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Evaluation of the Malnutrition-Inflammation Score in Kidney Transplant Recipients

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Background: Chronic protein-energy wasting, termed malnutrition-inflammation complex syndrome, is frequent in patients with chronic kidney disease and is associated with anemia, morbidity, and mortality in patients on maintenance dialysis therapy. The Malnutrition-Inflammation Score (MIS) recently has been developed and validated in dialysis patients.

Study Design: Observational cross-sectional study.

Setting & Participants: 993 prevalent kidney transplant recipients.

Predictor: MIS computed from change in body weight, dietary intake, gastrointestinal symptoms, functional capacity, comorbid conditions, decreased fat store/Systemic Global Assessment, signs of muscle wasting/Systemic Global Assessment, body mass index, serum albumin level, and serum transferrin level.

Outcomes: Markers of inflammation and malnutrition, including serum C-reactive protein, interleukin 6, tumor necrosis factor α, serum leptin, prealbumin, body mass index, and abdominal circumference. The relationship was modeled by using structural equation models.

Results: Mean age was 51 $\pm$ 13 years, 57% were men, and 21% had diabetes. Median time from transplant was 72 months. MIS significantly correlated with abdominal circumference ($r = -0.144$), serum C-reactive protein level ($r = 0.094$), serum interleukin 6 level ($r = 0.231$), and serum tumor necrosis factor α level ($r = 0.102$; $P < 0.01$ for all). A structural equation model with 2 latent variables (malnutrition and inflammation factor) showed good fit to the observed data.

Limitations: Single-center study, lack of information about vascular access, presence of nonfunctioning kidney transplant, relatively high refusal rate.

Conclusions: Our results confirm that MIS reflects both energy-protein wasting and inflammation in kidney transplant recipients. This simple instrument appears to be a useful tool to assess the presence of protein-energy wasting in this patient population.

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INDEX WORDS: Kidney transplant; protein-energy wasting; Malnutrition-Inflammation Score; validation.

Protein-energy wasting (PEW) and inflammation are closely associated in patients on maintenance dialysis therapy.[1-3] The mechanisms underlying this association have been scrutinized closely lately in an effort to uncover potential reasons behind the high mortality observed in this patient population. Chronic inflammation is common in patients with chronic kidney disease (CKD), in part because of possible genetic predisposition,[4,5] but also because of

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factors related to decreased kidney function and the standard dialysis procedure itself.[6,7] Inflammation is associated closely with uremic cachexia. Baseline serum C-reactive protein (CRP) level independently predicts changes in fat mass over time in patients on maintenance dialysis therapy.[8] In patients with CKD, inflammation can increase circulating concentrations of adipokines. Increased leptin levels induce the release of α-melanocyte–stimulating hormone in the central nervous system,[9,10] which in turn suppresses food intake and increases energy expenditure.[11] On the basis of a consistent association between inflammation and malnutrition, the constellation of the 2 conditions has been termed malnutrition-inflammation complex syndrome (MICS) or PEW.[1]

PEW is associated with adverse outcomes in various populations, including healthy elderly people,[12] patients with chronic obstructive pulmonary disease,[13] and surgical patients.[14] MICS also is an important risk factor in patients with non–dialysis-dependent CKD[15,16] and those on maintenance dialysis therapy.[2,17-19] Potential consequences of MICS in dialyzed patients include atherosclerosis,[20,21] oxidative stress,[22] erythropoietin hyporesponsiveness,[23,24] and increased morbidity and mortality.[3,25] To offset difficulties related to the measurement of inflammation in clinical practice, Kalantar-Zadeh et al[3] have developed a semiquantitative and easy-to-use scoring system, the Malnutrition-Inflammation Score (MIS), for the evaluation of MICS in dialyzed patients. The MIS was associated with measures of nutrition, inflammation, and also anemia and predicted hospitalization and mortality in patients on maintenance dialysis therapy.[3] Several factors can potentially induce PEW in kidney transplant recipients; the presence of the transplant, immune response to the transplant, rejection episodes, impaired kidney function, and immunosuppressive drugs all might contribute to the pathomechanism of PEW. Various markers of inflammation have been associated with lower hemoglobin levels,[26] erythropoietin resistance,[27] lumbar bone mass,[28] and new-onset diabetes[29] after kidney transplant. Despite the potentially important association between inflammation and multiple important outcomes,[30] detailed analysis and clinical application of this knowledge has been hampered by the lack of a clinically applicable, practical, and feasible method to assess the presence of MICS in kidney transplant patients.

