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Dimensions of Depressive Symptoms and Their Association With Mortality, Hospitalization, and Quality of Life in Dialysis Patients: A Cohort Study

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ABSTRACT

Objective: Unraveling specific dimensions of depressive symptoms may help to improve screening and treatment in dialysis patients. We aimed to identify the best-fitting factorial structure for the Beck Depression Inventory-II (BDI) in dialysis patients and to assess the relation of these structure dimensions with quality of life (QoL), hospitalization, and mortality.

Methods: This prospective study included chronic dialysis patients from 10 dialysis centers in five hospitals between 2012 and 2017. Dimensions of depressive symptoms within the BDI were analyzed using confirmatory factor analysis. To investigate the clinical impact of these dimensions, the associations between symptom dimensions and QoL, hospitalization rate, and mortality were investigated using logistic, Poisson, and Cox proportional hazard regression models. Multivariable regression models included demographic, social, and clinical variables.

Results: In total, 687 dialysis patients were included. The factor model that included a general and a somatic factor provided the best-fitting structure of the BDI-II. Only the somatic dimension scores were associated with all-cause mortality (hazard ratio of 1.7 [1.2–2.5], $p < .007$) in the multivariable model. All dimensions were associated with increased hospitalization rate and reduced QoL.

Conclusions: The somatic dimension of the BDI-II in dialysis patients was associated with all-cause mortality, increased hospitalization rate, and reduced QoL. Other dimensions were associated with hospitalization rate and decreased QoL. These findings show that symptom dimensions of depression have differential association with adverse clinical outcomes. Future studies should take symptom dimensions into account when investigating depression-related pathways, screening, and treatment effects in dialysis patients.

Key words: depression, dimensions, CKD, dialysis, mortality, hospitalization.

INTRODUCTION

Chronic kidney disease (CKD) is a highly prevalent health problem, affecting around 10% of the global population (1–3). End-stage renal disease requires lifesaving dialysis treatment or transplantation. Many patients on dialysis report severe psychological distress, such as depressive symptoms, with an estimated prevalence of up to 43% (2,4–6). Depression is underrecognized and undertreated in dialysis patients, which could be related to the overlap of depressive symptoms with symptoms of CKD (i.e., fatigue, loss of appetite) (6–11). The identification of specific dimensions of depression in these patients may increase our knowledge of the underlying mechanism and help to develop a more individualized screening and treatment approach. To address the issue of symptom diversity and subtyping, several attempts have been made to specify more homogenous subgroups within depression in somatically ill patient groups (12–14).

BDI = Beck Depression Inventory-II, **CFA** = Confirmatory Factor Analysis, **CFI** = comparative fit index, **CKD** = chronic kidney disease, **DSM** = Diagnostic and Statistical Manual of Mental Disorders, **G-S-C model** = general-somatic-cognitive dimensions of the BDI, **HR** = hazard ratio, **QoL** = quality of life, **RMSEA** = root mean square error of approximation, **SF-12** = 12-item Short Form Health Survey, **95% CI** = 95% confidence interval of the corresponding effect measure estimate

SDC Supplemental Content

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Major depressive disorder is a condition marked by the presence of different combinations of symptoms (15,16). Depression may well represent a diversity of dimensions that each has a separate pathophysiology, clinical course, and associations with adverse clinical outcomes, such as mortality. Dimensions of somatic and cognitive symptoms can easily be obtained using the Beck Depression Inventory (BDI) as a screening instrument (17). However, these dimensions of depressive symptoms may differ between populations (18). Clinical studies on the dimensional or factorial structure of depressive symptoms in dialysis patients are sparse. Chilcot et al. (14,19) examined several factor structures of the BDI-II in patients with various stages of end-stage renal disease and a recent study in hemodialysis patients and found a three-factor model: general-somatic-cognitive (G-S-C). This finding is in line with the study of Thombs et al. (20), who validated a comparable G-S-C factor model in patients with acute myocardial infarction. In cardiac patients, latent factor analyses distinguished a similar two main dimensional structures of depressive symptoms: somatic/affective and cognitive/affective (21–24). The somatic/affective dimension of depression was found to be associated with an increased risk of adverse cardiovascular outcomes in patients with heart disease (21,22,24,25). Data on the association between symptom dimensions and adverse clinical outcomes in dialysis patients are unknown. In general, depressive symptoms in dialysis patients are associated with an increased risk of hospitalization and mortality, and impaired health-related quality of life (QoL) (3,6,26). However, the results of studies investigating these associations are inconsistent. A recent meta-analysis by Farrokhi et al. (6) showed that only 15 of 31 studies found a significant association. The heterogeneity of these results could be explained by differences in cohort characteristics and measurement tools and by the complex and diverse nature of depression. More insight into the heterogeneous nature of depression and the clinical course with adverse clinical outcomes could lead to a better understanding of clinically relevant subtypes of depressive symptoms.

The first aim of this study was to identify the best-fitting factorial structure for the BDI-II in dialysis patients by means of confirmatory factor analysis (CFA). The second aim was to explore whether the identified factor dimensions are associated with adverse clinical outcomes. Based on the available literature in cardiac patients, we hypothesized that the somatic dimension of depression is more strongly associated with all-cause mortality, increased hospitalization rate, and reduced QoL in dialysis patients than the general and cognitive dimension.

