Anxiety Symptoms, Mortality, and Hospitalization in Patients Receiving Maintenance Dialysis: A Cohort Study

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Rationale & Objective: Anxiety symptoms are common in dialysis patients and have a large impact on quality of life. The association of anxiety symptoms with adverse clinical outcomes in dialysis patients is largely unknown. This study examined the association of anxiety symptoms with hospitalization and mortality in patients receiving maintenance dialysis.

Study Design: Prospective cohort study.

Setting & Participants: Maintenance dialysis patients treated at 10 dialysis centers in the Netherlands between 2012 and 2016.

Exposures: Time-varying symptoms of anxiety and depression using the Beck Anxiety Inventory and Beck Depression Inventory.

Outcomes: All-cause mortality, 1-year hospitalization rate, and hospital length of stay.

Analytical Approach: Cox proportional hazards and Poisson regression models adjusted for sociodemographic and clinical variables. Sensitivity analyses included multiple imputation of missing data and restriction to incident patients only.

Results: 687 patients were included, composed of 433 prevalent and 242 incident dialysis patients. Median follow-up time was 3.1 (IQR, 3.0-3.5) years, during which 172 deaths occurred. 22% of patients had anxiety symptoms and 42% had depressive symptoms. Anxiety symptoms were associated with all-cause mortality and 1-year hospitalization rate and length of stay in all multivariable models. Anxiety symptoms showed a clear dose-response relationship with mortality.

Limitations: Depression and anxiety often coexist and share symptoms. The observational design of this study limits inferences about causal mechanisms between anxiety and clinical outcomes.

Conclusions: Anxiety symptoms are independently associated with increased risk for mortality and 1-year hospitalization. Anxiety symptoms are a clinically relevant risk factor for morbidity and mortality in dialysis patients and warrant further research on effective treatment.

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Mood disorders are highly prevalent in patients with end-stage renal disease (ESRD) receiving dialysis,[1] with depressive and anxiety disorders considered the most common. The prevalence ranges from 38% to 53% for anxiety symptoms and 37% to 42% for depressive symptoms, when using a cutoff value in self-report questionnaires.[1-11] Both depressive and anxiety symptoms in dialysis patients are frequently underdiagnosed and untreated.[3,12] These psychiatric comorbid conditions have an important impact on patients' quality of life and are possibly associated with adverse medical outcomes.[1,6,8,12,13]

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During the last 20 years, multiple prospective studies in dialysis patients have provided support for an association between depressive symptoms and adverse outcomes, such as mortality.[14] Although most of the studies available focused on depressive symptoms and their complications, there has been little attention on anxiety symptoms in patients with kidney disease. Furthermore, the few studies available showed that anxiety symptoms were unchanged during extended follow-up, indicating that anxiety symptoms may be persistently high in a substantial number of dialysis patients.[10] A study of peritoneal dialysis patients indicated that anxiety is a significant predictor for mortality (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.0-4.5, after adjustment for confounders).[15] Furthermore, a study in non–dialysis-dependent patients with chronic kidney disease showed a significant association between anxiety symptoms and mortality.[16] To our knowledge, the association between anxiety and adverse clinical outcomes has not been systematically investigated in dialysis patients.

The primary aim of this study is to investigate the association between anxiety symptoms and mortality in dialysis patients. Additionally, this study aims to investigate the association between anxiety and 1-year hospitalization rate and length of stay. For comparison, the association between depressive symptoms and adverse clinical outcomes is investigated in the same manner as anxiety in this cohort. It is important to gain insight into the magnitude of these mental health problems and the associated adverse outcomes to improve treatment and quality of life.

Methods

Study Cohort

Data were obtained from DIVERS (Depression Related Factors and Outcomes in Dialysis Patients With Various

Ethnicities and Races Study). This is an observational prospective-cohort study of dialysis patients from 10 dialysis centers in the Netherlands. The cohort consists of both prevalent and incident dialysis patients included between June 2012 and October 2016. All patients who met the inclusion criteria were approached for study participation during dialysis treatment or during an outpatient appointment. Inclusion criteria were being at least 18 years of age and having a dialysis vintage of at least 90 days. Patients who were unable to fill in self-reported questionnaires were excluded. To improve generalizability, all questionnaires and variables were available in Dutch, English, Turkish, and Moroccan Arabic translations.

