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Serum Ferritin Is a Marker of Morbidity and Mortality in Hemodialysis Patients

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• **We tested the hypothesis that a high concentration of serum ferritin, a frequently used marker of iron stores in dialysis patients and an acute-phase reactant, may be a marker of morbidity and mortality in these patients. To evaluate the impact of ferritin on morbidity and mortality, we reviewed the 6-month hospitalization rates in our dialysis patients retrospectively and subsequently reviewed the mortality among these patients over a 12-month period of time prospectively. One hundred one adult hemodialysis patients (59 men and 42 women; age, 54 ± 15 years) who had been on hemodialysis for 38 ± 27 months were studied. All but 5 patients were on intravenous iron with similar iron administration pattern. In the retrospective cohort, ferritin's correlation coefficients for hospitalization days and frequency (both $r = +0.39$, $P < 0.001$) were higher compared with the albumin correlations for hospitalization days ($r = -0.31$, $P = 0.001$) and frequency ($r = -0.28$, $P = 0.005$) and correlation coefficients remained similarly significant after case-mix adjustment. In the prospective study, the "predeath" value of serum ferritin for 17 deceased patients (891 ± 476 ng/mL) was higher than both their "initial" value (619 ± 345 ng/mL, $P = 0.007$) and the mean ferritin value of 84 surviving and withdrawing patients (639 ± 358 ng/mL, $P = 0.001$). Although Cox proportional hazard analysis showed a significant odds ratio of death only for serum albumin and not for ferritin, logistic regression analysis using the predeath values confirmed the significant impact of both decreased serum albumin and increased serum ferritin as markers of dialysis mortality. After case-mix adjustment, the relative risks of death for a 500 ng/dL increase in serum ferritin was 2.71 (95% confidence interval, 1.06 to 7.02) and for a 0.5 g/dL decrease in serum albumin was 4.48 (95% confidence interval, 1.77 to 11.33). Hence, serum ferritin is a strong predictor of hospitalization in dialysis patients. Although serum albumin is found to be a strong long-term marker of mortality in hemodialysis patients, an increase in serum ferritin appears to be a more reliable short-term marker of death over a 12-month period. Therefore, in the setting of uniform iron administration, a high serum ferritin may be a morbidity risk factor and a recent increase in serum ferritin may carry an increase in the risk of death in these patients.**

INDEX WORDS: Dialysis; ferritin; albumin; transferrin; anemia; acute-phase reactant; mortality; hospitalization.

SERUM FERRITIN is frequently used as a marker of iron stores in uremic patients.[1-4] Several studies have shown that a low serum ferritin concentration is a reliable indicator of iron deficiency among ESRD patients.[2,4] However, a high serum ferritin may not be an optimal indicator of "increased" iron stores among dialysis patients[5,6] because it is an acute-phase reactant and its increase in dialysis patients may be based on factors unrelated to iron stores such as inflammation and malignancy.[1,7] Some recent studies have indicated a significant association between increased serum ferritin and malnutrition[8] as well as resistance to recombinant human erythropoietin (rHu-EPO).[9] We compared serum ferritin with serum albumin and total iron binding capacity (TIBC) to study the hypothesis that increased concentrations of serum ferritin may be a prognostic marker of morbidity and mortality in dialysis patients. To evaluate this hypothesis, we studied the association between ferritin and semiannual hospitalization rates retrospectively and the annual mortality prospectively in a group of hemodialysis patients in an outpatient dialysis unit.

METHODS

Patients' Characteristics

The outpatient dialysis unit at San Francisco General Hospital provided chronic hemodialysis treatment to 104 adult patients. Among this group, 101 adult hemodialysis patients (59 men and 42 women) had been on dialysis for at

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least 3 months at the beginning of this study (mean ± standard deviation [SD], 38 ± 27 months). We obtained the semiannual hospitalization indices as well as demographic and laboratory data of all 101 patients retrospectively by reviewing the medical charts after the Institutional Review Board approved exemption from written consent. The patients' ages ranged from 22 to 85 years (56 ± 15 years) and included 47 African Americans, 29 Asians, 16 Hispanics, and 9 whites. Among the underlying renal diseases, more than two thirds of the patients had either hypertension (42%) or diabetes (34%).

