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Does Timing of Nephrology Referral Influence Outcome among Patients on Maintenance Hemodialysis in Cameroon?

Influence du délai de transfert chez le néphrologue sur le devenir des patients hémodialysés au Cameroun

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ABSTRACT

Objective. To assess the influence of the timing of nephrology referral on adverse outcomes in patients undergoing chronic haemodialysis (HD) and to identified associated factors to mortality in a referral hospital of Cameroon. **Methods.** A retrospective study including patients with ESKD who started HD in Douala general hospital from January 2008 to December 2011. Socio demographic and relevant clinical data including date of first nephrologists' consultation, stage of CKD at presentation, presumed aetiology of CKD and starting date of HD were reviewed. Early referral (ER) was defined as first nephrologists' consultation at least four months before initiation of HD, and LR as less than four months prior to dialysis. Study outcomes were morbidities, type of vascular access, withdrawal and mortality at one, three, six and twelve months on dialysis. **Results.** We recruited 188 participants. 66.5% of them were males, and the mean age was 46.8±14.7 years. ERs accounted for 29.8% of the population. Emergency dialysis on a temporary catheter was more frequent for LRs (p=0.000). During the period of dialysis, hospitalization and withdrawal rates were similar between both group (p= 0.76 and p=0.25). From zero to six months, the cumulative survival of ER patients was better (p=0.02) but at one year the difference was no longer significant (p=0.62). Factors associated to high mortality were male sex (p=0.007), diabetes mellitus (p= 0,006) hospitalization (p=0,002) and pulmonary oedema at initiation (p=0,004). **Conclusion.** One year outcome of HD patients is little modified by the timing of referral; it is more affected by co morbidity and initial morbidity.

RÉSUMÉ

Objectif. Décrire l'influence du moment du transfert en néphrologie sur le devenir des patients hémodialysés et identifier les facteurs associés à la mortalité de ces patients. **Méthodologie.** Il s'agit d'une étude rétrospective transversale analytique incluant les dossiers médicaux des patients ayant commencé l'hémodialyse chronique à l'Hôpital Général de Douala de Janvier 2008 à Décembre 2011. Les données sociodémographiques et cliniques (date de première consultation néphrologique, stade IRC au transfert, néphropathie de base, date initiation de dialyse). Le transfert était précoce (TP) si la première consultation néphrologique était supérieure à 4 mois avant l'initiation de la dialyse et tardif (TT) si inferieur à 4 mois. Le devenir était évalué à un, trois, six et douze mois. Le seuil de significativité était fixé à $p < 0.05$. **Résultats.** 188 patients ont été inclus dont 66.5% d'hommes. L'âge moyen était de 46,8±14,7 ans. Le TP concernait 29.8% des patients. Le taux d'abandon et d'hospitalisation était similaire dans les deux groups (p= 0.76 and p=0.25). Entre zéro et six mois, la survie cumulée était meilleure dans le groupe des TP par rapport au TT (p=0.02) ; mais à 12 mois, il n'y avait plus de différence significative entre les deux groupes (p=0.62). Les facteurs associés à la mortalité étaient le sexe masculin (p=0.007), le diabète sucré (p= 0,006), l'hospitalisation (p=0,002) et l'œdème pulmonaire à l'initiation de la dialyse (p=0,004). **Conclusion.** Le devenir à un an des patients hémodialysés chroniques est plus influencé par les comorbidités et la morbidité à l'initiation de la dialyse que par le moment du transfert du malade en néphrologie.

INTRODUCTION

Chronic kidney disease (CKD) is associated with a heavy human, clinical, and financial burden [1]. Despite advances in technology and treatment strategies, morbidity and mortality of patients with end stage kidney disease (ESKD) remains higher compared to the general population [2]. Factors present before and occurring after initiation of renal replacement therapy (RRT) could have an impact on patient outcomes. Amongst these factors timing of referral and pre dialysis care by nephrologists play a role [1]. There is no consensus on the definition of early and late referral. Generally late referral (LR) is defined as occurring when pre-ESKD management by a nephrologist could have been improved with earlier interactions[3]. Specifically authors defined LR when the first nephrology visit occurs within 1 to 6 months prior to dialysis initiation [4].

Many studies on the influence of the timing of nephrology referral in the pre-dialytic stage of CKD exist and the results are conflicting and still debating. For the majority the potential benefits of timely nephrology referral include identification of reversible causes of CKD, provision of treatments that may slow the progression of CKD, management of the complications of advanced CKD, allow adequate physical, social and psychological preparation to RRT and reduces the morbidity and mortality of patients [1,5–7].

Therefore LR in the contrary is costly, harmful for patients with increases morbidity and mortality in the 3 months and the first year on dialysis [4,8–12]. In the contrary in other studies timing of referral did not influence the outcome of patients on dialysis [13–15]. The difference across studies can be explain by many factors such as the different ways of operationalizing late referral, the variety in dialysis technical conditions , the difference in medical characteristics of patients and medical management among countries.

