How baseline, new-onset, and persistent depressive symptoms are associated with cardiovascular and non-cardiovascular mortality in incident patients on chronic dialysis

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ABSTRACT

Objective: Depressive symptoms are associated with mortality among patients on chronic dialysis therapy. It is currently unknown how different courses of depressive symptoms are associated with both cardiovascular and non-cardiovascular mortality.
Methods: In a Dutch prospective nation-wide cohort study among incident patients on chronic dialysis, 1077 patients completed the Mental Health Inventory, both at 3 and 12 months after starting dialysis. Cox regression models were used to calculate crude and adjusted hazard ratios (HRs) for mortality for patients with depressive symptoms at 3 months only (baseline only), at 12 months only (new-onset), and both at 3 and 12 months (persistent), using patients without depressive symptoms at 3 and 12 months as reference group.
Results: Depressive symptoms at baseline only seemed to be a strong marker for non-cardiovascular mortality (HR_{adj} 1.91, 95% CI 1.26–2.90), whereas cardiovascular mortality was only moderately increased (HR_{adj} 1.41, 95% CI 0.85–2.33). In contrast, new-onset depressive symptoms were moderately associated with both cardiovascular (HR_{adj} 1.66, 95% CI 1.06–2.58) and non-cardiovascular mortality (HR_{adj} 1.46, 95% CI 0.97–2.20). Among patients with persistent depressive symptoms, a poor survival was observed due to both cardiovascular (HR_{adj} 2.14, 95% CI 1.42–3.24) and non-cardiovascular related mortality (HR_{adj} 1.76, 95% CI 1.20–2.59).
Conclusion: This study showed that different courses of depressive symptoms were associated with a poor survival after the start of dialysis. In particular, temporary depressive symptoms at the start of dialysis may be a strong marker for non-cardiovascular mortality, whereas persistent depressive symptoms were associated with both cardiovascular and non-cardiovascular mortality.

Introduction

Evidence suggests that depressive symptoms are associated with mortality in patients with end-stage renal disease (ESRD) treated with dialysis therapy, even after adjustment for a wide array of covariates [1–5]. A few studies revealed that a stronger association with mortality is observed if depressive symptoms were assessed repeatedly instead of only once at the start of dialysis [6,7]. The relatively weak prognostic value of depressive symptoms for mortality when depressive symptoms are assessed only once at the start of dialysis compared with depressive symptoms assessed repeatedly may be attributed to the temporary adjustment to a stressful life event [8,9]. Most patients starting dialysis experience feelings of uncertainty about the future and grief about the apparent loss of renal function [10]. The occurrence of negative feelings however appears to diminish over time for the majority of patients, as most patients show resilience by adapting to the extensive demands of day to day dialysis therapy after a while [9,11,12]. Another explanation for why a repeated measure of depressive symptoms seems stronger associated with mortality is that the natural course of depressive symptoms includes remissions and relapses.

Probably, the various processes that link depressive symptoms and mortality may preferentially unfold if depressive symptoms persist

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over time. For example, persistent depressive symptoms may lead to the accumulation of social isolation [12,13], stress [10], and poor health behaviors, like smoking [14,15], lack of physical exercise [16,17], and a reduced adherence to medication [18] and fluid restrictions [19]. These health behaviors subsequently increase the risk for mortality. Besides influencing health behaviors, the continuous presence of depressive symptoms may be mutually related to a chronic disregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and chronic inflammation, which is associated with an increased risk for mortality as well [1]. Finally, depressive symptoms may vary over time as a result of the relative effectiveness of dialysis treatment, and the (lack of) prospect of a future transplantation.

To date, there is a lack of knowledge regarding whether different patterns of depressive symptoms are associated with differences in mortality in patients who receive chronic dialysis therapy. Moreover, no data are available about whether different courses of depressive symptoms are pathophysiologically associated with different causes of mortality. This is of interest since it has been hypothesized that persistent or new-onset depressive symptoms are especially associated with the pathogenesis of cardiovascular diseases [20,21]. The aim of the current study was to investigate the association between different courses of depressive symptoms with both cardiovascular and non-cardiovascular mortality in a Dutch nation-wide study among incident patients with ESRD treated with chronic dialysis therapy.