Iron Administration and Blood Transfusion

All but 5 patients received one course of intravenous (IV) iron repletion therapy at some point during the 6-month retrospective cohort, which consisted of 100 mg of iron dextran administered for 10 consecutive dialysis sessions (1 g total). Those 5 patients (including 4 surviving and 1 deceased patients) who did not receive parenteral iron had suspected or documented reactions to IV iron dextran and were receiving oral doses of iron sulfate. During the 12-month prospective cohort, 10 of 17 deceased patients (59%) received an additional iron repletion therapy within 6 months before their death. Among 84 survivors, 71 patients (85%) received additional repletion therapy within the first 9 months of the prospective cohort. During the last 3 months of the prospective cohort, the iron treatment policy of our dialysis unit changed in that all patients with a serum ferritin less than 800 ng/mL began receiving "maintenance" IV iron at 200 mg monthly. No deceased patient received maintenance iron therapy.

In the 6-month retrospective cohort, only 3 hospitalized patients received packed red blood cell (RBC) transfusion. During the 12-month prospective cohort, 5 surviving and 3 deceased patients received blood transfusion. However, no patient received any blood transfusion during the 4-week period before serum ferritin measurement.

The total weekly dose of rHu-EPO was calculated for each patient as the product of the dose and the weekly frequency (1 to 3 times per week).

Hospitalization

Hospitalization data during a 6-month period of time were obtained on all 101 hemodialysis patients retrospectively by reviewing the medical charts. Hospitalization was defined as any hospital admission that included at least one overnight hospital stay. The admission day was counted as 1 full hospitalization day, but the discharge day was not. Therefore, the minimum hospitalization per admission was 1 day. No exclusion criterion was used. Hence, all kinds of hospital admissions were counted, including access-related problems. For those few patients who were in a hospital at the start of the retrospective cohort, that hospitalization was not counted. For those patients who were still in a hospital at the end of the 6-month cohort, all hospitalization days of the last admission were counted. For 4 patients who were on dialysis less than 6 months, the presumed semiannual hospitalization data were calculated by using the adjusting factor "6/number of months." The "semiannual hospitalization days" were the sum of all hospitalization days during the 6-month retrospective cohort as defined above. The "semiannual hospitalization frequency" was the total number of hospital admissions during the same period irrespective of the length of each admission.

Laboratory Evaluation

All laboratory values, except for postdialysis blood urea nitrogen, were measured on all patients immediately before the hemodialysis session, at least 16 days after the last IV iron administration. Serum albumin, creatinine, blood urea nitrogen, TIBC to estimate transferrin, serum iron, transferrin saturation ratio (iron saturation ratio), and hematocrit were obtained monthly. Serum ferritin was measured quarterly. Postdialysis blood urea nitrogen of the same dialysis session was measured to calculate the urea reduction ratio (URR). Laboratory values were obtained by automated methods. The serum ferritin value was measured by an immunoradiometric assay with polyclonal reagents. All laboratory data were measured by Spectra Laboratories (Fremont, CA). Serum TIBC concentrations were used as a reliable estimate of transferrin values.[8] The URR was obtained as the indicator of the hemodialysis dose by calculating the percentage of intradialytic reduction of blood urea nitrogen as described elsewhere.[10] For the retrospective cohort, the mean values of monthly serum albumin, creatinine, TIBC, transferrin saturation ratio, and URR were calculated for each patient over a 6-month period of the cohort. To calculate mean serum ferritin, three quarterly ferritin values within a 7-month period were used, the first value of which being the serum ferritin value immediately before the start of the retrospective cohort. For 4 patients who had been on dialysis between 3 to 6 months, only two ferritin values were used to calculate the patient's mean ferritin concentration. During the prospective cohort, "predeath" serum albumin and TIBC values were obtained within the last 4 weeks before death. The predeath ferritin values were measured within the last 3 months before death on each deceased patient.

