Inflammation, Malnutrition, and Cardiac Disease as Predictors of Mortality in Hemodialysis Patients

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Abstract. Various studies suggest a strong association between nutrition and clinical outcome in hemodialysis (HD) patients. Several morbidity factors that *per se* increase the risk of a poor outcome, such as cardiovascular disease (CVD) and inflammation, may also cause malnutrition. Among laboratory parameters used to assess nutritional status, serum albumin appears to be a particularly strong predictor of morbidity and mortality. This study assessed the importance of nutritional status and inflammation and other comorbidity factors as predictors of mortality in HD patients. Nutritional status was evaluated in 128 HD patients by subjective global nutritional assessment (SGNA) and by measuring several anthropometric markers (actual body weight, percentage of actual body weight to desirable body weight, midarm muscle circumferences, triceps skinfold thickness), and serum albumin, plasma insulin such as insulin growth factor-1 and as a marker of inflammation, serum C-reactive protein (s-CRP) levels. The mortality during the next 36 mo was analyzed in relation to age, gender, CVD, SGNA, serum albumin, CRP, and several other factors by Kaplan-Meier analysis multivariate. Cox proportional hazard analysis was used to identify independent predictors of mortality. After 36 mo, 58 patients were still on HD treatment, 57 patients (45%) had died while receiving treatment, and 13 had received a kidney transplant. The main cause of death was CVD (58%), followed by infection (18%); malnutrition/cachexia was a rare direct cause of death (5%). Kaplan-Meier analysis showed that age, female gender, CVD, diabetes, SGNA, all anthropometric parameters, serum albumin, plasma insulinlike growth factor-1, and s-CRP were significant predictors of mortality. Analysis by the Cox model showed that age, gender, CVD, nutritional status (SGNA), and CRP were independent predictors of mortality at 36 mo. A low albumin level was not an independent predictor, although it was strongly associated with a reduced survival rate in the Kaplan-Meier analysis. Inflammation, malnutrition, and CVD appeared to contribute to increased mortality in a stepwise manner. The mortality at 36 mo was 0% when none of these complications was present, whereas the mortality was 75% in those patients with all three risk factors present at baseline. It is concluded that in addition to malnutrition and comorbidities (CVD, diabetes mellitus), inflammation (elevated s-CRP) is a significant independent risk factor for mortality in HD patients. Inflammation, malnutrition, and CVD appear to be interrelated, each additionally contributing to the high mortality in these patients.

Although maintenance dialysis therapy for end-stage chronic renal failure has been used for almost 40 yr, the mortality rate of dialysis patients remains unacceptably high (1,2). Several risk factors for this high rate have been identified, including advanced age, cardiovascular disease (CVD), and diabetes mellitus. CVD causes more than 50% of the deaths among maintenance dialysis patients, followed by infection (approximately 15%) (1,2).

The prevalence of protein-energy malnutrition in hemodialysis (HD) patients is high (23 to 73% in various studies) (3–7). Several recent reports have focused on the association between nutritional status and clinical outcome, providing support for the hypothesis that malnutrition may cause or contribute to mortality (6,8–15). In most of these studies, the evaluation of nutritional status was mainly based on measurements of serum albumin levels and other serum protein levels (8–11), but in a few, nutritional status was evaluated with anthropometry, subjective global nutritional assessment (SGNA), or total body nitrogen (13–15). Low protein intake (urea appearance rate) (16) and low relative body weight (6,17) have also been shown to be predictors of mortality in HD patients.

The role of nutrition as a mortality factor has not been clearly defined. Several morbidity factors that increase the risk of a poor outcome may also cause malnutrition, which may not be the direct cause of death but rather a marker of illness. Among laboratory parameters used to assess nutritional status, serum (s-) albumin levels appear to be a particularly strong predictor of mortality (8–12). However, although s-albumin is an index of nutritional status, reflecting visceral protein stores, its generation, distribution and elimination are affected by

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several non-nutritional factors, such as the state of hydration, capillary permeability, urinary and dialytic losses, infection, inflammation, and malignancies (18).

In 1998, we presented results of a cross-sectional study of nutritional status in 128 unselected HD patients aiming at identifying factors that predict malnutrition (7). We found that 65% of the patients were malnourished, as evaluated via SGNA. The patients with malnutrition were older, had lower levels of s-albumin, plasma insulinlike growth factor-1 (p-IGF-1), and s-creatinine than those with normal nutritional status. Signs of malnutrition were more common in patients with CVD than in those without CVD. Inflammation, as reflected by elevated serum C-reactive protein (s-CRP) levels, was more prevalent in the malnourished patients than in those with normal nutritional status, and s-CRP was negatively correlated with s-albumin.

