

# A Malnutrition-Inflammation Score Is Correlated With Morbidity and Mortality in Maintenance Hemodialysis Patients

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• Malnutrition inflammation complex syndrome (MICS) occurs commonly in maintenance hemodialysis (MHD) patients and may correlate with increased morbidity and mortality. An optimal, comprehensive, quantitative system that assesses MICS could be a useful measure of clinical status and may be a predictor of outcome in MHD patients. We therefore attempted to develop and validate such an instrument, comparing it with conventional measures of nutrition and inflammation, as well as prospective hospitalization and mortality. Using components of the conventional Subjective Global Assessment (SGA), a semiquantitative scale with three severity levels, the Dialysis Malnutrition Score (DMS), a fully quantitative scoring system consisting of 7 SGA components, with total score ranging between 7 (normal) and 35 (severely malnourished), was recently developed. To improve the DMS, we added three new elements to the 7 DMS components: body mass index, serum albumin level, and total iron-binding capacity to represent serum transferrin level. This new comprehensive Malnutrition-Inflammation Score (MIS) has 10 components, each with four levels of severity, from 0 (normal) to 3 (very severe). The sum of all 10 MIS components ranges from 0 to 30, denoting increasing degree of severity. These scores were compared with anthropometric measurements, near-infrared-measured body fat percentage, laboratory measures that included serum C-reactive protein (CRP), and 12-month prospective hospitalization and mortality rates. Eighty-three outpatients (44 men, 39 women; age,  $59 \pm 15$  years) on MHD therapy for at least 3 months ( $43 \pm 33$  months) were evaluated at the beginning of this study and followed up for 1 year. The SGA, DMS, and MIS were assessed simultaneously on all patients by a trained physician. Case-mix-adjusted correlation coefficients for the MIS were significant for hospitalization days ( $r = 0.45$ ;  $P < 0.001$ ) and frequency of hospitalization ( $r = 0.46$ ;  $P < 0.001$ ). Compared with the SGA and DMS, most pertinent correlation coefficients were stronger with the MIS. The MIS, but not the SGA or DMS, correlated significantly with creatinine level, hematocrit, and CRP level. During the 12-month follow-up, 9 patients died and 6 patients left the cohort. The Cox proportional hazard-calculated relative risk for death for each 10-unit increase in the MIS was 10.43 (95% confidence interval, 2.28 to 47.64;  $P = 0.002$ ). The MIS was superior to its components or different subversions for predicting mortality. The MIS appears to be a comprehensive scoring system with significant associations with prospective hospitalization and mortality, as well as measures of nutrition, inflammation, and anemia in MHD patients. The MIS may be superior to the conventional SGA and the DMS, as well as to individual laboratory values, as a predictor of dialysis outcome and an indicator of MICS. © 2001 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Dialysis; malnutrition; inflammation; nutritional assessment; hospitalization; mortality; near infrared; albumin; transferrin; C-reactive protein (CRP).

## Editorial, p. 1318

**T**HERE IS A HIGH prevalence of measures of both protein-energy malnutrition and inflammation in patients with end-stage renal disease (ESRD) who are undergoing maintenance hemodialysis (MHD).<sup>1-3</sup> These observations, made repeatedly by different researchers,<sup>1-4</sup> have led to coinage of the term malnutrition inflammation complex syndrome (MICS). Factors causing protein-energy malnutrition and proinflammatory cytokines, which themselves may cause anorexia, muscle wasting, hypoalbuminemia, refractory anemia, and, possibly, accelerated atherosclerosis, are apparent causes of MICS.<sup>5,6</sup> Several features of MICS, alone or in combination, are strong predictors of degree of sickness, as well as morbidity and mortality, in these patients.<sup>7,8</sup>

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Although many measures of malnutrition or inflammation correlate with clinical outcome, these values generally do not evaluate clinical condition and outcome in a combined way for an individual patient. Very few measures of malnutrition or inflammation give an overall rating of these clinical conditions. A comprehensive scoring system would be useful for this purpose if it was capable of risk-stratifying a patient with ESRD in a quantitative way for optimal management, yet be a practical and easy tool without cumbersome methods or sophisticated calculations.

We therefore attempted to develop a scoring system that is comprehensive and semiquantitative, but easy to use, for the evaluation of patients with ESRD. The present report describes such a system and our attempts to validate it in MHD patients by comparing it with conventional measures of nutritional state, inflammation, risk for hospitalization, and mortality.

## METHODS

### *Patients*

The outpatient chronic dialysis program at San Francisco General Hospital (San Francisco, CA) treated 91 adult MHD patients at the time of the study. Inclusion criteria were patients undergoing MHD for at least 3 months and aged 18 years or older. Three patients did not meet these criteria. Of 88 eligible MHD patients, 2 patients were hospitalized in other centers at the time of the study and 3 patients did not agree to participate. Therefore, 83 individuals (44 men, 39 women) agreed to enroll onto the study. The study was approved by the institutional review board, and written informed consent was obtained from all participants.

### *Conventional Subjective Global Assessment*

The Subjective Global Assessment (SGA) of nutritional states, as it is commonly used in nephrology, is a semiquantitative scoring system based on history and physical examination.<sup>9,10</sup> The history consists of five components: weight loss during the preceding 6 months, gastrointestinal (GI) symptoms, food intake, functional capacity, and comorbidities. Each of these features is scored separately as A, B, or C, reflecting well-nourished to severely malnourished categories. The physical examination includes two components: loss of subcutaneous fat and muscle wasting. (The presence of edema or ascites is the third component of the original SGA physical examination, usually not used for dialysis patients.) These two components are classified from 0 to 3, representing normal to severely abnormal. Data are scored subjectively, and patients are classified in terms of the three major SGA scores: A, well nourished; B, mild to moderate malnutrition; and C, severe malnutrition. Details on methods for SGA evaluation in dialysis patients are available as an appendix in a previously published article,<sup>10</sup> available on the

web site of the *American Journal of Kidney Diseases* (<http://www.ajkd.org>).

### *Dialysis Malnutrition Score*

Using components of the conventional SGA, one of the authors recently developed a quantitative scoring system, the Dialysis Malnutrition Score (DMS),<sup>11</sup> that consists of seven components of the conventional SGA: weight change, dietary intake, GI symptoms, functional capacity, comorbidity, subcutaneous fat, and signs of muscle wasting. Ascites and edema were deleted, and number of years of dialysis therapy (vintage) was added to the comorbidity component. Each component has a score ranging from 1 (normal) to 5 (severely abnormal). Thus, the DMS, ie, the sum of all seven components, is a number from 7 (normal) to 35 (severely malnourished); a higher DMS represents a greater degree of protein-energy malnutrition. In a recent preliminary report from a cross-sectional study using a different pool of patients, the DMS correlated significantly with anthropometric values and laboratory measures of nutritional status in MHD patients.<sup>11</sup>

### *Malnutrition Inflammation Score*

To attempt to make the scoring system more comprehensive and quantitative, evaluation criteria for the 7 DMS components were revised, and three new items were added: body mass index (BMI), serum albumin level, and total iron-binding capacity (TIBC). Moreover, the number of severity levels of each component was reduced from five to four levels because in the previous study, we noted that the fifth level of the DMS was almost never used.<sup>11</sup> Thus, the Malnutrition Inflammation Score (MIS) has 10 components, each with four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components ranges from 0 (normal) to 30 (severely malnourished); a higher score reflects a more severe degree of malnutrition and inflammation.