Epidemiological and Statistical Methods

The study is based on a combined retrospective and prospective cohort design. The retrospective cohort comprises the last 6 months before day 1 of the study and analyzes the hospitalization indices of 101 live patients as continuous outcome variables to represent morbidity. The prospective cohort includes the subsequent 12 months after day 1 and analyzes the mortality as a dichotomized outcome variable in the same group of patients. We used Pearson's correlation coefficient r for selected analyses. Total sample size required to achieve a statistical power of 0.8 ($\beta = 0.20$) is 85 patients for any correlation coefficient $r > 0.30$ based on a two-tailed P value between 0.05 and 0.01 and is 92 patients for any $r > 0.20$ if the P value is less than 0.01.[11] All P values less than 0.05 are viewed as statistically significant and P values between 0.10 and 0.05 are considered marginally significant. Fiducial limits are given as the mean ± SD. Multiple regression analyses including analysis of covariance were performed for the retrospective cohort to calculate the adjusted (partial) correlation coefficients for 5 major demographic features, ie, age, sex, race, dialysis months,

and underlying renal disease, as well as to control for other laboratory variables. The two-tailed Student's *t*-test and Pearson's chi-square test were used for group mean comparisons of continuous and binomial variables, respectively.

To calculate the relative risk of death in the prospective cohort, odds ratios and their 95% confidence intervals (95% CI) were obtained using both Cox proportional hazard and logistic regression methods to control for the above-mentioned demographic and laboratory variables. Whereas the Cox proportional hazard model was applied to the "initial" laboratory values, ie, mean values obtained during the retrospective cohort, and the time to death (survival analysis approach), the logistic regression model used the "predeath" values obtained during the prospective cohort for deceased cases and the "initial" values for the survivors and withdrawers, without accounting for the time to event (case-cohort approach).[12] Any 95% CI not including one was considered statistically significant. The Kaplan-Meier method was used to analyze the cumulative proportion surviving. All descriptive and multivariate statistics were performed using the statistical software package Stata for Windows 95 (version 5.0; Stata Corp, College Station, TX).

RESULTS

Table 1 shows a summary of data for all patients. The patients' ages and the number of dialysis months were obtained on the first study day (day 1), which is the temporal intercept of the 6-month retrospective and 12-month prospective cohorts. The unspecified laboratory values and those specified as "initial" values are the calculated mean values during the retrospective cohort. The "predeath" values are single laboratory values that were obtained during the prospective cohort before death. Race appears to have a marginal bearing on death, because the whites and Asians are represented slightly more than African Americans and Hispanics among the deceased patients. The "initial" mean serum albumin concentration of the retrospective cohort is the only laboratory value that is different between the deceased and surviving patients in the prospective cohort. Hospitalization frequency was slightly higher among those patients who died subsequently, but the total number of hospitalization days was not significantly different between the two groups.

Table 2 shows Pearson correlation coefficients (r) for relevant variables, including the 6-month mean values of the pertinent laboratory results.

Table 1. Relevant Demographic and Laboratory Characteristics of 101 Hemodialysis Patients at the Start of the Cohort

	All Patients	Survivors	Death Cases	*P* Value
No. of patients	101	84	17	
Male:female (% male)	59:42 (58%)	48:36 (57%)	11:6 (65%)	NS
Black:White (% black)	47:9 (47%)	42:6 (50%)	5:3 (29%)	0.09
Hispanic:Asian (% Hispanic)	16:29 (16%)	15:21 (18%)	1:8 (6%)	NS
Diabetes:HTN (%)	34:42 (34%)	28:36 (33%)	6:6 (35%)	NS
Iron repletion therapy (%)	96 (95%)	80 (95%)	16 (94%)	NS
Age (y)	54 ± 15	54 ± 16	57 ± 15	NS
Dialysis (mo)	38 ± 27	38 ± 29	36 ± 18	NS
Initial ferritin (ng/mL)	635 ± 354	639 ± 358	619 ± 345	NS
Predeath ferritin (ng/mL)			891 ± 476	0.01*
Initial albumin (g/dL)	3.85 ± 0.39	3.91 ± 0.35	3.55 ± 0.48	0.001
Predeath albumin (g/dL)			3.43 ± 0.52	0.001*
Initial TIBC (mg/dL)	198 ± 34	200 ± 33	188 ± 34	NS
Predeath TIBC (mg/dL)			180 ± 29	0.03*
Transferrin saturation (%)	32.1 ± 9.2	32.7 ± 9.2	29.1 ± 8.4	NS
Hematocrit (%)	32.7 ± 4.0	32.9 ± 3.7	31.5 ± 5.0	NS
rHu-EPO dose (U/wk)	9,040 ± 8,837	8,714 ± 8,534	10,647 ± 10,344	NS
URR (%)	65.7 ± 6.2	65.6 ± 6.2	66.2 ± 6.2	NS
Creatinine (mg/dL)	11.2 ± 3.3	11.2 ± 3.3	11.4 ± 3.8	NS
Hospitalization (d)	3.52 ± 6.66	3.26 ± 6.54	4.82 ± 7.30	NS
Hospitalization frequency	0.81 ± 1.41	0.70 ± 1.31	1.35 ± 1.80	0.08

