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A Low Serum Iron Level Is a Predictor of Poor Outcome in Hemodialysis Patients

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● **Background:** Iron administration has been implicated as a cause of poor clinical outcome in maintenance hemodialysis (MHD) patients. However, the role of low iron levels in the clinical outcome of MHD patients is not clear. **Methods:** We examined the predicting value of baseline serum iron level on prospective mortality and hospitalization in a cohort of all 1,283 MHD patients from 10 DaVita dialysis facilities in Los Angeles County, CA. **Results:** Patients aged 57.8 ± 15.2 years included 49% men, 45% Hispanics, 25% African Americans, and 53% patients with diabetes. During the first 3 months of the cohort, 97% of patients were administered erythropoietin (EPO) and 60% were administered intravenous iron (gluconate and/or dextran) at least once. During a 12-month follow-up, mortality was significantly greater (23%) in the lowest serum iron quartile ($<45.3 \mu\text{g/dL}$ [$<8.1 \mu\text{mol/L}$]) compared with other quartiles (10% to 12%). Multivariate Poisson and Cox models adjusted for demographic features, dialysis dose and vintage, serum albumin and ferritin and blood hemoglobin concentrations, and administered EPO and iron doses showed that both serum iron level and iron saturation ratio had significant, but inverse, associations with prospective mortality and hospitalization. There was a statistically significant trend toward greater rates of mortality and hospitalization with lower serum iron levels. This reverse association remained significant in a subcohort of 322 MHD patients after additional adjustments for comorbid conditions and serum C-reactive protein level to reflect inflammation. **Conclusion:** Low baseline serum iron indicators are associated with increased mortality and hospitalization in MHD patients independent of hemoglobin level, EPO and iron doses, indicators of nutrition and inflammation, and comorbid conditions. Clinical trials to examine the role of iron administration in improving morbidity and mortality by increasing serum iron levels in MHD patients are required. *Am J Kidney Dis* 43:671-684.

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INDEX WORDS: Serum iron; transferrin saturation ratio; mortality; hospitalization; hemodialysis (HD); reverse epidemiology; erythropoietin (EPO).

MORE THAN one quarter of a million maintenance hemodialysis (MHD) outpatients in the United States and many more in other countries continue to have poor clinical outcomes, including unacceptably high rates of mortality and hospitalization and low quality of life.¹ Markers of anemia, including low blood hemoglobin concentrations, are associated with poor outcome. Consequently, management of anemia by recombinant human erythropoietin (EPO) by increasing serum hemoglobin levels toward the target of 11.0 to 12.0 g/dL (110 to 120 g/L) are reported to improve all 3 of these outcome measures in MHD patients.²⁻⁶ However, much controversy exists with regard to the association between measures of iron stores or changes in these values by iron administration and clinical outcome in these individuals. Although in the pre-EPO area, iron overload was a major cause of morbidity in MHD patients, its significance in the post-EPO era has not been expressively examined. Conversely, it is not clear whether iron deficiency is significantly associated with outcome. Hence, we examined the association between baseline serum values of

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iron indices and prospective mortality and hospitalization in a large cohort and a subcohort of MHD patients.

METHODS

Patients

DaVita South Bay Cohort consists of 10 out-patient dialysis facilities in the Los Angeles South Bay area that are located within a 15-mile radius from Harbor-UCLA Medical Center and administered uniformly by DaVita Inc. This cohort has been followed up closely since October 2001, especially because it constitutes the base population for the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study.⁷⁻¹⁰ Approximately 360 MHD patients participate at any given time in the NIED Study and are randomly selected from more than 1,200 MHD patients of the DaVita South Bay Cohort (see NIED Study Web site; www.NIEDstudy.org for more details, as well as related publications⁷⁻¹⁰). Virtually all MHD patients from the 10 dialysis facilities were included in this cohort. The study was approved by the Institutional Review Committee of the Research and Education Institute at Harbor-UCLA Medical Center and was exempted from written consent requirements. The NIED Study cohort, which is essentially a subcohort of the DaVita South Bay Cohort, also was analyzed during the same period for comparison with the main cohort. The medical chart of each MHD patient in this subcohort was thoroughly reviewed by a nephrologist (K.K.-Z.), and data pertaining to underlying kidney disease, cardiovascular history, and other comorbid conditions were extracted as described elsewhere.^{8,9} A modified version of the Charlson comorbidity index, ie, without the age and kidney disease components, was used to assess the severity of comorbidity.^{11,12}

Mortality and Hospitalization

Patients were studied from October 1, 2001, to September 30, 2002. Their mortality was determined irrespective of the cause of death during the 12-month prospective period. Survival was verified by confirming the existence of the surviving patient in the database of the subsequent quarters after the end of the cohort study period, ie, after September 30, 2002. For all surviving patients, the right censorship cohort time was 12 months. For a surviving patient with a right censorship time less than 12 months, the cause of removal from the study was determined by reviewing the 12-month longitudinal data and included renal transplantation, quitting dialysis treatment, and transferring out of the dialysis cohort area. For patients who changed modality to peritoneal dialysis and remained in the cohort area, the follow-up for mortality watch was continued based on the intention-to-treat principle.

Hospitalization is defined as any hospital admission that included at least 1 overnight stay in the hospital. The admission day was counted as 1 full hospitalization day, but the discharge day was not. Therefore, the minimum duration of hospitalization per admission was 1 day. No exclusion criteria for determining hospitalizations were used, except for renal transplantation. Thus, all hospital admissions except for renal transplantation were counted. However, be-

cause the vast majority of dialysis access-related hospitalizations did not require overnight admission, essentially only access-related hospitalizations associated with other morbid conditions, such as infection or cardiovascular events, were included. For patients in the hospital at the start of this cohort study, that hospitalization was not counted. For patients still in the hospital at the end of the 1-year cohort study, all hospitalization days of the last admission were counted up to a maximum of 30 days. For patients who died and those who left the cohort during the prospective follow-up, hospitalization rates during the survival time were standardized by use of the multiplication factor, 12/survival time (in months). To remove the effect of outliers, a hospitalization frequency (H_F) more than 12 times/y was replaced by 12 times/y ($n = 17$), and any total hospitalization days (H_D) more than 120 days was replaced by 120 days ($n = 13$).

Three methods were used to assess the 12-month prospective hospitalization, as described in our previous reports.^{8,13} Annual H_F was the total number of hospital admissions during the 12-month prospective cohort irrespective of the length of each admission. Annual H_D was the sum of all hospitalization days of a given patient during the same 12-month period. Number of days at risk from the start of the cohort until the first hospitalization event (H_T) for each individual per year was assessed in a survival model, irrespective of additional subsequent hospitalizations. Accordingly, risk time for each individual is defined as days from study entry until the first hospitalization, a censoring event, or the study anniversary day occurs.

