Kidney International, Vol. 62 (2002), pp. 199–207

Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe

Antonio Alberto Lopes, Jennifer Bragg, Eric Young, David Goodkin, Donna Mapes, Christian Combe, Luis Piera, Philip Held, Brenda Gillespie, and Friedrich K. Port, for the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Department of Medicine, Federal University of Bahia, Brazil; University Renal Research and Education Association (URREA), and Kidney Epidemiology and Cost Center (KECC), University of Michigan, and Division of Nephrology, University of Michigan and VAMC, Ann Arbor, Michigan, USA; Amgen, Inc., Thousand Oaks, California, USA; Service de Néphrologie B, Center Hospitalier Universitaire de Bordeaux, Bordeaux, France; Hospital General Vall D'Hebron, Barcelona, Spain; and Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe.

Background. Depression is not uncommon among patients with end-stage renal disease (ESRD) being treated by hemodialysis. We investigated whether risk of mortality and rate of hospitalization may be predicted from physician-diagnosed depression and patients' self-reports of depressive symptoms.

Methods. Data were analyzed from the Dialysis Outcomes and Practice Patterns Study (DOPPS) for randomly selected ESRD patients being treated by hemodialysis in the United States (142 facilities, 2855 patients) and five European countries (101 facilities, 2401 patients). The diagnosis of depression during the past year was abstracted from the medical records. In addition, the patients were asked to indicate how much of their time over the previous four weeks they had felt (*1*) "so down in the dumps that nothing could cheer you up" and (*2*) "downhearted and blue." A response of "a good bit," "most," or "all" of the time were classified as depressed.

Results. The prevalence of depression was nearly 20%. The relative risks of mortality and hospitalization among depressed (vs. non-depressed), adjusted for time on dialysis, age, race, socioeconomic status, comorbid indicators and country were, respectively: 1.23 and 1.11 for physician-diagnosed depression, 1.48 and 1.15 for the "so down in the dumps" question, and 1.35 and 1.11 for the "downhearted and blue" question ($P < 0.05$ for all six relative risks). These associations were not significantly different between US and European patients.

Conclusions. Self-reported depression by two simple questions was associated with increased risks of mortality and hospitalization for hemodialysis patients. Future research needs to assess whether early identification and treatment of depression may help to improve quality of life and survival in hemodialysis patients.

Key words: depression, end-stage renal disease (ESRD), hemodialysis, hospitalization, mortality.

Received for publication October 23, 2001
and in revised form January 18, 2002
Accepted for publication February 12, 2002

In recent decades, important advances have been made in the treatment of patients with end-stage renal disease (ESRD) [1]. Despite these advances, mortality rate is still high and many patients have a low quality of life attributable to both physical and psychological disorders [2, 3]. Depression has been described as the most frequent psychological problem among patients with ESRD being treated by hemodialysis [2, 4]. Its prevalence varies widely across studies, which may reflect in part the use of different diagnostic criteria [5].

Accumulating evidence suggests that depression precedes the clinical onset of chronic diseases such as cancer and coronary artery disease (CAD) [6, 7]. There are data to support an association between depression and increased risk of mortality among patients with cancer and CAD [8–11]. The studies on hemodialysis patients have not been consistent about the association between depression and mortality risk, which may be due to the small power to test the research hypothesis [12–17]. In a study that included 56 ESRD patients being treated by hemodialysis or peritoneal dialysis, Patterson et al did not find a significant correlation between depression (assessed at the start of the follow-up by the Beck Depression Inventory) and mortality risk, either at one or two years of follow-up [15]. Kimmel et al studied 256 hemodialysis patients with a median follow-up time of 39 months and likewise did not find significant association between the baseline level of depression and mortality risk [16]. However, when they used multiple measures of depression assessed every six months and treated the variable as time-dependent, a significant association between depression and mortality risk was found.

We studied depression among hemodialysis patients in the context of the large-sample, multi-national Dialysis Outcomes and Practice Patterns Study (DOPPS). Using

nationally representative samples of facilities and hemodialysis patients from the United States and five European countries, we investigated whether the risks of death and hospitalization may be predicted from the presence of depression as diagnosed by physicians or patients' self-reports. The DOPPS data also were used to compare cause-specific rates of death between depressed and non-depressed patients and to identify patient characteristics correlated with depression.

METHODS

DOPPS is an international, prospective, observational study of hemodialysis practice patterns and associated outcomes. It is ongoing in the United States, Europe (France, Germany, Italy, Spain, and the United Kingdom), and Japan [18]. Nationally representative samples of dialysis facilities were recruited in each country. Within each facility, study patients were randomly selected. In each country the institutional review boards have approved the study. Informed patient consent was obtained in accordance with local requirements for each country. The overall design of the DOPPS has been published previously [18].

The present study included data from the United States (142 facilities) and Europe (101 facilities), but not Japan. The main analyses were restricted to 5256 patients who had a medical questionnaire (29 with missing information on depression diagnosis) completed by the nurse coordinator in the unit and who had responded to a patient questionnaire filled out by the patient himself or herself. Among these patients, 2855 (6321 patient-years) were treated in the United States and 2401 (3771 patient-years) were treated in Europe. Additional analyses were performed with the 4297 United States patients and 3022 European patients who had a completed medical questionnaire, independently of having a completed patient questionnaire. Data on years since ESRD onset, age, gender, race, socioeconomic status, laboratory tests, comorbid indicators, and patient outcome variables were recorded for each patient. The majority of data were collected at entry into the study, from July 1996 through December 1997 in the United States, and from May 1998 through November 1998 in Europe.