NOTE. The "initial" and unspecified laboratory values are the mean ± SD of the retrospective cohort, whereas "predeath" values are obtained during the prospective cohort.

Abbreviations: NS, statistically not significant ($P > 0.10$); HTN, hypertension.

* Student's *t*-test compared predeath values of the dead patients with the initial values of the survivors.

Table 2. Pearson Correlation Coefficients Between Pertinent Demographic and Laboratory Values Among 101 Hemodialysis Patients

	Age (y)	Dialysis (mon)	Ferritin	Albumin	TIBC (Transferrin)	Transferrin Saturation	Hematocrit	Creatinine	rHu-EPO
Dialysis (mo)	−0.06 ($P = 0.57$)								
Ferritin	0.38* ($P < 0.001$)	0.07 ($P = 0.46$)							
Albumin	−0.18† ($P = 0.08$)	0.07 ($P = 0.46$)	−0.08 ($P = 0.41$)						
TIBC (transferrin)	−0.31* ($P = 0.002$)	−0.23* ($P = 0.02$)	−0.38* ($P < 0.001$)	0.22* ($P = 0.03$)					
Transferrin saturation	−0.09 ($P = 0.37$)	0.15 ($P = 0.13$)	−0.03 ($P = 0.73$)	0.14 ($P = 0.17$)	−0.07 ($P = 0.52$)				
Hematocrit	0.06 ($P = 0.54$)	0.23* ($P = 0.02$)	0.01 ($P = 0.89$)	0.17† ($P = 0.09$)	0.06 ($P = 0.55$)	−0.05 ($P = 0.61$)			
Creatinine	−0.39* ($P < 0.001$)	0.17† ($P = 0.09$)	−0.19† ($P = 0.06$)	0.43* ($P < 0.001$)	0.20* ($P = 0.04$)	0.21* ($P = 0.04$)	−0.06 ($P = 0.58$)		
rHu-EPO	−0.06 ($P = 0.539$)	−0.05 ($P = 0.63$)	0.06 ($P = 0.55$)	−0.02 ($P = 0.81$)	−0.09 ($P = 0.36$)	−0.13 ($P = 0.20$)	−0.54* ($P < 0.001$)	0.19† ($P = 0.06$)	
Hospitalization (d)	0.28* ($P = 0.004$)	−0.06 ($P = 0.58$)	0.39* ($P < 0.001$)	−0.31* ($P = 0.001$)	−0.28* ($P = 0.004$)	−0.09 ($P = 0.37$)	−0.12 ($P = 0.23$)	−0.21* ($P = 0.04$)	0.18† ($P = 0.07$)
Hospitalization frequency	0.25* ($P = 0.01$)	−0.07 ($P = 0.49$)	0.39* ($P < 0.001$)	−0.28* ($P = 0.005$)	−0.28* ($P = 0.005$)	−0.11 ($P = 0.28$)	−0.10 ($P = 0.30$)	−0.22* ($P = 0.03$)	0.18† ($P = 0.07$)

NOTE. The laboratory values are the mean values during a 6-month period of time (retrospective cohort period).

* P value < 0.05 (significant).

† P value between 0.10 and 0.05 (marginally significant).