In the study presented here, we have analyzed to what extent the various nutritional and non-nutritional factors recorded in the aforementioned cross-sectional study predicted the clinical outcome, measured as mortality over a period of 36 mo. Preliminary results of this study were presented at the Annual Meeting of the American Society of Nephrology in 1995 (19), where we showed for the first time that an elevated s-CRP is a strong predictor of mortality in HD patients.

Materials and Methods

The 128 patients (76 men and 52 women) participating in the cross-sectional study preceding this follow-up study were treated at the various dialysis centers affiliated to the Renal Clinic, Huddinge University Hospital, Stockholm, Sweden. The median age was 65 yr (range, 26 to 84 yr), and the mean age was 61 yr. All patients were white. The causes of renal failure included the following: diabetic nephropathy ($n = 23$), chronic glomerulonephritis ($n = 38$), polycystic kidney disease ($n = 13$), pyelonephritis and interstitial nephritis ($n = 14$), and other diseases or unknown cause ($n = 40$). Thirteen patients with diabetes were dependent on insulin.

Seventy-seven patients (60%) had signs of CVD, peripheral vascular disease, or both (grouped as CVD) when entering the study. Twenty of these had had at least one myocardial infarction, 15 patients had ischemic heart disease but no prior myocardial infarction, 1 patient had an aortic aneurysm, 11 had peripheral atherosclerotic vascular disease, and 19 experienced chronic heart failure without clinical signs of ischemic heart disease. Six patients had cerebrovascular disease with neurologic symptoms after one or more strokes; all of these patients also had signs of CVD.

HD was performed three times weekly. Dialyzers with low-flux, modified cellulosic membranes (cellulose acetate or derivatized cellulose) were used in 94% of the patients. No major changes were made in the dialysis treatment and schedules during the follow-up period.

In the cross-sectional study preceding this follow-up study, SGNA was used to evaluate the overall protein-energy nutritional status (20,21). The SGNA includes six subjective assessments, three based on the patient's history of weight loss, incidence of anorexia and incidence of vomiting, and three based on the physician's grading of muscle wasting, presence of edema, and loss of subcutaneous fat. On the basis of these assessments, each patient was given a score that reflected the nutritional status as follows: 1 = normal nutritional status, 2 = mild malnutrition, 3 = moderate malnutrition, and 4 =

severe malnutrition. Nutritional status was also evaluated by anthropometric methods, including triceps skinfold thickness, midarm muscle circumference (MAMC), and hand-grip strength (HGS), as described previously (7). The anthropometric values were expressed as the percentage of the normal mean value for each gender, as found in 24 men and 20 women, all of whom were healthy subjects.

Actual body weight (ABW) was recorded after dialysis with the subjects lightly dressed and without shoes. A difference in ABW from normal was recorded as the percentage of ABW to desirable body weight (DBW). DBW, based on the patient's height, gender, and frame size, was obtained from the Metropolitan Life Insurance Company's height and weight tables (22,23). The cross-sectional study also included determinations of *inter alia* blood hemoglobin, total leukocyte count, s-albumin, s-urea, s-creatinine, p-IGF-1, and s-CRP, which were analyzed with routine methods as described earlier (7). Only s-CRP values greater than 10 mg/L were quantified by the laboratory. Venous blood samples were collected on a dialysis-free day immediately before the anthropometric measurements. Blood samples were also collected before and after HD for determination of urea. The outcome single-pool Kt/V_{urea} was calculated according to Daugirdas method (24), and the normalized protein equivalent of nitrogen appearance (nPNA) was assessed by urea kinetic modeling (25). Kt/V_{urea} and PNA were also "normalized" to the DBW as described elsewhere (7).

After the cross-sectional study, the patients were followed for 36 mo or until the patient died or had a renal transplant (within 36 mo). In patients who died, the primary cause of death was recorded, as obtained from the death certificate or patient records (in some cases, the autopsy protocol).

The Ethics Committee of Karolinska Institutet at Huddinge University Hospital approved the study protocol, and informed consent was obtained from all patients who participated in the cross-sectional study.

Statistical Analyses

Data are presented as mean ± SD. $P < 0.05$ was considered to be significant. The Kaplan-Meier test was used for analysis of survival. The data were censored for renal transplantation. Differences in survival were assessed with the log rank test. For the continuous variables, we compared survival of patients above and below the median (upper and lower 50th percentile). An exception was s-CRP, for which the median value could not be defined because CRP values less than 10 mg/L were not quantified. Therefore, for CRP, we compared survival of patients above and below the highest tertile (upper tertile *versus* sum of middle and lower tertile). All data analyses were performed with Statistica 5.5 for Windows (Statsoft Inc., Tulsa, OK).

