6 g/dL (reference: ≥4.6 g/dL) among National Health and Nutrition Examination Survey participants (N = 31 274).

Variable	Unadjusted			Adjusted		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age, y (per 10 y)	1.34	1.32−1.37	< 0.001	1.39	1.35−1.43	< 0.001
Female sex (vs. male)	3.33	3.13−3.54	< 0.001	3.97	3.63−4.35	< 0.001
Race (%)						
Non-Hispanic White	Ref			Ref		
Hispanic	0.88	0.82−0.93	< 0.001	0.85	0.77−0.95	< 0.001
Non-Hispanic Black	1.90	1.74−2.07	< 0.001	2.39	2.09−2.73	< 0.001
Other	0.86	0.75−0.98	< 0.001	1.15	0.92−1.44	0.38
Education (%)						
Some college	Ref			Ref		
<9th grade	1.26	1.14−1.39	0.01	1.04	0.89−1.22	0.42
9−11th grade	0.93	0.85−1.01	0.92	1	0.88−1.14	0.54
High school graduate/GED	0.94	0.87−1.02	0.99	1.04	0.93−1.17	0.41
College graduate	0.89	0.81−0.97	0.60	0.87	0.77−1.00	0.96
Smoking status (%)						
Never smoked	Ref			Ref		
Every day	0.79	0.72−0.86	0.09	1	0.87−1.15	0.06
Some days	0.53	0.46−0.62	< 0.001	0.79	0.63−0.99	0.09
Diabetes	2.43	2.14−2.74	0.01	1.43	1.19−1.73	0.23
Systolic BP (per 30 mm Hg)	1.42	1.34−1.51	< 0.001	0.89	0.82−0.97	0.007
Total cholesterol (per 100 mg/dL)	1.18	1.10−1.26	< 0.001	1.02	0.92−1.12	0.75
eGFR (per 10 mL/min/1.73 m^2)	0.87	0.86−0.88	< 0.001	0.95	0.94−0.97	< 0.001