METHODS

Study Cohort

Data were obtained from the DIVERS study, an observational, prospective cohort study among chronic dialysis patients in 10 dialysis centers of four urban teaching hospitals and one university hospital in the Netherlands. The cohort consists of both prevalent and incident dialysis patients, included between 2012 and 2017. All patients who met the inclusion criteria were approached for study participation during dialysis treatment or during an outpatient appointment. Patients were included if they were at least 18 years of age and had a dialysis vintage of at least 90 days. Patients who were unable to complete self-reported questionnaires by themselves or with help from a research nurse 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 ethical committees of all participating hospitals and was carried out in accordance with the Declaration of Helsinki.

Demographic, Social, and Clinical Data

At baseline, the following sociodemographic and clinical data were collected from electronic medical records: age, sex, dialysis modality and vintage, comorbidities (summarized in the Davies comorbidity score), primary cause of kidney disease, routine laboratory measures, transplantation waiting list, and medication use. Incident dialysis patients were defined as new patients on renal replacement therapy >90 and <180 days. The primary cause of kidney disease was classified according to the European Renal Association–European Dialysis and Transplant Association coding system, and causes were divided into four groups: diabetes mellitus, glomerulonephritis, renal vascular disease, and other (27). The level of comorbidity was defined according to the Davies comorbidity index, indicating no, intermediate, or severe comorbidity, and a seven-point severity scale (used in the multivariable analyses) (28).

We collected the following characteristics through self-reported questionnaires: ethnicity (defined as immigrant status based on the country of birth), marital status, children, educational level, working status, current smoking and alcohol use, and previous depression.

Depressive Symptoms

Depressive symptoms were measured using the BDI-II. (29) Respondents were asked to rate how much each of these symptoms had bothered them in the past week, on a scale ranging from 0 (not at all) to 3 (severely). The total score ranges from a minimum of 0 to a maximum of 63. The BDI was analyzed primarily using a cutoff value. Sensitivity analysis included the use of the continuous scores. The BDI has been validated in a large variety of cohorts with various depressive disorders, diagnosed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) (7). Two studies demonstrated that the BDI self-reported rating scale is a valid screening tool for detecting depression in dialysis patients. Dialysis patients were regarded as having a depressive disorder if they scored at least 13 points on the BDI (7,30). In the present study, the term "depression" refers to patients who scored above this predefined cutoff score for clinically relevant depressive symptoms (BDI $\geq$13), not to a clinical diagnosis. The internal consistency of the total BDI in dialysis patients is high (Cronbach $\alpha = .90$), and the test-retest reliability for 1 week is 0.75. (31)

Clinical Outcomes: QoL, Hospitalizations, and Mortality

The primary clinical end point of this study was all-cause mortality. Cause and time of death were collected with a maximum follow-up of 4 years. Cause of death was classified using the European Renal Association–European Dialysis and Transplant Association coding system. Data from baseline to 1 year after inclusion were used to calculate the hospitalization rate in number of hospitalizations per year. If a patient had been discharged from hospital and was admitted again on the same day, the hospital admittance was considered one event. QoL was measured using the 12-item Short Form Health Survey (SF-12), consisting of both a mental component score and a physical component score.

Statistical Analysis

Standard descriptive statistics were used to present baseline characteristics for the total study population depending on the variable and underlying distribution.

Factor Analysis

The factor structure of the BDI-II was analyzed using CFA with robust full-information maximum likelihood estimation. Full-information maximum likelihood estimation is robust for missing data and nonnormally

distributed data (32). The models were identified using the marker-item approach, which means that the loading of the first item of every subscale is fixed to 1 and its intercept is set to 0. Model fit was interpreted by inspecting fit indices, using the following rules of thumb: the comparative fit index (CFI) indicates acceptable fit greater than 0.900 and good fit greater than 0.950, the root mean squared error of approximation (RMSEA) indicates good fit less than 0.060, and the standardized root mean squared residual indicates good fit less than 0.080 (33). These fit indices should be considered in combination, so a good fit meets all these criteria (33). The best-fitting model was obtained by means of an iterative process, starting with factor models found in the literature (14,19,34) and adapting the model until adequate model fit was obtained. These analyses were performed in R (R Core Team), using the package lavaan (35).

Association With Adverse Clinical Outcomes

Univariable and multivariable regression models were used to investigate the association between the different dimensions of depressive symptoms and adverse clinical outcomes, including QoL, hospitalization, and all-cause mortality. General, cognitive, and somatic symptom dimensions were investigated in all regression models. Variables were included in a predefined stepwise manner to show the effect of the extra included variables on the effect estimates. The multivariable models included the following:

- Model 1: crude effect measure
- Model 2: adding sex, age, and ethnicity incident/prevalent to model
- Model 3: adding children yes/no, married yes/no, paid job yes/no, education level
- Model 4: adding dialysis vintage, dialysis modality (hemodialysis versus peritoneal dialysis), incident/prevalent, and the seven-point Davies comorbidity score (including diabetes mellitus, congestive heart failure, ischemic heart disease, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, cancer, and collagen vascular disease), laboratory measures (hemoglobin, albumin, Kt/V, and calcium)
- Model 5: adding physical component score of the QoL (SF-12)

All models used the dichotomous scores for the symptom dimensions as the outcome variable. Because no cutoff value for the cognitive and somatic symptom dimension is validated, the median value was used for dichotomization. For the general BDI score, a validated cutoff of 13 was used.

