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Prepare; before starting dialysis : outcomes in patients with CKD stage 4-5

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THE IMPACT OF SYMPTOMS ON HEALTH RELATED QUALITY OF LIFE IN ELDERLY PRE–DIALYSIS PATIENTS; EFFECT AND IMPORTANCE IN THE EQUAL STUDY

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Abstract

Introduction: Quality of life (QoL) is an important outcome in chronic kidney disease (CKD). Patients feel symptoms are an important determinant of QoL. However, this relation is unknown. The aims of this study were to investigate the impact of the number and severity of symptoms on quality of life in elderly pre-dialysis patients, assessed by both the effect of symptoms and their importance relative to kidney function, and other clinical variables on QoL.

Methods: The EQUAL Study is an ongoing European prospective follow-up study in late stage 4/5 CKD patients aged ≥65 years. We used patients included between March 2012 and December 2015. Patients scored their symptoms with the Dialysis Symptom Index, and QoL with the RAND-36 item Health Survey (RAND-36). The RAND-36 results in a physical component summary (PCS) and a mental component summary (MCS). We used linear regression to estimate the relation between symptoms and QoL at baseline and after six months, and to calculate the variance in QoL explained by symptoms.

Results: 1079 (73%) patients had a baseline questionnaire (median age 75, 66% male, 98% Caucasian) and 627 (42%) patients a follow- up questionnaire. At baseline, every additional symptom changed MCS with -0.81 (95% CI -0.91;-0.71), and PCS with -0.50 (95% CI-0.62;-0.39). In univariable analyses number of symptoms explained 22% of MCS variance and 11% of PCS variance, whereas eGFR only explained 1%.

Conclusions: In elderly CKD stage 4/5 patients symptoms have a substantial impact on QoL. This indicates symptoms should have a more prominent role in clinical decision making.

Introduction

Elderly patients with advanced chronic kidney disease (CKD) often have a poor quality of life (QoL).[1, 2] This is an important outcome in these patients since it predicts mortality and morbidity.[3-5] Although many definitions of QoL exist, it is commonly defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" which is determined by an individual's capacity to cope and to adapt.[6, 7]

In CKD patients clinical variables are considered important determinants for QoL.[8-12] However, kidney function, the most important biological factor in CKD and determinant for many treatment choices, does not influence QoL as much as expected. [12, 13] Although Pagels ***et al.*** and Chin ***et al.*** found a difference in QoL between patients with moderately severe versus severe CKD, no linear effect of eGFR on QoL has been observed.[12, 13] A possible explanation for this can be found in the conceptual model by Wilson ***et al***. which portrays QoL as the result of a chain of consecutive elements, passing from biological variables through symptom status through functional status to QoL.[14] From this model it could be inferred that factors earlier in the chain – affecting QoL through more intermediate variables – will have a weaker effect. The effect of biological factors, such as kidney function, is mediated by symptoms, which may thus be more important in determining QoL. The IDEAL study, where a large part of the CKD patients initiated dialysis based on symptoms instead of planned kidney function, illustrates this idea.[15]

CKD patients suffer from a wide range of physical and psychological symptoms. They can range from tiredness and itching to feeling anxious or irritable. Patients consider symptoms as one of the most important aspects of their disease, and both patients and nephrologists believe symptoms should be one of the main focuses in CKD research.[16-18] Nonetheless, research on symptoms and their effect on QoL in pre-dialysis patients is limited.[19, 20] A few notable exceptions suggest that an increase in symptoms is associated with a decrease in QoL. De Goeij ***et al***. found an increase in symptoms over time accompanied by a decrease in QoL in 436 pre-dialysis patients.[1] In a cross-sectional study by Abdel-Kader ***et al.*** symptoms were negatively correlated with QoL in 87 CKD stage 4/5 patients.[11]

This study aimed to fill this knowledge gap by investigating the impact of number and severity of symptoms on quality of life in pre-dialysis patients, assessed by both the effect of symptoms and their importance relative to kidney function and other clinical variables. In this study the word effect is used to investigate the relation between symptoms and QoL, an etiological research aim. The term relative importance is used when investigating the part of QoL that is determined by symptoms, a research aim more at the edge of etiological research.

