Uremic malnutrition is a predictor of death independent of inflammatory status

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Background. Several studies have pointed out the influence of nutritional parameters and/or indices of inflammation on morbidity and mortality. Often, these conditions coexist, and the relative importance of poor nutritional status and chronic inflammation in terms of predicting clinical outcomes in chronic hemodialysis (CHD) patients has not been clarified.

Methods. We undertook a prospective cohort study analyzing time-dependent changes in several established nutritional and inflammatory markers, and their influence on mortality in 194 CHD patients (53% male, 36% white, 30% with diabetes mellitus, mean age 55.7 ± 15.4 years) throughout a 57-month period. Serial measurements of serum concentrations of albumin, prealbumin, creatinine, transferrin, cholesterol, and C-reactive protein (CRP), as well as normalized protein catabolic rate, postdialysis weight, and phase angle and reactance by bioelectrical impedance analysis were performed every 3 months. Clinical outcomes were simultaneously assessed using indicators of mortality.

Results. Serum albumin, serum prealbumin, serum creatinine, and phase angle were significant predictors of all-cause mortality, even after adjustment for serum CRP concentrations. Serum CRP concentrations were not significantly associated with mortality. Serum albumin concentrations and phase angle were also independent predictors of cardiovascular deaths in the multivariate model.

Conclusion. The nutritional status of CHD patients predicts mortality independent of concomitant presence or absence of inflammatory response. Prevention of, and timely intervention to treat uremic malnutrition by suitable means are necessary independent of the presence and/or therapy of inflammation in terms of improving clinical outcomes in CHD patients.

Uremic malnutrition and chronic inflammation are highly prevalent in chronic hemodialysis (CHD) patients [1, 2]. These comorbid conditions tend to coexist, and

a number of CHD patients with elevated markers of inflammation tend to have higher incidence of uremic malnutrition [1]. Several studies also linked chronic inflammation and uremic malnutrition to clinical outcome separately [3–7]. Presence of each condition is identified as strong predictor of increased risk of death and hospitalization events. Nevertheless, there is ongoing controversy regarding the relative importance of these 2 conditions in terms of predicting mortality in CHD patients. Studies have shown that the predictive ability of serum albumin is dissipated when adjusted for the influence of C-reactive protein (CRP) [8]. Owen et al reported contrary findings, suggesting that serum albumin is a reliable indicator even when adjusted for CRP [9], albeit the follow-up in this particular study was limited to 6 months.

In order to clarify the relationship between uremic malnutrition, chronic inflammation, and their [independent] ability to predict mortality in CHD, we prospectively studied 194 CHD patients over a 57-month period, evaluating a broad range of nutritional markers and a marker of inflammatory response at multiple time points, and monitored death as a marker of long-term clinical outcome. Our results indicate that the presence of uremic malnutrition predicts mortality (all-cause and cardiovascular) independent of the presence of inflammation in CHD patients.

METHODS

Patients

Patients were recruited from Vanderbilt University Outpatient Dialysis Clinic. The study period was from January 1996 through December 2000. All prevalent patients in February 1996, and all incident patients thereafter (after 90 days of initiation), were asked to participate in this study. Enrollment period was from January 1996 to December 1999. A total of 194 patients on CHD therapy agreed to be followed and were included in this study. All patients were dialyzed with biocompatible membranes throughout the study period. Patients' routine laboratory parameters, such

Table 1. Patient characteristics

Gender (M/F)	102 (53.1%)/92 (46.9%)
Race (W/AA)	71 (35.8%)/123 (64.2%)
Age *years*	55.7 ± 15.4
Etiologic disease *N* (%)	
Diabetes mellitus	57 (29.38%)
Hypertension	36 (18.56%)
Glomerulonephritis	21 (10.82%)
Other	20 (10.31%)
Unknown	60 (30.93%)

as hemoglobin, serum phosphorus, and serum calcium were kept within acceptable ranges through established protocols. Recombinant human erythropoietin and intravenous iron (Dextran) were prescribed to keep hematocrit within the range of 33% to 36%. All patients underwent monthly formal urea kinetic modeling during the study period. Urea reduction ratio (URR) and Depner kinetics for Kt/V were used once a month during the study period to assess the dose of dialysis, with a goal of URR ≥70% and Kt/V ≥1.4. The minimum dialysis dose prescribed at the dialysis unit was single pool Kt/V ≥1.4, and the attending nephrologists determined the dialysis prescription for individual patients.

