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Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients

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Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients.

Background. Prealbumin (transthyretin) is a hepatic secretory protein thought to be important in the evaluation of nutritional deficiency and nutrition support. Prior studies have suggested that the serum prealbumin concentration is independently associated with mortality in hemodialysis patients, even with adjustment for serum albumin and other nutritional parameters.

Methods. To determine whether prealbumin was independently associated with mortality and morbidity (cause-specific hospitalization) in hemodialysis patients, we analyzed data on 7815 hemodialysis patients with at least one determination of serum prealbumin during the last three months of 1997. Unadjusted, case mix-adjusted, and multivariable-adjusted relative risks of death were calculated for categories of serum prealbumin using proportional hazards regression. We also determined whether the prealbumin concentration was associated with all-cause, cardiovascular, infection-related, and vascular access-related hospitalization.

Results. The relative risk (RR) of death was inversely related to the serum prealbumin concentration. Relative to prealbumin ≥ 40 mg/dL, the adjusted RRs of death were 2.41, 1.85, 1.49, and 1.23 for prealbumin <15 , 15–20, 20–25, and 25–30 mg/dL, respectively. The adjusted RRs of hospitalization due to infection were 2.97, 1.95, 1.81, and 1.61 for prealbumin <15 , 15–20, 20–25, and 25–30 mg/dL, respectively. The adjusted RRs of vascular access-related hospitalization were 0.48, 0.52, 0.58, and 0.71 for prealbumin <15 , 15–20, 20–25, and 25–30 mg/dL, respectively. While serum albumin was strongly associated with mortality and all-cause hospitalization, it was not associated with hospitalization due to infection, and lower levels were associated with higher rather than lower rates of vascular access-related hospitalization.

Conclusion. In hemodialysis patients, lower prealbumin concentrations were associated with mortality and hospitalization due to infection, independent of serum albumin and other clinical characteristics. Higher prealbumin concentrations were as-

sociated with vascular access-related hospitalization. In light of these findings, more intensive study into the determinants and biological actions of prealbumin (transthyretin) in end-stage renal disease is warranted.

Protein energy malnutrition (PEM) affects a large fraction of maintenance hemodialysis patients and is unequivocally associated with mortality and morbidity [1]. While difficult to define, PEM depends on several intersecting dimensions of health and disease, including reduced dietary intake, sarcopenia, and loss of subcutaneous fat (often referred to as “somatic mass”) and reduced concentrations of plasma proteins and leukocytes (often referred to as “visceral mass”) [2]. Inflammation directly affects the catabolism of plasma proteins as well as hepatic synthesis [3].

While serum albumin has proved to be a potent predictor of mortality and cardiovascular morbidity in patients with end-stage renal disease (ESRD), several studies have suggested that other plasma proteins, including prealbumin, have additive predictive value [4–9]. For example, we previously demonstrated a significant (2.5-fold) increase in risk among hemodialysis patients with prealbumin concentrations <20 mg/dL, but were unable to identify an optimal prealbumin concentration, or a level below which a definitive increase in risk could be identified [10]. Moreover, prior studies have focused only on mortality without consideration of hospitalization or other morbidities.

Therefore, we aimed to determine the risk profile associated with the spectrum of prealbumin concentrations in a large cohort of hemodialysis patients, using mortality as the principle outcome of interest. We also explored the association between prealbumin concentration and cause-specific hospitalization. We hypothesized that prealbumin would be independently associated with mortality and associated with hospitalization due to cardiovascular disease and infection.

Key words: prealbumin, mortality, dialysis, infection, vascular access, epidemiology.

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METHODS

Data source

The sample of patients was taken from the Fresenius Medical Care North America Patient Statistical Profile system. The database and methods of abstraction have been previously described [11]. The cohort consisted of patients on thrice weekly hemodialysis as of January 1, 1998 who had at least one determination of serum phosphorus and calcium during the last three months of 1997. Where repeated, all laboratory data were averaged to provide a better estimate of exposure. The sample included 40,538 patients. Of the 40,538 patients, 7815 (19.3%) had at least one serum prealbumin concentration during the three-month period. Patients with and without prealbumin determinations were compared to assess generalizability. Prealbumin was categorized a priori into seven categories in 5 mg/dL increments: <15, 15–20, 20–25, 25–30, 30–35, 35–40, and ≥ 40 mg/dL.

