

Health-related quality of life and symptom burden in patients on haemodialysis

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RUNNING TITLE: Health-related quality of life and symptom burden in haemodialysis patients

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ABSTRACT

Background. Patients on haemodialysis generally experience poor health-related quality of life (HRQoL) and a broad range of physical and mental symptoms, but it is unknown whether this differs between younger and older patients. We aimed to describe the trajectories of HRQoL and symptom burden of patients <70 and ≥70 years old, and to assess the impact of symptom burden on HRQoL.

Methods. In incident Dutch haemodialysis patients, HRQoL and symptoms were measured with the 12-item Short Form Health Survey and Dialysis Symptom Index. We used linear mixed models for examining the trajectories of HRQoL and symptom burden during the first year of dialysis, and linear regression for the impact of symptom burden on HRQoL.

Results. In 774 patients, the trajectories of physical HRQoL, mental HRQoL, and symptom burden were stable during the first year of dialysis. Compared with patients aged <70 years, patients ≥70 years reported similar physical HRQoL (mean difference -0.61, 95% CI -1.86; 0.63), better mental HRQoL (1.77, 95% CI 0.54; 3.01), and lower symptom burden (-2.38, 95% CI -5.08; 0.32). With increasing symptom burden, physical HRQoL declined more in older than in younger patients (β -.287 versus -.189, respectively, p -value for interaction = .007). For mental HRQoL, this decrease was similar in both age groups (β -.295 versus -.288, p = .847).

Conclusions. Older haemodialysis patients generally experience a better mental HRQoL and a (non-statistically significant) lower symptom burden, compared to younger patients. Their physical HRQoL declines more rapidly with increasing symptom burden.

Keywords: ageing, dialysis, end stage renal disease, kidney failure, patient-reported outcomes

KEY LEARNING POINTS

What was known:

- Dialysis often has a major impact on patients' lives, both physically, mentally, and socially.
- In older patients, health-related quality of life (HRQoL) and symptom burden deteriorate rapidly in the years preceding dialysis initiation after which a stabilisation is seen. However, it remains unknown whether the trajectories of HRQoL and symptom burden differ between younger and older patients.
- Symptoms play an important role in HRQoL, but it remains unknown if the impact of symptoms differs between younger and older dialysis patients.

This study adds:

- Younger (<70 years) and older (≥ 70 years) patients both have stable trajectories of HRQoL and symptom burden during their first year of haemodialysis. Older patients, however, generally experience better mental HRQoL and a lower symptom burden.
- Both the prevalence and severity of individual symptoms was lower among older patients, as compared with younger patients. Younger patients more often reported *feeling sad, lightheadedness, having difficulty concentrating, headaches, feeling irritable, nausea, feeling anxious, diarrhoea, and vomiting*. Older patients more often reported *leg swelling*.
- In older patients, the impact of symptoms on physical HRQoL is larger than observed in younger patients. For mental HRQoL, the effect was similar among both age groups.

Potential impact:

- Knowledge on HRQoL and symptom burden trajectories of both younger and older patients helps to inform patients on what to expect after dialysis is initiated: despite the impact of dialysis, haemodialysis patients – most notably, the older patients – showed no further deterioration of HRQoL during their first year of treatment.
- Because symptoms impact the physical HRQoL of older patients, adequate monitoring, discussing and treatment of symptoms is warranted.
- Future studies should assess which symptoms impact patients' HRQoL most and whether treatment of these symptoms would consequently improve HRQoL.

BACKGROUND

Dialysis-dependent patients generally experience a lower health-related quality of life (HRQoL) than the general population, patients with earlier stages of chronic kidney disease (CKD), and kidney transplant recipients.¹⁻³ Apparently, dialysis treatment, although often life-saving, has a major impact on patients' lives, both physically, mentally, and socially. HRQoL is often influenced by the presence of physical and emotional symptoms.⁴⁻⁷ On average, patients on dialysis experience a high symptom burden and report having more than 10 symptoms.⁸

Although the dialysis population is ageing rapidly, little is known about the trajectories of HRQoL and symptom burden of younger and older dialysis patients. A recent European study found a stabilisation of HRQoL and symptom burden after dialysis initiation in patients aged ≥ 65 years.^{9, 10} It is unknown whether the same holds true when including patients of all ages, including those younger than 65 years old. It is also currently unknown whether the impact of symptom burden on HRQoL differs between age groups. Therefore, we aimed to describe the trajectories of HRQoL and symptom burden of younger and older patients during the first year of dialysis, and to assess the impact of symptom burden on HRQoL in both age groups.

