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Original Article

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Comparing outcome predictability of markers of malnutrition–inflammation complex syndrome in haemodialysis patients

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Abstract

Background. Markers of malnutrition–inflammation complex syndrome (MICS) are reported to predict mortality and hospitalization in maintenance haemodialysis (MHD) patients. However, it is not clear which one is a more sensitive and stronger predictor of outcome.

Methods. We examined the utility of 10 markers of MICS as predictors of prospective mortality and hospitalization, which included malnutrition–inflammation score (MIS), a fully quantitative score adopted from subjective global assessment, and serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), albumin, prealbumin, total iron binding capacity, creatinine, total cholesterol and normalized protein nitrogen appearance. A cohort of 378 MHD patients, who were randomly selected from eight DaVita dialysis facilities in the South Bay Los Angeles area, was studied.

Results. Patients, aged 54.5 ± 14.7 years, included 53% men, 47% Hispanics, 30% African-Americans and 55% diabetics, who had undergone MHD for 37 ± 34 months. Over a 12-month follow-up, 39 patients died and 208 were hospitalized at least once. Multivariate Cox and Poisson models that included 11 covariates [gender, age, race, ethnicity, diabetes, dialysis vintage, Charlson co-morbidity index (CCI), insurance status, Kt/V, body mass index and history of cardiovascular disease] were explored for the highest quartiles of inflammatory markers or the lowest quartiles of nutritional markers. The magnitude of relative risk of death and hospitalization was greatest for MIS, CRP and IL-6. In extended multivariate models that included all 10 MICS markers and 11 additional covariates simultaneously, CRP, MIS and CCI were the only consistent predictors of mortality and hospitalization, and their outcome predictabilities were superior to serum albumin.

Conclusions. The MIS appears to be a useful, short-term tool to risk-stratify MHD patients and may circumvent the need for measuring inflammatory markers such as CRP or IL-6.

Keywords: cytokines; haemodialysis; hospitalization; mortality; malnutrition–inflammation complex syndrome; reverse epidemiology

Introduction

Patients undergoing maintenance haemodialysis (MHD) have a high prevalence of protein-energy malnutrition and inflammation. Since these two conditions often occur concomitantly in MHD patients, they have been referred to together as the 'malnutrition–inflammation complex syndrome' (MICS) [1,2] or 'malnutrition–inflammation atherosclerosis' (MIA) syndrome to emphasize its important association with atherosclerotic cardiovascular disease [3]. MICS is reported to correlate with poor outcome, including significantly greater rates of hospitalization and mortality in MHD patients [1,3]. Indeed, MICS may be the major cause of the paradoxical exposure–outcome association, also known as reverse epidemiology, of cardiovascular risk factors in maintenance dialysis patients when they are compared with the general population [4].

Although many measures of MICS such as serum albumin or C-reactive protein (CRP) correlate with clinical outcome, it is not clear which one these blood values has a superior outcome predictability compared with others. Moreover, such blood tests generally do not evaluate clinical condition and outcome in a combined way for an individual patient, and some of these tests such as CRP or pro-inflammatory cytokines are not measured routinely and are too expensive to be

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measured even sporadically. A comprehensive scoring system that is reproducible and based on available data can be useful for this purpose if it is capable of risk-stratifying MHD patients in a quantitative way for optimal management, yet be a practical and easy tool without cumbersome methods or sophisticated calculations.

To compare outcome predictability of markers of MICS, we examined the prospective associations between 10 indicators of MICS at the baseline of an MHD cohort, including eight blood tests, a urea kinetic-based measure and a nutritional–inflammatory scoring system, and several measures of clinical outcome including prospective mortality and hospitalization, in a group of MHD patients. This was performed during the first year of the NIED (Nutritional and Inflammatory Evaluation in Dialysis) Study, a National Institute of Diabetes, Digestive and Kidney Diseases-funded 5-year prospective, observational cohort study targeting up to 900 MHD patients.

Subjects and methods

Patients

Subjects participating in the NIED Study are 360–385 MHD patients at any given time, who originate from a pool of ~1200 MHD out-patients in eight DaVita, Inc. dialysis facilities in the South Bay Los Angeles area (DaVita South Bay Cohort) [5]. The NIED Study website at www.NIEDstudy.org has more details and the list of relevant publications [5–7]. Inclusion criteria were out-patients who had been undergoing MHD for at least 8 weeks, were 18 years or older and who signed a written consent form. Patients with a metastatic malignancy or terminal human immunodeficiency virus (HIV) disease were excluded. In the initial phase of the NIED Study (October 2001–March 2002), 385 patients from eight dialysis units signed the written consent form. Subsequently, blood samples were obtained from 378 of these individuals, because seven patients left the study (died, underwent transplantation or transferred out of the dialysis unit) by the time the study started. The patients were all receiving haemodialysis via high flux dialysers such as polysulfone, and their dialysis membranes were routinely re-used. The medical chart of each MHD patient was thoroughly reviewed by a nephrologist (K.K.-Z.) and data pertaining to underlying kidney disease, cardiovascular history and other co-morbid conditions were extracted. A modified version of the Charlson co-morbidity index, i.e. without the age and kidney disease components, was used to assess the severity of co-morbidity [8].

Malnutrition inflammation score (MIS)

Using the seven components of the conventional Subjective Global Assessment of Nutrition (SGA) [9], a semi-quantitative scale with three severity levels, and combining it with three new elements [body mass index (BMI), serum albumin, and total iron binding capacity (TIBC) to represent serum transferrin] in incremental fashion, the so-called 'malnutrition inflammation score' (MIS) with 10 components has been created (Figure 1) [10]. Each MIS component has four levels of severity from 0 (normal) to 3 (very severe). In a recent prospective study, the MIS was found to be a comprehensive scoring system with significant associations with prospective hospitalization and mortality as well as measures of nutrition, inflammation and anaemia in MHD patients and was superior to conventional SGA and to individual laboratory values as a predictor of dialysis outcome and an indicator of MICS [10].

Anthropometric evaluation

Body weight assessment and anthropometric measurements were performed while patients were undergoing haemodialysis treatment or within 5–20 min after termination of the treatment. Biceps skinfold (BSF) and triceps skinfold (TSF) thicknesses were measured with a conventional skinfold caliper using standard techniques. Mid-arm circumference (MAC) was measured with a plastic tape. Mid-arm muscle circumference (MAMC) was calculated from the formula: $\mathrm{MAMC} = \mathrm{MAC} - (3.1416 \times \mathrm{TSF})$. Height was obtained from the patient's chart.

