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Are Both Psychological and Physical Dimensions in Health-Related Quality of Life Associated with Mortality in Hemodialysis Patients: A 7-Year Taiwan Cohort Study

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Key Words
Depression · Disability, physical · Health-related quality of life · Hemodialysis · Taiwan

Abstract
Background: Psychological depression and physical disability are closely correlated in hemodialysis patients. A retrospective cohort study was conducted to examine the independent association of physical and psychological functioning with mortality in a hemodialysis cohort in Taiwan. ***Methods:*** A total of 888 stable hemodialysis patients were included. Patients completed two questionnaires: the 36-item Short Form Health Survey Questionnaire (SF-36, Taiwan Standard Version 1.0) and the Beck Depression Inventory (BDI, Chinese Version). Mortality outcomes were recorded for a seven-year follow-up period. ***Results:*** There were 303 deaths recorded. BDI scores were inversely related to all health-related quality of life (HRQoL) domains ($p < 0.001$). In the Cox-proportional hazard model, only poor physical dimension of HRQoL was independently associated with higher mortality. ***Conclusion:*** Poor physical dimension in HRQoL is a strong predictor of mortality among hemodialysis patients in Taiwan. Psychological depression is closely correlated with poor HRQoL but does not predict mortality.

Introduction

Both prolonging life expectancy and maintenance of good health-related quality of life (HRQoL) are objectives of clinical practice. In spite of advances in medicine and dialysis technology, chronic kidney disease stage 5 still results in extremely high mortality. Maximizing HRQoL in this population becomes a very important issue and deserves exploration.

The HRQoL is usually evaluated by self-reported questionnaires, which reflect the functioning status of the previous month. Such scores of HRQoL are composed of

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physical and psychological components and are associated with survival in previous studies [1–4]. The high levels of somatic symptoms, such as aching, poor appetite, and dizziness frequently reported by chronically ill hemodialysis patients may be transferred to mental dysfunction and even depression. A recent study of the dialysis population showed that medical co-morbidity preceded the depressive symptoms [5]. The psychological dysfunction may reflect physical disability but not a specific disease. In fact, previous study results of the association between physical and psychological functioning with survival are conflicting. The study by DeOreo [1] did not show that a low mental component scale (MCS) was associated with a higher death rate. In contrast, Kalantar-Zadeh et al. found a correlation between survival and mental functioning but not physical functioning [2].

We conducted this retrospective study to examine the exact association of physical and psychological functioning with survival. The main psychological dysfunction in the end-stage renal disease population is depression, so we also evaluated it by questionnaires. We hypothesized that psychological depression and physical dysfunction in HRQoL were independent predictors of mortality among hemodialysis patients.

Subjects and Methods

Subjects

This study was conducted at 14 hospitals and dialysis centers in northern Taiwan. Patients were enrolled consecutively from September 2001 to August 2002. The inclusion criteria were hemodialysis for more than three months before this study, age more than 18 years old, and being able to independently answer the questionnaires. Patients with active psychiatric disease, recent infection, uncontrolled congestive heart failure (more severe than New York Heart Association functional class II), acute complications from uremia at the time of the study, cognitive impairment, or refusal to join the study were excluded.

Biochemical and hematological parameters were obtained by mid-week predialysis blood samples within one month of this study. Other clinical variables, including duration on hemodialysis, primary renal disease, and comorbid diseases were also documented.

This study was approved by the ethical committees of all included hospitals and was monitored by the institutional review board of National Taiwan University Hospital.

Questionnaires

After written informed consent was obtained, patients were asked to complete two questionnaires by themselves: (1) the 36-item Short Form Health Survey Questionnaire (SF-36, Taiwan Standard Version 1.0) to survey HRQoL, and (2) the Beck Depression Inventory (BDI, Chinese Version) to rate the severity of depressive symptoms. The questionnaires were given to patients on the midweek day. Patients completed the questionnaires on that day or returned them at their next hemodialysis session.

The SF-36 is an instrument commonly utilized to measure QOL in dialysis populations [1–4]. It includes eight scales: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Low scores in the eight domains indicate lower quality of life. These eight scales have been compressed into two primary summary scales: the physical component scale (PCS) and the MCS.

The BDI is a standard self-administered questionnaire used to screen patients for depression [6] and is used in the assessment of depression in ESRD patients [7, 8]. BDI scores of 14–19 represent a mild degree of depression, scores of 20–28 a moderate degree, and scores of 29–60 a severe degree of depression.

