Depressive symptoms but not chronic pain have an impact on the survival of patients undergoing maintenance hemodialysis

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Abstract

Introduction: More than 1/3 of patients with end-stage renal disease who are in a chronic dialysis program suffer from chronic pain and depression/anxiety. The aim of the study was to determine the impacts of symptoms of depression/anxiety, chronic pain and quality of life (QoL) on 6-year patient survival.
Material and methods: Observational study of end-stage renal disease patients on maintenance hemodialysis ($n = 205$) who met the inclusion criteria. Patients from three dialysis centers in Lower Silesia were asked to complete a battery of validated questionnaires: the Hospital Anxiety and Depression Scale (HADS), the 36-item Short Form Health Survey Questionnaire, the Verbal Rating Scale (VRS) and the Visual Analog Scale (VAS). Clinical and biochemical data (dialysis adequacy) were recorded.
Results: One hundred thirty from 205 enrolled hemodialysis patients (63.4%) suffered from chronic pain. Patients with pain were on maintenance dialysis for longer times and had higher levels of parathyroid hormone, more depressive symptoms and a lower QoL than those without pain. In the 6-year period, 96 (46.8%) patients died. The most common cause of death was cardiovascular disease in 44 (45.8%) patients. Highly depressed patients (HADS depression score > 8) exhibited higher mortality (< 8 vs. > 8 points; $p = 0.016$) independent of age, diabetes, cardiovascular disease, C-reactive protein or albumin level.
Conclusions: Chronic pain, although common among hemodialysis patients, did not lower survival. Depressive symptoms are an important predictor for all-cause mortality in hemodialysis patients, with the relationship independent of nutritional or inflammatory status.

Key words: chronic pain, depressive symptoms, hemodialysis, quality of life, mortality.

Introduction

All-cause mortality among dialysis patients remains high despite improvements in technology and management of anemia and disturbances in calcium–phosphate metabolism. This is partly due to the increasing

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number of elderly patients with many comorbidities enrolled in dialysis programs [1]. The overall symptom burden of these patients is high and is similar to that of the end-of-life cancer population.

Determinants of mortality in patients with end-stage renal disease (ESRD) treated using hemodialysis include older age, nutritional status and comorbidities such as diabetes mellitus and inflammation [2, 3]. Psychosocial factors, such as depression [4, 5] and quality of life (QoL) covering self-reported bodily pain [6, 7], have also been associated with mortality in dialysis patients.

The prevalence of depression verified by a specialist in patients undergoing hemodialysis ranges from 5% to 30%, but depressive/anxiety symptoms are found in up to 54% of patients with chronic kidney disease (CKD) and congestive heart failure [4, 8–12]. The occurrence of depressive symptoms frequently begins with the onset of dialysis or even earlier in CKD of greater severity [13–15].

Although the problem of pain in ESRD patients has been recognized for more than 25 years, only a few studies, mainly focused on QoL, have investigated this subject. Pain is a common problem that has been both under-recognized and under-treated. Pain may be caused by underlying systemic diseases such as diabetic neuropathy or polycystic kidney disease, a comorbidity such as peripheral vascular disease or be due to routine aspects of renal replacement therapy (from needle insertions, or from muscle cramps during the procedure) and complications arising from dialysis access sites. Pain may result from calciphylaxis and renal osteodystrophy, which are unique to ESRD, or may develop during the patient's lifetime on dialysis. As in the general population, musculoskeletal pain is the most common symptom of chronic pain syndromes.

Some investigators have reported a higher prevalence of pain (51%–73%) among patients undergoing maintenance hemodialysis (Campbell *et al.*, unpublished data, 2006; Haggiag *et al.*, unpublished data, 2006), while others have reported a lower prevalence of pain (about 30–37%) in these patients [16]. Chronic pain is a known factor affecting QoL, and intense, prolonged, self-reported pain may mask or induce depression/anxiety symptoms in some patients [17]. Hence, the next question is: to what extent do chronic pain and/or depression influence the long-term outcome in ESRD patients?

In this study, we assessed the prognostic significance of chronic pain, depression/anxiety and QoL on 6-year survival in a cohort of clinically stable hemodialysis patients.

Material and methods

Design and patients

Initially, 240 ambulatory dialysis patients who met the inclusion criteria were asked to complete questionnaires concerning depression/anxiety symptoms, mental functioning, pain and quality of life in the period from February 2006 to May 2006. Patients were recruited from three dialysis centers in Lower Silesia, Poland (University Hospital $n = 82$; Municipal Hospital (public) $n = 49$; International Dialysis Center (private) $n = 97$; the recruitment process is shown in Figure 1. All patients received hemodialysis free of charge (i.e. paid for by the National Health Fund).