Each patient's medical record was assessed for diagnosis of depression within the past 12 months and this information was recorded on the DOPPS medical questionnaire. In addition, the patients completed the Kidney Disease and Quality of Life Short Form (KDQOL-SF™) in which they were queried about the presence and frequency of depressive symptoms during the previous four weeks. In particular, patients were asked to respond to the following two questions: (*1*) "have you felt so down in the dumps that nothing could cheer you up?" and (*2*) "have you felt downhearted and blue?" The six possible responses to these questions were: (*1*) none of the time, (*2*) a little of the time, (*3*) some of the time, (*4*) a good bit of the time, (*5*) most of the time, and (*6*) all the time. The last three options were considered indicative of depression. Dates of first hospitalization, death or withdrawal from dialysis were recorded. Patients also were classified by the following causes of death: cardiac, infectious, malignant, vascular (pulmonary embolus, cerebral vascular accident and hemorrhage), and other diseases.

Statistical methods

Depression was categorized and analyzed separately by the three criteria: physician diagnosis by medical record and the patient responses to the "so down in the dumps" and the "downhearted and blue" questions. The *t* test for independent samples and the chi-square test were used to compare means and proportions, respectively. The kappa statistic was used to assess agreement between measures of depression. A kappa value between 0.6 and 0.79 indicates high agreement, while a value below 0.2 indicates poor agreement [19].

Logistic regression analyses were performed to estimate adjusted associations between patient characteristics (demographic and socioeconomic factors, laboratory tests, comorbid indicators, and years on dialysis) and depression. The following laboratory factors and comorbid indicators were included in the analyses: serum albumin concentration, coronary artery disease, congestive heart failure, history of other cardiovascular problems (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 (HIV) or acquired immune deficiency syndrome (AIDS), neurologic disease (seizure, dementia, organic brain syndrome, Parkinson's disease), and gastrointestinal bleeding.

Cox models were used to estimate the relative risk of the two patient outcomes under study (time to first hospitalization following study entry and time to death) in relation to depression (both physician-diagnosed and self-reported), adjusted for demographic variables, laboratory tests, comorbid indicators and years on dialysis and stratified by country of residence [20]. For the Cox models with physician-diagnosed depression, two groups of adjusted models were used, one restricted to patients who filled out the patient questionnaire and another that included all patients. All statistical analyses were performed using SAS software (version 8; SAS, SAS Institute, Cary, NC, USA) [21].

RESULTS

In the analysis restricted to subjects who filled out the patient questionnaire, physician-diagnosed depression was

Table 1. Prevalence of depression diagnosed by physician and self-reported in Europe and the United States and agreement between measurements

Depression indicator	Prevalence of depression, % *n*/*N*			Kappa index	
	Europe	United States	Total	"Downhearted and blue"	"So down in the dumps"
Physician-diagnosed by medical record	16.2 (388/2401)	19.0 (543/2855)	17.7 (931/5256)	0.17	0.16
Self reported					
"Downhearted and blue"[a]	24.8 (576/2319)	18.5 (475/2562)	21.5 (1051/4881)	—	0.60
"So down in the dumps that nothing could cheer you up"[a]	22.6 (525/2324)	16.6 (429/2577)	19.5 (954/4901)	—	—

[a] Defined as good bit of the time or more frequent

reported in the medical records of 17.7% of patients; 16.2% of the 2401 patients from European centers and in 19.0% of the 2855 patients from United States centers (Table 1). Among the patients with a physician diagnosis of depression, treatment with antidepressive medication was observed for approximately 36.6% in the United States and 12.1% in Europe ($P < 0.0001$). This difference in prevalence between the United States and European patients was statistically significant ($P = 0.003$). Overall, the prevalence of physician-diagnosed depression was higher for patients with >1 year on dialysis (19.2%), but the difference was not significantly different as compared with patients dialyzed <3 months (17.5%) and 3 months to 1 year (17.8%).

Depression as measured by the "so down in the dumps" question was observed in 19.5% of patients; 22.6% of 2319 European patients and 16.6% of 2577 United States patients ($P < 0.0001$). For the "downhearted and blue" question, a total of 21.5% of patients were classified as depressed: 24.8% in Europe and 18.5% in the United States ($P < 0.0001$). Approximately 13.7% of the patients had a positive response to both questions and 26.8% were positive for at least one self-reported indicator of depression. For patients with time on dialysis <3 months, 3 months to 1 year and >1 year, the percentages of depression by the "so down in the dumps" question were 17.3%, 17.1% and 20.2%, respectively. The corresponding percentages of depression by the "downhearted and blue" question were 20.2%, 20.8% and 21.9%. For the "so down in the dumps" question, the difference in depression prevalence between 3 months to 1 year and >1 year was statistically significant ($P < 0.05$).

The percentage of agreement and the kappa index between physician diagnosed depression and depression by the "so down in the dumps" question were 74.2% and 0.16, respectively. The corresponding values for the agreement between physician diagnosed depression and depression by the "downhearted and blue" question were 73.6% and 0.17, respectively. The two self-reported indicators of depression, as measured by the two questions on the KDQOL-SF™, showed 87% of concordance and a kappa index of 0.60.

Correlates of physician-diagnosed depression restricted to those who filled out the patient questionnaire

The mean age was similar for patients with and without a physician diagnosis of depression. There were higher percentages of females and white patients in the group of depressed patients (Table 2). Depressed patients had a higher prevalence of coronary artery disease, congestive heart failure, other cardiac disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, lung disease, cancer (excluding skin cancer), gastrointestinal bleeding, and neurological disease. Lower percentages of the depressed patients were married and employed compared with non-depressed patients. On average, patients diagnosed with depression had been on dialysis several months longer than non-depressed patients and had lower serum albumin concentrations.