Methods

Study design and population

The European Quality study on treatment in advanced chronic kidney disease (EQUAL study) is an ongoing prospective cohort study in advanced CKD patients in six European countries: Germany, Italy, Poland, Sweden, The Netherlands and the United Kingdom. We included patients of 65 years and older with an eGFR that had dropped to 20 ml/min/1.73m^2 or lower for the first time during the last six months in patients referred to a nephrologist. Patients were eligible when they were followed in a nephrology clinic, but were excluded if the drop in eGFR resulted from an acute event, or if the patient had received any form of renal replacement therapy (RRT) in the past. Patients were followed until kidney transplantation, death, refusal for further participation, moving to a center not participating in the EQUAL study, loss to follow-up, or end of follow-up. For the current study end of follow-up was determined at the 29th of November 2016 and patients were censored when starting dialysis. A full description of the study has been published elsewhere.[21]

For our analyses we used the baseline and six months follow-up data of the patients who were recruited for the EQUAL study between March 2012 and December 2015 and filled in at least the QoL part of the patient questionnaire at baseline. The study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Data collection

The EQUAL study followed patients receiving routine medical care as provided by the nephrology clinic. Data were collected and entered into a web-based clinical record form that was developed for this specific purpose. The information included patients' demographics, ethnicity, kidney disease, comorbid conditions, diet and medication, physical examination, and laboratory data.

The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula, taking into account age, sex, race, and serum creatinine.[22] Primary kidney disease was classified by the treating nephrologist according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[23] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases. Educational level was classified into low (no education or primary school only), intermediate (primary and secondary school), and high (academic education).

All laboratory investigations and physical examinations were performed through standard protocols and procedures according to routine care at the local participating sites. In order to standardize these data, all participating centers completed a questionnaire to capture details on local laboratory methods, units of measurement and normal ranges. All data were then recalculated into one uniform unit of choice.

Additionally, data regarding the patient's lifestyle, marital status, QoL, as well as the presence and severity of uraemic symptoms were obtained via self-administered paper patient questionnaires. The list of uraemic symptoms was based on the Dialysis Symptom Index, which consists of 30 symptoms, and was complemented with the items bleeding, loss of weight, and loss of strength.[24] The patients had to score the presence of these symptoms over the past month. For each symptom experienced, patients subsequently rated how much they had been bothered by that symptom using a 5-point Likert scale with the options "not at all", "a little bit", "somewhat", "quite a bit", or "very much". The total number of symptoms resulted in a score that ranged from 0 to 33. The reported symptom severity was summarized in a score that ranged from 0 to 165 by counting the Likert scale points. Unreported symptoms were assigned a severity score of zero.[11]

QoL was measured with the RAND-36, a 36 item questionnaire measuring QoL on eight dimensions, resulting in an overall physical component score (PCS) and mental component score (MCS). The eight dimensions are physical functioning, role limitations due to physical problems, bodily pain, social functioning, role limitations due to emotional problems, mental health, general health, and vitality. To score a dimension at least half of the items in that dimension had to be completed.[25] The PCS and MCS were calculated using norm based scoring, which employs linear transformation to achieve standardized scores with a mean of 50 and a standard deviation of 10 for each dimension by using the United States population as a reference group.[26] Research has shown using the United States reference group is as good as using a Dutch reference group.[26]

Statistical analysis

Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed continuous variables, skewed continuous variables as median with interquartile range (IQR), and categorical variables as percentages.

Multiple imputation was used to minimize the risk of bias.[27] Missing values of number of symptoms, and symptom severity at baseline and after six months, as well as potential confounders at baseline were imputed (using 10 repetitions).

We conducted linear regression analyses to estimate the effect of number and severity of symptoms on the outcomes PCS and MCS. This was performed both at baseline and after six months of follow-up. All residuals were plotted to check the linearity assumption. To check the direction of the effect of symptoms on QoL we estimated the effect of baseline determinants on six months QoL, adjusted for baseline QoL using a linear regression analysis. Next, the effect of the difference in symptoms between baseline and six months of follow-up (delta symptoms) on the difference in QoL between baseline and six months of follow-up (delta QoL) was estimated with linear regression. All analyses were adjusted for the potential confounders: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, body mass index, primary kidney disease, albumin, and eGFR.