Cox proportional hazard analysis was used to assess independent predictors of survival. The validity of the proportional hazards assumption was considered for all variables, and variables for which the effect over time was not constant were not included in the final model (26). The likelihood risk ratio was used to judge whether the addition of a variable to a model added to that model significantly or not.

Results
Clinical Data

Initial clinical and dialysis data and serum biochemistries are shown in Table 1. As evaluated by SGNA, 46 patients had normal nutritional status, 65 patients were mildly malnourished, 15 had moderate and 2 patients had severe malnutrition—that is, in all, 82 of the patients (65%) showed signs of

Table 1. Clinical and dialysis data in 128 hemodialysis patients

Parameter	Value[a]
Age (yr)	61 ± 14
Mean blood pressure (mmHg)	99 ± 18
Time on HD (mo)	35 ± 46
Interdialytic weight gain (kg)	3.17 ± 1.66
Length of dialysis (h)	3.92 ± 0.55
Predialysis serum urea (mmol/L)	27 ± 7
Postdialysis serum urea (mmol/L)	9 ± 3
Dialyzer urea clearance (ml/min)	209 ± 20
nPNA (g/kg body wt per day)	1.14 ± 0.22
Kt/V_{urea}	1.37 ± 0.26
Dialysis-free day	
serum creatinine (μmol/L)	690 ± 211
standard bicarbonate (mmol/L)	24 ± 3
serum albumin (g/L)	33 ± 5

[a] Values are expressed as means ± SD.

malnutrition when entering the study. s-CRP ≥ 0 mg/L was present in 61 of the patients (48%).

Patient Survival and Causes of Death

After 36 mo, 58 patients were still on HD treatment, 57 patients (45%) had died while being treated, and 13 had received a kidney transplant. More women (60%) than men (34%) died during the follow-up period. The causes of deaths are shown in Table 2. The main cause of death was CVD (58%), followed by infection (18%). Twenty-eight (80%) of the 35 women with CVD died, but only 18 (43%) of the 42 men with CVD died ($P = 0.0011$; Fisher's exact test). Malnutrition/cachexia was a rare direct cause of death (5%). Sixteen (70%) of the 23 patients with diabetes died; 10 were women.

Comparison between Survivors and Nonsurvivors

Data from the initial cross-sectional study in the survivors and the nonsurvivors are presented in Table 3. The latter had a higher prevalence of CVD (70%) than the survivors (54%). Diabetes mellitus was also more common among the nonsurvivors (28%) than among the survivors (12%). The median

Table 2. Causes of death in 57 hemodialysis patients during 36 mo of follow-up

Parameter	n (%)
Cardiovascular disease	33 (58)
Infection/sepsis	10 (18)
Withdrawal from dialysis	5 (8)
Tumor	4 (7)
Cachexia	3 (5)
Gastrointestinal bleeding	2 (4)

length of time on HD treatment before entering the study was longer in the survivors (25 mo) than in the nonsurvivors (14 mo).

The nonsurvivors had a higher prevalence of malnutrition evaluated by SGNA (85%) than the survivors (44%), and they also had more marked anthropometric signs of malnutrition, with lower ABW, percentage of ABW to DBW, triceps skinfold thickness, MAMC, and HGS. The initial levels of serum creatinine, p-IGF-1, s-albumin, and blood hemoglobin, which may also reflect nutritional status, were lower in the nonsurvivors than in the survivors. Inflammation with s-CRP ≥ 15 mg/L was more prevalent in the nonsurvivors (44%) than in the survivors (13%). The former group also had higher blood leukocyte counts. Initial mean Kt/V_{urea} and nPNA, respectively, were not different in the survivors and nonsurvivors. However, when normalized to desirable body weight, Kt/V_{urea} and nPNA were lower in the nonsurvivors.

Kaplan-Meier Analysis of Survival

The cumulative survival was markedly dependent on age, with the highest mortality in older patients (Figure 1A). Women had higher mortality ($P < 0.001$) rate than men (data not shown). Patients with CVD had a higher mortality than those without (Figure 1B). The mortality rate was considerably higher ($P = 0.003$) in patients with diabetes mellitus than in patients without diabetes (curve not shown).

Sign of malnutrition as evaluated by SGNA was a significant predictor of mortality (Figure 2A), as were percentage of ABW to DBW ($P < 0.01$) and percentage of MAMC ($P < 0.001$) (data not shown). HGS was also a strong predictor of mortality (Figure 2B). The levels of s-albumin, p-IGF-1, and s-CRP (Figure 3, A through C) were strong predictors of mortality as well. Malnutrition (as assessed by SGNA), inflammation (s-CRP ≥ 15 mg/L; upper third tertile), and presence of CVD, which appear to be independent risk factors of mortality, frequently coincided (Figure 4A).

