ORIGINAL RESEARCH

Independent and Joint Associations of Nutritional Status Indicators With Mortality Risk Among Chronic Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Antonio Alberto Lopes, MD, PhD, Jennifer L. Bragg-Gresham, MS,† Stacey J. Elder, MS,† Nancy Ginsberg, RD,‡ David A. Goodkin, MD,† Trinh Pifer, MPH,† Norbert Lameire, MD,§ Mark R. Marshall, MBChB,** Yasushi Asano, MD,†† Tadao Akizawa, MD,‡‡ Ronald L. Pisoni, PhD, MS,† Eric W. Young, MD, MS,§§ and Friedrich K. Port, MD, MS†*

Objective: To consider the Kidney Disease Outcomes Quality Initiative recommendation of using multiple nutritional measurements for patients on maintenance dialysis, we explored data for independent and joint associations of nutritional indicators with mortality risk among maintenance hemodialysis patients treated in 12 countries.

Setting: Dialysis units in seven European countries, the United States, Canada, Australia, New Zealand, and Japan.

Main Outcome: Mortality risk.

Methods: We conducted a prospective cohort study of 40,950 patients from phases I to III of the Dialysis Outcomes and Practice Patterns Study (1996–2008). Independent and joint effects (interactions) of nutritional indicators (serum creatinine, serum albumin, normalized protein catabolic rate, body mass index [BMI]) on mortality risk were assessed by Cox regression with adjustments for demographics, years on dialysis, and comorbidities.

Results: Important variations in nutritional indicators were seen by country and patient characteristics. Poorer nutritional status assessed by each indicator was independently associated with higher mortality risk across regions. Significant multiplicative interactions (each $p \leq 0.01$) between indicators were also observed. For example, by using patients with serum creatinine 7.5–10.5 mg/dL and BMI 21–25 kg/m^2 as referent, BMI <21 kg/m^2 was associated with lower mortality risk among patients with creatinine >10.5 mg/dL (relative risk = 0.68) but with higher mortality risk among those with creatinine <7.5 mg/dL (relative risk = 1.38). The association of lower albumin concentration with higher mortality risk was stronger for patients with lower BMI or lower creatinine.

Conclusion: The joint effects of nutritional indicators on mortality indicate the need to use multiple measurements when assessing the nutritional status of hemodialysis patients.

**Department of Medicine, Federal University of Bahia, Salvador, BA, Brazil.*

†*Arbor Research Collaborative for Health, Ann Arbor, MI 48103.*

‡*Renal Research Institute, New York, NY 10128.*

§*Ghent University Hospital, Ghent, Belgium.*

***Middlemore Hospital, Auckland, New Zealand.*

††*Koga Red Cross Hospital, Koga, Ibaraki, Japan.*

‡‡*Showa University Hospital, Shingawa, Tokyo, Japan.*

§§*Veterans Affairs Ann Arbor Healthcare System/University of Michigan, Ann Arbor, MI 48105.*

The DOPPS is administered by Arbor Research Collaborative for Health. DOPPS I, II, and III have been supported by research grants from Amgen Inc. and Kyowa Hakko Kirin Co., Ltd. As of January 2009, the DOPPS is additionally funded by Genzyme Corp. Support is provided without restrictions on publications. Friedrich K. Port receives research funding for the DOPPS from Amgen Inc. and Kyowa Hakko Kirin Co Ltd. (additionally since 2009 from Genzyme Corp.). This manuscript was edited by Shauna Leighton, a medical editor employed by Arbor Research Collaborative for Health.

Address reprint requests to Dr. Antonio Alberto Lopes, Departamento de Medicina da Faculdade de Medicina da Universidade Federal da Bahia, Av. Reitor Miguel Calmon, s/n, Vale do Canela, Salvador, BA - CEP: 40110-100 Brazil. E-mail: aaslopes@ufba.br

1051-2276/$36.00

doi:10.1053/j.jrn.2009.10.002

OBJECTIVE NUTRITIONAL indicators, such as serum albumin, serum creatinine, body mass index (BMI), and normalized protein catabolic rate (nPCR), have been used to assess the nutritional status of patients with chronic kidney diseases.[1–5] The Kidney Disease Outcomes Quality Initiative (KDOQI) asserts, however, that none of these measures provides complete evaluation of nutritional status and therefore recommends a collective evaluation of multiple nutritional parameters for patients on maintenance dialysis.[6] The changes in conventional nutritional measures are apparently the result of different mechanisms, such as reduced protein intake and inflammation.[7,8] Thus, it is meaningful to assess the joint effects of these measures on the risk of death among dialysis patients. The evaluation of joint effects will provide insight into the value of using more than one measure to assess the nutritional status of hemodialysis patients, particularly when the objective is to identify patients at higher risk of death.

We examined data of more than 40,000 maintenance hemodialysis patients from 12 countries participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 1996 through 2008 using several conventional measures of nutritional status. To consider the KDOQI recommendation of using multiple measures of nutritional status for patients on maintenance hemodialysis, we investigated both independent and joint associations of nutritional indicators with mortality. We also assessed how nutritional status indicators vary by patient characteristics and by country in the DOPPS to provide a broad-based international perspective for this evaluation.