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; GED, general education development; OR, odds ratio; Ref, reference
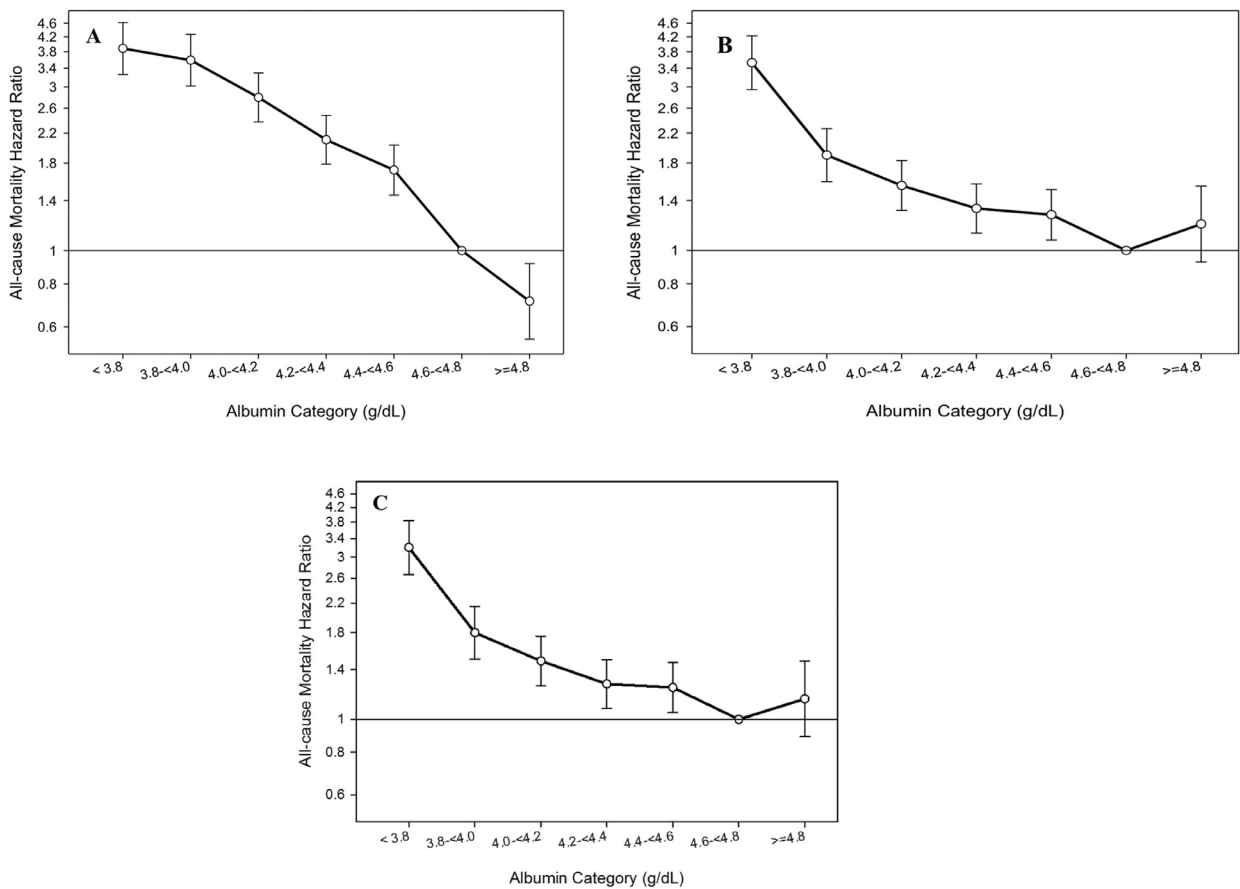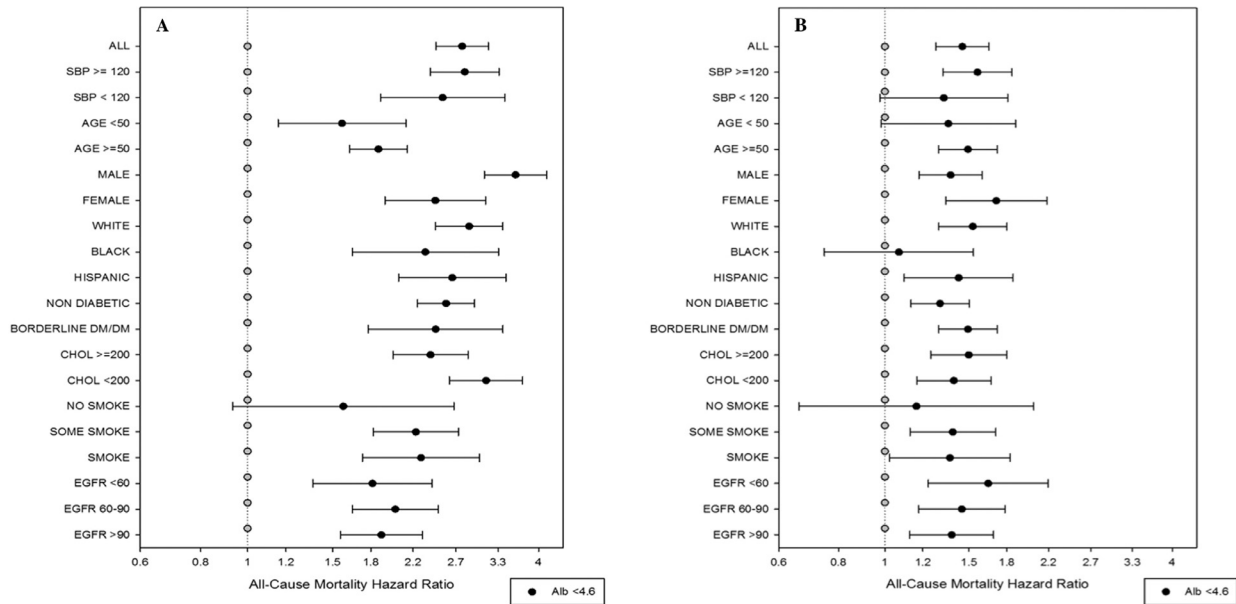

Fig. 2. Association among National Health and Nutrition Examination Survey participants (N = 31 274) between serum albumin concentrations and all-cause mortality in (A) an unadjusted model; (B) a case-mix model; and (C) a case-mix + estimated glomerular filtration rate model

