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Nutritional status in chronic dialysis patients : associations with development of disease and survival

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The association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition

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ABSTRACT

Background We investigated the effect of inflammatory and nutritional status on the association between serum albumin and mortality in hemodialysis (HD) and peritoneal dialysis (PD) patients.

Methods This was a prospective cohort study of patients incident dialysis in The Netherlands starting hemodialysis or peritoneal dialysis treatment. The presence of inflammation (CRP ≥ 5 or ≥ 10 mg/L), malnutrition (1-5 on the 7-point SGA) and a low protein intake (nPNA < 0.99 g/kg/d) were measured at three months after the start of dialysis. We ascertained all-cause mortality 2 years after the start of dialysis.

Results In total, 700 patients were included (age, 59 ± 15 years; 60% men; 454 starting HD, and 246 starting PD; serum albumin, 3.3 ± 0.7 g/dL). The 2-year mortality was 21%. In HD patients, the mortality risk (hazard ratio [HR], with 95% confidence interval [95% CI]) per unit decrease in serum albumin (g/dL) was 1.47 (95% CI, 1.07 to 2.00). Adjustment for SGA did not decrease this risk, whereas adjustment for nPNA decreased the HR to 1.45 (95% CI, 1.06 to 1.97). The mortality risk decreased to 1.30 (95% CI, 0.95 to 1.78) after adjustment for inflammation, and did not further decrease after additional adjustment for SGA and nPNA. Additional adjustment for age, sex, and comorbidity decreased the HR to 1.09 (95% CI, 0.79 to 1.51). In PD patients, the effects of the adjustments on the mortality risk of serum albumin (HR 1.38; 95% CI, 0.87 to 2.20) were similar.

Conclusion In dialysis patients, a 1-g/dL decrease in serum albumin was associated with an increased mortality risk of 47% in HD and 38% in PD patients. These mortality risks were in part explained by the inflammatory pathway. The mortality risks associated with serum albumin were not a consequence of malnutrition as measured with the SGA and nPNA. These findings imply that nutritional status cannot be assessed with precision by measurement of serum albumin in dialysis patients.

INTRODUCTION

Hypoalbuminemia is highly prevalent in patients with end-stage renal disease and is a strong predictor of mortality.¹⁻⁴ Current evidence suggests that the cause of low albumin levels, rather than hypoalbuminemia specifically, is responsible for the high morbidity and mortality among dialysis patients.^{5,6}

Investigations in dialysis patients of the determinants of serum albumin concentrations reported that metabolic acidosis, insulin resistance, hydration status, protein intake and protein losses in the dialysate are associated with hypoalbuminemia.^{5,7-9} Because serum albumin is also a negative acute-phase protein, inflammation also contributes to low albumin concentrations.^{6,10,11} It was shown that the positive acute-phase protein C-reactive protein (CRP) is strongly associated with serum albumin concentration in both hemodialysis and peritoneal dialysis patients.^{8,9} Furthermore, in predicting cardiovascular mortality, CRP superseded serum albumin.¹² These findings suggest that the acute-phase response may be largely responsible for the effect of hypoalbuminemia on mortality in dialysis patients.¹²⁻¹⁴

Although evidence indicates that malnutrition rarely causes loss of protein stores,^{13,14} several studies relating factors to serum albumin levels reported protein intake as a determinant of hypoalbuminemia.^{5,8,9,15,16} Furthermore, several intervention studies showed a positive effect of nutritional supplements on serum albumin concentrations,^{17,18} and even on mortality.¹⁸

Hence, in dialysis patients, serum albumin concentrations are considered to reflect both nutritional and inflammatory domains. However, it remains unclear whether the relation between hypoalbuminemia and mortality in dialysis patients is only in response to inflammation or also (in part) a consequence of malnutrition. Therefore, we investigated the effect of inflammatory and nutritional status on the strength of the association between serum albumin and mortality in hemodialysis and peritoneal dialysis patients.