Laboratory Evaluation

Routine blood samples were obtained in a uniform fashion in all 10 dialysis facilities within the first full week of a given month, eg, October 1 through 6, 2001, for the first cohort month. Single-pool Kt/V was used to represent weekly dialysis dose, and normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate, was calculated to estimate daily protein intake.^{14,15} Serum iron concentrations and iron saturation ratio were used as indices of iron stores. Total iron-binding capacity (TIBC) was considered to represent serum transferrin level.^{16,17} Iron saturation ratio was calculated based on the following formula:

$$\text{Iron saturation} = \text{serum iron/serum TIBC}$$

Blood hemoglobin was measured weekly to bimonthly. Serum ferritin and intact parathyroid hormone were measured at least once during the first week of October 2001. All other laboratory parameters were measured monthly. All laboratory measurements were performed by DaVita Laboratories (Deland, FL) by using automated methods, and average values for each laboratory test within the first 13 weeks of the cohort were calculated. Hence, laboratory data of the baseline database were 3-month-averaged values obtained between October 1 and December 31, 2001. Laboratory data were extracted and averaged using KLINLAB software, designed and operated by one of the coauthors of this report (R.S.L.). In subjects of the NIED subcohort, high-sensitivity C-reactive protein (CRP) was measured by means of a turbidometric immunoassay in which a serum sample is

mixed with latex beads coated with antihuman CRP antibodies forming an insoluble aggregate (WPCI, Osaka, Japan; in milligrams per liter; normal range, <3.0 mg/L).^{18,19}

Administered EPO and Iron

A computerized billing data registry was used to obtain doses and frequencies of medications used for the treatment of anemia, including EPO, iron dextran (InFeD; Watson, Inc, Corona, CA), iron gluconate (Ferrlecit; Watson, Inc), and iron sucrose (Venofer; American Regent, Shirley, NY). The total amount of medications administered to each patient within the first 13 weeks of the cohort was extracted. For EPO, average weekly dose, and for iron supplementation, average monthly dose, were calculated. The intravenous (IV) iron that was administered at baseline and during the first 8 to 10 months of the cohort to almost all MHD patients in the 10 DaVita dialysis facilities was iron gluconate (Ferrlecit). However, until 6 to 8 months before the start of the cohort, the only form of IV iron used in the dialysis facilities was iron dextran (InFeD) exclusively. Patients related to Kaiser Permanente Healthcare (almost 5% of the total cohort) did not switch from iron dextran to iron gluconate unless they were allergic to iron dextran. Almost no patient was administered iron sucrose (Venofer) during the first 8 to 10 months of the cohort. However, during the last 2 to 4 months of the cohort, there was a transition in almost all dialysis units from iron gluconate to iron sucrose, whereas Kaiser Permanente patients still remained on iron dextran therapy.

The decision about how much EPO and/or IV iron was administered to each MHD patient was made independently by at least 42 nephrologists who were in charge of dialysis treatment care for some of these 1,283 MHD patients. Most nephrologists were not aware of the period in which this study was conducted, but they mostly were familiar with iron and anemia guidelines of the Kidney Disease and Dialysis Outcomes Quality Initiative (K/DOQI) guidelines,^{7,20} ie, to achieve a targeted hemoglobin level of 11 to 12 g/dL (110 to 120 g/L) and/or a hematocrit of 33% to 36%. Eight nephrologists were randomly asked if they were aware of the K/DOQI guidelines and whether they used these recommendations to prescribe EPO and iron to their patients. All interviewed nephrologists were fully aware of the guidelines, but 2 nephrologists argued that they might withhold iron administration with ferritin levels greater than 500 ng/mL ($\mu\text{g/L}$), whereas 1 nephrologist would continue iron administration with ferritin levels as high as 1,200 ng/mL ($\mu\text{g/L}$).

Statistical and Epidemiological Methods

Conventional Student's *t*-test and analysis of variance were used to detect significant differences among continuous variables in 2 or more groups, when applicable. Chi-square and Kruskal-Wallis rank tests were used for categorical variables. We used Pearson's correlation coefficient *r* for analyses of associations between continuous variables and Spearman's rank test for categorical variables. Partial correlations adjusted for case-mix covariates were calculated by using linear multivariate models. To calculate the relative risk for first hospitalization (H_b) and death in the prospective

cohort, hazard ratios (HRs) and their 95% confidence intervals (CIs) were obtained by using Cox proportional hazard regression models. Covariates included age, sex, race (blacks versus others and Asians versus others), ethnicity (Hispanics versus others), diabetes, dialysis vintage (in months), insurance status (Medicaid versus others), body mass index (BMI), Kt/V (single pool), serum albumin and ferritin concentrations, blood hemoglobin level, average weekly dose of EPO, and monthly dose of IV iron. Plots of log (-log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption. Poisson regression models with the same covariates were used to evaluate the association between hospitalization data (H_b and H_f) and relevant predictors by calculating the hospitalization rate ratio (RR). A 95% CI not including 1.00 was considered statistically significant. Descriptive and multivariate statistics were performed using the statistical software Stata, version 7.0 (Stata Corp, College Station, TX). Fiducial limits are given as mean \pm SD. *P* less than 0.05 is considered statistically significant.

RESULTS

The main cohort consisted of 1,283 MHD patients at baseline who were followed up for a total of 1,077 patient-years. The subcohort included 322 MHD patients who were among 385 NIED Study participants with complete iron- and anemia-related values. Table 1 lists relevant demographic, laboratory, and dialysis treatment-related data at baseline for both the main cohort and subcohort. In the main cohort, 49% of patients were men. Approximately a quarter of the patients were African American, and almost half were Hispanic. More than half of all 1,283 MHD patients had diabetes mellitus. Patients had an average age of 57.8 years and had undergone dialysis treatment for 41 months (dialysis vintage). Three-month averaged values for pertinent laboratory data also are listed in Table 1. Data in the subcohort were similar, but *t*-test for differences between the main cohort and subcohort showed mostly statistical significance caused by large sample sizes.

During the 12-month prospective follow-up, 179 patients died, consistent with an annual mortality rate of 14.0% in the main cohort, whereas the mortality rate was 10.5% in the subcohort, indicating that somewhat healthier patients were selected in the NIED Study subcohort. During the same period, 23 MHD patients received a kidney transplant, 150 patients transferred out of the cohort area, 3 patients withdrew from dialysis therapy voluntarily, and 4 patients changed treatment modality to peritoneal dialy-

Table 1. Demographic, Laboratory, and Clinical Data in MHD Patients From 10 DaVita Dialysis Facilities in the South Bay Los Angeles Area