The MIS would be an excellent tool to assess PEW; however, it has never been assessed in kidney transplant recipients. Before its widespread application in this special patient population, it has to be shown that it is correlated with serum markers of inflammation and nutritional status. To this end, we analyzed the association of MIS with nutritional and inflammatory markers, such as abdominal circumference and concentrations of serum prealbumin and leptin, serum CRP, interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α). Furthermore, we wanted to show that the MIS reflects both inflammation and wasting; in other words, that the MIS measures MICS. To test this hypothesis, we built structural equation models to analyze the complex network of associations between the different malnutrition markers and inflammatory cytokines and the MIS itself.

METHODS

Patient Population and Data Collection

All prevalent kidney transplant recipients 18 years or older (n = 1,214) who were followed up at a single transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University, Budapest, Hungary, on December 31, 2006, were invited to participate in this observational study. Exclusion criteria were acute rejection within the last 4 weeks, present hospitalization, transplant in the previous 3 months, acute infection, or bleeding. The baseline assessment was conducted between February 2007 and August 2007 (Malnutrition-Inflammation in Transplant-Hungary [MINIT-HU] Study).

Demographic data and details of medical history were collected at enrollment, when information about age, sex, menopause status, cause of CKD, and transplant-related data, including immunosuppressant medication use, weight, height, abdominal circumference, and comorbid conditions, including the modified Charlson Comorbidity Index (CCI),[31] were obtained. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[32]

The study was approved by the Ethics Committee of Semmelweis University. Before enrollment, patients received detailed written and verbal information regarding the aims and protocol of the study and gave written consent to participate.

Malnutrition-Inflammation Score

The MIS[3] has 10 components, each with 4 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 status. In contrast to the original MIS, we did not include dialysis vintage in the score in this analysis; only comorbidity was computed. Thus, comorbid conditions were scored as 0 if no medical illnesses were present except CKD; as 1 for mild comorbidity, excluding such major comorbid conditions as congestive heart failure class III or IV, severe coronary artery diseases, clinically evident AIDS, moderate to severe chronic obstructive pulmonary disease, and metastatic malignancies; as 2 for moderate comorbidity (including 1 of the diseases listed under major comorbid conditions); and as 3 for 2 or more major comorbid conditions. All Subjective Global Assessments were performed by a physician (M.E.C.) according to conventional Subjective Global Assessment guidelines.[33,34]

Laboratory Data

Laboratory data were extracted from charts and the electronic laboratory database of the hospital. The following laboratory parameters were tabulated: hemoglobin, serum CRP, total cholesterol, triglycerides, ferritin, transferrin, albumin, prealbumin, creatinine, and serum urea nitrogen.

Serum samples also were collected at the time of the baseline assessment and stored at −70°C for future use. From these samples, high-sensitivity IL-6, TNF-α, and leptin were measured using immunoassay kits based on solid-phase sandwich enzyme-linked immunosorbent assay (R&D Systems, www.rndsystems.com).

Comorbid Conditions

We used the modified Charlson Comorbidity Index,[31,35] which is a weighted scoring system based on the presence or absence of each of 17 variables. Earlier, it has been reported that the Charlson Comorbidity Index was a predictor of survival in kidney transplant patients.[31] Because one of the variables is the presence of moderate to severe kidney disease, the minimum score for all patients with end-stage renal disease is 2. Thus, in patients with end-stage renal disease, scores range from 2 to a possible maximum of 33.