Before inclusion, all patients gave written informed consent. This study was approved by the medical ethics committees of all participating hospitals and was carried out in accordance with the Declaration of Helsinki.

Demographic and Clinical Data

At baseline, the following sociodemographic and clinical data were collected from electronic medical records: age, sex, dialysis modality and vintage, comorbid conditions (summarized in the Davies comorbidity score), transplant waiting list status, and current medication use. Incident dialysis patients were defined as new patients on renal replacement therapy for more than 90 and less than 180 days. The primary cause of kidney disease was classified according to the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) coding system and divided into 4 groups (diabetes mellitus, glomerulonephritis, renal vascular disease, and other).[17] The level of comorbidity was defined according to the Davies comorbidity index.[18]

We collected the following characteristics through self-reported questionnaires: immigrant status (defined by using the country of birth), marital status, children, educational level, employment status, current smoking and alcohol use, and previous depression. Quality of life was measured using the 12-Item Short Form Health Survey (SF-12).

Assessment of Exposure: Anxiety and Depression

Anxiety and depressive symptoms were assessed using self-questionnaires, the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI), respectively. Respondents were asked to rate how much each of these symptoms bothered them in the past week, on a scale ranging from 0 (not at all) to 3 (severely). The total score has a minimum of 0 and maximum of 63.

BDI and BAI scores were analyzed primarily as continuous variables because cutoff values vary between studies. For additional analysis and interpretation of the association, a cutoff value was used: BDI score ≥ 13 and BAI score ≥ 16, respectively. Both the BDI and BAI have been validated in a large variety of cohorts with various anxiety and depressive disorders diagnosed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (SCID-1), including cohorts with other long-term somatically ill patients.[19-22] The BAI has high internal consistency (Cronbach $\alpha = 0.92$) and test-retest reliability over 1 week of 0.75.[21,22] For the BDI, a cutoff value of 13 has been validated in a Dutch cohort of dialysis patients.[23] For the BAI, the cutoff of 16 was based on the manual provided by Beck and Steer[20] indicating "clinically significant" anxiety symptoms. Additionally, a severity index for anxiety has been used to investigate dose-response associations. Time-varying variables of anxiety and depression include the baseline and 6-month-interval scores of the BAI and BDI.

Assessment of Clinical Outcome: 1-Year Hospitalization and Mortality

Cause of death, time of death, and 1-year hospitalization rate and length of stay data were collected from electronic medical records for a maximum of 4 years. Cause of death was classified using the ERA-EDTA coding system.[17] Data from baseline to 1 year after inclusion were used in the analysis for the 1-year hospitalization (number of admissions) and hospital length of stay (number of days). When a patient was discharged from the hospital and then admitted again the same day of discharge, the hospital admission was considered as 1 event.

Statistical Analysis

Standard descriptive statistics were used to present baseline characteristics. To investigate changes in visit-levels of anxiety and depression, we used 2 mixed-effects models with a random intercept and random slope with time as a covariate. Time to event was defined as time between inclusion of the patient and date of death or censoring. Patients who underwent kidney transplantation were censored at the time of transplantation. Cox proportional hazard models were used to calculate HRs to determine the hazard of anxiety and depressive symptoms on mortality. The primary analyses on mortality use time-varying continuous scores of the BDI and BAI; the other analyses use baseline information on anxiety and depressive symptoms.

Multivariable adjustment of these HRs was performed to adjust for possible confounding. An a priori sequential order in the regression models was used to examine the effect of these variables on the association of anxiety and depressive symptoms with mortality. The association between anxiety and depression with number of hospitalizations per year (count data) was investigated using Poisson regression models. Multivariable analyses included age, sex, immigrant status, marital status, ever had children (yes/no), low formal education (yes/no), employment, dialysis vintage, incident/prevalent dialysis status, dialysis modality, current smoking, current alcohol use, and the 7-point Davies score. Primary analyses include separate models for anxiety symptoms and depressive symptoms.