The Institutional Review Board approved the study protocol, and informed consent was obtained from study patients. Patients' characteristics are depicted in Table 1.

Study design

This was a prospective cohort of 194 CHD patients. The study consisted of serial (every 3 months) measurements of serum albumin, serum prealbumin, serum creatinine, serum transferrin, serum total bicarbonate (tCO_2), serum CRP, normalized protein catabolic rate (nPCR), body mass index (BMI), and the bioelectrical impedance analysis (BIA)-derived nutritional markers phase angle and reactance. There were no specific interventions in patient care related to the study. Mortality was recorded and documented as "all-cause mortality," as well as "specific-cause" mortality (grouped as cardiovascular, infection, and other causes).

Methods

Sample collections were completed within the first week of each month of data analysis in a nonfasting state before the hemodialysis session (Monday or Tuesday). On the day of the sample collection, patients underwent BIA at approximately 30 minutes after completion of hemodialysis. C-reactive protein (high sensitivity) was measured using nephelometric analysis at the Vanderbilt University Medical Center clinical chemistry laboratory. The other measurements were done at a specialized ESRD clinical and special chemistry laboratory (Spectra Laboratories, San Juan, CA, USA). Serum albumin

was analyzed using bromcresol green technique. Serum prealbumin was analyzed by an antigen-antibody complex assay, and serum transferrin was analyzed by turbidimetric reading (Hitachi 717; Boehringer Mannheim, Indianapolis, IN, USA). Bioelectrical Impedance analysis was performed using a hand-held device (Quantum BIA 101 Q; RJL Systems, Clinton Township, MI, USA) [10]. Resistance and reactance values obtained from BIA were processed into Cyprus 1.2 software system (RJL Systems), allowing the calculation of body composition parameters, including phase angle and reactance.

Statistical analysis

Analyses of study results focused on estimating the association between the continuous variables serum albumin, serum prealbumin, serum creatinine, serum transferrin, serum CRP, nPCR, phase angle, and reactance with a binary outcome (mortality). The primary end point in this study was all-cause mortality, and the secondary end point was cardiovascular mortality. Associations between study variables at baseline with mortality were performed with the generalized linear model. Multivariate analyses of time-dependent changes in study variables across time points, as well as tests of associations between these changes with mortality, were completed by using the restricted/residual maximum likelihood-based mixed effect model to adjust the intracorrelation effect for the patients who had multiple follow-up measurements [11, 12]. We included possible two-way interactions in this model for testing the statistical significance of interactions. The model used was selected based on Akaike's Information Criterion [13]. In addition to evaluating the study variables at baseline, we also averaged these variables across all time points for each patient to obtain a "grand mean." With its inherent limitations, we believe the "grand mean" is a more comprehensive representation of the study variables than the single baseline value for an individual patient. Comparisons between patients who survived with those who died according to the grand mean study variables were done using the Student *t* test for normally distributed data, and the Mann-Whitney *U* test for non-normally distributed data. Associations of the grand mean with all-cause mortality, as well as with cardiovascular mortality, were tested using survival analyses. These were completed with log-rank tests and presented with Kaplan-Meier tables in univariate models. All tests of significance were two-sided, and differences were considered statistically significant when *P* value was less than 0.05. All data were expressed as mean ± SD. SAS version 8.02 (Cary, NC, USA) was used for all analyses.

RESULTS

One hundred and ninety-four patients were included in this study (Table 1). Throughout the study period

Table 2. The baseline and 6-month interval levels of study parameters (mean ± SD)