Table 4
Association between sAlb and all-cause mortality in unadjusted, case-mix, and case-mix + eGFR + CRP models among National Health and Nutrition Examination Survey participants (N = 31 274)

sAlb (g/dL)	Unadjusted HR (95% CI)	Case-mix HR (95% CI)	Case-mix + eGFR HR (95% CI)	Case-mix + eGFR + CRP HR (95% CI)	No. of deaths	No. of participants
<3.8	3.88 (3.26−4.62)	3.53 (2.04−4.23)	3.20 (2.67−3.84)	2.96 (2.47−3.57)	400	2656
3.8 to <4.0	3.59 (3.01−4.27)	1.90 (1.59−2.27)	1.80 (1.51−2.15)	1.75 (1.47−2.10)	403	3133
4.0 to <4.2	2.79 (2.37−3.29)	1.55 (1.31−1.83)	1.49 (1.26−1.76)	1.46 (1.23−1.73)	596	5595
4.2 to <4.4	2.10 (1.79−2.48)	1.33 (1.12−1.56)	1.27 (1.07−1.50)	1.26 (1.06−1.48)	627	7275
4.4 to <4.6	1.72 (1.45−2.03)	1.27 (1.07−1.51)	1.24 (1.04−1.47)	1.23 (1.04−1.46)	501	6559
4.6 to <4.8	Ref	Ref	Ref	Ref	188	3864
≥4.8	0.71 (0.55−0.92)	1.19 (0.93−1.54)	1.15 (0.89−1.48)	1.15 (0.89−1.49)	88	2192

CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Ref, reference; sAlb, serum albumin

Fig. 3. (A, B) Subgroup analyses of association between serum albumin concentrations <4.6 g/dL (reference: ≥4.6 g/dL) with all-cause mortality in an unadjusted model among National Health and Nutrition Examination Survey participants (N = 31 274)

Table 5
Subgroup analyses of the association between sAlb concentration of <4.6 g/dL (Ref: ≥4.6 g/dL) with all-cause mortality in unadjusted (Panel A) and case-mix (Panel B) models among National Health and Nutrition Examination Survey participants (N = 31 274).

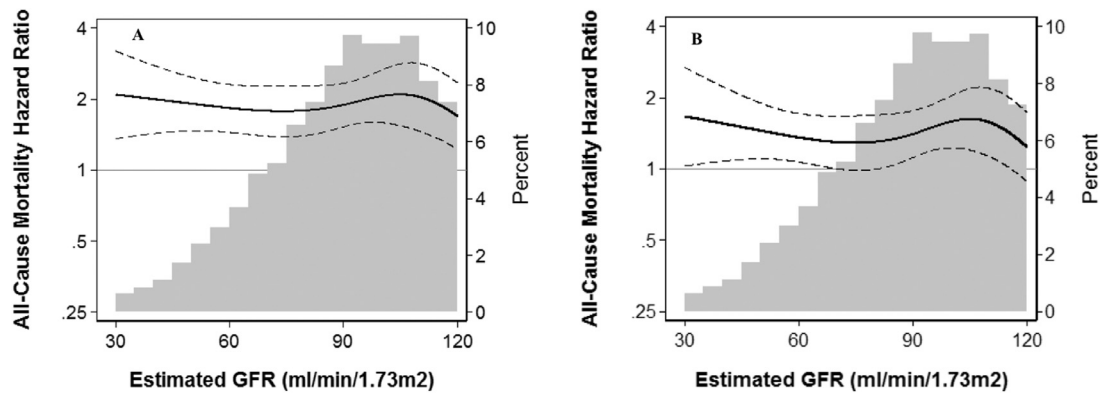|	Unadjusted		Case-mix adjusted	
	HR	95% CI	HR	95% CI
Systolic BP < 120 mm Hg	2.53	1.88−3.41	1.33	0.98−1.81
Systolic BP ≥120 mm Hg	2.81	2.39−3.31	1.56	1.32−1.85
Age ≥50 y	1.87	1.63−2.14	1.49	1.30−1.72
Age <50 y	1.57	1.16−2.13	1.36	0.98−1.88
Female sex	2.45	1.93−3.11	1.71	1.34−2.18
Male sex	3.58	3.09−4.16	1.37	1.18−1.60
Race, Hispanic	2.65	2.05−3.42	1.43	1.10−1.86
Race, Non-Hispanic Black	2.33	1.65−3.31	1.07	0.75−1.53
Race, Non-Hispanic White	2.87	2.44−3.37	1.53	1.30−1.80
Borderline diabetes/diabetes	2.45	1.78−3.38	1.49	1.30−1.72
Nondiabetic	2.58	2.25−2.95	1.30	1.13−1.50
Total cholesterol < 200 mg/dL	3.12	2.62−3.71	1.40	1.16−1.67
Total cholesterol ≥ 200 mg/dL	2.39	2.00−2.86	1.50	1.25−1.80
Smoke every day	2.29	1.73−3.02	1.37	1.02−1.83
Smoke some days	2.23	1.82−2.73	1.39	1.13−1.71
Smoke not at all	1.58	0.93−2.67	1.16	0.66−2.05
eGFR ≥ 90 mL/min/1.73 m²	1.89	1.56−2.30	1.38	1.13−1.69
eGFR 60 to <90 mL/min/1.73 m²	2.02	1.65−2.48	1.45	1.18−1.79
eGFR <60 mL/min/1.73 m²	1.81	1.37−2.41	1.65	1.23−2.20
CRP < 1.0 mg/dL	2.55	2.22−2.94	1.32	1.14−1.53
CRP ≥ 1.0 mg/dL	2.18	1.20−3.98	1.60	0.86−2.97

BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Ref, reference; sAlb, serum albumin

Similarly, in case-mix adjusted models, we observed that sAlb concentrations of <4.6 g/dL were associated with a higher mortality risk across all subgroups, except for those age <50 y, of non-Hispanic Black race/ethnicity, and with systolic blood pressure <120 mm Hg (Fig. 3B and Table 5). In sensitivity analyses stratified by CRP level, the unadjusted analyses showed that lower sAlb-higher mortality associations were present in both those with low (<1.0 mg/dL) versus elevated CRP levels (≥1.0 mg/dL); however, upon adjustment for case-mix covariates, the associations persisted in those with low CRP levels, but were attenuated to the null in those with elevated CRP levels (Table 5).

In both the unadjusted and case-mix adjusted spline analyses that examined the association of sAlb as a continuous variable and mortality risk across varying levels of eGFR, we observed that sAlb concentrations of <4.6 g/dL were associated with a higher death risk across the entire spectrum of kidney function (reference: sAlb ≥ 4.6 g/dL; Figs. 4A and B).

Discussion

In this nationally representative sample of U.S. adults, crude analyses showed that incrementally lower sAlb concentrations of <4.6 g/dL were associated with an increasingly higher death risk, whereas higher sAlb concentrations of ≥4.8 g/dL were associated

Fig. 4. Association between low serum albumin concentrations <4.6 g/dL (reference: ≥4.6 g/dL) and all-cause mortality across varying estimated glomerular filtration levels in (A) unadjusted and (B) case-mix adjusted models

with greater survival. After accounting for differences in case-mix covariates, eGFR, and inflammatory markers (i.e., CRP), we observed a consistent and potent association between lower sAlb concentrations and death, such that sAlb concentrations in the lowest category (i.e., sAlb < 3.8 g/dL, typically considered to be within the normal range) were associated with a two- to threefold higher death risk. However, associations between higher sAlb concentrations of ≥4.8 g/dL and mortality were attenuated to the null. Upon examining the association of sAlb concentrations with mortality across relevant clinical characteristics, we observed robust relationships across most subgroups. Notably, lower sAlb-higher mortality associations were observed across the entire spectrum of eGFR.

Our findings are consistent with those of other studies examining the relationship between sAlb concentrations and mortality in the general population. In a seminal study of the NHANES I cohort, sAlb concentrations of ≥4.5 g/dL compared with ≤4.1 g/dL were associated with greater survival in men of White and Black race/ethnicity and among women age 45 y to 74 y [1]. An analysis of the non-Hispanic White Framingham Offspring Study cohort similarly concluded that sAlb concentrations of <4.5 g/dL compared with ≥4.7 g/dL were associated with an increased all-cause mortality risk in women [7]. In a more recent study of >1.7 million insurance applicants from a healthy adult population, sAlb concentrations were examined within separate age and sex strata such that the middle 50% of sAlb values specific to each group served as the reference [8]. For each age and sex strata, sAlb concentrations lower than the middle 50% of sAlb values for the respective groups were associated with a higher mortality risk.

Similar to the aforementioned studies, we observed a strong association between lower sAlb concentrations within the normal range (<4.6 g/dL) with a higher mortality risk in the overall cohort. However, to our knowledge, ours is the first study to observe a robust association between lower sAlb concentrations (<4.6 g/dL) with a higher mortality risk across the entire spectrum of kidney function in both categorical analyses and as a continuous spline, including those with lower levels of eGFR (<60 mL/min/1.73 m²). Patients with CKD are particularly predisposed to lower circulating albumin concentrations owing to alterations in albumin synthesis/turnover from concurrent illnesses, inflammation, and metabolic acidosis [9].