Elderly patients had higher ferritin but lower creatinine, TIBC, and albumin values and showed higher rates of hospitalization. Patients on dialysis for a longer period of time had lower serum TIBC but slightly higher hematocrit values. Mean serum ferritin concentration had a strong, inverse correlation with serum TIBC ($r = -0.38$) and a weaker inverse correlation with serum creatinine but no correlation with serum albumin. However, the mean serum creatinine, TIBC, and hematocrit values were significantly correlated with the mean serum albumin among hemodialysis patients. Anemic patients required higher doses of rHu-EPO.

Correlation coefficients between hospitalization data and pertinent laboratory measurements can be obtained from Tables 2 and 3. Mean serum ferritin had the highest correlation with both semiannual hospitalization days and frequency of hospitalization during the same period of time ($r = 0.39$). Mean serum albumin, TIBC, and creatinine values also had significant but weaker correlations with hospitalization indices compared with ferritin. Table 3 compares the raw (unadjusted) and adjusted correlation coefficients by using multivariate regression analysis after controlling for age, sex, race, dialysis months, and underlying renal disease. Serum ferritin is the strongest independent predictor for both hospitalization days and frequency of hospitalization (both $r = +0.32$, $P < 0.01$), even after accounting for age, sex, race, dialysis duration, underlying disease, and three other laboratory variables. Mean serum albumin had a weaker correlation with hospitalization days ($r = -0.25$) and no significant correlation with hospitalization frequency after controlling for other variables. Both mean serum TIBC and creatinine lost their statistical significance as predictors of hospitalization after controlling for the above-mentioned characteristics. Moreover, after dividing the patients into four quarters according to ascending ferritin values, the number of days and the frequency of hospitalization were proportionately increased in higher ferritin quarters, but albumin concentrations did not differ significantly among these groups. The negative, significant correlation between serum TIBC and ferritin was confirmed. Moreover, serum ferritin values over 600 were significantly associated with higher hospitalization rates.

Table 3. Comparison Between Raw (Unadjusted) and Controlled (Adjusted) Correlation Coefficients for Four Statistically Significant Mean Laboratory Values Versus Semiannual Hospitalization Days and Frequency Among 101 Hemodialysis Patients

	Hospitalization Days		Hospitalization Frequency	
	Raw *r*	Adjusted *r*	Raw *r*	Adjusted *r*
Ferritin	0.39*	0.32*	0.39*	0.32*
Albumin	−0.31*	−0.25†	−0.28*	−0.19
TIBC (transferrin)	−0.28*	−0.12	−0.28*	−0.13
Creatinine	−0.21†	−0.01	−0.22†	−0.01

NOTE. The "adjusted" values are based on one combined regression model that controls for five demographic factors (age, sex, race, dialysis months, and underlying renal disease) and all four laboratory values against each other.

* *P* value < 0.01.

† *P* value between 0.05 and 0.01.

During the prospective follow-up, 17 patients died (average time to death, 5.9 ± 3.8 months) and 6 patients left the cohort, including 1 patient who underwent renal transplant, 2 patients who changed dialysis modality to peritoneal dialysis, and 3 patients who were transferred to other dialysis units. None of the 6 patients who left the cohort died during the study period. Compared with the "initial" values (mean values during the 6-month period before the prospective study), the "predeath" albumin did not change significantly (3.55 ± 0.48 and 3.43 ± 0.52 g/dL, respectively). This was also the case for serum TIBC. However, the predeath serum ferritin value for deceased patients was 44% higher than the initial mean ferritin value (891 ± 476 versus 619 ± 345 ng/mL, respectively) and the difference was statistically significant ($P = 0.007$), despite the small number of deceased patients (Figs 1 and 2). In contrast, almost no change occurred in these laboratory values among the survivors in the prospective cohort when the initial laboratory values were compared with their corresponding values after 9 months (Fig 2). Moreover, the ferritin concentration in the survivors after 9 months (678 ± 404 ng/mL) was still significantly lower than the predeath ferritin concentration of the deceased patients ($P = 0.03$; Fig 2). This trend underscores the importance of