Subjects and Methods

Subjects

The data were from adult maintenance hemodialysis patients (aged ≥18 years) enrolled in phases I to III of the DOPPS. The DOPPS is an international, prospective, observational study based on nationally representative samples of randomly selected dialysis facilities.[9,10] DOPPS I data (308 facilities) were collected in five European countries (France, Germany, Italy, Spain, and the United Kingdom), Japan, and the United States. Data collection began in 1996 in the United States, 1998 in Europe, 1999 in Japan, and continued into 2001. DOPPS II (322 facilities) was initiated in 2002 and continued through 2004. It included dialysis facilities from the DOPPS I countries as well as facilities from Australia, Belgium, Canada, New Zealand, and Sweden. DOPPS III (301 facilities) was initiated in 2005 with data collection completed in 2008. DOPPS III included the same 12 countries as DOPPS II.

Within each participating facility, 20–40 patients were randomly selected, depending on facility size. This study used a sample of 40,950 patients who were on maintenance hemodialysis for at least 3 months. Patients departing from the study typically were replaced every 4 months by randomly selected patients who had entered the dialysis unit since the time of the prior random selection. For between-country comparisons of nutritional status, only data from a prevalent cross section of patients on hemodialysis for at least 3 months at the time of a facility's entry into DOPPS III were used.

Nutritional Indicators

The following indicators of nutritional status were assessed: serum creatinine concentration, serum albumin concentration, nPCR, BMI, and appearance of cachexia. Laboratory methodology has not been standardized in the DOPPS.

Statistical Methods

Multivariable logistic regression was used to identify patient characteristics and regions associated with the odds of cachectic appearance, lower concentrations of serum albumin (≤3.5 vs. >3.5 g/dL), lower serum concentration of creatinine (≤7.5 vs. >7.5 mg/dL), lower nPCR (≤0.9 vs. >0.9 g/kg/day), and lower BMI (≤22 vs. >22 kg/m^2). Cox regression was used to assess whether poorer nutritional status by each indicator was associated with the risk of all-cause and cause-specific death (death due to cardiovascular and infectious causes). Cox models were stratified by country and study phase. To assess for joint effects (multiplicative interactions) between nutritional indicators on mortality risk separate Cox models were used. The p values for the interaction terms were based on the product of two continuous variables (serum albumin × serum creatinine): BMI × serum albumin and serum creatinine × BMI. Logistic and Cox regression models were adjusted for facility clustering and the effects of age, black race, sex, marital status, living situation (living with spouse or friends, alone or in nursing homes),

years on dialysis, being seen by a dietitian, ability to eat independently, dialysis dose by single-pool Kt/V (spKt/V), 14 comorbid conditions (cancer [other than skin], cerebrovascular disease, congestive heart failure, coronary artery disease, other cardiovascular disease, diabetes mellitus, gastrointestinal bleed, HIV/AIDS, hypertension, lung disease, neurological disease, peripheral vascular disease, psychological disorders, recurrent cellulitis/gangrene), catheter as vascular access and neutrophil:lymphocyte ratio >4. Neutrophil:lymphocyte ratio was included in the analysis as a proxy for inflammation that has been found to be associated with mortality and serum albumin concentration.[8,11] All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics of patients in the overall study sample and stratified by three regions. The results stratified by region were based only on the DOPPS III cross-sectional sample. The time since first dialysis was longer for patients treated in Japan than for those treated in other regions. Japan was also the country with the highest percentage of patients living with a spouse or friends and with the lowest prevalence rates for the majority of comorbidities. North America (Canada and the United States) had the highest prevalence of reported comorbidities.

As shown in Table 2, there was large variation in the mean values of indicators of nutritional status across countries. Mean serum creatinine varied from 7.7 ± 2.3 in Sweden to 11.0 ± 2.8 mg/dL in Japan, mean albumin from 3.48 ± 0.48 in Sweden to 4.02 ± 0.50 g/dL in Germany, nPCR from 0.93 ± 0.21 in Germany to 1.12 ± 0.25 g/kg/day in Australia/New Zealand, and BMI from 20.9 ± 3.2 in Japan to 27.7 ± 6.9 kg/m^2 in the United States. The percentage of patients with cachectic appearance varied from 3.6% in Japan to 18.0% in the United Kingdom.

Table 3 shows adjusted odds ratios (AOR) for the associations between patient characteristics and baseline indicators of nutritional status. Each odds ratio was adjusted for variables listed in the table and also for DOPPS phase and country. The difference in sample sizes among nutritional indicators is explained by missing values. In general, older patients had higher odds of poorer nutritional status as indicated by a lower concentration of serum creatinine (≤7.5 mg/dL), lower concentration of serum albumin (≤3.5 g/dL), lower nPCR (≤1.0 g/kg/day), and being considered cachectic. However, older patients had lower adjusted odds of BMI ≤22 kg/m^2. Males had significantly lower odds of serum creatinine ≤7.5 mg/dL, serum albumin ≤3.5 g/dL, and BMI ≤22 kg/m^2. As compared with patients of other races, blacks had higher odds of nPCR <1.0 g/kg/day but lower odds of serum creatinine concentration ≤7.5 mg/dL and BMI ≤22 kg/m^2. These associations by race were similar when the analysis was restricted to patients treated in the United States. For some measurements, significantly higher adjusted odds of poorer nutritional status were observed for patients who were not married, living in nursing homes, had ≤1 year on dialysis, did not eat independently or had a spKt/V ≤1.2. The presence of a dietitian in the dialysis unit was associated with lower odds of a patient having low albumin and being considered cachectic. A neutrophil:lymphocyte ratio >4 was associated with higher odds of cachectic appearance, BMI ≤22 kg/m^2, having serum creatinine concentrations ≤7.5 mg/dL, and serum albumin concentration ≤3.5 g/dL. In general, the odds of having at least one measurement indicative of poorer nutritional status were significantly higher for patients with comorbidities, except for hypertension. Gastrointestinal bleeding, neurologic disease, and psychological disorders were comorbidities significantly associated with higher odds of having a serum creatinine ≤7.5 mg/dL, serum albumin ≤3.5 g/dL, BMI ≤22 kg/m^2, and cachectic appearance.

