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Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

Donna L. Mapes, Antonio Alberto Lopes, Sudtida Satayathum, Keith P. McCullough, David A. Goodkin, Francesco Locatelli, Shunichi Fukuhara, Eric W. Young, Kiyoshi Kurokawa, Akira Saito, Jürgen Bommer, Robert A. Wolfe, Philip J. Held, and Friedrich K. Port

Amgen, Inc., Thousand Oaks, California; Department of Medicine, Federal University of Bahia, Bahia, Brazil; University Renal Research and Education Association (URREA), Ann Arbor, Michigan; Division of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy; Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; Department of Veterans Affairs Medical Center and Division of Nephrology, University of Michigan, Ann Arbor, Michigan; Tokai University School of Medicine, Bohseidai Isehara, Kanagawa, Japan; Department of Nephrology, University of Heidelberg, Heidelberg, Germany; and Kidney Epidemiology and Cost Center and Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan

Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS).

Background. We investigated whether indicators of health-related quality of life (HRQOL) may predict the risk of death and hospitalization among hemodialysis patients treated in seven countries, taking into account serum albumin concentration and several other risk factors for death and hospitalization. We also compared HRQOL measures with serum albumin regarding their power to predict outcomes.

Methods. We analyzed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, prospective, observational study of randomly selected hemodialysis patients in the United States (148 facilities), five European countries (101 facilities), and Japan (65 facilities). The total sample size was composed of 17,236 patients. Using the Kidney Disease Quality of Life Short Form (KDQOL-SF™), we determined scores for three components of HRQOL: (*1*) physical component summary (PCS), (*2*) mental component summary (MCS), and (*3*) kidney disease component summary (KDCS). Complete responses on HRQOL measures were obtained from 10,030 patients. Cox models were used to assess associations between HRQOL and the risk of death and hospitalization, adjusted for multiple sociodemographic variables, comorbidities, and laboratory factors.

Results. For patients in the lowest quintile of PCS, the adjusted risk (RR) of death was 93% higher (RR = 1.93, $P < 0.001$) and the risk of hospitalization was 56% higher (RR = 1.56, $P < 0.001$) than it was for patients in the highest quintile level. The adjusted relative risk values of mortality per 10-point lower HRQOL score were 1.13 for MCS, 1.25 for PCS, and 1.11 for KDCS. The corresponding adjusted values for RR for first hospitalization were 1.06 for MCS, 1.15 for PCS, and 1.07 for KDCS. Each RR differed significantly from 1 ($P < 0.001$). For 1 g/dL lower serum albumin concentration, the RR of death adjusted for PCS, MCS, and KDCS and the other covariates was 1.17 ($P < 0.01$). Albumin was not significantly associated with hospitalization (RR = 1.03, $P > 0.5$).

Conclusion. Lower scores for the three major components of HRQOL were strongly associated with higher risk of death and hospitalization in hemodialysis patients, independent of a series of demographic and comorbid factors. A 10-point lower PCS score was associated with higher elevation in the adjusted mortality risk, as was a 1 g/dL lower serum albumin level. More research is needed to assess whether interventions to improve quality of life lower these risks among hemodialysis patients.

Key words: DOPPS, end-stage renal disease (ESRD), hemodialysis, hospitalization, mortality, quality of life.

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The concept of health-related quality of life (HRQOL) takes into account patient well-being as expressed by both the physical and psychologic (or mental) domains of health. HRQOL may be affected by several factors, including the clinical manifestations of diseases, the side effects of treatments, and the quality of the relationships of the patient with family members and health care providers [1]. In addition to providing information about individual well-being at a given moment, the assessment of HRQOL may help identify an individual's risk for certain outcomes. Impaired quality of life may be a cause or a marker of developing cardiovascular disorders and other important outcomes, such as death and hospitalization [2–5].

There is evidence that HRQOL predicts outcomes among hemodialysis patients [6, 7]. A study of 1000 patients at three dialysis facilities in the United States reported an association between lower scores in the physical component of quality of life and higher risk of death and hospitalization at least until the next 24 months [6]. A larger study, involving 5256 patients at 243 dialysis facilities in the United States and Europe, presented evidence that the psychologic or mental components of quality of life predict death and hospitalization in hemodialysis patients [8]. Self-reported depression, as assessed by questions from the mental health scale of the Kidney Disease and Quality of Life Short Form (KDQOL-SF™) [9], was significantly associated with a higher risk of death and hospitalization, even after taking into account serum albumin concentration and several other risk factors.

This study provides additional evidence of the relationships between HRQOL and hemodialysis outcomes. It was developed to verify whether different components of HRQOL are associated with the risks of death and hospitalization among hemodialysis patients. We also compared HRQOL and serum albumin regarding predictive power for death and hospitalization.

METHODS

The data used for the analysis were from the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, prospective, observational study of hemodialysis practice patterns and associated outcomes [10, 11]. Nationally representative samples of dialysis facilities were recruited in five European countries (France, Germany, Italy, Spain, and the United Kingdom), Japan, and the United States. Within each participating facility, study patients were randomly selected, and, within each country, the appropriate Institutional Review Boards approved the study. Informed patient consent was obtained in accordance with local requirements. The overall design of the DOPPS has been published previously [10].

The present study included data from 148 facilities in the United States, 101 facilities in Europe, and 65 facilities in Japan, with a total sample size of 17,236 patients (10,030 with complete information on HRQOL measures). The data regarding HRQOL, sociodemographic factors, comorbidities, laboratory values, and treatment factors were collected at patient entry into the study. Data collection began in 1997 in the United States, 1998 in Europe, and 1999 in Japan. Patients were replaced as they left participating facilities for reasons of death, transplantation, change in treatment modality, withdrawal from dialysis, recovery of renal function, or transfer to another facility.

The patient responses to the KDQOL-SF were used to determine scores of the kidney disease component summary (KDCS), the mental component summary (MCS) and the physical component summary (PCS). The scales for MCS and PCS were derived from eight different subscales, originally developed for the SF-36 Short-Form Health Survey (SF-36): (*1*) physical functioning, (*2*) role-physical, (*3*) bodily pain, (*4*) general health, (*5*) vitality, (*6*) social functioning, (*7*) role-emotional, and (*8*) mental health [12].