To investigate possible interaction between anxiety and depression scores and mortality, the product term of BAI*BDI was added to the model using baseline scores for the BAI and BDI. Due to the possibility of "adjusting for sequelae," we did not include time-varying variables of

Table 1. Baseline Characteristics

Characteristic	All Patients (N = 687)[a]	Anxiety[b]		Depression[c]	
		No (n = 395)	Yes (n = 113)	No (n = 305)	Yes (n = 228)
Demographic					
Age, y	65 ± 15	65 ± 15	62 ± 14	64 ± 16	64 ± 14
Male sex	424 (62%)	238 (62%)	71 (63%)	208 (68%)	143 (63%)
Immigrant	300 (48%)	163 (43%)	67 (61%)	124 (42%)	123 (56%)
Country of birth					
European	366 (58%)	244 (64%)	45 (41%)	193 (65%)	109 (49%)
Sub-Saharan Africa	22 (4%)	13 (3%)	2 (2%)	15 (5%)	5 (2%)
Northern Africa/Western Asia	54 (9%)	19 (5%)	17 (16%)	17 (6%)	24 (11%)
Southern Asia/South Eastern Asia	57 (9%)	33 (9%)	14 (13%)	24 (8%)	21 (10%)
South America/Caribbean	131 (21%)	75 (20%)	32 (29%)	50 (17%)	62 (28%)
Social					
Married	316 (52%)	207 (52%)	55 (49%)	172 (57%)	114 (50%)
Has children	474 (78%)	306 (78%)	87 (78%)	233 (77%)	179 (79%)
Low formal education[d]	127 (22%)	90 (24%)	19 (17%)	51 (17%)	51 (23%)
Not employed	534 (89%)	336 (86%)	107 (95%)	258 (85%)	207 (91%)
Renal and Dialysis					
Incident dialysis patient[e]	240 (36%)	142 (37%)	33 (30%)	122 (40%)	77 (34%)
Vintage of prevalent group, mo	13 [4-47]	11 [4-45]	28 [5-57]	8 [4-39]	15 [4-48]
Treatment modality:					
Hemodialysis	592 (88%)	336 (88%)	100 (89%)	271 (89%)	198 (87%)
Peritoneal dialysis	80 (12%)	47 (12%)	12 (11%)	34 (11%)	30 (13%)
Primary kidney disease					
Diabetic nephropathy	155 (24%)	82 (23%)	38 (36%)	56 (20%)	65 (30%)
Renal vascular disease	163 (26%)	100 (28%)	18 (17%)	71 (26%)	50 (23%)
Glomerulonephritis	70 (11%)	40 (11%)	11 (10%)	35 (13%)	22 (10%)
Other	247 (39%)	140 (39%)	40 (37%)	115 (42%)	79 (37%)
AVG or AVF[f]	435 (65%)	246 (64%)	73 (65%)	231 (76%)	167 (73%)
Kt/V_{urea} at baseline	2.0 [1.5-3.6]	2.0 [1.5-3.4]	1.7 [1.4-3.6]	2.0 [1.4-3.6]	1.8 [1.5-3.1]
Residual diuresis > 100 mL/24 h	475 (71%)	277 (72%)	68 (61%)	219 (72%)	161 (71%)
On waiting list for Tx					
Yes	201 (30%)	124 (32%)	30 (27%)	104 (34%)	69 (30%)
No, for medical reasons	425 (63%)	235 (61%)	71 (63%)	179 (59%)	148 (65%)
No, by patient preference	46 (7%)	24 (6%)	11 (10%)	22 (7%)	11 (5%)
Clinical					
Current smoking	108 (18%)	68 (18%)	23 (21%)	53 (18%)	48 (21%)
Current alcohol use	161 (27%)	110 (28%)	27 (24%)	101 (29%)	36 (23%)
Davies comorbidity score					
Low comorbidity	183 (27%)	109 (29%)	24 (21%)	90 (31%)	51 (23%)
Moderate comorbidity	370 (55%)	212 (55%)	58 (52%)	156 (53%)	133 (59%)
Severe comorbidity	119 (18%)	62 (16%)	30 (27%)	49 (17%)	43 (19%)
Comorbid conditions					
Diabetes mellitus	284 (42%)	154 (40%)	58 (52%)	117 (38%)	105 (46%)
Chronic heart disease	111 (17%)	59 (15%)	24 (21%)	46 (15%)	49 (22%)
Peripheral vascular disease	84 (13%)	53 (14%)	12 (11%)	34 (11%)	34 (15%)

(Continued)

both depression and anxiety into the same model.[24,25] A grouping variable was made to divide patients into 4 mutually exclusive groups: only depression, only anxiety, none, and both anxiety and depression.[26] Sensitivity analyses included the use of only incident dialysis patients in the main analyses of the continuous BAI and BDI scores and clinical outcomes. Additional sensitivity analyses included investigating the association between exposure and mortality using predefined cutoff values for anxiety (BAI score ≥ 16), depression (BDI score ≥ 13), and comorbid anxiety plus depression (patients with both BAI score ≥ 16 and BDI score ≥ 13).