Method

Patients

Data were collected within the framework of The Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD), a prospective observational study among incident patients receiving hemodialysis (HD) and peritoneal dialysis (PD) in 38 centers in The Netherlands included between 1997 and 2007. The study was approved by all local medical ethics committees and all patients gave written informed consent before inclusion. Patients were included in NECOSAD if they were ≥ 18 years of age and had no previous history of renal replacement therapy. For the present study, we selected all patients who had survived the first 12 months on dialysis and completed questionnaires about depressive symptoms both at 3 and 12 months after the initiation of dialysis.

Measures

Depressive symptoms were assessed 3 and 12 months after the start of dialysis using the Mental Health Inventory (MHI). That MHI is the Mental Health scale of the Medical Outcomes Survey Short-form 36. The MHI has been validated as a reliable measure of depressive symptoms in different populations [22–25]. It includes 5 items questioning how often during the past month patients had felt 'downhearted and blue', 'calm and peaceful', 'happy', 'nervous', and 'so down in the dumps that nothing could cheer them up'. Items were scored on a six-point scale, varying from all of the time to none of the time. The scores were summed and transformed to a scale ranging from 0 to 100. The reliability of the scale was good (at 3 months Cronbach's α = .84; at 12 months Cronbach's α = .85). Depressive symptoms were assessed in dichotomous manner using a cut-off of 52 (depressive symptoms were considered to be present when the MHI scores were ≤52). This cut-off showed a good specificity and sensitivity for detecting clinically significant depressive symptoms in patients with chronic illness [26], and has been used previously in studies in patients on dialysis [6,27,28].

Four courses of depressive symptoms were distinguished: no depressive symptoms (no depressive symptoms at 3 and at 12 months), baseline depressive symptoms only (only depressive symptoms at 3 months), new-onset depressive symptoms (only depressive symptoms

at 12 months), and persistent depressive symptoms (depressive symptoms at 3 and at 12 months).

At the start of dialysis, data were collected on sociodemographics and primary cause of renal disease. The primary cause of kidney disease was classified according to the ERA-EDTA coding system [29]. Twelve months after the start of dialysis, dialysis modality (i.e., HD or PD), and comorbidities were recorded (i.e., the presence of diabetes mellitus, having a history of myocardial infarction, angina pectoris, congestive heart failure, peripheral vascular disease, or cerebrovascular accident). The following data were collected at 12 months after the start of dialysis: residual glomerular filtration rate (rGFR) (calculated as the mean renal clearance of creatinine and urea corrected for body surface area (mL/min/1.73 m^2)), serum albumin level, hemoglobin, plasma phosphorus, intact parathyroid hormone (iPTH), and plasma creatinine.

End points

Causes of death were determined by the patients' nephrologist and classified according to the codes of the ERA-EDTA registry [29], which is widely adopted by nephrologists and renal registries around the world [30], and has been applied in previous studies [e.g., 31,32]. Cardiovascular mortality was defined as death due to the following causes: myocardial ischemia and infarction, hyperkalemia, hypokalemia, cardiac failure, fluid overload, cerebrovascular accident, hemorrhage from a ruptured vascular aneurysm, cardiac arrest, mesenteric infarction, and cause of death uncertain/unknown. All other causes of mortality were designated as being non-cardiovascular, i.e., death due to the following causes: infection, malignancy, suicide or refusal of further treatment, cachexia, and miscellaneous.

Statistical analysis

T-tests and chi-square tests were used to compare sociodemographic and clinical characteristics between (a) patients who completed both questionnaire and patients who did not complete the questionnaire at 12 months, and (b) patients who did not have depressive symptoms at 3 and 12 months and patients who reported depressive symptoms at least once at 3 months or at 12 months (i.e., baseline, new-onset or persistent). Analyses of variance and chi-square tests were used to assess differences in patient characteristics between the groups with depressive symptoms.