Near infrared interactance

To evaluate the percentage of body fat and lean body mass, the near infrared (NIR) interactance [11] was performed at the same time as the anthropometric measurements. A commercial NIR interactance sensor (portable Futrex 6100®, Gaithersburg, MD) was used. NIR measurements were performed by placing a Futrex® sensor on the non-access upper arm for several seconds, after entering the required data (date of birth, gender, weight and height) from each patient. NIR measurements of body fat are shown to correlate significantly with SGA and other nutritional measures in MHD patients [11].

Laboratory evaluation

Blood samples were obtained and coincided chronologically with the quarterly blood tests of DaVita facilities. The single-pool Kt/V was used to represent the weekly dialysis dose, and the normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), was calculated to estimate the daily protein intake. All routine laboratory measurements were performed by DaVita Laboratories (Deland, FL) using automated methods, and the average values for each laboratory test within the 13 week study period were calculated and used for data analyses in this study. Serum albumin and transferrin concentrations used in the MIS were also 3 month averaged values.

Serum C-reactive protein (CRP) and cytokines including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) were measured as indices of the degree of inflammation. The high sensitivity CRP was measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with anti-human CRP antibodies forming an insoluble aggregate (WPCI, Osaka, Japan; mg/l, normal range <3.0 mg/l) [12]. High sensitivity IL-6 and TNF-α immunoassay kits based on a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) using recombinant

MALNUTRITION INFLAMMATION SCORE (M.I.S.)			
(A) Patients' related medical history:			
1- Change in end dialysis dry weight (overall change in past 3-6 months):			
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%
2- Dietary intake:			
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
3- Gastrointestinal (GI) symptoms:			
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
4- Functional capacity (nutritionally related functional impairment):			
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
5- Co-morbidity including number of years on Dialysis:			
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) Physical Exam (according to SGA criteria):			
6- Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
7- Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous):			
0	1	2	3
Normal (no change)	mild	moderate	Severe
(C) Body mass index:			
8- Body mass index: BMI = Wt(kg) / Ht^2(m)			
0	1	2	3
BMI≥20 kg/m^2	BMI: 18-19.99 kg/m^2	BMI: 16-17.99 kg/m^2	BMI<16 kg/m^2
(D) Laboratory Parameters:			
9- Serum albumin:			
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
10- Serum TIBC (total Iron Binding Capacity): ♣			
0	1	2	3
TIBC≥ 250 mg/dL	TIBC: 200-249 mg/dL	TIBC: 150-199 mg/dL	TIBC: <150 mg/dL
Total Score = sum of above 10 components (0-30):			

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

♣ Suggested equivalent increments for serum transferrin are: >200 (0), 170-200 (1), 140-170 (2), and <140 mg/dL

Fig. 1. Components of the comprehensive MIS.

human IL-6 and TNF-α were used to measure serum pro-inflammatory cytokines (R&D Systems, Minneapolis, MN; normal range IL-6, < 9.9 pg/ml; TNF-α, < 4.7 pg/ml) [5]. CRP and cytokines were measured in GCRC Core Laboratories of Harbor-UCLA Medical Center. Serum pre-albumin and total cholesterol concentrations were measured via automated methods in the Harbor-UCLA Clinical Laboratory.

Hospitalization

Hospitalization data during the 12 month period following the completion of the above measurements were obtained on all 378 MHD patients. Hospitalization was defined as any hospital admission that included at least one overnight stay in the hospital. The admission day was counted as one full hospitalization day, but the discharge day was not. Therefore, the minimum duration of hospitalization per

admission was 1 day. Since the vast majority of dialysis access-related hospitalizations did not require overnight admission, essentially only those access-elated hospitalizations that were associated with other co-morbid conditions were included such as infection or cardiovascular events. For those patients who were in a hospital at the end of the 1 year cohort, all hospitalization days during this last admission were counted. The annual hospitalization days were the sum of all hospitalization days of a given patient during the 12 month prospective cohort as defined above. The annual hospitalization frequency was the total number of hospital admissions during the same period irrespective of the length of each admission.

Moreover, the number of days at risk from the start of the study until the first hospitalization event for each individual per year was assessed. Accordingly, the risk time for each individual is defined as the days from study entry until the first hospitalization, a censoring event or a study anniversary day occurs. A patient's risk period was truncated 3 days prior to a kidney transplant in order to avoid attributing the transplant-related hospitalization to the observed days to event.

Statistical methods

We used Pearson's correlation coefficient r for analyses of associations between continuous variables. To calculate the relative risks of first hospitalization or death for each of the 10 MICS indicators, we obtained hazard ratios (HRs) of the highest (for inflammatory markers) or lowest (for nutritional markers) quartiles of each of these markers using Cox proportional hazard models after controlling for 11 covariates including age, gender, race (Blacks *vs* others), ethnicity (Hispanics *vs* others), insurance status (Medicaid *vs* others), diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose (single-pool Kt/V), BMI and history of cardiovascular disease. Plots of log [−log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption. Kaplan–Meier analyses were utilized to assess the statistically significant differences in surviving proportions. Multivariate Poisson regression analyses were used in a similar fashion to calculate hospitalization rate ratios after adjusting for the above-mentioned covariates. Fiducial limits are given as mean ± SD. All relative risks include 95% confidence interval (CI) levels. A P-value <0.05 or a 95% CI that did not span 1.0 was considered to be statistically significant. Descriptive and multivariate statistics were carried out with the statistical software 'Stata 7.0' (Stata Corporation, College Station, TX).

Results

Table 1 shows the pertinent demographic, laboratory and clinical data in the 378 MHD patients. Men comprised 53% of the study population, which was heavily dominated by Hispanics (47%). Over half of the patients (55%) had diabetes mellitus and almost the same proportion a history of cardiovascular disease including a myocardial infarction, coronary artery procedures such as angioplasty or surgery, congestive heart failure, or peripheral vascular disease including amputation as documented in their charts and/or obtained by questionnaires. The average annual mortality rate was 10.9% in this cohort, in that over half of the patients (20 out of 39) had a recoded cardiovascular cause of death. Fifty-five percent of the patients were hospitalized at least once during the 12 month follow-up. Patients were on average 54.5 years old and had been on dialysis for 37 months.

