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File ID 81526
Filename Chapter 2.1 Clinical condition

SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type Dissertation
Title Determinants of outcome dialysis
Author K.J. Jager
Faculty Faculty of Medicine
Year 2000
Pages 159
ISBN 9090-1402-47

FULL BIBLIOGRAPHIC DETAILS:

<http://dare.uva.nl/record/85780>

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Chapter 2.1

Clinical condition

Jager KJ, Merkus MP, Boeschoten EW, Dekker FW, Stevens P, Krediet RT, on behalf of the NECOSAD Study Group: Dialysis in the Netherlands: the clinical condition of new patients put into a European perspective. *Nephrol Dial Transplant* 14:2438-2444, 1999

Abstract

Background and Purpose. The unadjusted annual mortality rate among prevalent Dutch dialysis patients increased from 1981 to 1992. Part of this increase may be attributed to the aging of the dialysis population, but hardly any data were available on other important prognostic features of new Dutch dialysis patients, such as comorbidity and other aspects of their clinical condition. The aim of the present study was to obtain these data and to put them into a European perspective.

Methods. Two hundred and fifty consecutive new patients were included in this prospective multicenter study. Data were collected three months after start of dialysis. Multivariate linear regression analysis was used to explain the variability of parameters of nutritional state and blood pressure.

Results. Mean age was 57 years, comorbid conditions were present in 51%, diabetes mellitus in 18% and cardiovascular disease in 28%. Decreased protein intake was related to diminished residual renal function. Our patients did not have more comorbidity than Dutch patients participating in a European study some years earlier. Comparison with other studies was complicated by the use of different definitions of comorbidity and of selected patient populations.

Conclusions. Despite the fact that Dutch dialysis patients have become older and the incidence of diabetic nephropathy has increased, no conclusions could be drawn on a concomitant increase in comorbidity. This patient group may serve as a reference population to study future changes in patient case-mix within the Netherlands. Furthermore, the use of common international definitions of comorbidity is needed to be able to make comparisons of survival data.

Introduction

Between 1981 and 1992 the number of patients on dialysis treatment for end-stage renal disease (ESRD) in the Netherlands has doubled.¹ Despite major improvements in dialysis technology, the unadjusted annual mortality rate among prevalent patients increased from 10.5 to 18.8% during this same period.¹ Both developments were not unique to the Netherlands, but were the expression of a world-wide trend. Explanations for the increase in the number of patients include greater acceptance to therapy of older and sicker patients, reduced mortality from other conditions and possibly a higher incidence of kidney disease.² At the same time, advanced age and increased comorbidity seem the obvious causes for the growing mortality of prevalent patients, although a change in other patient characteristics or in treatment patterns cannot be excluded.

The aging and increased sickness are in part illustrated by the following figures. In the United States, the mean age of new dialysis patients has increased from 55 years in 1984 to 59 years in 1992, while the incidence of diabetes mellitus as primary renal disease rose from 27 to 36% and that of hypertension from 25 to 30%.^{3,4} In Europe, the mean age of adult patients starting renal replacement therapy increased from 46 years in 1977 to 57 years in 1992, whereas the incidence of ESRD due to diabetes mellitus grew from 4 to 17% and that due to renal vascular disease from 7 to 14%.⁵ A similar trend occurred in the Netherlands,^{5,6} although the incidence of ESRD caused by diabetes was somewhat lower than in the rest of Europe: 12% in 1992.⁶

Data on the non-renal comorbidity of the US patients starting dialysis are collected by the United States Renal Data System. Also other investigators evaluated the incidence and sometimes the growth in the number of comorbid conditions in the US^{7,8} and Canada.^{9,10} Less is known on the presence of comorbid conditions in Europe. Neither the registry of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) nor the Dutch renal replacement registry (RENINE) routinely collect these data. Yet, especially comorbidity will influence the outcome of renal replacement therapy. Therefore, Khan et al. recently stated that unadjusted comparisons between survival data from different centers or countries are at best meaningless and at worse misleading because of the potential imbalances in age, comorbidity, etc., in different patients.¹¹ The same holds for the comparison of survival data over time. The aim of this study was therefore to obtain more data on the clinical condition of patients starting dialysis in the Netherlands and to put these into a European perspective.