Survival time was defined as the number of days between 12 months after starting dialysis and death or censoring, i.e. transfer to a nonparticipating dialysis center, withdrawal from the study, renal transplantation, recovery of kidney function, or reaching the end of the follow-up period at April 2011. Cumulative mortality curves for cardiovascular mortality and non-cardiovascular mortality were calculated using competing risk analysis regarding cause of mortality, as patients dying of cardiovascular causes are no longer at risk to die of non-cardiovascular causes, and vice versa [33]. Cox proportional hazards analysis was used to assess the association between depressive symptoms and all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality. Hazard ratios (HR) for mortality with accompanying 95% confidence intervals (95% CI) were calculated for patients with depressive symptoms at 3 and 12 months, and subsequently for patients with depressive symptoms at baseline only, new-onset depressive symptoms, and persistent depressive symptoms with patients without depressive symptoms as reference group. In addition, HRs of patients who reported depressive symptoms at least at one time point were compared with patients who did not have depressive symptoms at 3 and 12 months. Adjustments were made for age, sex, marital status, having children, ethnicity, educational level, being employed, dialysis modality, primary cause of renal disease, comorbidities at 12 months (that is, diabetes mellitus, angina pectoris, cerebrovascular accident, peripheral vascular disease, myocardial infarction and congestive heart failure),

and rGFR and laboratory values (that is, serum albumin, hemoglobin, phosphorus, iPTH, and creatinine) determined at 12 months after the initiation of dialysis. The full set of measures for the adjusted analyses was available for 64.1% of the patients. Variables had less than 5% missing values, except for rGFR which was missing for 18.8%. In order to increase precision of the estimates and to decrease bias missing values were imputed using multiple imputation techniques [34,35] using standard multiple imputation methods (10 repetitions) in SPSS statistical software version 17.0 (SPSS, Chicago, IL). The Cox regression models were fitted to each of the imputed datasets and results were averaged by using Rubin's rules [36]. All P-values are reported two-sided and were considered significant at a <0.05 level.

Sensitivity analyses

Several sensitivity analyses were conducted. First, we checked whether the pattern of results regarding the association with mortality and depressive symptoms at 3 months and at 12 months remained similar if depressive symptoms were analyzed as a continuous variable. Secondly, we ran all analyses after excluding patients of whom the cause of death was unknown. The reason for this is that deaths with an uncertain/unknown cause, were designated as cardiovascular deaths, which may lead to an overestimation of the number of cardiovascular deaths [32]. Third, sensitivity analyses were performed in which we did not censor for transplantation. The reason for this is that censoring for transplantation may introduce selection bias, as patients who receive a renal transplant are usually healthier than patients who have not. Fourth, the presence of baseline depressive symptoms and new-onset depressive symptoms was determined in a more stringent manner to avoid classifying patients without meaningful changes over time (e.g., shifting from MHI = 53 to MHI = 51 over time). In this analysis, we respectively excluded patients with depressive symptoms at baseline only and patients with new-onset depressive symptoms if they showed a decrease or increase of less than 10 points between 3 months and 12 months, respectively (10 points equaled 0.5 standard deviation). Finally, sensitivity analyses were conducted to check whether results are similar if we additionally adjusted for comorbidities, treatment modality and laboratory values at 3 months (instead of at 12 months only).

Results

In total, 1528 patients completed the MHI at 3 months, of whom 1077 completed the 12-month follow-up questionnaire as well. Of the 451 patients who did not complete the questionnaire at 12 months, 215 patients had died, 114 had received a renal transplantation, and 15 patients had a recovery of renal function. Furthermore, 20 patients were lost because they were transferred to a dialysis center that did not participate in the NECOSAD study or because their dialysis center discontinued study participation. Finally, 63 patients refused further participation in the NECOSAD study and 24 patients were still included in the NECOSAD study but did not complete the MHI at 12 months. The 87 patients who discontinued participation in the NECOSAD study or who did not complete the MHI at 12 months had a better renal function ($P = .017$) and reported more depressive symptoms at 3 months ($P = .025$) than the group of 1077 patients who did complete the follow-up measure. On all other sociodemographic and clinical characteristics at 3 months, no differences were observed between those two groups.