The picture in developing countries is less known. Given the limited access to healthcare, the lack of the systematic practice of referrals and level of awareness on CKD, the low number of nephrologists and the lack of health insurance in most countries, LR is a major concern and the rate is extremely high [15–17] . In Brazil 60.3% of patients were referred late and with one year mortality rate of 47.8% versus 20.5% of ER patients (p= 0.035) [16]. In Cameroon, a single centre study revealed that 82.8% of patients with CKD were referred late to the nephrologists with a consequent high rate of hospitalizations and emergency dialysis on first nephrology visit [17]. However the impact of this LR on dialysis outcomes is not known in our setting where dialysis is partially self-funded. We hypothesized that late referral increased morbidity and mortality of patients in our setting. We therefore assessed the influence of the timing of nephrology referral on adverse outcome in the first year on HD and identified other factors associated to mortality of these patients in Cameroon.

METHODS

Study setting

The study was carried out in the dialysis unit of the Douala General hospital, a tertiary referral hospital with 360 beds which offers care to a population of 13 million inhabitants of the littoral region of Cameroon. At the time of the study, the centre was equipped with 17 haemodialysis Generators Fresenius 4008S, polysulfone dialyzers and bicarbonate dialysate used. The centre does not practice dialyzer reuse. The patients undergo two weekly sessions of 4 hours. Dialysis is partially state-funded such that patients contribute 5000 XAF per dialysis session. However routine tests and medications such as erythropoietin, transportation are self-funded by patients. The personnel of centre at the time of the study was composed of one nephrologist, two general practitioners and twelve nurses.

Participants

The study included patients with ESKD who started HD between 1st January 2008 and 31st December 2011. Patients transferred to other dialysis centres, lost to follow up or with missing data on first nephrology visit were excluded from the study. Patients' clinical and HD charts were retrospectively reviewed for sociodemographic data (gender, age) and relevant clinical data including date of first visit to the nephrologist, stage of CKD on first nephrology visit, aetiology of CKD, number of nephrologist visits and interval between first nephrology visit and initiation of dialysis. Laboratory parameters at the initiation of HD were noted. The type of vascular access, and morbidities were noted at initiation, one, three, six and twelve months of dialysis, while mortality was noted at 1, 3, 6 and 12 months. The Charlton's co morbidity score was used to quantify the co morbidity burden in the patients [18]. ER was defined as first nephrologist consultation at least 4 months before the initiation of HD, and LR as less than 4 months prior to dialysis. Initial emergent dialysis was defined as the need for dialysis within 24 hours of admission. Outcome measures were morbidities, type of vascular access, withdrawal and mortality at 1, 3, 6 and 12 months on dialysis.

Ethical approval was obtained from the ethical review board of the Douala University.

Statistical analysis

Analyses were done using the statistical package software SPSS 17.0.0, 2008. The Fisher exact test was used to compare categorical variables, and Student t-test and Mann-Whitney U test for quantitative variables. Quantitative variable are expressed as mean, median and percentage. Logistic regression analysis was used to look for associated factors to mortality within the first year after the dialysis onset. A p value < 0.05 was considered as statistically significant.

RESULTS

211 patients initiated dialysis during the period under study of which 23 were excluded for missing relevant data. We therefore reviewed medical records of 188 participants including 66.5% males; their mean age was 46.8±14.7 years. Fifty-six (29.8%) were ER while 132 (70.2%) were LR. The mean duration between the time of referral and dialysis initiation was 302.2± 11.9 days in the ER group and 50.17 ± 4.6 days in the LR (p=0.000).The main presumed aetiologies of ESKD were hypertension (32.4%), diabetes mellitus (25.5%) and chronic glomerulonephritis (16.5%) with no difference between both groups. The aetiology was unknown in 18.09% and 81.3% of patients had low to moderate co morbidity index (Table 1).