Cause-specific mortality rates were calculated using person-years and ERA-EDTA mortality codes. This study is

Table 1 (Cont'd). Baseline Characteristics

Characteristic	All Patients (N = 687)[a]	Anxiety[b]		Depression[c]	
		No (n = 395)	Yes (n = 113)	No (n = 305)	Yes (n = 228)
Psychiatric and Quality of Life					
Previous depression	27 (4%)	12 (3%)	6 (5%)	9 (3%)	12 (5%)
BDI score	12.9 ± 9.5	9.9 ± 7.4	22.7 ± 14.2	6.4 ± 3.4	21.6 ± 8.1
Depressive symptoms (BDI ≥ 13)	228 (42%)	110 (30%)	80 (83%)	—	—
BAI score	10.3 ± 10.1	6.0 ± 4.5	25.4 ± 9.5	5.6 ± 6.0	16.3 ± 10.9
Anxiety symptoms (BAI ≥ 16)	113 (22%)	—	—	16 (6%)	80 (42%)
HRQoL (SF-12)					
PCS score	38.1 ± 11.1	38.2 ± 10.5	40.0 ± 11.2	40.2 ± 10.3	32.9 ± 9.4
MCS score	48.9 ± 10.8	50.9 ± 9.5	33.0 ± 10.1	53.0 ± 7.7	41.8 ± 10.9

Note: Values are presented as mean ± standard deviation, median [interquartile range], or frequency (percentage).
Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; HRQoL, Health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey; Tx, transplantation.
[a]There were 56 of 687 participating patients who gave permission only to collect data from electronic medical records and did not provide consent for self-report measurement of anxiety, depression, and more. Details on missing values can be found in Table S6.
[b]Defined as BAI score < 16 vs ≥16.
[c]Defined as BDI score < 13 vs ≥13.
[d]Low formal education: highest level of education is high school or less.
[e]Less than 180 days on dialysis.
[f]Versus central venous catheter, for hemodialysis patients only.

not powered to analyze cause-specific mortality in regression models.

Missing Values

To maximize the generalizability of study results from this cohort, participating patients had the option to participate in a nonquestionnaire part of the study. These patients gave consent only to gather information from their electronic patient file without filling in self-reported questionnaires. This provided us with data for characteristics of patients who were otherwise excluded. To assess the impact of missingness on results, missing values for BAI and BDI scores were imputed by using multiple imputation techniques (10 repetitions) as sensitivity analysis.

All statistical analyses were performed using SPSS for Windows, version 24 (IBM Corp).

Results

Baseline Characteristics

A total of 687 dialysis patients were included in this cohort study. Table 1 describes baseline characteristics for all patients and stratified by levels of anxiety and depressive symptoms (BAI score ≥ 16 vs <16 and BDI score ≥ 13 vs <13). The cohort consisted of 433 (64%) prevalent and 240 (36%) incident dialysis patients. Prevalent patients had a median dialysis vintage of 13 (interquartile range [IQR], 4-47) months. Mean age was 65 ± 15 (standard deviation) years, 62% of patients were men, and 48% of patients were immigrants. The cohort had follow-up for a maximum of 4 years, with a median follow-up of 3.1 (IQR, 3.0-3.5) years. A total of 173 (25%) patients died during follow-up.

The group of patients with high anxiety symptoms seemed to differ from the group of patients with low anxiety in immigrant status, diabetes prevalence, depressive symptoms, and Mental Component Summary score on the SF-12, a health-related quality-of-life questionnaire. No major differences were found in social characteristics, vascular access, treatment modality, residual diuresis, and SF-12 Physical Component Summary score.