Depressive symptoms at 3 months and 12 months

Of the 1077 patients who completed both questionnaires, 96 patients had depressive symptoms at baseline only (8.9%), 97 patients had new-onset depressive symptoms (9.0%), 117 patients had persistent depressive symptoms (10.9%), and 767 patients had no depressive symptoms (71.2%).

Table 1 shows sociodemographic and clinical characteristics of the four groups. Patients who reported depressive symptoms at least at one time point, differed in several respects from patients without depressive symptoms. Compared with patients without depressive symptoms, patients with depressive symptoms at 3 months and/or 12 months were older ($P = .009$), more often female ($P = .010$), lower educated ($P < .001$), more often non-employed ($P < .001$), and more often treated with HD instead of PD ($P = .016$). Furthermore, these patients had more comorbidities (diabetes mellitus $P < .001$,

angina pectoris $P < .001$, cerebrovascular accident $P = .022$), and lower levels of serum albumin ($P < .001$), creatinine ($P < .001$), and hemoglobin ($P = .014$).

Patients with persistent depressive symptoms seemed to suffer from more severe depressive symptoms: At 3 months they reported more severe depressive symptoms than patients with depressive symptoms at 3 months only ($P = .001$), and at 12 months they had more severe depressive symptoms than patients with depressive symptoms at 12 months only ($P = .001$). Among the three groups with depressive symptoms patients, differences were observed regarding serum albumin ($P = .047$), creatinine ($P = .008$), and phosphorus ($P = .046$). Patients with depressive symptoms at baseline only had higher levels of serum albumin and lower phosphorus than patients with new-onset or persistent depressive symptoms. In addition, patients with persistent depressive symptoms had a lower level of creatinine than patients with depressive symptoms at baseline only or new-onset depressive symptoms. No other differences in sociodemographic, clinical and laboratory variables were observed among the three groups with depressive symptoms.

Depressive symptoms and mortality

Among 1077 study patients, 479 deaths (44.5%) occurred during follow-up, of which 215 deaths were related to a cardiovascular cause (44.9%). Both at 3 months and at 12 months depressive symptoms were related to cardiovascular mortality (3 months $HR_{adj} = 1.66$, 95% CI 1.19–2.31; 12 months $HR_{adj} = 1.82$, 95% CI 1.31–2.53), and non-cardiovascular mortality (3 months $HR_{adj} = 1.71$, 95% CI 1.28–2.30; 12 months $HR_{adj} = 1.49$, 95% CI 1.10–2.02). Differences in all-cause, cardiovascular and non-cardiovascular mortality were observed across the four groups (Fig. 1), with patients without depressive symptoms having the lowest mortality risk. Compared with patients without depressive symptoms, patients with depressive symptoms at 3 and/or 12 months had both a higher cardiovascular mortality risk ($HR_{adj} = 1.74$, 95% CI 1.28–2.35), and a higher non-cardiovascular mortality risk ($HR_{adj} = 1.70$, 95% CI 1.29–2.23). Table 2 depicts crude and adjusted HRs for mortality for patients with different courses of depressive symptoms with patients without depressive symptoms as reference group. After adjustment, patients with depressive symptoms at baseline only had a 1.91-fold (95% CI 1.26–2.90) increased risk for non-cardiovascular mortality compared with patients without depressive symptoms, whereas cardiovascular mortality was moderately increased ($HR_{adj} = 1.41$, 95% CI 0.85–2.33). Patients with new-onset depressive symptoms had a moderately increased risk for cardiovascular mortality ($HR_{adj} = 1.66$, 95% CI 1.06–2.58) and an increased risk for non-cardiovascular mortality ($HR_{adj} = 1.46$, 95% CI 0.97–2.20). Finally, patients with persistent depressive symptoms had a 2.14-fold (95% CI 1.42–3.24) increased risk for cardiovascular and a 1.76-fold (95% CI 1.20–2.59) increased risk for non-cardiovascular mortality compared with patients without depressive symptoms (see Table 2).