Variable	Main Cohort (n = 1,283)	Subcohort (n = 322)
Sex (% male)*	48.9	53.6
Race (% blacks)*	25.3	28.9
Ethnicity (% Hispanics)*	44.9	48.5
Insurance (% Medicaid)	20.7	21.1
Diabetes mellitus (%)	53.2	56.5
Mortality (% annual)*	14.0	10.5
Hospitalized at least once (%)*	57.1	50.9
History of cardiovascular disease	NA	50.6
Charlson comorbidity index	NA	2.08 ± 1.51
Age (y)*	57.8 ± 15.2	54.1 ± 14.7
Cohort time (mo)	10.1 ± 3.4	10.3 ± 3.4
Dialysis vintage (mo)*	40.8 ± 40.4	37.5 ± 34.9
Postdialysis weight (kg)	71.3 ± 19.7	73.2 ± 19.7
BMI (kg/m ²)	26.4 ± 6.5	26.6 ± 6.3
Kt/V (single pool)	1.57 ± 0.30	1.58 ± 0.28
nPNA (nPCR; g/kg/d)	1.05 ± 0.25	1.05 ± 0.22
Blood hemoglobin (g/dL)	11.91 ± 0.98	11.94 ± 0.98
Serum albumin (g/dL)*	3.81 ± 0.38	3.85 ± 0.33
TIBC (μg/dL)	200.0 ± 42.0	201.3 ± 35.8
Ferritin (ng/mL)	685 ± 480	655 ± 473
Iron (μg/dL)	63.6 ± 28.4	65.9 ± 23.9
Iron saturation ratio (%)	31.2 ± 11.1	32.6 ± 10.4
CRP (mg/L)	NA	6.1 ± 7.8
Annual hospitalization frequency	1.9 ± 2.8	1.8 ± 3.0
Annual hospitalization days*	11.5 ± 27.1	8.7 ± 24.7
EPO weekly dose (U/w)*	16,879 ± 13,645	13,868 ± 11,386
Iron gluconate dose (mg/mo)	153.8 ± 195.4	165.9 ± 201.8
Iron dextran dose (mg/mo)	11.6 ± 68.0	12.2 ± 49.6

NOTE. Count data expressed as percent, and continuous data expressed as mean ± SD. Postdialysis weight, BMI, Kt/V, and most laboratory measures are 3-month-averaged values based on all measurements during the first 13 weeks of the cohort. To convert hemoglobin and albumin in g/dL to g/L, multiply by 10; ferritin in ng/mL to μg/L, multiply by 1; iron in μg/dL to μmol/L, multiply by 0.179.

Abbreviations: NA, data not available; nPCR, normalized protein catabolic rate.

* $P < 0.05$ for t -test between the main cohort and subcohort.

sis in the main cohort. Of 1,283 MHD patients in the main cohort, 732 patients (57.1%) were hospitalized at least once during the 12-month follow-up. Annual H_F was 1.9 times/patient/y, and total H_D were an average of 11.5 d/patient/y. Average administered EPO dose during the first 3 months of the cohort was 16,879 U/patient/wk. In the subcohort, more than half the patients had a history of cardiovascular disease, whereas the same data were not available in the main cohort. Charlson comorbidity index and serum CRP levels also were exclusively assessed in the subcohort.

Table 2 lists data pertaining to anemia management medications in the main cohort. All except 33 patients were administered EPO. Although

Table 2. Medications Administered in the Management of Anemia in 1,283 MHD Patients During the First 3 Months of the Main Cohort

Medication Type and Status	No.	Percent
EPO	1,250	97.4
EPO without IV iron	537	41.9
IV iron dextran	54	4.2
IV iron gluconate	727	56.7
IV iron sucrose	0	0.0
Two IV irons concurrently	24	1.8
IV iron without EPO	14	1.1

NOTE. Each count indicates that the medication in question was administered at least once during the 3-month interval.

Table 3. Correlation Coefficients Between Serum Iron Indices and Relevant Laboratory Measures, Anemia, Protein Intake, Dialysis Dose, BMI, and Administered Doses of EPO and IV Iron

	Serum Iron	Iron Saturation Ratio
Serum albumin	+0.22*/+0.16*	+0.03/+0.03
TIBC	+0.33*/+0.42*	-0.16*/-0.10*
Ferritin	+0.05/+0.06†	+0.15*/+0.15*
CRP‡	-0.13†/-0.11†	-0.04/-0.03
Blood hemoglobin	+0.21*/+0.18*	+0.10*/+0.18*
WBC count	-0.18*/-0.14*	-0.17*/-0.16*
nPNA (nPCR)	+0.21*/+0.17*	+0.11*/+0.07†
Kt/V (single pool)	+0.16*/+0.15*	+0.16*/+0.19*
BMI	-0.12*/-0.08*	-0.17*/-0.15*
EPO (U/wk)	-0.25*/-0.20*	-0.16*/-0.14*
IV iron gluconate (mg/mo)	-0.14*/-0.10*	-0.19*/-0.17*

NOTE. In each entry, the first correlation coefficient is bivariate (unadjusted) and the second is multivariate adjusted for age, sex, race, ethnicity, diabetes, dialysis vintage, and insurance status in 1,283 MHD patients of the main cohort.

Abbreviations: nPCR, normalized protein catabolic rate.

* $P < 0.01$

† P between 0.01 and 0.05.

‡Correlations with CRP level are in the subcohort of 322 MHD patients.

more than half the patients were administered IV iron at least once during the first 3 months of the cohort, 42% of all MHD patients were administered EPO without iron supplementation. Only 4% of patients were administered iron dextran, and these were essentially Kaiser Permanente patients; 57% were administered iron gluconate, and no patient was administered iron sucrose. Only 1% of patients ($n = 14$) were administered some dose of IV iron without EPO during the same interval. Data in the subcohort were similar (not shown here).

Table 3 lists correlation coefficients between serum iron indices and relevant variables in the main cohort. Serum albumin level significantly, but weakly, correlated with serum iron level, but not with iron saturation ratio. Serum TIBC had a positive and strong correlation with serum iron level ($r = +0.45$), but a negative correlation with iron saturation ratio, indicating the confounding effect of TIBC as the denominator of the iron saturation ratio formula. Serum ferritin level did not have a significant association with serum iron level, but correlated with iron saturation.

Both iron indices correlated positively with hemoglobin level, Kt/V, and nPNA and negatively with white blood cell (WBC) count, BMI, and administered doses of EPO and IV iron. However, most of these correlations were weak. Correlations were very similar in the subcohort; these data are not shown except for serum CRP level, which had a weak, but inverse, correlation with serum iron level, indicating that a low serum iron level tended to be associated with inflammation in MHD patients.

Table 4 lists mortality and hospitalization in 4 quartiles of serum iron level and iron saturation ratio. Patients in the lowest serum iron quartile ($<45.5 \mu\text{g/dL}$ [$<8.1 \mu\text{mol/L}$]) had a mortality rate virtually twice that in other quartiles (23% versus 10% to 12% in the main cohort; $P < 0.001$). Hospitalization indices also were significantly higher in the lowest serum iron quartiles. The same trend was seen for the lowest quartile of iron saturation ratio ($<24\%$), but with a less impressive P . Annual mortality rate was 19% in the lowest iron saturation quartile compared with the other 3 quartiles, which had a mortality rate of 11% to 13% ($P = 0.02$). Similarly, hospitalization measures were greater in the lowest iron saturation quartile. Figures 1 and 2 show cumulative proportions of surviving patients in 4 quartiles of serum iron level and iron saturation ratio, respectively. In both figures, the lowest quartile had significantly worse survival, and Kaplan-Meier P for serum iron level and iron saturation ratio were <0.001 and 0.03, respectively.