The questions used for the KDCS are not part of the SF-36. They were included in the KDQOL-SF to take into account particular health-related concerns of individuals with kidney diseases and end-stage renal disease (ESRD) patients treated by dialysis [9]. The scale for the KDCS was derived by 11 subscales [9]: (*1*) symptoms/problems (muscle soreness, chest pain, cramps, itchy skin, shortness of breath, faintness or dizziness, lack of appetite, and problems with vascular access), (*2*) effects of kidney disease on daily life, (*3*) burden of kidney disease, (*4*) work status, (*5*) cognitive function, (*6*) quality of social interaction, (*7*) sexual function, (*8*) sleep, (*9*) social support, (*10*) dialysis staff encouragement, and (*11*) patient satisfaction. Because of the weighting used, the scales of the PCS ranged from −1.73 to 76.28 and the MCS scales ranged from −1.27 to 80.74. For KDCS, the scales ranged from 0 to 100.

Statistical methods

All analyses were performed within the population groups (United States, Europe, and Japan) as well as overall. Cox models were used to estimate the relative risk (RR) of the two patient outcomes (death and first hospitalization after initiation of the study) for every 10-point lower score of each of the three quality-of-life components and their subscales. In one set of models, all patients were included, independent of the duration of the follow-up. For the other two sets of models, restrictions were made based on duration of follow-up in order to evaluate the disjoint short-term versus long-term effects. One set looked at follow-up censored at 6 months; the other set considered only patients with follow-up >6 months. Models were developed to assess the association between HRQOL and outcomes in subgroups as defined by age (<60 years versus ≥ 60 years), region (United States, Europe, and Japan), time on dialysis at study start (3 months or less, 4 months to less than 1 year, 1 year to less than 2 years, and 2 or more years), and serum albumin level (<3.5 g/dL, 3.5 to 3.9 g/dL, and ≥ 4 g/dL). Cox adjusted RR values for death and hospitalization were estimated by comparing quintiles of HRQOL scores, using the highest quintile as referent. Similar models were used to assess the RR of death and hospitalization by quintiles of albumin. Missing data were handled with indicator variables.

The models were stratified by country of hemodialysis treatment and diabetes and adjusted for age, gender, socioeconomic factors, body mass index (BMI), predialysis systolic blood pressure, treatment with epoetin, dial-

ysis dose by the equilibrated Kt/V (eKt/V) [13], type of vascular access, laboratory tests, comorbidities, and time on dialysis [14]. The following laboratory factors and comorbidities were included in the Cox models: predialysis serum albumin, creatinine, phosphorus and hemoglobin concentrations, normalized protein catabolic rate (nPCR), coronary artery disease, congestive heart failure, other cardiac disorders (cardiac arrest, arrhythmia, permanent pacemaker, pericarditis, prosthetic heart valve), hypertension, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, lung disease, cancer (excluding skin cancer), infection with the human immunodeficiency virus or AIDS, gastrointestinal bleeding, neurologic disease (seizure, dementia, organic brain syndrome, Parkinson's disease), psychiatric disease, recurrent cellulitis, and dyspnea. The following socioeconomic variables were included in the regression models: living status (living alone, living with family/friends, living in nursing home, homeless/prisoner), marital status (married or not), education (high school or lower grade, attended college), employment status (for ages 18 to 60 years), and yearly household income (less than $5,000; $5,001 to $10,000; $10,001 to $20,000; $20,001 to $40,000; $40,001 to $75,000 and more than $75,000). Equivalent income categories were provided on the European and Japanese questionnaires based on United States monetary exchange rates in 1998 for Europe, and exchange rates in 1999 for Japan. All statistical analyses were performed using SAS software, version 8 [15].

RESULTS

Baseline characteristics

Among 17,236 patients included in DOPPS, 10,030 (58.2%) completed all the questions of the KDQOL-SF. The percentages of patients with complete responses to the KDQOL-SF in Europe, Japan, and the United States were, respectively, 74.8% ($N = 4591$), 68.5% ($N = 2784$), and 47.6% ($N = 9861$). Tables 1 and 2 show the distribution, within the DOPPS sample, of baseline characteristics that were used in the adjusted Cox models, both for the whole sample and stratified by patients with complete or incomplete response to the KDQOL-SF. In the whole sample, the mean age of the patients was 60.5 ± 15.2 years. Males were 57.4% of the sample. Approximately half of the patients were receiving dialysis for less than 1 year, 38% had diabetes mellitus, and 21% were reported as having psychiatric disorders. Patients who did not complete all items of the KDQOL-SF were significantly older ($P < 0.001$) and had lower levels of albumin, creatinine, hemoglobin, and nPCR. These patients also had a significantly shorter time on dialysis therapy ($P < 0.001$), lower levels of BMI, lower predialysis systolic blood pressure, lower eKt/V, and higher prevalence of several comorbidities.

Comparisons of death and hospitalization risks by patient response to the KDQOL-SF

We also compared patients who answered all questions on the KDQOL-SF ($N = 10,030$) with those patients who provided an incomplete response or no response ($N = 7206$). For the latter group, the risk of death was more than two times higher (RR = 2.51, 95% CI = 2.35 to 2.69, $P < 0.001$) and the risk of hospitalization was 33% higher (RR = 1.33, 95% CI = 1.26 to 1.41, $P < 0.001$) compared with patients who responded to all items. These associations remained statistically significant even after adjustment for sociodemographic variables, laboratory values, comorbidities, treatment factors, time on dialysis, and country. The adjusted risk of death was 40% higher for patients who did not complete all items of the questionnaire than for those who did (RR = 1.40, 95% CI = 1.29 to 1.51, $P < 0.001$). The adjusted risk of hospitalization was estimated as 12% higher for those who did not respond to all questions on the KDQOL questionnaire (RR = 1.12, 95% CI = 1.04 to 1.20, $P = 0.003$).