In the logistic regression model (Table 3), blacks and patients of other races were less likely than whites to have physician-diagnosed depression. The adjusted odds ratios (AOR) for blacks and other races were 0.44 and 0.40, respectively. Men were significantly less likely to have physician-diagnosed depression than women (AOR = 0.82). Greater likelihood of diagnosed depression was significantly associated with younger age, unemployment, lower level of serum albumin and the presence of coronary artery disease, congestive heart failure, other cardiac disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, lung disease, cancer, gastrointestinal bleeding, and neurological disease.

Correlates of self-reported depression

Blacks were less likely than whites to have self-reported depression (Table 2). The proportions of whites and patients of "other races" (excluding blacks) were higher in depressed than in non-depressed patients by the "so down in the dumps" question. Patients classified as depressed by "so down in the dumps" were also more likely to be diabetic, have lung disease, or not have finished high school. Patients who had attended college were less likely to report feeling "so down in the dumps" a good bit of the time or more frequently.

Table 2. Characteristics of the patients according to physician-diagnosed and self-reported depression

	Depression indicator					
	Physician-diagnosed		"So down in the dumps"		"Downhearted and blue"	
	Yes (N = 931)	No (N = 4325)	Yes (N = 954)	No (N = 3947)	Yes (N = 1051)	No (N = 3830)
Mean age in years (SD)	58.9 (15.1)	60.0 (15.3)[c]	59.6 (15.2)	59.5 (15.3)	60.0 (15.1)	59.5 (15.3)
Male *%*	50.5	56.2[b]	51.5	56.6[b]	52.8	56.5[b]
Race *%*						
Black	17.4	23.0[a]	16.5	22.1[a]	16.1	22.4[a]
White	78.6	71.0[b]	76.5	72.8[b]	77.4	72.4[b]
Other race	4.0	6.0[b]	7.0	5.1[b]	6.5	5.2
Socioeconomic factors *% for yes*						
Live alone	17.0	16.4	16.5	16.6	17.2	16.4
Married	50.8	55.2[b]	57.0	54.7	56.4	54.8
Did not finish high school	43.0	42.3	50.4	40.2[a]	50.2	40.1[a]
Attended college	15.3	15.2	11.0	17.0[a]	12.3	12.7[b]
Employed (ages <60)	12.8	23.2[a]	12.3	23.8[a]	15.4	22.9[a]
Comorbidities *% for yes*						
Coronary artery disease	48.8	37.3[a]	37.9	39.0	39.8	38.7
Congestive heart failure	43.9	32.9[a]	34.6	34.2	35.3	34.0
Other cardiac disease	44.8	33.4[a]	36.7	34.7	37.8	34.5[c]
Hypertension	80.1	78.2	75.2	79.4[b]	74.8	79.5[b]
Cerebrovascular disease	22.7	13.6[a]	16.9	14.6[c]	17.0	14.7[b]
Peripheral vascular disease	31.9	21.4[a]	25.1	22.8	27.1	22.2[b]
Diabetes mellitus	39.8	31.4[a]	36.7	31.3[b]	38.4	30.6[a]
Lung disease	15.7	10.6[a]	13.6	11.1[b]	13.7	11.0[b]
Cancer, excluding skin cancer	10.7	8.8[b]	8.7	9.1	8.8	9.1
HIV/AIDS	0.8	0.7	0.4	0.7	0.3	0.8[c]
Gastrointestinal bleeding	10.7	6.5[a]	8.9	6.4[b]	7.7	6.6
Neurological disease	14.2	7.3[a]	9.0	8.1	8.9	8.2
Median years on dialysis	2.66	2.41[b]	2.70	2.44[c]	2.55	2.48
Serum albumin *g/dL (SD)*	3.81 (0.45)	3.85 (0.46)[b]	3.83 (0.46)	3.86 (0.44)[b]	3.82 (0.46)	3.86 (0.45)[b]

[a] $P < 0.0001$, [b] $P < 0.05$, [c] $0.05 < P < 0.10$

Table 3. Logistic regression associations between baseline patient characteristics and depression

	Depression indicator					
	Physician-diagnosed		"So down in the dumps"		"Downhearted and blue"	
Characteristic	AOR	P value	AOR	P value	AOR	P value
Age *per 10 years older*	0.79	<0.0001	0.92	0.0119	0.91	0.0014
Male vs. female	0.82	0.0223	0.94	0.0607	0.89	0.1708
Race vs. White						
Black	0.44	<0.0001	0.69	0.0007	0.67	0.0001
Other race	0.40	<0.0001	1.47	0.0177	1.14	0.4347
Socioeconomic factors						
Live alone vs. not alone	1.11	0.3914	1.05	0.7143	1.11	0.3745
Married vs. not married	0.87	0.2101	1.13	0.2039	1.08	0.3962
Did not finish vs. finish high school	1.09	0.3147	1.50	<0.0001	1.50	<0.0001
Some college vs. no college	1.05	0.7178	0.84	0.1875	0.91	0.4683
Employed, ages <60 vs. not	0.59	0.0008	0.57	0.0004	0.68	0.0078
Comorbidities *yes vs. no*						
Coronary artery disease	1.22	0.0368	0.89	0.2115	0.90	0.2370
Congestive heart failure	1.30	0.0046	0.96	0.6703	1.03	0.7626
Other cardiac disease	1.40	0.0002	1.08	0.3823	1.16	0.0955
Hypertension	1.04	0.7383	0.76	0.0064	0.72	0.0006
Cerebrovascular disease	1.58	<0.0001	1.16	0.1772	1.16	0.1705
Peripheral vascular disease	1.31	0.0064	1.06	0.5561	1.18	0.0886
Diabetes mellitus	1.35	0.0012	1.29	0.0063	1.38	0.0004
Lung disease	1.44	0.0019	1.34	0.0169	1.31	0.0235
Cancer, excluding skin cancer	1.41	0.0119	0.96	0.8022	1.02	0.8637
HIV/AIDS	1.88	0.1646	0.78	0.6543	0.31	0.1250
Gastrointestinal bleeding	1.50	0.0039	1.48	0.0067	1.11	0.4750
Neurological disease	1.61	0.0002	1.06	0.6721	1.02	0.8722
Years on dialysis *per 1 year*	1.02	0.1551	1.01	0.1783	1.00	0.8418
Serum albumin *per 0.1 g/dL*	0.99	0.0101	0.99	0.0936	0.98	0.0065

AOR is odds ratio adjusted for all other variables listed.