Transplant-Related Data and Donor Characteristics

Transplant-related data extracted from the medical records included the following information: present medications (including present immunosuppressive treatment), transplant "vintage" (ie, time elapsed from the time of transplant), previous time on dialysis therapy, type of transplant (deceased or living related), history of acute rejection, HLA mismatch, panel reactive antibody titer, cold ischemic time, donor age and sex, and history of delayed transplant function. Delayed transplant function was defined as the need for 1 or more hemodialysis sessions in the first week after transplant.[36]

Immunosuppressive Therapy

Standard maintenance immunosuppressive therapy generally consisted of prednisolone, either cyclosporine A microemulsion formulation or tacrolimus, combined with mycophenolate mofetil or azathioprine or sirolimus.

Statistical Analysis

Data were summarized using proportions, mean ± standard deviation, or median and interquartile range, as appropriate. Continuous variables were compared using *t* test or Mann-Whitney *U* test, as appropriate.

Associations between the MIS versus continuous sociodemographic and clinical variables and also between MIS versus serum markers of inflammation and nutritional status were assessed using Pearson or Spearman correlation analysis. Furthermore, analysis of variance or Kruskal-Wallis H test was used to compare continuous variables in quartiles of MIS. In all statistics, 2-sided tests were used.

Structural equation modeling with the asymptotically distribution free method was used to test goodness of fit of 1- and 2-factor models describing the relationship of abdominal circumference and levels of leptin, prealbumin, CRP, IL-6, and TNF-α with MIS. For this analysis, we transformed TNF-α and leptin values by multiplying by 5 and dividing by 5, respectively, to make variances comparable to the variances of other variables. We initially hypothesized that a 2-factor model would best describe this relationship. Model χ^2, also called discrepancy, is presented, which is the most commonly used fit test indicating that the theoretical model fits the given data. A range of goodness-of-fit statistics also was computed for model comparison. The goodness-of-fit index, adjusted goodness-of-fit index, and Bentler comparative fit index increase to a maximum of 1.00 when there is perfect fit. Values around 0.95 indicate a good fit. Root mean square error of approximation is a measure that penalizes for lack of parsimony in the model, which is useful because more complex models produce better fit than simpler ones. Schumacker and Lomax[37] suggest that a root mean square error of approximation ≤0.05 indicates good model fit. Subsequently, we also built a more parsimonious model including only abdominal circumference, CRP level, and IL-6 level. Statistical analysis was carried out using SPSS 15.0 (SPSS Inc, www.spss.com) and Amos 16.0 software (SPSS Inc).

RESULTS

Demographics and Baseline Characteristics of the Sample

Of 1,214 eligible patients, 205 (17%) refused to participate in the study and 16 (1%) were excluded based on exclusion criteria. The study population therefore included 993 patients. There were fewer men in those who refused to participate (57% vs 67%; $P < 0.01$), but there was no significant difference in age between the 2 groups (51 ± 13 vs 52 ± 13 years).

Baseline patient characteristics are listed in Table 1. The most prevalent underlying kidney disease was chronic glomerulonephritis (23%). Prevalences of other kidney diseases were diabetic nephropathy, 5%; autosomal dominant polycystic kidney disease, 18%; chronic pyelonephritis and tubular

