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Association of Pre-End-Stage Renal Disease Serum Albumin With Post-End-Stage Renal Disease Outcomes Among Patients Transitioning to Dialysis

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Abstract

Objective: Serum albumin is a marker of malnutrition and inflammation and has been demonstrated as a strong predictor of mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. Yet, whether serum albumin levels in late-stage CKD are associated with adverse outcomes after the transition to ESRD is unknown. We hypothesize that lower levels and a decline in serum albumin in late-stage CKD are associated with higher risk of mortality and hospitalization rates 1 year after transition to ESRD.

Design and Methods: This retrospective cohort study included 29,124 US veterans with advanced CKD transitioning to ESRD between 2007 and 2015. We evaluated the association of pre-ESRD (91 days before transition) serum albumin with 12-month post-ESRD all-cause, cardiovascular, and infection-related mortalities and hospitalization rates as well as the association of 1-year pre-ESRD albumin slope and 12-month post-ESRD mortality using hierarchical multivariable adjustments.

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Results: There was a negative linear association between serum albumin and all-cause mortality, such that risk doubled (hazard ratio [HR]: 2.07, 95% confidence interval [CI]: 1.87, 2.28) for patients with the lowest serum albumin <2.8 g/dL (ref: ≥4.0 g/dL) after full adjustment. A consistent relationship was observed between serum albumin and cardiovascular and infection-related mortality, and hospitalization outcomes. An increase in serum albumin of >0.25 g/dL/year was associated with reduced mortality risk (HR: 0.76, 95% CI: 0.63, 0.91) compared with a slight decline in albumin (ref: >−0.25 to 0 g/dL/year), whereas a decline more than 0.5 g/dL/year was associated with a 55% higher risk in mortality (HR: 1.55, 95% CI: 1.43, 1.68) in fully adjusted models.

Conclusions: Lower pre-ESRD serum albumin was associated with higher post-ESRD all-cause, cardiovascular, and infection-related mortalities and hospitalization rates. Declining serum albumin levels in the pre-ESRD period were also associated with worse 12-month post-ESRD mortality.

Introduction

PROTEIN–ENERGY WASTING (PEW), a condition characterized by metabolic and nutritional changes leading to depleted stores of protein and energy, has been considered as one of the strongest indicators of death in chronic kidney disease (CKD) and maintenance hemodialysis patients.[1–3] Serum albumin is a protein synthesized by the liver, whose synthesis and thereby serum levels are impacted by conditions related to both nutrition (protein intake) and inflammation.[4–6] Many studies have indicated hypoalbuminemia in CKD and end-stage renal disease (ESRD) patients as a strong indicator of PEW.[1,3,7] Lower serum albumin levels have been associated with higher all-cause and cardiovascular (CV) death risk in nondialysis-dependent CKD patients.[8–11] In maintenance hemodialysis patients, low baseline serum albumin is a potent predictor of adverse outcomes such as lower health-related quality of life and higher hospitalization rates and death risk.[12–16] In chronic dialysis patients, in addition to the mortality–predictability of serum albumin measured at a single point in time, time-varying hypoalbuminemia independently predicts all-cause and CV mortalities.[12] Furthermore, studies examining change in serum albumin in ESRD patients found that declining albumin levels in ESRD were associated with higher mortality, whereas increasing levels reduced this risk.[12,17–19]

Patients with advanced CKD transitioning to ESRD have particularly high mortality rates within the first months after transition.[20,21] The management of health status in late-stage CKD before transition to ESRD (pre-ESRD) may help improve posttransition outcomes. To date, no study examining the associations of serum albumin levels during those pre-ESRD stages with mortality outcomes after transition to ESRD has been performed. We hypothesized that lower serum albumin and a decline in serum albumin before the initiation of dialysis are associated with higher early mortality risk and hospitalization outcomes posttransition.

Methods

Study Population and Data Source

The study population was derived from the United States Renal Data System (USRDS) Special Study Center Transition of Care in CKD (TC-CKD), which aimed to investigate incident ESRD US veterans who transitioned to ESRD between October 1, 2007, through March 30, 2015. Of the original population of 102,477 veterans derived from the United States Renal Data System (USRDS) records, we excluded patients without data on follow-up (n = 2,153) or date of birth (n = 6). We subsequently identified 29,124 patients for the main analytical cohort, who had serum albumin measured in the patient quarter (91-day period) immediately before the transition to ESRD, also referred to as quarter 1 (Appendix Fig. 1). We further identified a subcohort of 1,828 patients with serum albumin and urinary albumin-to-creatinine ratio measured in the patient quarter before transition to ESRD. For our slope analyses, we excluded an additional 4,583 patients from the main analytical cohort, who only had 1 albumin measurement during the 1-year pre-ESRD period and 244 patients with an outlier albumin slope estimate (<−1.37545 [0.5th percentile] or >0.64053 [99.5th percentile]). Hence, the resulting secondary analytical cohort was comprised of 24,297 patients (Appendix Fig. 2). Given the nonintrusive nature, patient anonymity, and large sample size, the requirement for written informed consent was waived and the study was approved by the Memphis and Long Beach Veterans Affairs Medical Centers Institutional Review Boards.

Demographic, Clinical, and Laboratory Measurements

Baseline patient characteristics of this study cohort (including date of birth, sex, race, and ethnicity) were extracted from a composite of USRDS Patient and Medical Evidence files, Veterans Affairs (VA) databases, and Centers for Medicare and Medicaid Services (CMS) databases. Data on marital status and the primary cause of ESRD were solely collected from VA and USRDS records, respectively. VA and CMS data were used to determine preexisting comorbidity status and Charlson Comorbidity Index (CCI). Race groups were categorized as Caucasian, African American, and other.

Most laboratory measurements, including serum albumin, were obtained from the VA Decision Support System National Data Extracts Laboratory Results file. C-reactive protein (CRP) was extracted from VA Corporate Data Warehouse LabChem file. Estimated glomerular filtration rate (eGFR) was calculated with the CKD Epidemiology Collaboration formula.[22] Corrected calcium was calculated with the calcium correction formula.[23] Data on body mass index were obtained from the VA Corporate Data Warehouse Vital Signs file. All laboratory measurements during the patient quarter immediately before ESRD transition were averaged into a single measurement used as baseline levels in analyses. Kidney function decline or eGFR slope over the 1 year period before transition was calculated using a mixed-effects (random intercept and slope) model.

Exposure Measurement

The main exposure of this study was pre-ESRD quarterly averaged albumin. Baseline pre-ESRD albumin was categorized into 8 groups: (1) <2.8, (2) 2.8 to <3.0, (3) 3.0 to <3.2, (4)

3.2 to <3.4, (5) 3.4 to <3.6, (6) 3.6 to <3.8, (7) 3.8 to <4.0, and (8) ≥4.0 g/dL. Serum albumin ≥4.0 g/dL was set as the reference group. In additional analyses, we calculated albumin slope over a period of 1 year before transition using a mixed-effects (random intercept and slope) model. We categorized albumin slope estimates into five groups: (1) ≤ −0.5, (2) −0.5< to ≤−0.25, (3) −0.25< to ≤0, (4) 0< to ≤0.25, and (5) >0.25 g/dL/year. A change in serum albumin of −0.25< to ≤0 was set as the reference group.