Subjects and methods

Patients

ESRD patients older than 18 years, who started chronic dialysis as their first renal replacement therapy and survived the first three months on dialysis, were eligible for the study. From 13 Dutch centers we included consecutive patients, who started dialysis between 1 October 1993 and 1 April 1995. These patients were participating in the Netherlands Cooperative Study on the Adequacy of Dialysis, phase 1 (NECOSAD-1), a prospective multicenter cohort study.

Data collection

Primary renal disease and comorbidity. Renal disease was classified according to the codes of the ERA-EDTA Registry. Comorbid conditions present at the start of dialysis were scored. Cardiovascular disease was recorded when one of the following conditions had been present: angina pectoris, myocardial infarction, class III to IV congestive heart failure, or peripheral vascular disease. Systemic disease was considered to be present in patients with diabetic nephropathy, hypertensive nephrosclerosis, lupus nephritis, amyloidosis, and scleroderma. The comorbidity risk for patient survival was expressed as Davies risk score,¹² whereas the combined risk of comorbidity and age was estimated as Khan risk score.¹³

Blood pressure, functional status and well-being. In hemodialysis (HD), blood pressure was measured before and after dialysis over a period of two weeks. The systolic and the diastolic pressures were averaged. In peritoneal dialysis (PD), blood pressure was measured at a routine visit in the outpatient clinic. Mean arterial blood pressure was calculated as diastolic blood pressure + 1/3 (systolic blood pressure minus diastolic blood pressure).

Functional status and well-being were determined by the Karnofsky index, scored by a physician or a nurse, and by the 36-Item Short Form Health Survey Questionnaire (SF-36),^{14,15} which was completed by the patients. The scales of the SF-36 were combined into a physical component summary score (PCS-score). Higher scores in these instruments indicate a better functional status and well-being.

Laboratory investigations. Blood tests included plasma urea, plasma creatinine, hemoglobin, serum albumin, calcium and phosphate. In HD, the blood samples were taken prior to a dialysis session.

Nutritional status. Nutritional status was assessed by the body mass index (BMI), percentage of lean body mass (% LBM), serum albumin, and an estimation of dietary protein intake. Percentage of LBM was determined by measurement of skinfold thickness at four sites (biceps, triceps, subscapular and iliac) by trained nurses. In HD patients these assessments took place after a dialysis session. The dietary protein intake was estimated as protein equivalent of nitrogen appearance

(PNA) (in HD, PNA (g/24 hr) = 9.35 * urea generation rate (mg/min) + 0.294 * urea distribution volume (l)¹⁶; in PD, PNA (g/24hr) = 19 + 0.2134 * urea appearance (mmol/24hr)¹⁷) normalized to actual body weight (nPNA). The urea distribution volume (V) was determined by the formulae of Watson et al. for total body water.¹⁸ Anthropometric parameters and serum albumin were combined to a malnutrition index, corrected for age, sex, height and frame size, as described by Harty et al.,¹⁹ but without the use of the subjective global assessment. A score of 11 or higher was defined as severe malnutrition.

Renal function and therapy. In HD, urine was collected during the interdialytic interval and in PD during 24 hr. From this collection daily urine volume, renal Kt/V_{urea}, renal creatinine clearance, and residual GFR (rGFR) were calculated. The latter was defined as the mean of the urea and creatinine clearances. Hemodialysis Kt/V_{urea} was estimated using a second-generation Daugirdas formula.²⁰ Peritoneal Kt/V_{urea} and creatinine clearance were calculated from a 24-hour dialysate collection. Data on medication were collected from the medical records.