Figure 1 shows our scoring sheet, which consists of four sections (nutritional history, physical examination, BMI, and laboratory values) and 10 components. The history section includes 5 components adopted from the original SGA.<sup>9</sup> Weight change is determined as the change in edema-free posthemodialysis body weight in the past 6 months. The lowest score (0) is given if weight loss is less than 0.5 kg or there is an increase in body weight. Score 1 indicates a minor loss of at least 0.5 kg, but less than 1.0 kg. Score 2 is given for weight loss of at least 1.0 kg, but less than 5% of body weight, and score 3 indicates weight loss of 5% or greater.

Dietary intake is scored 0 if it is the usual intake of solid foods, with no recent decrease in amount or quality of meals. A score of 1 indicates a slightly suboptimal solid diet, 2 indicates a full-liquid diet or moderate decrease in food intake, and 3 indicates a daily nutrient intake that would be incompatible with life on a chronic basis.

GI symptoms are scored 0 if the patient has a good appetite and no GI symptoms; 1, mildly decreased appetite or mild nausea; 2, occasional vomiting or other moderate GI symptoms, such as abdominal pain; and 3, diarrhea, frequent vomiting, or severe anorexia.

Functional capacity is scored 0 for normal functional capacity or a considerable improvement in level of previous functional impairment. A score of 1 indicates mild or occa-

<b>COMPREHENSIVE MALNUTRITION INFLAMMATION SCORE</b>			
<b>(A) Patients' related medical history:</b>			
<b>1- Change in end dialysis dry weight (overall change in past 3-6 months):</b>			
0	1	2	3
No decrease in dry weight or weight loss <0.5 kg	Minor weight loss (>0.5 kg but <1 kg)	Weight loss more than one kg but <5%	Weight loss >5%
<b>2- Dietary intake:</b>			
0	1	2	3
Good appetite and no deterioration of the dietary intake pattern	Somewhat sub-optimal solid diet intake	Moderate overall decrease to full liquid diet	Hypo-caloric liquid to starvation
<b>3- Gastrointestinal (GI) symptoms:</b>			
0	1	2	3
No symptoms with good appetite	Mild symptoms, poor appetite or nauseated occasionally	Occasional vomiting or moderate GI symptoms	Frequent diarrhea or vomiting or severe anorexia
<b>4- Functional capacity (nutritionally related functional impairment):</b>			
0	1	2	3
Normal to improved functional capacity, feeling fine	Occasional difficulty with baseline ambulation, or feeling tired frequently	Difficulty with otherwise independent activities (e.g. going to bathroom)	Bed/chair-ridden, or little to no physical activity
<b>5- Co-morbidity including number of years on Dialysis:</b>			
0	1	2	3
On dialysis less than one year and healthy otherwise	Dialyzed for 1-4 years, or mild co-morbidity (excluding MCC*)	Dialyzed >4 years, or moderate co-morbidity (including one MCC*)	Any severe, multiple co-morbidity (2 or more MCC*)
<b>(B) Physical Exam (according to SGA criteria):</b>			
<b>6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):</b>			
0	1	2	3
Normal (no change)	mild	moderate	Severe
<b>7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):</b>			
0	1	2	3
Normal (no change)	mild	moderate	Severe
<b>(C) Body mass index:</b>			
<b>8- Body mass index: BMI = Wt(kg) / Ht<sup>2</sup>(m)</b>			
0	1	2	3
BMI >20 kg/m <sup>2</sup>	BMI: 18-19.99 kg/m <sup>2</sup>	BMI: 16-17.99 kg/m <sup>2</sup>	BMI <16 kg/m <sup>2</sup>
<b>(D) Laboratory Parameters:</b>			
<b>9- Serum albumin:</b>			
0	1	2	3
Albumin ≥ 4.0 g/dL	Albumin: 3.5-3.9 g/dL	Albumin: 3.0-3.4 g/dL	Albumin: <3.0 g/dL
<b>10- Serum TIBC (total Iron Binding Capacity): *</b>			
0	1	2	3
TIBC > 250 mg/dL	TIBC: 200-249 mg/dL	TIBC: 150-199 mg/dL	TIBC: <150 mg/dL
<b>Total Score = sum of above 10 components (0-30):</b>			

\*MCC (Major Comorbid Conditions) include CHF class III or IV, full blown AIDS, severe CAD, moderate to severe COPD, major neurological sequelae, and metastatic malignancies or s/p recent chemotherapy.

\* Suggested equivalent increments for serum transferrin are: >200 (0), 170-199 (1), 140-169 (2), and <140 mg/dl

Fig 1. Components of the comprehensive MIS.

sional difficulty with baseline ambulation or feeling tired frequently; 2, difficulty with independent activities; and 3, restriction to light activity or a persistent bed- and/or chair-bound state.

As in the modified SGA version (DMS), comorbidity includes vintage (number of years on dialysis therapy) because the element of time may have a bearing on the degree of malnutrition and inflammation.<sup>10,12</sup> Thus, comorbidity is

scored 0 if there are no other medical illnesses and the patient has undergone hemodialysis therapy for less than 1 year; 1, mild comorbidity, excluding such major comorbid conditions (MCCs) as congestive heart failure class III or IV, severe coronary artery diseases, clinically evident acquired immunodeficiency syndrome, moderate to severe chronic obstructive pulmonary disease, and metastatic malignancies, or dialysis therapy for 1 to 4 years; score 2, moderate comorbidity (including one of the diseases listed under MCCs) or dialysis therapy for more than 4 years; and score 3, two or more MCCs. The existence of diabetes per se is not accounted for if the previously mentioned comorbidities do not exist. Instead, comorbidities that may be a risk for poor outcomes in patients with diabetes are examined individually.

The physical examination section consists of two components. Body fat stores are scored by assessing subcutaneous fat deposition in four body areas, ie, below the eyes, triceps and biceps areas, and chest. Signs of muscle wasting are obtained by briefly examining seven sites: the temple, clavicle, scapula, ribs (intercostal spaces), quadriceps, knee, and interosseous muscles. For each of these two components, a score of 0 through 3, representing normal to severe changes, is assigned according to conventional SGA guidelines based on criteria specified elsewhere.<sup>9,10</sup>

We added a body weight function adjusted for height to the scoring system because it has predictive value for dialysis mortality.<sup>7</sup> BMI, a ratio of end-dialysis weight (in kilograms) to height squared (in square meters), was selected to represent height-standardized weight.<sup>13,14</sup> BMI was graded in four levels, 0 through 3, representing BMI greater than 20, 18 to 19.99, 16 to 17.99, and less than 16 kg/m<sup>2</sup>, respectively.