The patients were accordingly divided into 4 groups on the basis of whether 0, 1, 2, or 3 of these risk factors were present, and Kaplan-Meyer analysis was performed for each group. Of the 128 patients, 13 had none of these risk factors and all survived, whereas mortality increased progressively with the number of risk factors present—as high as 75% over 3 yr in the group with 3 risk factors (Figure 4B). Kt/V_{urea} and nPNA did not predict survival when the upper and lower 50th percentiles were compared. However, all eight patients with $Kt/V_{urea} < 1.0$ died within 36 mo.

Cox Proportional Hazard Analysis of Survival

The Cox model was used to identify independent significant predictors of survival (Table 4). Because for CRP the 50th percentile could not be defined (the majority of patients had CRP < 10 mg/L—*i.e.,* not quantified by the laboratory), the material was divided into tertiles, and the highest tertile was compared with the sum of the middle and lowest tertile. Age, female gender, CVD nutritional status (by SGNA), and CRP were significant independent predictors of mortality. Low al-

Table 3. Comparison between initial data in survivors and nonsurvivors showing significant differences

Parameter	Survivors ($n = 58$)	Nonsurvivors ($n = 57$)	P
Gender, M/F	41/17	26/31	
Age (yr)	56 ± 14	69 ± 9	0.0001[a]
Patients with malnutrition (%)	44%	85%	0.0001[b]
Patients with CVD (%)	41%	80%	0.003[b]
Patients with diabetes (%)	4 (40%)	6 (60%)	NS
Desirable body weight (%)	102 ± 15	89 ± 13	0.002
Midarm muscle circumference (%)	98 ± 9	90 ± 11	0.01[a]
Hand-grip strength (%)	62 ± 25	47 ± 25	0.008
nPNA (g/kg body weight per day)[c]	1.12 ± 0.24	1.09 ± 0.21	NS
Kt/V$_{urea}$	1.40 ± 0.28	1.35 ± 0.28	NS
Plasma IGF-1 (ng/ml)	213 ± 99	135 ± 98	0.03[c]
Serum albumin (g/L)	34 ± 4	31 ± 4	0.004[a]
Blood hemoglobin (g/L)	105 ± 14	93 ± 14	0.01[a]
Serum creatinine (μmol/L)	713 ± 199	622 ± 202	0.01[a]
Blood leucocyte count (10^9/L)	6 ± 2	8 ± 3	0.02[a]
Serum C-reactive protein (mg/L ≥15)	13%	44%	0.003[b]

[a] *t* test.
[b] Chi-square test.
[c] nPNA, normalized protein equivalent of nitrogen appearance.

bumin level was not an independent predictor in the Cox analysis, although it was strongly associated with a reduced survival rate in the Kaplan-Meier analysis.

Discussion

The cross-sectional study of nutritional status in HD patients, upon which this follow-up study is based, has been reported in detail elsewhere (7). We intended to include all 164 HD patients treated at the Huddinge University Hospital and its satellite units who had undergone dialysis for more than 2 wk at the time of that study. However, we failed to recruit 36 patients, representing 22% of the population, because they refused to participate or they were not referred by the staff. Nevertheless, we believe that the population studied was representative of the whole population because age, gender distribution, diagnoses of renal disease, and dialysis data in the patients who did not participate was about the same as in the participating patients.

Typical features of this population were racial homogeneity (all were white), high median age (65 yr), and high prevalence of CVD (60%) and malnutrition (65%). High age and CVD may both have contributed to the relatively high 3-yr mortality rate of 45%. In our statistical analysis, age was the most significant independent predictor of mortality. CVD was also a strong independent predictor of mortality and the most common cause of death in the 57 patients who died within 36 mo. These findings are in general agreement with other reports, which have analyzed risk factors and causes of death in HD patients (1,2).

Gender may be another factor associated with clinical outcome. In most studies and also in the large European and American registers, male gender is found to be a risk for increased mortality in patients with end-stage renal disease (1,2,8). However, in the study presented here, the mortality was higher in women than in men when analyzed via Fisher's exact test as well as in the univariate and Cox analyses. Goldwasser *et al.* (9) also reported a higher mortality rate in women than in men and attributed this difference mainly to the women being older, but in our study, they were of about the same age as the men. However, the women had a higher prevalence of CVD, and the mortality in the women with CVD was higher than that of men. Moreover, diabetes mellitus was also more common in women than in men.

Nutritional Status and Clinical Outcome

The results of this study confirm that nutritional status predicts mortality. Malnutrition, as assessed by SGNA, anthropometric (ABW, percentage of ABW to DBW, MAMC, triceps skinfold thickness, HGS) and biochemical measurements (s-albumin, p-IGF-1, s-creatinine) was much more prevalent at the start of the study in the patients who subsequently died than in the survivors. Moreover, the Kaplan-Meier curves showed that each of these factors were significant predictors of mortality.

