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Early referral to a nephrologist is associated with better long-term outcome of chronic dialysis patients

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ABSTRACT

Background: To evaluate the influence of timely referral to a nephrologist on long-term outcome of chronic dialysis patients.

Methods: The outcome of chronic kidney disease (CKD) patients starting dialysis in our hospital was evaluated according to age, gender, race, diabetes, glomerular filtration rate (GFR), dialysis access, haemoglobin and albumin at the start of dialysis as well as the pattern of referral to a nephrologist.

Results: 101 patients (mean age: 61.57 years, 69 men, 95 Caucasian, 32 diabetic, 61 early referrals (ER)) were evaluated. Median follow-up was 716.59 days. Dialysis access ($p<0.0001$), referral pattern ($p<0.0029$), age ($p<0.005$) and diabetes ($p<0.05$) correlated with 3-year patient survival. After adjusting for clinical variables, age, dialysis access and the pattern of referral to a nephrologist were independent predictors of mortality ($p=0.025$). Patients younger than 65 years [relative risk (RR), 0.44; 95% confidence interval (CI) 0.23 to 0.82] and patients with a permanent access (RR, 0.55; 95% CI 0.28 to 0.98) had a lower risk of death while LR patients (RR, 2.02; 95% CI 1.08 to 4.19) were at increased risk of death.

Conclusion: Early referral to a nephrologist is associated with the greater long-term survival of chronic dialysis patients.

Key-Words:
Dialysis; outcome; timely referral to a nephrologist.

INTRODUCTION

Despite modern renal replacement therapy, the mortality of chronic kidney disease (CKD) patients remains unacceptably high[1].

Many risk factors develop in the pre-dialysis period and are associated with a greater mortality in subsequent dialysis[1]. Cardiovascular disease is the major cause of death of dialysis patients and many cardiovascular risk factors such as anaemia, hypertension, left ventricular hypertrophy and secondary hyperparathyroidism develop and progress during earlier stages of renal disease. Hypoalbuminemia, a strong predictor of death and hospitalization in dialysis patients, is a common comorbidity of CKD patients starting dialysis[2]. A placed long-term vascular access at dialysis initiation correlates with outcome[3].

According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NFK-DOQI) guidelines recently released for CKD[4], expected interventions during the pre-dialysis period include the evaluation and treatment of such risk factors as hypertension and anaemia, referral to a nephrologist and preparatory treatments for beginning dialysis, such as the placement of a vascular access[5].

Several recent studies focusing on pre-dialysis care suggested that pre-dialysis management is suboptimal, taking into consideration the high prevalence of anaemia and underuse of erythropoietin[6-9], hypoalbuminemia[1,2] and the significant proportion of CKD patients who start dialysis with a tempo-

rary catheter[1,2,5,10]. However, early referral to a nephrologist seems to be associated with a better control of anaemia[1,9] and a higher proportion of patients starting dialysis with a permanent vascular access[1,11]. Despite several studies reporting a significant impact of timely referral to a nephrologist on short and midterm outcome of CKD patients after beginning dialysis[12-15], the influence of early referral to a nephrologist on long-term patient survival remains unclear. The purpose of this study is to evaluate the influence of timely referral to a nephrologist on the long-term outcome of chronic dialysis patients.

SUBJECTS AND METHODS

We evaluated prospectively all CKD patients who started chronic dialysis, either haemodialysis or peritoneal dialysis, in our hospital for the first time, between January 1st and December 31st 2001. Hospital de Santa Maria (HSM) is a highly specialized referral and teaching hospital (Faculty of Medicine, University of Lisbon) serving a population of almost 1000000 inhabitants. CKD was considered whenever a slowly progressive kidney disease was documented at least over the last three months before the start of dialysis. Patients who recovered renal function after the initiation of dialysis, patients with no previous medical follow-up or patients with acute or chronic disease who started dialysis were excluded from analysis. All CKD patients who began dialysis in HSM are referred to dialysis units outside the Hospital except those who chose peritoneal dialysis or are infected with human immunodeficiency virus or do not belong to any social security system. These patients remain as outpatients in the HSM dialysis unit. However, patients dialysed in the associated dialysis units keep their link to the HSM for vascular access issues and hospitalization.

One week after the initiation of dialysis we reviewed all medical records to ascertain baseline demographic information (age, gender, race) and clinical variables (weight, aetiology and date of diagnosis of renal disease, timing of referral to a nephrologist, date of dialysis initiation, dialysis modality, initial dialysis access and use of erythropoietin). Patients were considered early referred (ER) if they were referred to a nephrologist at least 4 months before the start of dialysis and late referred (LR) if less than 4 months. We used a 4 month cut-off for late referral because it has been employed in other studies[1,12,15,16]. Laboratory data at last medical visit or at first dialysis (serum creatinine, haemoglobin level, serum albumin, serum iron, serum ferritin and total iron binding capacity) were also collected.