Variable	Baseline $N = 194$	M6 $N = 189$	M12 $N = 174$	M18 $N = 144$	M24 $N = 108$	M30 $N = 83$	M36 $N = 66$	M42 $N = 52$	M48 $N = 25$
Salb *g/dL*	3.70 ± 0.5	3.78 ± 0.4	3.81 ± 0.4	3.82 ± 0.4	3.79 ± 0.4	3.82 ± 0.4	3.80 ± 0.4	3.80 ± 0.4	3.98 ± 0.4
SCr *mg/dL*	9.1 ± 3.9	9.7 ± 3.7	10.2 ± 3.3	10.2 ± 3.3	10.2 ± 3.4	10.3 ± 3.3	10.4 ± 3.5	10.8 ± 3.7	11.4 ± 3.2
Spreal *mg/dL*[a]	31.4 ± 8.9	33.3 ± 9.3	33.5 ± 8.8	34.3 ± 10.0	33.5 ± 10.3	34.2 ± 9.1	32.9 ± 9.8	33.1 ± 8.3	36.3 ± 10.1
Strans *mg/dL*	186 ± 39	177 ± 33	176 ± 34	165 ± 32	162 ± 34	158 ± 32	163 ± 33	166 ± 35	177 ± 36
Schol *mg/dL*	182 ± 44	174 ± 38	170 ± 38	175 ± 40	171 ± 41	168 ± 36	169 ± 36	161 ± 38	161 ± 36
Phang *degrees*	5.4 ± 1.7	5.6 ± 1.8	5.4 ± 1.8	5.6 ± 2.0	5.9 ± 2.0	6.3 ± 2.0	6.0 ± 1.9	6.3 ± 1.8	6.7 ± 1.6
React *ohms*	50 ± 16	52 ± 16	51 ± 15	54 ± 18	57 ± 18	59 ± 16	59 ± 19	60 ± 16	62 ± 16
Pst HD wt *kg*[a]	76 ± 22	76 ± 21	77 ± 20	77 ± 22	79 ± 22	81 ± 20	85 ± 20	84 ± 18	78 ± 17
CRP *mg/dL*	1.4 ± 2.1	1.2 ± 1.8	1.6 ± 2.4	1.8 ± 2.4	1.7 ± 2.6	2.4 ± 2.6	2.0 ± 3.2	3.8 ± 1.1	1.9 ± 2.3
NPCR *g/kg/d*	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2

Abbreviations are: Salb, serum albumin; SCr, serum creatinine; Sprealb, serum prealbumin; Strans, serum transferrin; Schol, serum cholesterol; Phang, phase angle; React, reactance; Pst HDwt, post hemodialysis weight; CRP, serum C-reactive protein; nPCR, normalized protein catabolic rate.

[a]$P < 0.05$ for trend over 48 months.

50 patients (22 male, 28 female) died, 23 patients transferred out, 10 patients received kidney transplants, and 7 patients switched to peritoneal dialysis. Data were collected until patients were censored from the study (study period completion, transfer, transplant, or death). Mean follow-up was 36 months (range 6–57 months). Overall survival during the study period was 89% at 24 months, 77% at 36 months, 54% at 48 months, and 47% at 57 months. This unexpectedly high survival rate might be due to an unintentional selection bias towards inclusion of healthy subjects in the study. Causes of death were cardiovascular for 23 patients, infectious for 15 patients, and other causes for 9 patients. The cause of death was unknown for 3 patients.

Baseline values of nutritional markers predict mortality

We examined the 5-year predictive power of each study variable at baseline. Our results confirmed those previously published, in that baseline values of the nutritional markers serum albumin, serum prealbumin, serum creatinine, phase angle, and postdialysis weight significantly and negatively predicted all-cause mortality during the study period ($P < 0.01$ for all). Contrarily, CRP values at baseline were positively associated with mortality in this population, with a marginal statistical significance ($P = 0.06$).

Time-dependent changes in study variables

Mean (± SD) values of study parameters at baseline and at 6-month intervals (up to 48 months) are depicted in Table 2. The baseline concentration was 3.70 ± 0.48 g/dL for serum albumin, 9.1 ± 3.9 mg/dL for serum creatinine, 31.4 ± 8.9 mg/dL for serum prealbumin, 186 ± 39 mg/dL for serum transferrin, 5.4 ± 1.7 degrees for phase angle, 50 ± 16 ohms for reactance, and 1.4 ± 2.1 mg/dL for CRP. Most of the study variables were stable with the exception of slight, but statistically significant, increases in postdial-

Table 3. The mean values for each study parameter grouped according to survivors and nonsurvivors

	Survivors	Nonsurvivors
CRP *mg/dL*	1.6 ± 1.3	1.9 ± 1.3
Salb *g/dL*	3.8 ± 0.3[a]	3.6 ± 0.3
Screat *mg/dL*	10.1 ± 3.3[a]	8.4 ± 2.4
Sprealb *mg/dL*	34.2 ± 7.7[a]	28.5 ± 6.6
Post-HD weight *kg*	80.1 ± 21.1[a]	70.2 ± 21.1
Phase angle *degrees*	6.0 ± 1.4[a]	4.4 ± 1.4

[a]Denotes significant difference vs. nonsurvivors.

ysis body weight and serum prealbumin concentrations during the study period ($P < 0.05$ for both).