The fourth MIS section includes two laboratory values. Serum albumin level is frequently a strong predictor of mortality among patients with ESRD,<sup>15,16</sup> and hypoalbuminemia may represent a response to inflammation (acute-phase reaction),<sup>17,18</sup> as well as low protein intake. Serum TIBC reflects serum transferrin concentration and correlates significantly with nutritional state in dialysis patients,<sup>10</sup> although it also changes with inflammation and iron store fluctuations. Therefore, these two laboratory values now comprise 20% of the total MIS score (see Fig 1 for details).

In this study, a trained physician (K.K.-Z.) scored each patient within 5 to 15 minutes before anthropometric measurements were performed. To evaluate the degree of reproducibility, the same physician repeated the MIS assessment after 1 week on a subset of 15 patients without reference to the first MIS evaluation. The correlation coefficient (*r*) between the two MIS assessments was 0.91, denoting a good degree of reproducibility.

### *Anthropometric Evaluation*

Body weight assessment and anthropometric measurements were performed 5 to 20 minutes immediately after the termination of a hemodialysis treatment. Biceps skinfold and triceps skinfold (TSF) thickness were measured using a conventional skinfold caliper, described elsewhere.<sup>19,20</sup> Midarm circumference (MAC) was measured with a plastic tape. All anthropometric measurements were performed by a single trained physician (K.K.-Z.) three times in rapid succession on the non-access-containing arm of each dialysis

patient, and the three measurements were averaged to give the final result. Midarm muscle circumference (MAMC) was calculated from the formula<sup>20</sup>:

$$\text{MAMC} = \text{MAC} - (3.1415 \times \text{TSF})$$

Height was obtained from the patient's chart.

### *Near-Infrared Interactance*

To evaluate the percentage of body fat and lean body mass, near-infrared interactance (NIR)<sup>14,20</sup> was performed at the same time as anthropometric measurements. A commercial NIR sensor (portable Futrex 5000; Futrex Inc, Gaithersburg, MD) was used. NIR measurements were performed by placing a Futrex sensor on the nonaccess upper arm for several seconds after entering the required data (sex, weight, height, and body frame size) from each patient, stipulating that physical activity levels were uniform for all patients. It previously was shown that NIR measurements of body fat correlate significantly with the SGA and other nutritional measures in MHD patients.<sup>14,20</sup>

### *Hospitalization*

Hospitalization data during the 12-month period after the completion of these measurements were obtained on all 83 hemodialysis patients. Hospitalization was defined as any hospital admission that included at least one 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 criterion was used. Thus, hospital admissions for a variety of disorders were counted. However, because the vast majority of dialysis access-related hospitalizations did not require overnight admission, essentially only those access-related hospitalizations complicated by other morbid events, such as infection or cardiovascular complications, were included. For the few patients in a hospital at the start of the 6-month cohort, that hospitalization was not counted. For patients who were still in a hospital at the end of the 1-year cohort, all hospitalization days of the last admission were counted. For 9 patients who died and 6 patients who left the cohort during the prospective 12-month follow-up, hospitalization indices during the survival time were standardized by using the factor 12/survival time (in months).

Three methods were used to assess the 12-month prospective hospitalization as clinical outcomes. Annual hospitalization frequency ( $H_1$ ) was the total number of hospital admissions during the 12-month prospective cohort, defined previously, regardless of the length of each admission. Annual hospitalization days ( $H_2$ ) were the sum of all hospitalization days of a given patient during the same period. The number of days at risk from study start to the first hospitalization event for each individual per year was assessed in a survival model ( $H_3$ ). Accordingly, risk time for each individual is defined as days from study entry until the first hospitalization, a censoring event, or a study anniversary day occurs. A patient's risk period is truncated 3 days before transplantation to avoid attributing the transplantation-related hospitalization to observed days to event.

### Laboratory Evaluation

Laboratory values, except for postdialysis serum urea nitrogen levels used to calculate urea reduction ratio, were measured immediately before the dialysis session at least 16 days after the last intravenous administration of iron. Serum C-reactive protein (CRP) was measured as an indicator of an inflammatory state and assessed by the immunoturbidimetric method (Hitachi 747). The lower-limit sensitivity of the CRP assay is 6.9 ng/mL. For patients with a reported CRP level less than 6.9 ng/mL, an arbitrary average of 3.4 ng/mL was used for statistical analyses. Laboratory values were obtained by automated methods. All laboratory measurements were performed by Spectra Laboratories (Fremont, CA).

### Statistical and Epidemiological Methods

The initial cross-sectional study included 83 patients who were subsequently followed up as a 12-month prospective cohort to evaluate hospitalization data as continuous outcome variables and mortality as a dichotomized outcome. We used Pearson's correlation coefficient  $r$  for selected analyses between continuous variables. Student's  $t$ -test (two-tailed) was used for group mean comparisons between men and women. Pearson's correlation  $r$  was used to determine the significance and strength of associations. Spearman's rank correlation also was used for such variables with nonparametric features as SGA, race, and underlying diseases, and results were compared with Pearson's  $r$ . Multivariate regression analysis was performed to obtain partial (adjusted) correlations controlled for sex, age, race, and renal disease.

To calculate the relative risk for first hospitalization and death in the prospective cohort, hazard ratios and 95% confidence intervals (CIs) were obtained using Cox proportional hazard models to control for the previously mentioned demographic variables. A 95% CI not including 1.00 is considered statistically significant. The Cox proportional hazard-calculated  $R^2$  (also known as pseudo- $R^2$ ) was used for comparison with other multivariate correlations. Plots of  $\log(-\log[\text{survival rate}])$  against  $\log(\text{survival time})$  were performed to establish the validity of the proportionality assumption. Each multivariate model included one outcome (dependent) variable and five predicting (independent) variables, ie, age, sex, race, underlying kidney disease, and the variable under study for that particular model. Therefore, the general multivariate model for Cox regression is:

$$\lambda(t) = \lambda_0(t)[\exp(b_1\text{age} + b_2\text{sex} + b_3\text{race} + b_4\text{disease} + b_5X)]$$

where  $\lambda$  is the estimated hazard,  $t$  is time to event or censorship,  $b_1$  through  $b_5$  are coefficients of the model terms, and  $X$  is the predicting variable, including the MIS result, its components, or other variables (SGA, DMS, BMI, NIR body fat, Kt/V, or a pertinent laboratory measurement). Therefore, the association between each predicting variable and outcomes (first hospitalization or death) was studied through separate multivariate models, but with uniform case-mix adjustment for each model.