In the main cohort, we conducted multivariate Cox proportional hazard and Poisson regression models that included demographic features (sex, age, race, ethnicity, insurance status, and dialysis vintage); 3-month averaged values for dialysis dose, indices of serum iron, albumin, and ferritin and blood hemoglobin concentrations; and administered EPO and iron doses. Models in the subcohort also included all these covariates, as well as history of cardiovascular disease, Charlson comorbidity score, and serum CRP level (only mortality models are shown for the subcohort). Among variables related to iron status, baseline serum ferritin level and 3-month-averaged administered IV iron did not predict mortality (results not shown). However, both serum iron level and iron saturation ratio had significant, but inverse,

Table 4. Quartiles of Serum Iron Levels and Iron Saturation Ratio

	1st (lowest) Quartile	2nd Quartile	3rd Quartile	4th (highest) Quartile	P*
Serum iron level					
No. of patients	322	317	318	317	
Range of serum iron ($\mu\text{g/dL}$)	11.0-45.3	45.5-58.0	58.3-75.7	76.0-331.5	NA
Mean \pm SD ($\mu\text{g/dL}$)	36.7 \pm 6.6	51.8 \pm 3.5	66.3 \pm 4.9	99.9 \pm 30.9	NA
Mortality \dagger (main cohort; %)	23.0	12.3	9.7	10.4	<0.001
Mortality \dagger (subcohort, n = 322; %)	24.4	2.4	8.6	7.1	<0.001
Hospitalized \geq 1 time \dagger (%)	66.7	57.4	54.1	49.8	<0.001
Annual H _F \ddagger	2.4	1.8	1.5	1.5	<0.001
Annual H _D \ddagger	14.9	10.4	8.5	8.8	<0.001
Iron saturation ratio					
No. of patients	325	335	310	307	
Range of iron saturation (%)	5.7-23.7	24.0-29.7	30.0-37	37.3-88.5	NA
Mean \pm SD (%)	19.5 \pm 3.2	26.8 \pm 1.8	33.1 \pm 2.0	46.5 \pm 9.6	NA
Mortality \dagger (main cohort)	18.7%	12.8%	10.6%	13.4%	0.023
Mortality \dagger (subcohort, n = 322)	17.1	10.3	7.4	7.1	0.091
Hospitalized \geq 1 time \dagger	64.9%	58.2%	52.2%	52.1%	0.002
Annual H _F \ddagger	2.1	2.0	1.6	1.6	0.014
Annual H _D \ddagger	13.7	10.5	9.2	9.1	0.020

NOTE. In each section, the second data row shows range of the iron store indicator in the 4 consecutive quartiles and the third row, mean values. Data pertain to the main cohort of 1,283 MHD patients, unless specified. To convert iron in $\mu\text{g/dL}$ to $\mu\text{mol/L}$, multiply by 0.179.

*P based on chi-square or analysis of variance (test of trend is not included).

\dagger Rates of mortality and hospitalization (at least once) are within the 12 months of prospective follow-up.

\ddagger Annual H_F and H_D are adjusted for left-censored cohort time when applicable (see text).

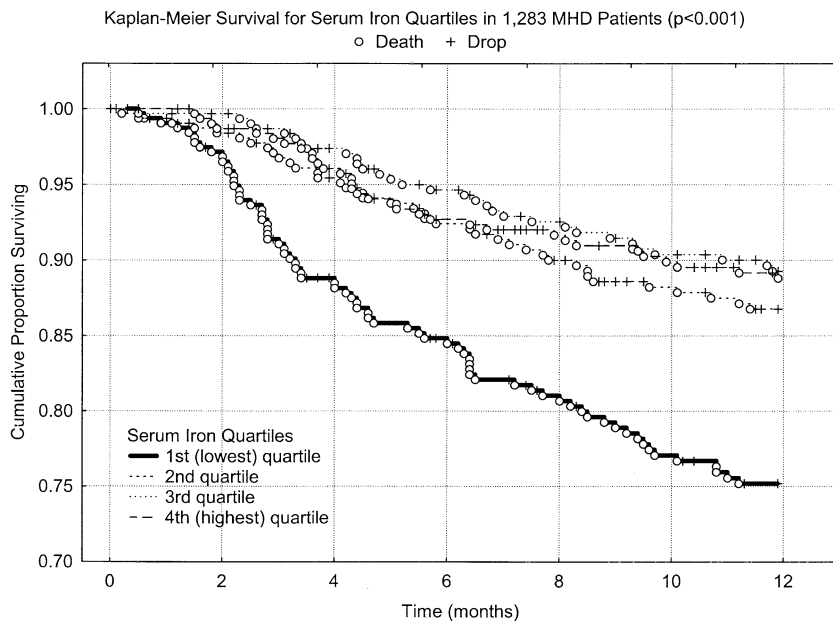


Fig 1. Cumulative proportions of surviving patients in 4 quartiles of serum iron concentrations (3-month average at the beginning of the cohort) in 1,283 MHD patients of the main cohort. Patients in the lowest serum iron quartile had the greatest mortality (Kaplan-Meier $P < 0.001$).

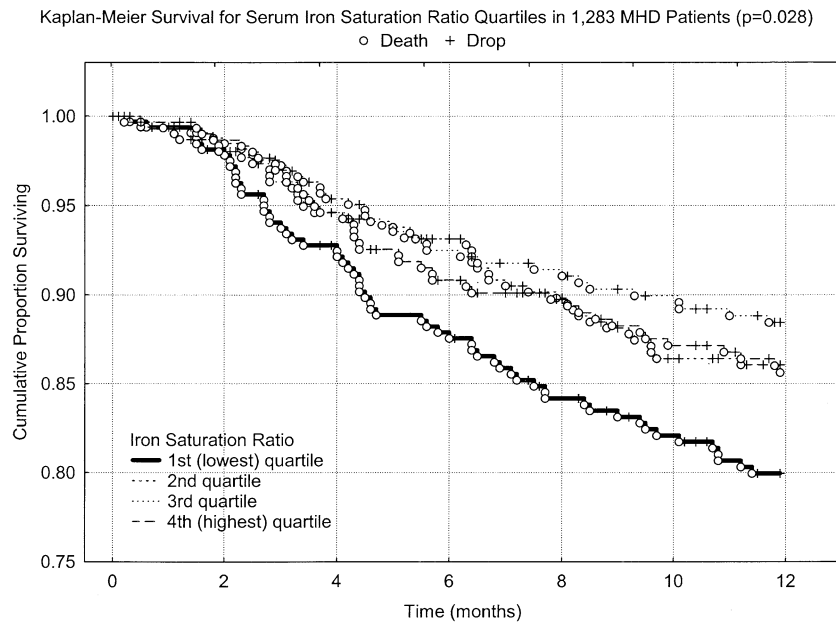


Fig 2. Cumulative proportions of surviving patients in 4 quartiles of serum iron saturation ratio (3-month average at the beginning of the cohort) in 1,238 MHD patients of the main cohort. Patients in the lowest serum iron quartile had the greatest mortality (Kaplan-Meier $P = 0.028$).

associations with prospective mortality and hospitalization.