METHODS

Study design

The Netherlands Cooperative Study on the Adequacy of Dialysis-II (NECOSAD-II) is an observational, prospective cohort study of incident dialysis patients that has been performed since 1997 in 38 dialysis centers in The Netherlands. At 3 months after the start of dialysis, blood samples are taken for routine hospital measurements, and additional serum aliquots are frozen and stored for future analyses. Dates and causes of mortality are immediately reported during follow-up. Survival time is defined as the number of days between 3 months after the start of the dialysis, considered as the baseline of the study, and the date of death, or the date of censoring because of loss to follow-up (kidney transplantation or transfer to a nonparticipating dialysis centre), the end of the follow-up as of January 1, 2007, or at a set maximum of 2 years.

Patients

End-stage renal disease patients at least 18 years old, and beginning their first renal replacement therapy, were eligible. The medical ethical committees of all participating dialysis centers approved the study, and all participants gave written, informed consent before inclusion. All patients who started chronic hemodialysis or peritoneal dialysis treatment between February 1997 and September 2001, and from whom a blood sample was taken at 3 months after the start of dialysis, were included in the present analysis (n=856).

Data collection

Baseline demographic data and clinical data such as age, sex, body mass index (BMI), ethnicity, primary kidney disease, and comorbidities were recorded in the patients' files. Primary kidney diseases and causes of death were classified according to the coding system of the European Renal Association – European Dialysis and Transplantation Association.¹⁹ The comorbidity index of Khan et al. was calculated, in which age and number of comorbid conditions are combined into three mortality-risk groups: low, medium or high.²⁰

A blood sample was taken the same day before a dialysis session, and urine was collected during the interdialytic interval. The residual glomerular filtration rate was calculated from the mean of creatinine and urea clearance, and adjusted for body surface area (mL/min/1.73 m²).

In January 2002, the serum concentrations of albumin and CRP were determined in the stored blood samples at a central laboratory. Serum albumin was measured by means of an immunonephelometric method (Hoffman-La Roche; expressed in g/dL). The between-assay coefficient of variation (CV) was 6%, and the detection limit was 4 mg/dL. The CRP concentrations were measured using a commercial immunoturbidimetric assay, with a detection limit of 3 mg/L. The between-assay CV was 1.8%. The within-run CV was 1.8%, the run-to-run CV 1.7%, and day-to-day CV 2.8%. On the basis of serum CRP concentration at 3 months after the start of dialysis, patients were divided into three categories: CRP<5 mg/L, 5≤CRP<10 mg/L and CRP≥10 mg/L. We defined the presence of inflammation as a serum concentration of CRP of ≥10 mg/L.^{21;22}

Nutritional status was measured with the 7-point subjective global assessment of nutritional status (SGA), a modification of the SGA originally described by Detsky et al.²³ Trained research nurses of the dialysis centers scored patients' recent weight change, dietary intake, and gastro-intestinal symptoms, conducted a physical examination of loss of subcutaneous fat mass and muscle wasting according to a standardized protocol, and assigned a summary score of 1 to 7.^{24;25} In this study, we combined the severely and moderately malnourished groups (scores of 1 to 5) to define the presence of malnutrition. Daily protein intake was estimated in peritoneal dialysis patients from their urea excretion in urine and dialysate according to Bergström et al.,²⁶ and expressed as normalized protein equivalent of nitrogen appearance (nPNA). In hemodialysis patients PNA was calculated from the increase in plasma urea between two subsequent dialysis sessions, using a single pool model,²⁷ and was also normalized to standard body weight. We defined low protein intake as nPNA<0.99 g/kg/d, and BMI was calculated as weight (kg) divided by height (m) squared.