HGS is a reliable, easily performed and cheap estimate of nutritional status and protein loss (27) and is reported to be a strong predictor of postoperative complications in surgical patients (28). We found in our cross-sectional study that HGS is related to other nutritional parameters in HD patients (7), and similar results are reported in patients with chronic renal failure who are not on dialysis (29). The results of this study demonstrate that reduced HGS is a strongly significant predictor of increased mortality in HD patients.
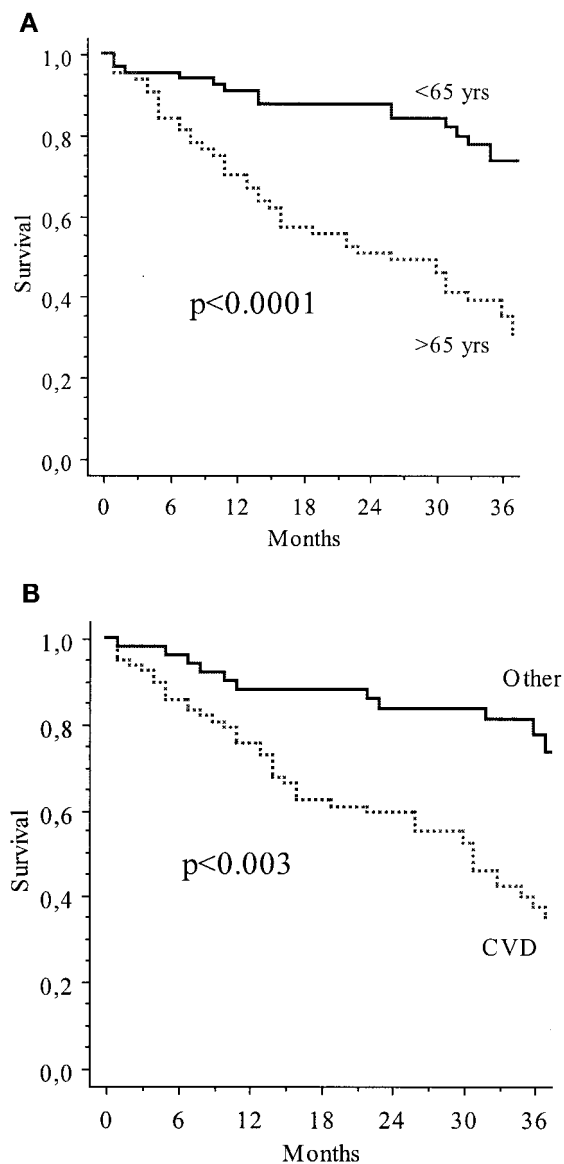
Figure 1. Kaplan-Meier survival curves for patients above and below the median of age of 65 yr (A) and patients with and without cardiovascular disease (B).
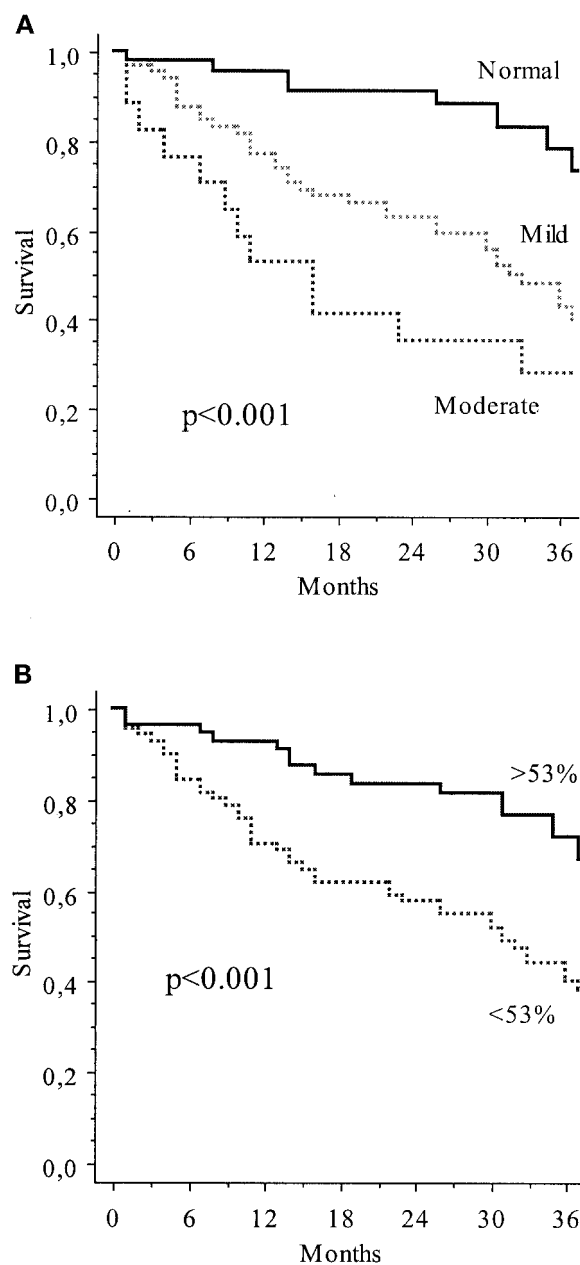