Table 1. Patient Characteristics

	All Patients (n = 993)	MIS Quartiles				*P*
		MIS Median = 1	MIS Median = 2	MIS Median = 4	MIS Median = 7	
Age (y)	51 ± 13	48 ± 13	51 ± 12	53 ± 12	54 ± 12	<0.001
Men (%)	57	66	55	53	47	<0.001
Time since last transplant (mo)	72 (75)	57 (76)	78 (78)	74 (68)	94 (78)	<0.001
Dialysis vintage (mo)	20 (29)	20 (29)	18 (31)	23 (32)	19 (29)	0.3
Estimated GFR (mL/min/1.73 m^2)	51 ± 21	56 ± 18	53 ± 20	48 ± 21	42 ± 23	<0.001
Presence of diabetes (%)	21	14	22	27	26	<0.001
Hemoglobin (g/dL)	13.5 ± 1.7	13.9 ± 1.5	13.8 ± 1.7	13.3 ± 1.5	12.5 ± 1.8	<0.001
Cholesterol (mg/dL)	212 ± 49	211 ± 45	215 ± 48	214 ± 50	213 ± 59	0.8
Triglycerides (mg/dL)	150 (114)	151 (110)	154 (128)	142 (124)	144 (107)	0.9
Transferrin (g/L)	2.36 ± 0.46	2.47 ± 0.4	2.43 ± 0.51	2.3 ± 0.43	2.11 ± 0.47	<0.001
Ferritin (μg/L)	161 (303)	153 (229)	140 (281)	167 (342)	227 (554)	<0.001
Panel reactive antibody titer (%)	0 [0-85]	0 [0-85]	0 [0-85]	0 [0-85]	0 [0-85]	0.5
Cold ischemic time (min)	1,248 ± 349	1,216 ± 372	1,239 ± 332	1,277 ± 363	1,286 ± 293	0.07
History of delayed transplant function (%)	26	26	24	25	30	0.3
History of acute rejection (%)	34	31	30	37	42	0.005
HLA mismatches (%)						0.08
0	1	1	1	1	0	
1	5	6	6	4	3	
2	22	24	18	21	22	
3	46	44	48	46	47	
4	21	21	23	21	22	
5	4	3	3	6	5	
6	1	1	1	1	1	

Note: Unless otherwise indicated, values are shown as mean ± standard deviation, percentage, median (interquartile range), or median [range]. Conversion factors for units: serum cholesterol in mg/dL to mmol/L, ×0.02586; serum triglycerides in mg/dL to mmol/L, ×0.01129; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; hemoglobin in g/dL to g/L, ×10; transferrin in g/L to mg/dL, ×100. No conversion necessary for ferritin in μg/L and ng/mL.

Abbreviations: GFR, glomerular filtration rate; MIS, Malnutrition-Inflammation Score.

interstitial disease, 13%; and hypertensive nephropathy, 6%. Other or unknown underlying kidney disease accounted for 35%. At the time of enrollment, 81% of patients were using prednisolone, 50% were using cyclosporine A, 40% were using tacrolimus, 78% were using mycophenolate mofetil, and 4% were using sirolimus. Average cold ischemic time was 21 hours, delayed transplant function was present in 26%, and a history of acute rejection (cumulative) was present in 34% of patients. Only 4% of donors were living related. Mean age of donors was 43 ± 14 years.

Baseline Nutritional and Inflammation Characteristics

Baseline values of nutritional and inflammation markers are listed in Table 2. The distribution of MIS is shown in Fig 1.

IL-6 level, but not TNF-α level, positively correlated with age ($\rho = 0.247$; $P < 0.001$). Serum CRP level also showed a weak positive correlation with age ($\rho = 0.146$; $P < 0.001$). Abdominal circumference showed a moderate positive correlation ($R = 0.299$; $P < 0.001$), serum leptin level showed a

Table 2. Association Between Quartiles of MIS and Inflammation and Nutritional Parameters

	All Patients (n = 993)	MIS Quartile				P
		MIS Median = 1	MIS Median = 2	MIS Median = 4	MIS Median = 7	
Weight (kg)	75 ± 16	79 ± 15	78 ± 15	75 ± 15	67 ± 15	<0.001
Abdominal circumference (cm)	99 ± 14	100 ± 13	101 ± 15	98 ± 15	94 ± 15	<0.001
BMI (kg/m^2)	27 ± 4.9	28 ± 4.6	28 ± 4.7	27 ± 4.9	25 ± 4.9	<0.001
CRP (mg/L)	3.1 (5.4)	2.9 (4.0)	3.0 (5.6)	3.3 (6.0)	3.6 (6.8)	0.1
Albumin (g/dL)	4 ± 0.4	4.2 ± 0.3	4 ± 0.4	3.9 ± 0.4	3.7 ± 0.4	<0.001
Prealbumin (mg/dL)	34.6 ± 7.6	35.9 ± 7.3	34.4 ± 7.3	33.8 ± 7.6	33.1 ± 8.3	<0.001
IL-6 (ng/L)	2.09 (2.37)	1.79 (1.83)	2.18 (1.97)	2.35 (3.00)	2.64 (3.36)	<0.001
Leptin (μg/L)	15.1 (25.3)	14.9 (22.7)	19.6 (31.2)	17.7 (29.9)	9.8 (20.7)	<0.001
TNF-α (ng/L)	2.06 (1.34)	1.99 (1.17)	2.07 (1.40)	2.02 (1.30)	2.27 (1.64)	0.01