Quality of Life

QoL was investigated using the SF-12 total scores in linear regression models.

Hospitalization

Hospitalization numbers were presented as count data, displaying the number of hospitalizations during the first year after inclusion (number/year). The association between depressive symptoms and hospitalization was studied using Poisson regression models.

Mortality

Median survival time was calculated using the life table method (Kaplan-Meier). Time to event was calculated using the moment of inclusion as starting point. Patients who, at the end of their follow-up, were lost to follow-up, were transplanted, or had recovery of renal function were censored. The hazard ratio (HR) for survival for the different dimensions was estimated using Cox proportional hazards analysis. To allow for direct comparison between groups of patients, we divided the population into binary (lowest-highest) cognitive, and somatic dimensions.

Dose-response association between the symptom dimensions and mortality was investigated by using the quartiles of the symptom scores and the continuous scores as the independent variable.

Sensitivity analyses included stratified analyses of incident and prevalent dialysis patients, including a test for multiplicative and additive interaction (36,37).

Missing Values

To avoid bias, missing values of the BDI were imputed using multiple imputation techniques (10 repetitions) as a sensitivity analysis.

All statistical analyses were performed using SPSS for Windows version 24.

RESULTS

Baseline Characteristics

In total, 687 dialysis patients were included in this prospective cohort study. Table 1 describes the baseline characteristics. Baseline demographic and clinical variables had <5% missing values. The overall percentage of missing questions on the BDI was 4.6%. The cohort consisted of 433 (63%) prevalent and 253 (37%) incident dialysis patients, 62% of the patients were men, and the mean age was 64 (±15) years. The cohort had a follow-up for a maximum of 4 years, with a median follow-up of 3.1 years (interquartile range, 3.0–3.5). In total, 173 participants died during this study. The primary causes of end-stage renal failure were diabetic nephropathy (24%), renal vascular disease (26%), and polycystic kidney disease (6%). Total comorbidity scores were divided into low (27%), intermediate (55%), and severe (18%). The most prevalent comorbidities were diabetes and hypertension, with prevalence rates of 42% and 64%, respectively. Most of the patients had children (78%), 52% were married, 38% had a low education level, and 89% of this cohort did not have paid work. Four percent of the dialysis patients reported a depression in the past, and 10% used antidepressant medication at baseline. A third (34%) of the patients described a self-perceived need of a psychologist now or in the future. Mean (standard deviation) BDI scores were 12.9 (9.6), with 43% of the patients having depressive symptoms above the predefined threshold (BDI-II ≥13).

Factor Analysis to Identify Symptom Dimensions of Depression

This study investigated existing factor models and searched for the best-fitting factor model in a cohort of chronic dialysis patients. Existing factor models did not yield an adequate fit in this sample (Table 2). The model of Chilcot et al. (19) did not converge. In an iterative process, we tried one-factor, two-factor, and three-factor models, also including bifactor models as proposed by Beck and Steer (17) and Chilcot et al. (19). We found no evidence for a separate cognitive or affective factor in the factor analyses. The best-fitting model comprised one overall general depression factor that included all items, and an orthogonal somatic factor (Table 2). This model showed acceptable fit (CFI = 0.934, RMSEA = 0.052; Table 2). The process for obtaining this model can be found in the R code (Supplemental Digital Content 1, http://links.lww.com/PSYMED/A571). In conclusion, the best-fitting factor model for this cohort of chronic dialysis patients includes a general and a somatic symptom dimension.

Association Between Symptom Dimensions and Adverse Clinical Outcomes

The second step in the analyses focused on which symptom dimensions were the most important risk factor for adverse clinical outcomes. Only the somatic dimension of depressive symptoms in the BDI showed a significant association with all-cause mortality, where the general and cognitive dimensions did not, as shown in