Nutritional markers are overall associated with mortality

We initially compared the overall means of study variables between survivors and nonsurvivors by averaging all measurements for each individual patient over time, and then averaging according to survivor status (grand mean). Table 3 shows mean values (± SD) of study variables in survivors and nonsurvivors (all-cause mortality). All averaged nutritional markers were significantly different between the 2 groups (i.e., patients who died had lower averaged levels of serum albumin, serum creatinine, serum prealbumin, phase angle, reactance, and body weight during the study period compared to patients who survived). The inflammation marker CRP was higher in patients who died, but the difference did not reach statistical significance (1.95 ± 1.35 vs. 1.59 ± 1.30, respectively, $P > 0.05$).

Patients were then grouped according to quartiles of the "grand mean" serum concentrations of albumin, prealbumin, creatinine and CRP to perform univariate survival analyses. Figures 1, 2, and 3 depict Kaplan-Meier survival tables for quartiles of serum albumin, serum prealbumin, and serum creatinine. As can be seen, there is a significant difference in survival status comparing highest versus lowest quartile by log-rank test ($P < 0.001$),
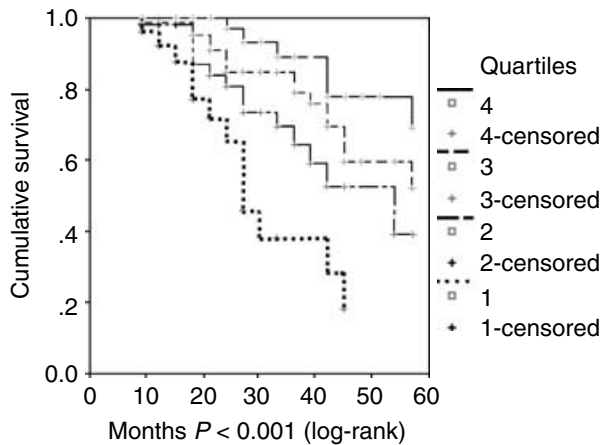
Fig. 1. Kaplan-Meier survival curves for quartiles of mean serum albumin during the study period. *P* < 0.001 for Q4 vs. Q1, by log-rank test.
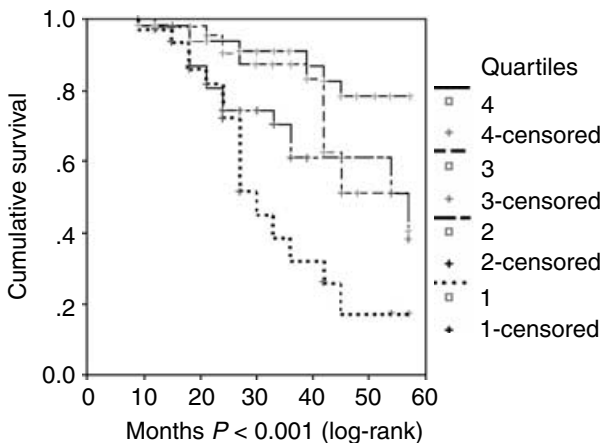

Fig. 2. Kaplan-Meier survival curves for quartiles of mean serum prealbumin during the study period. *P* < 0.001 for Q4 vs. Q1, by log-rank test.

Fig. 3. Kaplan-Meier survival curves for quartiles of mean serum creatinine during the study period. *P* < 0.001 for Q4 vs. Q1, by log-rank test.

Fig. 4. Kaplan-Meier survival curves for quartiles of mean CRP during the study period. *P* = 0.275 for Q4 vs. Q1, by log-rank test.

which starts to be evident after 20 months. A similar analysis with CRP showed no significant survival difference comparing highest versus lowest quartiles of serum CRP (Fig. 4, *P* = 0.275). Remarkably, patients in the lowest quartile of both serum albumin and serum prealbumin displayed a mortality rate of more than 20% at 2 years, and close to 80% at 4 years of follow-up.