Relative risks of death and hospitalization per 10-point lower HRQOL score and 1 g/dL lower serum albumin concentration

As shown in Table 3, HRQOL was found to be significantly associated with the risk of death and hospitalization ($P < 0.001$). The increase in the unadjusted mortality risk for each 10-point lower HRQOL score was 47% for PCS (RR = 1.47; 95% CI = 1.41 to 1.54), 16% for MCS (RR = 1.16; 95% CI = 1.12 to 1.21), and 15% for KDCS (RR = 1.15; 95% CI = 1.11 to 1.18). For each 10-point lower HRQOL score, the mortality risk (stratified by country and diabetes and adjusted for the covariates listed in Table 1) increased 25% for the PCS (RR = 1.25; 95% CI = 1.20 to 1.30), 13% for the MCS (RR = 1.13; 95% CI = 1.09 to 1.17), and 11% for KDCS (RR = 1.11; 95% CI = 1.08 to 1.13). For hospitalization, the unadjusted RR values for each 10-point lower HRQOL score were 1.25 (95% CI = 1.21 to 1.28) for PCS, 1.09 (95% CI = 1.07 to 1.11) for MCS, and 1.10 (95% CI = 1.08 to 1.13) for KDCS. The adjusted RR values were 1.15 (95% CI = 1.12 to 1.19) for PCS, 1.06 (95% CI = 1.04 to 1.08) for MCS, and 1.07 (95% CI = 1.05 to 1.09) for KDCS.

The associations between HRQOL and outcomes were stronger in Japan than in Euro-DOPPS or the United States, with the highest RR observed for PCS (Table 3). The adjusted RR for the association between PCS and mortality was approximately 37% higher in Japan than the United States and 33% higher in Japan than Euro-DOPPS. In Japan, the adjusted RR of hospitalization related to PCS was approximately 22% higher compared with the United States and 12% higher com-

Table 1. Sociodemographic variables and years on dialysis at study start[a]

	All (N = 17,236)	Filled out entire KDQOL-SF: Yes (N = 10,030)	Filled out entire KDQOL-SF: No (N = 7206)	P value
Age *years*	60.5 ± 15.2	58.9 ± 14.9	62.8 ± 15.3	<0.0001
Male	57.4	57.6	56.9	0.5885
Median years on dialysis	1.04	1.48	0.43	<0.0001
Socioeconomic factors[b]				
Yearly income[c]				<0.0001
<$5000	13.9	13.6	16.8	
$5001–$10,000	26.3	26.3	27.8	
$10,001–$20,000	27.5	27.6	27.5	
$20,001–$40,000	21.6	21.9	20.2	
$40,001–$75,000	7.9	7.9	8.1	
>$75,000	2.8	2.7	3.5	
Education				<0.0001
High school or less	60.0	63.9	54.2	
Attended college	40.0	36.1	45.8	
Occupational status				<0.0001
Employed	17.2	20.2	11.9	
Retired	38.5	36.8	41.4	
Disabled	18.9	17.1	22.2	
Unemployed	9.8	9.2	10.9	
Homemaker, never employed	15.5	16.7	13.6	
Living status				<0.0001
Living alone	14.8	14.7	14.9	
Living with family/friends	79.2	82.0	75.0	
Living in nursing home	5.7	3.1	9.7	
Homeless/prisoner	0.3	0.2	0.3	

KDQOL-SF is Kidney Disease Quality of Life-Short Form.

[a] Results are represented by the mean ± SD or %, unless specified to be median. The yes column indicates the sample used for the analysis.

[b] Data on income, education, occupational status, and social support indicators were unknown or missing for 57.8%, 5.0%, 23.7%, and 4.1% of the patients, respectively

[c] Yearly income was collected on the same patient questionnaire on which quality of life was based. These percentages represent the patients who completed this part, but not the entire patient questionnaire.

pared with Euro-DOPPS. The PCS scores were also significantly higher among patients from Japan than those from Euro-DOPPS and the United States ($P < 0.001$). The associations between HRQOL scores and the two outcomes, death and hospitalization, were similar in the United States and Euro-DOPPS.

Table 3 also shows the RRs of death and hospitalization per 1 g/dL lower concentration of serum albumin, using Cox models adjusted for the variables listed in Tables 1 and 2 and all three summary measures of HRQOL (PCS, MCS, and KDCS). As observed for the HRQOL summary measures, the associations between albumin and adverse outcomes were stronger in Japan than in the other treatment locations. A 10-point lower PCS was associated with similar or higher elevation in the adjusted mortality risk, as was a 1 g/dL lower serum albumin level. Albumin was not significantly associated with the adjusted risk of hospitalization in models that included all three HRQOL summary measures.

In models adjusted for all variables listed in Tables 1 and 2, but not for HRQOL measures, a lower level of albumin was significantly ($P < 0.001$) associated with a higher risk of death and marginally significantly associated with hospitalization ($P = 0.05$) among patients who have completed the KDQOL-SF. Among this same group of respondents to the KDQOL-SF, the adjusted (not adjusted for HRQOL measures) RRs of death and hospitalization per 1 g/dL lower concentration of serum albumin were 1.20 (95% CI = 1.08 to 1.33) and 1.08 (95% CI = 1.00 to 1.16), respectively. Among patients who did not complete the KDQOL-SF, the lower level of albumin was significantly associated with death ($P < 0.001$) and hospitalization ($P = 0.003$); in this group of nonrespondents to the KDQOL-SF, the RR per 1 g/dL lower concentration of albumin was 1.22 (95% CI = 1.11 to 1.35) for death and 1.12 (95% CI = 1.04 to 1.22) for hospitalization (these results are not shown in the table). The RRs of the associations between albumin level and outcomes (death and hospitalization) did not differ significantly between patients who completed all questions of the KDQOL-SF and those who did not ($P > 0.1$).

The associations of lower HRQOL scores with higher risks of death and hospitalization were not significantly different between patients younger than 60 years of age and those 60 years or older. Likewise, adjusted RR values did not differ significantly among those with serum albumin <3.5 g/dL, 3.5 to 3.9 g/dL, and ≥4 g/dL. Similarly, the adjusted associations between HRQOL and outcomes did not vary significantly by time on dialysis: ≤3 months, 4 months to less than 1 year, 1 year to less than 2 years, and 2 or more years (data not shown).