Table 1. Demographic, laboratory, anthropometric, co-morbidity and nutritional values (mean ± SD) in 378 MHD patients at the start of the NIED Study cohort

Variable	Mean ± SD
Gender: male (%)	53.2
Race: African Americans (%)	29.6
Ethnicity: Hispanics (%)	47.2
Diabetes mellitus (%)	55.1
Insurance status: Medicaid (%)	19.7
History of cardiovascular disease (%)	50.8
Annual mortality (%)	10.9
Hospitalized at least once (%)	55.1
Hospitalization frequency (per year)	1.8 ± 3.0
Hospitalization days (per year)	10.0 ± 28.4
Age (years)	54.5 ± 14.7
Dialysis vintage (months)	36.7 ± 33.9
Body mass index (kg/m^2)	26.6 ± 6.2
Kt/V (single pool)	1.57 ± 0.28
Charlson co-morbidity index	2.0 ± 1.5
Blood haemoglobin (g/dl)	11.90 ± 0.99
Ferritin (ng/ml)	654 ± 470
Transferrin saturation ratio (%)	33.8 ± 39.4
Iron (μg/dl)	64.7 ± 28.1
Phosphorus (mg/dl)	5.9 ± 1.5
Urea nitrogen (mg/dl)	66.4 ± 16.9
Triceps skinfold (mm)	9.9 ± 7.9
Biceps skinfold (mm)	17.7 ± 9.3
Mid-arm muscle circumference (cm)	28.7 ± 5.1
NIR body fat (%)	26.4 ± 10.8

NIR = near infra-red interactance.

Table 2 includes descriptive statistics for the 10 markers of protein-energy malnutrition and/or inflammation. The MIS was measured in 346 MHD patients (92%), since 32 patients either left the study or refused to undergo evaluation. The mean value of the MIS was 6.3 ± 3.9 (SD), while 25% of all patients had a score >8, corresponding to the highest MIS quartile. Figure 2 shows the distribution of MIS. The median CRP was 4.36 mg/l, which was higher than the normal range for the general population (<3.0 mg/dl). A similar trend was found for IL-6 and TNF-α. Table 3 shows bivariate correlation coefficients (r) among the same markers of MICS. The MIS had weak to moderate but statistically significant correlations with all but serum cholesterol and TNF-α. The three serum inflammatory markers (CRP, IL-6 and TNF-α) had weak correlations among each other and different correlation coefficients with other measures, indicating that these three measures reflected different aspects of inflammatory status. These 10 MICS markers did not have significant or persistent correlations with other measures of nutritional status such as anthropometric values or body fat (data not shown here).

Table 2. Ten markers of MICS that were examined in this study as 'outcome predictors' in 378 MHD patients

Variable	*n*	Mean	SD	25th %	50th % (median)	75th %
MIS (0–30)	346	6.3	3.9	4	5.5	8
nPNA (nPCR) (g/kg/day)[a]	372	1.05	0.22	0.89	1.05	1.20
Serum albumin (g/dl)[a]	378	3.85	0.33	3.63	3.83	4.10
Pre-albumin (mg/dl)	365	28.1	9.5	21	28	34
Creatinine (mg/dl)[a]	377	10.8	3.4	8.6	10.5	12.8
Cholesterol (mg/dl)	368	143.4	47.0	115.5	140.5	172.0
TIBC (μg/dl)[a]	375	199.6	36.9	174	196	224
CRP (mg/l)	374	6.42	7.79	1.82	4.36	8.4
Interleukin-6 (pg/ml)	373	22.60	56.57	4.96	8.65	17.91
TNF-α (pg/ml)	372	8.38	6.44	4.92	7.02	9.255

nPNA = normalized protein nitrogen appearance; nPCR = normalized protein catabolic rate; TIBC = total iron binding capacity.
[a]These measures are based on the 3-month averaged values for each patient.

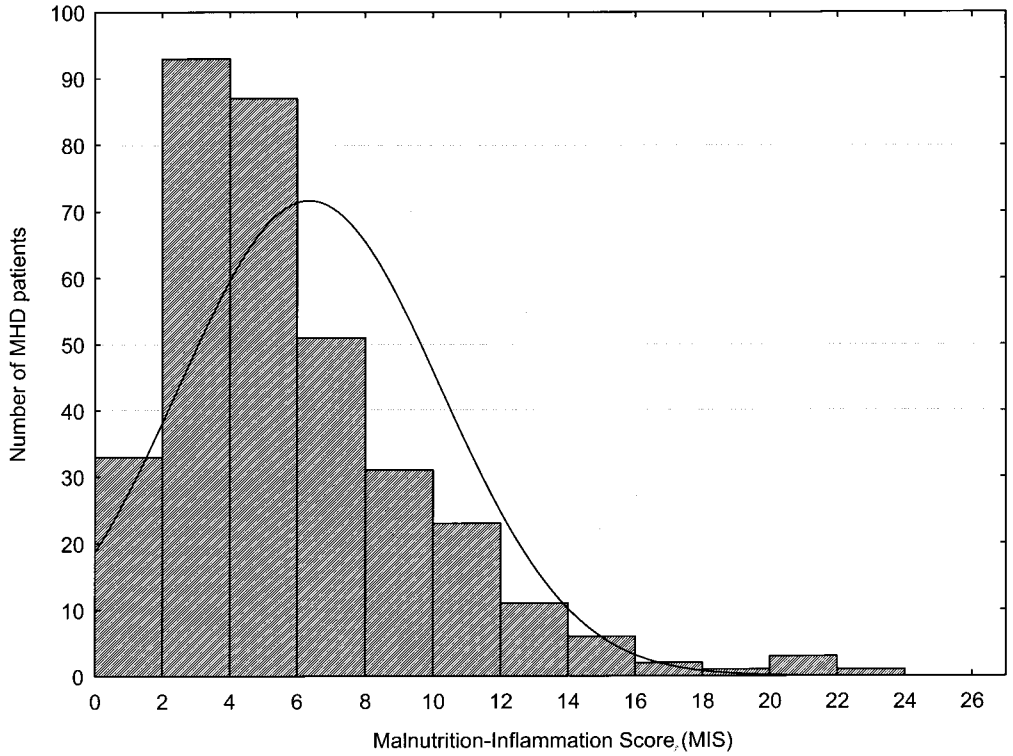

Fig. 2. Distribution of the MIS among 346 MHD patients.

Tables 4–7 show relative risks of mortality and hospitalization for eight selected markers of MICS. Serum creatinine and nPNA are not included in these four tables since their associations with outcome measures were not significant, less persistent and/or weaker than the others. Each marker is divided into four almost equal quartiles. The risk of poor outcome in the fourth quartile was examined in different modalities. While the sorting direction for serum levels of albumin, pre-albumin, cholesterol and TIBC was from highest to lowest value—hence the fourth quartile is the lowest quartile—sorting had an opposite direction for inflammatory markers and MIS, so that the fourth quartile was the lowest quartile. This approach led to commensurate relative risks that were all >1. Kaplan–Meier *P*-values are also listed for survival analyses, i.e. in Tables 4 and 5. In general, the highest quartiles of serum IL-6 and CRP levels and MIS, and the lowest quartile of serum albumin concentrations had the strongest relative risks of death and hospitalization. Table 8 shows the ranking of the relative risks of the fourth quartile (*vs* others) for comparison. IL-6 was the strongest predictor of mortality followed by MIS and CRP, indicating that the highest quartiles of these three measures were associated with a 3- to 4-fold increase in death risk. The MIS was the strongest predictor of first hospital admission. With regard to rate ratio of hospitalization (frequency and days per year), CRP and IL-6 were the strongest predictors, but MIS remained among the next