Changes in nutritional markers overtime predict all-cause mortality

We looked at the predictive power of the changes in nutritional markers over the study period by multivariate mixed model, including serum concentrations of albumin, prealbumin, creatinine, and CRP, in addition to case-mix adjustments (age, gender, race). We found that changes in serum albumin, serum creatinine, and serum prealbumin over time were strong predictors of all-cause
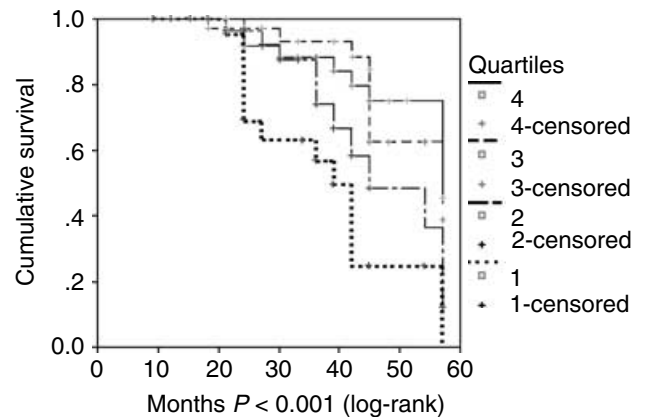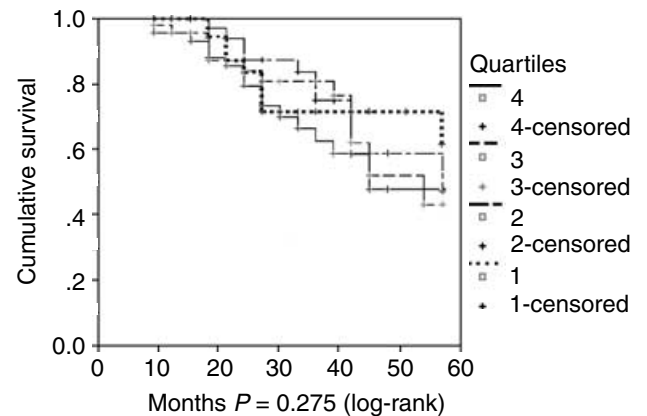
mortality even after CRP (with and without log transformation) was incorporated into the model (*P* < 0.01 for all). When analyzing the same group of covariates by time-dependent Cox regression, serum albumin, prealbumin, and creatinine were still strong predictors, with serum prealbumin at a lesser extent (*P* = 0.06). Table 4 depicts the parameter estimates of the changes with hazard ratios and level of significance of each variable. Based on these estimates, in practical terms, a decrease of 0.31 g/dL in serum albumin concentration [i.e., the difference from the means in fourth (4.17 g/dL) and third quartiles (3.86 g/dL)] was associated with an increased relative risk of death of 6.3. Likewise, a decrease in serum albumin of 0.28 g/dL, which is the difference from the means in third (3.86 g/dL) and second quartiles (3.58 g/dL), was associated with a relative risk of death of 8.1 (Fig. 5). Similar strong associations between decreases in serum prealbumin and increased risk of death were observed (data not shown).

Table 4. Relationship between changes in study variables over the study period with mortality

Variable	Parameter estimate	Standard error	Hazard ratio	P value
Albumin	−29.12	14.33	0.000	**0.042**
Prealbumin	−1.71	0.93	0.181	**0.068**
Phase angle	−1.93	2.45	0.145	0.448
Creatinine	−6.15	2.65	0.002	**0.020**
CRP	1.15	1.14	3.174	0.309
Age	0.059	0.02	1.060	**0.001**
Gender	−0.103	0.39	0.902	0.790
Race	0.430	0.41	1.537	0.290

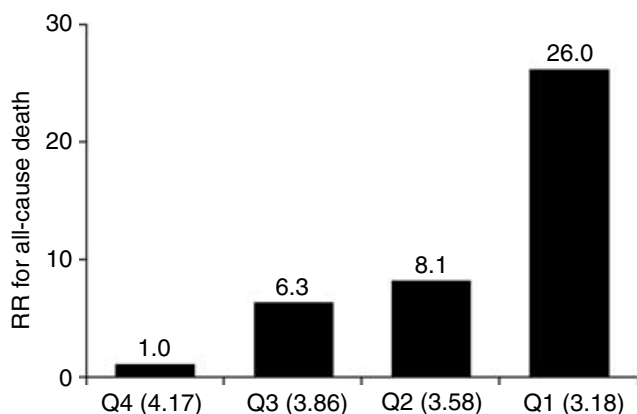Bolded numbers denote $P < 0.15$ in multivariate time-dependent Cox regression model.