Outcome Assessment

The outcomes of interest were the first 12-month post-ESRD all-cause mortality, the first 12-month post-ESRD CV mortality, the first 12-month post-ESRD infection–related mortality, and the first 12-month post-ESRD hospitalization rate. CV and infection-related causes of death were extracted from USRDS records. Information on all outcomes and censoring events were obtained from VA, CMS, and USRDS records. Patients were followed from the date of initiation of ESRD until death, kidney transplantation, loss to follow-up, or the date of final follow-up for all patients (12-month post-ESRD transition or September 1, 2015 for all-cause mortality or hospitalization rate and July 31, 2015 for cause-specific mortality). Loss to follow-up was determined as the last date of use of CMS or VA services.

Statistical Analysis

Patient baseline demographic and clinical characteristics are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or percentages as appropriate for the total cohort and stratified by serum albumin groups. Linear trends for patient baseline characteristics were tested across albumin groups. Cox proportional hazards models were used to evaluate the association of albumin (baseline or slope) with early posttransition all-cause, CV, and infection-related mortalities over 12-month follow-up. Finally, Poisson regression models were used to evaluate the relationship of pre-ESRD averaged serum albumin with 12-month hospitalization rate.

For each outcome in the main analysis, 3 hierarchical models of adjustment were used: (1) Model 1, unadjusted; (2) Model 2, adjusted for case-mix covariates: age, sex, race, ethnicity, marital status, CCI, anemia, atrial fibrillation depression, hyperlipidemia, ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease (rheumatic disease), peptic ulcer disease, paraplegia and hemiplegia, AIDS and HIV, liver disease, diabetes mellitus, cancer and primary cause of ESRD; and (3) Model 3, adjusted for case-mix + malnutrition-inflammation complex syndrome (MICS), which included all covariates in Model 2 plus baseline laboratory measures of hemoglobin, bicarbonate, phosphorus, white blood cell count, alkaline phosphatase, body mass index, potassium, cholesterol, eGFR, and corrected calcium. We defined Model 3 as the primary model of interest. In the subcohort of 1,828 patients with quarter 1 pre-ESRD serum albumin and urinary albumin-to-creatinine ratio, we used the following hierarchical models of adjustment: (1) Model S1, unadjusted; (2) Model S2, adjusted for patient demographics and comorbidities: age, sex, race, ethnicity, marital status, CCI, anemia, atrial fibrillation, depression, hyperlipidemia, ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, cancer, diabetes

mellitus, and liver disease; (3) Model S3, including Model S2 and baseline eGFR measurements; whereas (4) Model S4, also included all covariates in Model S3 and natural logarithmic transformed urinary albumin-to-creatinine ratio. Model S4 was defined as the primary model of interest. In slope analyses, the first available serum albumin measurement in the 1-year period before ESRD transition was added as a covariate to all adjustment models. Furthermore, eGFR slope was calculated and adjusted for in Model 4, case-mix + MICS + first albumin measurement + eGFR slope. We defined Model 4 as the primary model of interest in the slope analyses. Baseline demographic and clinical characteristics of patients who are included in the slope analyses are presented as mean ± SD, median (IQR) or percent as appropriate and stratified by slope groups. Linear trends for patient baseline characteristics were tested across slope groups.

Associations of hypoalbuminemia (albumin <3.5 g/dL) with all-cause mortality were examined across strata of a *priori* selected clinical characteristics using Model 3 adjustments. In sensitivity analysis, we also examined associations of albumin with all-cause mortality using restricted cubic splines with 4 knots at 5th, 35th, 65th, and 95th percentiles. Furthermore, we examined the association between albumin and all-cause mortality over an extended follow-up period that lasted until September 1, 2015. To illustrate trajectories of quarterly averaged albumin across transition to dialysis (1-year pre- and posttransition), we used a mixed-effects regression model and stratified trajectories by the baseline albumin groups.

Missing categorical data on patient characteristics, including marital status, were <0.2% and were handled by creating missing categories. There were 13 patients (<.01% of the total cohort) with missing comorbid data who were categorized as absence of condition for each comorbidity. Missing values for laboratory measurements (including 40% of patients for cholesterol, 33% for phosphorus, 11% for alkaline phosphatase, and <10% for other laboratories) were imputed using multiple imputation. Very few patients had data on CRP (n = 2,702) and urinary albumin-to-creatinine ratio (n = 1,828); we therefore did not use CRP and urinary albumin-to-creatinine ratio as a covariate in adjusted models in the main analysis, but provided data on CRP and urinary albumin-to-creatinine ratio distribution according to baseline albumin groups in the appendix (Appendix Table 1A and B). All analyses were conducted using SAS Enterprise Guide, version 7.1 (Cary, NC) and STATA version 14.2 (StataCorp, College Station, TX).

Results

Baseline Demographic, Clinical, and Laboratory Characteristics

In the 29,124 US veterans transitioning to ESRD included in this study, patients were aged 67 ± 11 years (mean ± SD) and included 2% females, 33% African Americans, and 74% patients with diabetes mellitus (Table 1). In the quarter before transition to ESRD, patients had an average serum albumin of 3.3 ± 0.6 g/dL. Patients with lower serum albumin were more likely to be younger, African American, not married, have a lower prevalence of coronary artery disease, myocardial infarction, cancer and hyperlipidemia, and yet have a higher prevalence of liver disease, AIDS/HIV infection, and depression (Table 1). Moreover, patients with lower serum albumin were more likely to also have decreased concentrations

of blood hemoglobin, serum sodium, uric acid, and uncorrected calcium, whereas they were more likely to have higher values for WBC, hemoglobin A1c, alkaline phosphatase, glucose, platelets, phosphorus, albumin-corrected calcium, CRP (Appendix Table 1A), and urinary albumin-to-creatinine ratio (Appendix Table 1B).

Serum Albumin Trajectories 1-Year Before and After ESRD Transition

In the pre-ESRD period, patients with higher baseline serum albumin showed a gradually increasing trend toward higher serum albumin levels as they transitioned to ESRD, whereas the lower baseline serum albumin groups displayed a trend toward decreasing serum albumin as they approached ESRD (Fig. 1). Patients with the lowest baseline albumin (<2.8 g/dL) had the steepest decline of serum albumin before dialysis initiation. Posttransition, there was a slight regression to the mean whereby serum albumin in the higher baseline albumin groups decreased, and serum albumin in the lower baseline albumin groups increased. Subsequently, serum albumin levels across all strata initially increased and then plateaued over quarters of the post-ESRD follow-up. Throughout the years of the pre- and post-dialysis periods, the hierarchical order of the albumin groups was maintained, and the differences among groups remained relatively constant.