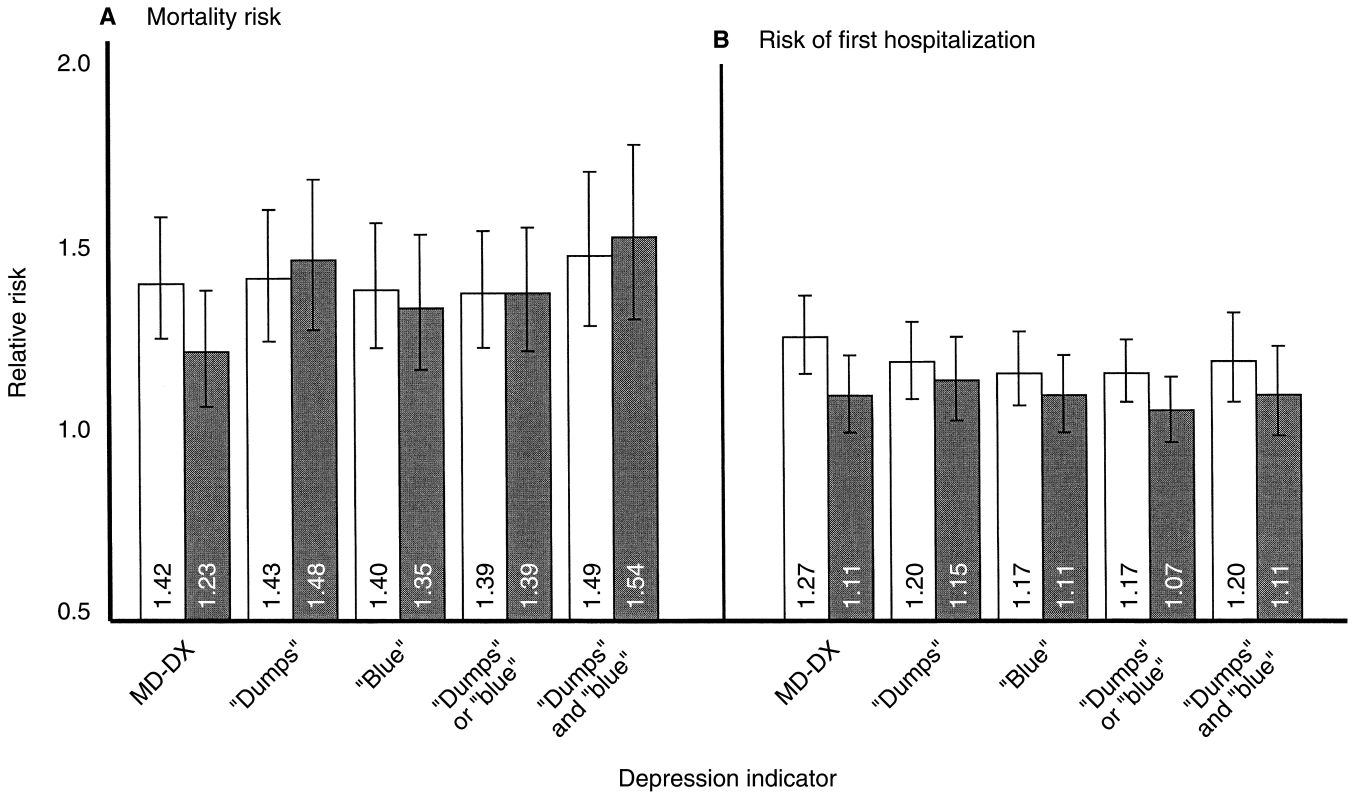

Fig. 1. Unadjusted (□) and adjusted (■) relative risks of mortality and first hospitalization for depressed as compared to non-depressed patients. Three indicators of depression were used: physician diagnosis (MD-DX) and two self-reported indicators, "so down in the dumps" ("dumps") and "downhearted and blue" ("blue"). The numbers printed on each bar represent the point estimate of the relative risk. The vertical lines represent the upper and lower limits of the 95% confidence intervals of the relative risks. The adjusted Cox models included the factors listed in Table 2, and were stratified by country.

The logistic regression model (Table 3), revealed that younger age, the presence of diabetes mellitus, lung disease, gastrointestinal bleeding, not being diagnosed as hypertensive, having finished high school, and not being employed were independently and significantly associated with a higher likelihood of self-reported depression as measured by the "so down in the dumps" question. In contrast to physician-diagnosed depression, the likelihood of self-reported depression as measured by the "so down in the dumps" question was lower for whites than for patients of "other races" (excluding blacks). Compared to whites, blacks had a lower likelihood of depression, as measured by physician-diagnosis and by both self-report questions. With the exception of gastrointestinal bleeding, the associations between comorbid conditions and depression were very similar for the results of both the "downhearted and blue" and the "so down in the dumps" self-report questions.