In the total sample, diabetics had lower odds of having BMI ≤22 kg/m^2 or being considered cachectic. Analysis of the association between the odds of nutritional indicator by diabetic status was also performed by age at the onset of end-stage renal disease (ESRD): <35 years, 35–44 years, and ≥45 years. The prevalence of diabetes mellitus by age at ESRD onset was 13.2% for ages <35, 26.1% for ages 35–44 years, and 43.1% for ages ≥45 years (data not shown in the table). As shown in Table 3, the association between diabetic status and lower odds of BMI ≤22 kg/m^2 was stronger for ages ≥45 years; odds ratios were 0.78 ($p < 0.05$) for ages <35, 0.67 ($p < 0.0001$) for ages 35–44, and 0.43 ($p < 0.0001$) for ages ≥45 years). The odds of cachectic appearance were significantly lower among diabetic than among nondiabetic patients in the age group ≥45 years (OR = 0.7, $p <$

Table 1. Baseline Characteristics and Comorbidities by Region

	Entire Sample N = 40,950	DOPPS III Sample* Europe and A/NZ** n = 4,102	North America n = 2,212	Japan n = 1,752
Age, mean (SD)	62.0 (14.9)	64.2 (14.4)	62.0 (15.4)	62.4 (12.4)
Gender (% male)	58.0	58.1	55.2	60.0
Race (% black)	13.1	1.7	30.5	0.0
Married (%)	56.6	57.8	45.9	69.1
Eat independently (%)	95.5	97.1	96.4	96.3
Saw dietitian in prior 6 months (%)	53.0	36.0	84.1	25.8
Living with spouse/friends (%)	75.3	72.0	69.5	84.7
Living alone (%)	15.7	18.9	20.0	11.3
Living in nursing home (%)	5.0	4.2	6.6	2.2
Kt/V ≤1.2 (%)	17.6	11.7	8.2	23.6
Years on dialysis; mean(SD)	3.6 (5.2)	5.1 (5.7)	4.1 (4.1)	8.3 (7.0)
Years on dialysis; median	1.5	3.2	2.8	6.3
Neutrophil:lymphocyte > 4 (%)	19.1	20.4	16.0	16.6
Catheter as access (%)	26.3	18.8	26.8	0.3
Comorbidities (%)				
Cancer, other than skin	11.4	14.2	12.2	8.8
Cerebrovascular disease	16.6	19.4	18.5	13.5
Coronary artery disease	44.6	51.7	67.4	41.3
Other cardiovascular disease	33.6	42.1	36.4	32.9
Diabetes mellitus	38.0	31.1	53.3	31.7
Gastrointestinal bleed	6.2	4.9	6.1	4.0
HIV/AIDS	0.6	0.5	1.0	0.6
Hypertension	78.2	78.7	88.2	71.9
Lung disease	11.2	13.3	19.0	2.6
Neurological disease	10.0	11.4	13.6	10.0
Peripheral vascular disease	24.9	31.3	33.4	17.5
Psychiatric disorder	18.1	11.8	20.1	3.6
Recurrent cellulitis/gangrene	7.6	9.4	10.9	4.1

*The DOPPS III is a prevalent cross section of patients on dialysis for at least 3 months. The entire sample contains replacement patients.

**A/NZ, Australia and New Zealand.

0.0001) and a nonsignificant trend to higher odds of cachectic appearance was observed among diabetics in the age group <35 years.

Table 4 shows adjusted odds ratios of associations between country of hemodialysis treatment and indicators of nutritional status in the initial cross section using the United States as the referent country. Each odds ratio was adjusted for all covariates in Table 3 and DOPPS study phase. Compared to the United States, the adjusted odds of

Table 2. Nutritional Status Indicators Based on a Prevalent Cross Section of DOPPS III

	Creatinine (mg/dL), mean (SD)	Albumin (g/dL), mean (SD)	nPCR (g/kg/day), mean (SD)	BMI (kg/m^2), mean (SD)	% Cachectic
Australia/New Zealand (n = 497)	8.4 (2.4)	3.75 (0.45)	1.12 (0.25)*	27.2 (6.3)	10.9
Belgium (n = 472)	8.5 (3.0)	3.76 (0.46)	1.01 (0.26)*	25.2 (5.0)*	14.8
Canada (n = 508)	8.1 (2.6)*	3.58 (0.46)*	1.00 (0.24)	26.7 (6.6)*	7.1
France (n = 515)	8.3 (2.3)	3.69 (0.47)*	1.09 (0.27)*	24.3 (5.0)*	12.0
Germany (n = 556)	8.7 (2.9)	4.02 (0.50)*	0.93 (0.21)	26.1 (5.0)*	5.5
Italy (n = 507)	9.0 (2.5)*	3.83 (0.50)	1.06 (0.24)*	24.2 (4.5)*	10.1
Japan (n = 1,752)	11.0 (2.8)*	3.83 (0.41)	1.02 (0.20)*	20.9 (3.2)*	3.6*
Spain (n = 627)	8.5 (2.4)	3.83 (0.44)	1.10 (0.26)*	24.6 (4.5)*	8.5
Sweden (n = 512)	7.7 (2.3)*	3.48 (0.48)*	1.02 (0.26)*	25.3 (5.0)*	11.7
United Kingdom (n = 416)	8.5 (2.6)	3.77 (0.45)	0.98 (0.22)	25.4 (5.4)*	18.0*
United States (n = 1,704)	8.7 (3.1)	3.80 (0.43)	0.96 (0.24)	27.7 (6.9)	9.4

*Significantly different from the United States ($p < 0.05$).