All analyses including only baseline variables were performed in patients with a QoL patient questionnaire at baseline. Analyses including baseline and six months follow-up variables were performed in patients with a QoL patient questionnaire at baseline and after six months of follow-up. To simplify clinical interpretation we have added the effects of number and severity of symptoms on PCS and MCS per quartile, using the interquartile range for number and severity of symptoms.

Lastly, we calculated the impact of symptoms on QoL using linear regression analysis to calculate the explained variance as a measure of importance. In this analysis we defined different variable clusters: demographics (sex, age, ethnicity, education level, country of residence), comorbidities (diabetes mellitus, cardiovascular disease, myocardial infarction, malignancy, psychiatric disease) and primary kidney disease, eGFR, other laboratory measurements (albumin, hemoglobin, proteinuria), symptom number, and symptom severity. These clusters were included both separately with a univariable analysis and stepwise with a multivariable analysis. This way, the impact of each of these variables as well as their additive effect could be calculated. In addition to the estimated associations, this analysis gives more clinical context and demonstrates the relative importance of different determinants of QoL. The explained variance was calculated at baseline, after six months, and for change in symptoms and change in QoL.

To test the robustness of the results we performed several sensitivity analyses. First, we stratified all analyses by sex, since the occurrence of symptoms as well as the perceived QoL might differ between men and women and thereby affect the associations between symptoms and QoL. Second, we repeated all analyses without using multiple imputation for missing values. Third, we repeated all analyses only using multiple imputation for baseline confounders, not for symptom number or severity. Fourth, we repeated the linear regression analysis at baseline only including patients with a patient questionnaire at baseline and after 6 months of follow-up. Finally, we calculated the explained variance without the symptoms fatigue, feeling sad, feeling nervous, and feeling anxious since these are both symptoms and part of the SF-36 and thereby might influence the explained variance. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0 for Windows.

Results

Patient characteristics

Of the 1486 patients in EQUAL by the 31th of December 2015, 1079 (73%) filled in the QoL part of the baseline patient questionnaire and 627 (42%) filled in the QoL part of the patient questionnaire at baseline and after six months of follow-up. Missing symptom number and symptom severity were imputed. Of the 452 patients missing QoL at 6 months of follow-up, 40 already started dialysis, 61 died, 29 withdrew from the study, 7 received a kidney

Table 1. Baseline characteristics in patients with a patient questionnaire at baseline (n=1079) and in patients with a patient questionnaire at baseline and follow–up (n=627)

	QoL questionnaire at baseline, n=1079	QoL questionnaire both at baseline and 6 months, n=627
Sex, male	66	65
Age, years	75 (70-80)	76 (70-80)
Ethnicity		
Caucasian	98	98
Black	1	1
Other	1	1
Primary Kidney Disease		
Glomerular disease	10	9
Tubulo-interstitial disease	9	10
Diabetes Mellitus	20	18
Hypertension	35	37
Other/ unknown	28	26
Education [a]		
Low	30	28
Intermediate	48	48
High	17	21
Other	3	3
Marital status, married or living together	64	64
Diabetes Mellitus, yes [b]	40	37
Hypertension, yes [c]	89	90
Cerebrovascular Disease, yes	15	15
Myocardial Infarction, yes	18	17
Malignancy, yes	21	22
Psychiatric disease, yes	7	6
Body Mass Index, kg/m^2	28 (25-31)	29 (25-31)
Index eGFR, ml/min/1.73m^2 [d]	17.1 (3.1)	17.4 (2.7)
eGFR baseline, ml/min/1.73m^2 [d]	19.0 (5.5)	19.7 (5.3)
Serum albumin, g/L	37.6 (5.8)	37.7 (5.4)
Hemoglobin, mmol/L	7.2 (1.0)	7.3 (1.0)
Proteinuria, g/24h	1.9 (0.6-6.3)	1.6 (0.5-4.9)