Statistical analyses

Mean values with standard deviations (SDs) were calculated for continuous variables. Categorical variables were expressed in proportions. All analyses were performed separately for patients starting hemodialysis or peritoneal dialysis. Univariate linear regression analysis was used to estimate the relationship of serum albumin with nPNA and logarithmically transformed CRP (log CRP) at baseline. The Kruskal-Wallis test was used to compare serum albumin per SGA category at baseline. Hemodialysis and peritoneal dialysis patients were divided into quartiles of serum albumin concentrations at baseline. Observed survival per quartile of serum albumin was computed by the Kaplan-Meier method. Cox regression analysis was used to calculate hazard ratios (HRs, equivalent to relative risks of mortality), with 95% confidence intervals (95% CIs) per unit of decrease in serum albumin (g/dL). We adjusted this association once for nutritional status, once for protein intake, and once for inflammatory status of the patients (Figure 1).

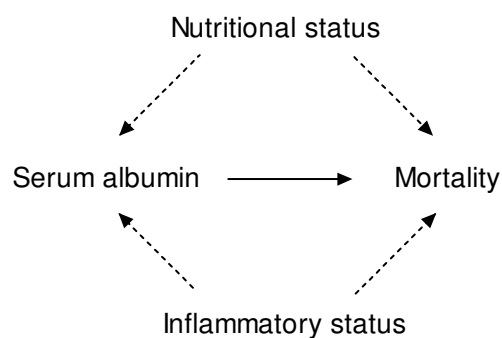


Figure 1. The observed association between serum albumin and mortality (black arrow) is possibly caused by nutritional status, and/or by inflammatory status (broken arrows).

For this purpose, SGA, nPNA and CRP were categorized according to our definitions, and were included in turn as covariates in the model. For example, when the association between serum albumin and mortality disappeared after adjustment for covariate X, it meant that the association is explained by factor X, and that serum

albumin lies within the causal pathway between X and mortality. If the association remained, we concluded that the mortality risk associated with serum albumin was independent from factor X. Afterward, we included all covariates at the same time in one model, to estimate the association of serum albumin with mortality after adjustment for SGA, nPNA and CRP. Finally, the model was adjusted for age, sex and comorbidity. We used SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL) for all analyses.

RESULTS

Patient characteristics

Of 856 patients with available blood samples, serum CRP concentrations were determined in 842 patients who began dialysis in NECOSAD between February 1997 and September 2001. Serum albumin concentrations were determined in 839 of these patients. Of these, 23 patients did not complete the SGA at 3 months. In addition, information on nPNA was missing in 116 patients. Thus, 700 patients (454 starting hemodialysis [HD] and 246 starting peritoneal dialysis [PD]) were included in the analysis. The mean age (SD) was 59 (15) years, the mean BMI was 24.7 (4.1) kg/m², and 60% were men. The main causes of chronic kidney disease were diabetes mellitus (15% of patients), glomerulonephritis (13% of patients), and renal vascular diseases (18% of patients). According to our definitions, at baseline, 25% of patients were malnourished, 34% had low protein intake, and 31% suffered from inflammation.

The hemodialysis patients were older, more often women, and more often at high risk according to the comorbidity index of Khan et al.²⁰ (Table 1). The mean serum albumin concentration was lower in the peritoneal dialysis patients. At baseline, serum albumin concentration was inversely related to log CRP in HD patients ($r = -0.209$, $p < 0.01$) and PD patients ($r = -0.109$, $p < 0.01$), less strong, positively to nPNA (HD, $r = 0.066$, $p = 0.16$; PD, $r = 0.111$, $p = 0.08$), and not to SGA (HD, $p = 0.87$; PD, $p = 0.61$). Cross-sectional plots for the total population are given in Figure 2A-C.

Table 1. Baseline characteristics of 454 hemodialysis patients and 246 peritoneal dialysis patients at the start of dialysis

	HD	PD
N	454	246
Age (y)	63 ± 13	52 ± 14
Sex (% men)	57	67
BMI (kg/m ²)	24.7 ± 4.3	24.8 ± 3.9
Primary kidney disease (%)		
Glomerulonephritis	10	20
Diabetic nephropathy	16	14
Renal vascular disease	21	13
rGFR (ml/min/1.73 m ²)	3.4 ± 2.6	4.3 ± 2.9
Comorbidity* (% high)	29	15
Serum albumin (g/dL)	3.4 ± 0.7	3.2 ± 0.8
SGA (% 1-5)	29	17
nPNA (g/kg/d)	1.01 ± 0.22	1.02 ± 0.23
nPNA < 0.99 g/kg/d (%)	51	49
CRP (mg/L)	12.6 ± 19.8	10.0 ± 19.7
CRP < 5 mg/L (%)	44	52
5 ≤ CRP < 10 mg/L (%)	20	24
CRP ≥ 10 mg/L (%)	36	24