Table 3. Pair-wise correlation coefficients (r) among 10 markers of MICS in 378 MHD patients

	MIS	Albumin[a]	Pre-albumin	TIBC[a]	Cholesterol	Creatinine[a] (nPCR)[a]	nPNA	CRP	IL-6
Albumin[a]	**−0.48**[b] ($P<0.001$)	1							
Pre-albumin	**−0.26** ($P<0.001$)	**+0.45** ($P<0.001$)	1						
TIBC[a]	**−0.44**[b] ($P<0.001$)	**+0.27** ($P<0.001$)	+0.10 ($P=0.05$)	1					
Cholesterol	−0.01 ($P=0.8$)	+0.02 ($P=0.7$)	**+0.25** ($P<0.001$)	−0.03 ($P=0.6$)	1				
Creatinine[a]	**−0.21** ($P<0.001$)	**+0.33** ($P<0.001$)	**+0.34** ($P<0.001$)	+0.03 ($P=0.5$)	**−0.12** ($P=0.02$)	1			
nPNA (nPCR)[a]	**−0.11** ($P=0.04$)	**+0.24** ($P<0.001$)	+0.15 ($P=0.01$)	+0.09 ($P=0.08$)	+0.02 ($P=0.7$)	**+0.22** ($P<0.001$)	1		
CRP	**+0.13** $P=0.02$)	**−0.12** ($P=0.02$)	**−0.11** ($P=0.03$)	**−0.15** ($P=0.01$)	−0.09 ($P=0.09$)	−0.02 ($P=0.7$)	−0.04 ($P=0.5$)	1	
IL-6	**+0.22** ($P<0.001$)	**−0.17** ($P<0.001$)	**−0.21** ($P<0.001$)	−0.09 ($P=0.08$)	−0.02 ($P=0.6$)	−0.09 ($P=0.1$)	+0.05 ($P=0.3$)	+0.10 ($P=0.06$)	1
TNF-α	+0.06 ($P=0.3$)	−0.02 ($P=0.7$)	**−0.11** ($P=0.04$)	−0.07 ($P=0.2$)	−0.09 ($P=0.1$)	+0.06 ($P=0.2$)	−0.02 ($P=0.8$)	**+0.15** ($P=0.005$)	**+0.16** ($P=0.002$)

Related P-values are shown in parentheses after each r value. With the exception of the MIS, all other values are serum concentrations. Statistically significant r values ($P<0.05$) are in bold.
[a]These measures are based on the 3-month averaged values for each patient.
[b]Strong associations between the MIS and serum albumin and TIBC concentrations are probably due to mathematical collineraity, since these two laboratory values are parts of the MIS.
TIBC = total iron binding capacity; nPNA = normalized protein nitrogen appearance; nPCR = normalized protein catabolic rate.

Table 4. Associations between baseline nutritional and inflammatory markers and the risk of death over the 12-month follow-up period, as reflected by mortality hazard ratios (HRs) and 95% confidence intervals (CIs) in 378 MHD patients

Mortality	Status of the fourth quarter (lowest or highest)	HR across all four quartiles (first to fourth)	HR for the fourth *vs* the first quartile	HR for the fourth quartile *vs* the rest	Kaplan–Meier P for four quartiles
Albumin (g/dl)[a]	Lowest (<3.63 g/dl)	**1.84** (1.27–2.68) $P=0.001$	**9.80** (1.93–49.70) $P=0.006$	**2.24** (1.13–4.44) $P=0.02$	0.0002
Pre-albumin (mg/dl)	Lowest (<21 mg/dl)	1.17 (0.84–1.64) $P=0.4$	2.18 (0.63–7.50) $P=0.2$	1.79 (0.90–3.55) $P=0.09$	0.04
Cholesterol (mg/dl)	Lowest (<115.5 mg/dl)	1.14 (0.84–1.56) $P=0.4$	1.80 (0.65–4.96) $P=0.3$	1.62 (0.78–3.37) $P=0.2$	0.6
TIBC (mg/dl)[a]	Lowest (<174 mg/dl)	1.28 (0.94–1.74) $P=0.12$	1.46 (0.56–3.85) $P=0.4$	1.80 (0.93–3.51) $P=0.08$	0.2
CRP (mg/l)	Highest (>8.4 mg/l)	**1.81** (1.27–2.59) $P=0.001$	**6.31** (1.76–22.60) $P=0.005$	**3.27** (1.67–6.41) $P=0.001$	0.005
IL-6 (pg/ml)	Highest (>17.9 pg/ml)	**2.23** (1.52–3.26) $P<0.001$	**27.44** (3.52–213.74) $P=0.002$	**3.97** (2.02–7.79) $P<0.001$	0.00003
TNF-α (pg/ml)	Highest (>9.26 pg/ml)	1.19 (0.88–1.62) $P=0.3$	1.94 (0.73–5.13) $P=0.2$	1.81 (0.89–3.70) $P=0.10$	0.8
MIS (0–30)	Highest (>8)	**1.64** (1.17–2.31) $P=0.005$	**4.91** (1.81–13.30) $P=0.002$	**3.83** (1.82–8.04) $P<0.001$	0.0002

Multivariate HR values are based on Cox proportional hazard regression models and adjusted for age, gender, race (Blacks *vs* others), ethnicity (Hispanics *vs* others), insurance status (Medicaid *vs* others) diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose (single-pool Kt/V), BMI and history of cardiovascular disease. All models are based on Poisson regression analyses.
[a]Serum albumin and TIBC concentrations are based on 3-month averaged values for each patient.
TIBC = total iron binding capacity.