Values are given as a percentage, means (±SD) or median (IQR).
Missings: baseline group; marital status 15, education 14, proteinuria 852, albumin 101, BMI 63, hemoglobin 12; baseline and six months group: marital status 9, proteinuria 517, albumin 56 BMI 32, hemoglobin 7 [a] Defined as: low, no education or primary school only; intermediate, primary and secondary school; high, academic education. [b] Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [c] Defined as either the presence of hypertension as primary kidney disease or a history of hypertension. [d] eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula. Index eGFR; eGFR at time of study inclusion, eGFR baseline; eGFR at baseline measurement.
QoL: Quality of life

transplantation, and 3 patients had not yet reached the 6 months follow-up measurement. The other 312 (29%) patients were defined as non-responders. Patients with complete follow-up had a median age of 76 (IQR 70-80), 65% were male, and 98% were Caucasian (table 1). Sixty-four percent of these patients were married or living together, 28% had a low education level, 48% an intermediate education level, and 21% a high education level. Hypertension was present in 90%, a malignancy in 22%, and a psychiatric disease in 6% of these patients. In the 1079 patients with a baseline questionnaire these numbers were virtually the same. Supplemental table 1 shows the baseline characteristics for the 312 patients where follow-up questionnaires were missing.

Table 2 shows the number of symptoms, symptom severity, MCS, and PCS at baseline and after six months of follow-up for complete cases. The numbers showed only small changes over the first six months. In figure 1 the prevalence of symptoms with the severity score per symptom at baseline are shown. The most prevalent symptoms at baseline were fatigue, a decreased interest in sex, and loss of strength. “A decreased interest in sex” and “difficulty becoming sexually aroused” were the symptoms that scored the most “very much bother” as symptom severity score. After six months (figure 2) the most prevalent symptoms and the most severe symptoms remained unchanged.

Table 2. Symptom and QoL descriptives at baseline and after 6 months

	QoL questionnaire at baseline, n=1079	QoL questionnaire at baseline and 6 months, n=627		
	Baseline	Baseline	6 months	Scale
Symptom number	12.6 (6.5) n=819	12.4 (6.2) n=460	13.5 (7.2) n=460	0-33
Symptom severity	33 (18 to 51) n=720	33 (19 to 48) n=407	36 (19 to 57) n=407	0-165
MCS	50.3 (10.9) n=1079	50.6 (10.4) n=627	48.3 (11.7) n=627	50 (10)*
PCS	34.8 (12.1) n=1079	35.1 (11.4) n=627	36.5 (9.8) n=627	50 (10)*

Values are given as means ± SD or median (interquartile range)

*standardized score mean (standard deviation)

QoL; quality of life, MCS; Mental Component Summary, PCS: Physical Component Summary

Example questions: Symptom number: In the past month have you experienced any of the following symptoms? Muscle cramps; yes/no

Symptom severity: In the past month have you experienced any of the following symptoms? If yes, how much did it bother you

MCS: During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

PCS: During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

The effect of symptoms on QoL

Table 3 shows the association between symptoms and QoL at baseline. With every additional symptom the MCS changed with -0.81 (95% CI -0.91 to -0.71) and the PCS with -0.50 (95% CI -0.62 to -0.39). The association between symptom severity and MCS was -0.23

Figure 1. Symptom prevalence and scoring according to 5 Likert scale at baseline (n=1079)