*Comorbidity according to Khan comorbidity score

BMI=Body mass index, rGFR=residual Glomerular filtration rate, HD=hemodialysis, SGA=Subjective global assessment of nutritional status, nPNA=normalized protein nitrogen appearance, CRP=C-reactive protein.

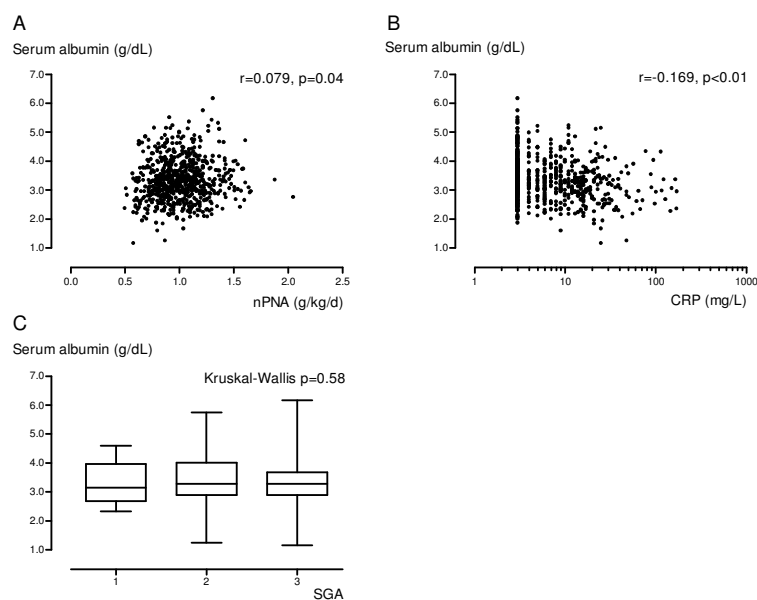


Figure 2. Cross-sectional relations at baseline in 700 dialysis patients of A: Serum albumin and nPNA, B: Serum albumin and log CRP and C: Serum albumin and SGA in three categories (1=severe malnutrition, score of 1-3; 2=moderate malnutrition, score of 4-5; 3=normal nutritional status, score of 6-7).

Serum albumin and mortality

In two years after the start of dialysis, 134 patients died, 66 because of cardiovascular causes (98 events in the HD group, and 36 events in the PD group). The cumulative mortality of the total population in 2 years was 21%. Figure 3 shows the Kaplan-Meier curves for hemodialysis (Figure 3A) and peritoneal dialysis (Figure 3B) separately. Both HD and PD patients with a serum albumin concentration in the lowest quartile had a significantly poorer survival than patients in the higher quartiles of serum albumin.