Literature search. A Medline search was performed to retrieve references of studies providing information on comorbidity in dialysis patients and published in the English language over the period of January 1985 to June 1998. Dialysis, survival or mortality, comorb*, and adult were used as search terms. From the retrieved references we selected studies that fulfilled the following criteria:

(1) information present on comorbid conditions at the start of renal replacement therapy of ESRD patients receiving dialysis, other than data on primary renal diseases; (2) no restriction made to a subgroup of the adult dialysis population; the only selection permitted was one on treatment modality; and (3) European patient population.

Analytical methods

Demographic and clinical characteristics were used to explain the variability of parameters of nutritional state and blood pressure in multivariate linear regression. A two-sided P-value less than 0.05 was considered statistically significant.

Results

Demography, primary renal disease and comorbidity

Of 267 patients who met the inclusion criteria, 250 were included in the study (94%). Eleven patients refused to participate and the physical, psychological or social condition of six patients was so serious that collection of essential parameters, such as residual renal function or anthropometry, was not possible. Table 1 shows data on demography, renal disease and comorbidity. Thirty seven percent of the patients were aged ≥ 65 years. Renal vascular disease was the most

Table 1. Demography, renal disease, comorbidity and risk scores (% or means (SD)).

| <i>Factor</i> | | |
|--|--|---------|
| <i>Demography</i> | | |
| Age | | |
| Mean (years) | | 57 (15) |
| ≥ 65 years (%) | | 37 |
| Sex (% male) | | 58 |
| <i>Renal disease, comorbidity and risk scores</i> | | |
| Renal disease (%) ^a | renal vascular disease | 23 |
| | diabetes mellitus | 15 |
| | glomerulonephritis | 12 |
| | other | 50 |
| Comorbidity (%) | | |
| Diabetes mellitus | | 18 |
| Malignancy | | 6 |
| Cardiovascular disease | | 28 |
| | ischemic heart disease | 15 |
| | angina pectoris | 10 |
| | myocardial infarction | 9 |
| | congestive heart failure (NYHA III/IV) | 5 |
| | peripheral vascular disease | 17 |
| Cerebrovascular accident | | 8 |
| Systemic disease | | 30 |
| No. of comorbid conditions, out of a number of 14 (%) ^a | | |
| | 0 | 12 |
| | 1 | 29 |
| | ≥ 2 | 59 |
| Risk scores ^a | | |
| Khan | low risk | 47 |
| | medium risk | 30 |
| | high risk | 22 |
| Davies | grade I (0 conditions) | 49 |
| | grade II (1-2 conditions) | 44 |
| | grade III (3-4 conditions) | 7 |
| Current smoker (%) | | 28 |

^a values may not total 100% because of rounding off.

Table 2. Blood pressure levels, functional status and well-being (% or means (SD)).

| <i>Factor</i> | | |
|---|--------|----------|
| <i>Blood pressure</i> | | |
| Systolic blood pressure (mm Hg) | | 145 (19) |
| Diastolic blood pressure (mm Hg) | | 83 (10) |
| Mean arterial pressure (mm Hg) | | 104 (11) |
| <i>Functional status and well-being</i> | | |
| Karnofsky index | 80-100 | 68 |
| | 70 | 16 |
| | 20-60 | 16 |
| SF-36 physical component summary score | | 39 (9) |

frequent cause of ESRD. Of the patients ≤ 60 years, 47% had two or more comorbid conditions. All patients with diabetes mellitus had one or more comorbid conditions besides their diabetes. Fifty-one percent of the patients had comorbid conditions according to the Davies risk score.

Blood pressure levels and functional status

Data on blood pressure levels and functional status are shown in Table 2. A systolic blood pressure of 160 mm Hg or higher was found in 24% of the patients. Systolic blood pressure was higher in patients with hypertension/renal vascular disease or diabetes as primary renal disease. These conditions explained the variance in systolic pressure for 7%. A diastolic pressure of 90 mm Hg or higher was found in 32%. Diastolic pressure was lower in older patients and in those with a medium or high Khan risk score. The variance explained by these variables was 13%.