The primary ICD-9-CM code for each hospitalization was recorded. Cardiovascular hospitalization incorporated the following ICD-9-CM codes: 390–459 (diseases of the circulatory system), 518.4 (acute pulmonary edema), 276.6 (fluid overload), 785 (symptoms involving cardiovascular system), 786.5 (chest pain), 780.2 (syncope and collapse), and 798 (sudden death). Infection-related hospitalization included the following ICD-9-CM codes: 001–139 (infectious and parasitic diseases), 320–324 (meningitis and encephalitis), 421 (endocarditis), 480–486 (pneumonia), 590 (infections of the kidney), 680–686 (infections of the skin and subcutaneous tissue), and 790.7 (bacteremia). Vascular access-related (non-infection-related) hospitalization included ICD-9-CM codes 996.1 and 996.70, 73, and 74.

Several confounding variables were included in the analyses. Age, sex, race, or ethnicity, diabetes, and vintage (time since initiation of dialysis) were considered to represent “case mix.” Laboratory variables included parameters of mineral metabolism [phosphorus, calcium, and parathyroid hormone (PTH)], hematologic status (hemoglobin and ferritin), and other markers of nutritional status [serum albumin, predialysis blood urea nitrogen (BUN), creatinine, cholesterol, and bicarbonate]. Body size was estimated using body weight, body surface area, or Quetlet’s (body mass) index. Dialysis dose was estimated using the urea reduction ratio (URR) or the indexed or nonindexed urea clearance \times time product (Kt/V_{urea} and Kt_{urea}).

Statistical analyses

Continuous variables were expressed as mean \pm standard deviation or median with interquartile range and compared with parametric [Student *t* test or analysis of variance (ANOVA)] or nonparametric tests (Wilcoxon rank sum test or the Kruskal–Wallis test), where ap-

propriate. Categorical variables were expressed as proportions and compared with the χ^2 test. We calculated unadjusted survival rates using the Kaplan–Meier product limit method. Unadjusted, case mix-adjusted, and multivariable-adjusted survival analyses were performed using the proportional hazards regression model. Relative risks (RR) and 95% confidence intervals (95% CI) were calculated from model parameter coefficients and standard errors, respectively. Multivariable models were constructed with backward variable selection, using $P < 0.05$ for variable retention. Plots of $\log(-\log[\text{survival rate}])$ against $\log(\text{survival time})$ were performed to establish the validity of the proportionality assumption. Effect modification was evaluated by including multiplicative interaction terms for selected variables. Factors not included in multivariable models were reentered individually to evaluate for residual confounding ($>10\%$ change in the parameter estimate for prealbumin or albumin). There were few missing laboratory data except for PTH ($N = 1566$, 20%) and cholesterol ($N = 1946$, 25%). To avoid a significant loss of power we categorized these data and included missing indicator variables in regression models. Patients who underwent kidney transplantation ($N = 337$, 4.3%), recovered kidney function ($N = 34$, 0.4%), transferred dialysis facilities ($N = 1071$, 13.7%), withdrew from dialysis ($N = 303$, 3.9%), or were lost to follow-up for unknown reasons ($N = 4$, 0.05%) were censored. Two-tailed P -values < 0.05 were considered statistically significant. Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Clinical characteristics of patients with and without prealbumin determinations

To determine whether there were material differences in patients who did and did not have determinations of serum prealbumin during the evaluation period, we compared baseline characteristics of the two populations ($N = 7815$ and $N = 32,723$, respectively, shown in Table 1). Many of the differences were relatively small, although statistically significant, owing to the large sample sizes. Patients who were tested were less likely to be African American (34.3% vs. 45.1%, $P < 0.0001$). The mean age was only slightly higher in tested patients. Testing was unrelated to sex or diabetes. Among tested patients, the median vintage was lower; body weight, Quetlet’s index, serum creatinine, and albumin were significantly lower, although modestly so.