Patients meeting the following criteria were eligible for inclusion: (i) > 6 months on dialysis, (ii) standard hemodialysis (low-flux) three times a week, (iii) not hospitalized at the time of assessment, (iv) no physical impairments that would prevent the completion of the questionnaires. If blindness or an inability to write due to skeletal deformities was the only physical impairment, assistance in completing the questionnaires was provided. Exclusion criteria were: (i) dementia based on medical records or as assessed by the Mini-Mental State Examination (MMSE) that
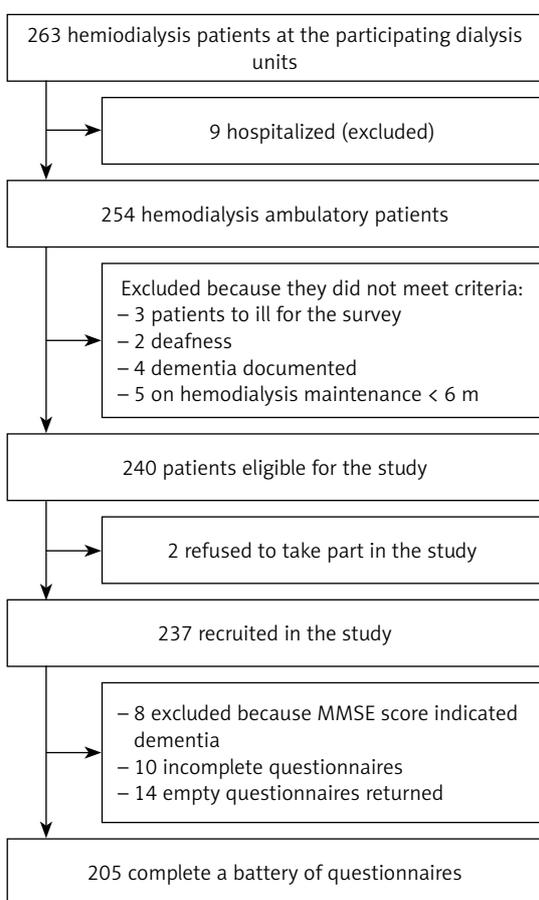
Figure 1. Study flow chart

was provided for all patients 65 years and above, (ii) addiction to alcohol/psychoactive drugs, (iii) antidepressive treatment.

In the MMSE assessment, the cut-off for dementia in patients 65 years and older with higher education was ≥ 27 points, while for those with a low education level it was ≥ 23 points.

The study was approved by the Bioethics Committee of the Wroclaw Medical University.

Clinical parameters

In addition to demographic factors, baseline clinical data were recorded from electronic/written medical records and included cause of ESRD, maintenance dialysis, presence of residual diuresis, blood pressure, hemoglobin level, serum albumin, calcium–phosphorus product, parathyroid hormone (PTH), C-reactive protein (CRP) and parameters reflecting dialysis dose and adequacy. The aforementioned routine laboratory tests were performed at the hospitals' central analytical laboratory as part of standard patient care.

Methods

Participants completed a battery of previously validated questionnaires in the Polish language as well as a demographic appendix and anamnesis pain sheet. The Hospital Anxiety and Depression Scale (HADS:A and HADS:D), the 36-item Short Form Health Survey Questionnaire (SF-36) and the MMSE (for those 65 years or older) were provided. Two pain measurement tools (Verbal Rating Scale (VRS) and Visual Analog Scale (VAS)) were used to identify patients with chronic pain.

Pain assessment

Patients were asked to record their current level of pain (as assessed on a four-point categorical VRS and on a VAS consisting of a horizontal 100-mm line) on a questionnaire [18, 19]. The VRS in this study consisted of a series of adjectives reflecting varying degrees of pain severity ranging from "no pain" to "the most extreme pain". Patients circled the adjective that best described how severe their pain was. Numbers were provided along with adjectives – none (0), mild (1–3), moderate (4–6), severe (7–10) – to enhance interpretation of the scale. Additionally, a question about the first appearance of pain over time was incorporated. Chronic pain was defined as pain intensity reaching ≥ 1 point(s) in both scales (more than 10 mm in the VAS and with at least "mild" being circled in the VRS) lasting more than 3 months. When less than 10 mm was marked in the VAS or "none" circled in the VRS, the patient was transferred to the group without chronic pain.