MATERIALS AND METHODS

Study design and population

For this study, data from the *Dutch nocturnal and home dialysis study to improve clinical outcomes* (DOMESTICO) were used, a nationwide observational cohort study in the Netherlands and Belgium with 59 participating centres. The rationale and design of DOMESTICO was published previously.¹¹ In summary, DOMESTICO will assess differences between patients on home dialysis with in-centre dialysis in terms of quality of life, clinical outcomes, and costs. Patients of ≥ 18 years who started maintenance dialysis from December 2017 onwards were included. Patients with a life expectancy of less than 3 months or an expected kidney transplantation within 3 months were excluded. For the present substudy, we included all patients who started in-centre haemodialysis prior to January 19th, 2021, as DOMESTICO is currently ongoing. This allowed for a minimum follow-up duration of 1 year. This manuscript adheres to the *STrengthening the Reporting of OBservational studies in Epidemiology* (STROBE) guidelines.¹² (Supplementary Table S1)

Patient-reported outcome measures (PROMs)

For the present study, we used data on HRQoL and symptoms collected at dialysis initiation, after 3 months, 6 months, and 12 months. Patients filled in questionnaires on paper or using online forms, if needed with help of others, as long as patients themselves provided the answers. HRQoL was measured using the 12-item Short Form Health Survey (SF-12).^{13,14} The SF-12 is summarised into a Physical Component Summary score and a Mental Component Summary score, hereafter referred to as physical HRQoL and mental HRQoL. These scores range from 0-100 with higher scores indicating better HRQoL. Both scores are norm-based with the mean of 50 being standardised to the US general population. Symptoms were measured using the kidney disease-specific Dialysis Symptom Index (DSI), consisting of the 30 most common physical and emotional symptoms in this population.¹⁵ Patients indicated the presence of each symptom (yes/no) and, if present, the symptom's severity on a 5-point Likert scale ranging from 1 ('not at all bothersome') to 5 ('very bothersome'). An overall symptom burden score was calculated by summation of the severity of each of the 30 symptoms, resulting in an overall score ranging from 0 ('no symptoms') to 150 ('30 symptoms with a maximal severity').¹⁶

Statistical analyses

The main determinant for all analyses was age at dialysis initiation, which was dichotomised to <70 years (reference) and ≥70 years (comparison). This cut-off value for age was determined *a priori* and based on comparability with other large nationwide study initiatives.¹⁷

HRQoL at dialysis initiation was compared between age groups using unpaired t-tests. The trajectory of HRQoL during the first year of dialysis treatment was examined using linear mixed models while incorporating all available measurements for individual patients. This allowed us to describe the trajectory of HRQoL for younger and older patients (i.e. within-groups results) and to compare these two age groups (i.e. between-groups comparison). Age (dichotomised) was used as a fixed covariate. To detect differences in the trajectories of HRQoL between both groups, an interaction with time was added to the model. Results were not adjusted for expected between-group differences, such as sex and comorbidities, because of the descriptive nature of these analyses. Results of the between-groups comparison were reported as the mean difference over the 1-year observation period.

The presence and severity of symptoms at the start of dialysis treatment were compared between patients <70 and ≥70 years old using chi-squared tests. The overall symptom burden at dialysis initiation was compared using a t-test. The trajectory in symptom burden during the first year of dialysis treatment was examined using linear mixed models, with similar methodology as the assessment of HRQoL. Again, the trajectories of symptom burden for both age groups were described and a comparison made between younger and older patients.