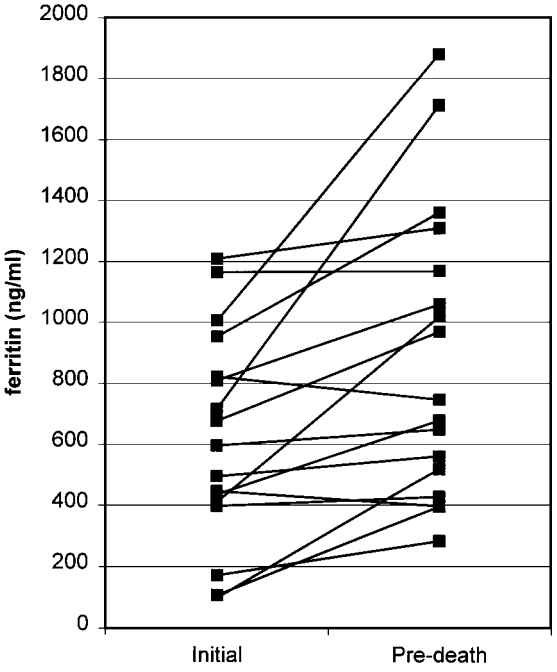

Fig 1. Changes in serum ferritin values in 17 hemodialysis patients who died within a 12-month period of time.

a recent increase in serum ferritin as a risk factor for death within a 12-month period.

Table 4 lists the odds ratios (OR) and 95% CI of death using two different methods. The survival method using the Cox proportional hazard regression analysis is based on the "initial" values at the start of the prospective cohort and the time to death. The logistic regression method compares the impact of the "predeath" values for the deceased patients with the initial values of the surviving and withdrawing cases but does not account for the element of time to event and is based on a case-cohort approach. Both methods control for age, sex, race, dialysis months, and underlying renal disease. We used predetermined increments that are most relevant for each laboratory value, ie, 0.5 g/dL decrease in serum albumin, 500 ng/mL increase in serum ferritin, and 50 mg/dL decrease in serum TIBC, and studied their impact on death.

Using a separate survival regression for each laboratory value, only serum albumin had significant bearing on death (for 0.5 g/dL decrease in serum albumin: OR = 2.11; 95% CI, 1.29 to 3.46). By using one single combined survival model for all three laboratory measurements and, hence, controlling for each other, not only the relative risk of death for each 0.5 g/dL decrease in serum albumin remains significant (OR = 2.31; 95% CI, 1.40 to 3.81), but the impact of serum TIBC on survival becomes evident, so that for each 50 mg/dL decrease in serum TIBC there is a significant relative risk of death of 3.35 (95% CI,1.23 to 3.35). Survival model analysis failed to show the survival impact of "initial" ferritin values on the subsequent death in our study (Table 4). Therefore, the initial values of both serum albumin and TIBC appear to be "long-term" predictors of death among hemodialysis patients but ferritin values do not.

When logistic regression models are used separately for each laboratory variable, the "predeath" values of all three laboratory measurements are significantly associated with the relative risk of death (Table 4). However, when a single combined model was used to control the effect of all three laboratory results against each other, predeath values of serum TIBC did not have any bearing on death, whereas albumin and ferritin did. The adjusted relative risk of death for each 0.5 g/dL decrease in serum albumin was 4.48 (95% CI, 1.77 to 11.33) and that of a 500 ng/mL increase in serum ferritin was 2.71 (95% CI, 1.06 to 7.02). Therefore, recent changes in both serum albumin and ferritin appear to be reliable, "short-term" predictors of death in dialysis patients.

DISCUSSION

We showed in this study in hemodialysis patients that serum ferritin correlates with hospitalization indices and is a strong marker of hospitalization days and frequency compared with serum albumin and other laboratory values. Moreover, this study suggests that hyperferritinemia may also be a marker of dialysis mortality and that a recent increase in serum ferritin may be associated with imminent risk of death among this group of patients. These associations do not appear to have any relationship with the amount of the administered iron.

