ORIGINAL ARTICLE

Late nephrologist referral and mortality assotiation in dialytic patients

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ABSTRACT

Introduction: Chronic kidney disease is defined by the progressive loss of renal function. Interventions in early stages significantly improve the prognosis of patients with chronic kidney disease, reducing the mortality, and many studies show that early nephrologist referral reduces the mortality rate. **Objective:** To analyze the characteristics of the patients in dialysis and the time between the first consultation in the dialysis clinic and the beginning of the dialytic program. **Methods:** It was made a cohort retrospective study with two analysis axis: the social and epidemiological characteristics of the patients in hemodialysis and the time between the first consultation in the clinic and the beginning of the dialytic program. Analytical and descriptive methods where used to compare these data with the early referral and the mortality 12 months after the dialysis onset. **Results:** One hundred and one patients were analized. The mortality rate of the early and lately referred patients was 47.8% and 20.5%, respectively (HR = 2.38; IC = 1.06-5.36; p = 0.035). Concerning the patients which initiated the dialysis with catheter and arteriovenous fistula, the mortality was respectively 51.4% and 10.3% (HR = 4.61; IC = 1,54-13,75; p = 0.006). **Conclusion:** The referral timing was predominantly late. The late referral was associated with a greater mortality. Other variables associated with a greater mortality were age of 70 or more, presence of diabetes and the use of catheter by the dialysis onset.

Keywords: dialysis; renal insufficiency, chronic; survival analysis.

INTRODUCTION

Chronic kidney disease (CKD) is a complex disease with significant impact on quality of life, longevity, use of medical resources, and public health spending.[1] In the United States population, the prevalence of patients with CKD is 16.8%.[2] In Brazil, it has been estimated that 5.09% of the individuals over 60 have CKD.[3] The prevalence of end-stage renal disease in the United States is 0.4%,[2] while in Brazil it is estimated that 97,586 patients on dialysis have CKD.[4]

The National Kidney Foundation (NKF)[5] advises every patient with a glomerular filtration rate lower than 60 ml/min/1.73 m^2 (CKD stage 3) or proteinuria to seek care from a nephrologist when proper assessment or the recommended therapy cannot be delivered by a general practitioner.[6] The Royal College of Physicians[7] and the Brazilian Ministry of Health[8] recommend that patients with CKD stages 4 and 5 (< 30 ml/min/1.73 m^2) be referred to a nephrologist.

Despite the protocols for referral to a nephrologist and the existing therapies, patient mortality rates remain high.[9] Recent studies have shown that late referral (LR) to a nephrologist (referral occurring < 90

days prior to the initiation of dialysis)[10-14] is associated with death. These studies have shown that early intervention significantly improves the prognosis of patients with CKD, reduces their short and long-term death rates and length of hospitalization, and positively impacts patient quality of life.[1,5,6,10-14]

Given the lack of information on this topic in Brazil and the association between timely referral and death rates, this study looked into the time between the first consultation in the dialysis center and the start of dialysis, the sociodemographic and clinical characteristics of the included patients, and the impact these factors had on mortality 12 months after the initiation of dialysis.

Method

Two perspectives were considered in the analysis carried out in this retrospective cohort study: (1) the socio-epidemiological and clinical profile of dialysis patients, and (2) the time between the first consultation in the dialysis unit and the start of dialysis.

The study included patients with chronic kidney disease who started dialysis in 2008 to 2011. Patients who started dialysis before 2008, individuals who had undergone dialysis in other centers, subjects who had been undergone kidney transplantation, individuals on dialysis prior to 2008 who came back for treatment in 2008 to 2011, and individuals with missing information in their records were excluded.

The following data were collected to describe the socio-epidemiological profile of the enrolled patients: birthdate, date of first visit to the clinic, start date of dialysis in the clinic, date of first catheter implantation, date of first arteriovenous fistula (AVF) implantation, gender (male or female), type of reimbursement (public or private insurance), city of origin (Itajaí or other cities), associated diseases (*diabetes mellitus* [DM], hypertension, or other specified diseases), and death within a year of the start of

dialysis (date of death). The difference between the start date of dialysis and the date of the first consultation with a nephrologist in the clinic was calculated in days. Patients referred to a nephrologist less than 90 days to the start of dialysis were typified as LR, whereas subjects referred to a nephrologist 90 or more days prior to the start of dialysis were categorized as early referrals (ER). Lack of standardization in the medical records prevented workup data from being included in the study.