The difference in the fraction of African Americans among tested and nontested patients confounded the differences in baseline nutritional indicators. For example, among African Americans, testing was unrelated to the mean serum albumin concentration ($P = 0.33$), and patients who were tested had marginally higher serum

Table 1. Clinical characteristics of patients with and without prealbumin determinations

| | +Prealbumin (N = 7815) | -Prealbumin (N = 32,723) | P value |
|---|---------------------------|-----------------------------|---------|
| Age years | 61.5 ± 15.1 | 60.3 ± 15.1 | <0.0001 |
| Sex% female | 51.0% | 51.3% | 0.61 |
| Race/ethnicity% | | | <0.0001 |
| Caucasian | 46.2% | 35.3% | |
| African American | 34.3% | 45.1% | |
| Hispanic | 16.4% | 16.0% | |
| Other | 3.2% | 3.6% | |
| Diabetes% | 46.5% | 46.5% | 0.93 |
| Vintage years | 1.61 (0.76–2.80) | 1.72 (0.77–3.00) | <0.0001 |
| Weight kg | 71.5 ± 18.1 | 72.4 ± 18.7 | <0.0001 |
| Quetelet's (body mass) index kg/m ² | 26.4 ± 7.4 | 26.7 ± 7.8 | 0.0012 |
| Bicarbonate mEq/L | 20.6 ± 3.0 | 21.1 ± 3.0 | <0.0001 |
| BUN mg/dL | 59.1 ± 16.6 | 59.0 ± 16.5 | 0.54 |
| Creatinine mg/dL | 9.3 ± 3.3 | 9.7 ± 3.3 | <0.0001 |
| Albumin g/dL | 3.84 ± 0.40 | 3.86 ± 0.40 | <0.0001 |
| Cholesterol mg/dL | 169 ± 42 | 171 ± 42 | 0.0005 |
| Hemoglobin g/dL | 10.5 ± 1.1 | 10.4 ± 1.1 | 0.002 |
| Ferritin µg/L | 406 (202–675) | 415 (209–686) | 0.0001 |
| URR% | 68.4% ± 7.6% | 68.7% ± 7.3% | 0.0004 |
| Phosphorus mg/dL | 5.8 ± 1.6 | 5.8 ± 1.6 | 0.51 |
| Calcium mg/dL | 9.1 ± 0.8 | 9.0 ± 0.8 | 0.0005 |
| PTH pg/mL | 132 (60–295) | 153 (68–348) | <0.0001 |

Note: mean ± standard deviation except for vintage, ferritin, and PTH (median, interquartile range).

creatinine concentrations than those not tested (11.0 ± 3.5 vs. 10.8 ± 3.4, $P = 0.04$).

Crude mortality rates were higher in the tested population (22.5% vs. 19.8% in the nontested population, $P < 0.0001$). However, after adjusting for baseline covariates, the risk associated with prealbumin testing was attenuated and race-dependent. Among African Americans, testing for prealbumin was significantly associated with mortality (RR 1.17, 95% CI 1.08 to 1.29), whereas among non-African Americans, the association between prealbumin testing and mortality was weak (RR 1.06, 95% CI 0.99 to 1.12). Thus, the cohort with prealbumin data appeared to be somewhat sicker than the general hemodialysis population.

Distribution and correlates of prealbumin

The mean serum prealbumin was 32.0 ± 8.8 mg/dL. The mean serum prealbumin was significantly higher with younger age, and significantly higher in men (32.9 vs. 31.1 mg/dL in women, $P < 0.0001$), African Americans (33.9 vs. 30.9 in whites, $P < 0.0001$), and among persons without diabetes (33.3 vs. 30.5 mg/dL in persons with diabetes, $P < 0.0001$). Table 2 shows the distribution of patient characteristics by categories of prealbumin concentration. Serum prealbumin concentrations were directly related to other parameters of nutritional status, including body weight and laboratory proxies of nutritional status and dietary intake (i.e., predialysis blood urea nitrogen, creatinine, albumin, phosphorus, and bicarbonate).