Outcome Data Collection

All patients were monitored until September 2008. Date and cause of death were obtained by retrospectively reviewing the medical records. Survival was analyzed as the time from enrollment to death. Patients were censored from contributing additional survival analysis following renal transplantation, switching to peritoneal dialysis, or transfering to other dialysis facility.

Statistics

The patients' characteristics are presented as mean ± SD. The independent t test was used to find confounding variables associated with future mortality. Cumulative survival curves stratified by depression severity and four equal quartiles of PCS and MCS were constructed using the Kaplan-Meier method. The survival rates were compared using the log-rank test. The confounding effects of other variables were corrected using the Cox-proportional hazard model. A two-tailed $p < 0.05$ was considered statistically significant. All calculations were performed using a standard statistical package (SPSS 15.0 for Windows; SSPS Inc., Chicago, Ill., USA).

Results

Baseline Characteristics and QoL of Surviving and Deceased Patients

There were 2,185 hemodialysis patients at the time of recruitment, and a total of 775 patients were excluded because of failing to fulfill inclusion criteria or having one of the exclusion criteria. There were 1,410 patients invited into the study, 888 patients completed the questionnaires and were enrolled into the follow-up cohort. The response rate was 63.0%. This study cohort was predominantly female (56.2%) with an average age of 57.9 ± 13.1 years. There were 242 (27.3%) diabetic patients. At the end of follow-up, a total of 303 deaths were recorded. The baseline characteristics of deceased, surviving, and all patients are listed in table 1. The deceased group was older ($p < 0.001$), had more men ($p = 0.042$), more diabetics ($p < 0.001$), and more chronic hepatitis C ($p = 0.005$). The

Table 1. Patient demographic features and relevant laboratory data

	All patients	Surviving patients	Deceased patients	p
Number	888	585	303	
Age, years	57.9 ± 13.1	54.8 ± 13.3	63.7 ± 10.5	<0.001
Women	499 (56.2)	156 (51.5)	343 (58.6)	0.042
HD vintage, months	48.7 ± 45.0	49.8 ± 46.8	46.4 ± 41.3	0.284
Diabetics	242 (27.3)	119 (20.3)	123 (40.3)	<0.001
Hypertension	432 (48.6)	281 (48.0)	151 (49.8)	0.611
BMI	22.0 ± 3.3	22.0 ± 3.1	21.9 ± 3.8	0.827
Hepatitis C	174 (19.6)	99 (16.9)	75 (24.8)	0.005
Hepatitis B	76 (8.6)	53 (9.1)	23 (7.6)	0.458
Biochemical parameters				
Albumin, g/dl	4.1 ± 0.8	4.1 ± 0.4	3.9 ± 0.4	<0.001
Hematocrit, %	29.8 ± 4.3	29.9 ± 4.3	29.6 ± 4.4	0.297
Creatinine, mg/dl	10.3 ± 2.3	10.8 ± 2.2	9.5 ± 2.2	<0.001
UN, mg/dl	74.5 ± 19.2	75.9 ± 18.9	72.0 ± 19.5	0.004
Uric acid, mg/dl	7.7 ± 3.7	7.8 ± 4.4	7.6 ± 1.5	0.441
Calcium, mg/dl	9.3 ± 1.5	9.3 ± 1.4	9.1 ± 1.6	0.055
Phosphorus, mg/dl	5.1 ± 2.0	5.2 ± 2.1	4.8 ± 1.5	0.008
AST, IU/l	20.9 ± 14.2	19.8 ± 13.6	23.0 ± 15.1	0.002
ALT, IU/l	20.4 ± 24.1	19.2 ± 21.3	22.8 ± 28.5	0.062
Iron, μg/dl	72.0 ± 57.7	72.5 ± 65.3	71.0 ± 39.1	0.723
Ferritin, ng/ml	526.2 ± 515.2	511.1 ± 473.5	555.5 ± 587.3	0.230
Triglyceride, mg/dl	170.3 ± 130.2	170.5 ± 133.8	169.9 ± 123.1	0.951
Total cholesterol, mg/dl	187.9 ± 46.9	189.2 ± 45.5	185.4 ± 49.4	0.260
Intact PTH, pg/ml	172.3 ± 219.6	187.3 ± 229.0	143.9 ± 197.9	0.007
URR, %	74.0 ± 8.5	74.4 ± 8.3	73.3 ± 8.8	0.06

Data are numbers (percent) or means ± SE, as appropriate. HD = Hemodialysis; BMI = body mass index; UN = urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PTH = parathyroid hormone; URR = urea reduction rate.

serum albumin ($p < 0.001$), creatinine ($p < 0.001$), urea nitrogen ($p = 0.004$), phosphorus ($p = 0.008$), and intact parathyroid hormone ($p = 0.007$) were higher in the surviving patients.