TABLE 1. Baseline Characteristics

Characteristic	All Patients (*n* = 687)
Demographic	
Age, M (SD), y	64 (16)
Sex (men), *n* (%)	424 (62)
Ethnicity (immigrant patients), *n* (%)	300 (49)
Smoking currently (yes), *n* (%)	108 (18)
Smoking >3 mo in lifetime, *n* (%)	373 (63)
Needed help in filling in questionnaires, *n* (%)	138 (27)
Children (yes), *n* (%)	474 (78)
Low education, *n* (%)	227 (38)
Not employed, *n* (%)	534 (89)
Renal and dialysis	
Incident dialysis patients, *n* (%)	253 (37)
Prevalent dialysis patients, *n* (%)	433 (63)
Dialysis vintage of prevalent group, median (IQR), mo	13 (4–46)
Treatment modality, *n* (%)	
Hemodialysis	601 (88)
Peritoneal dialysis	84 (12)
Primary renal disease, *n* (%)	
Diabetic Nephropathy	155 (24)
Renal vascular disease	163 (26)
Glomerulonephritis	70 (11)
Other	247 (39)
Vascular access (only HD patients), *n* (%)	
Shunt	508 (85)
Kt/V urea at baseline, M (SD)	2.6 (1.5)
On waiting list for Tx, *n* (%)	203 (29)
No because of medical reasons	436 (63)
No because of patient preference	46 (7)
Clinical	
Davies comorbidity score, *n* (%)	
Low comorbidity	183 (27)
Moderate comorbidity	228 (55)
Severe comorbidity	533 (18)
Comorbidities, *n* (%)	
Diabetes mellitus	288 (42)
Chronic heart disease	114 (17)
Peripheral vascular disease	84 (12)
Laboratory measures, M (SD)	
Kt/V per week	2.6 (1.5)
Albumin, M (SD), g/L	37.0 (5.3)
Calcium, M (SD), mmol/L	2.3 (0.2)
Hemoglobin, M (SD), mmol/L	7.1 (0.8)
Psychiatric	
Receiving psychological care at baseline, *n* (%)	27 (4)
Previous depression in life (self-reported), *n* (%)	27 (4)
Current use of antidepressants, *n* (%)	65 (9)
Self-perceived need of a psychologist (yes), *n* (%)	60 (10)
Willing to talk to a psychologist in the future (yes), *n* (%)	190 (34)
Already in contact with a psychologist (yes), *n* (%)	24 (5)
Depressive symptoms (BDI), continuous score, M (SD)	12.9 (9.6)
BDI cutoff ≥13, *n* (%)	228 (43)
Health-related quality of life (SF-12), M (SD)	
SF-12 physical component mean summary score	38.1 (11.1)
SF-12 mental component mean summary score	48.9 (10.9)

Continued on next page

TABLE 1. *(Continued)*

BDI = Beck Depression Inventory; HD = hemodialysis; IQR = interquartile range; M (SD) = mean (standard deviation); SF-12 = 12-item Short Form Health Survey; Tx = therapy.

the survival plots in Figure 1. All dimensions (general, cognitive, and somatic) showed a significant association with hospitalization and QoL, as shown in Table 3.

Patients with the highest somatic subgroup score (somatic score ≥7) showed a significant association with mortality (HR = 1.5 [95% confidence interval [CI] = 1.1–2.1]) and hospitalization (rate ratio = 1.4 [95% CI = 1.2–1.6]). The cognitive and general symptom dimension showed a similar association with hospitalization, as shown in Table 3. In a multivariable model (model 4 in Table 3), adjusting for many comorbidities, the associations between the symptom dimensions with mortality and hospitalization showed only a minor change, which highlights the independent nature of the associations. Model 5 in Table 3 showed an additional adjustment for the physical component score of the QoL questionnaire SF-12. The same trend for hospitalization is visible for all dimensions, where both the crude and fully adjusted models showed no major difference.

There seems to be a clear dose-response association between the somatic dimension and mortality, as shown in Table 4 where the quartiles of the dimensions are used. In addition to the dichotomization of the dimension scores, we analyzed the association between the continuous symptom scores with mortality. The continuous somatic score showed an association with mortality with an HR of 1.048 (95% CI = 1.009–1.089, $p = 0.02$). The continuous cognitive score did not show an association (HR = 0.995 [95% CI = 0.967–1.024, $p = 0.7$]).

As a sensitivity analyses, we compared the main analyses between incident and prevalent dialysis patients, as shown in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/PSYMED/A572). The tests for interaction indicated that there is no interaction between incident status and symptom dimension scores (the exposures) on all-cause mortality (the primary outcome) on both an additive and a multiplicative scale. Stratified results show that a) the effect of depressive symptoms on hospitalization is stronger in incident patients compared with prevalent patients for all dimensions, b) the effect of the somatic dimension on mortality is more pronounced in incident patients, and c) the effect on QoL does not show major differences in all dimensions between incident and prevalent patients.

TABLE 2. Performance of Dimensional Models in DIVERS Compared with the Existing Literature

	DIVERS		Chilcot et al. (14,19)		Thombs et al. (20)	
Dimension Models	CFI	RMSEA	CFI	RMSEA	CFI	RMSEA
Somatic/affective-cognitive (38)	0.896	0.065	0.955	0.058	0.92	0.07
General-somatic-cognitive (Chilcot et al. (19)	[a]	[a]	0.983	0.037	0.92	0.07
General-somatic (DIVERS, 2019)	0.934	0.052	—	—	—	—

CFI = comparative fit index; RMSEA = root mean square error of approximation.

CFI ≥ 0.90 indicates adequate (or okay) fit, and CFI ≥ 0.95 indicates good fit (37). RMSEA < 0.06 is considered to demonstrate good fit (39).

[a] Did not converge.

All symptom dimensions showed associations with QoL scores, but the association was more pronounced for the somatic dimension ($\beta = -2.3$) than for the cognitive and general dimensions ($\beta = -1.4$ and $\beta = -1.08$, respectively). In conclusion, only the somatic symptom dimension showed significant associations with hospitalization rate and mortality, whereas the cognitive and general symptom dimension did not.

DISCUSSION

This study identified a general and a somatic dimension structure in dialysis patients. The somatic dimension showed an association with hospitalization, mortality, and QoL, in contrast to the cognitive and general dimension.