Rates of death and first hospitalization as restricted to those who filled out the patient questionnaire

Among the subjects who filled out the patient questionnaire, 1613 deaths were observed (16 deaths per 100 patient-years): 1146 deaths among the United States patients (18.2 deaths per 100 patient-years) and 467 among the European patients (12.4 deaths per 100 patient-years; $P < 0.0001$). First hospitalization after study entry was observed for 3409 patients with a hospitalization rate of approximately 67 cases per 100 patient-years: 1973 hospitalizations among United States patients (67.3 first hospitalizations per 100 patient-years) and 1436 among European patients (67.6 first hospitalizations per 100 patient-years; $P = 0.4567$). The rates of death and first hospitalization were not significantly different between depressed patients who received and those who did not receive antidepressive medication. The associations between depression and death and depression and first hospitalization did not differ significantly between the United States and European patients.

Physician-diagnosed depression and outcomes as restricted to those who filled out the patient questionnaires

Mortality. Figure 1 shows the estimates of the unadjusted and adjusted associations between physician-diagnosed depression and the mortality risk. In the unad-

justed model, the mortality risk was 42% higher in patients with depression (RR = 1.42, 95% CI = 1.27 to 1.60; $P < 0.0001$). A reduction in the RR was observed after the factors listed in Table 2 and country of residence were included in the model (RR = 1.23, 95% CI = 1.08 to 1.40; $P < 0.0001$). The adjusted RR for the mortality risk was similar and remained statistically significant after removing patients on antidepressive medication (RR = 1.25, 95% CI = 1.08 to 1.45; $P = 0.0028$).

Patients with physician-diagnosed depression, as compared with those without the diagnosis of depression, had a significantly ($P < 0.0001$) higher withdrawal rate (3.7 vs. 2.3 per 100 patient-years). Patients with physician-diagnosed depression also had significantly higher rates of death attributed to cardiac (10.4 vs. 8.2 cases per patient-years; $P = 0.0027$), infectious (3.3 vs. 2.2 cases per 100 patient-years; $P = 0.0066$) and vascular (2.6 vs. 1.5 cases per 100 patient-years; $P = 0.0022$) causes. The death rate attributed to malignant diseases also was higher for patients with physician diagnosis of depression, but the difference did not reach statistical significance ($P = 0.3682$).

First hospitalization. Figure 1 also shows estimates of the association between physician-diagnosed depression and the risk of first hospitalization. In the unadjusted model, the risk of hospitalization was significantly higher among patients with physician-diagnosed depression (RR = 1.27, 95% CI = 1.17 to 1.38, $P < 0.001$). The RR decreased, but remained statistically significant, after the demographic factors, socioeconomic variables, comorbid indicators, years on dialysis and country of residence were included in the model (RR = 1.11, 95% CI = 1.01 to 1.22, $P < 0.04$). The adjusted RR for first hospitalization was similar and remained significant after removing patients on antidepressive medication (RR = 1.12; 95% CI = 1.02-1.23; $P = 0.0235$).

Physician-diagnosed depression and outcomes including those who did not fill out the patient questionnaire

Including the subjects who did not fill out the patient questionnaire, the prevalence of physician-diagnosed depression was 18.7%. Among these patients the rate of death was approximately 20 cases per 100 patient-years, and the rate of first hospitalization was 68 cases per 100 patient-years. The adjusted RRs of the associations between physician-diagnosed depression and outcomes were 1.27 (95% CI = 1.15 to 1.42; $P < 0.0001$) and 1.14 (95% CI = 1.05-1.24; $P = 0.002$) for mortality and first hospitalization, respectively. These data are not shown.

Self-reported depression and patient outcomes

Mortality. As shown in Figure 1, self-reported depression as measured by the "so down in the dumps" question was associated with increased risk of mortality in the unadjusted model (RR = 1.43; 95% CI = 1.26 to 1.62, $P < 0.0001$) in a pattern similar to that observed for physician-diagnosed depression. In contrast to physician-diagnosed depression, however, the association between self-reported depression by the "so down in the dumps" question and mortality did not decrease after all covariates were included in the model (RR = 1.48; 95% CI = 1.29 to 1.70; $P < 0.0001$).

Patient self-reported depression as measured by the "downhearted and blue" question also was associated with increased risk of mortality. In the unadjusted model, the risk of death was 40% higher among those classified as depressed by the "downhearted and blue" question (RR = 1.40; 95% CI = 1.24 to 1.58; $P < 0.0001$). This association remained significant (RR = 1.35; 95% CI = 1.18 to 1.55; $P < 0.0001$) after the inclusion of all covariates in the Cox model.

By comparing patients who had a positive response to either the "so down in the dumps" or "downhearted and blue" questions with the other subjects, similar RRs were observed in the unadjusted (RR = 1.39; 95% CI = 1.24 to 1.56; $P < 0.0001$) and adjusted (RR = 1.39; 95% CI = 1.23 to 1.57; $P < 0.0001$) models. The unadjusted (RR = 1.49; 95% CI = 1.30 to 1.72; $P < 0.001$) and adjusted (RR = 1.54; 95% CI = 1.32 to 1.79; $P < 0.0001$) RRs of mortality were higher when patients with a positive response for both depression indicators were compared to the rest of the sample.

Patients self-classified as depressed had significantly ($P < 0.01$) higher rates of withdrawal from dialysis, for both the "so down in the dumps" (3.6 and 2.2 per 100 patient-years) and the "downhearted and blue" questions (3.1 and 2.2 per 100 patient-years). Also for both self-reported indicators of depression the rates of death for major causes (that is, cardiac, infectious, vascular and malignant diseases) were higher for those classified as depressed. A statistical significant difference, however, was only observed for cardiac causes: 8.0 and 6.0 per 100 patient-years for depressed and non-depressed, respectively ($P < 0.01$).