The study design was approved by the Research Ethics Committee of the Vale do Itajaí University (UNIVALI) and granted permit CAAE: 07541412.5.0000.0120 on October 5, 2012. Data collection took place at the Itajaí River Valley dialysis reference clinic from November of 2012 to February of 2013. Data sets were extracted through software program NephroSys 2.376® and treated on Microsoft Excel 2007®; software program Epi Info 3.5.4® was used for statistical analysis and calculation of the relative risks (RR) between each variable and ER, the Kaplan-Meier curves and Cox regression for the hazard ratio (HR) multivariate analysis of the deaths occurred within a year of the start of dialysis in relation to the number of survivors. Statistical significance was attributed to results with a $p < 0.05$.

Results

Description

Three hundred and one patients started dialysis at the reference clinic between January 1, 2008 and December 31, 2011. One hundred and ninety were excluded, 134 (44.5%) for prior treatment in other clinics and 56 (18.6%) due to missing medical record data. The remaining 111 (36.9%) were enrolled in the study.

Table 1 shows patient demographic data. Enrolled patients had a mean age of 61 years, and 25.2% of them were 70 or older. The most prevalent diseases were hypertension (75.7%) and *diabetes mellitus* (48.6%), and 35.1% of

the patients had both *diabetes mellitus* and hypertension.

Early referral to a nephrologist (90 or more days prior to the start of dialysis) occurred in 39.6% of the cases, and late referral (less than 90 days to the start of dialysis) in 60.3%. AVF was the method of choice to start dialysis in 35.1% of the patients. The overall mortality rate one year after the start of dialysis was 36.9%.

THE RELATIONSHIP BETWEEN TIMELINESS OF REFERRAL AND SOCIO-EPIDEMIOLOGICAL AND CLINICAL FACTORS

Table 1 shows the main associations between timeliness of referral and socio-epidemiological and clinical variables. Early referrals were observed in 44.4% of diabetic patients and in 35.1% of non-diabetic patients (RR = 1.27; p = 0.31). In terms of patient age, early referrals were seen in 39.8% of the individuals aged less than 70 years and in 39.3% of the subjects aged 70 or older (RR = 1.01; p = 0.96). Early referrals were also seen in 69.2% of the patients started on dialysis with an AVF and in 23.6% of the subjects started with a catheter (RR = 2.93; p ≤ 0.0001).

TIMELINESS OF REFERRAL AND DEATH

Death was the outcome for 47.8% of late referral patients and 20.5% of early referral patients (HR = 2.38, CI = 1.06-5.36; p = 0.035) (Graph 1).

SOCIO-EPIDEMIOLOGICAL AND CLINICAL PROFILE *VERSUS* DEATH RATES

Table 2 shows the correlations between socio-epidemiological and clinical factors and death. Death was the outcome for 60.7% of the patients aged 70 years or older and 28.9% of the subjects aged less than 70 years (HR = 3.99, CI = 2.01-7.90; p = 0.0001). More than two fifths (44.4%) of the diabetic patients and 29.8% of the non-diabetic subjects died (HR = 2.70, CI = 1.36-5.36; p = 0.004). Death was the outcome for 39.3% of the hypertensive patients and 29.6% of the individuals without hypertension (HR = 0.88; p = 0.77).