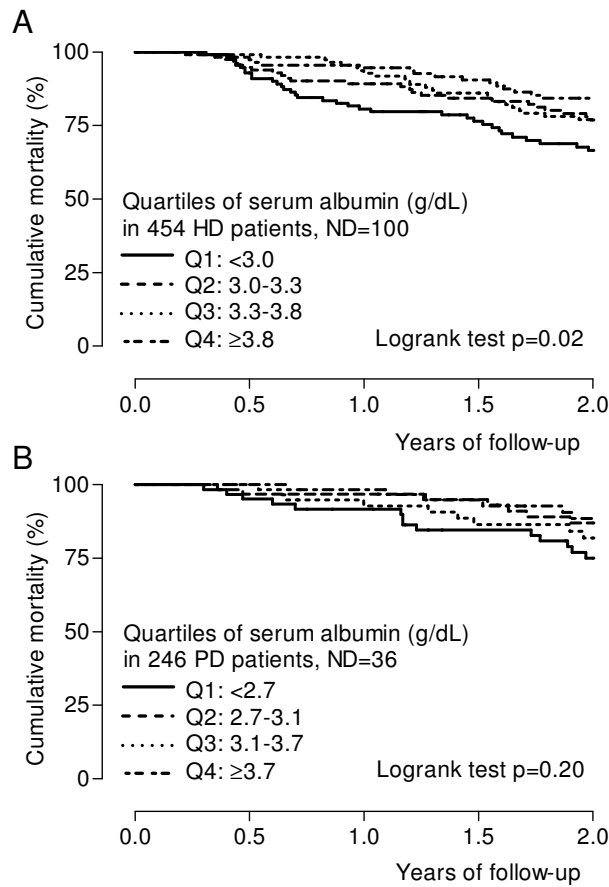


Figure 3. Kaplan-Meier curves in 454 hemodialysis (HD) patients (Figure A) and 246 peritoneal dialysis (PD) patients (Figure B) per quartile of serum albumin at baseline during the first two years of chronic dialysis treatment. ND=number of deaths in two years of follow-up.

The univariate HRs (with 95% CIs) of all variables are shown in Table 2. The first row in Table 3 shows the crude HRs of serum albumin during the first 2 years of chronic dialysis treatment per unit decrease in serum albumin (g/dL) in HD (HR, 1.47; 95% CI, 1.07 to 2.00) and PD (HR, 1.38; 95% CI, 0.87 to 2.20) patients. Adjustment for SGA did not decrease this HR, whereas adjustment for nPNA decreased the HR to 1.45 (95% CI, 1.06 to 1.97) in HD patients, and 1.32 (95% CI, 0.83 to 2.10) in PD patients. The mortality risk decreased to 1.30 (95% CI, 0.95 to 1.78) in HD and 1.17 (95% CI, 0.75 to 1.81) in PD patients after adjustment for inflammation, and did not further decrease after additional adjustment for SGA and nPNA (Table 3, model 9). In this model, nutritional status (HD, 1.55; 95% CI, 1.03 to 2.35; PD, 2.29; 95% CI, 1.12 to 4.69) and inflammation (CRP \geq 10 mg/L; HD, 2.62; 95% CI, 1.61 to 4.25; PD, 2.52; 95% CI, 1.15 to 5.53) remained independently associated with 2-year all-cause mortality (nPNA HD, 1.43; 95% CI, 0.95 to 2.16; nPNA PD, 1.65; 95% CI, 0.81 to 3.39). Additional adjustment for age, sex and comorbidity further decreased the HR to 1.09 (95% CI, 0.79 to 1.51) in HD patients, and 0.95 (95% CI, 0.63 to 1.43) in PD patients.

Table 2. Univariate relative mortality risks (hazard ratios with 95%-confidence intervals) of nutritional, inflammatory and clinical variables during the first two years of chronic dialysis treatment in 454 hemodialysis and 246 peritoneal dialysis patients.

Variables	HR (95%-CI)	
	HD patients	PD patients
Albumin (g/dL decrease)*	1.47 (1.07-2.00)	1.38 (0.87-2.20)
SGA (score 1-5)†	1.65 (1.10-2.47)	2.79 (1.39-5.58)
nPNA (<0.99 g/kg/day)†	1.57 (1.05-2.36)	2.08 (1.04-4.15)
CRP** (vs CRP<5 mg/L)	1	1
5 \geq CRP<10 mg/L	1.67 (0.91-3.07)	0.91 (0.34-2.41)
CRP \geq 10 mg/L	3.04 (1.90-4.88)	3.52 (1.69-7.31)
Age (year)*	1.04 (1.02-1.06)	1.05 (1.03-1.08)
Sex (men)†	1.19 (0.80-1.79)	1.35 (0.65-2.79)
Comorbidity‡ (vs low risk)	1	1
Medium risk	3.83 (1.86-7.89)	6.96 (2.33-20.81)
High risk	6.61 (3.24-13.48)	15.23 (5.09-45.59)

*Unit of hazard ratios

†Groups of patients tested against the opposite reference category

**C-reactive protein, with patients with a CRP<5 mg/L as reference

‡Kahn comorbidity score, with patients at low risk as reference

SGA=Subjective global assessment of nutritional status, nPNA=normalized Protein nitrogen appearance, CRP=C-reactive protein, HD=hemodialysis.