Tables 5 through 8 indicate relative risk for mortality and hospitalization for both serum iron level and iron saturation ratio. In each table, the first 2 rows show relative risk for each $10\text{-}\mu\text{g/dL}$ ($1.8\text{-}\mu\text{mol/L}$) decrease in serum iron level or 10% decrease in iron saturation ratio in the main cohort and subcohort, respectively. The third row indicates relative risk across all 4 quartiles from lowest to highest; the next row, lowest versus highest; and the last row, lowest versus all other quartiles in the main cohort. Both unadjusted and multivariate-adjusted relative risk values are calculated for comparison. Table 5 lists a multivariate mortality HR of 1.71 (95% CI, 1.06 to 2.77; $P = 0.03$) when risk for death in the lowest serum iron quartile is compared with the highest quartile and an HR of 1.56 (95% CI, 1.12 to 2.19; $P = 0.009$) when the lowest serum iron quartile is compared with the rest.

Tables 6 through 8 list relative risks for hospital admission for 3 measures of hospitalization in the same format as Table 5. All HRs for the first hospital admission (H_T) were consistently and significantly greater for decreasing values of serum iron level and iron saturation ratio and their lowest quartiles (Table 6). Poisson regression models indicated greater H_F and H_D RRs for lower values of serum iron and iron saturation

ratio (Tables 7 and 8). Figures 3 and 4 show Kaplan-Meier cumulative proportions of nonhospitalized patients over time for days before the first hospital admission (H_T) in the main cohort. As shown in Fig 3, the lowest quartile for serum iron levels had significantly higher numbers of H_T (Kaplan-Meier $P < 0.001$). A similar trend for nonhospitalized patients was observed for the lower 2 quartiles of iron saturation ratio compared with the higher quartiles (Fig 4). Finally, it is important to note that in all models, amount of administered iron did not show an association with outcome.

DISCUSSION

In a prospective observational study of 1,283 MHD patients from 10 uniformly administered DaVita dialysis facilities in the South Bay Los Angeles area, we show that low, rather than high, baseline values of serum iron and iron saturation ratio were consistently associated with poor clinical outcome, including significantly greater rates of mortality and hospitalization. These significant and strikingly inverse associations were independent of demographic features, markers of nutrition and inflammation (such as serum ferritin and albumin levels), anemia (serum hemoglobin level), and administered doses of EPO and IV iron. In the subcohort, we also showed that these inverse associations were independent of comorbid conditions, measured by Charlson

Table 5. Mortality Risk During the 12 Months of Prospective Follow-Up Indicated by HRs Based on Cox Proportional Hazard Regression Analyses

Serum Iron and Risk for Death	Unadjusted HR	Multivariate-Adjusted HR	Iron Saturation Ratio and Risk for Death	Unadjusted HR	Multivariate-Adjusted HR
Serum iron (for each 10- μ g/dL decrease; main cohort, n = 1,283)*	1.15 (1.07-1.23) <i>P</i> < 0.001	1.07 (1.01-1.14) <i>P</i> = 0.036	Iron saturation ratio (for each 10% decrease; main cohort, n = 1,283)*	1.11 (0.96-1.28) <i>P</i> = 0.145	1.15 (1.00-1.33) <i>P</i> = 0.056
Serum iron (for each 10- μ g/dL decrease; subcohort, n = 322)†	1.40 (1.13-1.73) <i>P</i> = 0.002	1.31 (1.07-1.62) <i>P</i> = 0.008	Iron saturation ratio (for each 10% decrease; subcohort, n = 322)†	1.38 (0.94-2.04) <i>P</i> = 0.104	1.59 (1.10-2.23) <i>P</i> = 0.014
Serum iron quartiles (across decreasing quartiles)*	1.40 (1.22-1.61) <i>P</i> < 0.001	1.20 (1.04-1.40) <i>P</i> = 0.015	Iron saturation ratio quartile (across decreasing quartiles)*	1.16 (1.01-1.32) <i>P</i> = 0.034	1.17 (1.01-1.35) <i>P</i> = 0.035
Lowest serum iron quartile (<i>v</i> highest quartile)*	2.34 (1.61-3.67) <i>P</i> < 0.001	1.71 (1.06-2.77) <i>P</i> = 0.028	Lowest iron saturation ratio quartile (<i>v</i> highest quartile)*	1.45 (0.98-2.16) <i>P</i> = 0.065	1.33 (0.84-2.11) <i>P</i> = 0.228
Lowest serum iron quartile (<i>v</i> all others)*	2.34 (1.74-3.16) <i>P</i> < 0.001	1.56 (1.12-2.19) <i>P</i> = 0.009	Lowest iron saturation ratio quartile (<i>v</i> all others)*	1.57 (1.15-2.14) <i>P</i> = 0.004	1.52 (1.09-2.13) <i>P</i> = 0.014

NOTE. Each entry includes the HR for first hospital admission, (95% CI), in parentheses, and related *P*. Data pertain to the main cohort of 1,283 MHD patients, unless specified. To convert iron in μ g/dL to μ mol/L, multiply by 0.179.

*Multivariate-adjusted models in the main cohort (n = 1,283) include age, sex, race (blacks versus others and Asians versus others), ethnicity (Hispanics versus others), diabetes, dialysis vintage (in months), insurance status (Medicaid versus others), BMI, Kt/V (single pool), serum albumin and ferritin concentrations, blood hemoglobin level, average weekly dose of EPO, and monthly doses of IV iron (iron gluconate and/or iron dextran).

†Models in the subcohort (n = 322) include all these covariates for the main cohorts plus history of cardiovascular disease, Charlson comorbidity score, and serum CRP level.

comorbidity score and history of cardiovascular disease, and inflammation, measured by serum CRP level. Serum iron level had a stronger association with inverse outcome compared with serum iron saturation ratio.

Among 3 indicators of iron stores that are routinely (monthly to quarterly) measured in all dialysis facilities in the United States, serum iron concentration is used less frequently than serum ferritin level or iron saturation ratio for monitoring iron status in MHD patients. The National Kidney Foundation-K/DOQI guidelines have extensive recommendations and comprehensive discussions about serum ferritin level and iron saturation ratio pertaining to their use in monitoring iron stores in dialysis patients, but almost no coverage for serum iron concentration itself in this regard.²⁰ Iron saturation ratio is a mathematical product of 2 measured serum components, ie, serum iron level divided by TIBC. Serum TIBC is a negative acute-phase reactant and a marker of malnutrition-inflammation complex syndrome

(MICS) and poor outcome in MHD patients.^{17,21,22} Hence, unlike in the general population, the use of iron saturation ratio may not be as helpful as serum iron level by itself for monitoring iron status in MHD patients. The value of the iron saturation ratio can be confounded significantly by protein-energy malnutrition and/or inflammation because its denominator, ie, TIBC, is a nutritional and/or inflammatory marker.^{23,24} This may explain why in our study, discovered inverse associations were stronger for serum iron level than for iron saturation ratio. Conversely, serum ferritin is a positive acute-phase reactant and levels may be increased in MICS regardless of iron status.^{22,25} Hence, serum ferritin level may be an even less useful marker of iron status.²⁵ Finally, serum iron level itself is inferior to such reference standard indicators of iron stores as bone marrow iron.²⁶

Serum iron is believed to be a reliable indicator of iron stores in the general population. However, some diurnal and day-to-day varia-

Table 6. Relative Risk for H_T During the 12 Months of Prospective Follow-Up Indicated by HRs Based on Cox Proportional Hazard Regression Analyses