Table 3. Adjusted Odds Ratios of the Associations Between Patient Characteristics and Baseline Indicators of Nutritional Status in DOPPS I, II, and III

	Creatinine ≤7.5 vs. >7.5 mg/dL (n = 36,071)	Albumin ≤3.5 vs. >3.5 g/dL (n = 32,443)	BMI ≤22 vs. >22 kg/m^2 (n = 34,242)	nPCR <1.0 vs. ≥1.0 g/kg/day (n = 23,172)	Cachectic Yes vs. No (n = 36,747)
Age 45–64 (vs. <45 years)	1.53**	1.24**	0.64**	1.02	1.23*
Age ≥65 (vs. <45 years)	2.92**	1.54**	0.70**	1.51**	1.64**
Male (vs. female)	0.51**	0.79**	0.85**	1.03	0.94
Black (vs. other)	0.36**	0.98	0.87*	1.32**	1.06
Black (vs. other) only in the United States	0.37**	1.01	0.86*	1.30**	1.06
Married (vs. not married)	0.89*	1.02	0.81**	0.99	0.79**
Living alone (vs. with spouse/friends)	0.96	0.93	1.03	1.05	0.95
In nursing home (vs. with spouse/friends)	1.60**	1.30**	1.26*	0.96	1.25*
Dietitian (yes vs. no)	0.95	0.85**	1.00	1.00	0.87*
Eat independently (yes vs. no)	0.62**	0.59**	0.82*	0.91	0.39**
Kt/V ≤1.2 (vs. >1.2)	0.97	1.01	0.61**	2.69**	1.00
Years on dialysis (≤1 year vs. >1 year)	3.72**	1.79**	0.87**	1.35**	1.21**
Neutrophil:lymphocyte > 4	1.19**	1.35**	1.15*	0.95	1.26**
Catheter as access (yes vs. no)	1.31**	2.14**	1.13**	1.21**	1.92**
Comorbidities (yes vs. no)					
Cancer (other than skin)	1.02	1.21**	1.10*	1.06	1.28**
Congestive heart failure	1.21**	1.16**	1.12**	0.96	1.28**
Cerebrovascular disease	1.13*	1.02	1.08*	1.03	1.10*
Coronary artery disease	1.07*	0.97	0.94*	1.11*	0.96
Other cardiovascular disease	1.14**	1.03	1.13**	0.98	1.17*
Diabetes mellitus (DM)–All	1.84**	1.30**	0.46**	1.07*	0.72**
DM–Age at ESRD start <35 yr	2.22**	1.92**	0.78*	1.31	1.21
DM–Age at ESRD start 35–44 yr	1.93**	1.72**	0.67**	1.33*	0.87
DM–Age at ESRD start ≥45 yr	1.78**	1.22**	0.43**	1.02	0.7**
Gastrointestinal bleed	1.15*	1.33**	1.12*	1.13*	1.77**
HIV/AIDS	1.05	2.41**	1.21	1.27	2.10**
Hypertension	0.79**	0.85**	0.95	0.93*	0.80**
Lung disease	1.26**	1.04	1.23**	1.17*	1.38**
Neurological disease	1.24**	1.28**	1.43**	1.15*	1.42**
Peripheral vascular disease	1.24**	1.05	1.09*	1.12*	1.20**
Psychological disorder	1.21**	1.16**	1.17**	1.17*	1.76**
Recurrent cellulitis/gangrene	1.23**	1.44**	1.05	1.02	1.37**

Each odds ratio was adjusted for the other variables in the table, DOPPS study phase and country using logistic regression.

*$p < 0.05$.

**$p < 0.0001$.

Table 4. Adjusted Odds Ratio (AOR) of the Associations Between Country and Baseline Indicators of Poorer Nutritional Status in DOPPS I, II and III, Using the United States as the Referent Country

	Creatinine ≤7.5 vs. >7.5 mg/dL		Albumin ≤3.5 vs. >3.5 g/dL		BMI ≤22 vs. >22 kg/m^2		nPCR <1.0 vs. ≥1.0 g/kg/day		Cachectic Yes vs. No	
	AOR	*p*-value	AOR	*p*-value	AOR	*p*-value	AOR	*p*-value	AOR	*p*-value
Country (vs. United States)										
Australia/New Zealand	0.86	0.19	1.42	0.03	0.89	0.24	**0.50**	<0.0001[a]	**2.26**	<0.0001[a]
Belgium	0.78	0.03	0.88	0.42	1.06	0.43	**0.67**	0.0004[a]	1.30	0.14
Canada	1.02	0.86	**1.96**	<0.0001[a]	0.93	0.37	0.81	0.05	1.05	0.80
France	0.78	0.02	1.25	0.12	**1.43**	<0.0001[a]	**0.50**	<0.0001[a]	**2.49**	<0.0001[a]
Germany	1.13	0.24	**0.61**	0.0005[a]	0.89	0.14	1.16	0.22	1.28	0.11
Italy	**0.54**	<0.0001[a]	0.92	0.57	**1.34**	<0.0001[a]	**0.40**	<0.0001[a]	**1.82**	0.0001[a]
Japan	**0.29**	<0.0001[a]	1.22	0.02	**8.96**	<0.0001[a]	**0.72**	<0.0001[a]	1.12	0.36
Spain	0.88	0.13	1.03	0.84	1.13	0.08	**0.41**	<0.0001[a]	1.33	0.07
Sweden	1.23	0.06	**3.27**	<0.0001[a]	1.12	0.15	0.67	0.002	1.49	0.02
United Kingdom	0.987	0.21	1.11	0.45	1.12	0.09	1.01	0.93	**2.54**	< 0.0001[a]
Phase (DOPPS I vs. III)	**0.78**	<0.0001[a]	**1.43**	<0.0001[a]	**1.51**	<0.0001[a]	**0.70**	<0.0001[a]	1.22	0.06
Phase (DOPPS II vs. III)	1.00	0.87	**1.45**	<0.0001[a]	**1.19**	<0.0001[a]	**0.85**	0.004[a]	**1.40**	0.0003[a]