Figure 2. Kaplan-Meier survival curves for patients with normal nutritional status ($n = 46$), mild malnutrition ($n = 65$), and moderate to severe malnutrition ($n = 17$) based on subjective global nutritional assessment (A) and for patients with hand-grip strength (HGS) above and below the median of the percentage of the normalized HGS (B).

Malnutrition and CVD

In most studies, including this one, CVD is the most common cause of death (approximately 50%) (12,30–32), followed by infection (15 to 20%), whereas malnutrition/cachexia is a rare cause of death, despite its role as a strong mortality predictor (1,2). This raises the question to what extent malnutrition directly increases the mortality risk; perhaps it is more of a marker of other types of illness with a poor prognosis. In our cross-sectional study, we found that HD patients with CVD were more frequently malnourished than were patients without CVD, as evaluated by SGNA and anthropometric and biochemical parameters (7). Foley *et al.* (12) reported that hypoalbuminemia was associated with the development of *de novo* and recurrent cardiac failure and ischemic cardiac disease in HD and in patients on continuous ambulatory peritoneal dialysis, which also suggests that malnutrition and CVD are interrelated, although s-albumin is far from an ideal indicator of nutritional status.

Several studies in patients without renal failure have showed that even mild chronic heart failure may lead to malnutrition and that proinflammatory cytokines may be involved in this process by stimulating protein catabolism and causing anorexia (33–36). Inflammation may also be a common factor for the development of malnutrition and CVD. Malnutrition may ag-
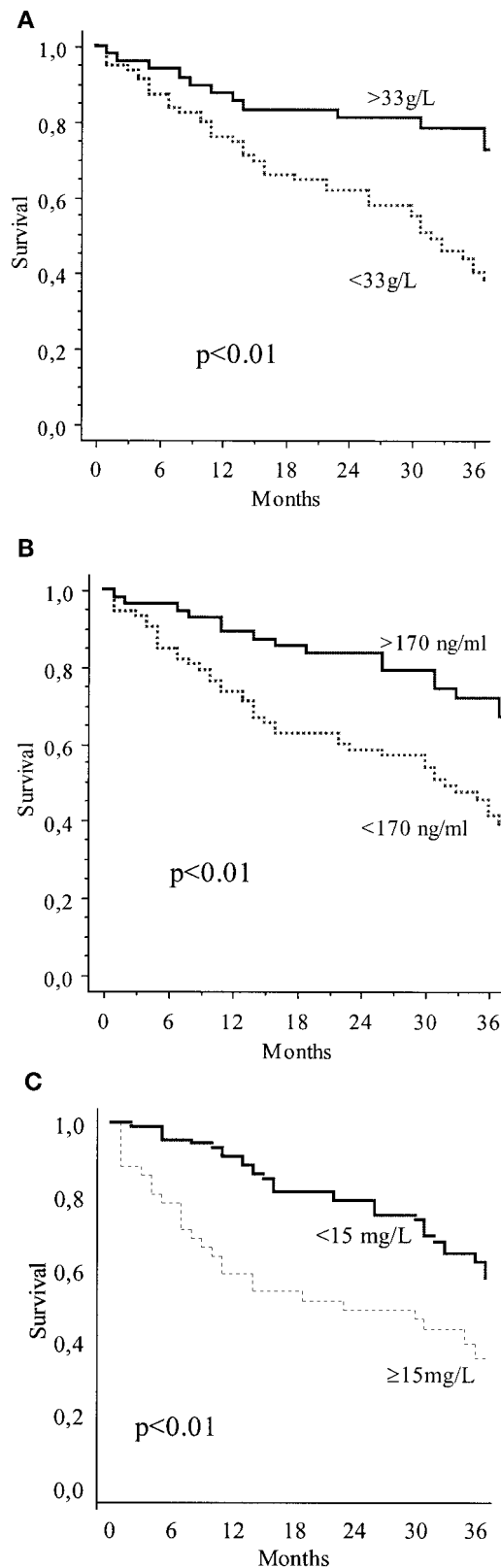
Figure 3. Kaplan Meier survival curves. (A) Patients above and below the median of serum albumin. (B) Patients above and below the median of plasma insulinlike growth factor-1. (C) Patients above and below the highest tertile ($\geq$15 mg/L) of serum C-reactive protein. Note that for C-reactive protein, the median value could not be defined because of the insensitivity of the laboratory method (see Results).