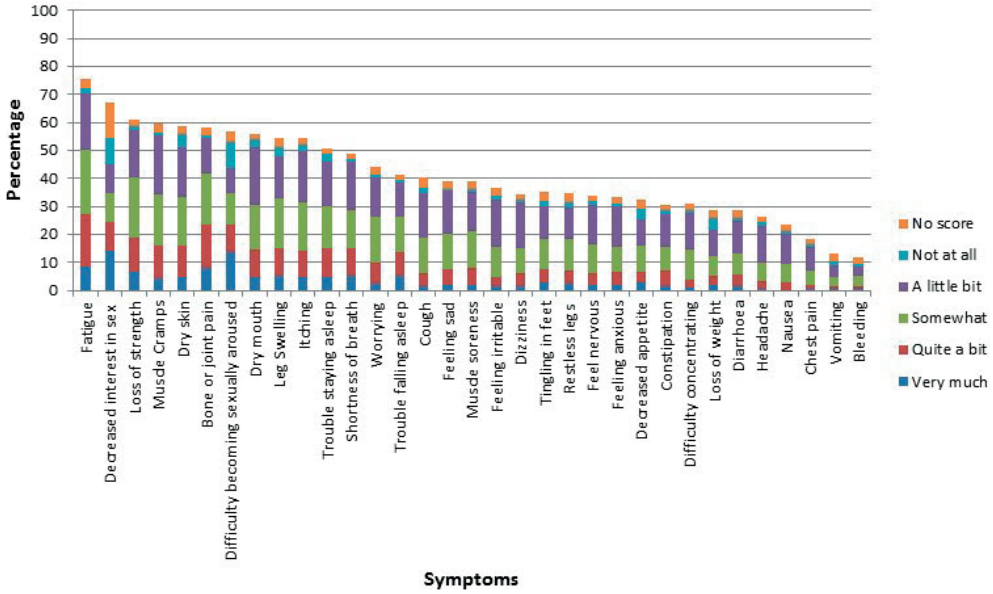

Figure 2. Symptom prevalence and scoring according to 5 Likert scale at six months follow-up (n=627)

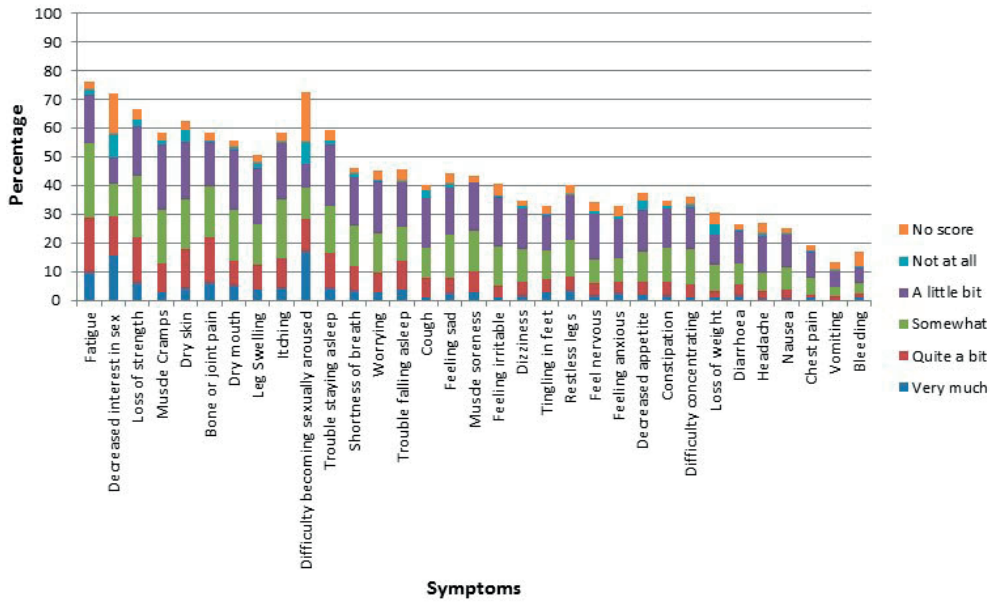

Table 3. Effect size per point increase of symptom number and severity on MCS and PCS at baseline (n=1079)

	MCS	PCS
Symptom number, crude	-0.80 (-0.90 to -0.70)	-0.64 (-0.76 to -0.53)
Symptom number, adjusted*	-0.81 (-0.91 to -0.71)	-0.50 (-0.62 to -0.39)
Symptom severity, crude	-0.22 (-0.25 to -0.19)	-0.22 (-0.25 to -0.19)
Symptom severity, adjusted*	-0.23 (-0.26 to -0.20)	-0.18 (-0.21 to -0.15)

*Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary

(95% CI -0.26 to -0.20) and -0.18 (95% CI -0.21 to -0.15) for PCS. After six months results were similar (results not shown). Table 4 shows the effect of symptom number and severity on QoL over time. After adjustment, one extra symptom at baseline changed MCS at six months of follow-up with -0.42 (95% CI -0.59 to -0.25), and PCS with -0.15 (95% CI -0.24 to -0.05). With every point increase in symptom severity at baseline the change in MCS at six months of follow-up was -0.14 (95% CI -0.19 to -0.09), and for PCS this was -0.05 (95%

Table 4. Effect size per point increase in symptom number and severity on MCS and PCS six month changes (n=627)

	M6 MCS	M6 PCS
Baseline symptom number, crude*	-0.42 (-0.58 to -0.26)	-0.16 (-0.26 to -0.06)
Baseline symptom number, adjusted**	-0.42 (-0.59 to -0.25)	-0.15 (-0.24 to -0.05)
Baseline symptom severity, crude*	-0.13 (-0.18 to -0.09)	-0.05 (-0.08 to -0.02)
Baseline symptom severity, adjusted**	-0.14 (-0.19 to -0.09)	-0.05 (-0.07 to -0.02)

*Adjusted for: baseline QoL
**Adjusted for: baseline QoL, age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary, QoL; Quality of Life

Table 5. Linear regression; effect size of change in symptom number and severity on change in MCS and PCS (n=627)

	Change in MCS	Change in PCS
Change in symptom number, crude	-0.48 (-0.67 to -0.29)	-0.22 (-0.35 to -0.09)
Change in symptom number, adjusted	-0.51 (-0.71 to -0.31)	-0.22 (-0.36 to -0.08)
Change in symptom severity, crude	-0.18 (-0.24 to -0.11)	-0.09 (-0.14 to -0.05)
Change in symptom severity, adjusted	-0.18 (-0.25 to -0.12)	-0.09 (-0.14 to -0.04)

Adjusted for: age, sex, ethnicity, country of residence, educational level, diabetes mellitus, cerebrovascular disease, myocardial infarction, hypertension, malignancy, psychiatric disease, BMI, primary kidney disease, albumin, and eGFR.
MCS; Mental Component Summary, PCS: Physical Component Summary

CI -0.07 to -0.02). Table 5 shows the association between the change in symptom number and severity during the first six months of follow-up and the change in QoL during those six months. The association was -0.51 (-0.71 to -0.31) for symptom number and MCS, -0.22 (-0.36 to -0.08) for symptom number and PCS, -0.18 (-0.25 to -0.12) for symptom severity and MCS, and -0.09 (-0.14 to -0.04) for symptom severity and PCS. All negative numbers indicate a decrease in QoL.

Although these effect sizes seem quite small, they are clinically relevant effects. This is illustrated by the changes in QoL per quartile of symptom number and symptom severity. For example, the change from quartile one to quartile three for symptom number and MCS at baseline is over 8 points (Supplemental table 2, 3 and 4).

The importance of symptoms in explaining QoL

Tables 6a and 6b show the R^2 for the different variable clusters that influence QoL, both separately and stepwise at baseline. In the univariable analysis symptom number and

Table 6a. Explained variance for MCS and PCS, for the separate variable clusters (n=1079)

	R^2 MCS	R^2 PCS
Demographics	0.02	0.12
Comorbidities+ PKD	0.02	0.04
eGFR	0.01	0.01
Other lab measurements	0.02	0.01
Symptom number	0.22	0.11
Symptom severity	0.21	0.16

Demographics: sex, age, ethnicity, education level, country of residence
Comorbidities + PKD: diabetes mellitus, cerebrovascular disease, myocardial infarction, malignancy, psychiatric disease, primary kidney disease
Other laboratory measurements: albumin, hemoglobin, proteinuria
MCS; Mental Component Summary, PCS: Physical Component Summary

Table 6b. Explained variance for MCS and PCS, for the stepwise combined variable clusters (n=1079)