TABLE 1	PATIENT DISTRIBUTION ACCORDING TO SOCIO-EPIDEMIOLOGICAL AND CLINICAL FACTORS AND RR OF ER FOR EACH VARIABLE		
Variables	Total population	Percent of ER	RR	p
Gender			1.29	0.27
Female	41 (36.9%)	46.3%		
Male	70 (63.1%)	35.7%		
Age			1.01	0.96
< 70 years	83 (74.8%)	39.8%		
≥ 70 years	28 (25.2%)	39.3%		
Reimbursement			1.42	0.27
Private insurance	13 (11.7%)	53.8%		
Public insurance	98 (88.3%)	37.8%		
City of origin			1.5	0.13
Itajaí	74 (66.7%)	44.6%		
Other cities	37 (33.3%)	29.7%		
Diabetes mellitus			1.27	0.31
Diabetic	54 (48.6%)	44.4%		
Non-diabetic	57 (51.3%)	35.1%		
Hypertension			0.69	0.14
Hypertensive	84 (75.7%)	36.5%		
Non-hypertensive	27 (24.3%)	51.9%		
Vascular access			2.93	< 0.0001
AVF	39 (35.1%)	69.2%		
Catheter	72 (64.8%)	23.6%		
Timeliness of referral			-	-
Early	44 (39.6%)	-		
Late	67 (60.3%)	-		

More than half (51.4%) of the patients started on dialysis with a catheter and 10.3% of the

Graph 1. Survival curves according to timeliness of referral.
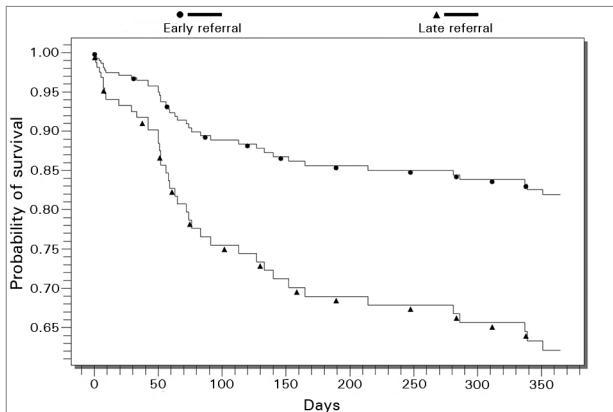
subjects given an AVF died (HR = 4.61; CI = 1.54-13.75; p = 0.006) (Graph 2).

Discussion

Most of the 111 patients included in the study were males, aged less than 70 years, served by public health insurance, and with residence in Itajaí. Hypertension ranked first and DM second in the list of prevalent conditions. Late referrals were observed in most of the cases; catheters were the preferred method to start patients on dialysis; and the overall mortality rate was high.

Gonçalves et al.[13] carried out a study at the Federal University of São Paulo with 101 patients, in which ER was defined as consultation with a nephrologist 90 or more days prior to the start of dialysis. Similarly to our study, late referrals were observed in 58.4% of the cases and catheters were placed in 71.3% of the included patients at the start of dialysis.

Early referrals were more frequent in non-Brazilian studies. The occurrence of late referrals ranged between 27% and 42% in studies with a cutoff point of three or four months to tell early from late referrals.[10,12,14-18]

The overall mortality rate found in this study was 36.9%. Other studies comprising populations with similar mean ages, prevalence of diabetes, and LR ranging between 34% and 42%, described death rates of 6% to 29%,[15,16,18] indicating that LR may have been particularly important in determining the death rate of patients in our study.

The analysis of the factors related to ER and LR in this study showed that the only factor statistically correlated with ER was placement of an AVF at the start of dialysis (RR = 2.93, $p \leq 0.00001$, a positive correlation).

Several studies have correlated AVF with LR or ER. Kim et al.[15] described early referrals in 43.7% and late referrals in 52% of the patients started on dialysis with a catheter (p = 0.009). Lorenzo et al.[18] found that 73% of early referral and 30% of late referral patients had AVFs implanted at the start of dialysis.

A study carried out in Mexico by Kazmi et al.[16] described a correlation between private health care (including private health insurance) and timeliness of referral. Private care was strongly correlated with ER (p < 0.0001).

Winkelmayer et al.[19] described a correlation between older age and LR (65-74 years: odds ratio [OR] = 1.73, p < 0.001; > 85 years, OR = 2.66, p < 0.001). The authors also reported correlations between LR and hypertension, and LR and DM, describing a higher probability of early referrals (OR = 0.47, p < 0.001; and OR = 0.82, p = 0.02, respectively).

The correlations between the included variables and death within 12 months of the start of dialysis were also considered in our study. The variables statistically correlated with higher mortality rates were age of 70 years or more, presence of *diabetes mellitus*, use of a catheter at the start of dialysis, and LR.