Depression and Anxiety Symptoms

The HADS [20] was developed as a tool for the identification of anxiety disorders and depression in patients in non-psychiatric hospital clinics. It consists of 14 items equally divided between anxiety and depression subscales. Each item is rated on a scale of 0 to 3. Responders choose the response that most accurately describes how they have been feeling during the past. For both anxiety and depression scores, 0–7 is considered normal, 8–10 mild and > 10 severe anxiety or depression. A review of several studies has shown that HADS has good psychometric properties (e.g. internal reliability and test–retest reliability) and is also capable of effectively assessing anxiety and depressive disorders in various health settings and in the general population [11, 21].

All included patients were treated according to the intention-to-treat principle. Study patients who scored ≥ 8 in the HADS:A (the anxiety subscore of the HADS) as well as in HADS:D (the depression subscore of the HADS) were referred to a psychiatrist for confirmation of depression/anxiety disorders and treatment.

Quality of life

The Medical Outcome Study (MOS) 36-item Short Questionnaire Health Survey (SF-36 or RAND 36) was administered to evaluate general quality of life. This assessment tool consists of the following generic items: general health perception (GH), physical functioning (PF), role limitations caused by physical health problems (RP), bodily pain (BP), vitality or energy (VT), mental health or emotional well-being (MH), role limitations caused by emotional health problems (RE) and social functioning (SF) [22]. SF-36 has been translated and validated in many countries and for different chronic illnesses including ESRD [23, 24].

Follow-up and survival analysis

Patients were followed for 6 years after enrollment. Survival time was calculated as the number of months from the baseline assessment until death.

In the statistical analysis, kidney transplantation, transfer out of the facility and change of dialysis modality were recorded as censored observations.

The primary end-point was all-cause mortality. Causes of death were defined according to the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) coding system [25].

Statistical analysis

Differences between groups were analyzed using ANOVA or the Mann-Whitney *U* test for con-

tinuous variables and the χ^2 test for categorical variables. A two sided *p*-value less than 0.05 was considered statistically significant.

Kaplan-Meier analysis was used to estimate survival from the time of pain/depression/QoL assessment to 6 years after evaluation. Univariate analysis was performed using log-rank tests to compare Kaplan-Meier survival curves. Cox proportional hazards regression was used to predict survival. The day of study recruitment was taken as the starting point for the analysis of patient survival (prevalent patient survival).

Results

Two hundred fifty-four prevalent ambulatory dialysis patients were considered for screening, of whom 205 were finally enrolled in the study (see study flow chart in Figure 1).

The response/consent rate was 205/240 (85.4%). Eight patients older than 65 years were not eligible because of a high MMSE score (indicating cognitive deficits), ten questionnaires were incomplete and 14 patients did not respond. Finally, 205 patients (41.5% female) with an average age of 60.3 ±13.8 years (age range: 19–87 years) were enrolled in the study as well as for survival analysis. A summary of demographic and clinical data is shown in Table I. Other clinical and biochemical measures for the entire cohort are displayed in Tables II and III.

Chronic pain

One hundred thirty (63.4%) maintenance hemodialysis patients suffered from chronic pain of any cause as reported in the two tools of pain measurement (≥ 10 mm in the VAS and at least "mild" pain in the VRS).

Based on patients' responses in the anamnesis pain questionnaire, 84% of patients with pain (108) had bone–joint–muscle pain. The locations of pain were as follows: head 26% (35), neck and shoulders 20.6% (27), back 13.7% (18), lumbar region 25% (33), chest 10% (13), bones in general 6.8% (9), lower extremity 28% (7), knee 15%

Table I. Baseline demographics and clinical characteristics (*n* = 205)

Parameter	*N* or mean ± SD	Percentage or median
Gender, female/male	85/120	41.5 (58.5%)
Age	60.3 ±13.8	Median 60 (range: 19–87)
Maintenance hemodialysis [months]	50.9 ±58	Median 26 (range: 7–300)
Residual diuresis (> 300 ml/day)	79	38.5%
Cause of ESRD:	(*n*)	(%)
Glomerulonephritis	55	26.8
Diabetic nephropathy	46	22.4
Hypertensive nephropathy	45	22
Polycystic kidney disease	22	10.7
Pyelonephritis	16	7.9
Other/unknown	21	10.2
Comorbidities:	(*n*)	(%)
Hypertension	119	58
Cardiovascular disease[a]	134	65
Diabetes mellitus	48	23.4
Vascular access:	(*n*)	(%)
Native AVF single needle	17	8.3
Native AVF two needles	157	76.6
Temporal catheter	7	3.4
Permanent catheter	22	10.7
PTFE prosthesis	2	1

[a]*Cardiovascular disease: stroke, myocardial infarction/revascularization, heart failure, coronary heart disease, peripheral occlusive artery disease, aortic aneurysm. AVF – arteriovenous fistula, ESRD – end-stage renal disease, PTFE – polytetrafluoroethylene.*