Sensitivity analyses

Analyses to assess whether depressive symptoms were associated with mortality at 3 and at 12 months were repeated with depressive symptoms as a continuous variable (reversed score). This did not change the pattern of results (cardiovascular mortality: at 3 months $HR_{adj} = 1.0009$, 95% CI [1.001–1.016], at 12 months $HR_{adj} = 1.015$, 95% CI [1.007–1.023]; non-cardiovascular mortality: at 3 months $HR_{adj} = 1.014$, 95% CI [1.008–1.021], at 12 months $HR_{adj} = 1.012$, 95% CI [1.005–1.019]).

Secondly, the cause of death was unknown for 87 patients who died during follow-up. Cox regression analyses in which patients with an unknown cause of death were excluded did not reveal different results (data not shown). In the third sensitivity analysis we found that 372 patients were censored during follow-up because they received a kidney transplantation. These patients reported fewer depressive symptoms at 3 and 12 months than patients who did not receive a renal transplantation during follow-up ($P < .001$). Analyses in which we did not censor for transplantation did not reveal different results (data not shown). Subsequently, we excluded all patients from the baseline only group (n = 20) and the new-onset group (n = 19) who showed a decrease, respectively an increase of less than 10 points in the MHI score. This more stringent designation of depressive symptoms did not change the pattern of results; only the association between new-onset depressive symptoms and cardiovascular mortality became somewhat more pronounced (patients with depressive symptoms at baseline only compared with patients without depressive symptoms: cardiovascular mortality, $HR_{adj} = 1.45$, 95% CI 0.82–2.56; non-cardiovascular mortality, $HR_{adj} = 2.02$, 95% CI 1.28–3.20; patients with new-onset depressive symptoms compared with patients without depressive symptoms: cardiovascular mortality, $HR_{adj} = 1.78$, 95% CI 1.10–2.88; non-cardiovascular mortality, $HR_{adj} = 1.37$, 95% CI 0.87–2.17). In the last sensitivity analysis we found that results did not materially change when we additionally adjusted for comorbidities, treatment modality and laboratory values at 3 months (data not shown).

Discussion

Our study adds up to the growing evidence suggesting that depressive symptoms among patients on dialysis are associated with poor survival [1–5]. In the current study we showed that all patterns of depressive symptoms over time pose a risk factor for mortality:

that is, depressive symptoms at the start of dialysis therapy only, new-onset depressive symptoms, and persistent depressive symptoms. This means that patients who were only depressed in the first period after starting dialysis remain at a higher risk for mortality than patients without depressive symptoms. Interestingly, depressive symptoms at baseline only, seemed to be a strong marker for especially non-cardiovascular mortality (1.91-fold increased risk), whereas cardiovascular mortality was only slightly increased among these patients. In contrast, new-onset depressive symptoms were moderately associated with both cardiovascular and non-cardiovascular mortality. Furthermore, patients with persistent depressive symptoms seemed to suffer from more severe depressive symptoms at each time point than patients with depressive symptoms at baseline only and new-onset depressive symptoms. Persistent depressed symptoms were strongly associated with both cardiovascular and non-cardiovascular mortality.

Perhaps different courses of depressive symptoms are associated with different pathophysiological pathways to explain mortality. Depressive symptoms may be harmful from both behavioral and biological perspectives. For example, multiple ongoing stressors associated with chronic dialysis therapy, such as loss of occupation and social functioning, decreased physical, cognitive and sexual functioning, and the experience of a decline in kidney function can induce chronic feelings of hopelessness and depression [1,37]. These persistent depressive symptoms may lead to mortality by influencing poor illness behaviors such as persistence of smoking, and less physical exercise [14–17]. Depressive symptoms also predict low adherence rates with medication intake [18] and fluid restrictions [19] in patients on dialysis, which are risk factors for mortality as well

[38,39]. Besides affecting detrimental illness behaviors, persistent stress and depressive symptoms seem bi-directionally related to immune system activity [1,5]. For example, depressive symptoms are associated with pro-inflammatory cytokines [40–42], which may disregulate the HPA axis by cortisol, resulting in an increase in immune activation [43,44]. Finally, depressive symptoms may be a consequence rather than the cause of a poor medical trajectory. In line with this, patients with depressive symptoms at 3 and/or 12 months had more often comorbidities (e.g., diabetes mellitus), and showed lower levels of albumin, creatinine, and hemoglobin. Although adjusted analyses controlled for a wide array of sociodemographic, medical and laboratory characteristics, it is still possible that prevalent or incident disease characteristics explain a part of the association between depressive symptoms and mortality.