Using predefined cutoff scores, 22% of patients had anxiety and 42% had depressive symptoms. Comorbid depressive and anxiety symptoms were present in 18% of patients. The majority of patients with anxiety symptoms had depressive symptoms above the cutoff value. Within the anxiety group, 27% of patients reported severe depressive symptoms. Table 2 shows mean anxiety and depressive symptom scores during follow-up. Repeated measurements of depression and anxiety after 6 months showed a progressive drop out due to death (26%), transplantation (21%), moving to another center (5%), and other, such as motivational reasons. Mixed-model analyses showed no significant changes in BDI and BAI scores between the 6-month time points.

Anxiety and Depressive Symptoms and All-Cause Mortality

Anxiety symptoms showed an association with all-cause mortality. The hazard coefficient indicated that a 1-point greater BAI score was associated with a 5.1% greater risk for all-cause mortality, as shown in Table 3 (HR, 1.051; 95% CI, 1.016-1.088; P = 0.004). For depressive symptoms, the same trend is visible: each 1-point greater BDI score was associated with 4.3% greater risk for all-cause mortality (HR, 1.043; 95% CI, 1.004-1.083; P = 0.03).

When confounders are introduced into the model, including a large number of medical comorbid conditions, the regression coefficient showed only minor changes in HR. Table 3 shows individual effects of the confounders on the association between anxiety and mortality as adjusted in an a priori sequential order.

Table 2. Longitudinal Psychosocial Measurements

Characteristic	Baseline (n = 643)	6 mo (n = 440)	12 mo (n = 341)	18 mo (n = 239)	24 mo (n = 164)	30 mo (n = 86)
Anxiety symptoms: BAI score	10.3 ± 10.1	9.7 ± 8.9	9.7 ± 9.9	9.8 ± 9.2	10.2 ± 10.0	10.7 ± 10.1
Depressive symptoms: BDI score	12.9 ± 9.5	12.8 ± 9.6	12.4 ± 9.9	14.0 ± 10.6	13.9 ± 10.8	13.9 ± 9.9
HRQoL (SF-12)						
PCS score	38.1 ± 11.1	36.7 ± 10.2	37.3 ± 10.4	35.1 ± 10.6	33.9 ± 9.8	33.2 ± 9.9
MCS score	48.9 ± 10.8	48.5 ± 10.6	48.2 ± 10.2	48.2 ± 10.7	48.7 ± 10.7	47.4 ± 11.9

Note: Values are presented as mean ± standard deviation. Mixed-model analyses showed no significant changes in the BDI and BAI scores between the 6-month-interval time points. BDI: estimate of 0.174 (−0.036 to 0.383) on change in BDI score per 6 months ($P = 0.1$). BAI: estimate of −0.133 (−0.361 to 0.096) on the change in BAI score per 6 months ($P = 0.3$).
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; HRQoL, Health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey.

Additional analyses using predefined cutoff values and the severity index of anxiety and depressive symptoms showed similar results, which are shown in Tables S1 to S3. Both anxiety and depressive symptoms showed a dose response: higher burden of symptoms was associated with higher risk for all-cause mortality.

Interaction Between Anxiety and Depressive Symptoms and Cause-Specific Mortality

The interaction term of anxiety*depression was not significant when introduced in regression models using baseline anxiety and depression scores, with $P = 0.4$ in the univariable and $P = 0.6$ in the multivariable models, respectively. These results indicate that there is no interaction between anxiety and depression on mortality in this cohort.

Cause-specific mortality rates were stratified by the presence of anxiety or depression, as shown in Table S4. Patients with anxiety or depression have higher rates of cardiovascular mortality and withdrawal from dialysis therapy compared with patients without anxiety or depression.

Anxiety and Depressive Symptoms and 1-Year Hospitalization Data

Both anxiety and depressive symptoms were significantly associated with number of hospitalizations and length of stay in both in the univariable and multivariable models, as shown in Tables 4 (1-year hospitalization rate) and S5 (length of stay). The coefficient indicated that a 1-point greater score (for either BAI or BDI) was associated with 1.8% greater 1-year hospitalization rate. The majority (52%) of patients had at least 1 hospitalization during the first year of follow-up, with 16% having 3 or more hospitalizations. Median hospital length of stay was 6 (IQR, 2-14) days.