Pre-ESRD Serum Albumin and 12-Month Post-ESRD Mortality

During the first 12 months after the transition to ESRD, 6,236 patients died with a crude mortality rate of 25.6 deaths (95% confidence interval [CI]: 24.7, 26.0) per 100 person-years. In addition, 468 patients (2%) were transplanted, and 2,027 (7%) were lost to follow-up during the first-year posttransition. Patients with lower serum albumin during the last 91 days before dialysis initiation had higher rates of all-cause mortality after dialysis initiation (Appendix Table 2). This linear inverse association between baseline pre-ESRD albumin and 12-month post-ESRD all-cause mortality (Appendix Table 2 and Fig. 2A) persisted across all models of adjustment. In fully adjusted models, patients with albumin <2.8 g/dL had a 2-fold higher risk of all-cause mortality (hazard ratio [HR] [95% CI]: 2.07 [1.87, 2.28]) compared with patients with a serum albumin ≥4.0 g/dL. Sensitivity analyses using restricted cubic spline models also showed a linear inverse association across all models of adjustments (Appendix Fig. 3). In a subcohort of 1,828 patients with pre-ESRD serum albumin and urinary albumin-to-creatinine ratio, we also observed a linear inverse association in a model adjusted for demographics, comorbidities and baseline eGFR. Additionally adjusting for urinary albumin-to-creatinine ratio did not alter the association in this subcohort (Appendix Fig. 4).

Results were similar under a longer period of follow-up time until September 1, 2015 (median [IQR]: 1.7 [0.6, 3.3] years). Furthermore, hypoalbuminemia (<3.5 g/dL) was consistently associated with a higher risk of 12-month all-cause mortality across all strata of clinical characteristics and laboratory measurements (Fig. 3). Of note, associations of hypoalbuminemia with mortality were significantly higher in patients who had a lower CCI score, or did not suffer from CV disease, classified as presence of at least one of the following comorbidities: ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, or cerebrovascular disease (Appendix Table 3 and Fig. 3).

Baseline serum albumin concentrations also exhibited similar inverse associations with 12-month CV mortality and 12-month infection-related mortality (Appendix Table 2 and Fig. 2B and C). In fully adjusted models, patients with albumin <2.8 g/dL had the highest risk of early CV mortality (HR [95% CI]: 2.10 [1.77, 2.49]) and early infection-related mortality (HR [95% CI]: 2.62 [1.85, 3.72]; ref: albumin ≥4.0 g/dL).

Pre-ESRD Serum Albumin and 12-Month Post-ESRD Hospitalization

In the first 12 months after transition to ESRD, patients had a median (IQR) of 1 (0, 3) hospitalizations. Across all levels of adjustment, baseline pre-ESRD serum albumin displayed an approximately linear inverse relationship with hospitalization rate (ref: albumin ≥4.0 g/dL; Appendix Table 2 and Fig. 2D). After full adjustment, lower albumin levels (<2.8 g/dL) were associated with a 50% higher rate of hospitalizations (incidence rate ratio [95% CI]: 1.50 [1.45, 1.56]).

Twelve-Month Pre-ESRD Serum Albumin Slope and 12-Month Post-ESRD Mortality

We then examined trajectories of 12-month pre-ESRD albumin and their associations with first 12-month posttransition mortality by calculating pretransition serum albumin 12-month slopes in 24,297 patients (83% of the cohort), who had at least 2 serum albumin measurements within the 12-month period before ESRD (Appendix Fig. 2). The median (IQR) rate of change in pre-ESRD albumin was −0.2 (−0.42, −0.06) g/dL/year. Patients with steeper albumin slope decline had a higher prevalence of chronic pulmonary disease, atrial fibrillation, cancer, myocardial infarction, and peripheral vascular disease; and had a lower prevalence of anemia, hyperlipidemia, and diabetes mellitus. Furthermore, patients with a steeper albumin slope decline during the quarter before transition were more likely to have higher levels of baseline eGFR, WBC, and CRP, yet lower measurements of baseline serum albumin. However, there was no significant difference in urinary albumin-to-creatinine ratio between the 5 albumin slope groups (Appendix Table 4). In unadjusted models, patients with the steepest 12-month pre-ESRD serum albumin decline (≤−0.5 g/dL/year) had the highest risk of 12-month posttransition all-cause mortality (HR [95% CI]: 1.94 [1.80, 2.09]) compared with a modest to no decline in albumin (−0.25 < to ≤0 g/dL/year; Appendix Table 5 and Fig. 4). Whereas, an increase in albumin slope over the 12-month pre-ESRD period was associated with lower unadjusted mortality risk compared with the reference. These linear inverse associations remained robust after further adjustment, including kidney function decline, where the steepest albumin decline was associated with the highest risk of all-cause mortality compared with the referent group (HR [95% CI]: 1.55 [1.43, 1.68]).

Discussion

In our cohort of 29,124 US veteran patients transitioning to ESRD, we observed an inverse association between pre-ESRD serum albumin level in the quarter before transition and 12-month post-ESRD all-cause, CV, and infection-related mortality. Patients with low serum albumin <2.8 g/dL had the highest mortality risk compared with the reference group of serum albumin >4.0 g/dL. Pre-ESRD serum albumin also exhibited an inverse linear relationship with hospitalization rates. In a subcohort of 1,828 US veterans with quarter 1 pre-ESRD serum albumin and urinary albumin-to-creatinine ratio, the inverse linear

association remained after adjusting for urinary albumin-to-creatinine ratio. In addition, a steeper 1-year pre-ESRD decline in serum albumin levels of more than −0.5 g/dL/year was associated with a higher 12-month posttransition all-cause mortality risk, whereas an increase in serum albumin levels was associated with lower mortality risk. These relationships were consistent across multiple levels of adjustment and in subgroup analyses. To the best of our knowledge, this is the first study examining the association of serum albumin concentrations and its change in advanced CKD patients with early outcomes after transitioning to ESRD.

Serum albumin is a well-known biomarker used to assess the clinical condition of patients undergoing renal replacement therapy, and hypoalbuminemia, which may reflect both malnutrition and inflammation; and is a known independent predictor of mortality among those on dialysis.[18,24] In our cohort, late-stage CKD patients with lower pre-ESRD serum albumin levels were more likely to have comorbidities such as diabetes, congestive heart failure, and a higher CCI. Previous studies have similarly reported lower serum albumin concentrations in patients with more severe diseases.[11,25] Moreover, in dialysis patients, lower serum albumin concentrations have been associated with reduced physical activity, and sicker patients are less likely to be physically active.[26]

Serum albumin concentration is determined by the rate of liver synthesis and breakdown as well as blood volume distribution (hyper vs. hypovolemia). Thus, levels might be influenced by multiple factors, such as protein intake, which may promote/stimulate albumin synthesis, in contrast to higher oncotic pressure or inflammation, which may lead to a reduction of albumin levels.[5,6,27–29] Declining serum albumin concentration may also be a marker of kidney function decline and worsening fluid overload, which can have a dilutional effect on serum albumin concentrations. In our cohort, however, patients with lower pre-ESRD serum albumin concentrations did not necessarily have lower eGFR rates. Likewise, advanced CKD patients with a 1-year pre-ESRD decline in serum albumin had higher eGFR values than patients with an increase in 1-year pre-ESRD serum albumin. In healthy individuals, about 20% to 30% of hepatocytes in the liver are engaged in albumin synthesis, and synthesis efforts can reactively be increased by 200% to 300%.[30] Whether this protective mechanism could partially explain our observation remains to be determined. Moreover, worsening metabolic acidosis, indicated by lower serum bicarbonate, can also create a catabolic state via the breakdown of proteins and amino acids. Corrective measures in dialysis patients may reverse these effects.[31–35] In our cohort, patients with lower pre-ESRD serum albumin concentrations were more likely to have metabolic acidosis as indicated by a lower serum bicarbonate level.