DISCUSSION

The present study showed that 2 years after the start of dialysis, a 1-g/dL decrease in serum albumin was associated with a 47% increased mortality risk in HD patients, and a 38% increased mortality risk in PD patients. These mortality risks were in part explained by the inflammatory pathway, but not by malnutrition as measured with SGA and nPNA. Furthermore, in the final model, inflammation and nutritional status remained risk factors of all-cause mortality, whereas serum albumin did not. These findings imply that nutritional status predicts mortality, but cannot be assessed with precision by measurement of serum albumin.

This study is, to the best of our knowledge, the first to investigate the effects of adjustment for markers of both nutritional and inflammatory status on the strength of the association between serum albumin and mortality. With this approach, our results extend earlier findings about CRP as a more powerful predictor of mortality for HD patients than hypoalbuminemia.^{12,28}

In our study, patients starting PD treatment had lower serum albumin concentrations, possibly because of losses in the dialysate.^{9,29} Furthermore, they were younger and healthier than the patients starting HD. The Kaplan-Meier curves showed that in both HD and PD, patients in the lowest quartile of serum albumin had the worst survival, implying similar effects of serum albumin on mortality. These effects changed similarly after adjustment for nutrition and inflammation in HD and PD patients, although confidence intervals were wider in the PD population because of the smaller sample size. Although the magnitude and direction of the associations were similar in HD and PD patients, we present the results separately for the two modality groups because they may differ in many ways,²⁹ and because PD patients may present the healthiest and most motivated patients, as indicated by their differences at baseline.

The associations we found in PD and HD patients, of 1.38 and 1.47 per g/dL decrease in serum albumin, respectively, with all-cause mortality in 2 years of follow-up, are weaker compared to the 3-to-4 times increased risk reported in

earlier studies.^{1,2} The association with mortality may be more pronounced among patients with lower levels of serum albumin. When the total patient population was divided into quartiles based on serum albumin levels at baseline, the lowest quartile (<2.9 g/dL) was associated with a 1.74 (95% CI, 1.08 to 2.80) increased mortality risk, compared with the highest quartile of serum albumin (>3.8 g/dL), which is still lower than in earlier reports. Differences in study design and methodology may contribute to this potential discrepancy. Moreover, earlier populations with low serum albumin levels may have been more diseased in general. Because of such differences between populations, comparisons of relative mortality risks between studies are complex.

nPNA made a minor contribution to the associations between serum albumin and mortality. Moreover, protein intake did not contribute to the mortality risk after adjustment for inflammation. A possible explanation is that inflammation and protein intake may be related via appetite. Appetite is known to be reduced in the presence of inflammation, possibly leading to lower dietary intakes in patients.³⁰ The relationship between protein intake and serum albumin concentrations may thus be confounded by inflammation.

Table 3. Univariate and multivariate relative mortality risks (hazard ratios with 95%-confidence intervals) of serum albumin per g/dL decrease during the first two years of chronic dialysis treatment in 454 hemodialysis and 246 peritoneal dialysis patients.