Glomerular filtration rate (GFR) at the start of dialysis was estimated using the Cockroft-Gault formula[17]. GFR was cut-off at 10.5 mL/min/1.73m^2, haemoglobin level at 11 g/dL and serum albumin at 35 g/L according to K-DOQI guidelines[4]. Transferrin saturation (TSAT) was defined as the rate between serum iron and total iron binding capacity. Adequate iron status was defined as a serum ferritin ≥100μg/L and a TSAT ≥20%, functional iron deficiency as a serum ferritin ≥100μg/L and a TSAT ‹20% and absolute iron deficiency as a serum ferritin ‹100μg/L. In order to evaluate outcome, a questionnaire was mailed to the dialysis units where those patients had been sent for dialysis (either haemodialysis or peritoneal dialysis) and the clinical status as of June 30th 2004 was ascertained.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as the percentages of number of cases. Comparisons between ER and LR patients were made using the Student's t-test for continuous variables and chi-square test or Fischer exact test for categorical variables. Survival rates were calculated according to age (‹65 *vs* ≥65 years), gender, race, diabetes, GFR (‹10.5 *vs* ≥10.5 mL/min/1.73m2), dialysis access (temporary *vs* definitive), haemoglobin (Hb) level (‹11 *vs* ≥11 g/dL), serum albumin (‹35 *vs* ≥35 g/L), referral pattern (ER *vs* LR) and dialysis units using the Kaplan-Meier method. Comparisons between the survival curves for each variable were made using the log-rank method. Multivariate Cox regression analysis was performed to evaluate the relationship of each independent variable to the risk of death. No evidence suggested that the proportional hazards assumption in the multivariate model had been violated. Patients were censored when they received a renal transplant. Statistical significance was considered whenever p‹0.05.

RESULTS

In 2001, 101 CKD patients (mean age 61.57±17.36 years, range 21-94 years, 69 men, 95 Caucasian) started chronic dialysis at our hospital. Table I summarizes clinical and laboratory data at the start of dialysis.

Sixty-one patients were ER. Fifty-seven patients were followed-up for more than 1 year and 4 patients less than 1 year but more than 4 months. Forty patients were LR.

Dialysis initiation and modality

Thirty-eight percent of ER patients (n=23) and 37.5% of LR patients (n=15) started dialysis with a GFR higher than 10.5 mL/min/1.73m^2 (p=ns).

Haemodialysis was initiated in 97% of patients whereas peritoneal dialysis was initiated only in 3 patients. All patients who started peritoneal dialysis were ER. Interestingly, 4 patients who previously chose peritoneal dialysis started haemodialysis for acute reasons and changed later to peritoneal dialysis. Among patients who started haemodialysis, 91 were referred to 14 dialysis units associated with HSM and 7 continued their treatment as outpatients in HSM.

Vascular Access

Only 40.6% of patients (n=41) had a permanent dialysis access ready for use at the initiation of dialysis, either an arteriovenous fistula (AVF) in 30 patients, a vascular graft in 8 patients and a peritoneal dialysis catheter in 3 patients. Fifty-nine percent of patients (n=60) started dialysis with a catheter, a tunnelled long-term, 7 patients and a temporary catheter, 53 patients.

Type of dialysis access differed according to timing of referral to a nephrologist. Fifty-nine percent of ER patients (n=36) had an AVF, a graft or a peritoneal dialysis catheter at the beginning of dialysis, which is in contrast to 12.5% of LR patients (n=5) (p<0.0001).

Anaemia management

Seventy-three percent of ER patients (n=45) and 77.5% of LR patients (n=31) had an Hb level lower than 11 g/dL (p=ns). Only 14.8% of ER patients (n=9) and 5% of LR patients (n=2) had an Hb level between 11 and 12 g/dL (p=ns), as recommended in the K-DOQI guidelines[4].

Only 28.7% of patients (n=29) started erythropoietin treatment before dialysis, most of them (89.6%) ER patients. Among those patients, 62% (n=18) still had an Hb level lower than 11 g/dL.

At the beginning of dialysis, 36% of ER patients (n=22) and 60% of LR patients (n=24) had an adequate iron status (p=0.031).

Nutritional Status

Forty-eight percent of ER patients (n=29) and 35% of LR patients (n=14) had a serum albumin higher than 35 g/L (p=ns).