Prealbumin and mortality

Figure 1 shows the relative risks (RR) of mortality associated with prealbumin concentration, considering serum prealbumin ≥40 mg/dL as the referent category. The unadjusted results showed significantly increased RRs (95% CI) for all categories of prealbumin below 40 mg/dL: 6.72 (5.35 to 8.48), 4.12 (3.44 to 4.94), 2.82 (2.39 to 3.23), 2.04 (1.73 to 2.40), 1.58 (1.38 to 1.86), and 1.37 (1.15 to 1.63) for prealbumin <15, 15–20, 20–25, 25–30, 30–35, and 35–40 mg/dL, respectively. The RRs were attenuated with adjustment for case mix, although all categories of prealbumin retained a significantly higher RR than the referent category. On multivariable analysis, including serum albumin and other nutritional parameters, the adjusted RRs were 2.41 (1.84 to 3.16), 1.85 (1.50 to 2.27), 1.49 (1.24 to 1.78), and 1.23 (1.04 to 1.47), for prealbumin categories of <15, 15–20, 20–25, and 25–30 mg/dL, respectively. The RR associated with prealbumin 30–35 mg/dL was increased by 16%, but not significantly so. Other predictors of mortality included: advanced age, male sex, white race, diabetes, longer dialysis vintage, lower body weight, hemoglobin, and serum albumin and creatinine, and higher phosphorus, calcium, and PTH (Table 3). There were U- or J-shaped relations among mortality and bicarbonate, ferritin, and URR.

Prealbumin, albumin, and hospitalization

There were 4805 hospitalizations recorded. Lower prealbumin concentrations were associated with an increased risk of all-cause hospitalization. The RRs were 1.95 (1.60 to 2.37), 1.67 (1.48 to 1.89), 1.55 (1.40 to 1.72), 1.30 (1.18 to 1.42), and 1.17 (1.07 to 1.28) for prealbumin <15, 15–20, 20–25, 25–30, and 30–35, respectively. As above, the RRs of all-cause hospitalization were attenuated with adjustment for case mix, although RRs for all categories of prealbumin remained significantly higher than the referent category. The multivariable RRs of all-cause hospitalization were 1.58 (1.29 to 1.93), 1.37 (1.20 to 1.56), 1.32 (1.18 to 1.47), and 1.15 (1.04 to 1.27), for prealbumin categories of <15, 15–20, 20–25, and 25–30 mg/dL, respectively. Other predictors of all-cause hospitalization were older age, white race, diabetes, lower body weight, lower hemoglobin, bicarbonate, and URR and higher ferritin.

Cardiovascular hospitalization

There were 1180 cardiovascular hospitalizations recorded. The association between prealbumin concentration and cardiovascular hospitalization was of marginal statistical significance (RR 1.08, 95% CI 1.01 to 1.15 per 10 mg/dL decrease), and was not significant after multivariable adjustment (RR 1.07, 95% CI 0.99 to 1.15). Other predictors of cardiovascular hospitalization were