In addition, inflammation may lead to and originate in PEW, given that protein malnutrition may act as an inflammatory stimulus.[1,36,37] In dialysis patients, serum albumin levels have been well correlated with both other markers of nutrition (such as normalized protein nitrogen appearance [protein catabolic rate] as well as markers of inflammation [interleukin-6]).[6] Inflammation is associated with atherosclerosis[38] and thereby might lead to higher CV mortality, which has also been observed among CKD patients.[39] Other biomarkers of inflammation (such as interleukin-6, interleukin-10, and CRP) have also been linked to adverse outcomes in CKD and dialysis patients.[40–43] Likewise, in our study lower

albumin was associated with higher inflammatory markers (CRP and WBC levels). Previous studies have also similarly reported an inverse correlation between neutrophil count and serum albumin.[18] In addition, the lowest pre-ESRD serum albumin group (<2.8 g/dL) had the highest CV mortality risk in our analysis.

Another consideration is that diets recommended to CKD patients consist of low plant fiber and symbiotic organisms (found in yogurt and cheese), which could lead to changes in the gut's microbiome with various complications including increased concentration of uremic toxins.[44] Uremic toxins provide yet another link to chronic inflammation and are themselves associated with higher CV burden and worse outcomes in kidney disease.[45] Conversely, in our cohort, late-stage CKD patients with lower pre-ESRD serum albumin were more likely to have lower blood urea nitrogen concentrations. Although preserving kidney function in the setting of advanced CKD may be hard to accomplish, either preserving residual kidney function or initiating dialysis might attenuate the aforementioned conditions and result in improved appetite and consequently improved health status. Concordantly, serum albumin concentration increases in incident dialysis patients independently of residual kidney function in the first years after dialysis initiation.[46,47] We can further add that in a 1-year pre-ESRD and 1-year post-ESRD trajectory analysis of serum albumin stratified by quarter 1 pre-ESRD serum albumin groups, lower baseline albumin groups especially showed an increase in serum albumin after the initiation of renal replacement therapy. Higher baseline groups, however, declined slightly after dialysis initiation. Interestingly, the hierarchical order of the baseline albumin groups was maintained throughout the entire observation time. Moreover, the underlying mechanism relating malnutrition to mortality is less understood. Some have speculated that malnutrition leads to diminished muscle function[1,48] and reduced ability to absorb nutrients,[49] as well as increased inflammation.[50,51] Approximately, 47% of patients in our cohort had a decline in serum albumin ≥0.25 g/dL during the 12-month period before ESRD transition, which may indicate a progressively worsening health status as CKD progresses. A steeper decline in serum albumin was associated with a higher death risk, which was independent of kidney function decline and factors related to malnutrition and inflammation. These results may indicate that the decline in serum albumin is associated with sustained damage beyond the change in physiology because of declining renal function. In contrast, 18% of patients in our cohort experienced an increase in serum albumin in the year before ESRD transition, which was associated with a lower mortality risk. These patients had higher phosphorus levels, which might indicate better nutritional status. In dialysis patients, nutritional oral supplements were associated with an increase in serum albumin.[52–54] Conversely, patients with declining renal function may receive diuretic medications leading to hypovolemia and the appearance of an increasing albumin.

Another possible link between serum albumin and adverse outcomes could be its function as an extracellular antioxidant molecule, given its ability to bind various types of toxic substances and thus limit their harmful effects.[55,56] Previous studies have shown that lower levels of albumin are associated with higher levels of biomarkers of oxidative protein damage.[55,56] Oxidative stress is a hallmark of CKD, and it may play an important role in the morbidity and mortality associated with kidney disease.[57] There are numerous mechanisms by which oxidative stress may cause morbidity and mortality including its impact on both inflammation and endothelial cell dysfunction thereby increasing CV risk and several other

complications of CKD.[58] In our cohort, associations between albumin and outcomes persisted after adjustment for markers of malnutrition and inflammation; however, information on inflammatory markers such as CRP or interleukin-6 was limited or unavailable. In addition, we did not have direct measurements of markers of oxidative stress.

Strengths of our study include the large population size and capture of comprehensive data on comorbidity status in the pre-ESRD period. In addition, given the availability of repeated measures, we were able to calculate the change in serum albumin before transition to ESRD. However, several limitations of our study should be noted. Patients included in our study were those who were using the VA health care system and its laboratory services in the year before transition to dialysis; thereby study results may not be externally valid to other populations. Younger VA patients are most likely veterans of the Gulf War and, therefore, suffering from different medical and/or mental conditions in comparison to older veterans. This could provide an explanation why in our cohort, patients with lower serum albumin levels were paradoxically more likely to be younger although it has been reported that albumin decreases with increasing age.[59] These younger patients may have a higher burden of comorbidities or worse nutrition, which may explain this finding. In addition, our study might be susceptible to survivor bias, as we are only able to investigate patients who survived the late CKD to post-ESRD transition period. Because of the design of our cohort, we were unable to examine CKD patients who died before transitioning to ESRD, which may limit generalizability. Thus, our study cohort may consist of a “relatively healthy’’ subset of late CKD patients. It is also important to note that we are unable to completely exclude sources of residual confounding by unmeasured variables such as inflammatory cytokines (e.g., interleukin-6), nutrition intake/lifestyle, and frequency of acute events such as infections. An important modifier of serum albumin is proteinuria, and hence, it may influence the serum albumin–mortality association. In our subcohort, adjusting for urinary albumin-to-creatinine ratio did not alter the pre-ESRD serum albumin-mortality association.

In addition, slopes were calculated using linearity assumptions and may be affected by acute episodes (e.g., hospitalizations), which could also explain the observed associations. Finally, because of the observational study design, we cannot draw conclusions about the causal associations between serum albumin levels or the rate of serum albumin change with mortality and hospitalizations.

In conclusion, we showed that pre-ESRD serum albumin is associated with early post-ESRD mortality outcomes. Furthermore, a decline in serum albumin in the year before transition was associated with higher posttransition all-cause mortality risk.