Missing Values

Table S6 describes the amount of missing items per variable and a stratified baseline table for patients with a complete BAI (n = 507) versus patients with missing items on the BAI (n = 180). Baseline demographic and clinical variables extracted from the electronic patient file had <5% missing values. The overall percentage of missing items on returned questionnaires was 4.6% for the BDI and 7.8% for the BAI. Missing data on self-reported questionnaires consisted of: (1) patients who participated in the non-questionnaire part of this study (8% of total cohort), (2) patients with missing items on the BAI (14%) and BDI (12%), and (3) patients with a completely missing BAI (4%) and BDI (2%) score. Sensitivity analyses, using multiple imputation of missing items and questionnaires, showed no major differences compared to the complete case analyses.

Table 3. Association of Time-Varying Anxiety and Depression With Mortality With Sequential Adjustment

	Time-Varying Anxiety Symptoms	Time-Varying Depressive Symptoms
Model 1 (crude)	1.050 (1.018-1.083) $P = 0.002$[a]	1.032 (0.998-1.067) $P = 0.07$
Model 2: model 1 + age, sex	1.055 (1.023-1.087) $P = 0.001$[a]	1.034 (1.000-1.069) $P = 0.05$[a]
Model 3: model 2 + ethnicity	1.055 (1.024-1.088) $P < 0.001$[a]	1.040 (1.004-1.077) $P = 0.03$[a]
Model 4: model 3 + marital status, children, educational level, employment	1.056 (1.024-1.089) $P = 0.001$[a]	1.040 (1.004-1.077) $P = 0.03$[a]
Model 5: model 4 + dialysis vintage, modality, incident or prevalent patient	1.056 (1.024-1.089) $P = 0.001$[a]	1.039 (1.002-1.076) $P = 0.04$[a]
Model 6: model 5 + smoking, alcohol	1.057 (1.023-1.093) $P = 0.001$[a]	1.044 (1.006-1.082) $P = 0.02$[a]
Model 7 (fully adjusted): model 6 + comorbid conditions[b]	1.051 (1.016-1.088) $P = 0.004$[a]	1.043 (1.004-1.083) $P = 0.03$[a]

Note: Cox proportional hazard models investigating the association of anxiety or depression (separate models) with mortality using an a priori sequential order approach to include possible explanatory variables. Values are presented as hazard ratio (95% confidence interval) for mortality per 1-point greater score. For each 10-point greater score, using the fully adjusted model, the associated mortality risk is 64% greater for the Beck Anxiety Inventory, and 52% greater for the Beck Depression Inventory.
[a]Statistical significance.
[b]Davies comorbidity score includes diabetes mellitus, congestive heart failure, ischemic heart disease, peripheral disease, chronic obstructive pulmonary disease, liver disease, cancer, and collagen vascular disease.

Table 4. Association of Baseline Anxiety and Depression with 1-Year Hospitalization Rate With Sequential Adjustment

	Baseline Anxiety Symptoms	Baseline Depressive Symptoms
Model 1 (crude)	1.021 (1.013-1.028) $P < 0.001$	1.022 (1.014-1.030) $P < 0.001$
Model 2: model 1 + age, sex	1.021 (1.013-1.028) $P < 0.001$	1.023 (1.015-1.031) $P < 0.001$
Model 3: model 2 + ethnicity	1.018 (1.011-1.026) $P < 0.001$	1.021 (1.012-1.029) $P < 0.001$
Model 4: model 3 + marital status, children, educational level, employment	1.020 (1.012-1.027) $P < 0.001$	1.021 (1.013-1.030) $P < 0.001$
Model 5: model 4 + dialysis vintage, modality, incident or prevalent patient	1.018 (1.011-1.026) $P < 0.001$	1.021 (1.012-1.030) $P < 0.001$
Model 6: model 5 + smoking, alcohol	1.021 (1.012-1.029) $P < 0.001$	1.021 (1.012-1.030) $P < 0.001$
Model 7 (fully adjusted): model 6 + comorbid conditions[a]	1.018 (1.009-1.026) $P < 0.001$	1.018 (1.009-1.027) $P < 0.001$

Note: Poisson regression models investigating the association of anxiety or depression (separate models) with 1-year hospitalization using an priori sequential order approach to include possible explanatory variables. Values are presented as rate ratio (95% confidence interval) for 1-year hospitalization per 1-point greater score, along with *P* value. All *P* values were statistically significant. For each 10-point greater score, using the fully adjusted model, the associated 1-year hospitalization rate is 20% greater for the Beck Anxiety Inventory and 20% greater for the Beck Depression Inventory. Interaction was investigated in an additional model (model 8): when the interaction term anxiety*depression was introduced in model 7, including both the baseline depressive and anxiety scores, the *P* value was not significant ($P = 0.3$).
[a]Davies comorbidity score includes diabetes mellitus, congestive heart failure, ischemic heart disease, peripheral disease, chronic obstructive pulmonary disease, liver disease, cancer, and collagen vascular disease.