Table 2. Clinical characteristics by prealbumin concentration

| | <15 (N = 170) | 15–20 (N = 524) | 20–25 (N = 1022) | 25–30 (N = 1512) | 30–35 (N = 1736) | 35–40 (N = 1411) | ≥ 40 (N = 1440) | P value |
|------------------------------------|------------------|--------------------|---------------------|---------------------|---------------------|---------------------|--------------------|---------|
| Age years | 64.8 | 66.1 | 63.8 | 63.6 | 61.1 | 60.6 | 56.8 | <0.0001 |
| Sex% female | 53.5% | 56.9% | 54.2% | 51.7% | 50.8% | 47.3% | 38.6% | <0.0001 |
| Race/ethnicity% | | | | | | | | |
| Caucasian | 50.6% | 53.2% | 49.5% | 53.0% | 47.1% | 42.4% | 36.1% | |
| African American | 29.4% | 25.6% | 27.5% | 27.1% | 33.2% | 39.3% | 46.9% | |
| Hispanic | 18.2% | 18.1% | 19.6% | 17.2% | 16.8% | 14.3% | 13.8% | |
| Other | 1.8% | 3.1% | 3.4% | 2.8% | 2.9% | 4.0% | 3.3% | |
| Diabetes% | 55.3% | 56.9% | 58.4% | 51.4% | 45.6% | 43.4% | 32.5% | <0.0001 |
| Vintage years | 1.37 | 1.27 | 1.38 | 1.62 | 1.63 | 1.65 | 1.69 | <0.0001 |
| Weight kg | 67.9 | 67.5 | 68.0 | 70.2 | 71.8 | 73.2 | 75.3 | <0.0001 |
| Quetelet's index kg/m ² | 25.4 | 25.2 | 25.4 | 26.2 | 26.5 | 27.0 | 27.2 | <0.0001 |
| Bicarbonate mEq/L | 21.5 | 21.6 | 21.0 | 20.9 | 20.6 | 20.3 | 19.9 | <0.0001 |
| BUN mg/dL | 44.3 | 49.6 | 53.7 | 56.3 | 60.0 | 62.7 | 66.4 | <0.0001 |
| Creatinine mg/dL | 6.3 | 7.0 | 7.9 | 8.5 | 9.4 | 10.2 | 11.5 | <0.0001 |
| Albumin g/dL | 3.12 | 3.41 | 3.62 | 3.78 | 3.88 | 3.98 | 4.11 | <0.0001 |
| Cholesterol mg/dL | 124 | 142 | 155 | 167 | 173 | 179 | 186 | <0.0001 |
| Hemoglobin g/dL | 9.8 | 10.0 | 10.2 | 10.4 | 10.6 | 10.6 | 10.7 | <0.0001 |
| Ferritin µg/L | 406 | 370 | 388 | 381 | 391 | 415 | 432 | <0.0001 |
| URR% | 66.2% | 67.6% | 67.7% | 68.8% | 68.5% | 68.8% | 68.3% | 0.002 |
| Phosphorus mg/dL | 5.1 | 5.3 | 5.6 | 5.7 | 5.9 | 5.9 | 6.0 | <0.0001 |
| Calcium mg/dL | 8.6 | 8.8 | 8.9 | 9.0 | 9.1 | 9.2 | 9.3 | <0.0001 |
| PTH pg/mL | 106 | 126 | 124 | 125 | 132 | 143 | 149 | 0.0005 |

Note: mean ± standard deviation except for vintage, ferritin, and PTH (median, interquartile range).

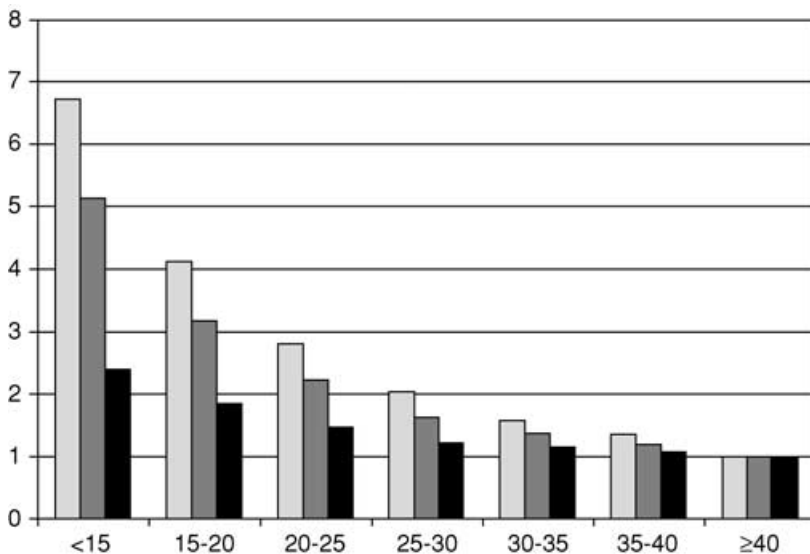


Fig. 1. The relative risk of death associated with serum prealbumin concentration. Light gray bars are unadjusted. Medium gray bars are case mix-adjusted (age, sex, race or ethnicity, diabetes, and vintage). Black bars are multivariable-adjusted (case mix + body weight, dialysis dose, and serum concentrations of creatinine, albumin, bicarbonate, hemoglobin, ferritin, phosphorus, calcium, and PTH).

advanced age, diabetes, higher concentrations of phosphorus, calcium, and ferritin, and lower concentrations of bicarbonate. The serum albumin was not associated with cardiovascular hospitalization in this cohort ($P = 0.70$).