Outcomes

Nine patients (mean age 74.22±12.7 years, range 56-90 years, 7 men, 9 Caucasian, 4 ER) were lost to follow-up. Thirty-eight patients (mean age 68.63±13.1 years, range 28-93 years, 24 men, 38 Caucasian, 20 ER) died and 5 received a renal transplant.

Median follow-up after the initiation of dialysis was 716.59±439.49 days. Cumulative survival of ER patients was 82% at 1 year, 71% at 2 years and 69% at 3 years compared to 50%, 40% and 40% for LR patients (p<0.0029) (Figure 1). Outcome of patients with a long-term dialysis access ready for use at the initiation of dialysis, either AVF, graft or a peritoneal dialysis catheter, was greater than those who started dialysis with a temporary or tunnelled long-term catheter; survival of patients with a long-term dialysis access was 91% at 1 year and 85% at 2 and 3 years compared to 58% at 1 year, 43% at 2 years and 41% at 3 years for patients starting dialysis with a catheter (p<0.0001) (Figure 2). Statistically significant differences in 3-year patient survival were found when comparing patients according to age (p<0.005) or to diabetes (p<0.05) but no differences were achieved when comparing patients according to gender, race, GFR, Hb level, serum albumin and dialysis units. Multivariate Cox regression analysis showed that age, dialysis access and the pattern of referral

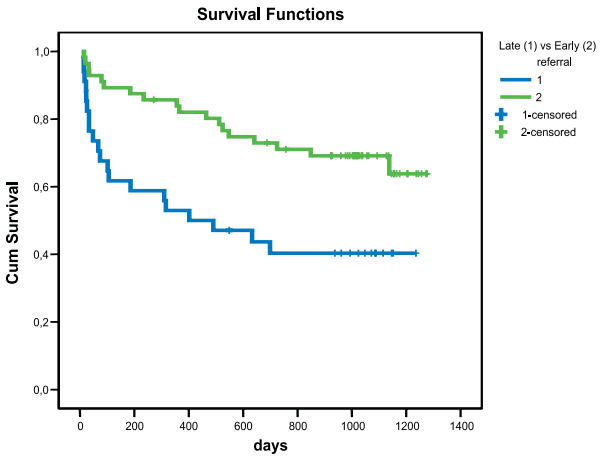

Figure 1

Kaplan-Meier survival analysis of late referral (1) and early referral (2) patients (p<0.0029, log-rank)

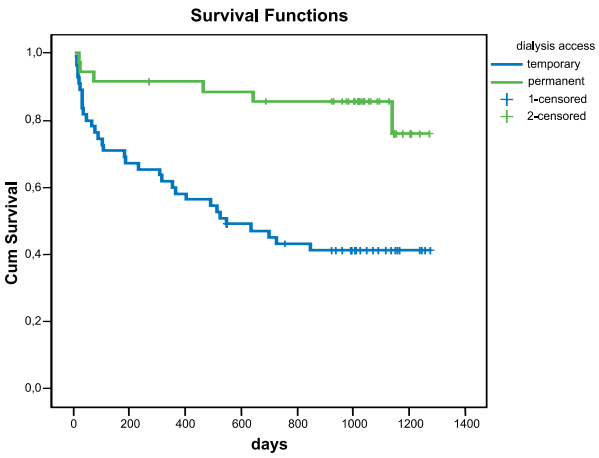

Figure 2

Kaplan-Meier survival analysis of patients with a temporary (long-term or temporary catheter) (1) or a permanent (arteriovenous fistula, graft or peritoneal dialysis catheter) (2) dialysis access at the beginning of dialysis (p<0.0001, log-rank)

to a nephrologist were independent predictors of mortality (p=0.025). Patients younger than 65 years [relative risk (RR), 0.44; 95% confidence interval (CI) 0.23 to 0.82], patients starting dialysis with a permanent dialysis access (RR, 0.55; 95% CI 0.28 to 0.98) had a significantly lower risk of death while LR patients (RR, 2.02; 95% CI 1.08 to 4.19) were at significantly increased risk of death.