Symptom Dimensions of Depressive Symptoms in Dialysis Patients

CFA showed that the general-somatic (G-S) bifactor model had the best overall fit (CFI = 0.950, RMSEA = 0.046). In previous studies, latent factor analyses distinguished two main dimensions of depressive symptoms in somatically ill patients: somatic and cognitive (S-C), with or without a general factor (G-S-C). However, we found very weak factor loadings for the cognitive factor in this dialysis cohort, as shown in Table 5. Furthermore, the G-S-C factor model did not show a good model fit, as shown in Table 2. When we compare the factor loadings in this study with the factor loadings of Chilcot et al. (14,19) and Thombs et al. (20), we did not find major differences, as shown in Supplemental Table 2 (Supplemental Digital Content 3, http://links.lww.com/PSYMED/A573). Both Chilcot et al. and Thombs et al. found relatively low factor loadings for the cognitive items (19,20,23). Our findings suggest that the G-S (general-somatic) symptom dimension is a well-fitting and appropriate bifactor model for the BDI-II in dialysis patients.

Several factors might play a role in the poor performance of the G-S-C models in our cohort, as proposed by Beck and Steer (17), Thombs et al. (20), and Chilcot et al. (14,19).

First, our population might differ from the existing literature in patient characteristics and symptom distribution. Dialysis patients are older and have a higher comorbidity score compared with the populations where the original scales and dimensions were developed. Furthermore, the somatic burden in dialysis patients is usually higher compared with other somatically ill patient groups, such as diabetes and cardiology patients. This does not explain the discrepancy, however, with the cohort from Chilcot et al. (19) in dialysis patients. A possible explanation could be the ethnic differences between our cohorts. There is a lack of data on ethnic differences in depressive symptoms in general and specifically in symptom dimensions. As Chilcot et al. stated in 2008, it is important to take cultural and ethnic differences into account before generalizing the results to all populations. Our cohort consists of 49% immigrant patients, which could lead to altered symptom scoring, altered symptom dimensions, and differential associations with adverse clinical outcomes.

Second, there might be a difference in symptom distribution compared with the existing literature. Because most studies do not report the symptom distribution of the BDI in their cohort, we were unable to compare this directly with, for example, cardiology patients. To allow future studies to compare their symptom distribution, we added the symptom distribution of the BDI-II in this cohort in Table 6. This table shows that the somatic symptoms are highly prevalent compared with the cognitive symptoms when compared with the symptom distribution of psychiatric patient cohorts (18).

Third, the dialysis session itself could interfere with self-reported symptoms, both cognitive and somatic. Chilcot et al. (39) found a high level of agreement between onsite and offsite measurement of the BDI; however, patients scored significantly higher on the somatic component of the BDI while filling in the questionnaires during the dialysis sessions. Although the differences were relatively small (only one point on the somatic scale), it could lead to altered scoring, especially on the somatic dimension. We do not know if this could also lead to altered associations. To the best of our knowledge, no studies have compared onsite and offsite self-reported questionnaires when investigating associations with adverse outcomes.

Association Between Dimensions and Adverse Clinical Outcomes

Only the somatic symptom dimension showed a significant association with mortality in the multivariable models. All symptom dimensions (cognitive, somatic, and general) showed associations with hospitalization rate and QoL, as visually shown in Figure 2. These findings are in line with a study of de Jonge et al. (24), who reported that somatic/affective symptom dimensions of depression were associated with an increased risk of adverse cardiovascular death in patients with heart disease. The general dimension of depressive symptoms showed no significant association with mortality in our cohort. Although multiple studies and a meta-analysis indicated that depressive symptoms were associated with mortality in CKD and hemodialysis patients, studies show heterogeneous