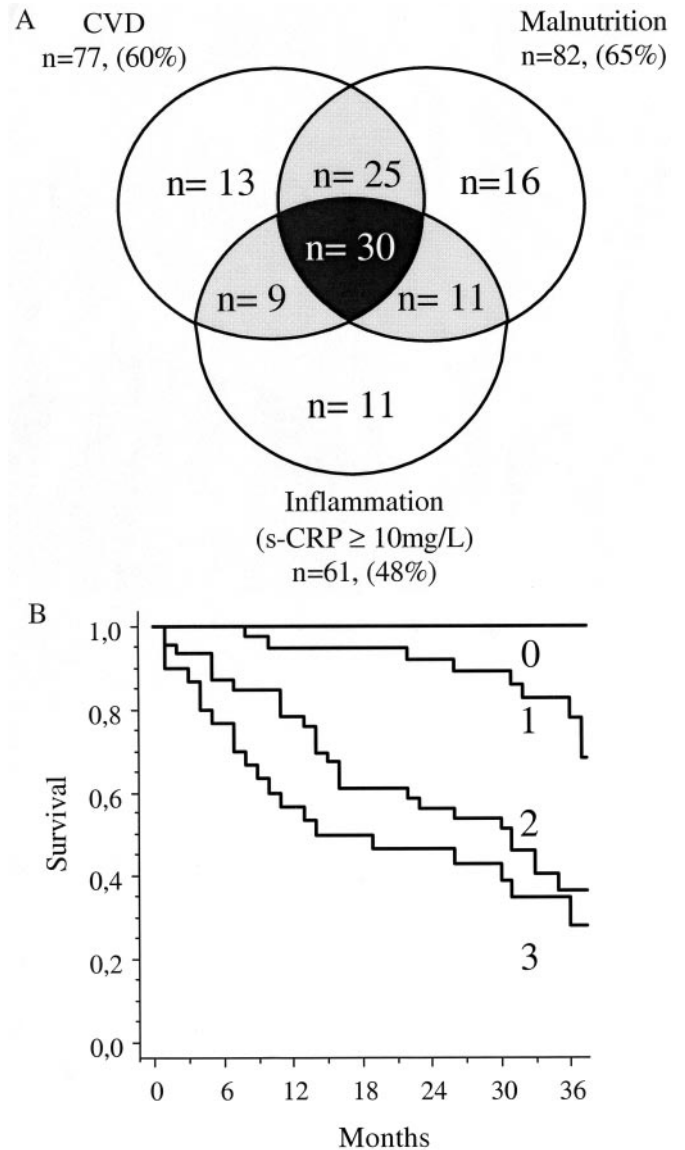

Figure 4. (A) Signs of malnutrition as assessed by subjective global nutritional assessment, inflammation (serum C-reactive protein $\geq$10 mg/L) and presence of cardiovascular disease (CVD) were common in the 128 hemodialysis patients, and each of these factors seemed to be an independent risk factor of mortality. (B) The patients were divided into 4 groups on the basis of whether they exhibited 0 ($n = 13$), 1 ($n = 39$), 2 ($n = 46$), or 3 ($n = 30$) of these risk factors, and Kaplan-Meyer analysis was performed for each group. Log-rank test shows that there were significant differences in survival between groups 0 and 2 ($P = 0.0007$), 0 and 3 ($P = 0.0003$), 1 and 2 ($P < 0.0002$), and 1 and 3 ($P = 0.0001$), but not between groups 0 and 1 ($P = 0.07$) and 2 and 3 ($P = 0.29$).

gravate heart failure by inducing morphologic and functional deterioration of the myocardium, as in patients with malnutrition and in experimental studies (37,38). Malnutrition has recently been identified as an independent risk factor for mortality in patients with heart failure (36).

The results of the Cox analysis in this study show that malnutrition was a significant independent predictor of mor-

Table 4. Cox proportional hazards analysis of factors predicting mortality in hemodialysis patients after a follow-up period of 36 mo

Parameter[a]	Relative Mortality Ratio	95% Confidence Interval	Probability
Age (yr)	1.04	1.01–1.06	0.0038
Gender (F *versus* M)	2.04	1.19–3.50	0.009
CVD *versus* no CVD	2.43	1.22–4.84	0.01
SGNA score	1.13	1.01–1.27	0.034
CRP groups low + middle *versus* high tertile	1.81	1.04–3.12	0.034
(Serum albumin [g/L])[b]	(0.97)	(0.89–1.04)	(0.39)

[a] CVD, cardiovascular disease; SGNA, subjective global nutritional assessment; CRP, C-reactive protein. χ^2 test = 52.3.