Descriptive and multivariate statistics were performed using the statistical software Stata, version 5.0 (Stata Corp,

College Station, TX), and all results were verified using a second statistical software, Statistica for Windows, release 5.1 (StatSoft Inc, Tulsa, OK). Fiducial limits are given as mean  $\pm$  SD.  $P$  less than 0.05 is considered statistically significant,  $P$  between 0.05 and 0.10 is considered marginally significant, and  $P$  greater than 0.10 is not significant.

## RESULTS

Table 1 lists clinical and laboratory data. Ages ranged from 22 to 87 years (mean,  $55.8 \pm 15.3$  [SD] years), and vintage (duration of chronic intermittent dialysis therapy) varied from 4 months to 12 years (mean,  $43 \pm 33$  months). Dry body weight ( $69.1 \pm 19.6$  kg) was the average edema-free weight immediately at the end of the hemodialysis session. Interdialytic weight gain was  $1.74 \pm 0.56$  kg. Four patients were not administered erythropoietin; the rest of the patients were administered intravenous erythropoietin in doses ranging from 3,000 to 36,000 U/wk (mean,  $7,928 \pm 7,730$  U/wk). Seventy-eight patients were administered a maintenance dose of iron dextran (200 mg/mon) intravenously, and the other patients were administered oral iron preparations. Women were an average of 11 years older than men. Skinfold measurements, percentage of body fat, and Kt/V were greater in women, whereas MAMC, lean body weight, and serum creatinine levels were greater in men. The three scoring systems (SGA, DMS, and MIS) were not significantly different between men and women.

Table 2 lists correlation coefficients of the three nutritional scoring systems and relevant variables. Among the three nutritional scoring systems, the MIS was the most powerful for predicting prospective hospitalization (adjusted correlations, 0.45 for hospitalization days and 0.46 for frequency of hospitalization). SGA tended to correlate more strongly with skinfold thickness, MAC, and percentage of body fat. Both the DMS and MIS had similar correlations with skinfold measurements and body fat, although the MIS showed stronger correlations with midarm measurements, lean body mass, and BMI. Almost all laboratory values correlated more strongly with the MIS compared with the DMS or SGA. Serum creatinine level and hematocrit did not have a significant correlation with the SGA or DMS, but correlated significantly with the MIS. This suggests that malnourished MHD patients with greater MISs have lower

serum creatinine levels and more profound anemia. However, it should be reiterated that the MIS already contains two laboratory values; therefore, its correlation with these and other laboratory measures is expected to be stronger, at least in part because of mathematical coupling. Serum CRP levels did not correlate with the DMS and correlated only weakly with the SGA. However, CRP levels correlated more strongly with the MIS ( $r = 0.41$ ;  $P < 0.01$ ), suggesting that the MIS may not only reflect severity, but also degree of inflammation. All three nutritional scoring systems had positive correlations with age, denoting the tendency of older patients to have more severe degrees of protein-energy malnutrition and inflammation. Because albumin level, BMI, and possibly transferrin level have been reported to predict dialysis outcome, we elected to compare the MIS with these values, although we acknowledge that a correlation may

be caused at least partly by mathematical coupling.

Table 3 lists correlations of a diverse variety of measures with hospitalization rates. Only those values that showed at least one statistically significant correlation with any hospitalization rate are listed in this table. Serum albumin level is the only value with slightly greater correlation coefficients than those for the MIS. Serum CRP, cholesterol, ferritin, and creatinine levels also have statistically significant correlations with hospitalization rates, although correlations were not as strong as those with serum albumin level or the MIS.

During the 12-month follow-up, nine patients died (average time to death,  $6.9 \pm 2.7$  months). Six patients left the cohort; three patients underwent renal transplantation, two patients changed dialysis modality to peritoneal dialysis, and one patient was transferred to another location. Forty-

**Table 1. Characteristics of 83 MHD Patients**

	All Patients	Men	Women	P
No. of patients	83	44	39	—
Race (black/Hispanic/Asian)	40/20/19	22/9/10	18/11/9	NS
Age (y)	55.8 $\pm$ 15.3	50.8 $\pm$ 15.2	61.5 $\pm$ 13.4	0.002
Vintage (dialysis mon)	43.1 $\pm$ 32.9	42.9 $\pm$ 31.7	43.3 $\pm$ 34.6	NS
Conventional SGA (1-3)	2.0 $\pm$ 0.7	1.8 $\pm$ 0.7	2.1 $\pm$ 0.7	NS
DMS (7-35)	12.1 $\pm$ 3.2	11.5 $\pm$ 3.3	12.7 $\pm$ 2.9	NS
MIS (0-30)	8.3 $\pm$ 4.2	7.5 $\pm$ 4.6	9.2 $\pm$ 3.7	NS
Annual hospitalization frequency ( $H_1$ )*	1.99 $\pm$ 3.14	2.58 $\pm$ 3.88	1.33 $\pm$ 1.84	NS
Annual hospitalization days ( $H_2$ )*	12.7 $\pm$ 24.3	15.5 $\pm$ 25.9	9.5 $\pm$ 9.0	NS
Triceps skinfold (mm)	14.7 $\pm$ 10.7	10.7 $\pm$ 8.2	19.2 $\pm$ 11.5	0.001
Biceps skinfold (mm)	10.5 $\pm$ 7.6	8.7 $\pm$ 6.7	12.6 $\pm$ 8.0	0.02
MAC (cm)	26.6 $\pm$ 4.6	27.0 $\pm$ 4.1	26.1 $\pm$ 5.1	NS
MAMC (cm)	21.9 $\pm$ 3.4	23.6 $\pm$ 2.9	20.0 $\pm$ 2.9	0.001
NIR-measured body fat (%)	28.0 $\pm$ 8.1	24.2 $\pm$ 6.9	32.2 $\pm$ 7.2	0.001
Weight (lb)	151.0 $\pm$ 45.6	157.8 $\pm$ 45.9	143.3 $\pm$ 44.6	NS
Lean body mass by NIR (lb)	106.9 $\pm$ 26.2	117.9 $\pm$ 25.0	94.4 $\pm$ 21.8	0.001
BMI (kg/m <sup>2</sup> )	24.7 $\pm$ 6.4	24.3 $\pm$ 6.1	25.2 $\pm$ 6.8	NS
Serum				
Albumin (g/dL)	3.8 $\pm$ 0.5	3.8 $\pm$ 0.5	3.8 $\pm$ 0.4	NS
Creatinine (mg/dL)	10.5 $\pm$ 3.1	11.5 $\pm$ 3.3	9.3 $\pm$ 2.4	0.002
Cholesterol (mg/dL)	165.2 $\pm$ 33.7	159.6 $\pm$ 31.7	171.4 $\pm$ 35.2	NS
TIBC (mg/dL)	180.0 $\pm$ 36.8	187.1 $\pm$ 42.8	171.9 $\pm$ 26.9	NS
Transferrin (mg/dL)	159.1 $\pm$ 36.5	165.6 $\pm$ 44.2	151.6 $\pm$ 23.7	NS
Ferritin (ng/mL)	826 $\pm$ 472	747 $\pm$ 442	916 $\pm$ 494	NS
Iron (mg/dL)	63.3 $\pm$ 28.8	67.2 $\pm$ 27.3	58.8 $\pm$ 30.2	NS
Transferrin saturation (%)	34.9 $\pm$ 13.8	36.1 $\pm$ 12.6	33.7 $\pm$ 15.1	NS
Hematocrit (%)	33.7 $\pm$ 4.4	34.4 $\pm$ 4.5	32.9 $\pm$ 4.3	NS
CRP (ng/mL)	18.2 $\pm$ 42.0	22.2 $\pm$ 56.1	13.6 $\pm$ 14.4	NS
Kt/V	1.37 $\pm$ 0.27	1.31 $\pm$ 0.25	1.45 $\pm$ 0.29	0.02
rHuEPO dose (U/wk)	7,928 $\pm$ 7,730	9,159 $\pm$ 9,368	6,538 $\pm$ 5,088	NS