Using logistic regression, each odds ratio was adjusted for all variables in Table 3 and DOPPS phase.
Bold AORs indicate $p < 0.005$.
[a]To correct for multiple comparisons between countries *p*-values <0.005 should be considered statistically significant.

having a lower serum creatinine (≤7.5 mg/dL) were significantly lower for patients treated in Belgium, Japan, Italy, and France. Significantly lower adjusted odds (compared to the United States) were observed for serum albumin ≤3.5 g/dL in Germany, and significantly higher adjusted odds were observed in Australia/New Zealand, Japan, Sweden, and Canada. Compared to the United States, the adjusted odds of BMI ≤22 kg/m^2 were significantly higher for Japan, France, and Italy. The adjusted odds of nPCR <1.0 g/kg/day were also much lower in Australia/New Zealand, Belgium, France, Italy, Japan, Spain, and Sweden than in the United States. The adjusted odds of cachectic appearance were significantly higher for Australia/New Zealand, France, Italy, Sweden, and the United Kingdom than for the United States.

Table 5 shows Cox regression results for unadjusted and adjusted relative risks of all-cause mortality by region in relation to indicators of poor nutritional status. In the models without adjustments for covariates, each measure of poorer nutritional status was significantly associated (each $p < 0.0001$) with a higher risk of death. For the whole DOPPS cohort, the risk of death increased by 16% (relative risk [RR] = 1.16) for each 1-mg/dL lower serum creatinine concentration; by 20% (RR = 1.20) per 0.3-g/dL lower serum albumin; by 20% (RR = 1.20) for each 5-kg/m^2 lower BMI; and by 7% (RR = 1.07) per 0.1-g/kg/day nPCR. The mortality risk was more than twofold higher (RR = 2.40) for patients diagnosed with cachexia. Adjustment for comorbidities reduced the magnitude of the associations between nutritional indicators and mortality risk but the associations remained statistically significant except for nPCR in North America (United States and Canada).

In the cross-sectional sample of patients in DOPPS III, the observed cardiovascular- and infection-related death rates per 100 patient-years were, respectively, 5.65 and 2.43 in the United States, 4.18 and 2.97 in Europe/Australia/New Zealand, and 1.92 and 1.36 in Japan. Septicemia was reported for 55.3% of the patients with infection-related death. Figure 1 shows the relationship of nutritional indicators with the adjusted relative risks of death due to cardiovascular- and infection-related causes. The associations of lower serum albumin and cachectic appearance with a higher risk of death were stronger for infection-related

Table 5. Relative Risk (RR) of All-Cause Mortality Associated With Worse Nutritional Status, by Region

	Serum Creatinine per 1-mg/dL lower		Serum Albumin per 0.3-g/dL lower		BMI per 5-kg/m^2 lower		nPCR per 0.1-g/kg/day lower		Cachectic (yes vs. no)	
	RR	*p*-value	RR	*p*-value	RR	*p*-value	RR	*p*-value	RR	p-value
Unadjusted Relative Risk										
Europe/Australia /New Zealand	1.17*,†	<0.0001	1.20*	<0.0001	1.19*	<0.0001	1.11*,†	<0.0001	2.71*,†	<0.0001
Japan	1.24	<0.0001	1.48	<0.0001	1.98	<0.0001	1.18	<0.0001	5.57	<0.0001
United States/Canada	1.14*	<0.0001	1.18*	<0.0001	1.19*	<0.0001	1.04*	<0.0001	2.09*	<0.0001
All countries	1.16	<0.0001	1.20	<0.0001	1.20	<0.0001	1.07	<0.0001	2.40	<0.0001
Adjusted Relative Risk										
	RR	*p*-value	RR	*p*-value	RR	*p*-value	RR	*p*-value	RR	p-value
Europe/Australia /New Zealand	1.10*,†	<0.0001	1.13*	<0.0001	1.20*,†	<0.0001	1.05*,†	<0.0001	1.72*,†	<0.0001
Japan	1.17	<0.0001	1.34	<0.0001	1.81	<0.0001	1.13	<0.0001	3.27	<0.0001
United States/Canada	1.06*	<0.0001	1.12*	<0.0001	1.14*	<0.0001	1.01*	0.4682	1.36*	<0.0001
** All countries	1.09	<0.0001	1.14	<0.0001	1.17	<0.0001	1.03	<0.0001	1.57	<0.0001

*Significantly different from Japan ($p < 0.05$).
**Adjusted for all variables in Table 3 and stratified by DOPPS phase.
†Significantly different from United States and Canada ($p < 0.05$); nPCR, normalized protein catabolic rate; n = 36,722.

causes than for cardiovascular-related causes. By contrast, lower BMI was more strongly associated with a higher risk of death due to cardiovascular-related causes than to infection-related causes. Lower nPCR was significantly associated with higher risk of death due to infection-related causes but not to cardiovascular-related causes.