Finally, the impact of overall symptom burden on physical and mental HRQoL at dialysis initiation was assessed using linear regression analysis. To compare the impact of age (dichotomised), an interaction term with the symptom burden score was added to the model.

Categorical variables are displayed as frequencies with percentages. Normally distributed variables are displayed as means with standard deviations (SD) and non-normally distributed variables as medians with interquartile ranges (IQR). All analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA), except for the linear mixed models, which were performed using Stata version 14 (Stata Corp LLC, College Station, TX, USA). A significance level (alpha) of .05 was used and results of the longitudinal analyses were reported with 95% confidence intervals (CI). In the longitudinal analyses, missing values were assumed to be missing at random and estimated using multiple imputation.¹⁸ Up to 10 iterations and predictive mean matching using 20 imputed datasets were used. The imputation model included patients' age and sex, moment of measurement and all individual responses on both the SF-12 and the DSI. Questionnaires with >50% missing answers were considered insufficient and were excluded.¹⁹

Sensitivity analyses

Four sensitivity analyses were performed. We performed 2 sensitivity analyses for the longitudinal assessment of HRQoL and symptom burden by 1) excluding patients who died and 2) excluding patients who did not complete the 1-year follow-up (i.e. patients who died, received a kidney transplant, withdrew their consent, withdrew from dialysis, or had recovery of kidney function). This was done since younger and older patients are potentially at an unequal risk for not completing the 1-year follow-up due to expected differences in mortality risk and probability of receiving a kidney transplant. We performed 2 additional sensitivity analyses for the longitudinal analyses to assess 3)

the effect of multiple imputation, using complete case analysis, and 4) the influence of the selected cut-off for age by using a different age-contrast (i.e. age <50 versus ≥80 years).

RESULTS

In total, 777 patients started in-centre haemodialysis of which 3 patients were excluded because they did not fill in any questionnaires. This led to a total of 774 included patients of whom 381 (49.2%) were <70 years and 393 (50.8%) were ≥70 years old. Baseline characteristics are shown in Table 1. Most notably, older patients more often had renovascular and diabetic kidney disease, were living together, had a low educational level, and had more comorbidities. One-year follow-up was complete for 622 patients (80.4%, Supplementary Table S2). Younger patients more often received a kidney transplant (9.2%, compared with 5.3% in patients ≥70 years old) while older patients more often died (7.6%, compared with 3.1% in patients <70 years old).

HRQoL at haemodialysis initiation

At baseline, physical HRQoL was similar for both age groups: 35.3 ± 9.6 and 35.3 ± 10.1 for patients aged <70 and ≥70 years, respectively ($p = .972$). Mental HRQoL, however, was significantly higher among older patients: 45.7 ± 10.5 for patients <70 years and 47.6 ± 9.7 for patients ≥70 years old ($p = .014$).

Trajectory of HRQoL after haemodialysis initiation

When comparing the two age groups, during the first year of dialysis, physical HRQoL scores of older patients were comparable with those of younger patients (mean difference -0.61, 95% CI -1.86; 0.63, $p = .334$). However, the mental HRQoL of older patients was higher compared with younger patients (mean difference 1.77, 95% CI 0.54; 3.01, $p = .005$). In other words, older patients reported a 1.77 points higher mental HRQoL score during the first year of dialysis treatment.

The trajectories of HRQoL scores are shown in Figure 1. Physical HRQoL slightly increased for patients aged <70 years throughout the first year of dialysis while it remained stable for patients ≥70 years old. Mental HRQoL increased slightly in both groups. The interaction term for time and age was statistically significant for physical HRQoL, indicating a different trend in physical HRQoL over time between younger and older patients. This can be seen in Figure 1: between 3 and 6 months,

when patients <70 years had an increase in HRQoL whereas patients ≥70 years had a decrease. For mental HRQoL, no significant differences in trends over time between age groups were detected.