Abbreviations: NS, not significant; rHuEPO, recombinant human erythropoietin.

\*Hospitalization days and frequency of hospitalization are 12-month prospective data.

six patients were admitted at least once during this time.

Table 4 lists hazard ratios and 95% CIs of first hospitalization using Cox proportional hazard models based on initial values at the start of the prospective cohort and time to first hospital admission ( $H_3$ ). The model controls for age, sex, race, and underlying renal disease to estimate relative risks. Only those values with statistically significant relative risks for death ( $P < 0.05$ ) are listed in Table 4. Among the three scoring systems, the MIS showed the strongest association with  $H_3$ . The relative risk for first hospital admission for each 10-unit increase in MIS was 3.83 (95% CI, 1.85 to 7.94;  $P < 0.001$ ). The DMS had a weaker association. Among other variables, serum albumin level was a strong predictor of  $H_3$  (hazard ratio, 4.48; 95% CI, 2.16 to 9.28;  $P = 0.001$ ). Serum CRP level also showed a statisti-

cally significant association with  $H_3$ , and serum creatinine level had a marginal association. All other clinical, laboratory, and demographic variables did not show a statistically significant association with  $H_3$  based on Cox proportional hazard modeling.

Table 5 lists hazard ratios and 95% CIs of death using Cox proportional hazard models in a similar approach as described for  $H_3$ . Only those values with statistically significant relative risks for death ( $P < 0.05$ ) are listed in Table 4, except for the DMS ( $P = 0.06$ ), mentioned here for comparison with other scoring systems. Among the three scoring systems, the MIS showed the strongest association with prospective mortality. The relative risk for death for each 10-unit increase in MIS was 10.43 (95% CI, 2.28 to 47.64;  $P = 0.002$ ). The SGA had a weaker association, and the DMS did not have a statistically signifi-

**Table 2. Raw and Adjusted Correlation Coefficients of Three Major Nutritional Scoring Systems and Pertinent Laboratory, Anthropometric, Demographic, and Hospitalization Data**

Correlation Coefficient ( <i>r</i> ) for	SGA	DMS	MIS	Change in <i>r</i> From DMS to MIS (%)
Hospitalization frequency ( $H_1$ )	0.35*	0.30* (0.36*)	0.39* (0.46*)	+30 (+28)
Hospitalization days ( $H_2$ )	0.34*	0.30* (0.34*)	0.41* (0.45*)	+37 (+32)
Triceps skinfold	-0.40*	-0.30* (-0.48*)	-0.29* (-0.47*)	-3 (-2)
Biceps skinfold	-0.44*	-0.35* (-0.47*)	-0.34* (-0.48*)	+3 (+2)
MAC	-0.50*	-0.40* (-0.42*)	-0.46* (-0.49*)	+15 (+16)
MAMC	-0.27†	-0.25† (-0.20)	-0.34* (-0.33*)	+56 (+65)
NIR body fat (%)	-0.35*	-0.27† (-0.58*)	-0.24† (-0.56*)	-11 (-3)
Lean body weight	-0.39*	-0.35* (-0.34*)	-0.40* (-0.43*)	+25 (+26)
BMI	-0.49*	-0.42* (-0.44*)	-0.45* (-0.49*)	+7 (+11)
Serum				
Albumin	-0.31*	-0.27† (-0.27)	-0.50* (-0.51*)	+92 (+88)
Creatinine	-0.14	-0.13 (-0.04)	-0.33* (-0.24†)	+154 (+500)
Cholesterol	-0.03	-0.02 (-0.06)	-0.02 (-0.11)	0 (+83)
TIBC	-0.26†	-0.27† (-0.21)	-0.47* (-0.42*)	+74 (+100)
Transferrin	-0.26	-0.29* (-0.23†)	-0.46* (-0.42*)	+59 (+83)
Ferritin	0.27†	0.34* (0.28†)	0.30* (0.23†)	-12 (-17)
Hematocrit	-0.08	-0.16 (-0.16)	-0.25† (-0.24†)	+56 (+50)
Iron	-0.06	-0.12 (0.05)	-0.23† (-0.12)	+92 (+120)
CRP	0.24†	0.20 (0.19)	0.40* (0.41*)	+100 (+116)
Kt/V	-0.06	-0.04 (-0.08)	-0.04 (-0.08)	0 (0)
Vintage (dialysis mon)	0.28	0.28† (0.33*)	0.19 (0.21)	-32 (-36)
Age	0.31*	0.33*	0.34*	+3
Race	0.01	0.01	0.01	0
Sex	0.16	0.18	0.20	+11
Renal disease	0.00	0.04	0.04	0

NOTE. Adjusted correlation coefficients (for age, race, sex, and underlying renal disease) in parentheses. Last column shows percentage of change in *r* from DMS to MIS. A positive percentage denotes change toward one ( $\pm 1$ ), or increase in correlation, whereas a negative percentage indicates change toward null; or decrease in correlation. Prospective hospitalization data (days and frequency) are annual.

\* $P < 0.01$ .

† $P$  between 0.05 and 0.01.