Infection-related hospitalization

There were 567 hospitalizations attributed to infection. Lower prealbumin concentrations were associated with an increased risk of hospitalization due to infection. Adjusted RRs were 2.97 (1.88 to 4.70), 1.95 (1.36 to 2.80), 1.81 (1.33 to 2.47), and 1.61 (1.20 to 2.16) for prealbumin <15, 15–20, 20–25, and 25–30 mg/dL, respectively.

The RR associated with prealbumin 30–35 mg/dL was increased by 24%, but not significantly so. Of the 567 hospitalizations due to infection, 234 (41%) were associated with pneumonia and 141 (25%) separately coded for bacteremia or sepsis. There was no association between serum albumin (and other laboratory variables) and the risk of hospitalization due to infection.

Vascular access-related hospitalization

Finally, we examined the associations among prealbumin, albumin, and vascular access-related (non-infection-related) hospitalization ($N = 696$). Lower prealbumin concentrations were associated with a

Table 3. Prealbumin and other predictors of mortality on multivariable analysis

| Factor | RR | 95% CI | P-value |
|----------------------------------|------|--------------|---------|
| Prealbumin referent 40 mg/dL | | | |
| <15 mg/dL | 2.41 | 1.84 to 3.16 | <0.0001 |
| 15–20 mg/dL | 1.85 | 1.50 to 2.27 | <0.0001 |
| 20–25 mg/dL | 1.49 | 1.24 to 1.78 | <0.0001 |
| 25–30 mg/dL | 1.23 | 1.04 to 1.47 | 0.017 |
| 30–35 mg/dL | 1.16 | 0.98 to 1.37 | 0.09 |
| 35–40 mg/dL | 1.08 | 0.90 to 1.29 | 0.40 |
| Age per decade | 1.28 | 1.24 to 1.33 | <0.0001 |
| Male referent female | 1.26 | 1.14 to 1.38 | <0.0001 |
| Race or ethnicity referent white | | | |
| African American | 0.90 | 0.80 to 1.00 | 0.06 |
| Hispanic | 0.83 | 0.73 to 0.94 | 0.003 |
| Other | 0.75 | 0.57 to 1.00 | 0.047 |
| Diabetes referent no diabetes | 1.21 | 1.11 to 1.33 | <0.0001 |
| Vintage referent <2 years | | | |
| 2–5 years | 1.17 | 1.04 to 1.31 | 0.008 |
| ≥5 years | 1.27 | 1.07 to 1.52 | 0.007 |
| Body weight per 10 kg | 0.91 | 0.89 to 0.94 | <0.0001 |
| Creatinine per mg/dL | 0.93 | 0.91 to 0.95 | <0.0001 |
| Albumin per 0.1 g/dL | 0.94 | 0.93 to 0.96 | <0.0001 |
| Hemoglobin per g/dL | 0.88 | 0.85 to 0.92 | <0.0001 |
| Calcium per mg/dL | 1.17 | 1.10 to 1.24 | <0.0001 |
| Phosphorus per mg/dL | 1.09 | 1.06 to 1.13 | <0.0001 |
| PTH per 100 pg/mL | 1.01 | 1.00 to 1.03 | 0.03 |

In addition to the factors noted above, there were curvilinear associations between URR and mortality ($P = 0.004$ and $P = 0.0007$) for linear and quadratic terms, bicarbonate and mortality ($P = 0.0007$ and $P = 0.003$ for linear and quadratic terms), and ferritin and mortality ($P < 0.0001$ and $P = 0.0005$ for linear and quadratic terms).

decreased risk of vascular access–related hospitalization. Adjusted RRs were 0.48 (0.25 to 0.90), 0.52 (0.35 to 0.77), 0.58 (0.43 to 0.78), 0.71 (0.55 to 0.92) for prealbumin <15, 15–20, 20–25, and 25–30 mg/dL, respectively. In contrast, higher serum albumin was associated with a decrease in the risk of access-related hospitalization (adjusted RR 0.72, 95% CI 0.58 to 0.90 per 1 g/dL increase).