Serum ferritin, which can be easily measured with a blood test via an immunoradiometric assay, has emerged as a leading candidate marker for iron stores.[1] Several studies have shown that a low serum ferritin has a high specificity to detect iron deficiency in dialysis patients receiving rHu-EPO.[2,4] However, an increased serum

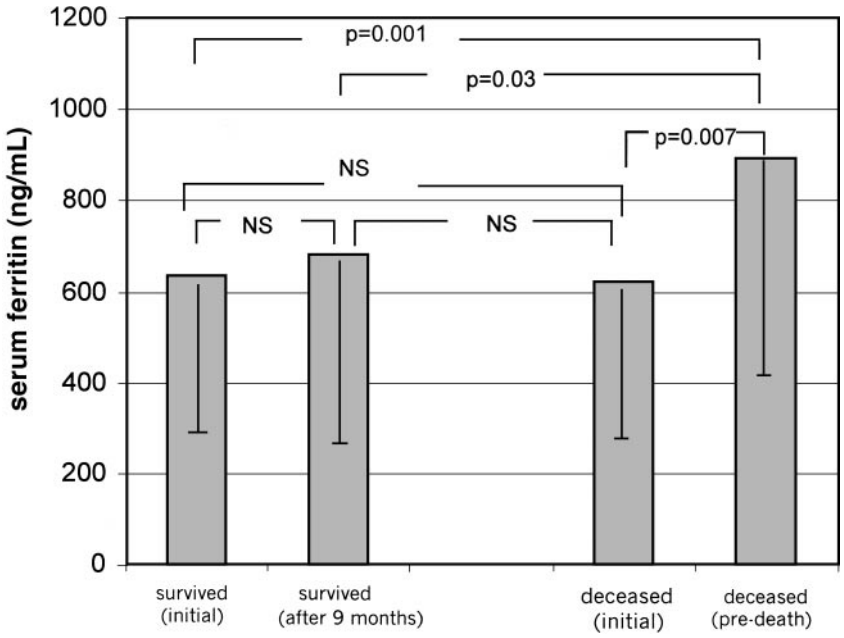

Fig 2. Comparison between mean serum ferritin concentration in surviving and deceased patients (NS, statistically not significant; ie, *P* > 0.10).

ferritin may not be a reflection of increased iron stores.[5,13]

The clinical significance of serum ferritin in dialysis patients may be somewhat different than in the general population, and the current guidelines to use serum ferritin for hemochromatosis screening might be flawed when applied to the dialysis population.[7] Hyperferritinemia in dialysis patients may denote circumstances not related to iron stores.[5,14] In nonuremic patients, an increased serum ferritin is occasionally used as a marker of malignancy, such as in neuroblastoma[15] or renal cell carcinoma.[16] In dialysis patients, hyperferritinemia is associated with rHuEPO resistance.[9] Uremic patients with high serum ferritin concentrations were reported to be more anemic.[17] Severely malnourished dialysis patients were found to have higher serum ferritin levels.[8] Several studies in the past had denoted an association between dialysis morbidity, including risk of infection, and iron overload represented by a high serum ferritin.[18] However, such inferences may be flawed, because the hyperferritinemia-associated morbidity could have reflected an independent prognostic factor rather than being due to iron overload.[5]

Serum ferritin results from the leakage of tissue ferritin, an intracellular iron storage pro-

Table 4. Relative Risk (Odds Ratio) of Death for Decreased Serum Albumin, Increased Serum Ferritin, and Decreased Serum TIBC Based on Cox Proportional Hazard and Logistic Regression Analyses

	Survival Analyses (using "initial" values)		Logistic Regressions (using "predeath" values)	
	Separate Survival Analyses	Combined Survival Analysis	Separate Logistic Regressions	Combined Logistic Regression
Albumin (decreased by 0.5 g/dL)	2.11 (1.29-3.46)*	2.31 (1.40-3.81)*	4.76 (2.02-11.23)*	4.48 (1.77-11.33)*
Ferritin (increased by 500 ng/mL)	1.01 (0.45-2.26)	1.00 (0.44-2.29)	2.83 (1.30-6.19)*	2.71 (1.06-7.02)*
TIBC (decreased by 50 mg/dL)	2.51 (0.92-6.83)	3.35 (1.23-9.12)*	4.50 (1.38-14.68)*	2.89 (0.81-10.35)

NOTE. All models are controlled for demographic factors (age, sex, race, dialysis months, and underlying renal disease). In "separate" analyses, each regression model is based on only one single laboratory value (albumin, ferritin, or TIBC), whereas in "combined" analysis, one single regression model is used for all three laboratory values and, hence, they are all controlled for each other. The values in parentheses are 95% CI.