Presence and severity of symptoms and overall symptom burden at haemodialysis initiation

At dialysis initiation, patients aged <70 years more often reported *feeling sad, lightheadedness, having difficulty concentrating, headaches, feeling irritable, nausea, feeling anxious, diarrhoea, and vomiting* (Figure 2). Patients aged ≥70 years more often reported *leg swelling*. Mean symptom severity scores for all individual symptoms of patients <70 years were comparable with or higher than those of patients ≥70 years (Supplementary Figure S1). The mean overall symptom burden at dialysis initiation was higher in patients <70 years compared with patients ≥70 years old (35.7 ± 22.7 versus 31.6 ± 19.2 respectively, $p = .013$).

Trajectory of overall symptom burden after haemodialysis initiation

During the first year of haemodialysis, older patients reported somewhat lower symptom burden scores compared with younger patients, although this difference was not statistically significant (mean difference -2.38 , 95% CI $-5.08; 0.32$, $p = .084$). The trajectory of symptom burden is shown in Figure 3. Both among younger and older patients, symptom burden decreased slightly during the first 3 months and thereafter stabilised. The interaction with time was statistically significant, indicating a different trend between both age groups, which can be seen in Figure 3: the symptom burden of patients <70 years slightly decreased between 3 and 6 months, and then slightly increased between 6 and 12 months. For patients ≥70 years, this was the opposite.

Impact of symptom burden on HRQoL at haemodialysis initiation

In younger patients, the overall symptom burden score explained 18.7% of the variance of the physical HRQoL (Figure 4). In older patients, this was 28.6%. With increasing symptom burden, the decline in physical HRQoL was smaller in younger patients compared with older patients (β $-.189$ versus $-.287$, respectively, p -value for interaction $.007$).

For mental HRQoL, the explained variance by the symptom burden score was more comparable for younger and older patients (37.1% and 31.2%, respectively). With increasing symptom burden, the decline in mental HRQoL was similar between younger and older patients (β $-.295$ and $-.288$, respectively, $p = .847$).

Sensitivity analyses

In summary, the sensitivity analyses showed that most results remained stable (Figure 5 and Supplementary Table S3), with one exception: when comparing patients <50 years old with patients aged ≥ 80 years (total $n = 215$), the estimated mean difference in physical HRQoL increased, with patients <50 years old having a better physical HRQoL.

DISCUSSION

Our study showed that older haemodialysis patients (≥ 70 years) had a similar physical HRQoL but a better mental HRQoL than younger patients (<70 years), at dialysis initiation and during their first year of treatment. During this year, HRQoL remained stable, both in younger and older patients. Regarding symptoms, older patients generally reported fewer symptoms and with lower severity, resulting in a lower overall symptom burden, but with increasing symptom burden, the physical HRQoL of older patients decreased more profoundly than observed in younger patients. The impact of symptoms on mental HRQoL was similar for both age groups.

Health-related quality of life

In general, the physical HRQoL of all patients in our cohort was significantly lower than observed in the general Dutch population (35.3 versus 50.3, respectively, using the SF-12), while for mental HRQoL the difference was less pronounced (46.6 versus 52.9).²⁰ This illustrates the substantial physical impact that kidney failure, its associated comorbidities, and dialysis treatment have on patients' lives, but also shows the remarkable mental resilience of dialysis patients. It is reassuring that patients, most notably older patients, are able to maintain their HRQoL, despite frequent hospital visits, risk of dialysis-related complications, and a high risk of mortality. Indeed, we perhaps would have expected greater decline of HRQoL among the older patients as they are particularly susceptible to these risks. Previous studies in incident haemodialysis patients assessing the effect of age are scarce and found contradictory results. One study found that increasing age was associated with worse physical HRQoL, measured 3 months after dialysis initiation.²¹ For mental HRQoL, no association with age was found. In the Dutch NECOSAD study, 7 out of 8 subdomains of the SF-36 were negatively associated with age, also measured 3 months after the start of dialysis.²² The