Table 2. Treatment, laboratory and comorbidity factors at study start[a]

	All (N = 17,236)	Filled out entire KDQOL-SF: Yes (N = 10,030)	Filled out entire KDQOL-SF: No (N = 7,206)	P value
Albumin *g/dL*[b]	3.6 ± 0.6	3.7 ± 0.5	3.5 ± 0.6	<0.0001
Creatinine *mg/dL*[b]	9.1 ± 3.4	9.5 ± 3.3	8.4 ± 3.5	<0.0001
Phosphorus *mg/dL*[b]	5.7 ± 1.9	5.8 ± 5.6	5.6 ± 2.0	<0.0001
Hemoglobin *g/dL*[b]	10.2 ± 1.7	10.3 ± 1.7	10.2 ± 1.7	<0.0001
Epoetin *U/kg/week*	162 ± 123	147 ± 115	185 ± 131	<0.0001
Predialysis systolic blood pressure *mm Hg*	150 ± 26	151 ± 25	149 ± 26	<0.0001
Body mass index	24.0 ± 5.4	24.0 ± 5.3	24.1 ± 5.5	<0.0001
eKt/V	1.19 ± 0.29	1.20 ± 0.28	1.17 ± 0.29	0.0126
nPCR	1.03 ± 0.28	1.04 ± 0.28	0.99 ± 0.97	<0.0001
Coronary heart disease	38.3	34.4	43.7	<0.0001
Congestive heart failure	33.8	29.5	39.9	<0.0001
Other cardiac disorders	30.8	29.8	32.3	0.0007
Hypertension	75.3	76.1	74.2	<0.0001
Cerebrovascular disease	16.1	13.4	19.8	<0.0001
Peripheral vasculopathy	22.0	19.5	25.6	<0.0001
Diabetes mellitus	37.8	33.9	43.0	<0.0001
Lung disease	10.7	9.3	12.6	<0.0001
Cancer, excluding skin	9.8	8.9	11.1	0.0003
HIV	0.8	0.6	1.1	0.0403
Gastrointestinal bleeding	7.0	5.9	8.5	<0.0001
Neurologic disease	8.4	6.5	11.0	<0.0001
Psychiatric disease	20.9	18.9	23.8	<0.0001
Recurrent cellulitis	7.3	5.9	9.2	<0.0001
Dyspnea	25.3	22.1	29.7	<0.0001
Type of vascular access				<0.0001
Fistula	54.7	62.5	42.1	
Graft	24.0	22.1	27.0	
Permanent catheter	12.0	8.6	17.4	
Temporary catheter	9.3	6.8	13.4	

Abbreviations are: eKt/V, equilibrated Kt/V; nPCR, normalized protein catabolic rate; HIV, seropositive for the human immunodeficiency virus; KDQOL-SF, Kidney Disease Quality of Life-Short Form.

[a]Results are represented by the mean ± SD or %

[b]Values are predialysis at study start

Table 3. Relative risk (RR) of death and hospitalization per 10-point lower HRQOL score and 1 g/dL lower serum albumin concentration, by total group and treatment location

HRQOL measure	Mean ± SD	RR of death (95% CI): Unadjusted	RR of death (95% CI): Adjusted	RR of hospitalization (95% CI): Unadjusted	RR of hospitalization (95% CI): Adjusted
Total group					
MCS	44.9 ± 11.9	1.16 (1.12–1.21)[c]	1.13 (1.09–1.17)[c]	1.09 (1.07–1.11)[c]	1.06 (1.04–1.08)[c]
PCS	35.3 ± 10.8	1.47 (1.41–1.54)[c]	1.25 (1.20–1.30)[c]	1.25 (1.21–1.28)[c]	1.15 (1.12–1.19)[c]
KDCS	63.5 ± 13.0	1.15 (1.11–1.18)[c]	1.11 (1.08–1.15)[c]	1.10 (1.08–1.13)[c]	1.07 (1.05–1.09)[c]
Albumin	3.64 ± 0.57	1.43 (1.31–1.57)[c]	1.17 (1.05–1.30)[b]	1.23 (1.15–1.32)[c]	1.03 (0.95–1.11)
Europe					
MCS	42.7 ± 11.8	1.15 (1.07–1.24)[c]	1.09 (1.02–1.17)[a]	1.08 (1.04–1.13)[c]	1.04 (1.00–1.08)
PCS	35.5 ± 10.5	1.60 (1.46–1.74)[c]	1.24 (1.13–1.37)[c]	1.28 (1.22–1.34)[c]	1.19 (1.13–1.25)[c]
KDCS	62.8 ± 12.5	1.17 (1.11–1.24)[c]	1.10 (1.03–1.17)[b]	1.11 (1.07–1.15)[c]	1.06 (1.02–1.11)[b]
Albumin	3.84 ± 0.59	1.50 (1.25–1.80)[c]	1.23 (0.98–1.54)	1.26 (1.12–1.42)[c]	1.06 (0.95–1.20)
Japan					
MCS	44.5 ± 11.5	1.34 (1.07–1.67)[b]	1.14 (0.92–1.43)	1.16 (1.09–1.24)[c]	1.08 (1.02–1.14)[b]
PCS	41.7 ± 9.0	2.36 (1.91–2.93)[c]	1.66 (1.27–2.16)[c]	1.55 (1.41–1.69)[c]	1.33 (1.21–1.47)[c]
KDCS	65.5 ± 11.8	1.47 (1.22–1.76)[c]	1.24 (1.02–1.51)[a]	1.24 (1.17–1.32)[c]	1.13 (1.06–1.21)[c]
Albumin	3.77 ± 0.43	2.96 (1.87–4.68)[c]	1.43 (0.80–2.54)	1.67 (1.24–2.25)[c]	1.19 (0.88–1.61)
United States					
MCS	46.5 ± 11.8	1.16 (1.11–1.21)[c]	1.13 (1.08–1.17)[c]	1.08 (1.05–1.11)[c]	1.05 (1.02–1.08)[c]
PCS	32.7 ± 10.6	1.41 (1.34–1.48)[c]	1.21 (1.16–1.27)[c]	1.17 (1.13–1.21)[c]	1.09 (1.04–1.13)[c]
KDCS	63.2 ± 13.7	1.13 (1.09–1.16)[c]	1.10 (1.06–1.14)[c]	1.07 (1.04–1.10)[c]	1.05 (1.02–1.08)[b]
Albumin	3.54 ± 0.56	1.41 (1.28–1.55)[c]	1.16 (1.02–1.31)[a]	1.18 (1.08–1.28)[c]	0.99 (0.90–1.09)

Abbreviations are: HRQOL, health-related quality of life; MCS, mental component summary; PCS, physical component summary; KDCS, kidney disease component summary; CI, confidence interval.