Discussion

This study investigates the effect of anxiety and depressive symptoms on clinical outcomes in dialysis patients. Anxiety and depressive symptoms are highly prevalent in this dialysis cohort, remained high during follow-up, and were associated with mortality, likelihood of hospital admission, and increased hospital length of stay. After adjustment for several confounders, including clinical comorbid conditions, these associations showed no major changes.

Studies on anxiety and depressive symptoms report a wide range in prevalence, which could be explained by the use of different measurement tools, different cutoff values, and differences in patient characteristics. A review of 55 studies by Murtagh et al[7] in 2007 in long-term dialysis patients reported a weighted average prevalence of anxiety symptoms of 38%, which is in line with results from the current study.[2,8] The few studies available on the longitudinal development of anxiety and depressive symptoms showed mixed results. Overall, our results indicate that anxiety and depressive symptoms tend to remain high, once elevated, and are not likely to be self-limiting. Studies by Ng et al[10] and Cukor et al[27] showed the same trend.

Our findings differ from that of Chilcot et al,[28] who showed that depressive symptoms were higher at the start of dialysis treatment. Sensitivity analyses in this cohort using only incident dialysis patients showed no major differences with prevalent patients in the clinical course of both anxiety and depressive symptoms.

Although the impact of anxiety symptoms on quality of life has been well established, the impact on adverse clinical outcomes is less known.[12] Studies investigating the association between anxiety and mortality in dialysis patients are scarce and small. A study by Griva et al[15] (n = 201) in peritoneal dialysis patients from Singapore showed that anxiety is an important predictor of mortality, with an HR of 2.1 (95% CI, 1.0-4.5). A smaller study by Preljevic et al[4] (n = 103) did not show a significant association between SCID-I anxiety diagnosis and mortality or between comorbid anxiety plus depression and mortality. Although this study by Preljevic et al[4] had a long follow-up of almost 4 years, it was underpowered, with only 18 patients having anxiety disorder and a total of 6 mortality events in these groups.[4] The present study found an association between anxiety symptoms and mortality in both the baseline and time-dependent analysis. The use of this time-dependent variable takes the possible fluctuating anxiety states or scores into account, thus supporting the possible association between (persistent) anxiety symptoms and mortality.

The association between depressive symptoms and mortality has been well studied. The meta-analysis by Farrokhi et al[14] reported an overall significant association between depression and mortality (HR, 1.5; 95% CI, 1.3-1.7) in dialysis patients. Depressive symptoms and mortality showed mixed results in our analyses. When using the crude model, the association of time-varying or baseline BDI score with mortality was not significant (Table 3; HR, 1.032 [95% CI, 0.998-1.067]; P = 0.07). The fully adjusted model using time-varying BDI score showed a significant association with mortality (Table 3; HR, 1.043 [95% CI, 1.004-1.083]; P = 0.03). For interpretation of the main analyses, it is important to take into account that use of a time-varying risk factor gives a relatively short-term effect measure compared to using fixed baseline risk factors.[25] Sensitivity analyses in our cohort using a pre-defined BDI cutoff score of 13 to define depression showed a nonsignificant HR of 1.20 (95% CI, 0.82-1.75; P = 0.3).

Several factors may play a role when comparing our results with the meta-analysis: (1) the meta-analysis

showed high heterogeneity, (2) the percentage of immigrant patients in our study is substantially higher compared with most studies in the meta-analysis, (3) our study uses the relatively low cutoff score for the BDI (ie, 13), and (4) the authors of the meta-analysis state that possible publication bias may play a role in the reporting of nonsignificant results. With these points in mind, results from this study fit well within the funnel-plot described by Farrokhi et al.[14]

In general, it is difficult to isolate the unique role of anxiety and depressive symptoms because of the overlap between somatic symptoms from ESRD and psychiatric symptoms. The interplay between anxiety, depression, and clinical outcome is complex and difficult to evaluate. Most patients who scored high on anxiety symptoms also scored high on depressive symptoms. This indicates that scores of depression and anxiety are likely to overlap when screening is implemented.