Table 5. Associations between baseline nutritional and inflammatory markers and the risk of first hospital admission over the 12-month follow-up period, as reflected by first hospitalization hazard ratios (HRs) and 95% confidence intervals (CIs) in 378 MHD patients

First hospital admission	Status of the fourth quarter (lowest or highest)	HR across all four quartiles (first to fourth)	HR for the fourth *vs* the first quartile	HR for the fourth quartile *vs* the rest	Kaplan–Meier *P* for four quartiles
Albumin (g/dl)[a]	Lowest (<3.63 g/dl)	**1.24** (1.08–1.42) $P=0.003$	**2.34** (1.38–3.95) $P=0.002$	1.37 (1.00–1.88) $P=0.05$	0.00003
Pre-albumin (mg/dl)	Lowest (<21 mg/dl)	**1.16** (1.02–1.33) $P=0.03$	1.54 (0.97–2.46) $P=0.07$	1.34 (0.98–1.82) $P=0.07$	0.009
Cholesterol (mg/dl)	Lowest (<115.5 mg/dl)	1.03 (0.91–1.18) $P=0.6$	1.12 (0.73–1.71) $P=0.61$	1.62 (0.78–3.35) $P=0.2$	0.4
TIBC (mg/dl)[a]	Lowest (<174 mg/dl)	1.08 (0.95–1.23) $P=0.2$	1.31 (0.88–1.96) $P=0.2$	**1.44** (1.06–1.96) $P=0.02$	0.3
CRP (mg/l)	Highest (>8.4 mg/l)	**1.33** (1.17–1.53) $P<0.001$	**2.49** (1.57–3.93) $P<0.001$	**1.92** (1.42–2.59) $P<0.001$	0.00003
IL-6 (pg/ml)	Highest (>17.9 pg/ml)	**1.24** (1.09–1.42) $P=0.001$	**1.87** (1.22–2.84) $P=0.004$	**1.62** (1.20–2.19) $P=0.002$	0.0008
TNF-α (pg/ml)	Highest (>9.26 pg/ml)	0.96 (0.84–1.09) $P=0.5$	0.80 (0.53–1.20) $P=0.3$	1.13 (0.82–1.56) $P=0.4$	0.12
MIS (0–30)	Highest (>8)	**1.31** (1.15–1.50) $P<0.001$	**2.41** (1.58–3.69) $P<0.001$	**2.02** (1.44–2.81) $P<0.001$	0.00003

Multivariate HR values are based on Cox proportional hazard regression models and adjusted for age, gender, race (Blacks *vs* others), ethnicity (Hispanics *vs* others), insurance status (Medicaid *vs* others) diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose (single pool Kt/V), BMI and history of cardiovascular disease. All models are based on Poisson regression analyses.
[a]Serum albumin and TIBC concentrations are based on 3-month averaged values for each patient.
TIBC = total iron binding capacity.

strongest hospitalization predictors, with the exception of serum cholesterol that had a slightly stronger association with hospitalization frequency than the MIS (Table 8). Figures 3–5 compare the mortality predictability of the four quartiles of MIS, IL-6 and CRP, respectively.

In order to detect the independent predictive values of all 10 markers of MICS, we constructed more extensive models that included continuous values of all 10 MICS markers and the 11 above-mentioned covariates simultaneously. Table 9 shows the results of extensive models. The MIS and serum levels of CRP were the only two variables that had statistically significant and strong independent associations with the prospective risk of hospitalization and mortality after all variables were adjusted for each other in the above-mentioned extensive models. Serum albumin had an independent association with hospitalization frequency and days but not with mortality or first hospital admission. Among 11 covariates, Charlson co-morbidity index had strong and significant associations with all outcome measures.

Discussion

We showed that in a cohort of 378 MHD patients from eight uniformly administered dialysis facilities in the Los Angeles area, a nutritional–inflammatory scoring system known as MIS and some inflammatory markers such as CRP and IL-6 had superior utility in predicting poor clinical outcome when 10 markers of MICS, including these three measures, were compared with each other. Although serum albumin concentration remained a strong predictor of poor outcome in separate models, the MIS and serum levels of CRP were the only significant and persistent predictors of mortality and hospitalization in combined statistical models. These findings may have clinical implications in risk-stratifying MHD patients and their management.

Protein-energy malnutrition and inflammation, independently or concurrently together as MICS or MIA, are common occurrences in MHD patients [1]. MICS is associated with poor clinical conditions and worse outcomes in these patients. The confounding effect of MICS on the associations between traditional risk factors such as obesity and hypercholesterolaemia and clinical outcome is so strong that it even reverses these associations. Hence, a low, rather than a high, BMI or serum cholesterol level is associated with mortality in MHD patients. This phenomenon is known as reverse epidemiology [4]. Nevertheless, despite this known effect of MICS on poor outcome, there is almost no uniform method to assess the nutritional and inflammatory status of dialysis patients in an outcome-

Table 6. Associations between baseline nutritional and inflammatory markers and prospective hospitalization frequency, i.e. total number of hospital admissions, over the 12-month follow-up period, as reflected by hospitalization frequency rate ratios (RRs) and 95% confidence intervals (CIs) in 378 MHD patients

Hospitalization frequency	Status of the fourth quarter (lowest or highest)	RR across all four quartiles (first to fourth)	RR for the fourth *vs* the first quartile	RR for the fourth quartile *vs* the rest
Albumin (g/dl)[a]	Lowest (<3.63 g/dl)	**1.31** (1.22–1.41) $P < 0.001$	**2.57** (1.94–3.41) $P < 0.001$	**1.52** (1.31–1.77) $P < 0.001$
Pre-albumin (mg/dl)	Lowest (<21 mg/dl)	**1.19** (1.11–1.27) $P < 0.001$	**1.78** (1.39–2.28) $P < 0.001$	**1.41** (1.21–1.65) $P < 0.001$
Cholesterol (mg/dl)	Lowest (<115.5 mg/dl)	**1.19** (1.11–1.27) $P < 0.001$	**1.84** (1.48–2.28) $P < 0.001$	**1.57** (1.34–1.83) $P < 0.001$
TIBC (mg/dl)[a]	Lowest (<174 mg/dl)	1.12 (1.05–1.19) $P = 0.001$	1.41 (1.14–1.74) $P = 0.001$	1.23 (1.06–1.44) $P = 0.007$
CRP (mg/l)	Highest (>8.4 mg/l)	1.34 (1.25–1.43) $P < 0.001$	2.40 (1.91–3.02) $P < 0.001$	1.81 (1.57–2.10) $P < 0.001$
IL-6 (pg/ml)	Highest (>17.9 pg/ml)	1.31 (1.23–1.40) $P < 0.001$	2.10 (1.69–2.60) $P < 0.001$	1.70 (1.46–1.97) $P < 0.001$
TNF-α (pg/ml)	Highest (>9.26 pg/ml)	1.03 (0.97–1.10) $P = 0.3$	0.97 (0.78–1.20) $P = 0.8$	1.00 (0.85–1.19) $P = 0.9$
MIS (0–30)	Highest (>8)	**1.22** (1.14–1.30) $P < 0.001$	**1.72** (1.38–2.15) $P < 0.001$	**1.53** (1.30–1.81) $P < 0.001$

Multivariate RR values are based on Cox proportional hazard regression models and adjusted for age, gender, race (Blacks *vs* others), ethnicity (Hispanics *vs* others), insurance status (Medicaid *vs* others) diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose (single pool Kt/V), BMI and history of cardiovascular disease. All models are based on Poisson regression analyses.
[a]Serum albumin and TIBC concentrations are based on 3-month averaged values for each patient.
TIBC = total iron binding capacity.

oriented fashion. Several indices of protein-energy malnutrition are available, ranging from well-known anthropometric measurements to more elaborate techniques, such as dual-energy X-ray absorptiometry [13]. However, the reliability of these methods in detecting protein-energy malnutrition, their practicability and their outcome predictability are not convincing. Moreover, methods to measure inflammatory state among dialysis patients are not well studied, and elaborate laboratory methods to measure diverse pro-inflammatory cytokines are costly and still controversial, which confines their use to a few research centres.