[a]$P < 0.05$

[b]$P < 0.01$

[c]$P < 0.001$

Table 4. Adjusted[a] relative risk (RR) of death and hospitalization per 10-point lower score for PCS, MCS, and KDCS, with all three health-related summary measures of HRQOL in the Cox models

HRQOL measure	RR of death (95% CI)		RR of hospitalization (95% CI)	
	Not adjusted for albumin	Adjusted for albumin	Not adjusted for albumin	Adjusted for albumin
PCS	1.29 (1.23–1.35)[c]	1.29 (1.23–1.35)[c]	1.15 (1.11–1.19)[c]	1.15 (1.11–1.18)[c]
MCS	1.13 (1.08–1.18)[c]	1.13 (1.08–1.18)[c]	1.05 (1.02–1.08)[c]	1.05 (1.02–1.08)[b]
KDCS	0.98 (0.94–1.02)	0.98 (0.94–1.02)	1.00 (0.97–1.03)	1.00 (0.97–1.03)

Abbreviations are: HRQOL, health-related quality of life; MCS, mental component summary; PCS, physical component summary; KDCS, kidney disease component summary; CI, confidence interval.

[a] All Cox models were adjusted for the summary measures of HRQOL and the variables listed in Tables 1 and 2

[b] $P < 0.01$

[c] $P < 0.001$

Associations between HRQOL and outcomes, restricted by follow-up duration

In the models restricted to patients censored at 6 months and patients with more than 6 months of follow-up, RR values were similar to values in the unrestricted models (Table 3), for both death and hospitalization. For each 10-point reduction in score in the 6-month censored models, the adjusted RR values for death were 1.33 (95% CI = 1.23 to 1.43) for PCS, 1.17 (95% CI = 1.09 to 1.25) for MCS, and 1.15 (95% CI = 1.08 to 1.22) for KDCS. For hospitalization, the corresponding values of RR for PCS, MCS and KDCS were 1.18 (95% CI = 1.14 to 1.23), 1.08 (95% CI = 1.05 to 1.12), and 1.08 (95% CI = 1.05 to 1.11), respectively. Each RR value was statistically significant for $P = 0.001$. In the models restricted by >6 months of follow-up, the adjusted RR values for death were 1.26 (95% CI = 1.20 to 1.32, $P < 0.001$) for PCS, 1.14 (95% CI = 1.10 to 1.19, $P < 0.001$) for MCS, and 1.12 (95% CI = 1.08 to 1.16, $P < 0.001$) for KDCS. For hospitalization the corresponding RR values for PCS, MCS, and KDCS were 1.13 (95% CI = 1.08 to 1.17, $P < 0.001$), 1.04 (95% CI = 1.00 to 1.07), and 1.07 (95% CI = 1.04 to 1.11), respectively.

Associations between HRQOL and outcomes with the inclusion of more than one summary measure in the Cox models, with and without the inclusion of albumin

In Cox models adjusted for all variables listed in Tables 1 and 2 (except albumin), and with the inclusion of all three summary measures of HRQOL (MCS, PCS, and KDCS), both PCS and MCS were significantly related to death and hospitalization (Table 4). For every 10-point lower PCS score, the risk of death increased by 29% (RR = 1.29; 95% CI = 1.23 to 1.35, $P < 0.001$) and the risk of hospitalization increased by 15% (RR = 1.15; 95% CI = 1.11 to 1.19, $P < 0.001$). The RRs of death and hospitalization related to 10-point lower MCS score were 1.13 (95% CI = 1.09 to 1.18, $P < 0.001$) and 1.05 (95% CI = 1.02 to 1.08, $P = 0.002$), respectively. Significant associations with outcomes were not observed for KDCS in models simultaneously adjusted for MCS and PCS.

The inclusion of albumin in the Cox models that included all three HRQOL summary measures did not change the RRs of death and hospitalization (Table 4). In these models, PCS and MCS remained significantly associated with death and hospitalization and no association was observed between KDCS and the outcomes. By contrast, KDCS was significantly associated with mortality risk in models where it was included with only one other indicator of HRQOL (either PCS or MCS). KDCS was also significantly associated with hospitalization in the model that included PCS but not in the model that included MCS.

Adjusted relative risks of death and hospitalization for KDQOL-SF subscales

Table 5 shows the adjusted RR of death and hospitalization for every 10-point lower HRQOL score for the 19 subscales of the KDQOL-SF. Each of the eight subscales that make up PCS and MCS scores were significantly and independently associated with death and hospitalization ($P < 0.05$). The adjusted RR per 10-point lower HRQOL score varied from 1.02 to 1.10. For the KDCS, the following subscales were significantly and independently associated with both mortality and hospitalization: symptoms/problems, effects of kidney disease on daily life, burden of kidney disease, work status, cognitive function, quality of social interaction, and sleep. Diminished sexual function, social support, and dialysis staff encouragement were significantly associated with risk of mortality but not of hospitalization. Patient satisfaction was not independently associated with either mortality or hospitalization.