* *P* value < 0.05.

tein shell with a molecular weight of approximately 450 kD, containing heavy (H) and light (L) subunits.[1] Serum ferritin is slightly different than tissue ferritin and contains little or no iron.[19] Whereas tissue ferritin clearly plays a role in intracellular iron handling, the role of serum ferritin is less clearly understood.[19] The level of ferritin in plasma represents the balance between its secretion, which is directly related to intracellular iron synthesis, and its clearance, mainly in liver and other organs.[1] However, liver dysfunction and inflammatory factors may interfere with the synthesis and clearance of ferritin, thereby increasing serum ferritin levels due to circumstances not related to iron metabolism.[19,20] During the acute-phase response, inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor (TNF) increase the synthesis of both H and L subunits of ferritin.[21,22] Rogers et al[21] showed that IL-1β induces ferritin gene expression by translational control of its mRNA, but this inflammatory induction of ferritin synthesis is different from iron-dependant ferritin gene expression. They showed that this inflammatory regulation of ferritin requires the background presence of cellular iron.[21] This important finding is consistent with several recent clinical and epidemiological findings that, in the setting of absolute iron deficiency, serum ferritin is almost always low[4,5] but once the minimal required iron is available, ferritin regulation becomes a function of non–iron-dependent factors.[21]

Current nephrology practice in the rHu-EPO era prescribes uniform, generous iron administration to dialysis patients receiving rHu-EPO.[23,24] Therefore, a commonly encountered high serum ferritin may be due to non–iron-related factors such as inflammation and malnutrition, both of which are highly correlated with dialysis morbidity and mortality.[25,26] Recently, we have shown that in uremic patients, serum ferritin values between 200 and 2,000 ng/mL are significantly correlated with C-reactive protein.[27] Inflammation-associated cytokines have been implicated in the pathogenesis of wasting syndrome,[28] which is associated with poor outcome. Yuen et al[29] have recently shown that C-reactive protein is a predictor of cardiovascular mortality in hemodialysis patients. These reports, along with our previous finding regarding the significant correlation between ferritin and malnutrition,[8] suggests that our current finding regarding the correlation between serum ferritin and dialysis outcome may be based on the fact that a high serum ferritin is a reflection of the "Malnutrition Inflammation Complex Syndrome"[25] in dialysis patients and, hence, a marker of morbidity and mortality in this group of patients. However, the small sample size and lack of C-reactive protein among laboratory values limit our study.

Whereas the role of ferritin as a marker of hospitalization was stronger than any other laboratory variables in our study, its role as a mortality marker was somewhat different when compared with albumin. Many studies, including ours, have confirmed a high dialysis mortality among hypoalbuminemic patients.[10,30] Our study suggests that an initially low serum TIBC (hypotransferrinemia) may also have a bearing on mortality. Unlike hypoalbuminemia, however, hyperferritinemia did not appear to be a "long-term" marker of mortality in our study. On the other hand, our study indicates that a recent increase in serum ferritin is a marker of possible dialysis mortality and, therefore, ferritin's role appears to be more of a "short-term" marker of mortality when compared with that of albumin. We found that, although initial serum ferritin values do not appear to have any role in predicting long-term mortality, the short-term ferritin changes can, in fact, be markers of dialysis death. The independent relative risk of death for any 500 ng/mg increase in serum ferritin during a 1-year follow-up is 2.71 in our study. This gives a more dynamic role to serum ferritin as a marker of death within a short period of time when compared with both serum albumin and serum TIBC, the two "long-term" mortality markers.

Our study suggests a significant role for hyperferritinemia in dialysis outcome. In the rHu-EPO era, when many dialysis patients are receiving generous doses of iron, an increased serum ferritin is a most puzzling finding for the clinician. In our study, such moderately high serum ferritin concentrations do not appear to reflect iron stores reliably but are more a reflection of the "Malnutrition Inflammation Complex Syndrome" and hence a marker of morbidity and mortality in dialysis patients. Our finding suggests that this may have a significant role in risk stratification

of the dialysis patient, although more longitudinal studies are required to establish the true association between serum ferritin and morbidity and mortality in dialysis patients. We suggest that a recent unexpected increase in serum ferritin concentration in any dialysis patient should be considered as a marker of "sickness."

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