**Table 3. Raw (bivariate) and Adjusted (multivariate) Correlation Coefficients for Hospitalization Rates to Compare Three Major Nutritional Scoring Systems With Anthropometric and Laboratory Variables**

Correlation Coefficient ( <i>r</i> ) for	Hospitalization Frequency (H <sub>1</sub> )	Hospitalization Days (H <sub>2</sub> )
MIS	0.39* (0.46*)	0.41* (0.45*)
DMS	0.30* (0.36*)	0.30* (0.34*)
SGA	0.35* (0.41*)	0.34* (0.38*)
NIR body fat (%)	-0.27† (-0.23†)	-0.17 (-0.14)
BMI	-0.22† (-0.24†)	-0.12 (-0.11)
Serum		
Albumin	-0.53* (-0.54*)	-0.54* (-0.54*)
Creatinine	-0.14 (-0.28†)	-0.25† (-0.34*)
Cholesterol	-0.22† (-0.20)	-0.30* (-0.28†)
Ferritin	0.23† (0.24†)	0.24† (0.24†)
Hematocrit	-0.17 (-0.23†)	-0.17 (-0.20)
Iron	-0.12 (-0.14)	-0.24† (0.26†)
CRP	0.41* (0.39*)	0.28† (0.27†)

NOTE. Case-mix-adjusted correlation coefficients (controlled for age, race, sex, and underlying renal disease) in parentheses.

\**P* < 0.01.

†*P* between 0.05 and 0.01.

cant hazard ratio. Among other variables, serum albumin level also was a strong predictor of mortality (hazard ratio, 7.21; 95% CI, 2.47 to 11.74; *P* = 0.001). Serum CRP, cholesterol, and creatinine levels also showed statistically significant associations with annual mortality. All other clinical, laboratory, and demographic variables did not show a statistically significant association with mortality based on Cox proportional hazard modeling.

**Table 4. Relative Risk for First Hospitalization According to Cox Proportional Hazard Model for Selected Variables With *P* Less Than 0.05**

Variable	Relative Risk for First Hospitalization (95% CI)	<i>P</i>
MIS (per 10-U increase)	3.83 (1.85-7.94)	<0.001
DMS (per 10-U increase)	3.68 (1.42-9.53)	0.007
SGA (per 1-U increase)	1.80 (1.17-2.78)	0.007
Serum albumin (per 1-g/dL decrease)	4.48 (2.16-9.28)	<0.001
Creatinine (per 1-mg/dL decrease)	1.13 (1.00-1.29)	0.052
CRP (per 10-ng/mL increase)	1.12 (1.05-1.194)	<0.001

NOTE. Magnitude of increments and direction of change in parentheses. Note that serum creatinine level also is mentioned here for comparison despite a *P* of 0.052.

**Table 5. Relative Risk for Death According to Cox Proportional Hazard Model for Selected Variables With *P* Less Than 0.05**

Variable	Relative Risk for Death (95% CI)	<i>P</i>
MIS (per 10-U increase)	10.43 (2.28-47.64)	0.002
DMS (per 10-U increase)	7.74 (0.94-64.02)	0.06
SGA (per 1-U increase)	3.90 (1.29-11.74)	0.02
Serum albumin (per 1-g/dL decrease)	7.21 (2.47-20.99)	0.001
Creatinine (per 1-mg/dL decrease)	1.33 (1.06-1.65)	0.01
Cholesterol (per 10-mg/dL decrease)	1.51 (1.10-2.09)	0.01
CRP (per 10-ng/mL increase)	1.13 (1.05-1.22)	0.001

NOTE. Magnitude of increments and direction of change in parentheses. Note that the DMS is mentioned here for comparison despite *P* of 0.06.

Table 6 lists case-mix-adjusted hazard ratios of both first hospitalization and death for all 10 components of the MIS, as well as the MIS itself. Each MIS component was entered in the Cox model as an incremental variable, consisting of a number between 0 and 3 (discussed previously). Six MIS components showed statistically significant hazard ratios for first hospitalization (H<sub>3</sub>), and 5 MIS components showed statistically significant hazard ratios for death. Subjective scores for subcutaneous fat and muscle wasting showed the strongest association with H<sub>3</sub>, and subcutaneous fat and functional capacity had the strongest association with mortality; however, the MIS was found to be a more powerful predictor of H<sub>3</sub> and mortality than any of its 10 components (Table 6).

Table 7 lists the stepwise development of the MIS model based on the addition of three components, albumin level, TIBC, and BMI, to the seven original components of the DMS. The first column shows the case-mix-adjusted (multivariate) correlation coefficients *R*<sup>2</sup> for hazard ratios for death (also known as pseudo-*R*<sup>2</sup> based on a Cox proportional hazard model). Subsequent columns are multivariate *R*<sup>2</sup>s for hospitalization indices (H<sub>1</sub> through H<sub>3</sub>), serum CRP level, hemoglobin level, MAMC, and NIR body fat percentage based on multivariate linear regression models, except for first hospitalization (H<sub>3</sub>), which, similar to hazard ratio for death, is based on a Cox model. The first seven rows show various combinations to model a scoring system based



**Table 6. Relative Risks (hazard ratios) for First Hospitalization and Death for the MIS and Its 10 Components for a One-Unit Increase Within Three Increments**

MIS Components	First Hospitalization		Death	
	Hazard Ratio (95% CI)	<i>P</i>	Hazard Ratio (95% CI)	<i>P</i>
1. Weight change	1.78 (1.14-2.79)	0.012	0.63 (0.16-2.40)	0.49
2. Dietary intake	1.05 (0.69-1.59)	0.82	1.88 (0.77-4.56)	0.17
3. GI symptoms	1.28 (0.92-1.762)	0.14	1.93 (0.96-3.89)	0.06
4. Functional capacity	1.52 (1.01-2.29)	0.049	2.97 (1.29-6.86)	0.01
5. Vintage and morbidity	1.01 (0.66-1.54)	0.96	2.14 (1.02-4.48)	0.05
6. Subcutaneous fat	1.77 (1.22-2.56)	0.003	3.45 (1.62-7.34)	0.005
7. Muscle wasting	1.86 (1.22-2.84)	0.004	2.67 (0.73-9.77)	0.14
8. BMI	1.52 (1.02-2.25)	0.04	0.71 (0.28-1.82)	0.48
9. Albumin	1.95 (1.33-2.88)	0.01	2.29 (1.06-4.94)	0.03
10. TIBC	1.60 (0.92-2.78)	0.09	2.39 (1.01-5.70)	0.05
MIS	3.83 (1.85-7.94)	<0.001	10.43 (2.28-47.64)	0.002

NOTE. Each component consists of a number between 0 and 3 (see text). Note that the MIS, a number between 0 and 30, also is divided into three equal increments (0 to 10, 11 to 20, and 21 to 30); thus, the hazard ratio of the MIS can be compared with those of its three-incremental components.

on the addition of one or more of the three previously mentioned elements (albumin, TIBC, BMI) to the first seven components (DMS\*). The eighth row is the full version of the MIS, composed of the DMS (shown as \*) and the three additional components. The ninth row represents a scoring model based on replacing albumin level by CRP level. The MIS had the strongest hazard ratio for H<sub>3</sub> and death, which clearly justifies the addition of all three new components together to achieve the best marker of mortality. Although the model without TIBC (model 6) had slightly stronger correlations with hospitalization rates (H<sub>1</sub> and H<sub>2</sub>) and body fat percentages,

the MIS was still superior, not only in terms of hazard ratio for H<sub>3</sub> and death, but also with regard to stronger correlations with CRP level, hemoglobin level, and MAMC. The MIS was not the strongest model in terms of correlation with the NIR-measured body fat percentage, but almost the most predictive model with regard to its correlation with MAMC.