Note: Values are shown as mean ± standard deviation or median (interquartile range). Conversion factor for serum albumin in g/dL to g/L, ×10.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin 6; MIS, Malnutrition-Inflammation Score; TNF-α, tumor necrosis factor α.

weak positive correlation ($\rho = 0.092$; $P = 0.004$), and serum prealbumin level showed a weak negative correlation with age ($R = -0.068$; $P = 0.03$).

IL-6, TNF-α, and CRP levels negatively correlated with eGFR (IL-6: $\rho = -0.156$; TNF-α: $\rho = -0.220$; $P < 0.001$ for both; and CRP: $\rho = -0.089$; $P = 0.005$). Similarly, serum prealbumin ($R = -0.263$; $P < 0.001$) and leptin ($\rho = -0.159$; $P < 0.001$) levels negatively correlated with eGFR.

Association Between MIS and Baseline Clinical Markers

Associations between MIS and several relevant clinical variables are listed in Table 1. MIS was associated positively with age, transplant vintage, presence of diabetes, serum ferritin level, and history of acute rejection (Table 1). Negative associations were found between MIS versus eGFR, hemoglobin level, and transferrin level (Table 1).

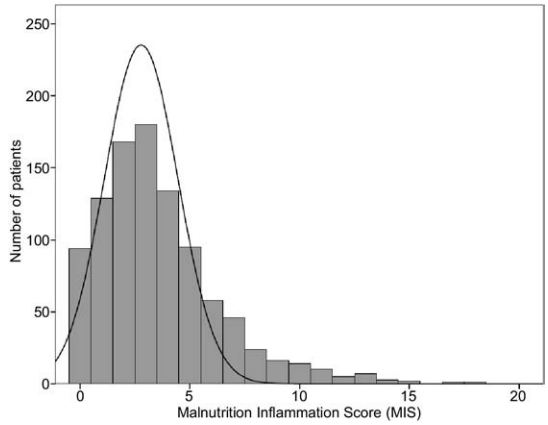

Figure 1. Distribution of Malnutrition-Inflammation Score.

Association Between MIS and Inflammation and Nutritional Markers

Associations between MIS and several relevant inflammation and nutritional markers are listed in Table 2. MIS showed significant negative correlations with abdominal circumference ($\rho = -0.144$; $P < 0.001$) and prealbumin level ($\rho = -0.165$; $P < 0.001$), whereas significant positive correlation was seen with IL-6 ($\rho = 0.231$; $P < 0.001$), TNF-α ($\rho = 0.102$; $P < 0.001$), and CRP levels ($\rho = 0.094$; $P = 0.003$).

Analysis of Individual Items of the MIS Scale

Table 3 lists descriptive statistics of individual items included in the scale and their contribution to the score. The "corrected item-total correlation" was highest for items related to dietary intake and also for elements of Subjective Global Assessment (decreased fat store and signs of muscle wasting).

Structural Equation Models for MIS

Structural equation models were fitted to our data in separate analyses postulating 1 or 2 (inflammation and malnutrition) latent variables. In the first model (Fig S1; available as online supplementary material associated with this ar-