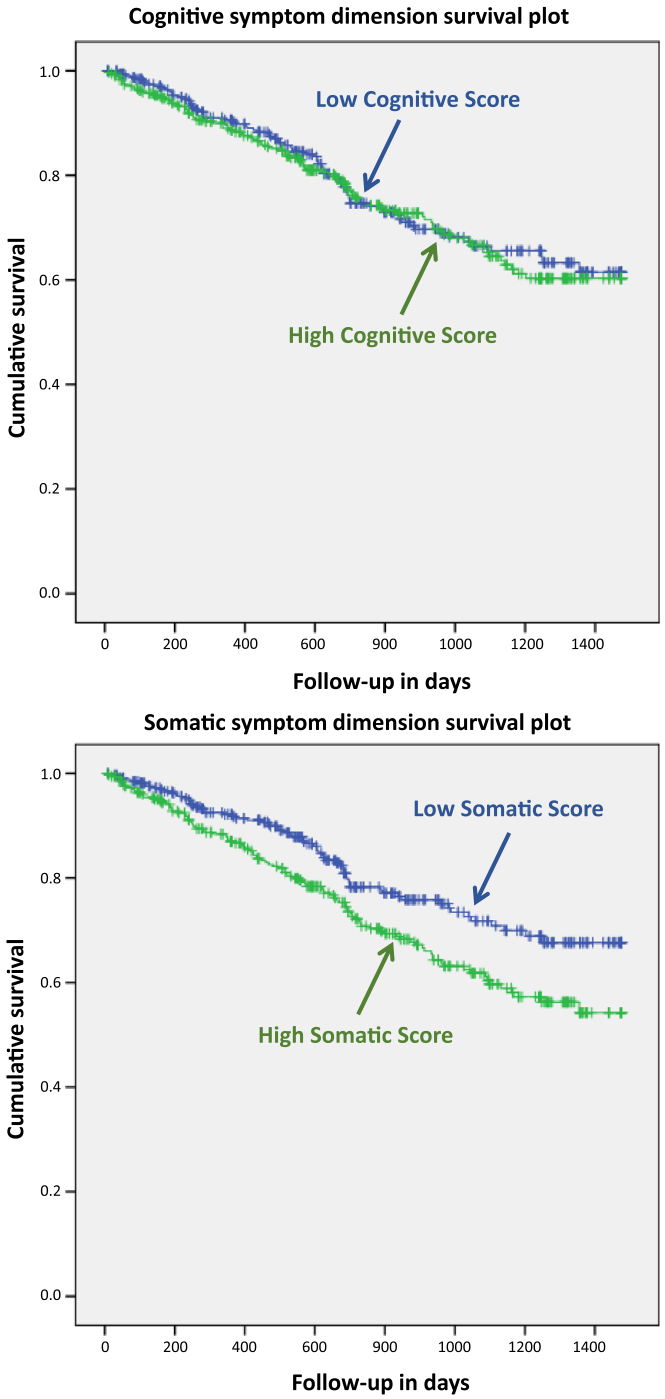

FIGURE 1. Kaplan-Meier survival plots for the cognitive and somatic symptom dimension. Color image is available only in online version (www.psychosomaticmedicine.org).

results (6). Our study did not find a significant association of the total BDI score with mortality. However, the results do not differ much from the meta-analysis when the CIs are compared: an HR of 1.3 (95% CI = 0.8–1.9; model 4 in Table 3) versus an HR of 1.5 (95% CI = 1.3–1.7) found in the meta-analysis. The authors state that this might be caused by between-study heterogeneity in reports of depressive symptoms, design, and analysis (6). In our study, we found a difference between incident and prevalent patients, with higher effect measures for the association between symptom dimensions and adverse clinical events in incident patients compared with prevalent patients; however, we found no evidence for interaction between incident status and symptom dimension on the primary outcome. Future studies should take these differences into account and adjust for this variable or provide stratified analyses.

To the best of our knowledge, there are no published data on the impact of symptom dimensions on adverse clinical outcomes

TABLE 3. Association Between Symptom Dimensions and Adverse Clinical Outcomes and Quality of Life

Sequential Modeling	Somatic Dimension (≥7)	Cognitive Dimension (≥3)	General BDI Score (BDI ≥ 13)
Mortality (HR + 95% CI)			
1. Univariable/crude	1.5 (1.1 to 2.1), $p = .007$	1.1 (0.8 to 1.4), $p = .67$	1.2 (0.8 to 1.7), $p = .36$
2. + Age, sex, ethnicity	1.6 (1.2 to 2.2), $p = .004$	1.3 (0.9 to 1.7), $p = .16$	1.4 (1.0 to 2.0), $p = .088$
3. + Social characteristics	1.7 (1.2 to 2.3), $p = .002$	1.3 (0.9 to 1.8), $p = .14$	1.4 (0.9 to 2.0), $p = .11$
4. + Dialysis, comorbidity, laboratory	1.7 (1.2 to 2.5), $p = .007$	1.3 (0.9 to 1.8), $p = .25$	1.3 (0.8 to 1.9), $p = .24$
5. + Physical component score SF-12	1.5 (1.0 to 2.3), $p = .03$	1.1 (0.7 to 1.6), $p = .79$	1.1 (0.7 to 1.8), $p = .60$
Hospitalization (RR + 95% CI)			
1. Univariable/crude	1.4 (1.2 to 1.6), $p < .001$	1.4 (1.2 to 1.6), $p < .001$	1.4 (1.2 to 1.7), $p < .001$
2. + Age, sex, ethnicity	1.3 (1.1 to 1.6), $p < .001$	1.4 (1.2 to 1.6), $p = .001$	1.4 (1.2 to 1.7), $p < .001$
3. + Social characteristics	1.3 (1.1 to 1.5), $p = .001$	1.3 (1.1 to 1.6), $p = .001$	1.4 (1.2 to 1.7), $p < .001$
4. + Dialysis, comorbidity, laboratory	1.3 (1.0 to 1.5), $p = .015$	1.4 (1.2 to 1.7), $p < .001$	1.5 (1.2 to 1.8), $p < .001$
5. + Physical component score SF-12	1.3 (1.0 to 1.5), $p = .015$	1.4 (1.2 to 1.7), $p < .001$	1.5 (1.2 to 1.8), $p < .001$
Quality of life (β + 95% CI)			
1. Univariable/crude	−9.7 (−12.3 to −7.1), $p < .001$	−11.7 (−14.3 to 9.2), $p < .001$	−18.3 (−20.9 to 15.7), $p < .001$
2. + Age, sex, ethnicity	−9.4 (−12.1 to 6.7), $p < .001$	−11.6 (−14.2 to 8.9), $p < .001$	−18.8 (−21.6 to 16.1), $p < .001$
3. + Social characteristics	−14.3 (−16.9 to 11.9), $p < .001$	−17.0 (−19.4 to 14.5), $p < .001$	−19.3 (−22.0 to 16.5), $p < .001$
4. + Dialysis, comorbidity, laboratory	−13.5 (−16.3 to 10.7), $p < .001$	−16.9 (−19.6 to 14.2), $p < .001$	−18.7 (−21.8 to 15.6), $p < .001$

BDI = Beck Depression Inventory; HR = hazard ratio; CI = confidence interval; SF-12 = 12-item Short Form Health Survey; RR = rate ratio.