The majority of the patients had a Karnofsky index of 80 or higher, which means they were able to carry out normal physical activity. Sixteen percent scored 60 or lower, indicating they needed at least some assistance in self-care.

Blood tests, nutritional status, renal function and therapy characteristics

Table 3 shows the results of the blood tests, and data on the nutritional status and residual renal function. As expected, most patients were anemic and the mean serum albumin level was in the low normal range. Multivariate analysis showed that dietary protein intake was lower in older patients and in patients with a lower rGFR. Age and rGFR explained 20% of the variance, 15 % of which was accounted for by the rGFR. We could not establish a relationship between rGFR

Table 3. Nutritional status and residual renal function (% or means (SD)).

| <i>Factor</i> | |
|---|------------|
| <i>Nutritional status</i> | |
| Hemoglobin (g/dl) | 10.8 (1.6) |
| Albumin (g/l) | 36.9 (5.4) |
| Calcium (mmol/l) | 2.4 (0.2) |
| Phosphate (mmol/l) | 1.8 (0.5) |
| Urea (mmol/l) | 26.2 (7.2) |
| Creatinine ($\mu\text{mol/l}$) | 841 (223) |
| nPNA (g/kg/24hr) | 1.0 (0.3) |
| Body mass index (kg/m ²) | 23.9 (4.1) |
| Lean body mass (%) | 74.8 (8.5) |
| Severe malnutrition (%) | 16 |
| <i>Renal function</i> | |
| rGFR (ml/min/1.73m ²) | 2.9 (2.3) |
| Renal Kt/Vurea (/wk) | 0.6 (0.5) |
| Renal creatinine clearance (l/wk/1.73m ²) | 40 (32) |
| Urine volume (ml/24 hr) | 674 (583) |

and other parameters of nutritional state such as BMI, albumin or percent LBM.

At baseline, 132 patients were treated by HD and 118 patients by PD. Mean total Kt/V_{urea} was 3.4 (1.0) (SD)/week in HD and 2.1 (0.5) in PD. In PD, mean total creatinine clearance was 83 (29) liter/week/1.73m². Antihypertensive medication was used by 64% and erythropoetin by 74% of the patients. Almost all patients received vitamin suppletion and phosphate binders.

Literature search

The Medline search for studies on the comorbidity in dialysis patients resulted in the retrieval of 101 documents. Seven publications out of these fulfilled the additional selection criteria.^{13, 21-26} One publication, which also matched the criteria but which was not found in the Medline search, was added.²⁷ The results are summarized in Table 4.

Discussion

Data from international registries show that patients starting dialysis have aged and become sicker over the last two decades as a result of wider acceptance criteria to treatment. This development has major implications for the mortality, morbidity and the quality of life of this group of chronically ill patients. Prevalent mortality rates in the Netherlands have indeed increased since the beginning of the eighties. Although data from the Dutch renal replacement registry, RENINE, show that the dialysis population in the Netherlands is aging and that the percentage of diabetic patients is growing, little is known on other important prognostic features of new dialysis patients, such as comorbidity and other aspects of the general clinical condition. The present study supplies such data for a group of 250 Dutch patients.

Time trends in comorbidity in the Netherlands

Comparison of the age and primary renal disease of our patients with the RENINE data (mean age 1992, 56.6 years; DM 1993-1995, 14.2%) suggests that our sample was representative for new Dutch dialysis patients in the years 1993 to 1995.^{5,6} Only two other studies reported information on the comorbid conditions of new Dutch dialysis patients.^{13,26} Struijk et al. reported a similar prevalence of systemic disease in a group of patients who started PD in the late eighties²⁶ as we did in our patient population. The Dutch Nijmegen/Veldhoven (NV) subgroup in the international study of Khan et al.¹³ comprised 267 patients starting renal replacement therapy on average six years earlier than our group. This NV subgroup was representative for the new Dutch dialysis patients in the late eighties with respect to age.⁵ At first sight, those patients seemed more sick than ours. For a valid comparison with our patient group we then excluded from the NV subgroup