Table 3. MIS Items by Quartiles and Items' Contribution to Scale

MIS Question	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	MIS Severity Level	MIS Quartile: MIS Median = 1	MIS Median = 2	MIS Median = 4	MIS Median = 7	*P*
1: Change in body weight	3.0294	5.645	0.248	0	95	80	64	35	<0.001
				1	2	6	6	7	
				2	3	12	25	29	
				3	0	2	5	29	
2: Dietary intake	3.5096	7.193	0.343	0	99	98	95	76	<0.001
				1	1	2	5	22	
				2	0	0	0	1	
				3	0	0	0	1	
3: GI symptoms	3.1824	6.774	0.195	0	84	64	59	40	<0.001
				1	15	35	34	43	
				2	1	1	7	14	
				3	0	0	0	3	
4: Functional capacity	3.2371	6.688	0.28	0	89	70	56	43	<0.001
				1	11	29	42	45	
				2	0	1	2	10	
				3	0	0	0	2	
5: Comorbid conditions	2.7609	6.551	0.184	0	59	27	23	14	<0.001
				1	36	60	54	50	
				2	5	13	20	33	
				3	0	0	3	3	
6: Decreased fat store/SGA	3.2644	6.219	0.444	0	93	81	63	37	<0.001
				1	7	19	36	43	
				2	0	0	1	17	
				3	0	0	0	3	
7: Signs of muscle wasting/SGA	3.3414	6.316	0.439	0	97	86	76	46	<0.001
				1	3	14	22	36	
				2	0	0	2	15	
				3	0	0	0	3	
8: BMI	3.5056	7.226	0.238	0	99	98	95	81	<0.001
				1	1	2	4	11	
				2	0	0	1	6	
				3	0	0	0	2	
9: Albumin	3.0395	6.401	0.241	0	81	54	46	24	<0.001
				1	18	40	43	49	
				2	1	5	9	22	
				3	0	3	2	5	
10: Transferrin	3.3181	6.832	0.199	0	92	82	75	58	<0.001
				1	7	15	17	26	
				2	1	2	8	12	
				3	0	1	0	4	

Abbreviations: BMI, body mass index; GI, gastrointestinal; MIS, Malnutrition-Inflammation Score; SGA, Subjective Global Assessment.

ticle at www.ajkd.org), we included all relevant variables (leptin level, abdominal circumference, prealbumin level, CRP level, IL-6 level, and TNF-α level). Goodness-of-fit statistics showed the best fit for the model with 2 latent variables ($\chi^2 = 6.072$; $P = 0.8$; root mean square error of approximation < 0.001 (90% confidence interval, 0-0.022); goodness-of-fit index = 0.997; adjusted goodness-of-fit index = 0.991; and comparative fit index = 1.000). Fig S1 shows pathways, standardized coefficients, and correlations for the 2–latent variable model. The covariance between the latent variable malnutrition and MIS was significantly different from zero (-2.02; $P < 0.001$) and correlation was -0.38. Similarly, covariance and correlation between the latent variable inflammation and MIS were 1.49 and 0.32 ($P < 0.001$), respectively. Subsequently, we

also built a more parsimonious model including only abdominal circumference, CRP level, and IL-6 level that also yielded a good fit (χ^2 = 0.595; $P = 0.4$; root mean square error of approximation < 0.001; goodness-of-fit index = 0.999; adjusted goodness-of-fit index = 0.993; and comparative fit index = 1.000; Fig S2). Covariance between the latent variable malnutrition and MIS was significantly different from zero (-1.03; $P < 0.001$) and correlation was -0.38. Similarly, covariance and correlation between the latent variable inflammation and MIS were 0.95 and 0.33 ($P < 0.001$), respectively.

DISCUSSION

We report data that confirm that MIS is a useful tool to measure nutritional status and inflammation and hence to assess MICS in kidney transplant recipients. The MIS was associated significantly with various nutritional and inflammation markers in these analyses, which supports the applicability of this simple scoring system in measuring MICS in this patient population. Furthermore, results of our structural equation modeling suggest that both inflammation and nutritional status are represented in the MIS. This is important because the pathways potentially leading to the clinical outcomes associated with MICS are complex and likely involve mechanisms related to both inflammation and PEW.[38]