Model	Covariates	Effect of serum albumin (HR (95%-CI) per g/dL decrease)	
		HD (n=454)	PD (n=246)
1	Univariate (Serum albumin)	1.47 (1.07-2.00)	1.38 (0.87-2.20)
2	1+ SGA (score 1-5)*	1.48 (1.09-2.01)	1.37 (0.87-2.16)
3	1+ nPNA (<0.99 g/kg/day)*	1.45 (1.06-1.97)	1.32 (0.83-2.10)
4	1+ CRP (in 3 categories)**	1.30 (0.95-1.78)	1.17 (0.75-1.81)
5	1+ SGA + nPNA	1.46 (1.08-1.98)	1.31 (0.83-2.05)
6	5+ BMI	1.47 (1.08-1.99)	1.25 (0.79-1.96)
7	1+ SGA + CRP	1.30 (0.95-1.78)	1.19 (0.77-1.84)
8	1+ nPNA + CRP	1.30 (0.95-1.78)	1.14 (0.74-1.78)
9	1+ SGA + nPNA + CRP	1.31 (0.96-1.78)	1.17 (0.76-1.80)
10	9+ age + sex	1.19 (0.86-1.64)	1.05 (0.69-1.61)
11	10+ comorbidity†	1.09 (0.79-1.51)	0.95 (0.63-1.43)

*Groups of patients tested against the opposite reference category

**C-reactive protein in 3 categories with a CRP<5 mg/L as reference category

†Khan comorbidity score

+ = model noted additionally adjusted for, SGA=Subjective global assessment of nutritional status, nPNA=normalized Protein nitrogen appearance, BMI=Body mass index, CRP=C-reactive protein, PKD=Primary kidney disease.

We used SGA and nPNA as markers of nutritional status. Although information on weight change is already included in the SGA, we adjusted the associations of serum albumin and mortality once for BMI as a marker of nutritional status, in addition to SGA and nPNA (Table 3, model 6). This extra adjustment for BMI did not affect the association between serum albumin and mortality in HD patients, further indicating that the mortality risk of serum albumin is not explained by malnutrition. In contrast to what was reported previously,¹⁻³ serum albumin was not an independent predictor of mortality risk in our study after adjustment for markers of nutritional status, protein intake and inflammation. In the final models, the HR of serum albumin per g/dL decrease was 1.09 (95% CI, 0.79 to 1.51) in HD patients, and 0.95 (95% CI, 0.63 to 1.43) in PD patients.

The present study has potential limitations. First, the use of nutritional supplements was not determined. Several intervention studies in dialysis patients showed an effect of nutritional supplements on serum albumin concentrations and on mortality.^{17,18} Therefore, it is not known to what extent the results of this observational cohort study may apply to patients receiving dietary intervention. Second, the choice of a 2-year follow-up may seem arbitrary. However, because serum albumin is variable over time, its short-term effects may be more important than its long-term effects. Although the association between serum albumin and mortality was stronger in the first year of follow-up and weaker in 3 years of follow-up, the effects of adjustment for inflammatory and nutritional status persisted in the same directions (data not shown).

Third, the present study focused on baseline serum albumin concentrations. If the cause of hypoalbuminemia is responsible for morbidity and mortality, changes in serum albumin may be especially important in predicting outcomes. In a study of time-varying effects of serum albumin on mortality, decreasing serum albumin values over time continued to have a strong association with outcomes, even after adjustment for surrogates of the malnutrition-inflammation complex syndrome.⁴ Other studies suggest that longitudinal changes in CRP are the strongest predictors of longitudinal changes in serum albumin,³¹⁻³³ which strengthens the findings in our study.

During the past few years, many studies suggested that malnutrition and inflammation may be pathophysiologically linked in patients with chronic renal failure.^{6,34,35} Inflammation may induce muscle proteolysis and catabolism, leading to a wasting illness.^{12,30} However, serum albumin concentrations, reflecting visceral protein mass, are not influenced by the process of muscle protein breakdown.¹⁴ Thus, whereas inflammation and malnutrition may be related, hypoalbuminemia does not seem to be part of that relationship. Current evidence on possible mechanisms suggests that hypoalbuminemia is most likely caused by the acute-phase response or the cause of the acute-phase response.^{6,10,33}

In conclusion, the mortality risk of serum albumin was partly explained by inflammation, but not by malnutrition. Furthermore, nutritional status and inflammation remained risk factors of all-cause mortality, whereas serum albumin did not. This research implies that nutritional status predicts mortality, but cannot be assessed with precision by measurement of serum albumin.

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