Although the SGA is an easy and reliable tool that has been validated prospectively to determine nutritional status and predict the degree of sickness, it is a semi-quantitative scale and consists of only three nutritional levels, restricting its reliability and precision [10,14]. Moreover, most components of the SGA do not have clear-cut definitions, and concrete guidelines do not exist. The MIS, on the other hand, is a practical and convenient scoring system that can be performed easily by a dietitian, trained nurse or physician within minutes. It is comprehensive enough and beyond the boundaries of history and simplified physical examination of the SGA, so that the MIS also reflects internal inflammation and predicts such clinically relevant outcomes as mortality and hospitalization. Moreover, the MIS does not require additional measurements such as anthropometry, nor does it include any other test rather than routine (monthly) laboratory measures [10]. In our current study, the MIS was compared with nine other markers of inflammation and malnutrition and found to have overall superiority to routinely available measures such as serum albumin and TIBC levels. The outcome predictability of the MIS was comparable with that of such costly and not routinely available tests as serum IL-6 and CRP concentrations. In our study, serum IL-6 and CRP were also found to have superior utility in predicting poor outcome. Indeed Figures 3–5 suggest that serum CRP and IL-6 concentrations provide a higher resolution among all groups with different prognosis, while the MIS may only discriminate between the highest quartile and the rest but not among the other three quartiles. Epidemiological studies indicate that in dialysis patients, increased serum CRP is at least as strong a predictor of morbidity and mortality as serum albumin [15]. Serum CRP is a known acute phase protein and a marker of increased cardiovascular events and poor outcome in both the general population [12] and dialysis patients [15]. Among pro-inflammatory cytokines, IL-6 is reported to have a central role in the pathophysiology of adverse effects of inflammation in patients with renal disease [16]. Increased

Table 7. Associations between baseline nutritional and inflammatory markers and prospective total hospitalization days, i.e. total number of days in hospital, over the 12-month follow-up period, as reflected by hospitalization days rate ratios (RRs) and 95% confidence intervals (CIs) in 378 MHD patients

Hospitalization	Status of the fourth quarter (lowest or highest)	RR across all four quartiles (first to fourth)	RR for the fourth *vs* the first quartile	RR for the fourth quartile *vs* the rest
Albumin (g/dl)[a]	Lowest (<3.63 g/dl)	**1.33** (1.30–1.37) $P < 0.001$	**2.83** (2.52–3.17) $P < 0.001$	**1.60** (1.51–1.70) $P < 0.001$
Pre-albumin (mg/dl)	Lowest (<21 mg/dl)	**1.10** (1.07–1.13) $P < 0.001$	**1.94** (1.74–2.17) $P < 0.001$	**1.10** (1.03–1.17) $P = 0.004$
Cholesterol (mg/dl)	Lowest (<115.5 mg/dl)	**1.18** (1.15–1.21) $P < 0.001$	**1.89** (1.74–2.06) $P < 0.001$	**1.57** 1.48–1.67) ($P < 0.001$
TIBC (mg/dl)[a]	Lowest (<174 mg/dl)	**1.16** (1.13–1.19) $P < 0.001$	**1.67** (1.54–1.82) $P < 0.001$	**1.41** (1.33–1.49) $P < 0.001$
CRP (mg/l)	Highest (>8.4 mg/l)	**1.53** (1.49–1.58) $P < 0.001$	**3.01** (2.75–3.31) $P < 0.001$	**2.39** (2.26–2.53) $P < 0.001$
IL-6 (pg/ml)	Highest (>17.9 pg/ml)	**1.38** (1.35–1.42) $P < 0.001$	**2.94** (2.68–3.22) $P < 0.001$	**1.83** (1.73–1.94) $P < 0.001$
TNF-α (pg/ml)	Highest (>9.26 pg/ml)	**1.11** (1.08–1.14) $P < 0.001$	**1.36** (1.25–1.50) $P < 0.001$	**1.13** (1.06–1.21) $P < 0.001$
MIS (0–30)	Highest (>8)	**1.27** (1.24–1.31) $P < 0.001$	**2.00** (1.83–2.19) $P < 0.001$	**1.67** (1.57–1.78) $P < 0.001$

Multivariate RR values are based on Cox proportional hazard regression models and adjusted for age, gender, race (Blacks *vs* others), ethnicity (Hispanics *vs* others), insurance status (Medicaid *vs* others) diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose (single pool Kt/V), BMI and history of cardiovascular disease. All models are based on Poisson regression analyses.
[a]Serum albumin and TIBC concentrations are based on 3-month averaged values for each patient.
TIBC = total iron binding capacity.

Table 8. Comparing relative risk of poor outcome among markers of MICS

Ranking (greatest magnitude)	Mortality	First hospital admission	Hospitalization frequency	Hospitalization days
First	IL-6 (3.97)	MIS (2.02)	CRP (1.81)	CRP (2.39)
Second	MIS (3.83)	CRP (1.92)	IL-6 (1.70)	IL-6 (1.83)
Third	CRP (3.27)	IL-6 (1.62)	Cholesterol (1.57)	MIS (1.67)
Fourth	Albumin (2.24)	TIBC (1.44)	MIS (1.53)	Albumin (1.60)
Fifth	TNF-α (1.81*)	Albumin (1.37)	Albumin (1.52)	Cholesterol (1.57)

For each MICS marker, the relative risk of the fourth quartile *vs* the rest is shown (see Tables 4–7).
*$P > 0.05$.

serum levels of IL-6 are also reported to be associated with increased mortality in both MHD and peritoneal dialysis patients [17]. Moreover, progression of carotid atherosclerosis during dialysis may be related to IL-6 levels [18]. However, even such acute phase reactants may be engendered during oxidative stress, which can happen in the setting of protein-energy malnutrition. Moreover, inflammatory markers have been shown to have a higher degree of temporal fluctuations when compared with serum albumin [19]. Nevertheless, the results of our study are consistent with more recent data indicating the superior reliability and sensitivity of serum concentrations of these inflammatory markers in predicting poor outcome.