Table I

Clinical characteristics

Variable	ER (n=61)	LR (n=40)	p
Age (years)	59.91±17.71	64.1±16.71	ns
Gender (male/female)	40/21	29/11	ns
Race (Caucasian/non-Caucasian)	57/4	38/2	ns
Aetiology of CKD (DN/non-DN)	21/40	11/29	ns
GFR[a] (<10.5/≥10.5mL/min/1.73m²)	38/23	25/15	ns
Access (temporary[b]/definitive[c])	25/36	35/5	0.0001
Haemoglobin (<11/≥11g/dL)	45/16	31/9	ns
Adequate iron status[d] (yes/no)	22/39	24/16	0.031
Functional iron deficiency[e] (yes/no)	23/38	6/34	0.025
Absolute iron deficiency[f] (yes/no)	16/45	10/30	ns
Erythropoietin therapy (yes/no)	26/35	3/37	0.0001
Albumin (<35/≥35g/L)	32/29	26/14	ns

ER – early referral patients; **LR** – late referral patients; **DN** – diabetic nephropathy; **non-DN** – without diabetic nephropathy. Diabetic nephropathy was considered whenever a past history of diabetes, proteinuria and slowly progressive renal dysfunction was present with no other obvious cause for CKD. [a]estimated according to Cockroft--Gault formula; [b]temporary or tunnelled long-term catheter; [c]arteriovenous fistula, vascular graft or peritoneal dialysis catheter. [d]adequate iron status was defined as a serum ferritin ≥100µg/L and a transferrin saturation (TSAT) ≥20%, [e]functional iron deficiency as a serum ferritin ≥100µg/L and a TSAT <20% and [f]absolute iron deficiency as a serum ferritin <100µg/L

DISCUSSION

This study shows that early referral to a nephrologist and a permanent dialysis access at the start of dialysis are associated with a better long-term survival of CKD patients.

Similarly to that reported in other recent studies[1,10], early referral to a nephrologist increased the likelihood of having a permanent access at the start of dialysis. As recommended by the K-DOQI guidelines[4], AVF was the most common initial permanent vascular access. This result is in sharp contrast with other studies[1,10] where vascular graft continues to be the most common permanent vascular access at the initiation of dialysis. The better outcome among patients beginning dialysis with a permanent dialysis access, as reported in the current study, might reflect the high porportion of patients starting dialysis with an AVF, which is associated with a lower mortality[18].

Despite several studies[1,9] suggesting that early referral to a nephrologist is associated with a lower prevalence of anaemia in pre-dialysis patients, no significant difference in Hb levels between ER and LR patients was found. An inadequate iron status among ER patients, jeopardizing the beneficial effects of erythropoietin therapy, could explain the similar high prevalence of anaemia between ER and LR patients.

In the current study, serum albumin has been employed as a surrogate marker of nutritional status. Contrary to that reported in other recent studies[1], we did not find a higher prevalence of malnourished patients among LR patients as compared to ER patients. The inexistence of other clinical and laboratory markers that allow a more adequate evaluation of the nutritional status could explain this result.

Timely referral to a nephrologist seems to be associated with a better pre-dialysis management and lower initial morbidity and mortality. However, the real impact of early referral to a nephrologist on long-term outcome of CKD patients remains unclear.

This study shows that timely referral to a nephrologist is associated with a significantly greater benefit to the long-term outcome of CKD patients starting dialysis, which is somehow in disagreement with other reports that failed to show an improved long-term survival among ER patients. Roubicek *et al* [12] showed that the referral pattern to a nephrologist did not influence the 1-year and 5-year survival of CKD patients on chronic dialysis. Gallego *et al* [13] reported that delayed nephrology referral was associated with a greater initial morbidity but not with a lower 3-year patient survival. Jungers *et al* [19] showed that 5-year patient survival was significantly lower among patients followed by a nephrologist for less than 6 months (59%) compared to those followed for 36 to 71 months (77.1%) and more than 71 months (73.3%), but similar to the patients followed by a nephrologist for 6 to 35 months (65.3%). Kessler *et al* [14] showed that early referral to a nephrologist was associated with a greater 3-month survival, but referral pattern had little influence on mortality among 90-day survivors. Contrary to the above cited studies, Stack *et al* [1] showed that early referral to a nephrologist was associated with a lower death risk at 1 and 2 years. ER patient survival was 89.1% at 1 year and 74.6% at 2 years which is similar to the reported in our cohort. However, we also demonstrate that improved ER patient survival persists beyond the second year of follow-up. We highlight that the current study has one of the longest patients' follow-up and evaluates incident patients starting dialysis, during a short period of observation, which reduces the variation in practice policies.

Finally, it should be stressed that despite suboptimal pre-dialysis nephrological care, timely referral to a nephrologist improved the long-term survival of dialysis patients. We hypothesized that improving nephrological care through better anaemia management, malnutrition correction and timely construction of AVF could even improve patient outcome.

In summary, this study shows that early referral to a nephrologist and a permanent dialysis access at the start of dialysis are associated with a better long-term outcome of CKD patients on chronic dialysis.

Conflict of interest statement. None declared.

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