More in-depth knowledge on characteristics of the relation between depressive symptoms and mortality (e.g. course, specific cause of mortality, short-term vs long-term effects on mortality) may also help to understand whether specific treatment strategies may be beneficial to patients. For example, it has been suggested that new-onset depressive symptoms in patients with myocardial infarction represent depressive symptoms with a different etiology. This type of depressive symptoms is associated with ongoing arteriovascular damage and a high cardiovascular mortality [45,46]. These patients seem to be resistant to several conventional psychiatric treatments for depression [46], as the type of depressive symptoms seems rather a symptom of detrimental cardiovascular disease than a conventional depressive disorder. In contrast, patients with other patterns of depressive symptoms may experience larger benefits from conventional depression treatment. For example, a multidisciplinary treatment intervention focusing on patients with

Table 1
Sociodemographic and clinical characteristics of patients with four patterns of depressive symptoms (DS)[a]

	No DS (n = 767)	DS at baseline only (n = 96)	New-onset DS (n = 117)	Persistent DS (n = 97)	P
DS continuous MHI score: M (SD)					
DS 3 months	79.1 (11.9)	44.6 (7.5)	67.7 (11.3)	39.6 (12.7)	<.001
DS 12 months	79.2 (12.1)	68.1 (11.7)	43.9 (8.2)	39.4 (11.8)	<.001
Sociodemographic characteristics					
Age: M (SD)	59.1 (14.9)	60.7 (13.1)	61.5 (12.7)	62.0 (13.0)	.089
Sex: male (%)	62.4	53.1	59.8	49.6	.029
Education: low (%)	51.8	66.0	64.9	67.0	<.001
Married: yes (%)	72.2	69.5	75.3	69.2	.744
Having children: yes (%)	78.1	80.0	77.1	78.1	.968
Employed: yes (%)	25.6	17.9	9.5	9.7	<.001
Ethnicity: Caucasian (%)	94.9	89.6	92.8	94.0	.002
Clinical					
Modality: hemodialysis (%)	60.1	66.7	66.0	70.7	.096
Primary cause of disease (%)					
Diabetes mellitus	11.4	16.7	16.5	20.5	.022
Glomerulonephritis	14.9	9.4	14.4	13.7	.541
Renal vascular disease	15.1	20.8	18.6	14.5	.431
Other	58.6	53.1	50.5	51.3	.208
Co-morbidity (%)					
Diabetes mellitus	15.3	16.7	26.8	27.6	<.001
Angina pectoris	8.5	21.9	22.7	19.8	<.001
Cerebrovascular accident	6.8	14.6	7.2	11.2	.031
Peripheral vascular disease	10.6	12.5	14.4	16.4	.248
Myocardial infarction	8.9	14.6	9.3	11.2	.319
Congestive heart failure	8.1	10.4	8.2	11.1	.743
Laboratory and rGFR: M (SD)					
Albumin (g/dL)	3.7 (0.5)	3.7 (0.5)	3.6 (0.5)	3.6 (0.5)	<.001
Hemoglobin (g/dL)	11.7 (1.3)	11.4 (1.4)	11.4 (1.6)	11.5 (1.7)	.063
Phosphorus (mmol/L)	1.8 (0.5)	1.7 (0.5)	1.9 (0.6)	1.9 (0.6)	.023
iPTH (pmol/L)	20.4 (24.7)	19.9 (27.1)	23.3 (29.9)	17.0 (20.6)	.342
Creatinine (μmol/L)	884.9 (257.3)	836.9 (259.4)	871.3 (240.5)	767.8 (241.9)	<.001
rGFR (mL/min/1.73 m^2)	2.9 (2.8)	3.3 (3.5)	2.3 (2.6)	3.2 (3.2)	.117

Used abbreviations: DS = depressive symptoms; MHI = mental health inventory; M = mean; SD = standard deviation; rGFR = residual glomerular filtration rate; iPTH = intact parathyroid hormone.