Practical Application

Lower pre-ESRD serum albumin and steeper decline in the 1-year before ESRD transition were associated with early mortality outcomes. Future studies are needed to determine if management of malnutrition and inflammation before transition to ESRD can improve health outcomes in the posttransition period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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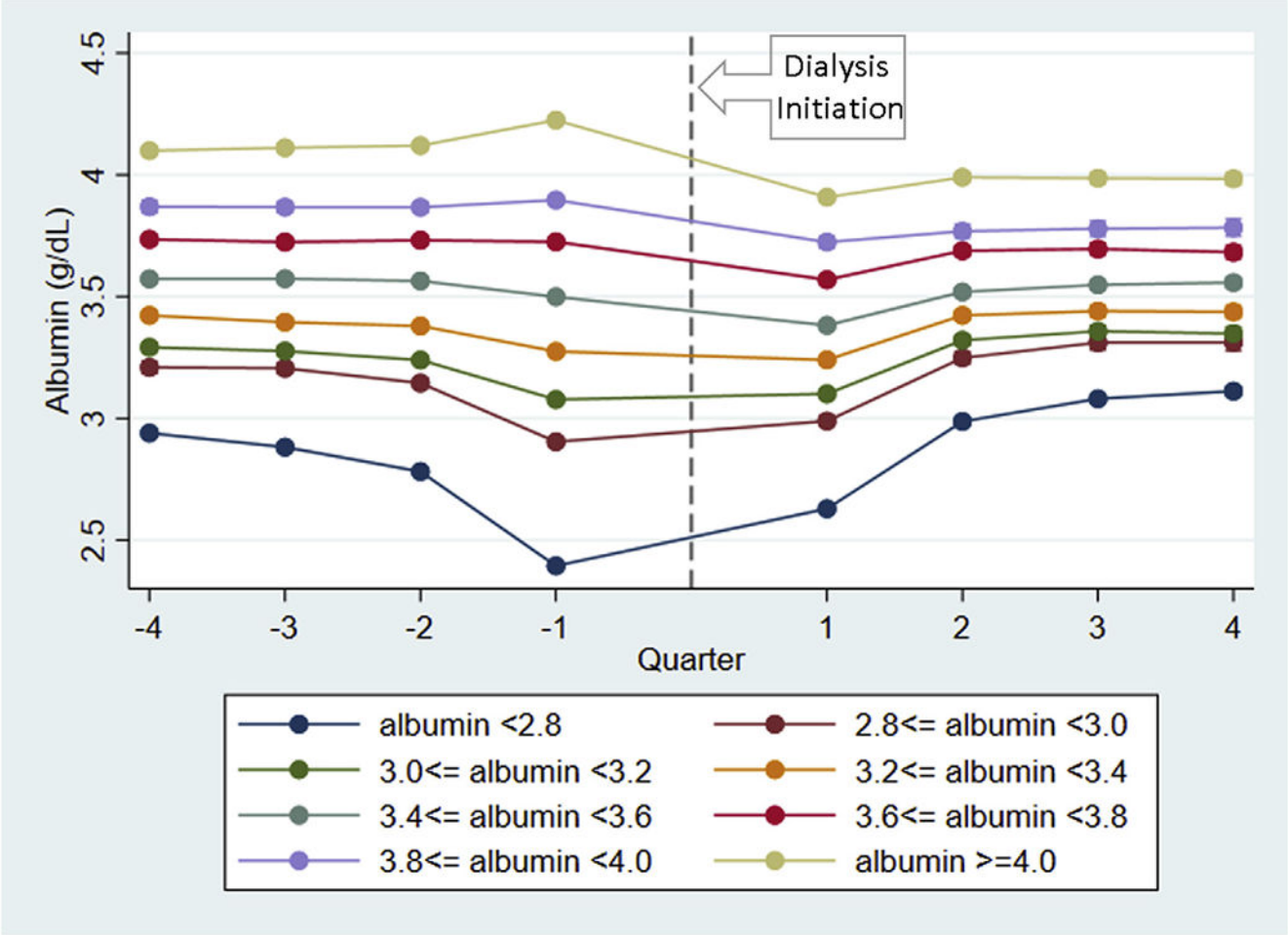

Figure 1.
Trajectories of quarterly population mean serum albumin (g/dL) concentrations during the 1-year pre- and post-ESRD period across baseline serum albumin groups.

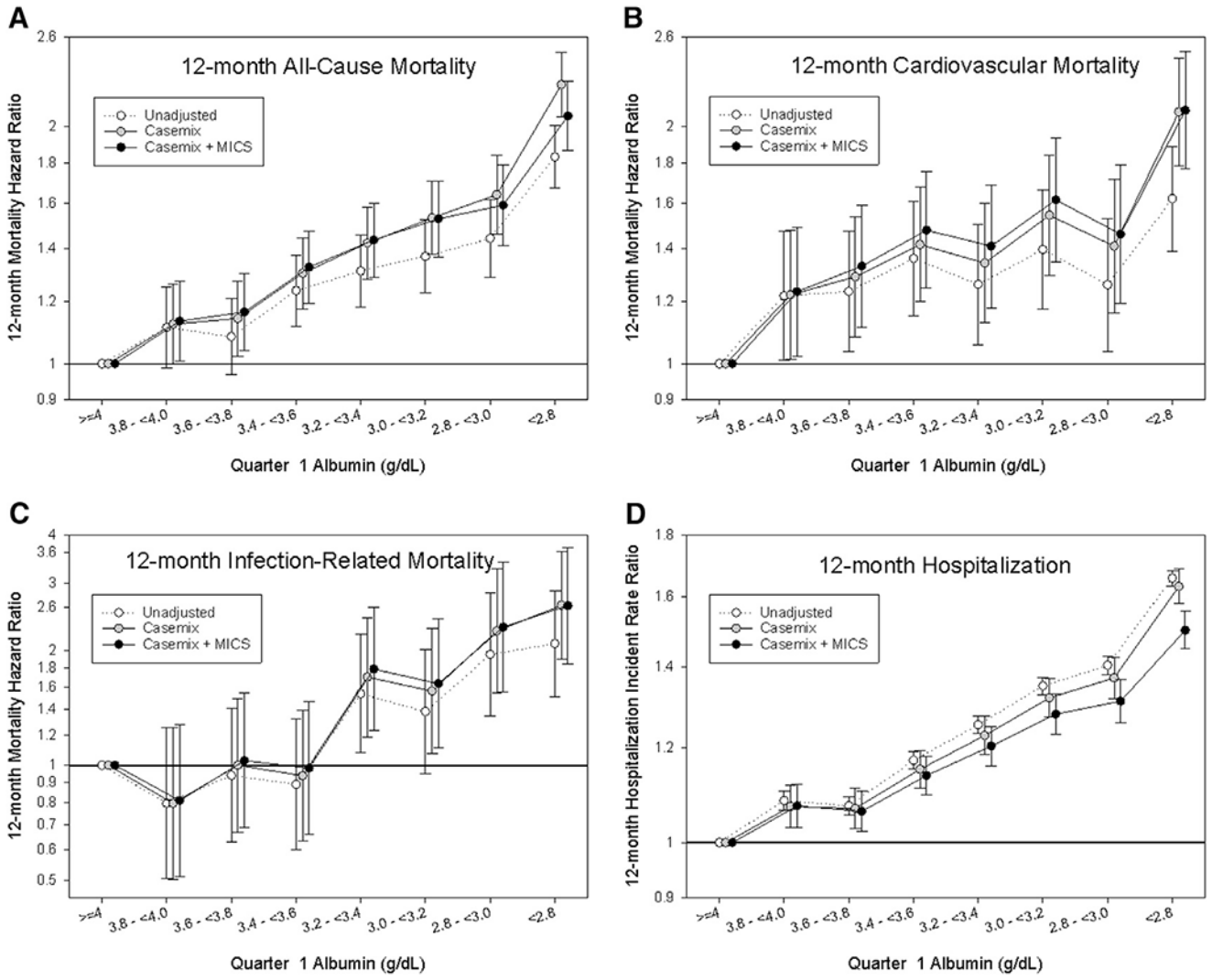

Figure 2.