Separate Cox models with coefficients of interaction were used to assess multiplicative joint effects of nutritional indicators on mortality risk (Fig. 2). All the tested joint effects (creatinine × albumin, BMI × albumin, and BMI × creatinine) were statistically significant ($p < 0.01$). As shown in Figure 2A, an excess mortality risk of more than 40% (RR = 1.46, $p < 0.05$) was observed for patients who had both lower serum creatinine (<7.5 mg/dL) and lower serum albumin (<3.5 g/dL) as compared with the referent category that was composed of patients who had serum creatinine 7.5–10.5 mg/dL and serum albumin 3.5–3.8 g/dL. However, compared with the reference category, serum albumin below 3.5 g/dL was not associated with mortality risk (RR = 1.01) when serum creatinine was >10.5 mg/dL. By using patients with serum albumin 3.5–3.8 g/dL who also had BMI 21–25 kg/m^2 as referent (Fig. 2B), an excess risk of 50% (RR = 1.50, $p < 0.05$) was observed for those with BMI <21 kg/m^2 who had serum albumin <3.5 g/dL. By contrast, the mortality risk was lower among patients with BMI <21 kg/m^2 who had serum albumin >3.8 g/dL compared with the referent category. Similarly, by using the group of patients who had serum creatinine 7.5–10.5 mg/dL and BMI 21–25 kg/m^2 as referent (Fig. 2C), it was observed that lower BMI (<21 kg/m^2) was associated with an excess mortality risk of 38% (RR = 1.38, $p < 0.05$) among those with serum creatinine <7.5 mg/dL. As observed for the joint effects between BMI and albumin, BMI <21 kg/m^2 was associated with reduction in the risk of death among those with serum creatinine >10.5 mg/dL, compared with the referent group, i.e., patients with BMI 21–25 kg/m^2 and creatinine 7.5–10.5 mg/dL.

Discussion

Using data from hemodialysis patients in 12 countries, our study shows important variations by country in nutritional status indicators. Countries with the lowest values for a specific nutritional indicator were not necessarily the ones with the lowest values for the other indicators. We also found important variations in nutritional indicators by patient characteristics. The adjusted odds of lower concentrations of serum creatinine and serum albumin were higher for patients who were older, female, living in nursing homes, had less than 1 year on dialysis, or had lower Kt/V. Significantly lower nutritional status as indicated by all five assessed measures was observed for patients with gastrointestinal bleeding, neurologic disease, psychological disorders or those receiving hemodialysis by catheter. Another factor associated with several measures of nutritional status was

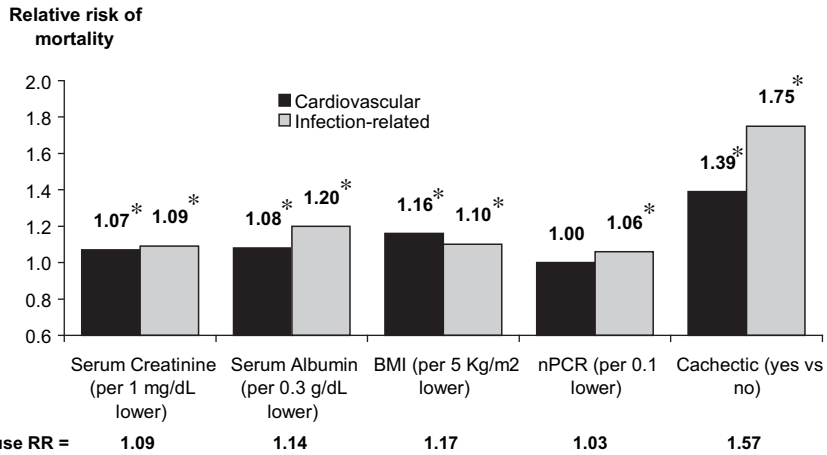

Figure 1. Adjusted relative risks of death due to cardiovascular and infection-related causes associated with nutritional indicators. BMI, body mass index; nPCR, protein catabolic rate; RR, relative risk. Relative risks were adjusted for age, sex, race, vintage, 14 summary comorbidities, neutrophil:lymphocyte ratio and dialysis by catheter. *$p < 0.01$.