Associations between HRQOL components (by quintiles) and outcomes, adjusted for albumin

Figure 1 shows the RRs for associations between HRQOL and the risk of mortality and hospitalization by quintiles of the scores of each HRQOL component, adjusted for the variables listed in Tables 1 and 2, including albumin. The highest quintile was used as reference. Both mortality and hospitalization increased significantly

Table 5. Adjusted relative risk (RR) of death and hospitalization per 10-point lower scores for mental component summary (MCS), physical component summary (PCS), and kidney disease component summary (KDCS) subscales

Subscales	RR of death (95% CI)	RR of hospitalization (95% CI)
For the physical and mental component summaries		
Physical functioning	1.10 (1.08–1.11)[c]	1.05 (1.04–1.06)[c]
Role—physical	1.03 (1.02–1.05)[c]	1.02 (1.02–1.03)[c]
Bodily pain	1.06 (1.04–1.08)[c]	1.05 (1.04–1.06)[c]
General health	1.10 (1.07–1.12)[c]	1.05 (1.04–1.07)[c]
Vitality	1.09 (1.07–1.12)[c]	1.05 (1.04–1.06)[c]
Social functioning	1.07 (1.05–1.09)[c]	1.03 (1.02–1.04)[c]
Role—emotional	1.03 (1.02–1.04)[c]	1.02 (1.01–1.03)[c]
Mental health	1.07 (1.05–1.09)[c]	1.04 (1.03–1.06)[c]
For the kidney disease component summary		
Symptoms/problems	1.08 (1.05–1.10)[c]	1.07 (1.06–1.09)[c]
Effects of kidney disease on daily life	1.05 (1.03–1.07)[c]	1.04 (1.02–1.05)[c]
Burden of kidney disease	1.04 (1.02–1.05)[c]	1.03 (1.01–1.04)[c]
Work status	1.02 (1.00–1.04)[a]	1.02 (1.01–1.03)[c]
Cognitive function	1.05 (1.03–1.08)[c]	1.02 (1.01–1.04)[b]
Quality of social interaction	1.03 (1.01–1.05)[b]	1.03 (1.01–1.04)[b]
Sexual function	1.02 (1.00–1.04)[a]	1.01 (1.00–1.02)
Sleep	1.05 (1.03–1.07)[c]	1.04 (1.02–1.05)[c]
Social support	1.02 (1.00–1.03)[b]	1.00 (0.99–1.01)
Dialysis staff encouragement	1.02 (1.01–1.04)[b]	1.01 (1.00–1.02)
Patient satisfaction	1.01 (0.99–1.03)	1.00 (0.99–1.02)

[a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$

from the highest to the lowest quintiles of the HRQOL component scores (P values for trend <0.001). For the PCS score, the adjusted risk of death was 93% higher (RR = 1.93) for patients in the lowest quintile (scores <25) compared with the highest quintile (scores >46). The adjusted risk of hospitalization was 56% higher (RR = 1.56) when comparing patients in the lowest and highest quintiles.

Adjusted relative risk of adverse outcome by quintiles of albumin and HRQOL summary measures, without adjustment for albumin

Figure 2 displays Cox-adjusted RR values of death and hospitalization by quintiles of each of the three HRQOL components and albumin, using the highest quintile as the referent category. Table 6 shows the range values of the quintiles and RR with the respective 95% CIs that were used for Figure 2. Only the data regarding patients with complete information for albumin and HRQOL were included in these Cox models. The RR values for the HRQOL components were adjusted for all covariates, except for albumin. PCS was the variable most strongly associated with both mortality and hospitalization.

DISCUSSION

This large international study shows highly significant associations between lower HRQOL scores and higher risk of death and hospitalization among hemodialysis patients. These inverse associations between HRQOL and outcomes were observed for all three components of the KDQOL-SF (i.e., MCS, PCS, and KDCS). These associations remained statistically significant after adjustment for several risk factors of death or hospitalization, including serum albumin concentration, sociodemographic characteristics, years on dialysis, type of vascular access, several comorbidities, and treatment factors [16–19]. Moreover, the adjusted associations between HRQOL and outcomes were similar among several subgroups, as defined by age (<60 years versus ≥60 years), albumin levels (<3.5 g/dL, 3.5 to 3.9 g/dL, and ≥4 g/dL), and time on dialysis (3 months or less, 4 months to less than 1 year, 1 year to less than 2 years, and 2 or more years). It should be noted, however, that the association between HRQOL and death was much stronger than the associations between HRQOL and hospitalization.

The adjusted associations between lower PCS score and higher risks of death and hospitalization differed by treatment location, being stronger in Japan than in Europe or the United States. The HRQOL scores varied less within Japan than within Europe or the United States. Thus, it is possible that a 10-point decrement represents a more profound deterioration of quality of life among Japanese patients and hence is associated with increased risk of adverse outcomes. It is important to assess whether variation in access to health care and in quality of care across dialysis facilities within each region (i.e., Japan, United States, and Europe) influences these findings.

PCS was the HRQOL component most strongly associated with both death and hospitalization. Patients in the lowest quintile of PCS had 93% higher adjusted risk