Table II. Baseline characteristics in the cohort, subgroups with pain (≥ 1 VRS and VAS) and without pain

Parameter	Cohort (n = 205)		No pain (n = 75)		Chronic pain (n = 130)		Pain vs. no pain (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	P-value
Maintenance HD [months]	50.9	58	36.1	43.3	64.9	67.8	0.001
Age [years]	60.3	13.8	62.7	14.1	58.9	13.6	0.060
24-h dieresis [l]	0.5	0.5	0.5	0.5	0.3	0.5	0.007
BMI [kg/m^2]	25.2	4.2	25.0	4.1	25.4	4.2	0.485
SBP before HD [mm Hg]	134.7	25.4	136.4	26.5	133.8	24.7	0.479
DBP before HD [mm Hg]	76.6	11.1	77.7	11.0	76.0	11.2	0.301
SBP after HD [mm Hg]	128.2	26.2	131.3	25.7	126.6	26.4	0.217
DBP after HD [mm Hg]	74.3	12.2	75.5	11.9	73.8	12.3	0.337
Albumin [g/dl]	3.7	0.5	3.6	0.4	3.7	0.5	0.153
Hemoglobin [g/dl]	10.9	2.5	10.6	1.6	11.1	2.8	0.214
CaxP	51.0	17.4	47.2	17.1	53.1	17.3	0.019
PTH [pg/ml]	375.0	501.3	215.6	181.6	467.0	595.9	< 0.001
URR	0.62	0.10	0.6	0.1	0.6	0.1	0.748
kt/V	1.14	0.26	1.1	0.2	1.2	0.3	0.171
kt/V weekly	3.49	0.59	3.4	0.6	3.5	0.6	0.154
Mean UF per session [ml]	2671.7	848.7	2610.7	857.9	2706.9	844.7	0.435
CRP [mg/l]	13.3	1.6	12.1	15.0	14.2	23.7	0.499
HADS:A	5.7	3.6	4.3	3.4	6.5	3.4	< 0.001
HADS:D	6.0	4.2	4.6	4.0	6.8	4.1	< 0.001
SF-36 GH	42.3	19.0	49.1	19.6	38.4	17.7	< 0.001
SF-36 BP	60.0	31.8	86.8	22.0	44.5	25.6	< 0.001
SF-36 PF	42.5	31.4	52.6	31.7	36.6	29.8	< 0.001
SF-36 RP	46.8	44.2	57.4	44.3	40.5	43.1	0.008
SF-36 RE	63.1	44.7	70.8	42.6	58.5	45.4	0.062
SF-36 VT	49.6	21.9	59.2	22.4	44.1	19.7	< 0.001
SF-36 MH	63.1	20.7	69.9	19.2	59.2	20.6	< 0.001
SF-36 SF	66.0	28.8	77.4	26.0	59.5	28.4	< 0.001

BMI – body mass index (calculated from post-dialysis body mass), SBP – systolic blood pressure, DBP – diastolic blood pressure, CaxP – calcium-phosphorus product, URR – urea reduction rate, UF – ultrafiltration, HADS – Hospital Anxiety and Depression Scale (HADS:A – anxiety, HADS:D – depression), SF-36 (Short Form 36 items) categories: GH – general health, PF – physical functioning, RP – role-physical limitation, RE – role-emotional limitation, BP – bodily pain, VT – vitality, MH – mental health, SF – social functioning.

(20), foot 23% (30), hand/wrist 7.6% (10), upper extremity 9.1% (12), abdomen 6.1% (8), hip 10% (14), calf cramps 53% (70). Some reported pain in more than one location (hence the sum of locations exceeds 100%). Moreover, 28% (37) of patients reported continuous pain with an exacerbation during the dialysis sessions. The average duration of chronic pain was 20 ±14 months, but often pain had persisted for 7 months prior to enrollment (the mode value was 7). Forty-three