Stepwise sequential modeling approach is used to investigate the associations of depressive symptoms with adverse clinical outcomes using cutoff values. The median value is used for the cognitive and somatic scores and BDI ≥ 13 for the general score. Social characteristics include children, paid job, education, and married. Dialysis characteristics include dialysis vintage, dialysis modality (hemodialysis versus peritoneal dialysis), incident or prevalent, and Davies comorbidity (0–7). Laboratory measures include hemoglobin, albumin, Kt/V, and calcium.

in dialysis patients. Our study showed that the somatic dimension was associated with all-cause mortality in dialysis. The association of this somatic dimension with adverse clinical outcomes shows no major changes after adjustment for demographic factors and extensive somatic comorbidity. The dose-response association further supports the association between the somatic dimension and adverse clinical outcomes. The cognitive dimension only showed an association with QoL and hospitalization and not with mortality.

Overlap Between Somatic Illness and Depressive Symptoms

In this field of research, it is important to take the interplay between somatic disease and psychiatric disease into account when investigating patient reported symptoms and the associations with adverse clinical outcomes. The overlap between depressive symptoms and somatic illness is complex, and psychiatric and somatic symptoms in dialysis patients often coexist and share (part) of their pathophysiology (9,10). In Figure 2, we tried to visualize these complex interactions. In this study, we performed several stepwise multivariable analyses on the association between depressive symptoms and clinical outcomes, as shown in Table 3. These analyses included a large set of clinical variables to be able to better interpret the possible confounding and shared causal pathways with each added step in the stepwise modeling. These results indicate that there is an independent effect of (dimensions of) depressive symptoms on clinical outcome, which highlights its clinical significance. These results are in line with a recent meta-analysis investigating the independent association between depression and mortality (6). The relationship of specific symptom dimensions of depressive symptoms with biochemical dimensions in chronic dialysis patients should be a topic of further research. Depression may well represent a diversity of dimensions, with each having separate pathophysiology, clinical course, and possibly different reaction to treatment. Depression and renal disease could have parallel inflammatory or hypothalamic-pituitary-adrenal axis pathways, as suggested by a wide range of studies investigating this relationship (40). Regardless of the underlying pathways, it is important that future studies focus on the effectiveness of treatment of these highly prevalent symptoms. Data from the current study suggest that improving the somatic symptom dimensions might have a larger impact on the associated adverse

TABLE 4. Investigating the Dose-Response Association Between Symptom Dimensions and Mortality

Quartiles of Scores	*n* (%)	Crude HR for Mortality
Somatic subscore		
0–25 (0–4)	145 (26)	1
25–50 (4–7)	161 (29)	1.29 (0.77–2.16), $p = .34$
50–75 (7–10)	129 (23)	1.63 (0.97–2.73), $p = .064$
75–100 (>10)	123 (22)	1.73 (1.03–2.90), $p = .037$
Cognitive subscore		
0–25 (0–1)	187 (33)	1
25–50 (1–3)	112 (20)	0.83 (0.51–1.34), $p = .44$
50–75 (3–8)	168 (30)	0.87 (0.57–1.32), $p = .51$
75–100 (>8)	103 (18)	0.80 (0.49–1.33), $p = .39$

HR = hazard ratio.

TABLE 5. Standardized Factor Loadings of the Modified G-S Model of the BDI

Depressive Symptoms From BDI-II	Factor 1 (General)	Factor 2 (Somatic)
Sadness	0.698	
Pessimism	0.659	
Sense of failure	0.673	
Dissatisfaction*/loss of pleasure**	0.743	
Guilt	0.589	
Punishment	0.477	
Self-dislike	0.670	
Self-accusations*/self-criticalness**	0.587	
Suicidal ideas	0.465	
Crying	0.529	
Agitation	0.579	
Loss of interest	0.675	
Indecisiveness	0.661	
Worthlessness	0.669	
Loss of energy	0.519	0.350
Changes in sleeping	0.338	0.420
Irritability	0.655	
Change in appetite	0.399	0.404
Concentration	0.575	0.331
Fatigue	0.521	0.428
Loss of libido		0.396

G-S = general-somatic; BDI = Beck Depression Inventory.

Only standardized factor loadings ≥0.30 are shown in the table.

* $p < .05$.

** $p < .01$.

clinical outcomes. However, to test this hypothesis, intervention studies should investigate the treatment effects on all dimensions of depressive symptoms.

Clinical Implications and Future Use of Symptom Dimensions

Our findings suggest that symptom dimensions need further attention in dialysis patients, both in research and in clinical practice. Although the factor analysis showed that the correlation between cognitive items was low, both the cognitive and somatic dimensions of depression showed associations with hospitalization and QoL. More studies are needed to draw solid conclusions regarding the dimensional structure of depressive symptoms in dialysis patients. Future studies could take the symptom dimensions into account when investigating associations between depression and adverse clinical outcomes, especially when investigating the association with mortality. Besides the cognitive and somatic dimensions, the results of this cohort study showed that the general factor is independently strongly correlated with all BDI-II items. This indicates that the BDI-II total score provides a good overall measurement of depressive symptoms in dialysis patients. More studies are needed to investigate the effectiveness of interventions on (specific dimensions of) depressive symptoms and adverse outcomes.