In a Cox model with both indicators of depression but without physician diagnosed depression, "so down in the dumps" was more strongly associated with mortality risk (adjusted RR = 1.36, $P = 0.0004$) than the "downhearted and blue" question (adjusted RR = 1.16, $P = 0.0897$). The question "so down in the dumps" (adjusted RR = 1.46, $P < 0.0001$) was also more strongly associated with mortality risk than physician diagnosed depression (adjusted RR = 1.20, $P = 0.0127$) when both variables were included in the same model.

In an analysis restricted to patients not taking antidepressive medication, the adjusted RR of mortality was 1.48 (95% CI = 1.28 to 1.72; $P < 0.0001$) for the "so down in the dumps" question and 1.34 (95% CI = 1.16 to 1.55; $P < 0.0001$) for the "downhearted and blue"

question. The associations between self-reported depression and mortality did not differ significantly between patients receiving and those not receiving antidepressive medications.

First hospitalization. For the "so down in the dumps" and the "downhearted and blue" questions, the unadjusted RRs of hospitalization were 1.20 (95% CI = 1.10 to 1.31; $P < 0.001$) and 1.17 (95% CI = 1.08 to 1.28; $P < 0.01$), respectively. The corresponding adjusted RRs were 1.15 (95% CI = 1.04 to 1.27; $P = 0.03$) and 1.11 (95% CI = 1.01 to 1.22; $P = 0.04$).

The unadjusted and adjusted RRs of first hospitalization were, respectively, 1.17 (95% CI = 1.09 to 1.26; $P < 0.001$) and 1.07 (95% CI = 0.08 to 1.16; $P = 0.12$) when depression was defined by a positive response to either the "so down in the dumps" or the "downhearted and blue" question. The corresponding unadjusted and adjusted RRs of first hospitalization comparing patients with a positive response for both indicator variables with the rest of the sample were 1.20 (95% CI = 1.09 to 1.33; $P = 0.0003$) and 1.11 (95% CI = 1 to 1.24; $P = 0.05$).

In a model with both indicators of depression, but without physician-diagnosed depression, "so down in the dumps" was marginally significantly (1.09, $P = 0.0855$) associated with first hospitalization and no significant association was observed for depression by the "downhearted and blue" question (RR = 1.06; $P = 0.3598$). The adjusted RRs of first hospitalization were 1.11 ($P = 0.0362$) for physician-diagnosed depression and 1.14 ($P = 0.0101$) for the "so down in the dumps" question, when both variables were in the model.

In an analysis restricted to patients not taking antidepressive medications, the adjusted RRs were 1.11 (95% CI = 1.01 to 1.24; $P = 0.0402$) and 1.09 (95% CI = 0.99 to 1.20; $P = 0.0951$) for the "so down in the dumps" and "downhearted and blue" questions, respectively. The associations between self-reported depression and hospitalization did not differ significantly between patients receiving and those not receiving antidepressive medications.

Trends in the risks of death and first hospitalization by the patient response to the indicators of depression

Figure 2 depicts the adjusted RR of death and first hospitalization by the six options of response to each of the two questions "so down in the dumps" and "downhearted and blue," using "none of the time" as the referent. A significant trend ($P < 0.001$) toward increased risk of mortality and first hospitalization was observed from "none of the time" to "all the time." The mortality risk was significantly higher ($P < 0.05$) even for those patients who responded to the "so down in the dumps" question with "little" or "some of the time," as compared with "none of the time." Patients who indicated that they felt "downhearted and blue" at least "a good bit of the time" had a significantly higher risk of mortality. Patients who responded "most of the time" or "all of the time" to either the "so down in the dumps" or the "downhearted and blue" question were significantly more likely to experience higher rates of hospitalization.

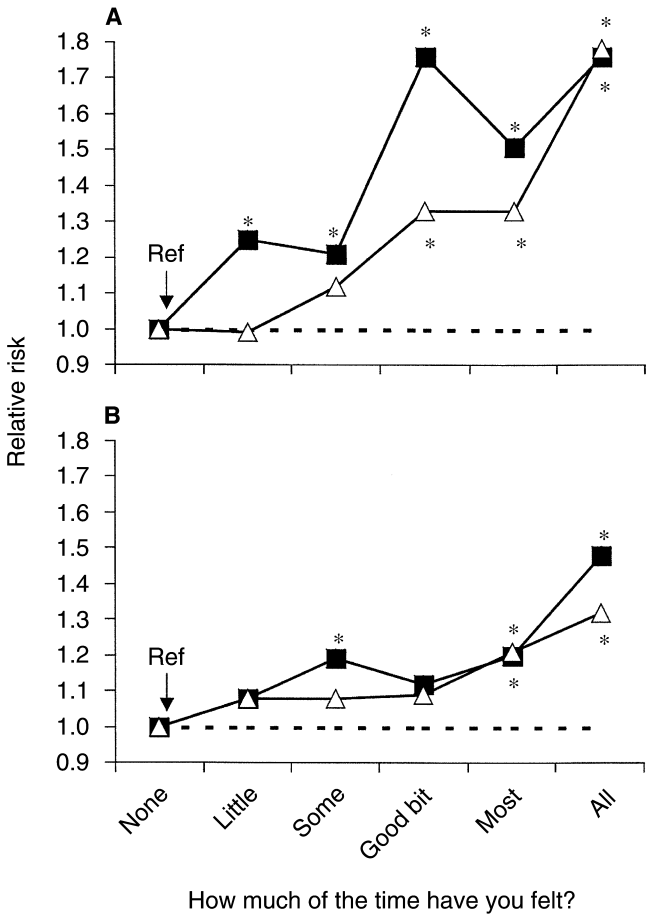

Fig. 2. Adjusted trend in the relative risk of death (*A*) and first hospitalization (*B*) according to level of depression assessed by the questions: (*1*) How much of time have you felt so down in the dumps that nothing could cheer you up (■), and (*2*) How much of the time have you felt downhearted and blue (Δ). "None of the time" is the referent (Ref) group. The dotted lines represent the relative risk (RR) expected under the null hypothesis (RR = 1). The adjusted Cox models included the factors listed in Table 2, and were stratified by country. Statistically significant RRs ($P < 0.05$) are identified with an asterisk (*). The risks of death and hospitalization showed a significant trend ($P < 0.001$) to increase from "none of the time" to "all of the time."