Jager et al.[17] described an association between DM and higher one-year mortality rates (HR = 1.9, CI = 1.4-2.6). The same was observed in patients aged 70 years or older (HR = 2.6, CI = 2.0-3.5). Kim et al.[15] looked into two-year mortality rates and also found a greater number of deaths among diabetic patients (HR = 4.74, CI = 1.73-13.00, p = 0.002).

Almost every paper included in our review showed a significant correlation between LR and higher mortality rates. As previously mentioned, the authors of these papers had different cutoff points for early and late referrals. In the studies that used cutoff points of three or four months, the

TABLE 2   CORRELATION BETWEEN ANALYZED VARIABLES AND DEATH RATE

Variables	One-year death rate	HR	CI	p
Gender		1.12	0.57-2.14	0.74
Female	36.6%			
Male	37.1%			
Age		3.99	2.01-7.90	0.0001
≥ 70 years	60.7%			
< 70 years	28.9%			
Reimbursement		3.44	0.95-12.47	0.06
Public insurance	38.8%			
Private insurance	23.1%			
City of origin		1.21	0.60-2.42	0.60
Itajaí	36.5%			
Other cities	37.8%			
Diabetes mellitus		2.70	1.36-5.36	0.004
Diabetic	44.4%			
Non-diabetic	29.8%			
Hypertension		0.88	0.38-2.01	0.77
Hypertensive	39.3%			
Non-hypertensive	29.6%			
Venous access		4.61	1.54-13.75	0.006
Catheter	51.4%			
AVF	10.3%			
Referral		2.38	1.06-5.36	0.035
Late referral	47.8%			
Early referral	20.5%			

HR: Hazard ratio; CI: Confidence interval; AVF: Arteriovenous fistula; LR: Late referral; ER: Early referral.

hazard ratio (HR) ranged between 1.44 and 10.77 after 12 months of follow-up.[10,13,16,17] The HR was kept within the same range in the studies with a two-year follow-up.[15,20]

In a meta-analysis published in 2007, Chan et al.[21] evaluated the correlations between 20 studies involving over 12,000 patients, and found that 13% ± 4% of early referral and 29% ± 5% of late referral patients died within 12 months of the start of dialysis (RR 2.08; 95% CI 1.31-3.31; p = 0.028).

The systematic review by Smart & Titus[1] included 27 studies with a total of 17,646 patients. Early referral patients had lower mortality rates at three months (OR = 0.51, CI = 0.44-0.59) and five years after the start of dialysis (OR = 0.45, CI = 0.38-0.53), both with a $p < 0.00001$.

CONCLUSIONS

Late referrals were predominantly described for the patients enrolled in our study. As also indicated in the literature, our study showed an association between ER and lower mortality rates 12 months after the start of dialysis. Age equal to or greater than 70 years, presence of *diabetes mellitus*, and use of a catheter at the start of dialysis were associated with higher death rates. The only variable statistically correlated with ER was placement of an AVF at the start of dialysis. The correlations between these indicators and other factors, such as workup and comorbidities, may, in a future study, shed light on other relevant observations.

Our findings showed that the condition in which the studied patients were referred to dialysis was far from ideal, and that modifiable factors such as LR and AVF may significantly improve their outcomes.

Graph 2. Survival curves according to type of vascular access. AFV: arteriovenous fistula.
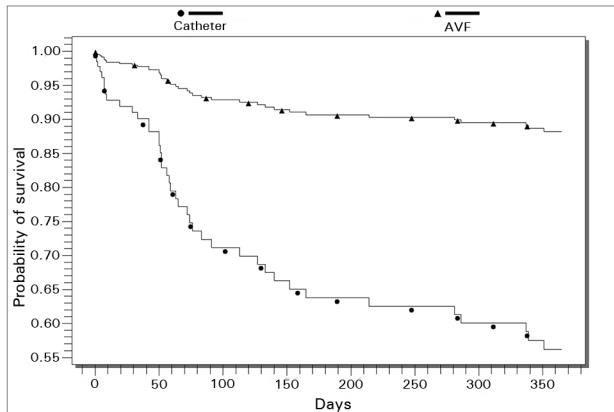
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