[a] No DS: 3 and 12 months MHI > 52; DS at baseline only: 3 months MHI ≤ 52, 12 months MHI > 52; New-onset DS: 3 months MHI > 52, 12 months MHI ≤ 52; persistent DS: 3 and 12 months MHI ≤ 52.
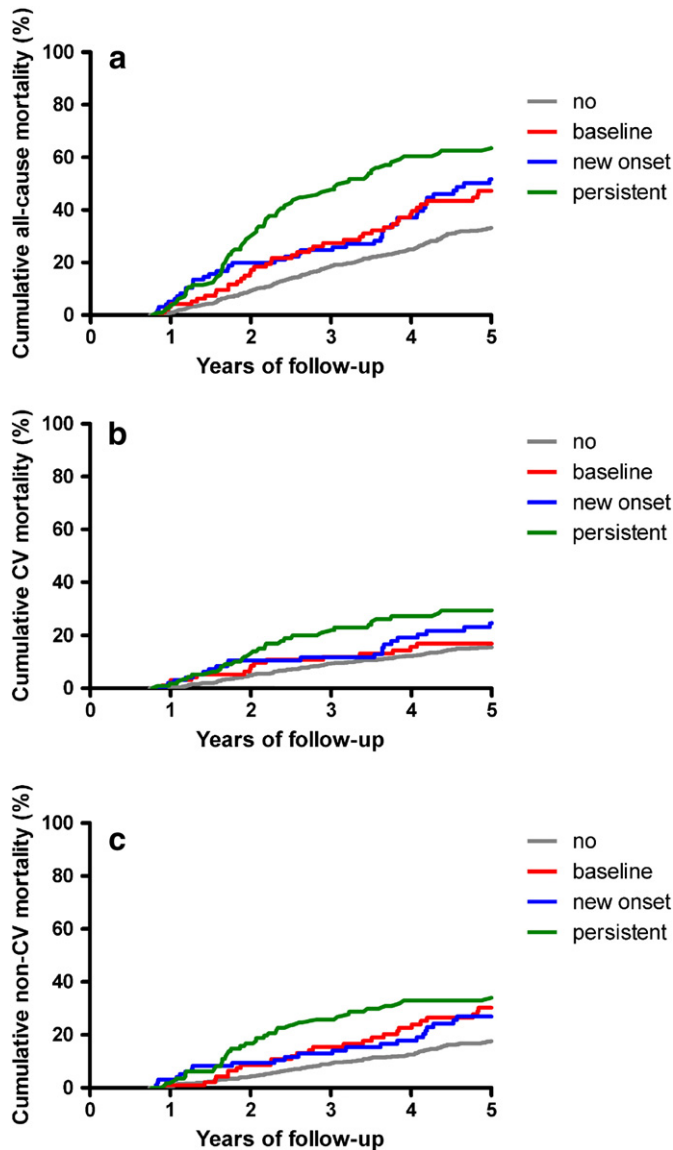
Fig. 1. Cumulative mortality curves for all-cause (a), cardiovascular (b), and non-cardiovascular (c) mortality for patients with different patterns of depressive symptoms.

Table 2
Patterns of depressive symptoms (DS)[a] and hazard ratios for all-cause, cardiovascular and non-cardiovascular mortality with patients without depressive symptoms as reference group

	Crude		Adjusted[b]	
	HR [95% CI]	P	HR [95% CI]	P
DS at baseline only				
All-cause mortality	1.44 [1.06–1.95]	.020	1.66 [1.20–2.29]	.002
Cardiovascular mortality	1.25 [0.77–2.02]	.363	1.41 [0.85–2.33]	.182
Non-cardiovascular mortality	1.59 [1.07–2.36]	.021	1.91 [1.26–2.90]	.002
New-onset DS				
All-cause mortality	1.85 [1.39–2.46]	<.001	1.54 [1.14–2.08]	.005
Cardiovascular mortality	1.89 [1.24–2.88]	.003	1.66 [1.06–2.58]	.026
Non-cardiovascular mortality	1.81 [1.23–2.68]	.003	1.46 [0.97–2.20]	.070
Persistent DS				
All-cause mortality	2.49 [1.92–3.23]	<.001	1.93 [1.46–2.57]	<.001
Cardiovascular mortality	2.56 [1.75–3.74]	<.001	2.14 [1.42–3.24]	<.001
Non-cardiovascular mortality	2.44 [1.71–3.48]	<.001	1.76 [1.20–2.59]	.004