European EQUAL study assessed HRQoL longitudinally and found that, after a marked deterioration in the year preceding dialysis, both physical and mental HRQoL stabilised shortly after dialysis was started.⁹ In a subgroup analysis for age, the trajectory was similar for patients of 65-74 years and ≥ 75 years old. Hence, our current study adds to this knowledge by showing that similar stabilisation is found in Dutch haemodialysis patients of all ages. In general, changes over time were small and likely clinically irrelevant: estimates of the minimally clinically important difference for HRQoL, measured with the SF-36, range from 2 up to 9 points, dependent on the population studied.^{23, 24}

Symptom burden

Older patients overall had a lower symptom burden, with an equal or lower prevalence and severity of nearly all individual symptoms compared with younger patients. So far, only two longitudinal studies assessed the potential influence of age on the symptom burden trajectory of patients with CKD. A French study found no association between age and 5-year symptom trajectories in nearly 2800 patients with eGFR < 60 mL/min/1.73m².²⁵ In the EQUAL study, patients of 65-75 years and ≥ 75 years old had a comparable trajectory of symptom burden after dialysis was started.¹⁰ Both results are in line with our findings, demonstrating a stable symptom burden during the first year of dialysis in both younger and older patients.

Impact of symptom burden on HRQoL

Our study found a strong impact of the overall symptom burden on HRQoL, with physical HRQoL being more affected in older patients compared with younger patients. A causal association between symptoms and HRQoL is biologically plausible. In the framework by Wilson and Cleary, symptoms directly influence a patient's functional status, in turn affecting the general health perception and ultimately HRQoL.²⁶ Indeed, previous studies described this association between symptoms and HRQoL but none compared younger and older patients.^{5, 7, 16} One study described that the physical HRQoL of dialysis patients of all ages is more profoundly influenced by either the number of symptoms or the symptoms' severity, as compared with mental HRQoL.¹⁶ Our study adds that the impact of symptoms on physical HRQoL is larger in patients ≥ 70 years, compared with younger patients.

Potential explanations

There are several potential explanations for the observed limited difference in physical HRQoL, mental HRQoL and symptoms between younger and older patients, even though older age often comes with more comorbidity, functional dependence, and higher dialysis-related risks. First, coping strategies may differ between younger and older patients. Older persons are generally better at emotional regulation, for example by avoiding stressors, positively reappraising the effects of negative events, adapting their daily life, adjusting their goals, and pacing their activity.²⁷ In a way, their past experiences help to cope with the increased burden that is associated with ageing, chronic illness, and the end of life. Second, social comparison, a behavioural strategy where people compare certain aspects of themselves to those of others, may also differ between the young and the old: younger patients with chronic illnesses are more often among healthier peers and, as such, their perception of their own health could be worse than older patients.^{28, 29} In addition, ageing is expected by the general population to be accompanied by physical deterioration. For younger adults, chronic health conditions are more likely to be regarded as abnormal events, influencing the person's perception of health. Third, the required adaptation to health problems often differs between younger and older patients since it is dependent on patients' social roles, life expectations, and goals. For example, younger patients are more often confronted with the risk of unemployment as their kidney function deteriorates while for many older patients, career responsibilities are no longer present or less influential. In younger patients, chronic illness may interfere with their desired central family role. In summary: it is possible that having better coping strategies, being around less healthy peers, and having less restraining social roles could have helped the older patients in our study to perceive their HRQoL more positively and their symptoms as less burdensome, compared with the younger patients.

Clinical interpretation and directives for future research

Our study has several clinical implications. Having data on the trajectory of HRQoL after dialysis initiation helps to inform patients about what to expect regarding the trajectory of HRQoL. Our observation that increasing symptom burden was associated with a lower physical HRQoL, most notably among older patients, suggests the importance of monitoring, discussing and, if possible, alleviating symptoms to improve HRQoL. Extra attention should be paid towards the symptoms that

are most common, burdensome, and modifiable. Future studies should assess if multidisciplinary treatment strategies to reduce symptom burden indeed result in improvement of HRQoL and which subgroups of patients are most likely to benefit. An example of such as study is currently ongoing in Australia and New Zealand.³⁰ In addition, the trajectory of individual symptoms should be studied, as potentially some symptoms are better alleviated with dialysis than others and symptoms might influence HRQoL differently.