Serum Iron and Risk for H _T	Unadjusted HR	Multivariate-Adjusted HR	Iron Saturation Ratio and Risk for H _T	Unadjusted HR	Multivariate-Adjusted HR
Serum iron (for each 10- μ g/dL decrease; main cohort, n = 1,283)*	1.08 (1.04-1.12) <i>P</i> < 0.001	1.04 (1.01-1.07) <i>P</i> = 0.007	Iron saturation ratio (for each 10% decrease; main cohort, n = 1,283)*	1.13 (1.06-1.22) <i>P</i> = 0.001	1.12 (1.04-1.20) <i>P</i> = 0.002
Serum iron (for each 10- μ g/dL decrease; subcohort, n = 322)†	1.10 (1.03-1.19) <i>P</i> = 0.007	1.07 (1.00-1.15) <i>P</i> = 0.054	Iron saturation ratio (for each 10% decrease; subcohort, n = 322)†	1.22 (1.04-1.43) <i>P</i> = 0.014	1.23 (1.05-1.44) <i>P</i> = 0.010
Serum iron quartiles (across decreasing quartiles)*	1.21 (1.13-1.29) <i>P</i> < 0.001	1.09 (1.01-1.16) <i>P</i> = 0.024	Iron saturation ratio quartile (across decreasing quartiles)*	1.15 (1.07-1.22) <i>P</i> < 0.001	1.12 (1.04-1.20) <i>P</i> = 0.002
Lowest serum iron quartile (<i>v</i> highest quartile)*	1.80 (1.47-2.20) <i>P</i> < 0.001	1.41 (1.12-1.79) <i>P</i> = 0.004	Lowest iron saturation ratio quartile (<i>v</i> highest quartile)*	1.46 (1.19-1.79) <i>P</i> < 0.001	1.36 (1.08-1.71) <i>P</i> = 0.008
Lowest serum iron quartile (<i>v</i> all others)*	1.59 (1.36-1.86) <i>P</i> < 0.001	1.21 (1.01-1.43) <i>P</i> = 0.033	Lowest iron saturation ratio quartile (<i>v</i> all others)*	1.34 (1.14-1.57) <i>P</i> < 0.001	1.22 (1.03-1.45) <i>P</i> = 0.020

NOTE. Each entry includes HR for H_T (95% CI), and related *P*. Data pertain to the main cohort of 1,283 MHD patients, unless specified. To convert iron in μ g/dL to μ mol/L, multiply by 0.179.

*Multivariate-adjusted models in the main cohort (n = 1,283) include age, sex, race (blacks versus others and Asians versus others), ethnicity (Hispanics versus others), diabetes, dialysis vintage (in months), insurance status (Medicaid versus others), BMI, Kt/V (single pool), serum albumin and ferritin concentrations, blood hemoglobin level, average weekly dose of EPO, and monthly doses of IV iron (iron gluconate and/or iron dextran).

†Models in the subcohort (n = 322) include all these covariates plus history of cardiovascular disease, Charlson comorbidity score, and serum CRP level.

tions in serum iron levels have been reported.²⁷ Serum iron levels may be decreased in conditions other than iron deficiency; the most frequent probably is the anemia associated with such chronic conditions as uremia. Chronic inflammation may be the reason for such a decrease in serum iron level under these conditions.^{7,28,29} Hypoferremia (ie, low serum iron level, not to be confused with hypoferritinemia) is observed not only during inflammation of various causes and neoplasia, but also during trauma, myocardial infarction, surgery, and stressful conditions.²⁹ The hypoferremic response was believed to be of protective value to the host against infection and neoplasia because suppression of the iron-withholding ability of the host by excess iron would be associated with a greater incidence and severity of infection and neoplasia.^{28,29} Excessive iron is considered deleterious because of its oxidative stress and predisposition

to infection in MHD patients. Such concerns probably have led to relatively conservative policies, including the K/DOQI guidelines, for iron administration to MHD patients. However, most reports concerning adverse effects of iron in MHD patients are based on in vitro studies.³⁰

The inverse association that we found between a relative iron deficiency status (serum iron < 45.5 μ g/dL [$<8.1 \mu$ mol/L]) and poor clinical outcome may be caused by the confounding effect of inflammation and malnutrition, also known as MICS. Nevertheless, the discovered associations remained statistically significant, consistent, and relatively strong, even after the use of such extensive multivariate models that adjusted for relevant covariates, including serum albumin and ferritin and blood hemoglobin levels. Even inclusion of such factors as WBC count (as an indicator of inflammation) and nPNA (as an indicator of protein intake) did not change the

Table 7. RR of H_F During the 12 Months of Prospective Follow-Up Based on Poisson Regression Analyses

Serum Iron and RR of H _F	Unadjusted RR	Multivariate-Adjusted RR*	Iron Saturation and RR H _F	Unadjusted RR	Multivariate-Adjusted RR*
Serum iron (for each 10- μ g/dL decrease; main cohort, n = 1,283)*	1.06 (1.04-1.08) <i>P</i> < 0.001	1.02 (1.01-1.04) <i>P</i> = 0.004	Iron saturation ratio (for each 10% decrease; main cohort, n = 1,283)*	1.10 (1.05-1.14) <i>P</i> < 0.001	1.07 (1.02-1.11) <i>P</i> = 0.002
Serum iron (for each 10- μ g/dL decrease; subcohort, n = 322)†	1.26 (1.22-1.31) <i>P</i> < 0.001	1.20 (1.15-1.25) <i>P</i> < 0.001	Iron saturation ratio (for each 10% decrease; subcohort, n = 322)†	2.01 (1.84-2.18) <i>P</i> < 0.001	1.86 (1.66-2.08) <i>P</i> < 0.001
Serum iron quartiles (across decreasing quartiles)*	1.16 (1.12-1.21) <i>P</i> < 0.001	1.04 (1.01-1.09) <i>P</i> = 0.034	Iron saturation ratio quartile (across decreasing quartiles)*	1.12 (1.08-1.16) <i>P</i> < 0.001	1.07 (1.03-1.11) <i>P</i> = 0.001
Lowest serum iron quartile (<i>v</i> highest quartile)*	1.53 (1.37-1.71) <i>P</i> < 0.001	1.22 (1.07-1.39) <i>P</i> = 0.003	Lowest iron saturation ratio quartile (<i>v</i> highest quartile)*	1.34 (1.19-1.50) <i>P</i> < 0.001	1.26 (1.11-1.43) <i>P</i> < 0.001
Lowest serum iron quartile (<i>v</i> all others)*	1.45 (1.33-1.58) <i>P</i> < 0.001	1.11 (1.01-1.23) <i>P</i> = 0.026	Lowest iron saturation ratio quartile (<i>v</i> all others)*	1.24 (1.13-1.35) <i>P</i> < 0.001	1.09 (0.99-1.19) <i>P</i> = 0.080

NOTE. Each entry includes the RR for H_F (95% CI), and related *P*. Data pertain to the main cohort of 1,283 MHD patients, unless specified. To convert iron in μ g/dL to μ mol/L, multiply by 0.179.