In our current study, we did not find a strong association between markers of protein-energy malnutrition such as nPNA or indicators of nutritional status such as the percentage of body fat or other anthropometric measures and clinical outcome. The former is in contrast to our recent data indicating a strong association between nPNA and outcome measures in MHD patients [20], while the latter is consistent with the majority of the studies in this field where no association has been found between anthropometric measures such as BSF, TSF or body fat percentage and

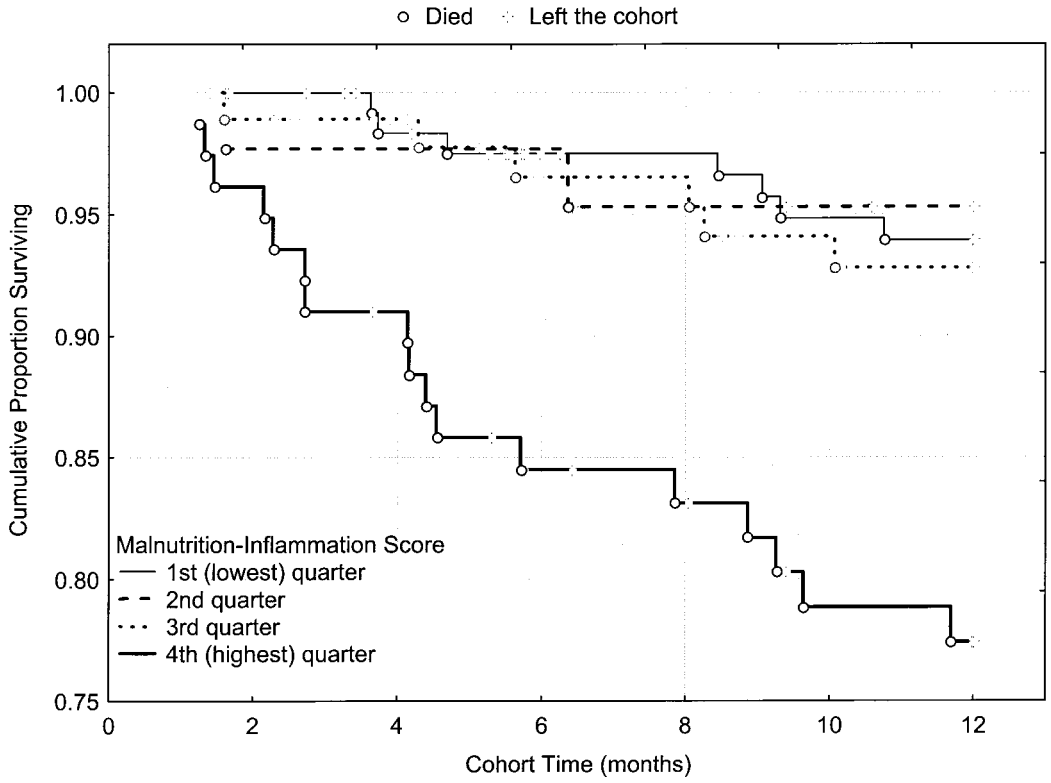

Fig. 3. Kaplan–Meier proportion of surviving patients comparing four quarters of the MIS in 346 MHD patients.

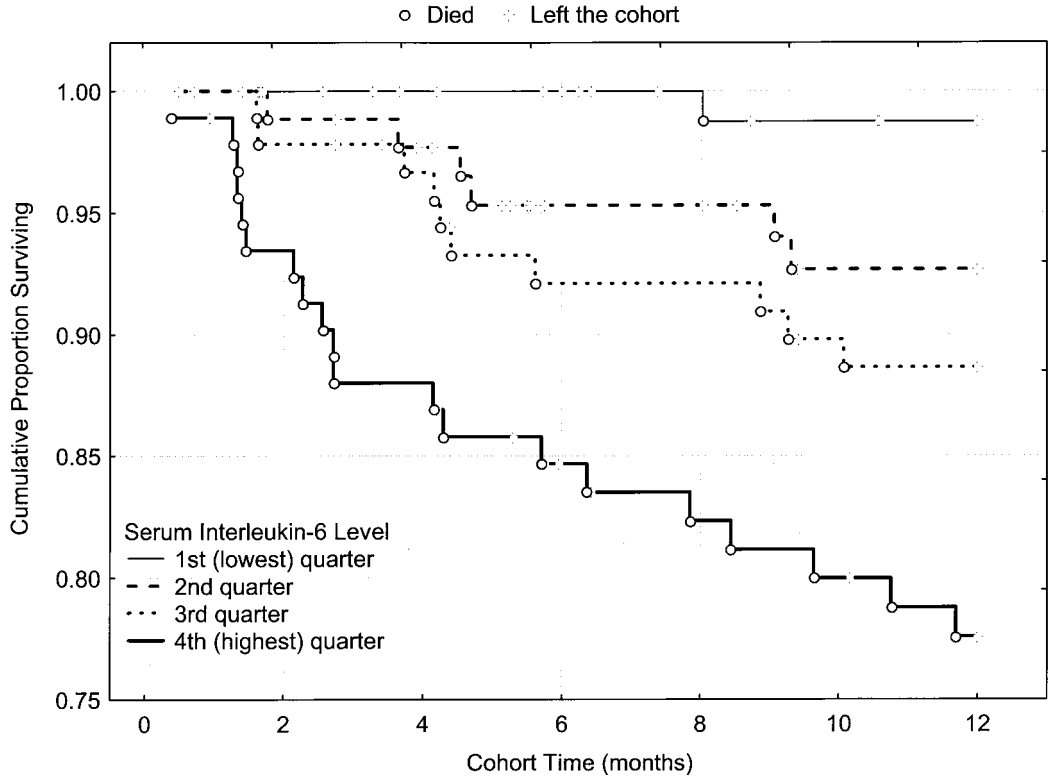

Fig. 4. Kaplan–Meier proportion of surviving patients comparing four quarters of serum IL-6 in 373 MHD patients.