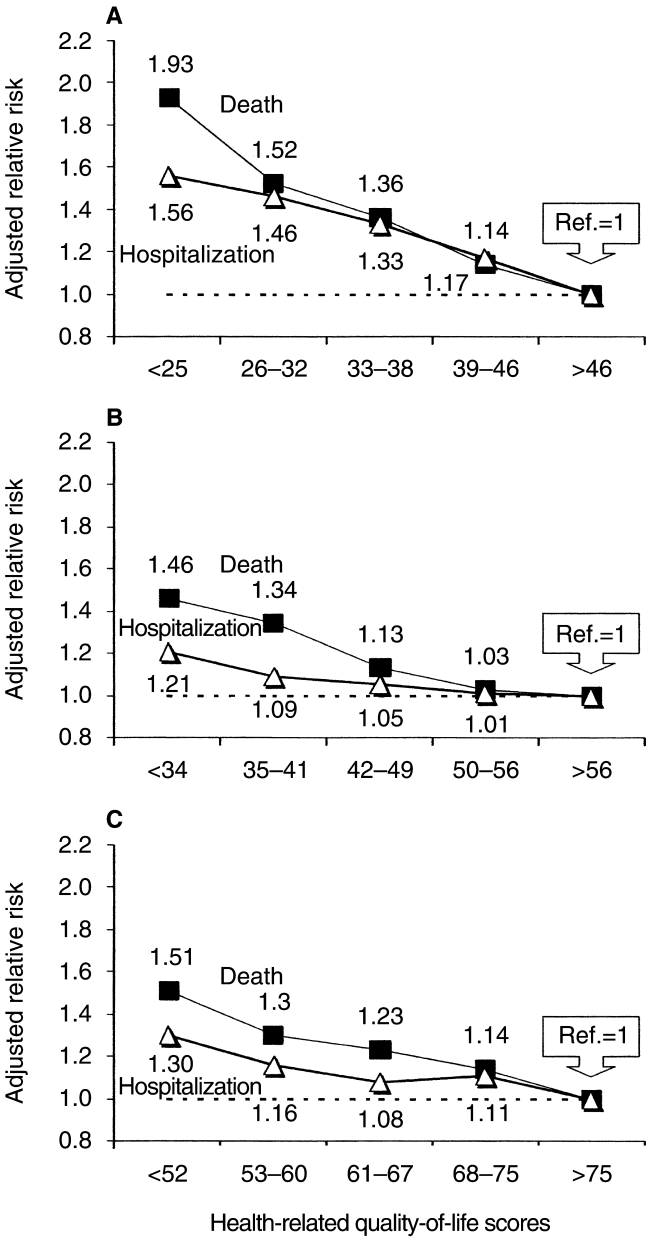

Fig. 1. Relative risks of death (■) and first hospitalization (Δ) by quintile of scores for each component of health-related quality of life (HRQOL), adjusted for all variables in Tables 1 and 2, including albumin, stratified by country and diabetes. The highest quintile is used as the reference group. For all six lines, there was a statistically significant trend (each $P < 0.001$) for the risks of both outcomes to increase with lower scores. (*A*) Physical component summary (PCS). (*B*) Mental component summary (MCS). (*C*) Kidney disease component summary (KDCS).

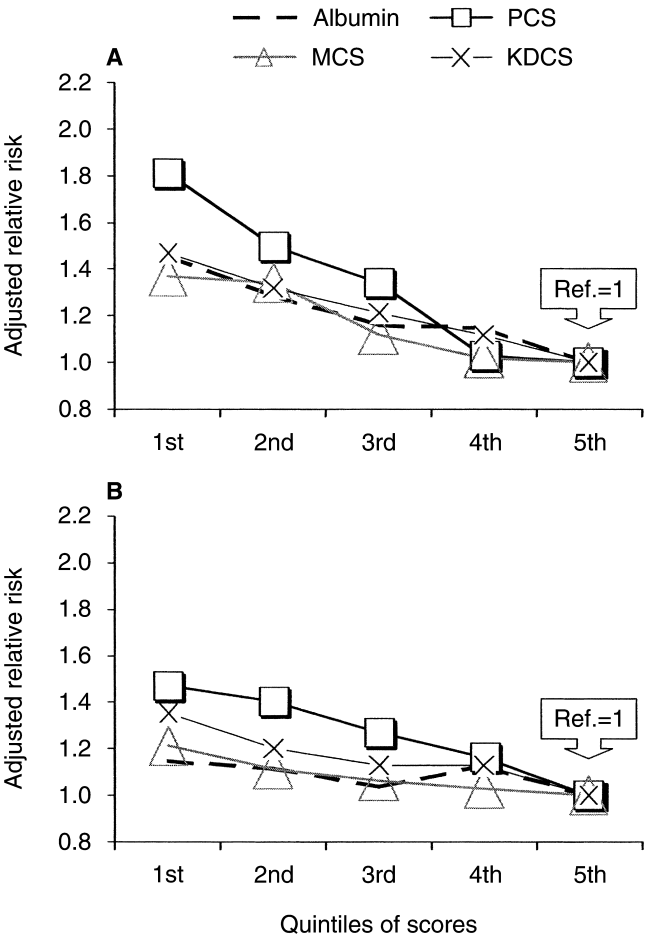

Fig. 2. Adjusted relative risks of death (*A*) and first hospitalization (*B*) by quintile of scores for each component of health-related quality of life (HRQOL) and for albumin, using the highest quintile as the reference group. For all eight lines, there was a statistically significant trend (each $P < 0.001$, except for hospitalization and albumin, which were $P < 0.05$) for the risks of both outcomes to increase with lower scores. Abbreviations are: MCS, mental component summary; PCS, physical component summary; and KDCS, kidney disease component summary.

of death and 56% higher adjusted risk of hospitalization when compared with those in the highest quintile. This finding is consistent with a previous investigation that has shown a stronger effect of PCS on death and hospitalization as compared with MCS [6]. It should be noted, however, that the effects of MCS on the two outcomes were independent of PCS and vice versa. Moreover, all subscales used for MCS and PCS were significantly associated with the outcomes. The effects of MCS and PCS were also independent of the KDCS and albumin. In fact, the increase in the mortality and hospitalization risks related to lower scores in MCS and PCS did not change when albumin was included in Cox models that contained all three summary measures of HRQOL and the variables included in Table 1 and Table 2. It is also important to note that even though KDCS, like MCS and PCS, predicts death and hospitalization independently of albumin, no association is observed between KDCS and outcomes in models that contain MCS and PCS. These results indicate that KDCS and albumin contribute little to predictions of death and hospitalization when information about PCS and MCS is available.

Several studies have shown that albumin is one of the

Table 6. Adjusted relative risk (RR) of death and hospitalization for quintiles of albumin and health-related quality of life (HRQOL) components

Quintile	Ranges of quintiles				RR of death (95% CI)				RR of hospitalization (95% CI)			
	Albumin	MCS	PCS	KDCS	Albumin	MCS	PCS	KDCS	Albumin	MCS	PCS	KDCS
1st	<3.4	<34	<25	<52	1.46[c] (1.22–1.74)	1.37[c] (1.18–1.59)	1.81[c] (1.49–2.20)	1.47[c] (1.26–1.72)	1.15[a] (1.01–1.30)	1.21[c] (1.10–1.33)	1.47[c] (1.30–1.67)	1.35[c] (1.21–1.51)
2nd	3.4–3.7	35–41	26–32	53–60	1.29[b] (1.08–1.54)	1.34[c] (1.15–1.58)	1.50[c] (1.24–1.80)	1.32[b] (1.12–1.56)	1.12 (1.00–1.26)	1.11[a] (1.01–1.22)	1.40[c] (1.25–1.58)	1.20[c] (1.08–1.33)
3rd	3.8–3.9	42–49	33–38	61–67	1.16 (0.96–1.39)	1.12 (0.96–1.31)	1.34[b] (1.10–1.63)	1.21[a] (1.04–1.42)	1.04 (0.93–1.17)	1.06 (0.95–1.17)	1.27[c] (1.14–1.42)	1.13[a] (1.02–1.25)
4th	4.0–4.1	50–56	39–46	68–75	1.15 (0.97–1.38)	1.02 (0.87–1.19)	1.03 (0.85–1.25)	1.12 (0.95–1.34)	1.13[a] (1.01–1.25)	1.03 (0.93–1.14)	1.16[b] (1.04–1.3)	1.13[a] (1.02–1.26)
5th	>4.1	>56	>46	>75	reference = 1	reference = 1	reference = 1	reference = 1	reference = 1	reference = 1	reference = 1	reference = 1