Vintage, prealbumin, and mortality

In addition to the effects of dietary intake and inflammation on prealbumin, the degree of kidney function may influence prealbumin concentrations. To explore whether residual kidney function was confounding the relations among prealbumin and outcomes, we tested whether the association between prealbumin and mortality was influenced by vintage, a reasonable proxy for residual kidney function. We also evaluated for effect modification by age, sex, race, or ethnicity and diabetes. No interaction terms were statistically significant ($P > 0.20$ for all interactions, individually or in combination).

Prealbumin and albumin combinations

To determine the predictive power of serum prealbumin across the range of serum albumin concentrations, we ranked both laboratory parameters into quintiles, and examined the RR of mortality associated with serum pre-

albumin concentrations within relatively narrow, fixed concentrations of albumin. The median within each prealbumin quintile was 20.7, 27.1, 31.9, 36.6, and 43.2 mg/dL. The median within each albumin quintile was 3.33, 3.67, 3.87, 4.07, and 4.30 g/dL. Figure 2 shows the RR of mortality for prealbumin quintiles within albumin quintiles. Lower prealbumin concentrations were associated with increased risk across the spectrum of serum albumin—particularly among patients at the extremes.

DISCUSSION

Prealbumin, also known as transthyretin, is a 54,000 D protein synthesized primarily by the liver. Its main function is to transport thyroxine and indirectly vitamin A, as it serves as a carrier protein for retinol-binding protein [12]. In humans, prealbumin has been shown to increase with increases in protein and calorie intake and to decrease when protein intake is inadequate [12]. In addition, albumin and prealbumin are negative acute-phase proteins. Serum concentrations of albumin and prealbumin decline in response to inflammation as a consequence at least in part of decreased synthesis [13, 14], although other factors such as altered vascular permeability affect the concentrations of these plasma proteins [15]. In contrast to serum albumin, the half-life of prealbumin is relatively short (approximately 2–3 days vs. 14–21 days) [16, 17]. It has therefore been suggested that prealbumin may be a more sensitive indicator of nutritional status than serum albumin [18, 19].

Several studies have demonstrated an association between prealbumin and mortality [4–10]. For example, Mittman et al [8] found that a serum prealbumin <30 mg/dL at the initiation of dialysis was associated with an increased risk of death in 258 dialysis patients (half on peritoneal, half on hemodialysis) followed over 10 years, even with adjustment for age, sex, race or ethnicity, diabetes, vintage, and other nutritional parameters. In an earlier report, prealbumin values <25 mg/dL were associated with mortality in unadjusted and case mix-adjusted analyses, but the multivariable results were significant only with prealbumin concentrations <20 mg/dL [10]. In the present study, we demonstrated a graded increase in the mortality risk across the spectrum of prealbumin concentrations, with significant increases in risk observable below 40 mg/dL (<30 mg/dL with multivariable adjustment), suggesting that optimal values are in excess of 30–40 mg/dL.

As before, we demonstrated that while albumin and prealbumin are directly correlated, both are strongly and independently associated with mortality. The disparate associations of albumin and prealbumin with cause-specific hospitalization are of particular interest. In this cohort, prealbumin concentration was associated with the risk of hospitalization due to infection, while