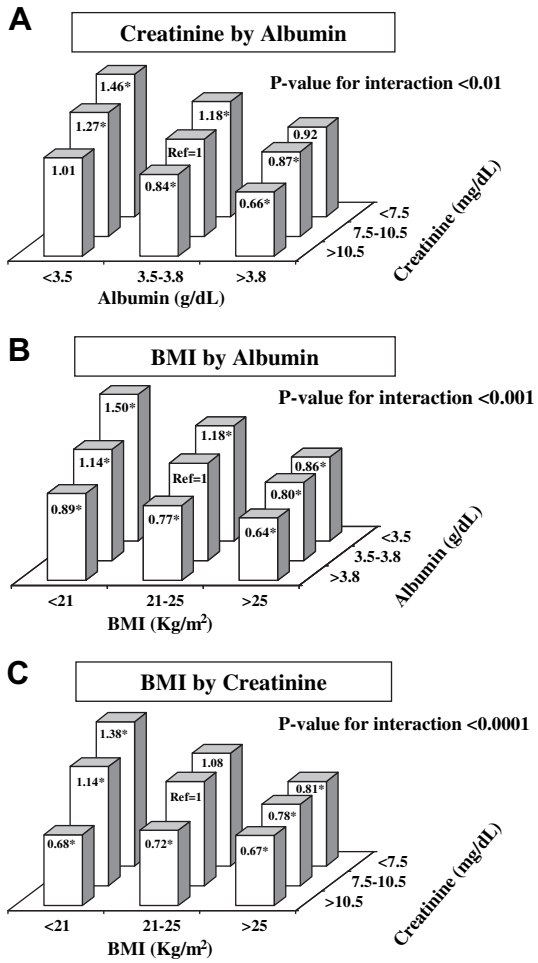

Figure 2. The relative risks of all-cause mortality due to the joint effects of nutritional indictors: A) Creatinine by Albumin, B) BMI by Albumin, C) BMI by Creatinine. Relative risks were adjusted for age, sex, race, vintage, 14 summary comorbidities, neutrophil:lympocyte ratio and dialysis by catheter. *p < 0.05 compared with the referent group; ref = referent group; BMI = body mass index.

neutrophil:lymphocyte ratio that was included in the present study as a proxy for inflammation.[11] Similar to a previous study, higher neutrophil:lymphocyte ratio was associated with lower serum albumin concentration.[8] Additionally, our results suggest that patients with higher neutrophil: lymphocyte ratio have also higher odds of cachexia, lower BMI, and lower serum creatinine concentration.

Differences in the direction of the associations among nutritional indicators and patient characteristics were observed in relation to race and diabetic status. Lower odds of serum creatinine ≤7.7 mg/dL and BMI ≤ 22 kg/m^2 were observed for blacks compared with patients of other races. By contrast, blacks had higher odds of nPCR <1.0 g/kg/day. These findings are consistent with previous studies that have shown higher serum creatinine and BMI but lower nPCR in blacks than in patients of other races.[12–14] The reason for these results on nutritional indicators by race is not clear but may be related to the fact that the various nutritional measures assess different aspects of body composition and are affected differently by factors related to dialysis treatment.[6]

Other interesting findings were the associations between diabetes and nutritional indicators for the total group and by age groups. In the total group, the odds of BMI ≤22 kg/m^2 or being diagnosed as cachectic were lower for diabetics than for nondiabetics. Our results indicate, however, that these results observed for the total group are largely explained by the stronger association of diabetes with lower odds of BMI ≤22 kg/m^2 or cachectic appearance in the age group ≥44 years. As suggested by a study developed in the United States, diabetes as cause of ESRD onset among patients older than 44 years of age is far more likely to be type 2 and rarely type 1.[15] The results regarding the comparisons of nutritional indicators by diabetic status observed in the present study might be explained by the strong associations of obesity with type 2 diabetes, which is more prevalent than type 1 diabetes, particularly among older ESRD patients.[15]

A strict definition of cachexia was not used in the present study. The patients were classified as undernourished or cachectic at enrollment in the study based on their general appearance. Despite the lack of more rigorous diagnostic criteria, cachexia was independently associated with higher mortality risk among patients treated in different regions. By assuming that misclassification of cachexia was nondifferential (random), we can expect that the associations between cachexia and mortality risk could be even stronger than the one described in the present study. A previous DOPPS analysis showed that cachexia appearance was associated, in a dose-response fashion, with lack of appetite, a factor that was found to be strongly associated with higher odds of several other indicators of poorer nutritional status and with higher risk of death.[16] Taken together, these data support the predictive validity of cachectic appearance to identify hemodialysis patients at higher risk of adverse outcomes. The results suggest that variations in the prevalence of cachexia

across regions could be partially explained by differences in patient characteristics. For example, in the unadjusted analysis, the prevalence of cachexia was significantly lower for patients treated in Japan than in the United States. After adjustment for patient characteristics, no significant difference was observed between Japan and the United States in the odds of cachexia.

A previous DOPPS publication found a lower mortality risk among patients treated in Japan than in patients treated in other regions, a finding not fully explained by differences in demographic factors and comorbidities.[17] The present analysis shows that both the mortality rate due to cardiovascular-related causes and the one due to infection-related causes were lower in Japan than in other regions. It is also worth noting that, in addition to the lower mortality risk, Japan displayed significantly stronger associations of nutritional indicators with mortality risk compared to other regions. In the DOPPS stronger associations were also observed between lower scores of health-related quality of life (HRQoL) and higher risk of death among hemodialysis patients treated in Japan than in other regions.[18] The reason for stronger associations of both nutritional markers and HRQoL measures with higher mortality risk in Japan than in other regions is a question for future studies.

Despite variations in nutritional indicators by patient characteristics and country, and the fact that laboratory methodology was not standardized, poorer nutritional status as indicated by each of the study measurements was found to be independently associated with a higher risk of death among patients treated in different regions. Moreover, significant joint effects of nutritional measures on mortality risk were observed. The described joint effects of nutritional indicators illustrate the importance of using more than one measurement of nutritional status to predict the risk of death among hemodialysis patients. Consistent with previous studies in patients on maintenance hemodialysis, lower BMI was associated with higher mortality risk.[1,4,19] The analysis of joint effects, however, suggests that the effect of BMI on mortality risk depends on the status of the patient regarding other nutritional indicators found to be strong risk factors of death in hemodialysis patients, such as serum creatinine and serum albumin.[4,20] It is worth noting that compared with the referent category (i.e., serum creatinine 7.5–10.5 mg/dL and BMI 21–25 kg/m^2), BMI <21 kg/m^2 was associated with lower mortality risk among patients with higher serum creatinine concentration (>10.5 mg/dL) but was associated with a higher mortality risk among those with lower serum creatinine concentration (<7.5 mg/dL). Similarly, the analysis of the joint effects between BMI and albumin showed that lower BMI (as compared with the referent BMI-albumin category) was associated with higher mortality among patients with lower serum albumin but not among those with higher serum albumin concentration. Hypoalbuminemia is strongly associated with higher risk of death among patients on maintenance hemodialysis.[21] Our results indicate, however, that the association between lower serum albumin and higher mortality risk among hemodialysis patients depends on the status of the patient regarding other nutritional indicators, particularly serum creatinine and BMI.