Table III. Characteristics of patients with depressive symptoms

Parameter	Diagnosis of depression by psychiatrist (*n* = 13)		HADS:D < 8 (*n* = 141)		HADS:D ≥ 8 (*n* = 62)		HADS:D < 8 vs. ≥ 8 (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	*P*-value
Maintenance HD [months]	67.3	78.6	53.3	56.9	56.7	70.9	0.634
Age [years]	49.8	16.8	55.0	16.1	57.6	15.0	0.302
24-h dieresis [l]	0.3	0.5	0.4	0.5	0.3	0.5	0.232
BMI [kg/m²]	26.2	2.5	25.0	4.3	25.7	3.9	0.177
SBP before HD [mm Hg]	137.9	17.8	132.7	23.9	139.2	27.9	0.090
DBP before HD [mm Hg]	77.5	7.5	75.7	10.8	78.5	11.7	0.068
SBP after HD [mm Hg]	132.9	21.2	128.0	25.4	128.8	28.1	0.994
DBP after HD [mm Hg]	74.2	7.9	74.5	12.0	74.1	12.5	0.895
Albumin [g/dl]	3.7	0.4	3.7	0.5	3.6	0.5	0.343
Hemoglobin [g/dl]	11.0	1.4	11.1	2.7	10.5	1.8	0.142
CaxP	46.4	13.1	51.0	17.4	51.8	18.6	0.933
PTH [pg/ml]	602.0	742.7	343.2	451.2	445.0	594.9	0.546
URR	0.6	0.1	0.6	0.1	0.6	0.1	0.850
kt/V	1.2	0.4	1.1	0.3	2.7	12.5	0.727
kt/V weekly	3.5	0.8	4.2	8.2	3.5	0.6	0.809
Mean UF per session [ml]	3166.7	957.6	2658.2	846.3	2701.6	859.8	0.555
CRP [mg/l]	22.9	26.6	12.8	20.3	15.7	21.9	0.473
VRS	2.9	2.3	1.8	2.3	3.3	4.6	0.001
HADS:A	8.0	4.7	4.6	2.6	8.1	4.3	0.006
HADS:D	9.1	3.1	3.7	2.2	11.1	2.9	< 0.001
HADS:A + D	17.1	5.4	8.4	3.9	19.2	5.9	< 0.001
SF-36 GH	38.3	21.2	46.1	19.2	34.3	16.0	< 0.001
SF-36 BP	39.8	27.4	65.7	30.5	48.2	31.4	0.007
SF-36 PF	37.1	26.7	49.6	30.9	27.1	26.8	0.109
SF-36 RP	37.5	47.1	49.3	43.6	41.4	45.4	0.845
SF-36 RE	50.0	48.2	71.7	40.5	44.6	47.9	0.699
SF-36 VT	34.6	18.9	55.0	20.4	38.3	20.9	0.011
SF-36 MH	42.3	18.4	68.8	18.5	50.9	20.1	0.010
SF-36 SF	53.1	25.6	70.7	26.2	55.8	31.8	0.269

BMI – body mass index (calculated from post-dialysis body mass), SBP – systolic blood pressure, DBP – diastolic blood pressure, CaxP – calcium-phosphorus product, URR – urea reduction rate, UF – ultrafiltration, VRS – mean intensity of pain, HADS – Hospital Anxiety and Depression Scale (HADS:A – anxiety, HADS:D – depression), SF-36 (Short Form 36 items) categories: GH – general health, PF – physical functioning, RP – role-physical limitation, RE – role-emotional limitation, BP – bodily pain, VT – vitality, MH – mental health, SF – social functioning.

percent of patients reported pain intensity as being "mild" in the VRS with a mean VAS of 3.07 ±1.2 × 10 mm, while 57% of responders indicated "moderate" pain in the VRS with a mean VAS of 5.01 ±1.3 × 10 mm.

Patients with chronic pain had been on maintenance dialysis for a longer period of time and demonstrated a lower residual renal function (diuresis). Moreover, patients reporting pain had higher levels of calcium–phosphorus product
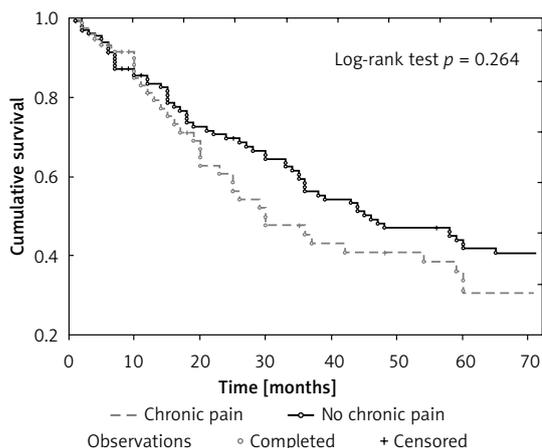
Figure 2. Comparison of survival in patients with ($n = 130$) and without ($n = 75$) chronic pain
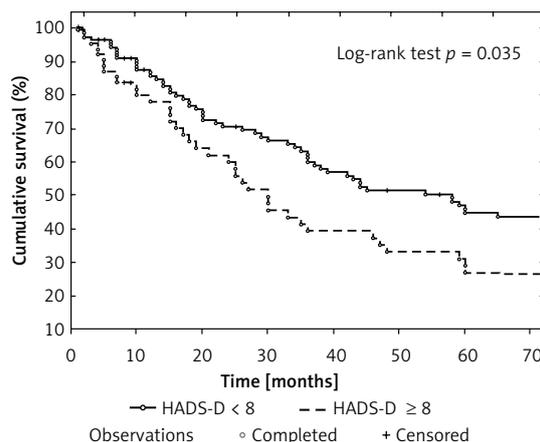
Figure 3. Comparison of survival in patients with high ($n = 62$) and low ($n = 141$) depression scores

(Ca × P) and PTH concentrations than those without pain (Table II). Both groups showed comparable indices of dialysis adequacy. Significant differences (pain versus no pain) were found in the anxiety (HADS:A), depression (HADS:D) and QoL scales (Table II).