DISCUSSION

Depression was independently associated with higher risks of mortality and hospitalization among hemodialysis patients enrolled in the DOPPS study, both in the United States and Europe. The association between depression and these outcomes remained statistically significant even after adjustments for demographic factors, years on dialysis, comorbidities and country of residence.

These results are consistent with those from other studies which have shown that depressed people are at increased risk for several diseases and related outcomes [8, 9, 22, 23]. A previous study on patients submitted to coronary artery bypass that used a research instrument similar to the one of the present study also found that patients with the highest levels of depressive symptoms according to the "so down in dumps" question had higher rates of hospital readmission [24].

In the logistic regression analysis, age was inversely related to depression. This finding is consistent with observations that showed a lower prevalence of depression among older people [25]. The data also were consistent with a lower likelihood of depression in blacks than in whites. It is important to assess whether this finding explains the lower mortality risk in black than in white ESRD patients treated by dialysis [3, 26, 27]. The odds of hypertension were lower in patients with self-reported depression, a finding that cannot be fully explained by the covariates included in the present analysis. A previous study has shown that in hemodialysis patients, low predialysis blood pressure and both high and low postdialysis blood pressure are associated with increased mortality [28]. The odds of diabetes mellitus, an important indicator of worsened prognosis in hemodialysis patients [29, 30], also were significantly higher among patients classified as depressed. Previous observations in patients without ESRD are also consistent with relationships of depression to the risk [31] and the prognosis of diabetes [32].

Our findings indicate that the two simple questions used as indicators of depression have predictive validity for important outcomes in hemodialysis patients. Methodological limitations of the present study and differences between our findings and those from previous studies, however, must be taken into consideration. In this study, depression was only assessed at the start of the follow-up. As depressive symptoms vary over time, we cannot be sure that our measures of depressive symptoms reflect an average level of depression for patients during the follow-up period [33]. Some data suggest that depression tends to be more severe during the first months of dialysis [5]. By contrast we found a tendency for a higher prevalence of depression, particularly by the "so down in the dumps" question, in patients with more than one year on dialysis.

Unfortunately, it was not possible to assess whether depression preceded the development of specific comorbidities. A previous study by Friend et al, however, showed that depression at the start of follow-up was associated with the development of hypoalbuminemia [34], a known risk factor for mortality in ESRD patients [35, 36]. In contrast, they did not find an association between initial albumin level and the development of depression.

It should be noted that the prevalence of physician-diagnosed depression and the death rate increased when subjects who have not responded to the patient questionnaire were included in the analysis. Moreover, the RR for both mortality and first hospitalization related to physician-diagnosed depression increased after including the patients with missing information on self-reported indicators of depression. This is consistent with the possibility that some patients did not respond to the questionnaire because they had more severe depressive symptoms. Thus, non-response may have contributed to reduce the strength of the associations between depression and the two hemodialysis outcomes.

The agreement between physician-diagnosed and each self-reported indicator of depression was low. It is important to observe, however, that the physician diagnosis of depression took into account the previous 12 months and might not reflect the actual situation of the patient at study start. Moreover, the presence of certain comorbidities could have influenced the physicians to diagnose depression in patients who were not self-classified as depressed. According to our results, however, the use of antidepressives for a fraction of patients should not have influenced the observed associations between self-reported depression and the outcomes.

Even though the rate of dialysis withdrawal was higher in depressed patients, the observed difference could not fully explain the association between depression and the mortality risk. Other causes of death, such as cardiac, vascular and infectious diseases also contributed to the higher mortality risk among depressed patients. Additional research is needed to assess whether the association between depression and hemodialysis outcomes is influenced by modifiable factors not fully addressed in the present study, such as poor patient compliance, poor nutrition, high phosphorus, and increased interdialytic weight gain [37–39].

In conclusion, depression was significantly and independently associated with increased risks of mortality and hospitalization in a representative sample of facilities and hemodialysis patients from the United States and Europe. This study provides evidence that even a single assessment of depression by simple questions can help identify hemodialysis patients at higher risk of death and hospitalization. We propose that these questions, particularly the "so down in the dumps" question, be used in clinical practice to identify hemodialysis patients with depressive symptoms so that they can receive more detailed evaluation and special psychosocial or medical attention to reduce the risks of hospitalization and death. As research instruments, these questions deserve to be considered for inclusion in future investigations. Clinical trials are warranted to assess whether interventions to prevent and control depression improve quality of life

and decrease the risks of death and hospitalization among hemodialysis patients.

ACKNOWLEDGMENTS

This study was supported by a grant from Kirin-Amgen. Dr. Lopes was supported by a grant (BEX2018/00-4) from the Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Ministry of Education of Brazil.