In Table 7, the ninth model, created by replacing albumin level with CRP level, had somewhat stronger correlations with MAMC, NIR body fat, and, of course, CRP level itself, but its correlations with death hazard ratio, all three hospitalization indices, and hemoglobin level were less

**Table 7. Adjusted Multivariate Correlation Coefficients**

	Hazard Ratio of Death	Hospitalization Frequency (H <sub>1</sub> )	Hospitalization Days (H <sub>2</sub> )	Hazard Ratio of First Hospitalization (H <sub>3</sub> )		CRP	Hemoglobin	MAMC	NIR Body Fat (%)
				Hospitalization (H <sub>3</sub> )	Hospitalization (H <sub>3</sub> )				
1) *	0.0747 (0.031)	0.1337 (0.001)	0.1486 (<0.001)	0.0366 (0.006)	0.0509 (0.045)	0.0332 (0.108)	0.0429 (0.067)	0.2752 (<0.001)	
2) * + ALB	0.1130 (0.005)	0.2111 (<0.001)	0.2305 (<0.001)	0.0466 (0.001)	0.0995 (0.005)	0.0680 (0.020)	0.0489 (0.050)	0.2186 (<0.001)	
3) * + TIBC	0.0807 (0.022)	0.1284 (0.001)	0.1533 (<0.001)	0.0383 (0.004)	0.0759 (0.014)	0.0377 (0.087)	0.0493 (0.049)	0.2636 (<0.001)	
4) * + BMI	0.0877 (0.016)	0.1537 (<0.001)	0.1340 (0.001)	0.0384 (0.003)	0.1011 (0.004)	0.0391 (0.081)	0.0691 (0.019)	0.3213 (<0.001)	
5) * + ALB + TIBC	0.1149 (0.004)	0.1972 (<0.001)	0.2275 (<0.001)	0.0474 (0.001)	0.1251 (0.001)	0.0703 (0.018)	0.0542 (0.039)	0.2111 (<0.001)	
6) * + ALB + BMI	0.1267 (0.003)	0.2271 (<0.001)	0.2066 (<0.001)	0.0479 (<0.001)	0.1550 (<0.001)	0.0724 (0.017)	0.0738 (0.015)	0.2615 (<0.001)	
7) * + TIBC + BMI	0.0932 (0.012)	0.1467 (<0.001)	0.1388 (0.001)	0.0399 (0.002)	0.1272 (0.001)	0.0430 (0.067)	0.0740 (0.015)	0.3057 (<0.001)	
8) * + ALB + TIBC + BMI (=MIS)	0.1280 (0.002)	0.2123 (<0.001)	0.2053 (<0.001)	0.0487 (<0.001)	0.1792 (<0.001)	0.0741 (0.015)	0.0777 (0.013)	0.2505 (<0.001)	
9) * + TIBC + BMI + CRP	0.1134 (0.005)	0.1724 (<0.001)	0.1572 (<0.001)	0.0448 (0.001)	0.2000 (<0.001)	0.0740 (0.015)	0.1032 (0.004)	0.2709 (<0.001)	

NOTE. *R*<sup>2</sup> and *P* for hazard ratios of death, three measures of hospitalization indices (H<sub>1</sub> through H<sub>3</sub>), serum CRP, hemoglobin, MAMC, and NIR body fat percentage to compare the DMS (shown by \*), which consists of the first seven components of the MIS, and its modified versions through the stepwise evolution toward the full version of the MIS by adding three additional components to the DMS (\*), ie, TIBC, albumin, and BMI. The ninth row is based on replacing albumin with CRP in the MIS. The case-mix-adjusted correlation coefficients *R*<sup>2</sup> are controlled for age, race, sex, and underlying renal disease. For each multivariate *R*<sup>2</sup>, *P* is listed in parentheses.

Abbreviation: ALB, albumin.

strong. Therefore, the original MIS with albumin level, not CRP level, appears to be a more useful scoring system. Other models also were constructed and evaluated, eg, one model based on the addition of CRP level to the 10 components of the MIS, thus including 11 components, and although most correlations improved as expected, the gain was minimal (data not shown). Moreover, CRP is not a routine laboratory value in many clinical institutions and dialysis centers. Therefore, in general, the MIS appears to be the best model with overall good correlation with outcome, as well as indices of inflammation, anthropometric values, and anemia.

### DISCUSSION

By combining components of the conventional SGA with BMI and two laboratory values, we developed a quantitative and comprehensive MIS, an easy and practical reproducible measure of assessing malnutrition and inflammation in a more objective way. The MIS is a comprehensive scoring system with significant strong correlations with prospective hospitalization indices, mortality, and surrogates for nutrition, inflammation, and anemia. It appears to reliably assess the nutritional and inflammatory status of MHD patients and may identify individuals at high risk for severe morbid or fatal events.

Malnutrition and inflammation are common occurrences in MHD patients, and the not yet well-defined MICS is associated with poorer clinical conditions and worse outcomes in this group of patients.<sup>2,5,6,21</sup> Nevertheless, there is no uniform method to assess the nutritional and inflammatory status of dialysis patients.<sup>22</sup> Several indices of malnutrition are available, ranging from well-known anthropometric measurements<sup>23</sup> to more elaborate techniques, such as dual-energy X-ray absorptiometry.<sup>24</sup> However, the reliability of these methods in detecting protein-energy malnutrition and their practicability are not convincing.<sup>11,25,26</sup> Moreover, methods to measure inflammatory state among dialysis patients are not well studied,<sup>27</sup> and more elaborate laboratory methods to measure diverse cytokines are costly and still controversial,<sup>18</sup> which confines their use to a few research centers.

Although the SGA is an easy and reliable tool that has been validated prospectively to determine nutritional status and predict the degree of sickness,<sup>28</sup> it is a semiquantitative scale and

consists of only three nutritional levels. This semiquantitative feature restricts the SGA's reliability and precision.<sup>11</sup> Moreover, most components of the SGA do not have clear-cut definitions, and concrete guidelines do not exist. Therefore, the final assessment of each SGA criterion is based solely on the subjective impression of the evaluator.<sup>10</sup>

The first quantitative version of the SGA, the DMS,<sup>11</sup> was a legitimate attempt to circumvent inherent problems of the SGA. The DMS was shown to correlate well with some anthropometric indices and BMI, as well as serum TIBC and albumin level.<sup>11</sup> Although preliminary data supported that the DMS offered more precision than the SGA, we continued our effort to optimize the tool. The goal is a practical and convenient scoring system that can be performed easily by a dietitian, trained nurse, or physician within minutes. However, it should be comprehensive enough to be beyond the boundaries of history and simplified physical examination of the SGA and DMS, that can also reflect internal inflammation and may predict such clinically relevant outcomes as mortality and hospitalization.