[b] Note that serum albumin was *not* a predictor of mortality in this analysis.

tality, suggesting that malnutrition is not simply an innocent bystander but rather may directly contribute to a fatal outcome, perhaps by aggravating the adverse effect of preexisting CVD and by increasing the susceptibility to infection.

In the study presented here, low s-albumin was a strong predictor of mortality in the univariate analysis, which is in agreement with several other reports. However, s-albumin was not an independent predictor in the Cox model, presumably because it depends on several factors, such as age, presence of CVD, nutritional status, and infection or inflammation, which may have a more direct effect on survival.

Inflammation as a Mortality Risk Factor

In our cross-sectional study, we observed that a large proportion of patients, especially those who were elderly or had CVD, had elevated s-CRP levels ($\geq$10 mg/L) (7). In our presentation of the preliminary results of the study presented here (19), we were the first to report that an elevated s-CRP is a strong independent predictor of increased mortality in HD patients. In the study presented here, an elevated s-CRP was identified by Cox proportional hazard analysis as a significant independent risk factor, suggesting that inflammation *per se* has an important effect on clinical outcome (Table 4). Several recent studies have confirmed that inflammation, as reflected by elevated levels of s-CRP or proinflammatory cytokines, are significant independent predictors of mortality in HD and patients on continuous ambulatory peritoneal dialysis (39–43).

When evaluating the role of an elevated s-CRP as a predictor of mortality, it should be pointed out that inflammation might be involved both in factors predisposing to malnutrition or hypoalbuminemia and to atherosclerotic CVD. Proinflammatory cytokines can adversely affect nutrition by inducing proteolysis in muscle, increasing energy expenditure, and inhibiting appetite (44). Hence, inflammation may be implicated as a causative factor for development of malnutrition in HD. This assumption is supported by our observation in the cross-sec-

tional HD study that inflammation and malnutrition were associated (7), which has been confirmed by others (40,45). We also reported that the s-CRP was negatively correlated with s-albumin, suggesting that inflammation had induced hypoalbuminemia as part of the acute-phase response. Other groups have made similar observations (39,45,46).

Several epidemiologic studies in the general population have found that inflammation, as assessed by elevated levels of s-CRP and plasma proinflammatory cytokines, are involved in the development of atherosclerotic CVD (47–49). Stenvinkel *et al.* (50) showed that there is a strong association between atherosclerosis, malnutrition, and an elevated s-CRP in patients with renal failure who were not on dialysis. The malnourished patients also had higher plasma levels of lipoprotein (a) and fibrinogen, two acute-phase reactants considered to be independent atherogenic factors in the general population (51). Zimmermann *et al.* (42) reported that inflammation (high s-CRP) in HD patients is associated with hypoalbuminemia and elevated levels of lipoprotein (a) and fibrinogen; in multivariate analysis, age and CRP remained powerful independent predictors of both overall death and cardiovascular death (43). The aforementioned observations suggest that inflammation, mediated by proinflammatory cytokines, may play a central role as common triggering causes of malnutrition and CVD in end-stage renal disease, thereby contributing to the high mortality.

Because malnutrition, inflammation, and CVD are significant independent risk factors of mortality that frequently coincide, one might expect that the death risk should increase in patients with more than one of these factors present. This indeed proved to be the case, as demonstrated by our results, showing that mortality increased progressively with the number of risk factors, being as high as 75% in 3 yr in those with all 3 risk factors present (Figure 4). Mortality was also high in the group of patients with 2 risk factors, among whom more than 50% had CVD, whereas mortality was considerably lower in patients with only 1 risk factor; survival was 100% in the few patients without any risk factors. It should be pointed out that we were unable to detect low-grade inflammation due to the insensitivity of the CRP method used, which may have led to an underestimation of the number of patients with inflammation in combination with the other risk factors.

The origin of inflammation in HD patients remains unclear. Chronic bacterial or viral infections and other inflammations are some of the factors held responsible for increased generation of cytokines (52). Loss of renal function may also play a more direct role, for the elevated serum levels of proinflammatory cytokines because in nondialyzed patients with chronic renal failure, the serum levels of these cytokines and their specific inhibitors increase with the reduction in glomerular filtration rate (53,54). A better understanding of the mechanisms for their generation and mode of action in dialysis patients is now needed so that new strategies may be developed to prevent their overproduction and eliminate or attenuate their harmful effects.

Acknowledgments

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