With this study, we aim to provide an important step in understanding the clinical significance of anxiety symptoms in dialysis patients. This study shows the univariable and multivariable effect of anxiety and depression on medical outcomes. Sociodemographic and clinical factors did not show a major impact on the associations with mortality in this cohort. This highlights the clinical significance of anxiety symptoms, in addition to depressive symptoms. Our results indicate that there is no evidence for interaction between anxiety and depression on mortality.

More insight into the causes of anxiety symptoms is necessary. Studies show a variety of possible factors that may play a role in the anxiety experience of patients, from short-term anxiety-inducing factors (such as frequent alarms from the dialysis machines and new clinic staff) to long-term factors (such as decreased social support).[8,10,29] These factors could be addressed in patient treatment.[8,30] In addition, more insight into the possible causal pathway between anxiety and mortality is necessary, including patient-related factors such as low treatment adherence and biochemical mechanisms. There are several plausible biochemical pathways through the hypothalamic-pituitary-adrenal axis and inflammatory pathways that show associations with severe mental health conditions in dialysis patients.[31] Furthermore, studies could differentiate between the impact of chronic anxiety versus newly developed anxiety due to ESRD.[29]

The results of this study need to be interpreted with possible limitations in mind. First, for studies investigating these symptoms it is important to take into account the overlap between depression, anxiety, and the kidney disease or medical comorbid conditions. Because these psychiatric and somatic comorbid conditions often coexist and share symptoms, it is difficult to measure the effect of a single disease.[12,32] In this study, we performed several stepwise multivariable analyses, including a large set of somatic variables and comorbid conditions. This enables us to give an indication of the independent effect of anxiety and depressive symptoms. However, it remains difficult to interpret the independent effect of anxiety due to the strong overlap with depression. Although the interaction term was not significant, thorough analysis of possible interaction in this cohort between anxiety and depression was not possible due to small groups of patients with only one exposure (only depression or only anxiety).

Second, this study uses self-reported anxiety and depressive symptoms and not a *DSM-IV* diagnosis. Furthermore, this study used time-varying continuous variables for the main analysis. However, for clinical interpretation, 10-point increments are more easily interpretable.

Third, missing data in this study are a possible limitation for the generalizability of these results. In this study, we included patients who were not willing to fill in self-reported questionnaires, which allowed us to assess the impact of missingness. Sensitivity analyses using multiple imputation of missing values on the BDI and BAI showed no major differences compared with the complete case analyses.

Last, we acknowledge that anxiety measurement tools in dialysis patients need to be used more often in these patients to fully understand the impact and validity in a broad range of patient groups with ESRD and ultimately provide cutoff values that can be used for screening. Although the BAI lacks validation in this specific patient group, it is one of the most accepted tools internationally to measure anxiety measures in clinical populations and has been validated in a number of different patient populations, including somatically ill patient groups.

Strengths include the prospective nature of data collection with high-quality follow-up data and use of time-varying risk factors. Furthermore, by using questionnaires in 4 languages, ethnic minorities have better representation compared with other studies. The multicenter nature of this study further improves the generalizability of our results.

Anxiety symptoms are highly prevalent and independently associated with increased risk for mortality, hospital admission rate, and hospital length of stay. This study provides clinicians and researchers with an indication of the clinical significance of anxiety in dialysis patients. Future studies should take anxiety symptoms into account when investigating mental health in dialysis patients. More research is needed to identify effective treatments for anxiety symptoms and provide the clinicians with the evidence for practical guidelines.

Supplementary Material

Supplementary File (PDF)

Table S1: Proportion of deaths during follow-up stratified by level of anxiety and depressive symptoms.

Table S2: Association of levels of anxiety and depression with mortality.

Table S3: Association of anxiety and depression with mortality using cutoff scores.

Table S4: Cause-specific mortality rates stratified by the presence of anxiety and depression.

Table S5: Association of anxiety and depression with length of stay in hospital.

Table S6: Description of missing values per baseline characteristic.

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