The MIS, although based on the SGA, contains three non-SGA components, ie, BMI, albumin level, and TIBC, scored in an incremental fashion (as integer numbers between 0 to 3); thus, the score will be compatible with the other already existing seven components of the SGA or DMS. Cross-sectional correlations between the MIS and both serum albumin ( $-0.51$ ) and transferrin levels ( $-0.42$ ) are stronger than those for the DMS ( $-0.27$  and  $-0.23$ , respectively), in part because these two laboratory values are components of the MIS. We used BMI as a simplified representative of height-standardized weight, which was found to be a predictor of dialysis mortality.<sup>7</sup> Serum albumin level is the strongest laboratory predictor of dialysis mortality, and hypoalbuminemia may reflect inflammation, as well as poor nutritional state.<sup>18</sup> Serum transferrin level, represented by TIBC, a laboratory value obtained monthly to quarterly on MHD patients in almost all dialysis units in the United States, is reported to be a reliable indicator of nutritional state in dialysis patients.<sup>10,29</sup> Despite the concern regarding mathematical coupling or collinearity, each of these three additional components (BMI, albumin level, and transferrin level) comprise only a small portion

of the total MIS, whereas the gain is appreciable and beyond a simple mathematical coupling.

The MIS correlated significantly with prospective hospitalizations and was found to be a predictor of death in MHD patients. Undoubtedly, improved correlations between the MIS and morbidity and mortality occur at least partly because of inclusion of such known markers of outcome as serum albumin level and BMI, which is the reason they were included in the MIS.

Correlation between the MIS and serum CRP level was relatively strong ( $r = 0.41$ ), possibly because serum albumin level, a component of the MIS, is known to correlate strongly with serum CRP level. Nevertheless, the DMS, which is essentially a quantitative version of the SGA, did not have a statistically significant correlation with CRP level ( $r = 0.19$ ), and correlation between the SGA and CRP level also was weak ( $r = 0.24$ ). Therefore, the MIS appears to be a marker of inflammation, as well as malnutrition, and thus an indication of severity of MICS.

Unlike the SGA and DMS, the MIS appears to be a marker of refractory anemia because correlation between the MIS and hematocrit is statistically significant, possibly because inflammation is associated with erythropoietin resistance in MHD patients.<sup>30,31</sup> Gunnell et al<sup>30</sup> reported that erythropoietin resistance occurs in the context of high ferritin and low transferrin levels, the pattern expected in the acute-phase response, not in iron deficiency. Moreover, low TIBC and high ferritin level are risk factors for morbidity and mortality in dialysis patients.<sup>32</sup> These findings further support our inclusion of serum TIBC (transferrin) in the MIS model.

In this study, as expected, serum albumin level also was found to have strong correlations with prospective hospitalization indices and mortality. However, the MIS had not only similar correlations with outcomes, but also correlated more strongly with anthropometric values and laboratory indicators of nutrition, inflammation, and anemia. As with a number of other laboratory and clinical measurements used to characterize a clinical state, different measurements may describe different aspects of a given disease and may not correlate well with each other. Therefore, the lack of a strong correlation between serum albumin level and anthropometric values is not unusual. It also should be stressed that serum albumin level is a component of the MIS;

therefore, mathematical coupling should contribute to the association between albumin level and the MIS. Nevertheless, 90% of the MIS is based on other (non-albumin related) variables. The average correlation between the MIS and all relevant clinical indices together was greater than that of albumin level, CRP level, and any other variable. Therefore, the MIS appears to be a more inclusive marker and a reflection of all aspects of nutrition and inflammation in dialysis patients and, at the same time, a strong predictor of morbidity and mortality in MHD patients.

Results of this preliminary study must be qualified in that sample size and duration of follow-up were rather small. Moreover, the two patients who did not participate in the study because of severe illness died shortly after the study began. Because their MIS score would have been very high, probably even stronger results would have been obtained for hospitalization and mortality if they had been included. Moreover, the effect of vintage (dialysis years) may be more complicated than the simple incremental contribution we used in MIS. Also, the BMI incremental scoring system ( $BMI > 20$  kg/m<sup>2</sup> is considered normal) may have been too restrictive and skewed because mean BMI was  $24.7 \pm 6.4$  kg/m<sup>2</sup>. Therefore, more than 60% of patients are scored as normal. Nevertheless, all these points are indicative of bias toward null, implying that with improvement of these criteria, even better correlations can be expected.

It should be recognized that most correlations were not particularly robust in the scoring systems evaluated in this study. Undoubtedly, construction of a metric to measure an underlying complex physiological state, such as malnutrition-inflammation complex, and the method for scale development are technically too sophisticated and at first may not appear to warrant the ad hoc approach presented here. However, it must be reiterated that the goal of this study is not to create a new score, but to further refine and validate what already existed, ie, the SGA. The task of developing a clinically relevant scale for malnutrition is a needed endeavor, and the SGA is a good place to start. The SGA has predictive and content validity, and it is increasingly accepted as a benchmark measure of nutritional risk.<sup>33</sup> Thus, the MIS is essentially an SGA-based system, with 70% of its components originating from the very conventional SGA and 30%

based on three additional components (albumin level, transferrin level, and BMI), which are frequently validated and generally accepted as markers of nutritional state in dialysis patients.

The purpose of assessing malnutrition and inflammation, the two major indicators of poor outcome in dialysis patients, is to identify patients at risk for complications and poor outcome. Such a risk-stratification strategy, conveniently based on a two-digit scoring system, would allow implementation of preventative interventions, such as additional nutritional counseling, dietary supplements, or psychosocial interventions.<sup>34</sup> This invented MIS incorporates advantages of the SGA and DMS while extending reliability, precision, and strength by adding three new components, which all have bearing on dialysis outcome. Time commitment and level of staff training are not increased.

Dialysis Outcome Quality Initiative guidelines recommend regular and uniform assessments of nutrition for all dialysis patients.<sup>33,35</sup> It is likely that increased attention to a global measure of nutritional and inflammatory status will improve patient outcome. This hypothesis could be tested by means of observational cohorts and/or randomized controlled trials in dialysis patients. Before such an intervention could be tested, a standardized, uniform, generally accepted method of assessing nutrition and inflammation must be adopted, a tool that is practical enough to be used ubiquitously, yet comprehensive enough to be a strong predictor of outcome. The MIS may be a means to that end. The current study suggests that the MIS may be superior to the conventional SGA and DMS. Nevertheless, more comparative and longitudinal studies are needed to assess the reliability of the scoring systems in detecting the presence or severity of MICS and their predictive value for morbidity and mortality in dialysis patients.

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