Fig. 5. Relative risk for all-cause death according to quartiles of mean serum albumin during the study period. Patients with serum albumin concentrations ≤3.18 g/dL were 26 times more likely to die of any cause compared with those with serum albumin concentrations ≥4.17 g/dL. $P < 0.001$ Q2, 3, and 4 vs. Q1.

Nutritional markers are predictors of cardiovascular mortality

Data were also analyzed according to specific causes of death. There were a total of 23 cardiovascular deaths during the study period. In univariate analyses, lower mean levels of serum albumin, serum prealbumin, serum creatinine, and phase angle at baseline were significant predictors of higher risks of cardiovascular mortality. Mean CRP (with and without log transformation) concentrations did not predict cardiovascular death in our study.

In multivariate models including grand mean values of serum albumin, serum prealbumin, serum creatinine, phase angle, CRP, and case-mix adjustment, serum albumin and phase angle were the only significant predictors of cardiovascular mortality, with phase angle displaying a very strong predictive power. As shown in Figure 6, a CHD patient in the lowest tertile for phase angle (mean 3.7 degrees) throughout the study period was 20 times more likely to die due a cardiovascular cause compared with a patient in the highest tertile (mean of 7.5 degrees).
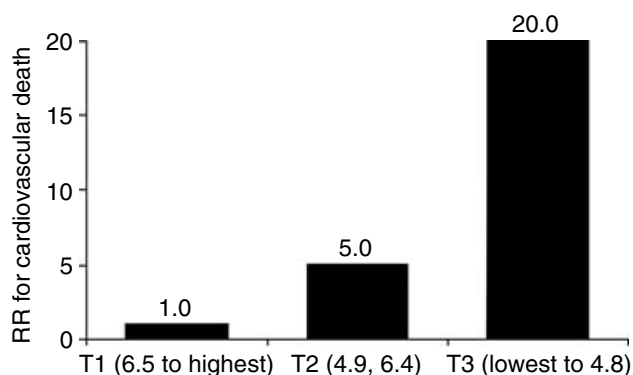

Fig. 6. Relative risk for cardiovascular death according to tertiles of mean phase angle during the study period. Patients with phase angle ≤4.8 degrees were 20 times more likely to die of cardiovascular complications compared with those with phase angle ≥6.5 degrees. $P < 0.001$ T3 vs. T1.

DISCUSSION

Markers of uremic malnutrition and inflammation not only tend to coexist, but are often inversely correlated in CHD patients [14, 15]. This observation has led investigators to believe that the nutritional markers are rather markers of overall health status with systemic inflammatory response syndrome (SIRS) as the primary driving force for changes in nutritional markers, resulting in problems with interpretation of the clinical relevance and importance of low levels of nutritional markers. Nevertheless, there are data to suggest that higher levels of DPI result in improvement in nutritional markers in the presence of inflammation [16]. This prospective cohort was designed to test the hypothesis that uremic malnutrition is associated with mortality in CHD patients independent of the presence of inflammatory response. The design was strengthened by utilization of a comprehensive array of nutritional markers along with multiple measurements of these variables over a relatively long study period. We were able to show that several nutritional markers, independent of the presence or absence of inflammatory response, were associated with mortality in our patient population. The implication of our study is that, although at times nutritional parameters such as serum albumin and serum prealbumin are indeed depressed in the presence of inflammation, most often they primarily reflect nutritional status, and that their association with adverse outcomes in relation to uremic malnutrition remains strong.

Several potential explanations can be speculated to interpret our results. It is most likely that nutritional status worsens over time due to multiple catabolic factors, including acute-phase response and associated morbid events, which ultimately results in increased risk of mortality in CHD patients [17]. Equally important, Kaysen et al [16] have shown that higher protein intake attenuates

the effects of inflammation. Further, poor nutritional status can also play a permissive role for the development of infections, which also activates inflammatory reaction. Therefore, poor nutritional status may also accelerate the adverse effects of inflammation on clinical outcomes. Nutritional support has been shown to improve protein and energy homeostasis, nutritional markers, and survival in chronic hemodialysis patients with low albumin levels, suggesting that poor nutritional status is an entity beyond the consequence of inflammation alone [18–20].