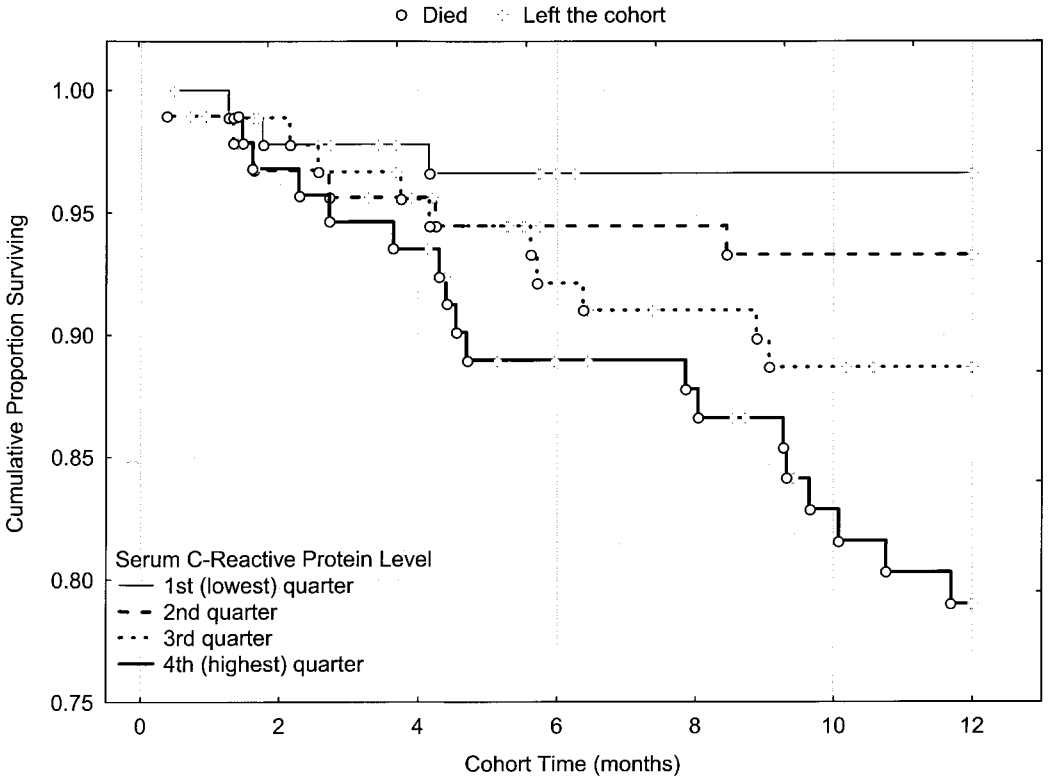

Fig. 5. Kaplan–Meier proportion of surviving patients comparing four quarters of serum C-reactive protein (CRP) in 374 MHD patients.

Table 9. Mortality and hospitalization predictability of markers of MICS using unifying multivariate models (Cox and Poisson) in 378 MHD patients

	Mortality (Cox)		First hospital admission (Cox)		Hospitalization frequency (Poisson)	
	z-Statistics	*P*-value	*Z*-Statistics	*P*-value	*Z*-Statistics	*P*-value
Markers of MICS						
MIS	**3.13**	**0.002**	**2.54**	**0.01**	**4.23**	**<0.001**
Serum CRP	**3.3**	**0.001**	**3.43**	**0.001**	**8.02**	**<0.001**
IL-6	−0.59	0.6	0.64	0.5	−0.18	0.9
TNF-α	0.37	0.7	−0.99	0.3	−1.55	0.12
Albumin	−1.07	0.3	−1.18	0.2	**−5.14**	**<0.001**
Pre-albumin	0.85	0.4	−0.46	0.6	1.36	0.2
Creatinine	0.65	0.5	0.39	0.7	0.77	0.4
Total iron binding capacity	0.86	0.4	0.57	0.6	1.03	0.3
Cholesterol	−0.27	0.8	0.25	0.8	−2.41	0.02
nPNA (nPCR)	−0.92	0.4	0.9	0.4	**4.26**	**<0.001**
Other covariates						
Charlson co-morbidity index	**3.75**	**<0.001**	**4.94**	**<0.001**	**7.82**	**<0.001**
Age	1.75	0.08	1.72	0.09	0.95	0.3
Gender	0.72	0.5	−1.13	0.3	**−4.1**	**<0.001**
Race (African Americans *vs* others)	1.72	0.09	−0.38	0.7	**−2.58**	**0.01**
Ethnicity (Hispanics *vs* others)	1.37	0.2	0.53	0.6	−1.13	0.3
Diabetes mellitus	−1.04	0.3	**−3.38**	**<0.001**	**−4.59**	**<0.001**
Dialysis vintage	−0.31	0.8	−0.06	0.9	−0.57	0.6
Insurance status (Medicaid)	0.72	0.5	−1.56	0.12	**−3.68**	**<0.001**
Body mass index	0.77	0.4	1.85	0.06	**2.92**	**0.003**
Kt/V (single pool)	0.66	0.5	−1.03	0.3	−1.46	0.2
History of cardiovascular disease	−1.79	0.07	**−2.85**	**0.004**	−0.94	0.3

nPNA: normalized protein nitrogen appearance; nPCR: normalized protein catabolic rate.

the outcome [21]. Our previous study pertaining to the utility of nPNA in predicting the clinical outcome was restricted to those MHD patients whose dialysis dose was above the usual target, i.e. Kt/V >1.20 [20]. This may explain the discrepancy between these two studies. Nevertheless, we have shown recently that other markers of inadequate food intake such as a low appetite are strong predictors of higher mortality and hospitalization in MHD patients [7]. Another important finding in our study was the strong and independent association between the Charlson co-morbidity index and all outcome measures, indicating, once again, the importance of co-morbid conditions in dialysis outcome and urgent need for more studies in this area.

Our current study should be qualified by the possibility of selection bias and its short-term interval of only 12 months. During the initial recruitment in eight dialysis units (with 1200 MHD patients), it is possible that only those MHD patients who were generally healthier or more health conscious agreed to participate (385 patients). This is evident from the fact that the annual mortality rate in these eight dialysis units in the same period of time was 15%, but in the 378 recruited MHD patients for the NIED Study was 10% (for a more comprehensive comparison, see [22]). Moreover, both incident and prevalent dialysis patients were studied simultaneously, which may lead to survival (incidence–prevalence) bias. However, a selection bias with such a direction or a survival bias would generally lead to a bias towards the null, so that without this type of bias our positive results would probably have been even stronger and the associations more prominent. Moreover, we did not account for fluctuation of serum CRP or cytokines over time, even though the follow-up time was only 12 months. To our knowledge, our study is the first one that compares the outcome predictability of such a large number of nutritional and inflammatory markers and uses both mortality and three distinct measures of hospitalization simultaneously in a relatively large sample of MHD patients. Moreover, this is the first time that utility of MIS in predicting clinical outcome has been examined comprehensively and in such a comparative fashion.

Undoubtedly, MICS/MIA is a major role player in poor clinical outcome of dialysis patients. Hence, it is imperative to find the best tool that can reliably identify MICS and its degree of severity in order to risk-stratify the patients accurately. Nevertheless, this preliminary step needs to be followed by efforts to treat MICS. There is a paucity of information concerning the effect of nutritional therapy or anti-inflammatory modalities on morbidity and mortality in dialysis patients [1]. Randomized clinical trials are needed to compare the effect of nutritional support and anti-inflammatory agents, both independently and combined with each other, in patients suffering from MICS, in order to improve poor outcome in dialysis patients [1]. To that end, a reliable tool to identify MICS and the degree of its severity is the most critical step.

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