Limitations

The results of this study should be interpreted with the following limitations in mind. First, this study is an observational cohort study, where possible causality between symptoms and adverse clinical outcomes cannot be determined. The results from this study indicate that symptom dimensions show differential associations and could be a relevant factor when investigating depression and assessing the effectiveness of treatment in future clinical trials. Second, we did not obtain the *DSM* diagnosis depression by means of a structured interview or clinical assessment. Therefore, these results refer to severity of depressive symptoms and not necessarily to a major depressive disorder. However, Chilcot et al. (30) and Loosman et al. (7) demonstrated that the BDI self-reported rating scale is a valid screening tool for detecting depression in dialysis patients, which they validated with a *DSM* diagnosis. Third, we included both incident and prevalent dialysis patients, creating a difference in baseline characteristics. However, the combination of both incident and prevalent patients improves the generalizability of our results to the entire dialysis population in clinical practice. Additional sensitivity analysis revealed that the risks of mortality and hospitalization are highest in the incident patients compared with the prevalent patient population. Fourth, depressive symptoms measured during a dialysis session can influence

TABLE 6. Prevalence and Mean Scores of BDI-II Items in This Cohort

BDI-II	% of Patients With This Symptom	M (SD)
Somatic dimension		
Loss of energy	89	1.39 (0.81)
Changes in sleeping	74	1.12 (0.89)
Change in appetite	61	0.83 (0.82)
Concentration	47	0.61 (0.75)
Fatigue	85	1.28 (0.86)
Loss of libido	70	1.36 (1.14)
Cognitive dimension		
Loss of interest[a]	35	0.48 (0.77)
Indecisiveness[a]	33	0.50 (0.82)
Irritability[a]	35	0.47 (0.72)
Sadness	28	0.39 (0.73)
Pessimism	47	0.75 (0.97)
Sense of failure	19	0.33 (0.76)
Dissatisfaction/loss of pleasure	54	0.73 (0.81)
Guilt	17	0.23 (0.59)
Punishment	14	0.30 (0.84)
Self-dislike	29	0.40 (0.70)
Self-accusations/self-criticalness	31	0.44 (0.46)
Suicidal ideas	11	0.14 (0.46)
Crying	31	0.48 (0.85)
Agitation	34	0.43 (0.71)
Worthlessness	28	0.38 (0.69)

BDI = Beck Depression Inventory; M (SD) = mean (standard deviation).

[a] Part of the somatic-affective dimension in the Beck and Steer model.

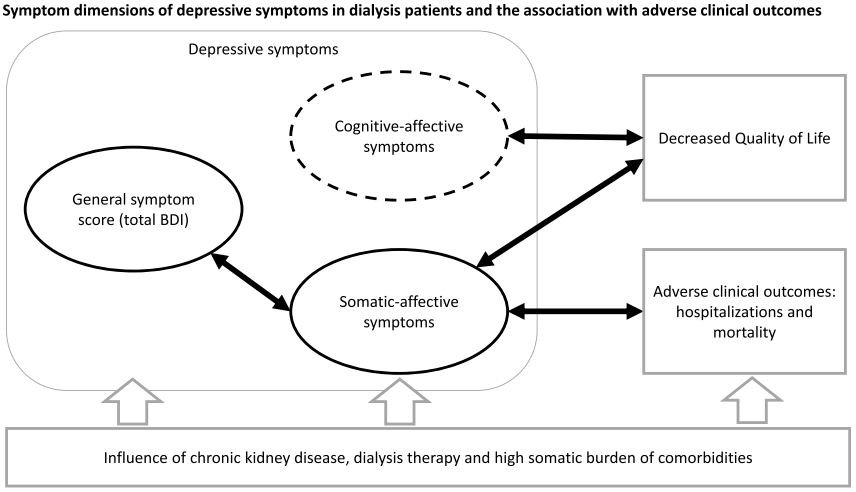

FIGURE 2. Model for relationship between depressive symptoms and adverse outcomes in chronic dialysis patients. BDI = Beck Depression Inventory.

the results because complaints about the dialysis therapy itself may overlap with somatic symptoms of depression. Finally, as a result of the use of self-reported scales, there are missing values. Although the overall percentage of missing values on the BDI-II was low, missing values and missing complete questionnaires were imputed as a sensitivity analysis to avoid bias.

CONCLUSIONS

Our findings demonstrated that the general-somatic dimension showed the best fit as a factor model for the BDI-II in dialysis patients. The cognitive dimension showed low factor loadings and a worse fit compared with the limited studies available. In line with the existing literature in other somatically ill patient groups, we found that the somatic dimension of depressive symptoms was associated with all-cause mortality, increased hospitalization rate, and reduced QoL. The cognitive dimension did not show an association with mortality. These findings show that symptom dimensions of depression have differential association with adverse clinical outcomes. Future studies should take symptom dimensions into account when investigating depression-related pathways, screening and treatment effects in dialysis patients.

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