Because the present study is not interventional, it can call attention to potentially modifiable nutritional factors associated with mortality risk but cannot prove if these associations are causal. The reported joint associations of nutritional indicators with mortality risk and variations in nutritional measures across countries and patient characteristics, however, support the KDOQI recommendation for using multiple measurements to assess the nutritional status of patients on maintenance dialysis.[6] The study also shows that there are differences in the strength of the associations between nutritional indicators and mortality risk depending on the specific cause of death. A lower BMI was more strongly associated with higher risk of death due to cardiovascular-related causes than infection-related causes. On the other hand, lower serum creatinine, lower serum albumin, and cachectic appearance were more strongly associated with higher risk of death due to infection-related causes than deaths due to cardiovascular-related causes. The data suggest that lower nPCR is associated with increased mortality risk due to infection-related causes but not to cardiovascular-related causes. Even though nutritional status was determined at the start of the follow-up, it is possible that the disease that caused death also contributed to malnutrition. The role of infection-related disease as a cause of malnutrition at the start of the follow-up should be viewed as more likely for chronic conditions such as HIV/AIDS and tuberculosis. However, the fact that septicemia was

cited for more than half of infection-related death supports the possibility that the infection was more often an acute complication, which is more likely to occur among hemodialysis patients with poorer nutritional status.[22]

Conclusion

This study indicates substantial differences across countries and patient characteristics in the nutritional status of hemodialysis patients, depending on which measurement is used. The study calls attention to the joint effects (interactions) between nutritional measurements on the risk of death among patients on maintenance hemodialysis. These joint effects indicate that the effects of a nutritional indicator on mortality risk may depend on the status of the patient regarding other nutritional measures. The results of the present study in maintenance hemodialysis patients treated in several countries support the use of more than one nutritional measure to improve the prediction of mortality risk, and suggest a greater emphasis on nutritional interventions to improve survival among these patients.

References

1. Lowrie EG, Huang WH, Lew NL: Death risk predictors among peritoneal dialysis and hemodialysis patients: a preliminary comparison. Am J Kidney Dis 26:220-228, 1995

2. Kalantar-Zadeh K, Kopple JD: Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. Am J Kidney Dis 38:1343-1350, 2001

3. Combe C, McCullough KP, Asano Y, et al: Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Dialysis Outcomes and Practice Patterns Study (DOPPS): nutrition guidelines, indicators, and practices. Am J Kidney Dis 44:39-46, 2004

4. Pifer TB, McCullough KP, Port FK, et al: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. Kidney Int 62:2238-2245, 2002

5. Blumenkrantz MJ, Kopple JD, Gutman RA, et al: Methods for assessing nutritional status of patients with renal failure. Am J Clin Nutr 33:1567-1585, 1980

6. Kidney Disease Outcome Quality Initiative: Clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 35:S1-S140, 2000

7. Depner TA, Daugirdas JT: Equations for normalized protein catabolic rate based on two-point modeling of hemodialysis urea kinetics. J Am Soc Nephrol 7:780-785, 1996

8. Thijssen S, Wystrychowski G, Usvyat L, et al: Determinants of serum albumin concentration analyzed in a large cohort of patients on maintenance hemodialysis. J Ren Nutr 17:70-74, 2007

9. Young EW, Goodkin DA, Mapes DL, et al: The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. Kidney Int 57(suppl 74):S74-S81, 2000

10. Pisoni RL, Gillespie BW, Dickinson DM, et al: The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. Am J Kidney Dis 44:7-15, 2004

11. Gomez D, Morris-Stiff G, Toogood GJ, et al: Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. J Surg Oncol 97:513-518, 2008

12. Hsu J, Johansen KL, Hsu CY, et al: Higher serum creatinine concentrations in black patients with chronic kidney disease: beyond nutritional status and body composition. Clin J Am Soc Nephrol 3:992-997, 2008

13. Fleischmann E, Teal N, Dudley J, et al: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int 55:1560-1567, 1999

14. Kaysen GA, Dubin JA, Muller HG, et al: Relationships among inflammation nutrition and physiologic mechanisms establishing albumin levels in hemodialysis patients. Kidney Int 61:2240-2249, 2002

15. Cowie CC, Port FK, Wolfe RA, et al: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 321:1074-1079, 1989

16. Lopes AA, Elder SJ, Ginsberg N, et al: Lack of appetite in haemodialysis patients–associations with patient characteristics, indicators of nutritional status and outcomes in the international DOPPS. Nephrol Dial Transplant 22:3538-3546, 2007

17. Goodkin DA, Young EW, Kurokawa K, et al: Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. Am J Kidney Dis 44:16-21, 2004

18. Mapes DL, Lopes AA, Satayathum S, et al: Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 64:339-349, 2003

19. Leavey SF, McCullough K, Hecking E, et al: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 16: 2386-2394, 2001

20. Lowrie EG, Lew NL: Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 15:458-482, 1990

21. Owen WF Jr, Lew NL, Liu Y, et al: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med 329:1001-1006, 1993

22. Vanholder R, Van Biesen W: Incidence of infectious morbidity and mortality in dialysis patients. Blood Purif 20:477-480, 2002