Analysis of 6-year survival in patients with any pain and in those without any reported pain did not show significant differences (Figure 2). Cox proportional hazards regression excluded pain as a factor influencing survival even when the subgroup of patients with moderate pain (≥ 4 in the VRS) was extracted and separately analyzed (log-rank test $p = 0.573$).

Anxiety and depression

Sixty-two patients with scores ≥ 8 points in the HADS were referred to a psychiatrist for confirmation of the diagnosis. Ten patients did not give consent for evaluation by a psychiatrist. Of the 52 evaluated patients, 13 (6%) were diagnosed with depressive/anxiety disorders.

There were no significant differences in distributions of demographic and clinical parameters between patients with high (≥ 8; $n = 62$) or low (< 8; $n = 143$) depression scores at baseline (Table III). The two groups differed in pain intensity (VRS ($p = 0.001$)) and in 4/8 categories of QoL (GH, BP, VT, MH; $p < 0.01$). Anxiety disorders were less prominent in the cohort than depressive disorders and showed no influence on cumulative survival.

Cox proportional hazards regression showed that depressive symptoms, scored in the HADS:D, were an important predictor of survival in univariate as well as multivariate analysis. A comparison of the cumulative survival of dialysis patients with high (≥ 8) and low (< 8) depression scores in the HADS:D revealed significantly better survival in less depressed patients (Figure 3; log-rank test $p = 0.035$).

An additional analysis of combined anxiety and depression symptoms (HADS:A + D) with a cut-off set at 13 points (< 13 vs. ≥ 13) showed no difference in terms of survival (log-rank $p = 0.121$) between the two groups.

Correlations

Negative correlations between pain (in the VRS) and QoL scores (higher VRS score = lower QoL) were observed in many categories: GH ($p = 0.009$; $R = -0.12$), BP ($p < 0.001$; $R = -0.54$), PF ($p = 0.05$; $R = -0.14$), RP ($p = 0.003$; $R = -0.21$), RE ($p = 0.003$; $R = -0.22$), VT ($p < 0.001$; $R = -0.29$), SF ($p < 0.001$; $R = -0.43$) and MH ($p < 0.001$; $R = -0.33$). Comparable results indicating slight-to-moderate negative correlations were found between the pain VAS and QoL categories (data not shown).

Positive correlations were found between the depression scale (HADS:D) and pain (assessed using the VAS or the VRS) (Table IV). Many SF-36 categories displayed moderate negative correlations with the depression score (HADS:D). The strongest significant correlations ($R = -0.52$) between QoL and depression scores were found for the mental (emotional) health and vitality categories (Table IV).

Mortality rates

During the follow-up period, 96 (46.8%) patients died. The most common cause of death was cardiovascular disease, accounting for 45.8% (44) of deaths. According to the ERA–EDTA coding system (COD group) [25], the causes of death were as follows: myocardial ischemia and infarction (27), heart failure (9), cardiac arrest (8), infections (11), malignancies (13), cerebrovascular accident (4), miscellaneous (4) and unknown/unavailable (20).

Survival analysis

During 6 years of follow-up, 102 patients were censored at various time points due to renal trans-

Table IV. Correlation coefficients for HADS:D, VAS, VRS and SF-36

Relation of variables	R	P-value
VAS and HADS:D	0.24	< 0.001
VRS and HADS:D	0.27	< 0.001
SF-36-GH and HADS:D	−0.43	< 0.001
SF-36-BP and HADS:D	−0.42	< 0.001
SF-36-PF and HADS:D	−0.42	< 0.001
SF-36-RP and HADS:D	−0.28	< 0.001
SF-36-RE and HADS:D	−0.39	< 0.001
SF-36-V and HADS:D	−0.52	< 0.001
SF-36-SF and HADS:D	−0.33	< 0.001
SF-36-MH and HADS:D	−0.52	< 0.001

VAS – current pain (visual analog scale), VRS – mean intensity of pain, HADS:D – depression score, SF-36 (Short Form 36 items) categories: GH – general health, PF – physical functioning, RP – role-physical limitation, RE – role-emotional limitation, BP – bodily pain, VT – vitality, MH – mental health, SF – social functioning.

plantation (24), transfer out of the facility (75), recovery of renal function (1) and change of dialysis modality (switch to peritoneal dialysis; 2).