Our study has several unique features compared to previously published studies evaluating the relationship between nutritional status, inflammation, and clinical outcome. These earlier studies almost exclusively relied on a one-time assessment of study variables with subsequent follow-up of clinical outcome. Among these, several studies indicated that the predictive ability of serum albumin as a nutritional marker on clinical outcome is dissipated when adjusted for the influence of CRP, a well-established marker of inflammation [8]. On the other hand, findings by Owen et al suggest that serum albumin is a reliable indicator of nutritional status even when adjusted for CRP, albeit follow-up was limited to 6 months in this study [9]. In addition to utilization of a single point measurement of the predictive variables, these studies examined the limited number of nutritional markers. In the present study, we used a wide combination of nutritional markers along with an inflammation marker (CRP) over a period of 57 months (4.7 years). For example, the associations between serum albumin and clinical outcome were confirmed with measurements of serum prealbumin, serum creatinine, and phase angle, all of which have been suggested as excellent markers of nutritional status in CHD patients [4, 21]. Furthermore, low levels of both serum albumin and phase angle have been independently associated with higher risk of death in CHD patients [4, 22].

Another important characteristic of our study is the sequential assessment of study variables over the follow-up period. The importance of trends in clinically relevant markers is emphasized by a recent study by Pifer et al [23], where decreases in serum albumin and creatinine over 6 months are associated with increased risk of death. The present study provides information on time-dependent changes in nutritional parameters in association with a well-established inflammatory marker in terms of predicting mortality. Further, the availability of sequential measurements of CRP provides a reasonable approach to overcome the variability associated with this marker [24].

An interesting finding of this study is that we were only able to find a significant relationship between all-cause mortality and inflammation using baseline measurements of CRP. This finding is consistent with recently published studies [25–27]. On the other hand, mean CRP concentrations throughout the study period, as well as changes in CRP over time, did not predict all-cause mortality, both in univariate and multivariate analyses. While the explanation of this finding is not clear, there are several possible reasons. CRP is a short-lived acute-phase protein and may not be the ideal inflammatory marker for long-term clinical outcome. In this respect, a recent report by Kaysen et al [28] reported more stable associations between 2 long-lived inflammatory markers and serum albumin. Another possible explanation is that CRP concentrations are highly skewed. While our results were not different even with the use of log transformation of CRP, a categorical analysis using certain cut-off values may provide alternative results [25]. Clearly, further studies with potentially larger sample sizes are needed to elucidate the relationship between chronic inflammation and long-term outcome in CHD patients, especially if CRP is used as the primary variable.

In this study, we also analyzed our results with regard to specific causes of mortality. Recent cross-sectional prospective studies suggested a link between the extent of inflammation and cardiovascular outcomes in CHD patients [7]. The direct effects of chronic inflammation on the progression of cardiovascular disease, especially atherosclerotic coronary artery disease, are well documented, and atherosclerosis is considered as an inflammatory disease [29]. In spite of these observations, we were not able to find a significant correlation between CRP and cardiovascular deaths in our study population. While this finding is somewhat unexpected and warrants further larger-scale studies, the analysis revealed an intriguing association between nutritional markers and cardiovascular mortality in our patient population. Specifically, phase angle and serum albumin displayed significant associations with cardiovascular death. These findings are consistent with the clinical observations in cross-sectional studies that hypoalbuminemia correlates with cardiovascular mortality in ESRD patients [30]. Our results suggest that serum albumin as a measure of nutritional status is associated with cardiovascular outcomes, rather than as a marker of inflammation.

In spite of the intriguing results that are presented, one should also consider potential limitations of this study. This study is based on a relatively small sample size, and represents a single practice, limiting generalizability of findings. We measured only one inflammatory marker and thus, our findings related to inflammation cannot be extrapolated to other markers. Furthermore, the present study did not assess baseline cardiac risks factors such as atherosclerosis or left ventricular hypertrophy, factors that might have affected mortality independently from the nutritional markers examined and accounted for the differences in mortality observed. Finally, this is an observational study without manipulation of exposure factors (nutrition and inflammation) and, therefore, no definitive

cause and effect relationship can be derived. The findings of the current study provide stimulating data that should lead to large-scale, prospective, randomized studies that evaluate nutritional and anti-inflammatory interventions in CHD patients aimed at improving clinical outcome.

CONCLUSION

We report that uremic malnutrition robustly predicts mortality independent of concomitant presence of inflammatory response. Based on our findings, we conclude that proper preventive and/or therapeutic measures should be employed to fight uremic malnutrition, regardless of the inflammatory status. Overall, comprehensive long-term assessments, prevention of uremic malnutrition by suitable means, and timely intervention to treat poor nutritional status and inflammation are imperative in terms of improving clinical outcome in CHD patients.

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