	R^2 MCS	R^2 PCS
1.Demographics	0.02	0.12
2. 1+Comorbidities+ PKD	0.04	0.16
3. 2+ eGFR	0.04	0.16
4. 3+Other lab measurements	0.06	0.17
5. 4+symptom number	0.26	0.24
6. 5+symptom severity	0.26	0.28

Demographics: sex, age, ethnicity, education level, country of residence.
Comorbidities + PKD: diabetes mellitus, cerebrovascular disease, myocardial infarction, malignancy, psychiatric disease, primary kidney disease
Other laboratory measurements: albumin, hemoglobin, proteinuria.
DM; diabetes mellitus, CVD; cardiovascular disease, MI; myocardial infarction, PKD; primary kidney disease

severity have an R^2 of 0.22 and 0.21 for MCS respectively, while eGFR has an R^2 of 0.01 and the other variables have a maximum R^2 of 0.02. For PCS the R^2 for symptom number and severity is smaller, 0.11 and 0.16, and demographic variables also explain a large part of the variance with an R^2 of 0.12. The R^2 for eGFR is again 0.01. When adding the variables stepwise in a multivariable analysis for MCS, symptom number significantly adds to the R^2 in addition to demographic and clinical variables, increasing the R^2 from 0.06 to 0.26. Symptom severity does not add more to this correlation. For PCS, the contribution of symptoms is smaller but also substantial. The R^2 increased from 0.17 to 0.24 with symptom number and up to 0.28 with symptom severity. In contrast, eGFR did not add to the R^2 in multivariable analyses, neither for MCS nor for PCS. Both after six months and for change between baseline and six months of follow-up symptom number and severity remained the variables with the largest R^2 in univariable analyses and contributed most to the R^2 in multivariable analyses. In these analyses eGFR did not contribute to the R^2 either.

Sensitivity analyses

Stratifying by sex showed a higher number and severity of symptoms and a lower QoL in women compared to men (supplemental table 5). The effect of symptoms on QoL did not show large differences between the different sexes (supplemental table 6, 7, 8). Repeating the analyses without multiple imputation showed similar results, as did the analyses when only using multiple imputation for baseline confounders. Repeating the baseline linear regression analysis with only the 627 patients who had a QoL questionnaire at baseline and after six months of follow-up showed no substantial differences in the results (supplemental table 9). Removing symptoms that are also part of the SF-36 changed the R^2 to 0.17 (symptom number) and 0.16 (symptom severity) in the univariable analysis for MCS at baseline. For PCS the R^2 changed to 0.12 and 0.18 in the univariable analysis. In the multivariable analysis the R^2 changed to 0.19 (symptom number) and 0.21 (symptom severity) for MCS, and to 0.25 and 0.29 for PCS.

Discussion

In this cohort of 1079 incident elderly pre-dialysis patients we found a wide range of symptom occurrence and severity. Most prevalent symptoms were fatigue, a decreased interest in sex, and loss of strength. Symptoms on sexuality scored highest on severity. Both an increase in number of symptoms and in symptom severity were associated with a decrease in QoL. In addition, baseline symptoms were related to QoL after six months of follow-up. The impact of symptoms on QoL is substantial, especially compared to eGFR which did not impact MCS or PCS at all.

Overall, effects on MCS were larger as compared with effects on PCS. We hypothesize this might be due to depressive symptoms having more impact on mental QoL as compared with physical QoL, due to the fact that a part of these symptoms are heavily reflected in MCS

questions, while the other symptoms do not have that much overlap with PCS questions. The sensitivity analysis in which the explained variance is calculated without overlapping symptoms seems to support this hypothesis. However, the analyses show only small changes as compared with the analyses including these overlapping symptoms.

The difference in impact on QoL between symptoms and eGFR we found supports the conceptual model by Wilson ***et al***. showing symptoms are a more determinant for QoL.[14] With this knowledge on symptom impact, a more prominent role for symptoms in clinical decision making in the pre-dialysis phase seems justifiable. That this is already happening has been illustrated by IDEAL, where symptoms overruled eGFR on the decision when to start RRT.[15] As far as we know there is no other research on the impact of symptoms on QoL in pre-dialysis patients.