The models for the mental component summary (MCS), physical component summary (PCS), and the kidney disease component summary (KDCS) were adjusted for all variables in Table 1 and 2, except for albumin.
[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$

strongest predictors of adverse outcomes, particularly death, in dialysis patients [17, 20]. Consistent with these previous observations, our study showed a strong association between low albumin and higher risk of death. Similar to HRQOL summary score, albumin level was less strongly associated with risk of hospitalization than with risk of death. De Oreo [6], in his study of HRQOL and dialysis outcomes, also found a much stronger association of albumin with mortality risk than with hospitalization (measured as hospital days). The reasons for a weaker association of both albumin and HRQOL with hospitalization are not clear, although they may be partly related to the complex interplay of factors that influence the decision for hospital admission. Local treatment or hospitalization policies and patient or family preferences, for instance, are factors that may influence hospitalization [21–25].

It is important to note that, according to the results of this study, the associations between lower HRQOL score and higher risk of death and hospitalization are not confounded by albumin. The comparisons by quintiles of albumin and by quintiles of HRQOL scores support the conclusion that MCS, PCS, and KDCS are at least as powerful as albumin in predicting death and hospitalization. Moreover, by treating HRQOL scores as a continuous variable, we showed that a 10-point lower PCS score was associated with a rise in mortality risk that was similar to (or even greater than) the risk associated with a 1 g/dL lower serum albumin level. This finding was observed in Europe, Japan, and the United States. It is important to note that the standard deviations of PCS and albumin for the total group were 10.8 and 0.57, respectively. Thus, 1 g/dL in albumin represents a larger change in the scale of the variable than 10 points in the PCS scale. These findings indicate that a relatively smaller difference in the PCS scale has a stronger effect on death and hospitalization than serum albumin concentration.

Quality of life is a critically important clinical outcome for hemodialysis patients. HRQOL measures provide information about the impact of the treatment on perceived well-being. More attention to the HRQOL instrument (e.g., KDQOL-SF) may help to identify not only biologic but also psychosocial factors to be the target of interventions aimed at improving the quality of life of a specific patient. This study additionally supports the use of HRQOL measures to identify patients who are at higher risk of adverse outcomes. Because the present study is observational, we cannot be sure whether the association between HRQOL and the outcomes are causal. Regardless of whether the relationship is causal or not, the data indicate that HRQOL can serve as a sensitive indicator of subsequent patient mortality and morbidity. If the relationship is causal, then interventions that can improve HRQOL might also be effective in

decreasing the risk of mortality and preventing other adverse outcomes in hemodialysis patients.

The associations between lower HRQOL score and higher risk of adverse outcomes (death and hospitalization) were strong and statistically significant, even after taking into account albumin and a large number of other covariates that are known to influence HRQOL, death, or hospitalization. Thus, it is unlikely that measured confounders caused the positive associations. However, since approximately 42% of the patients did not fill out all the questions of KDQOL-SF, we assessed the possibility that our results have been partly influenced by nonresponse bias. The nonresponse rates were approximately 52%, 32%, and 25% for patients treated in the United States, Japan, and Europe, respectively. Despite the large difference in nonresponse, similar patterns in the adjusted associations of HRQOL versus outcomes were observed for Europe and the United States, particularly for the associations MCS versus death, MCS versus hospitalization, and KDCS versus hospitalization (Table 3). Nonresponse to the KDQOL-SF was also more frequent among patients from the United States than Japan. However, the strongest associations between HRQOL and outcomes (death and hospitalization) were observed in Japan. Thus, it is unlikely that the strong associations between HRQOL and outcomes observed in these studies can be fully explained by information bias, due to the fact that respondents were in general healthier than nonrespondents to the KDQOL-SF.

In general, nonrespondents were older and had less time on dialysis, lower levels of serum albumin, higher risk of death and hospitalization, and higher prevalence of comorbidities. Their mortality risk was significantly higher, even with adjustments for the whole set of covariates. A lower HRQOL score is a plausible explanation for the higher risk of death for the nonrespondents. It is likely that those who did not answer all the questions of the KDQOL-SF had lower HRQOL, in which case we may be underestimating the association between lower HRQOL and the risk for the two outcomes (i.e., death and hospitalization). Another factor to be considered when interpreting our results is the validity of the HRQOL instrument itself. Previous data, however, give strong support to the use of the SF-36 and the KDQOL-SF as research instruments to assess HRQOL [9, 26–30]. Moreover, the internal consistency and reliability are similar among translations of the SF-36 and the KDQOL-SF [26, 30–32].

CONCLUSION

The three components of HRQOL (the MCS, PCS, and KDCS) have predictive validity for risk of both mortality and hospitalization; however, the associations between KDCS and outcomes can be explained by factors captured in the MCS and PCS. The results suggest that the HRQOL measures, particularly PCS, have a greater capacity to identify patients at greater risk for death and hospitalization than serum albumin, which has previously been recognized as a key marker among dialysis patients. Moreover, HRQOL seems to predict both shorter-term and longer-term outcomes. Future studies should assess factors related to change in HRQOL during hemodialysis treatment and the influence of such changes on the risk of mortality and hospitalization. It is also important to assess whether interventions that improve HRQOL also decrease the risk of death and hospitalization among hemodialysis patients.

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Reprint requests to Friedrich K. Port, M.D., M.S., University Renal Research and Education Association, 315 W. Huron Street, Suite 260, Ann Arbor, MI 48103.
E-mail: fport@urrea.org

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