Both PEW and chronic inflammation are highly prevalent in patients undergoing maintenance dialysis.[3] Because these 2 conditions often occur together, their combination has been referred to as malnutrition-inflammation complex syndrome (MICS) or malnutrition-inflammation atherosclerosis syndrome. MICS also was associated with oxidative stress,[39] erythropoietin resistance,[24,40] morbidity, and mortality[3, 41] in patients on maintenance dialysis therapy. Recently, it increasingly has been recognized that CKD and the complications of CKD are highly prevalent in kidney transplant recipients.[26,42] Our earlier results suggested that chronic inflammation may contribute to the high prevalence of posttransplant anemia[26] and also might contribute to negative clinical outcomes in this patient population.[43] A simple easy-to-use instrument to assess MICS in kidney transplant recipients would be invaluable for both outcomes research and everyday clinical practice.

The MIS has been developed by Kalantar-Zadeh et al[3] to measure MICS and has been validated in patients on maintenance dialysis therapy. This score showed associations with morbidity and mortality[3,41] in patients on maintenance dialysis therapy. In a recent publication, the MIS was used as the reference standard to validate 5 simplified nutritional screening tools in 422 Japanese hemodialysis patients.[44] To our knowledge, the MIS has not been assessed or used in kidney transplant patients.

To support the applicability of the MIS to measure MICS in kidney transplant patients, we correlated the score against accepted measures of nutritional status and inflammation. We measured biochemical parameters (leptin, IL-6, TNF-α, prealbumin, CRP, and transferrin) and anthropometric variables (body mass index and abdominal circumference) to assess both nutritional and inflammatory components of the MICS. Previous studies have shown that leptin,[45] IL-6,[41] TNF-α,[41] and the other measured variables reliably measure PEW. MIS correlated significantly with all measures of both inflammation and nutritional status in our data set. The strength and direction of associations between the MIS and these markers of MICS were similar in our study to those reported previously for patients on maintenance dialysis therapy,[41] suggesting that the MIS is a valid tool in kidney transplant recipients.

To further test the hypothesis that MIS meaningfully reflects both the inflammation and malnutrition components of MICS, we used structural equation modeling to analyze the complex association network between the different nutritional markers, inflammatory cytokines, and MIS. This method allows simultaneous modeling of multiple layers of independent- and dependent-variable constructs. Two different assumptions were tested in separate analyses. First, we assumed that the MIS represents 1 single latent variable. In the second model, 2 latent variables (malnutrition and inflammation) were postulated. The model assuming 2 latent variables showed better fit to the observed data, suggesting that the MIS reflects both the malnutrition and inflammation factors (Fig S1).

To our knowledge, this was the first study to assess the applicability of the MIS as an instrument to assess MICS in kidney transplant recipients. Our study is notable for enrolling a large number of patients and measuring several cytokines associated with nutritional status and inflammation. Use of structural equation modeling also allowed us to analyze the complex network between these variables and their association with MIS, which increases the biological reliability of our analysis.

However, several limitations should be considered when interpreting our results. Patients from a single center were enrolled; therefore, our results are not to be generalized without further considerations. Patients who were not participating in the study may have been different from participants, which is a potential source of bias. However, we believe it is unlikely that this would have qualitatively changed our results. Only white patients participated in this study, which may make comparisons with multiethnic populations difficult. Finally, we did not have information about various other parameters (such as percentage of body fat, lean body mass, prevalence of functioning vascular access, and presence of a nonfunctioning transplant) that also may be associated with MICS.[46,47]

In summary, we suggest that the MIS is a useful tool to assess MICS in kidney transplant recipients. The structural equation modeling analysis confirmed that the MIS reflects malnutrition and inflammation together in this patient population. Use of this scoring system could enhance outcomes research in kidney transplant recipients. MIS is an inexpensive and easy-to-use tool that can obviate the need for expensive cytokine measurements to assess MICS in epidemiologic studies. Additionally, MIS may be a useful tool in everyday clinical practice to increase quality of care. Studies assessing treatment options for MICS also could use this instrument.

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SUPPLEMENTARY MATERIALS

Figure S1: Structural equation model with 2 latent variables.

Figure S2: Parsimonious structural equation model with 2 latent variables.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.02.350) is available at www.ajkd.org.

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