Our results on the number of symptoms and symptom severity are in line with existing research in CKD patients.[17, 28-30] Almutary ***et al.*** performed a systematic review investigating symptom burden in CKD stage 4 and 5. They found seven studies on symptom burden in pre-dialysis patients. These studies showed a wide range of symptoms, with fatigue being the most common symptom, followed by pruritus and dry skin. Pre-dialysis patients had more psychological problems compared to patients on dialysis. The average number of symptoms ranged from 6 to 20, compared to 13 in our population.[17] Other research in 436 CKD patients of which 24.5% were in the pre-dialysis phase (mean age 52, 55% male), showed an average symptom number of 13 with fatigue and pain as most common symptoms. In this study "difficulty becoming sexually aroused" and "decreased interest in sex" were two of the most severe symptoms when experienced, which is in concordance with our study.[28]

Yong ***et al.*** performed a study in 179 end stage renal disease patients of which 45 were treated conservatively (mean age 73), looking both at symptom burden and at its relation to QoL. They found a negative correlation between symptom burden and QoL, which is similar to our study, although the CKD stage in this population differs from our population.[31] In a study by Abdel-Kader ***et al.*** symptom burden was negatively correlated with MCS but not with PCS, while symptom severity was negatively correlated with both MCS and PCS in 87 CKD stage 4/5 patients.[11] The lack of correlation between symptom burden and PCS in the latter study could be explained by the small population or by the lack of correction for confounding.

There is only one other study we know of that looks at symptoms and QoL over time.[1] De Goeij ***et al***. studied this relation in 436 pre-dialysis patients (median age 69, 66% male, mean eGFR 16.9ml/min/1.73 m^2). They found an increase in symptoms over time, and a decrease in QoL (both MCS and PCS). However, they did not directly assess the relation between symptoms and QoL over time. Although de Goeij ***et al.*** studied a longer period of time, their findings on symptoms and QoL are quite similar to our results.

The main strength of this study is the size of the study population. As far as we know this is the largest population of pre-dialysis patients in which the relation between symptoms

and quality of life has been evaluated. Another strength is the inclusion of incident pre-dialysis patients (who for the first time passed a pre-specified eGFR level), which decreased the risk of survival bias. In addition, the exclusion criteria for EQUAL are minimal, ensuring a wide range of elderly pre-dialysis patients were included, making the results generalizable to the clinical practice of pre-dialysis care for elderly patients.

The main limitation of this study is the duration of follow-up. In the future follow-up will be extended to at least four years, but for this study only the first six months of follow-up were available. Although this is a limitation, it is one of the first studies researching symptoms and QoL over time and thereby still an important contribution to the body of evidence on this subject. A second limitation is the number of non-responders after six months of follow-up. Due to this problem we had to restrict the number of patients in analyses involving the six months follow-up measurement. Another limitation is the use of the Dialysis Symptom Index as symptom questionnaire. This symptom questionnaire was developed and validated in dialysis patients. Since patient's follow-up continues during dialysis this questionnaire is a good choice for the entire EQUAL study. For this particular study in pre-dialysis patients the lack of validation in this group is a limitation. However, the Dialysis Symptom Index has been used in pre-dialysis populations before, with valid results.[32, 33] Finally, based on the model of Wilson which implies symptoms result in QoL, and on the measurements over time which gave us the opportunity to measure symptoms at an earlier moment compared to QoL, we interpreted our results as effects. However, we would like to emphasize the caution needed when interpreting our results as causal, and the possibility of methodological limitations, such as residual confounding, which could make causal interpretation very difficult.

In conclusion, this study showed an effect of symptoms on QoL, and quantified their relative importance. The prevalence and severity of symptoms in our population emphasizes the need for attention on symptoms during outpatient clinic visits. The effect of symptoms on a clinically relevant outcome measure indicates symptoms should have a more prominent role in clinical decision making and guidelines in CKD should emphasize this. Opportunities for future research include studying the impact of individual symptoms on QoL and testing whether interventions on symptoms improve QoL. Future results of the EQUAL study on the start of dialysis will give the opportunity to investigate the role of symptoms in that period more thoroughly.

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