Indeed, several seminal studies in the CKD population have observed a strong relationship between lower sAlb concentrations and higher mortality risk, particularly below the sAlb thresholds of approximately 3.5 g/dL and 4.0 g/dL [10−12]. In a meta-analysis pooling 38 studies of 265 330 dialysis-dependent patients with CKD, a significant inverse association between sAlb concentrations and all-cause and cardiovascular mortality has also been observed [13]. These

observations have informed clinical practice guidelines that advise on the maintenance of sAlb values of ≥4.0 g/dL in patients with advanced CKD (i.e., stage 5) [11,14]. In addition, the International Society of Renal Nutrition and Metabolism has included sAlb concentrations of <3.8 g/dL as one of three biochemical diagnostic criteria for protein−energy wasting [15].

However, our data suggest that, among U.S. adults with moderate CKD (i.e., eGFR < 60 mL/min/1.73 m²), sAlb concentrations typically considered within the normal range (i.e., sAlb < 4.6 g/dL) are linked with a higher death risk, and a more appropriate sAlb target may fall within approximately 4.6 to 4.8 g/dL. Notably, our case-mix adjusted analyses in the overall cohort demonstrated a survival benefit with sAlb concentrations of >4.8 g/dL, but after case-mix + eGFR adjustments, these associations were attenuated to the null. Given that some experts advise lower dietary protein consumption as a means to ameliorate CKD progression based on existing evidence [16−19], we would indeed caution against using higher protein consumption as a means to achieve higher sAlb concentrations in patients with CKD. Further studies are needed to confirm the optimal sAlb target across granular levels of kidney function and determine safe and effective interventions that can elevate sAlb concentrations in patients with CKD.

Another notable finding of our study was our observation of a differential association between sAlb concentration and mortality across racial/ethnic groups. Among other analyses of the general population examining sAlb concentrations and mortality, Djousse et al.'s study [7] included only non-Hispanic White participants, and although the study by Fulk et al. [8] examined age- and sex-specific sAlb references, differential race/ethnicity thresholds were not considered. In addition, although the analysis of the NHANES I cohort by Gillum et al. [1] found a similar relationship between sAlb concentrations and mortality among patients of black and White race/ethnicity, the NHANES I cohort did not separately distinguish participants according to Hispanic ethnicity at that time. In our study, although non-Hispanic Black patients had a higher likelihood of having low sAlb concentrations compared with non-Hispanic White patients, they did not demonstrate a higher risk of mortality associated with sAlb concentrations (<4.6g/dL). At this time, further studies are needed to determine the factors contributing to variations in sAlb concentrations across racial/ethnic groups, as well as their optimal sAlb targets.

The strengths of our study include its large sample size, granular examination of eGFR values, consideration of different racial/ethnic groups, and extended follow-up period to observe outcomes. However, several limitations of our study bear mention. First, given that sAlb concentration was measured at a single point

in time (i.e., baseline measurement only), we did not have repeated measures of sAlb concentrations as a proxy of nutritional and inflammatory status over time among participants. Hence, further studies examining the relationship between longitudinal sAlb concentrations and mortality as well as mortality in the general and CKD populations are needed. Second, sociodemographic characteristics and comorbidities (e.g., education, smoking status, diabetes status) were based on participants' self-report. Finally, the observational nature of this study prohibits causal inferences, and unmeasured confounders may have led to biased results.

Conclusions

Among a cohort of healthy U.S. adults, we observed that lower sAlb concentrations even within the normal range ($<$4.6 g/dL) are associated with a higher risk of all-cause mortality independent of case-mix characteristics and eGFR. Furthermore, we observed a robust association between lower sAlb concentrations ($<$4.6g/dL) with lower survival across a broad spectrum of eGFR levels. At this time, further studies are needed to determine safe and effective interventions that can elevate sAlb concentrations in patients with and without CKD and whether such interventions can improve survival in these populations.

CRediT authorship contribution statement

Amanda R. Brown-Tortorici: Conceptualization, Formal analysis, Writing - original draft, Funding acquisition. **Neda Naderi:** Writing - original draft, Writing - review & editing. **Ying Tang:** Formal analysis. **Christina Park:** Formal analysis. **Amy S. You:** Formal analysis. **Keith C. Norris:** Writing - review & editing. **Yoshitsugu Obi:** Formal analysis. **Elani Streja:** Conceptualization, Formal analysis. **Kamyar Kalantar-Zadeh:** Conceptualization, Writing - review & editing. **Connie M. Rhee:** Supervision, Writing - review & editing.

Declarations of Interest

None.

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