As shown in table 2, the surviving patients had less depressive mood ($p = 0.007$). The deceased group had lower scores for all eight HRQoL domains ($p \leq 0.001$). The two summary scores, PCS and MCS, were significantly lower among the deceased patients ($p < 0.001$ and $p = 0.002$, respectively).

Association between Depressive Mood and HRQoL

In the bivariate correlation analyses, BDI scores were inversely related to PCS scores ($r = -0.457$, $p < 0.001$) and MCS scores ($r = -0.627$, $p < 0.001$). The MCS scores were also directly related to PCS scores ($r = 0.281$, $p < 0.001$). Multivariate linear regression analysis was done to examine the independent associations between depressive mood and the eight domains of HRQoL. After correcting all the clinical variables, BDI scores had strong inverse association with all eight domains of HRQoL ($p < 0.001$; table 3).

Univariate Association between Mortality with Depressive Mood and HRQoL

For the preliminary analysis of the association between depressive mood and mortality, all the subjects were divided into four groups by BDI score: none, mild, moderate, and severe degree of depression. In the Kaplan-Meier analysis (fig. 1) the patients with severe depression had the highest mortality ($p = 0.007$, by log-rank test). The unadjusted Cox proportional hazards model (table 4) showed that numeric BDI score was also associated with mortality ($p = 0.002$).

For analysis of the association between HRQoL and mortality, all the subjects were divided into four equal quartiles according to their PCS and MCS scores for the SF-36. Quartile 1 had the lowest scores and quartile 4 had the highest. In both the MCS and PCS (fig. 2, 3) the pa-

Table 2. Association between SF-36 PCS and MCS scores with clinical characteristics

	Surviving patients (n = 585)	Deceased patients (n = 303)	p
BDI score	12.64 ± 10.11	14.73 ± 11.41	0.007
SF-36 domains			
Physical functioning	42.42 ± 9.45	36.94 ± 9.57	<0.001
Role – physical	41.84 ± 44.67	29.26 ± 43.11	<0.001
Bodily pain	72.45 ± 25.29	65.51 ± 29.64	<0.001
General health	45.24 ± 22.83	37.89 ± 24.21	<0.001
Vitality	51.51 ± 21.37	41.95 ± 22.90	<0.001
Social functioning	64.61 ± 24.75	53.31 ± 31.43	<0.001
Role – emotional	52.79 ± 45.71	42.06 ± 46.32	0.001
Mental health	61.35 ± 20.18	55.77 ± 22.89	<0.001
SF-36 summary scores			
PCS	42.42 ± 9.45	36.94 ± 9.57	<0.001
MCS	43.22 ± 11.22	40.61 ± 12.43	0.002

Table 3. Correlation between BDI scores and individual domains of SF-36

SF-36 domains	Standardized β coefficient	p
Physical functioning	–0.392	<0.001
Role – physical	–0.396	<0.001
Bodily pain	–0.464	<0.001
General health	–0.477	<0.001
Vitality	–0.548	<0.001
Social functioning	–0.476	<0.001
Role – emotional	–0.426	<0.001
Mental health	–0.606	<0.001

Corrected by age, gender, time on dialysis, hematocrit, presence of hepatitis C, diabetes mellitus, serum albumin, creatinine, urea nitrogen, phosphorus, and intact parathyroid hormone.