Table 4. European studies providing information on the comorbid conditions of dialysis patients at the start of renal replacement therapy.

| Country [Reference] | No of patients | Period of start RRT ^a | Mode of RRT ^a | Age (mean or median) | Renal disease DM (%) RVD (%) | DM ^b (%) | Cardiac/vascular disease (%) | Comorbid conditions (mean or % of patients) |
|------------------------|-------------------|--|-----------------------------|-------------------------|---------------------------------|------------------------|---|---|
| Sweden [21] | 274 | 1965-1975 1976-1979 1980-1985 1986-1987 | HD | 44 47 53 55 | - | - | - | 1.2 out of 10 conditions 1.2 out of 10 conditions 1.4 out of 10 conditions 1.4 out of 10 conditions |
| Italy [22] | 255 | 1974-1991 | HD/PD | 54 | 13 | 15 | CVD ^c , 27; PVD ^d , 2 | Mild, 18%; moderate, 49%; severe, 23% |
| [23] | 1296 | 1986-1987 | HD/PD | 56 | 10 | - | CD ^e , 12; VD ^f , 17 | Malnutrition, 2% |
| [24] | 578 | 1981-1993 | HD/PD | 59 | 9 | 9 | IHD ^g , 23; PVD, 20 | - |
| France [27] | 201 | 1983-1993 | PD | 55 | 18 | 23 | CVD, 44; IHD, 19; PVD, 10 | - |
| Spain [25] | 170 | 1986-1989 1990-1994 | PD | 48 58 | - | - | IHD, 18; PVD, 21 IHD, 20; PVD, 19 | > 1 out of 11 conditions, 48% > 1 out of 11 conditions, 52% |
| Five countries [13] | 1407 | 1985-1991 | HD/PD /Tx | 49-55 | 10-22 | 4-21 | IHD, 18-23; PVD, 2-17 | Low risk, 33-58%; medium risk, 28-37%; high risk, 14-34% |
| Netherlands [26] | 61 | 1986-1989 | PD | 57 | 13 | 10 | - | Systemic disease, 33% |
| [13] | 267 | 1985-1991 | HD/PD /Tx | 54 | 14 | 11 | IHD, 23; PVD, 17 | Low risk, 33%; medium risk, 33%; high risk, 34% |
| NF-COSAD-1 | 250 | 1993-1995 | HD/PD | 57 | 15 | 23 | CVD, 28; IHD, 15; PVD, 17 | 1 out of 14 conditions, 29%; ≥ 2 out of 14 conditions, 59%; systemic disease, 30% ^h ; low risk, 47% ^h ; medium risk, 30% ^h ; high risk, 22% ^h |

^a RRT, renal replacement therapy; ^b diabetes mellitus as renal disease or comorbid condition; ^c CVD, cardiovascular disease; ^d PVD, peripheral vascular disease; ^e CD, cardiac disease; ^f VD, vascular disease; ^g IHD, ischemic heart disease

all patients who died in the first 90 days of RRT. As a result, the mean age in that subgroup decreased to 52 years and the risk was reduced to low in 37%; medium in 34% and high in 29% of the patients. This still suggests more comorbidity in the NV subgroup than in our patient population. However, as we did not have information on the distribution of the comorbid conditions among the NV patients surviving the first three months of renal replacement therapy, our findings do not permit a conclusion with regard to a development in comorbidity since 1985.

Time trends in comorbidity in Europe

Comparison of our data with those of other European studies was only partly possible. In a Swedish single center study, Hylander et al.²¹ demonstrated an increase in age and a rise in the number of comorbid conditions from the sixties to the eighties. Rodriguez-Cormona et al.²⁵ of Spain also showed an increase in age, but an increase in comorbidity was less obvious. All other studies reported combined data over a period lasting from 2²³ to 17²² years and could therefore not be used to show a trend in time.