For the entire cohort, 1-, 2- 3-, 5- and 6-year patient survival on dialysis was 84% (SE = 0.03), 66% (SE = 0.04), 54% (SE = 0.04), 41% (SE = 0.04) and 37% (SE = 0.04), respectively.

Univariate analysis using log-rank tests to compare Kaplan-Meier survival curves or univariate Cox regressions (as appropriate) indicated that age (p = 0.008), serum albumin (p < 0.001), CRP level (p = 0.004) and depression (as assessed using the HADS-D (p = 0.016) and HADS:A + D (p = 0.041)) were significantly associated with survival. Other clinical and biochemical parameters, comorbidities (diabetes, cardiovascular burden) and pain as well as QoL outcome did not reach significance for patient survival.

The independent variables with a significant negative impact on 6-year survival according to the Cox proportional hazards regression model (Table V) were age (p = 0.041), lower albumin concentration (p = 0.018) and more depressive symptoms reported in HADS-D (p = 0.016). Addition of the VRS (mean intensity of pain) to the abovementioned model diminished the impact of depression on patient survival. This may have resulted from a significant correlation between the VRS and the HADS-D (Table IV).

Discussion

Bodily pain and psychiatric distress are common symptoms in patients undergoing chronic hemodialysis. In the European population of dialysis patients, the relationship between chronic pain, depressive symptoms and survival has not been thoroughly investigated.

In this three-center, prospective cohort study, a high prevalence of chronic pain (63.4%) was found. The most frequent complaints among our study subjects were of bone–joint–muscle pain (84%). When patients have a high PTH level, it is usually a consequence of secondary hyperparathyroidism resistant to treatment. Pain localized in the hand (uni- or bilateral) was linked to arteriovenous fistula (ischemia or steal syndrome) and, in those with more than 5 years of maintenance hemodialysis, it was related to secondary amyloidosis. Dialysis-related amyloidosis that is due to the accumulation of β_2-microalbumin (resulting from poor clearance in low-flux membranes) typically manifests as pain in the shoulder or hand (carpal tunnel syndrome).

A group of Italian investigators found that 37 of 100 hemodialysis patients had chronic pain. In their analysis, the predominant cause of chronic pain (24 of 37) was osteoarthritis [16]. In a multicenter QoL study of 165 United States (U.S.) hemodialysis patients, Kimmel *et al.* found that 21%

Table V. Cox proportional hazard regression model for 6-year survival time as a dependent variable

Model	Effect of	HR	95% CI	P-value
1	Age	1.015	0.943–1.052	0.041
	Serum albumin	0.581	0.305–1.274	0.018
	CRP	0.997	0.973–1.015	0.318
	HADS:D	1.055	0.944–1.121	0.016
2	Age	0.968	0.953–1.00	< 0.001
	Serum albumin	0.664	0.368–1.201	0.028
	CRP	0.997	0.973–1.015	0.428
	HADS:D	0.994	0.923–1.072	0.341
	VRS	1.010	0.911–1.080	0.553

VRS – verbal response scale (i.e. mean intensity of pain), HADS:D – depression score, CRP – C-reactive protein.

of the patients reported pain [22]; however, the nature of the pain was not evaluated.

In our study, patients with pain (even mild) showed worse self-reported QoL (i.e. lower scores) than patients without pain. A negative impact of pain on QoL has been reported previously [22, 26]. An association was also found between pain and depressive symptoms. On performing subgroup analyses, we found that 18.3% of the cohort with chronic pain of greater intensity (> 4 in VRS) also had depressive symptoms (HADS:D > 8). The occurrence of intense chronic pain not only diminishes QoL but may induce depression [5, 22, 26].

Finally, Cox regression analysis showed that pain of any intensity did not affect the 6-year survival of hemodialysis patients.

The main finding in this study is that depression is a key predictor of mortality in the cohort of hemodialysis patients. Higher scores in the HADS:D were independently associated with poorer survival (Figure 3). The impact on 6-year survival was equally as important as the impact of traditional well-known factors such as age or serum albumin (Table V). Riezebos *et al.* also analyzed the influence of depressive symptoms (using the HADS-D with a cutoff > 7) on the survival of Dutch dialysis patients. After adjustment for a series of clinical parameters, the association between depressive symptoms and mortality became even stronger [11].