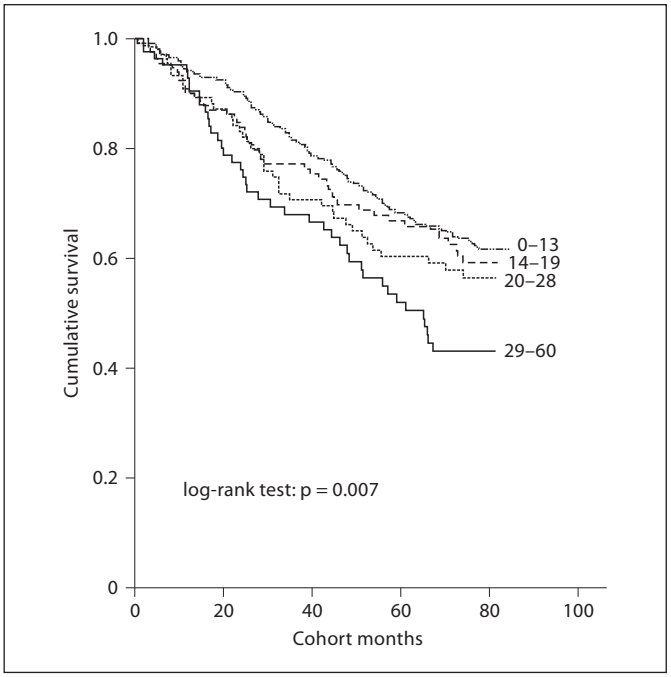

Fig. 1. Kaplan-Meier analysis showing association between BDI scores and survival.

tients with higher HRQoL had lower mortality ($p < 0.001$, log-rank test). Nonetheless, the unadjusted Cox proportional hazards model (table 4) showed that numeric MCS scores were not associated with mortality ($p = 0.140$).

Relative Risk of Death Adjusted by Depression and HRQoL

Because there were many differences in the clinical characteristics between the surviving and deceased group, all of these parameters were analyzed in the adjusted Cox proportional hazards model. Only higher PCS scores were associated with lower mortality (table 4). Even after converting the numeric HRQoL and BDI scores into four groups as previously described, MCS and BDI were still not associated with mortality (table 5). Only lower PCS quartiles were independently associated with higher mortality.

Discussion

Our study demonstrates that there is a strong association of the psychological dimension with the physical dimension of HRQoL among hemodialysis patients in Taiwan. The baseline depressive symptoms and MCS scores from the SF-36 do not independently predict mortality. Only PCS scores independently predict mortality. The patient self-reported physical component, rather than the psychological dimension, of quality of life is a better tool for routine clinical evaluation of Taiwan hemodialysis patients.

Patient self-reported questionnaires are widely used to assess HRQoL and depression. The major concerns of such evaluations are validity, reliability and predictability of major clinical outcomes. The above performances

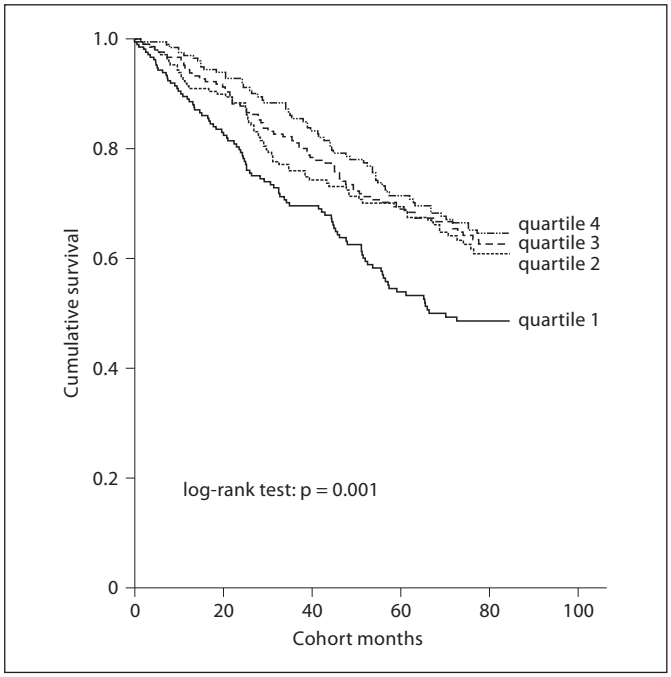

Fig. 2. Kaplan-Meier analysis showing association between MCS scores and survival.