Differences in case-mix within Europe

Only the study reported by Khan et al.¹³ allowed comparison of comorbidity between countries and centers. As they used common definitions of comorbid disease in new ESRD populations not selected for treatment modality, and therefore less subject to patient selection bias, these authors could show that Greek patients were younger and at a lower risk than patients from other countries.¹³ Although the NV subgroup had the highest percentage of high risk patients, the difference with other centers was not statistically significant.

Other patient and treatment characteristics

Other studies reported higher,^{21,28} similar^{29,30} or lower³¹⁻³³ blood pressures than were found in our patients. In the elderly patients we found a lower diastolic blood pressure. This finding is consistent with the age-related changes in blood pressure in the general population.³⁴ A survey performed by the ERA-EDTA registry showed that 83% of the dialysis patients were receiving antihypertensive medication.³⁵ According to European standards the use of antihypertensives in our patient population was therefore relatively low.

Studies reporting the functional status of new dialysis patients are lacking. The Karnofsky index in a Dutch group of prevalent patients who had been on dialysis for almost 4 years³⁶ was similar to that in ours. Another cross-sectional study was performed in patients who had already been on HD for a number of years, but who were still able to participate actively in their dialysis treatment.³⁷ In this selected group the Karnofsky index was higher than in our patients. So far, no European data are available on the functional status and well-being of dialysis

patients as assessed with the physical component summary score of the SF-36. DeOreo from the United States³⁸ reported a slightly lower score of 35 in 1000 new and prevalent HD patients with a mean age of 58 years, suggesting these patients were more impaired than ours. This difference may be explained by the fact that part of the US patients had already been on dialysis treatment for a longer period of time. However, most differences between our data and those from other studies remain difficult to interpret because other studies comprised cross-sectional samples of selected patients groups who were heterogeneous with respect to therapy history.

Three months after the start of dialysis rGFR was 2.9 ml/min/1.73m². Preliminary data from the USRDS Morbidity and Mortality study showed that rGFR was 4.9 ml/min in PD patients and 3.4 ml/min in HD patients at 60 days after the start of dialysis.³⁹ This suggests that US PD patients may have started dialysis relatively early. Three studies have reported mean residual creatinine clearances at the time of initiation of dialysis ranging from 4.3 to 6.9 ml/min.⁴⁰⁻⁴² This corresponds to 43-70 liter/week, which is slightly higher than the residual creatinine clearance of 40 liter/week/1.73 m² in our group. A part of this difference may be explained by the decrease in residual renal function during the first three months of dialysis treatment in our patients. On the other hand, the CANUSA study in PD patients reported a mean residual renal creatinine clearance of 39 liter/week/1.73m² at the start of dialysis.¹⁰ As the preservation of residual renal function in PD is relatively good,⁴² this suggests a creatinine clearance at three months after the start of dialysis similar to that in our group.

With regard to nutritional state, we confirmed the findings of both Ikizler et al. and Churchill who reported a decreased protein intake with diminished glomerular filtration rate.^{43,44} In our study rGFR explained a substantial percentage of variance in dietary protein intake, but relationships with other parameters of nutritional state were not found. Although Churchill showed such associations in PD patients, his analyses were univariate and the reported correlation coefficients were very low, suggesting even lower percentages of explained variance.

Conclusions

We conclude that information on comorbidity and other characteristics of dialysis patients is essential to evaluate the results of this therapy in the context of increasing prevalent annual mortality rates. New Dutch dialysis patients have become older and the incidence of diabetic nephropathy has increased. However, our findings did not permit a conclusion with regard to a concomitant increase in comorbidity. Our patient group was representative for new Dutch dialysis patients in the period 1993-1995 and may therefore serve as a reference population to study future changes in patient case-mix within the Netherlands. Comparison with data

from other studies are complicated by the use of different definitions of comorbidity and of selected patient populations. The development of common definitions of comorbid conditions, preferably including the possibility to indicate the severity of these conditions, as well as the use of an international standard for registration, are needed.

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