Reprint requests to Antonio A. Lopes, M.D., Ph.D., University Renal Research and Education Association, 315 W. Huron, Suite 260, Ann Arbor, Michigan 48103, USA.
E-mail: aaslopes@ufba.br or urrea@urrea.org

REFERENCES

1. Port FK, Orzol SM, Held PJ, Wolfe RA: Trends in treatment and survival for hemodialysis patients in the United States. *Am J Kidney Dis* 32:S34–38, 1998
2. Finkelstein FO, Finkelstein SH: Depression in chronic dialysis patients: Assessment and treatment. *Nephrol Dial Transplant* 15:1911–1913, 2000
3. Port FK: Morbidity and mortality in dialysis patients. *Kidney Int* 46:1728–1737, 1994
4. Kimmel PL: Psychosocial factors in dialysis patients. *Kidney Int* 59:1599–1613, 2001
5. Craven JL, Rodin GM, Johnson L, Kennedy SH: The diagnosis of major depression in renal dialysis patients. *Psychosom Med* 49: 482–492, 1987
6. Pratt LA, Ford DE, Crum RM, *et al*: Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* 94:3123–3129, 1996
7. Gallo JJ, Armenian HK, Ford DE, *et al*: Major depression and cancer: The 13-year follow-up of the Baltimore epidemiologic catchment area sample (United States). *Cancer Causes Control* 11: 751–758, 2000
8. Spiegel D: Cancer and depression. *Br J Psychiatry* 168 (Suppl 30):109–116, 1996
9. Mayou RA, Gill D, Thompson DR, *et al*: Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med* 62:212–219, 2000
10. Frasure-Smith N, Lesperance F, Gravel G, *et al*: Social support, depression, and mortality during the first year after myocardial infarction. *Circulation* 101:1919–1924, 2000
11. Irvine J, Basinski A, Baker B, *et al*: Depression and risk of sudden cardiac death after acute myocardial infarction: Testing for the confounding effects of fatigue. *Psychosom Med* 61:729–737, 1999
12. Kimmel PL, Weihs K, Peterson RA: Survival in hemodialysis patients: The role of depression. *J Am Soc Nephrol* 4:12–27, 1993
13. Wai L, Richmond J, Burton H, Lindsay RM: Influence of psychosocial factors on survival of home-dialysis patients. *Lancet* 2: 1155–1156, 1981
14. Shulman R, Price JD, Spinelli J: Biopsychosocial aspects of long-term survival on end-stage renal failure therapy. *Psychol Med* 19: 945–954, 1989
15. Peterson RA, Kimmel PL, Sacks CR, *et al*: Depression, perception of illness and mortality in patients with end-stage renal disease. *Int J Psychiatry Med* 21:343–354, 1991
16. Kimmel PL, Peterson RA, Weihs KL, *et al*: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int* 57:2093–2098, 2000
17. Burton HJ, Kline SA, Lindsay RM, Heidenheim AP: The relationship of depression to survival in chronic renal failure. *Psychosom Med* 48:261–269, 1986
18. 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
19. Lilienfeld DE, Stolley PD: *Foundation of Epidemiology*. New York, Oxford University Press, 1994
20. Allison PD: *Survival Analysis using the SAS System: A Practical Guide*. Cary, SAS Institute Inc., 1995
21. The SAS Institute: *SAS System for Windows* (version 8.0). Cary, SAS Institute Inc.
22. Takeida K, Nishi M, Miyake H: Zung's depression scale as a predictor of death in elderly people: A cohort study in Hokkaido, Japan. *J Epidemiol* 9:240–244, 1999
23. Ziegelstein RC, Fauerbach JA, Stevens SS, *et al*: Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med* 160:1818–1823, 2000
24. Saur CD, Granger BB, Muhlbaier LH, *et al*: Depressive symptoms and outcome of coronary artery bypass grafting. *Am J Crit Care* 10:4–10, 2001
25. Henderson AS, Jorm AF, Korten AE, *et al*: Symptoms of depression and anxiety during adult life: Evidence for a decline in prevalence with age. *Psychol Med* 28:1321–1328, 1998
26. USRDS: *United States Renal Data System 1999 Annual Data Report.* Bethesda, The National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, 1999
27. Cowie CC, Port FK, Rust KF, Harris MI: Differences in survival between black and white patients with diabetic end-stage renal disease. *Diabetes Care* 17:681–687, 1994
28. Port FK, Hulbert-Shearon TE, Wolfe RA, *et al*: Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis* 33:507–517, 1999
29. Lowrie EG, Lew NL, Huang WH: Race and diabetes as death risk predictors in hemodialysis patients. *Kidney Int* 42(Suppl 38): S22–S31, 1992
30. Mailloux LU, Bellucci AG, Mossey RT, *et al*: Predictors of survival in patients undergoing dialysis. *Am J Med* 84:855–862, 1988
31. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ: The prevalence of comorbid depression in adults with diabetes: A meta-analysis. *Diabetes Care* 24:1069–1078, 2001
32. de Groot M, Anderson R, Freedland KE, *et al*: Association of depression and diabetes complications: A meta-analysis. *Psychosom Med* 63:619–630, 2001
33. Gruenberg AM, Goldstein RD: Depressive Disorders, in *Psychiatry*, edited by Tasman A, Kay J, Lieberman JA, St. Louis, W.B. Saunders, 1997, pp 990–992
34. Friend R, Hatchett L, Wadhwa NK, Suh H: Serum albumin and depression in end-stage renal disease. *Adv Perit Dial* 13:155–157, 1997
35. Iseki K, Kawazoe N, Fukiyama K: Serum albumin is a strong predictor of death in chronic dialysis patients. *Kidney Int* 44:115–119, 1993
36. Leavey SF, Strawderman RL, Jones CA, *et al*: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. *Am J Kidney Dis* 31:997–1006, 1998
37. Leggat JE Jr, Orzol SM, Hulbert-Shearon TE, *et al*: Noncompliance in hemodialysis: Predictors and survival analysis. *Am J Kidney Dis* 32:139–145, 1998
38. Kimmel PL, Varela MP, Peterson RA, *et al*: Interdialytic weight gain and survival in hemodialysis patients: Effects of duration of ESRD and diabetes mellitus. *Kidney Int* 57:1141–1151, 2000
39. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis* 31:607–617, 1998