A high level of depressive symptoms was found among hemodialysis patients as assessed in the HADS questionnaire (62 patients had scores of 8 or more points). Of the 52 patients interviewed by an experienced psychiatrist, 13 (25%) were diagnosed with anxiety–depressive disorder. This accounts for 6% of the entire dialysis cohort, with possible under-scoring because 10 patients at high risk refused an interview diagnosis. Loosman *et al.* demonstrated that the HADS, a self-report rating scale, is a valid screening tool for detecting depression in ESRD patients [10]. HADS performs equally as well as the Beck Depression Inventory (BDI), which is also a self-report rating scale that includes somatic items.

Although a few studies involving a small number of patients showed no relationship between baseline depression scores and outcome [4, 27], most studies (using various self-reporting tools) underscored the impact of depression on mortality [14, 28–31].

There is no commonly accepted model that describes how depression increases the risk of morbidity (mainly cardiac) and mortality. Some authors report evidence of a link between depressive symptoms and major adverse cardiac events [8, 32]. The increased mortality in patients with depressive symptoms reported in a Dutch study was mainly due to a high incidence of infection-related deaths. This suggests a relationship between depression and inflammation or immune dysfunction. The relationship between depression and inflammation appears to be bidirectional [33]. Depression can result in the upregulation of inflammatory mediators as found in 50% of patients who receive interferon-α treatment [34]. In those patients, decreased brain concentrations of serotonin and dopamine resulted in the development of depression. The relationship between the altered serotonin levels seen in depressed patients and increased platelet aggregation and vasoconstriction (which can lead to coronary events) deserves mentioning. There are reports suggesting that depression is associated with changes in platelet function, and that selective serotonin reuptake inhibitors (SSRIs) may have antiplatelet activities [35, 36].

In another recent study on a relatively small group of hemodialysis patients, depression was not found to have any significant effect on the level of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α). Moreover, no significant improvements in cytokine levels were observed after the administration of antidepressant therapy [37].

Depression is associated with activation of the hypothalamic–pituitary–adrenal axis [38]. There is growing evidence regarding the role of cytokines in interrupting the negative feedback mechanism of the hormonal axis via cortisol, leading to immune system stimulation [39, 40].

Another important issue associated with depressive symptoms and lower survival is nonadherence to the medical regimen. In hemodialysis patients, nonadherence can take a variety of forms including regular fluid overload or noncompliance with dietary sodium restriction. These findings demonstrate a negative correlation between level of medication adherence and depressive symptoms. Patients with depressive symptoms report a greater feeling of hopelessness, compromising cognitive abilities. Hopelessness, cognitive distortions and fatigue produce negative expectations of the future and lead to inadequate fluid and dietary adherence behaviors [41]. Akman *et al.* found a doubled likelihood of dietary nonadherence in depressed CKD patients when compared to patients without depression [42]. The strong association between depressive symptoms and withdrawal from dialysis therapy noted in the Dialysis Outcomes and Practice Patterns Study (DOPPS) is particularly noteworthy [9].

On analyzing mortality in dialysis patients, we noticed a very high frequency (45.8%) of cardiovascular-related deaths. This has been reported in many ESRD registries worldwide [1]. Still, there remains a huge difference when mortality of dial-

M. Kusztal, E. Trafidło, K. Madziarska, H. Augustyniak-Bartosik, M. Karczewski, W. Weyde, M. Krajewska, J. Rymaszewska, M. Klinger

ysis patients is compared with that of the general population. For example, cardiovascular mortality rates in U.S. dialysis patients were found to be amplified by a factor of 5 to 500 (depending on the age group) when compared with that of the general population [43].

In the entire cohort 2-, 5- and 6-year survival in hemodialyzed patients was found to be 66%, 41% and 37%, respectively. This outcome is comparable to data published by the European registry (ERA–EDTA), although greater caution should be exercised when interpreting survival in prevalent dialysis patients as opposed to incident dialysis patients (the starting point is the date of dialysis onset). Nevertheless, according to a recent European registry for a hemodialysis cohort (2002–2006), 2- and 5-year patient survival was 68% and 36%, respectively [44].

One limitation of our study is the analysis of survival in prevalent dialysis patients (not incident dialysis patients). A potential bias is the unknown duration of depression in these patients prior to assessment.

In conclusion, our study underscores the fact that depression is an important psychosocial factor affecting not only QoL but also survival in hemodialysis patients. Chronic pain, although frequently observed among maintenance hemodialysis patients and often concomitant with depression, did not significantly lower the survival rate of these patients. The diagnosis and treatment of depression is a real challenge in hemodialysis patients; therefore, tools for screening depression/anxiety should be routinely used in these patients. It remains to be determined how pharmacological and nonpharmacological approaches to treating depressive symptoms will impact on morbidity and mortality in hemodialysis patients.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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