Associations of serum albumin (g/dL) with 12-month posttransition (A) all-cause, (B) cardiovascular, (C) infection-related mortality, and (D) hospitalization rates with hierarchical adjustments. Please note the inverse plotted x-axis for visual purposes. MICS, malnutrition-inflammation complex syndrome.

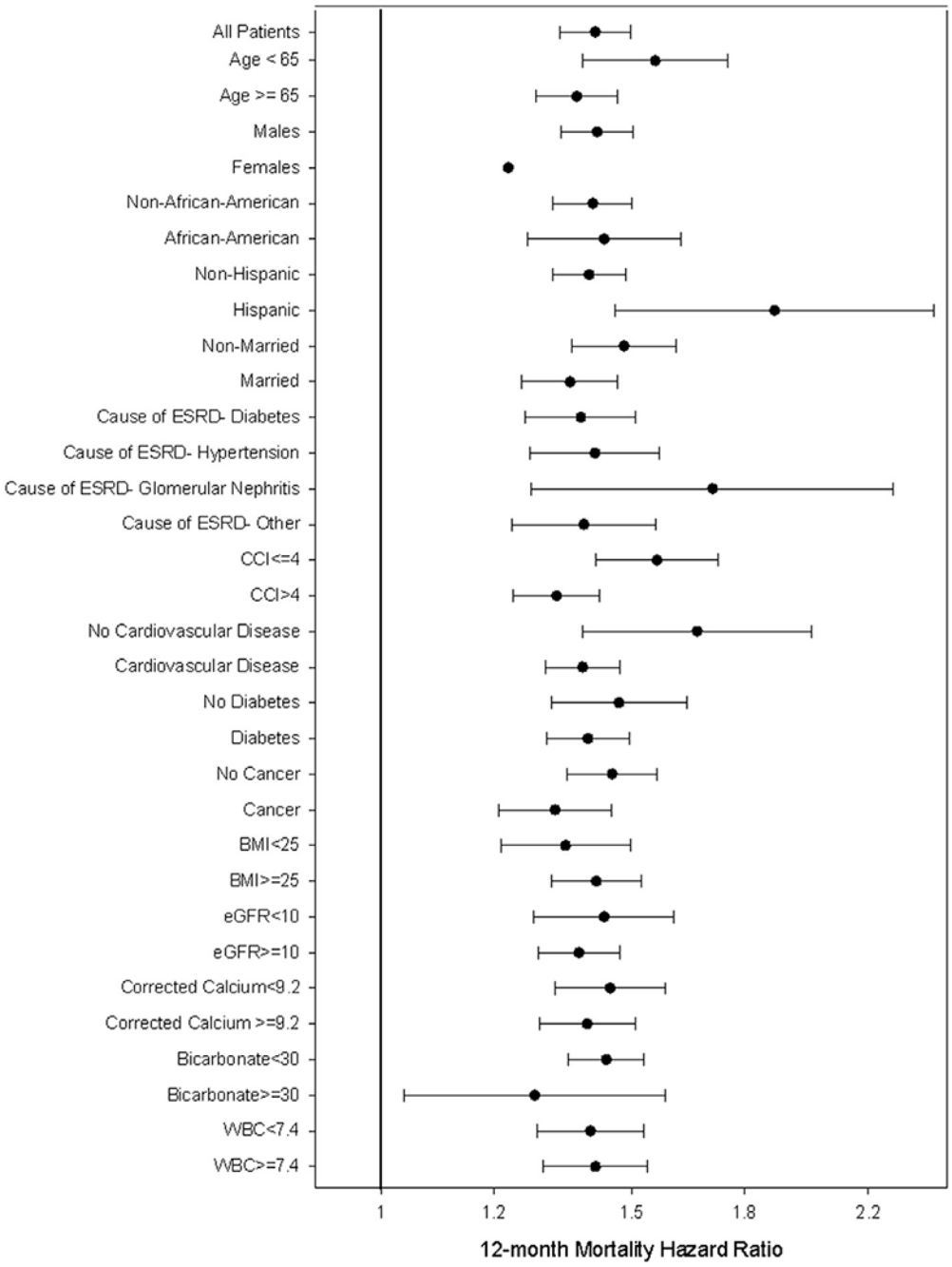

Figure 3.

Subgroups analyses examining the association of hypoalbuminemia (albumin <3.5 g/dL) with 12-month posttransition all-cause mortality in the fully adjusted model among 29,124 US veterans. Cardiovascular disease was defined as presence of at least one of the following comorbidities: ischemic heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease or cerebrovascular disease. ESRD, end-stage renal disease; CCI, Charlson comorbidity index; BMI, body mass index; eGFR, estimated glomerular filtration

rate; WBC, white blood cell. Confidence interval for female was removed because of small sample size