*Multivariate-adjusted models in the main cohort (n = 1,283) include age, sex, race (blacks versus others and Asians versus others), ethnicity (Hispanics versus others), diabetes, dialysis vintage (in months), insurance status (Medicaid versus others), BMI, Kt/V (single pool), serum albumin and ferritin concentrations, blood hemoglobin level, average weekly dose of EPO, and monthly doses of IV iron (iron gluconate and/or iron dextran).

†Models in the subcohort (n = 322) include all these covariates plus history of cardiovascular disease, Charlson comorbidity score, and serum CRP level.

strength or direction of the associations we found (data not shown). In the subcohort, 3 additional covariates, ie, degree of severity of comorbid condition, history of cardiovascular disease, and inflammation reflected by serum CRP level, were added to multivariate models, but serum iron level maintained its inverse and statistically significant association with outcome. Hence, a low serum iron level is an independent marker of poor outcome in MHD patients.

Very few in vivo studies have shown an association between iron administration or higher iron indices and poor outcome in MHD patients. In 79 MHD patients, Drueke et al³¹ found that an increased common carotid artery intima-media thickness, a marker of early atherosclerosis, was associated with plasma advanced oxidation protein products, serum ferritin, and annual IV iron dose administered. The investigators concluded that their findings indicated a significant role for oxidative stress in early atherosclerosis in MHD patients, which may be increased by IV iron.³¹

However, this observational study did not substantiate a cause-effect association between IV iron administration and worsening oxidative stress in these patients. In another longitudinal study of a similar number of MHD patients, an abrupt increase in serum ferritin levels was associated with increased mortality.²² However, in this study, all patients were administered a relatively uniform dose of IV iron. Hence, it was concluded that an increase in serum ferritin levels was related to acute-phase reaction and not IV iron administration.²² In another study by Feldman et al,³² there was a tendency to increased mortality in MHD patients administered greater doses of IV iron.

However, additional analyses by the same investigators of a large national data set from 1996 using novel epidemiological and statistical methods have not detected an association between iron administration and survival (H. Feldman, personal communication, November 2003). In our current study, we did not find an associa-

Table 8. RR of H_D During the 12 Months of Prospective Follow-Up Based on Poisson Regression Analyses

Serum Iron and RR of H _D	Unadjusted RR	Multivariate-Adjusted RR*	Iron Saturation and RR of H _D	Unadjusted RR	Multivariate-Adjusted RR*
Serum iron (for each 10- μ g/dL decrease; main cohort, n = 1,283)*	1.10 (1.09-1.10) <i>P</i> < 0.001	1.04 (1.03-1.05) <i>P</i> < 0.001	Iron saturation ratio (for each 10% decrease; main cohort, n = 1,283)*	1.17 (1.15-1.19) <i>P</i> < 0.001	1.14 (1.13-1.16) <i>P</i> < 0.001
Serum iron (for each 10- μ g/dL decrease; subcohort, n = 322)†	1.31 (1.28-1.33) <i>P</i> < 0.001	1.24 (1.21-1.26) <i>P</i> < 0.001	Iron saturation ratio (for each 10% decrease; subcohort, n = 322)†	1.88 (1.80-1.96) <i>P</i> < 0.001	1.68 (1.59-1.77) <i>P</i> < 0.001
Serum iron quartiles (across decreasing quartiles)*	1.21 (1.19-1.23) <i>P</i> < 0.001	1.06 (1.04-1.08) <i>P</i> < 0.001	Iron saturation ratio quartile (across decreasing quartiles)*	1.15 (1.14-1.17) <i>P</i> < 0.001	1.09 (1.07-1.11) <i>P</i> < 0.001
Lowest serum iron quartile (<i>v</i> highest quartile)*	1.69 (1.61-1.77) <i>P</i> < 0.001	1.39 (1.32-1.47) <i>P</i> < 0.001	Lowest iron saturation ratio quartile (<i>v</i> highest quartile)*	1.50 (1.43-1.57) <i>P</i> < 0.001	1.38 (1.31-1.46) <i>P</i> < 0.001
Lowest serum iron quartile (<i>v</i> all others)*	1.62 (1.56-1.67) <i>P</i> < 0.001	1.18 (1.13-1.22) <i>P</i> < 0.001	Lowest iron saturation ratio quartile (<i>v</i> all others)*	1.42 (1.37-1.47) <i>P</i> < 0.001	1.20 (1.15-1.24) <i>P</i> < 0.001

NOTE. Each entry includes the RR for H_T (95% CI), and related *P*. Data pertain to the main cohort of 1,283 MHD patients, unless specified. To convert iron in μ g/dL to μ mol/L, multiply by 0.179.

*Multivariate-adjusted models in the main cohort (n = 1,283) include age, sex, race (blacks versus others and Asians versus others), ethnicity (Hispanics versus others), diabetes, dialysis vintage (in months), insurance status (Medicaid versus others), BMI, Kt/V (single pool), serum albumin and ferritin concentrations, blood hemoglobin level, average weekly dose of EPO, and monthly doses of IV iron (iron gluconate and/or iron dextran).

†Models in the subcohort (n = 322) include all these covariates plus history of cardiovascular disease, Charlson comorbidity score, and serum CRP level.

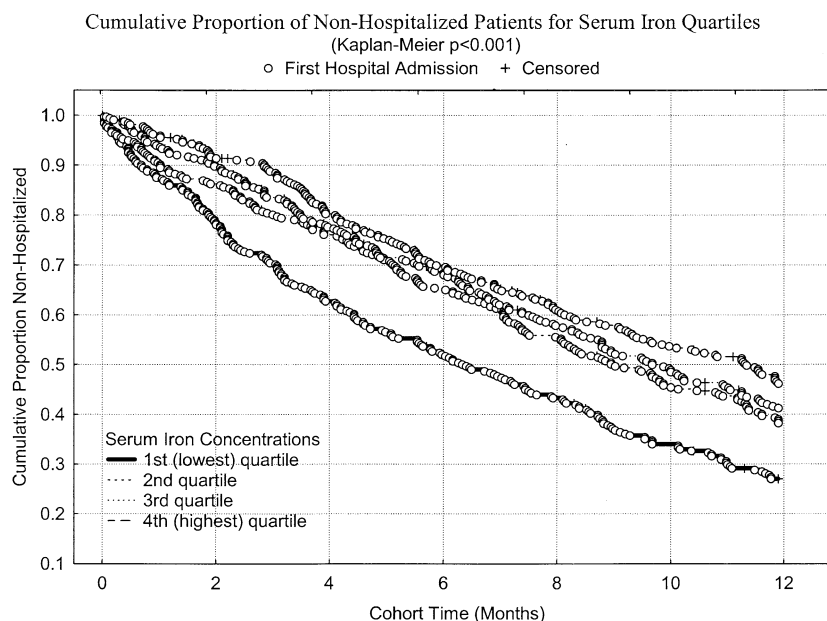


Fig 3. Cumulative proportions of nonhospitalized patients in 4 quartiles of serum iron concentrations (3-month average at the beginning of the cohort) in 1,283 MHD patients of the main cohort. Patients in the lowest serum iron quartile had the greatest first hospitalization incidence (Kaplan-Meier *P* < 0.001).