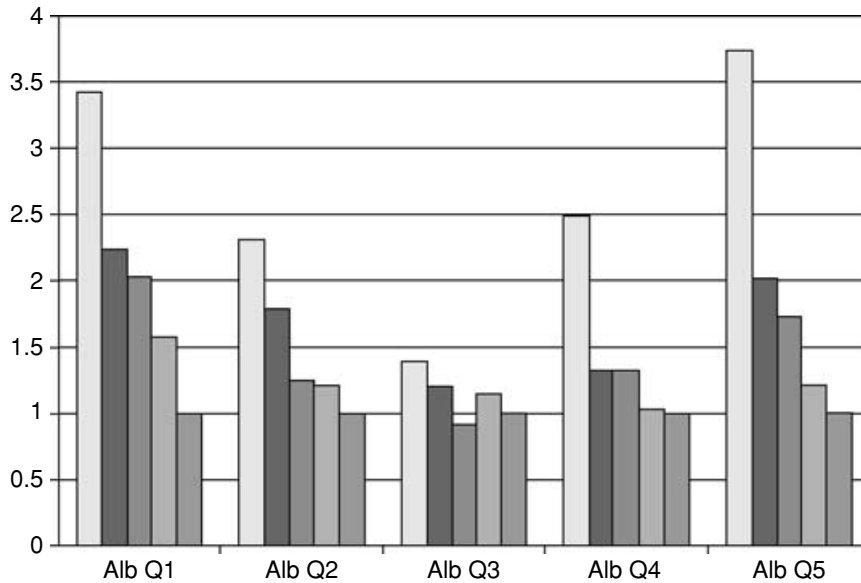


Fig. 2. The relative risk of death associated with serum prealbumin (in quintiles), stratified by quintiles of serum albumin (denoted as Alb Q1, Q2, Q3, Q4, and Q5).

albumin concentration was not. Since prealbumin is a negative acute-phase protein that is relatively short lived, it may be a particularly sensitive reflection of activation of the acute-phase response. Prior activation of the acute-phase response has been associated with decreased release of interleukin-6 and tumor necrosis factor- α when patients are subsequently challenged with an infectious agent, potentially explaining the increased risk of infection associated with low levels of prealbumin [20]. Patients with evidence of activation of the acute-phase response, as evidenced by increased concentrations of C-reactive protein, interleukin-6, and α -1-antitrypsin and decreased concentrations of prealbumin preoperatively experience a higher risk of postoperative infectious complications [21, 22]. Moreover, decreased levels of prealbumin and other negative acute-phase proteins are associated with decreased cellular-mediated immunity [23], abnormalities that may be reversed with parenteral nutrition [24].

Previous studies have demonstrated an association between hypoalbuminemia and vascular access thrombosis [25, 26]. We were initially surprised to observe a lower risk of vascular access-related hospitalizations with lower prealbumin concentrations. We cannot determine the mechanism underlying this association. Prealbumin may be a more sensitive indicator of acute hepatic dysfunction than albumin [27]. In a small study of cancer patients receiving cefoperazone, lower prealbumin concentrations were associated with hypoprothrombinemia [28]. While laboratory proxies of the coagulation cascade were not available on the 7815 patients described here, there was a strong association between prealbumin and cholesterol, another marker of the liver's synthetic capacity (Table 2). Moreover, median aspartate aminotransferase (AST) concentrations were significantly higher

among patients with low prealbumin concentrations, as was the proportion of patients with AST above the laboratory normal range (data not shown).

There are several limitations to the data presented here. First, residual confounding might dampen or enhance the relative risks described here. More precise estimates of risk associated with prealbumin concentrations might be obtained with additional adjustment for comorbidity and inflammatory markers, although these would be unlikely to extinguish the associations described. Second, because prealbumin concentrations were measured at baseline, some exposures may have been misclassified. Had prealbumin been analyzed as a time-dependent covariate, the magnitude of the relative risks would have probably been higher. Third, the use of primary ICD-9-CM diagnosis codes limits the capacity to identify associations between prealbumin and cause-specific hospitalization. There may have been additional hospitalizations for infection or vascular access that were not captured. In particular, the 270 (5.5%) hospitalizations coded with the primary ICD-9-CM code 585 (chronic renal failure) may have had informative secondary and tertiary ICD-9-CM codes. Finally, the study sample was restricted to hemodialysis patients, so that the associations described cannot be extrapolated to peritoneal dialysis patients or to persons with less severe degrees of chronic kidney disease.

CONCLUSION

In a cohort of 7815 hemodialysis patients, lower prealbumin concentrations were associated with mortality, all-cause hospitalization and, particularly, hospitalization for infection. These findings were independent of age, sex, race, diabetes, vintage, and other laboratory

factors, including serum albumin. Serum prealbumin concentrations >30–40 mg/dL were associated with the lowest risk of death. These data support the presence of unique pathophysiologic pathways within which prealbumin may operate, and suggest that monitoring of prealbumin should be incorporated into nutritional assessment and monitoring in dialysis units. Additional work is required to better understand the biological functions of prealbumin and the specific response of the protein to exogenous factors, such as uremia, starvation, and nutrition intervention.

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