Strengths and limitations

To our knowledge, this is the first study to directly compare HRQoL and symptom burden between younger and older dialysis patients, using a large prospective cohort that includes patients of all ages. By using multiple measurements within the first year, the trajectory of HRQoL could be studied in detail. By using linear mixed models, all measurements were included, even if patients died or withdrew within the first year. Multiple sensitivity analyses were performed to assess the robustness of our results. By combining SF-12 and the DSI, both generic and kidney disease-specific outcomes were measured. In the Netherlands, the DSI was chosen with input of the Dutch Kidney Patients Association as the standard in nephrological care for its brevity and completeness while being developed and validated in populations with advanced kidney disease.³¹

Our study has a few caveats. First, we only included patients on in-centre haemodialysis and it is unknown how generalisable our results are to patients receiving other types of dialysis treatment (i.e. home haemodialysis or peritoneal dialysis). Comparison between treatment modalities is often difficult as generally younger, less frail, and more functionally independent patients are started on home therapies. Second, we assessed only patients who started dialysis, while older and frailer patients are more likely to abstain from dialysis. Although previous studies demonstrated that patients who opt for conservative care have the potential to reach a comparable HRQoL as patients treated with dialysis, poor HRQoL could be associated with the odds to start dialysis.³² Hence, it's important not to causally apply our results to patients *prior to* their decision to start dialysis or not. The risk of selection bias after dialysis initiation appears to be limited in our study. Although older patients were more likely to die and younger patients more likely to receive a kidney transplant, and both odds are potentially associated with HRQoL, our sensitivity analyses showed results similar to our main analyses. Third, the trajectory of HRQoL and symptom burden after our 1-year study period remains

unknown. However, particularly for older patients, a year is still quite extensive due to the high risk of mortality: in our cohort, 5.4% died within the first year of dialysis. Finally, patients with a low HRQoL and/or a high symptom burden could choose to forego answering PROMs, potentially limiting the generalisability of the results to the whole haemodialysis population. This selection, however, is unlikely related to age as the exposure of interest.

Conclusion

In conclusion, younger and older haemodialysis patients experience HRQoL and symptoms differently, with older patients generally experiencing better mental HRQoL and a lower symptom burden. In both age groups, the association between symptoms and HRQoL is marked but physical HRQoL declines more rapidly with increasing symptom burden in older patients. Clinicians should discuss and treat individual symptoms where possible and future research should evaluate whether treatment of these symptoms also results in reduced symptom burden and consequently improvement of HRQoL.

CONFLICT OF INTEREST STATEMENT

A.E.S. received speaker fees from Baxter, outside the submitted work. W.J.B. received grant support from Zilveren Kruis Insurance, outside the submitted work. F.W.D. received grant support from Vifor, Astellas and Chiesi, outside the submitted work. A.C.A. received speaker fees from Baxter, Fresenius Medical Care Deutschland GmbH and Cablon Medical, and grant support from the Dutch Kidney Foundation and Baxter, outside the submitted work. M.v.O, A.C.A., M.v.B. and W.J.B. are investigators for the *DIALysis or not: Outcomes in older kidney patients with Gerlatric Assessment* (DIALOGICA) study, which is supported by Leading the Change, a Dutch healthcare efficiency evaluation project by Zorgevaluatie Nederland. All other authors declare they have no competing interests.

ETHICS STATEMENT

All patients provided written informed consent upon enrolment. Primary ethical approval was obtained from the medical research ethics committee of the VU University Medical Center Amsterdam, on December 7th, 2017 (reference number: 2017.491, NL63277.029.17).

AUTHORS' CONTRIBUTIONS

All authors were involved in the study design, data interpretation and drafting of the manuscript. A.A.B., A.E.S., F.W.D., B.v.J. and A.C.A. are primary investigators of DOMESTICO and involved in the data collection. M.v.O. performed the main analyses. A.A.B. performed the linear mixed models. All authors approved the final version.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission of the DOMESTICO steering committee.

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