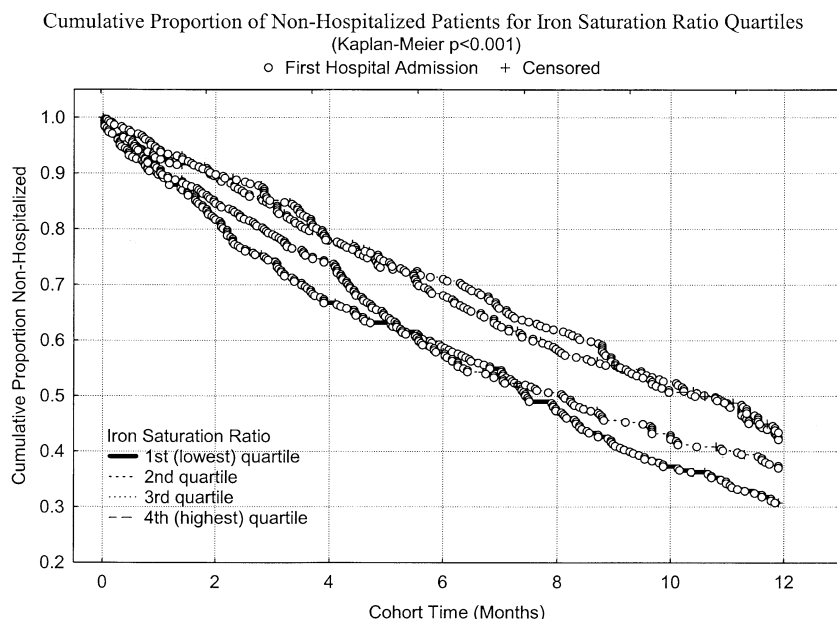


Fig 4. Cumulative proportions of nonhospitalized patients in 4 quartiles of iron saturation ratio (3-month average at the beginning of the cohort) in 1,283 MHD patients of the main cohort. Patients in the lowest iron saturation ratio quartile had the greatest first hospitalization incidence (Kaplan-Meier $P < 0.001$).

tion between amount of administered iron and mortality or hospitalization. Several studies in the past had denoted an association between dialysis morbidity, including risk for infection, and iron overload represented by a high serum ferritin level.³³ However, such inferences may be flawed because hyperferritinemia-associated morbidity could have reflected an independent prognostic factor, rather than being caused by iron overload. In other words, because serum ferritin is an inflammatory marker, its levels may be increased in the setting of infection. Infection per se may be the primary cause of death and also associated with hyperferritinemia as a secondary phenomenon. Thus, considering high ferritin level as the primary cause of increased mortality in the setting of inflammation or infection and implicating IV iron for that may be flawed as long as longitudinal studies do not show a temporal relationship between iron administration and poor outcome in MHD patients.

Our study should be qualified because it is observational, rather than interventional, and a mixed incident/prevalent MHD population was used. Moreover, despite its large sample size, MHD patients were on average several years younger than the average MHD patients in the US Renal Data System (USRDS).³⁴ This may explain a lower mortality rate in our study population compared with the USRDS. Moreover, we

had a greater prevalence of diabetes and more Hispanic patients than in the USRDS. Nevertheless, because essentially all MHD patients of the 10 studied dialysis facilities were included in our analyses, there was no selection bias, at least at study population level. Moreover, all dialysis facilities were under uniform administrative care, and all laboratory tests were performed in a single laboratory with optimal quality-assurance monitoring. Furthermore, we used 3-month-averaged measures, rather than 1 single measure at baseline, and we adjusted for dialysis vintage in all multivariate models. A switch from iron gluconate to sucrose toward the end of the cohort time was observed, but its confounding effect is less likely, although not impossible.

Another limitation of our study is the possible inclusion of cases with gastrointestinal bleeding, other sources of blood loss, or malignancies, which may lead to low serum iron levels and poor outcome. Moreover, MHD patients with intercurrent infection or systemic inflammatory diseases, in whom inflammation-induced hypoferrinemia can be observed, were not excluded. However, these cases are not too frequent to cause major confounding. Furthermore, we did not assess residual renal function, but it is less likely that serum iron level would be different based on urine output. Changes in fluid status may cause fluctuation in serum iron levels; how-

ever, all blood samples were drawn predialysis. Other analytical restrictions of our study may be that our design inherently precludes conclusions pertaining to cause-effect relationship. Moreover, we used conventional multivariate models that use a baseline measure to predict prospective events, a model that does not include time-varying components. Although time-varying or adjusted regression models may be of relevance for long-term cohorts, our follow-up interval was limited to only 12 months. It is very unlikely, although not impossible, that time-varying variables would exert significantly different exposure-outcome constellations within such a short period.

To our knowledge, this is the first study that shows an inverse association between serum iron level and poor outcome, which is in contrast to conventional expectation in MHD patients. However, this is not the first time that a "risk factor reversal" phenomenon was observed in these individuals.^{35,36} Decreased, rather than increased, BMI, blood pressure, or serum cholesterol, creatinine, and homocysteine levels have been associated with greater mortality rates in MHD patients.^{35,37} This phenomenon, also referred to as "reverse epidemiology," may now include yet another component, ie, the association between a low serum iron level and poor dialysis outcome.³⁵

Another potentially important observation in our study is that in more than 40% of MHD patients, anemia management was based solely on EPO, without IV iron administration during the entire 3 months of baseline. This may be a direct consequence of current conservative K/DOQI guidelines and caused by the known apprehension among nephrologists that iron is harmful. Conversely, only 14 patients (1.1%) were administered IV iron without EPO in the same observation period. Although our study is based exclusively on mere observational data and no cause-effect association can be inferred, it is consistent with the thesis that low iron status may be as harmful as, if not more harmful than, the so-called iron overload. In previously reported cases of hemochromatosis and/or hemosiderosis among dialysis patients, the observed serum ferritin levels were greater than the currently observed ranges in MHD patients, usually in the 3,000- to 10,000-ng/mL ($\mu\text{g/L}$) range

then.³⁸ To our knowledge, with widespread EPO administration to dialysis patients since the early 1990s, there have been much fewer, if any, reported cases of hemochromatosis or hemosiderosis in these patients despite rigorous use of IV iron.³⁸ Current guidelines to use such moderately increased serum ferritin levels (>200 to 300 ng/mL [$\mu\text{g/L}$]) for hemochromatosis screening in the general population are not applicable to the dialysis population.³⁹ Hence, K/DOQI guidelines advising against IV iron administration to dialysis patients with a moderately increased serum ferritin level, ie, the 800- to 2,000-ng/mL ($\mu\text{g/L}$) range, may need to be reconsidered and might deprive these possibly inflamed, but not iron-overloaded or even possibly iron deficient, patients of required iron supplementation. However, the observational nature of our study prompts caution in interpreting and generalizing our findings. Interventional studies, including randomized clinical trials, are required to ascertain whether: (1) in an MHD patient with a low serum iron level, IV iron administration can effectively increase serum iron levels; and (2) whether such an interventional increase in serum iron levels improves clinical outcome in these individuals.

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