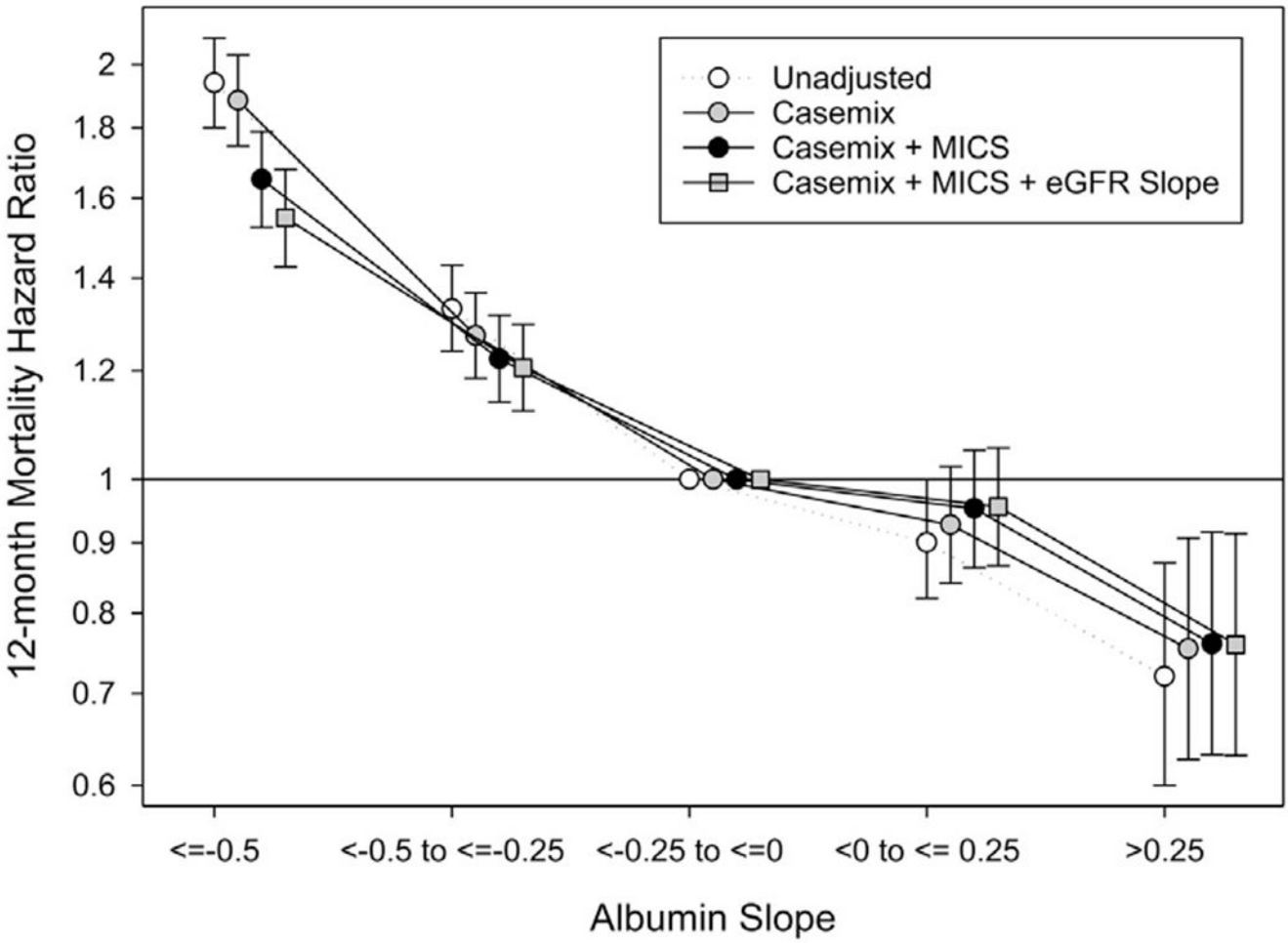

Figure 4.

The association of change of pre-ESRD serum albumin (g/dL/year) with 12-month posttransition all-cause mortality with hierarchical adjustments. ESRD, end-stage renal disease. eGFR, estimated glomerular filtration rate; MICS, malnutrition-inflammation complex syndrome.

Table 1.

Baseline Demographic and Clinical Characteristics of 29,124 US Veterans With ESRD Transitioning to Dialysis Stratified by Quarter 1 Pre-ESRD Serum Albumin

		Serum Albumin (g/dL)								
Variable	**Total**	**<2.8**	**2.8 to <3.0**	**3.0 to <3.2**	**3.2 to <3.4**	**3.4 to <3.6**	**3.6 to <3.8**	**3.8 to <4.0**	**$4.0**	***P* Value**
N (%)	29,124	5,722 (20)	2,405 (8)	3,256 (11)	3,618 (12)	4,080 (14)	3,495 (12)	2,723 (9)	3,825 (13)	
Age, mean ± SD	67 ± 11	64 ± 10	66 ± 10	67 ± 10	67 ± 11	68 ± 11	68 ± 11	69 ± 11	68 ± 12	<.001
Female, (%)	2	3	2	2	2	2	2	2	2	.02
Race (%)										<.001
Caucasian	64	58	61	61	61	63	66	69	73	<.001
African American	33	38	36	35	36	33	31	28	24	<.001
Other	3	4	4	4	3	3	3	3	2	<.001
Hispanic (%)	8	10	7	8	7	8	8	8	8	.01
Marital status (%)										.001
Single	10	12	11	10	10	9	8	8	8	<.001
Married	51	43	48	49	51	53	54	57	57	<.001
Divorced	29	36	32	30	30	27	28	25	25	<.001
Widowed	10	9	9	11	10	11	10	11	10	.13
Cause of ESRD (%)										
Diabetes	48	50	53	54	49	49	47	44	38	<.001
Hypertension	27	19	24	23	28	29	31	31	35	<.001
Glomerulonephritis	8	9	6	6	7	7	7	8	10	.15
Other	17	22	17	16	16	15	15	16	18	<.001
Comorbidities (%)										
Coronary artery disease	39	32	39	39	41	41	42	42	42	<.001
Myocardial infarction	27	23	28	28	28	28	29	28	27	<.001
Congestive heart failure	58	58	63	61	61	60	56	55	52	<.001
Ischemic heart disease	60	54	61	62	62	62	61	62	60	<.001
Atrial fibrillation	19	17	19	20	20	20	20	21	20	.0003
Peripheral vascular disease	46	45	46	47	47	48	46	48	45	.18
Cerebrovascular disease	38	34	40	38	38	39	39	38	38	.0005
Hypertension	98	96	98	98	98	99	98	98	98	<.001
Diabetes	74	77	79	79	76	75	72	71	66	<.001
Hyperlipidemia	83	80	84	84	85	85	86	86	85	<.001
Anemia	81	79	82	82	82	83	82	83	80	.006