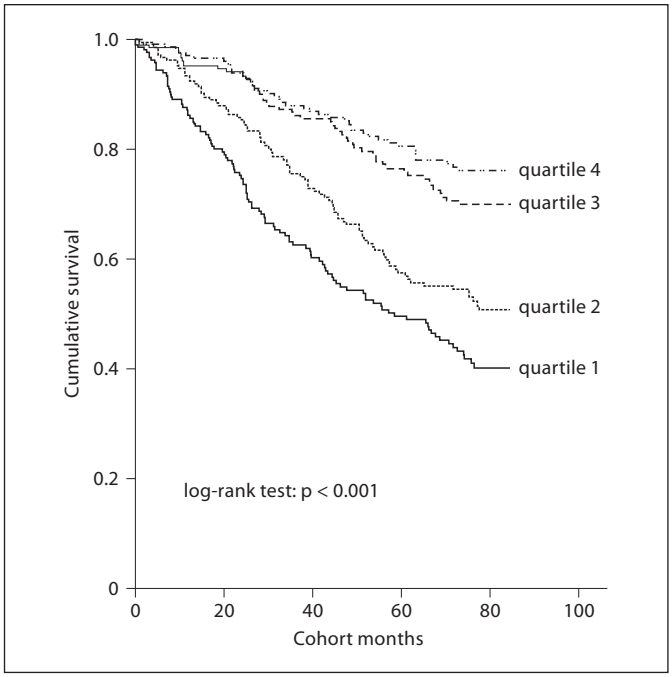

Fig. 3. Kaplan-Meier analysis showing association between PCS scores and survival.

Table 4. Relative risk (RR) of death per decreasing point in SF-36 summary score

	Mean ± SD	RR of death (95% CI)	
		unadjusted	adjusted
BDI score	13.36 ± 10.63	1.017 (1.006–1.027)[b]	1.004 (0.993–1.016)[a]
MCS score	42.33 ± 11.71	0.981 (0.969–0.993)[a]	0.989 (0.975–1.004)[a]
PCS score	40.54 ± 9.84	0.942 (0.927–0.957)[b]	0.971 (0.952–0.990)[b]

Adjusted by age, gender, serum albumin, creatinine, urea nitrogen, phosphorus, diabetes mellitus, aspartate aminotransferase, intact parathyroid hormone, diabetes, and hepatitis C.

[a] $p > 0.05$; [b] $p < 0.01$.

of these questionnaires differ by ethnic and racial groups [9, 10]. The instruments we used were the Chinese versions of SF-36 and BDI, both of which are validated [11–13]. We also assessed dialysis patients using these questionnaires in previous studies [14–16]. Thus, the HRQoL and depressive symptoms evaluations using the SF-36 and BDI among the Taiwanese hemodialysis cohort are reliable.

In this study, after adjusting for all the other variables, the BDI scores had significant negative correlation with the physical functioning domain of HRQoL (standardized β coefficient = –0.392, $p < 0.001$). Such association was affirmed as compound depression in previous research [17, 18]. How to differentiate medical disease leading to the depressive mood and somatic symptoms due to depression is difficult. Furthermore, such depressive disorders with coexistent medical illness are more resistant to treatment [19].

The relationship between HRQoL and outcomes obviously raises the question of the potential benefit of inter-

Table 5. Multivariate Cox proportional hazards models of independent predictors of mortality, overall significance p < 0.001

Variables	Unadjusted hazard ratios (95% CI)	p	Adjusted hazard ratios (95% CI)	p
Age, year	1.050 (1.039–1.061)	<0.001	1.035 (1.023–1.048)	<0.001
Gender (female vs. male)	1.375 (1.098–1.723)	0.006	0.573 (0.441–0.745)	<0.001
DM (yes vs. no)	2.142 (1.703–2.695)	<0.001	1.471 (1.127–1.920)	0.004
Albumin, g/dl	0.295 (0.222–0.390)	<0.001	0.434 (0.308–0.611)	<0.001
Creatinine, mg/dl	0.817 (0.778–0.859)	<0.001	0.884 (0.825–0.948)	0.001
UN, mg/dl	0.990 (0.983–0.996)	0.001	1.004 (0.996–1.011)	0.347
Phosphorus, mg/dl	0.873 (0.808–0.944)	0.001	0.986 (0.922–1.055)	0.688
Intact PTH, pg/ml	0.999 (0.998–1.000)	0.004	1.000 (0.999–1.001)	0.795
AST, IU/l	1.010 (1.004–1.017)	0.001	1.006 (0.999–1.014)	0.111
Hepatitis C (yes vs. no)	1.282 (0.988–1.664)	0.062	1.305 (0.951–1.790)	0.099
Quartiles of SF-36 PCS summary scores (compared to the 4th)				
1st	3.482 (2.445–4.959)	<0.001	1.857 (1.247–2.764)	0.005
2nd	2.424 (1.686–3.484)	<0.001	1.696 (1.136–2.533)	0.008
3rd	1.276 (0.845–1.909)	0.234	1.078 (0.703–1.652)	0.761
Quartiles of SF-36 MCS summary scores (compared to the 4th)				
1st	1.802 (1.307–2.484)	<0.001	1.418 (0.996–2.018)	0.120
2nd	1.205 (0.856–1.696)	0.286	1.080 (0.750–1.557)	0.797
3rd	1.114 (0.791–1.568)	0.536	0.883 (0.608–1.282)	0.807
Groups of BDI scores [compared to the group with severe symptoms (29–60)]				
No symptoms (0–13)	0.557 (0.396–0.783)	0.010	0.756 (0.516–1.109)	0.499
Mild symptoms (14–19)	0.641 (0.423–0.972)	0.036	0.766 (0.488–1.203)	0.535
Moderate symptoms (20–28)	0.713 (0.464–1.097)	0.124	0.882 (0.551–1.414)	0.678