[a] No DS: 3 and 12 months MHI > 52; DS at baseline only: 3 months MHI ≤ 52, 12 months MHI > 52; New-onset DS: 3 months MHI > 52, 12 months MHI ≤ 52; persistent DS: 3 and 12 months MHI ≤ 52.
[b] Adjusted for age, sex, marital status, having children, ethnicity, educational level, being employed, primary cause of renal disease, dialysis modality, the presence of diabetes mellitus, having a prior history of myocardial infarction, angina pectoris, congestive heart failure, peripheral vascular disease, or cerebrovascular accident at 12 months, and hemoglobin, iPTH, plasma phosphorus, serum albumin, rGFR, and creatinine at 3 and 12 months.

persistent depressive symptoms rather than patients with only one episode of depressive symptoms showed promising effects in patients with acute coronary syndrome [47].

The association between different time patterns of depressive symptoms and cardiovascular and non-cardiovascular mortality raises the question whether an adequate screening and treatment of depressive symptoms will improve the mortality in patients on dialysis. Meta-analyses in other chronic ill patient cohorts show that there is no evidence to date that routinely screening for and subsequently treating depressive symptoms enhances survival [48,49]. However, ameliorating depressive symptoms is in itself a valid therapeutic goal [2]. With an estimated prevalence of above threshold depressive symptoms being between 20% and 30%, the burden of depressive symptoms among patients on dialysis is extensive [1], whereas only a small minority of patients are adequately diagnosed and treated for depressive symptoms [2]. A reason why physicians may fail to recognize depressive symptoms is related to the considerable overlap between somatic depressive symptoms and the burden of uremic symptoms of chronic dialysis, such as decreased appetite, lack of energy, concentrating difficulties, and sleep disturbance [1]. This requires physicians to be aware of accompanying cognitive depressive symptoms, such as feelings of guilt, worthlessness, or suicidal thoughts as well [1,2]. Moreover, individuals who are vulnerable to depression will exhibit persistent negative biases in their thinking style [50]. A better recognition of the combination of cognitive and somatic depressive symptoms in patients on dialysis and whether they persist over time is needed.

Specific strengths of the current study are the nation-wide prospective study design with incident patients on dialysis, and the relatively large sample of patients with ESRD. Some limitations of the current study should also be noted. First, we relied on the MHI as measure of depressive symptoms. Although the MHI has been validated as a sound measure of depressive symptoms [22–25], the scale only measures a limited set of depressive symptoms and is not as commonly employed as, for example, the Beck Depression Inventory. However, a specific strength of the MHI is that it does not include somatic symptoms that can be attributed to both uremic symptoms of dialysis as well as to depressive symptoms. A practical advantage of the MHI is the brief format which makes it feasible for recurrent assessments in standard care protocols [51]. A second limitation is that we designed the four groups of depressive symptom courses based on measures at 3 and 12 months. This means that we only selected patients who had survived and who were not transplanted for at least one year after starting dialysis therapy. In addition to this possible selection bias, relevant information is lost by dichotomizing scores. Although it does make sense from a clinical point of view to classify patients as 'non-depressed' vs 'depressed', it can be questioned whether an objective definition of different courses over time can be obtained by applying a simple cut-off measure to identify clinically significant depressive symptoms which is based on two measurements. Moreover, patients may have had depressive symptoms before starting dialysis already or may suffer from intermittent depressive symptoms. Finally, our results regarding the specific cause of mortality should be interpreted with some caution, as the confidence intervals were rather wide. Future studies may consider taking into account a larger sample of patients with more frequent measurements over time to distinguish between patients with different courses of depressive symptoms.

In conclusion, different courses of depressive symptoms seem to be markers of mortality. The current study shows that even patients with depressive symptoms at the start of dialysis only are at increased risk for mortality.

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Conflict of interest

The authors have no competing interests to report.

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