	Serum Albumin (g/dL)									
Variable	**Total**	**<2.8**	**2.8 to <3.0**	**3.0 to <3.2**	**3.2 to <3.4**	**3.4 to <3.6**	**3.6 to <3.8**	**3.8 to <4.0**	**$4.0**	***P* Value**
Chronic pulmonary disease	50	48	52	51	52	52	50	49	48	.52
Connective tissue disease–rheumatic disease	6	5	7	6	6	6	6	6	5	.95
Peptic ulcer disease	9	9	9	9	9	9	9	10	9	.7
Liver disease	18	26	20	18	17	17	16	16	14	<.001
Cancer	28	25	26	27	28	29	29	29	28	<.001
AIDS/HIV	2	3	2	1	2	1	1	1	1	<.001
Paraplegia and hemiplegia	5	6	5	5	5	4	5	5	4	.001
Dementia	4	4	4	4	4	4	3	4	3	.12
Depression	36	41	37	37	36	36	35	33	30	<.001
CCI	5 (3, 7)	5 (3, 7)	5 (3, 7)	5 (3, 7)	5 (3, 7)	5 (3, 7)	4 (3, 7)	4 (3, 7)	4 (2, 6)	<.001
Serum laboratory values										
Albumin, g/dL	3.3 ± 0.6	2.4 ± 0.4	2.9 ± 0.1	3.1 ± 0.1	3.3 ± 0.1	3.5 ± 0.1	3.7 ± 0.1	3.9 ± 0.1	4.2 ± 0.2	<.001
Alkaline phosphatase, IU/L	83 (65, 110)	92 (70, 128)	86 (67, 113)	84 (66, 111)	83 (63, 109)	81 (64, 106)	81 (65, 105)	80 (63, 101)	79 (63, 101)	<.001
BMI, kg/m^2	30.0 ± 6.8	30.0 ± 7.1	30.2 ± 7.2	30.1 ± 6.9	30.2 ± 6.9	30.1 ± 6.7	30.0 ± 6.7	29.9 ± 6.6	29.6 ± 6.2	.49
BUN, mg/dL	67.7 ± 24.8	63.5 ± 24.3	67.7 ± 23.8	69.0 ± 24.1	70.0 ± 24.6	70.1 ± 24.4	68.7 ± 24.4	68.4 ± 25.6	66.7 ± 26.7	<.001
Calcium, mg/dL	8.6 ± 0.8	8.1 ± 0.7	8.3 ± 0.7	8.5 ± 0.7	8.6 ± 0.7	8.7 ± 0.7	8.8 ± 0.8	9.0 ± 0.7	9.2 ± 0.8	<.001
Corrected Calcium, mg/dL	9.2 ± 0.7	9.4 ± 0.7	9.2 ± 0.7	9.2 ± 0.7	9.2 ± 0.7	9.1 ± 0.7	9.1 ± 0.8	9.1 ± 0.7	9.0 ± 0.7	<.001
CRP, mg/L	2.4 (0.7, 7.6)	4.7 (1.1, 11.7)	2.4 (0.7, 7.7)	2.6 (0.8, 6.3)	1.9 (0.6, 5.4)	1.6 (0.5, 4.6)	1.2 (0.4, 3.2)	1.1 (0.3, 2.6)	0.7 (0.3, 1.8)	<.001
Total cholesterol, mg/dL	151.9 ± 51.7	162.3 ± 68.2	150.8 ± 50.4	148.7 ± 49.0	147.7 ± 48.3	147.2 ± 45.3	148.3 ± 44.4	148.8 ± 44.5	155.0 ± 45.9	.48
Bicarbonate, mEq/L	22.6 ± 4.1	22.3 ± 3.8	22.4 ± 4.0	22.5 ± 4.0	22.6 ± 4.1	22.5 ± 4.0	22.6 ± 4.2	23.0 ± 4.3	22.9 ± 4.3	<.001
eGFR, mL/min/1.73 m^2	11.6 (8.5, 16.2)	12.5 (9.1, 17.8)	11.5 (8.4, 15.8)	11.2 (8.5, 15.4)	11.3 (8.2, 15.4)	11.1 (8.2, 15.3)	11.5 (8.3, 15.8)	11.6 (8.5, 16.0)	11.8 (8.6, 17.0)	<.001
Hemoglobin, g/dL	10.2 ± 1.6	9.7 ± 1.4	9.8 ± 1.4	9.9 ± 1.5	10.1 ± 1.5	10.2 ± 1.5	10.5 ± 1.6	10.7 ± 1.7	11.0 ± 1.7	<.001
Hemoglobin A1c, %	6.8 ± 1.5	6.9 ± 1.7	6.8 ± 1.5	6.8 ± 1.5	6.8 ± 1.5	6.7 ± 1.4	6.7 ± 1.3	6.7 ± 1.4	6.6 ± 1.3	<.001
Sodium, mEq/L	138.8 ± 3.3	137.9 ± 3.4	138.4 ± 3.3	138.5 ± 3.3	138.8 ± 3.1	139.0 ± 3.1	139.2 ± 3.1	139.4 ± 3.2	139.7 ± 3.2	<.001
Platelet, ×10^9/L	205.7 ± 75.8	220.5 ± 90.1	208.6 ± 78.6	204.3 ± 73.6	201.7 ± 70.6	199.9 ± 69.8	199.8 ± 67.7	196.8 ± 65.0	202.6 ± 71.3	<.001
Potassium, mEq/L	4.5 ± 0.6	4.4 ± 0.5	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	<.001
Uric acid, mg/dL	8.2 ± 2.3	7.9 ± 2.4	8.1 ± 2.3	8.1 ± 2.4	8.3 ± 2.4	8.2 ± 2.2	8.2 ± 2.2	8.3 ± 2.2	8.3 ± 2.3	<.001
White blood cell, ×10^9/L	8.0 ± 4.0	8.8 ± 3.8	8.1 ± 3.4	8.0 ± 4.4	7.8 ± 2.9	7.8 ± 4.4	7.7 ± 5.1	7.5 ± 3.3	7.7 ± 4.1	<.001
Glucose, mg/dL	131.0 ± 48.0	135.2 ± 47.6	133.6 ± 47.9	134.5 ± 50.7	132.9 ± 46.7	129.8 ± 48.5	128.5 ± 47.9	128.4 ± 49.1	123.6 ± 44.9	<.001
HDL, mg/dL	39.1 ± 14.2	39.8 ± 16.0	39.2 ± 14.1	38.7 ± 14.2	39.3 ± 14.1	38.5 ± 13.9	38.6 ± 13.3	39.1 ± 12.9	39.2 ± 14.0	.17
LDL, mg/dL	84.7 ± 40.3	93.1 ± 52.4	85.2 ± 41.1	83.4 ± 38.6	81.7 ± 36.5	81.5 ± 36.1	81.6 ± 35.1	81.7 ± 35.0	85.1 ± 36.0	.0008
Phosphorus, mg/dL	5.4 ± 1.4	5.4 ± 1.6	5.5 ± 1.5	5.4 ± 1.4	5.4 ± 1.4	5.3 ± 1.4	5.3 ± 1.3	5.3 ± 1.3	5.2 ± 1.4	<.001
Triglyceride, mg/dL	145.1 ± 101.7	152.6 ± 110.6	137.8 ± 93.1	138.9 ± 95.4	139.1 ± 97.9	139.7 ± 99.3	144.2 ± 96.9	143.8 ± 101.2	156.8 ± 107.2	.05

	Serum Albumin (g/dL)									
Variable	**Total**	**<2.8**	**2.8 to <3.0**	**3.0 to <3.2**	**3.2 to <3.4**	**3.4 to <3.6**	**3.6 to <3.8**	**3.8 to <4.0**	**$4.0**	***P* Value**
Urinary albumin-to-creatinine ratio, mg/g	950.7 (173.7, 2,619.4)	2,427.9 (346.8, 4,990.2)	1,775.0 (247.4, 3,876.3)	1,401.6 (329.2, 3,004.8)	1,175.0 (239.9, 2,480.2)	754.9 (172.0, 2,108.0)	760.8 (169.0, 1,809.6)	509.5 (139.5, 1,438.0)	224.5 (37.3, 960.9)	<.001

BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson comorbidity index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; TSH, thyroid-stimulating hormone.

Values are expressed as mean ± SD, median (IQR), or percentage, as appropriate. SI conversion factors: to convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; calcium to mmol/L, multiply by 0.25; bicarbonate to mmol/L, multiply by 1.0.

Percentages might not add up to 100% because of rounding.