DM = Diabetes mellitus; UN = urea nitrogen; PTH = parathyroid hormone; AST = aspartate aminotransferase.

vention to improve HRQoL. Can the strategy to improve HRQoL not only alleviate subjective symptoms but also reduce mortality in the dialysis population? Previous studies have focused on higher hemoglobin targets [20, 21], exercise programs [22, 23], modifications in the dialysis treatment regimen [24, 25], and even antidepressant therapy [26, 27]. Preliminary evidence, mainly from studies in hemodialysis patients, suggests that exercise training improves arterial compliance, cardiac autonomic control, and left ventricular systolic function while decreasing inflammation, oxidative stress, and blood pressure levels [28]. But there is still no report demonstrating achievement of better survival by the above interventions. In fact, the intervention to improve HRQoL is time-consuming. Good patient adherence and sufficient resources in the entire patient care team are also needed. Also, more structured programs are needed to explore the impact of HRQoL intervention on medical outcomes.

This Taiwan cohort study did not show an independent association between the psychological dimensions of quality of life and mortality. Previous research results of dialysis populations regarding the association of psychological dimensions with mortality are conflicting [1, 2]. In a recent report of Japanese diabetic hemodialysis patients [29], PCS but not MCS scores from the SF-36 predicted survival. There are several possible reasons leading to such a discrepancy. Firstly, a higher than usual cutoff score for the BDI may be needed to define the exact depressive disorder in hemodialysis populations. The self-reported BDI questionnaire is easy to use in large-scale screening and research. But diverse BDI cutoff scores have been adopted in different studies [30]. The sensitivity and specificity of the BDI questionnaire are still undetermined in the hemodialysis population. Secondly, the depressive mood is not always persistent over time. In a study by Kimmel et al., only when depression was treated as a time-varying covariate based on periodic follow-up, but not baseline levels of depression symptoms, was the level of depression associated with mortality [7]. In the Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, baseline depressive mood was not associated with 2-year mortality,

but persistently depressive affect was associated with higher mortality [5]. Thirdly, the psychological dysfunction may reflect a physical disability but not a specific disease. Recent studies have shown that exercise training improved both the physical and psychological dimensions of HRQoL [22, 23]. It provides evidence that medical illness leads to depression, and association of depression with outcomes is only an epiphenomenon rather than depression leading to mortality [31]. Lastly, our result could be distorted by nonresponse bias. We had no available data about the nonresponders. The difference between responders and nonresponders in our survey could not be clarified. In a large international survey of HRQoL of dialysis populations, the risk of death of nonresponders was more than two times higher than that of responders [4]. In a survey of HRQoL of seniors, nonresponders had significantly more comorbidities and were older than the responders [32]. It is very likely that many severely depressed patients were reluctant to join the survey, so we were not able to determine the exact impact of psychological dysfunction on survival.

In conclusion, poor physical dimension of HRQoL predicts higher mortality in Taiwan hemodialysis patients. Although our study did not reveal that psychological dysfunction was associated with higher mortality among Taiwanese hemodialysis patients, it does not diminish the importance of psychological assessment. Quality of life itself represents the health status of every patient and it merits any effort to pursue it. The identification of psychological disorders requires a formal psychiatric interview and evaluation, along with evaluation of any physical disorders. Whether amelioration of physical disability is helpful for treatment of psychological disorders among hemodialysis patients deserves further study.

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