Table 1: Baseline characteristics of the study population

Variables	**Total. N=188**	**ER. N=56**	**LR. N=132**	***P***
Sociodemographic characteristics				
Age	46.8 ± 1.08	49.8 ± 1.80	45.5 ± 1.32	0.06
Men	125 (66.49%)	37 (66.07%)	88 (66.67%)	0.94
Female	63 (33.51%)	19 (33.93%)	44 (33.33%)	0.94
Mean duration from referral to initiation of HD	205.2 ± 14.97	302.2± 11.9	50.17 ± 4.6	<0.001
Mean eGFR at initiation	4.77±1.88 (n=167)	5.96±0.29 (n=55)	4.69± 1.31(n=112)	0.88
Mean Hemoglobin at initiation	7.80±1.90 (n=135)	8.07±1.82 (n= 52)	7.62±1.94 (n= 83)	0.19
Pulmonary edema at initiation	111 (59.68%)	27 (49.10%)	84 (64.12%)	0.17
Etiologies of CKD				
Hypertension	61 (32.45%)	17 (30.36%)	44 (33.33%)	0.69
Diabetes	48 (25.53%)	19(33.93%)	29(21.97%)	0.09
Unknown	34 (18.09%)	6 (10.71%)	28 (21.21%)	0.09
Chronic glomerulonephritis	31 (16.49%)	07 (12.50%)	24(18.18%)	0.34
Chronic interstitial nephritis	15 (07.98%)	08 (14.29%)	07(05.30%)	0.037
HIV	11 (5.85%)	03 (5.36%)	08 (6.06%)	0.85
Polykystosis	04 (2.13%)	01 (1.79%)	03 (2.27%)	0.83
Charlson Comorbidity score at initiation of dialysis (188)				
Low Comorbidity	106 (56.38%)	28 (50.00%)	78 (59.09%)	0.25
Moderate Comorbidity	47 (25.00%)	17 (30.36%)	30 (22.73%)	0.27
High Comorbidity	21 (11.17%)	5 (08.93%)	16 (12.12%)	0.53
Very high Comorbidity	14 (7.45%)	6 (10.71%)	8 (6.06%)	0.27
		Serology		
HIV(+)	11 (05.85%	03(05.36%)	08(06.06%)	0.86
Hepatitis B (+)	05(02.66%)	02 (03.57%)	03(02.27%)	0.62
Hepatitis C (+)	16(08.51%)	06 (10.71%)	10 (07.58%)	0.48
Modality of dialysis initiation				
Emergency Dialysis	162 (86.17%)	35 (62.50%)	127 (96.21%)	0.001
Temporary catheter	159 (84.57%)	31 (55.36%)	128 (96.97%)	0.001
Arteriovenous fistula	29 (15.43%)	25 (44.64%)	04 (03.03%)	0.001
Hospitalization	16 (08.94%)	02 (03.77%)	14 (11.11%)	0.18

At initiation of dialysis both groups were similar in comorbidity index, mean eGFR (ER= 5.96±0.29, LR = 4.69± 1.31, p=0.88), mean hemoglobin (ER= 8.07±1.82, LR=7.62±1.94 p=0.19) and prevalence of pulmonary oedema (49.1% vs 64.2%, p=0.17).Only 4 (3.03%) of the LR patients had a functional fistula at initiation of dialysis versus 25 (44.64%) of the ER patients (*p*= 0.000). Emergent dialysis was needed in many ER patients, but this was significantly higher in LR (62.50% vs 96.21%; p<0.001). Use of a temporary central venous catheter for the first dialysis was significantly more frequent in LR patients (96.9%) compared to ER (55.36%), p< 0.001 (Table 1)

Sixteen patients were lost of follow up at 12 months (table 2). While on dialysis, there was no difference in the two groups for hospitalization and withdrawal rate (p= 0.76 and p=0.25), but dialysis on a temporary catheter was significantly higher in the LR group at one month (p=0.049) but no difference was present after that period.

Table 2: Follow up or Outcome

Variables	Total. N=176	ER. N=53	LR. N=123	*P*
Withdrawal from dialysis				
1st Month	3 (1.60 %)	2 (3.57 %)	1 (0.76 %)	0.21
3rd Month	4 (2.13 %)	2 (3.57 %)	2 (1.52 %)	0.58
6th Month	6 (3.19 %)	2 (3.57 %)	4 (3.03 %)	1.00
12th Month	3 (1.60 %)	1 (1.79 %)	2 (1.52 %)	1.00
Hospitalization				
1st Month	15 (08.88%)	02 (03.92%)	13(11.02%)	0.14
3rd Month	08(05.16%)	01 (02.08%)	07 (06.54%)	0.44
6th Month	12(09.02%)	03 (06.98%)	09(19.00%)	0.57
12th Month	04 (03.28%)	01 (02.56%)	03 (03.61%)	0.76
Infections of dialysis catheter				
1st Month	47 (27.49%)	9 (17.31%)	38 (31.93%)	0.049
3rd Month	19(12.03%)	05(10.20%)	14(12.84%)	0.43
I 6th Month	11(08.15%)	04 (09.09%)	07 (07.69%)	0.78
12th Month	05(04.03%)	01(02.50%)	04(04.76%)	0.55
Pulmonary edema 1st Month	04 (01.74%)	00 (00.00%)	04 (02.50%)	0.25
Dialysis on temporary catheter				
1st Month	147 (83.52%)	30 (56.60%)	117 (95.12%)	0.0001
3rd Month	63(39.62%)	14(28.57%)	49(44.55%)	0.041
6th Month	31 (22.79%)	09 (20.45%)	22 (23.91%)	0.65
12th Month	21 (16.67%)	05 (12.50%)	16 (18.60%)	0.40

LR was not associated with increased hospitalization or withdrawal during the first year on dialysis. There was a trend towards more deaths in LR compared to ER patients between 0- 6 months (table 3) of dialysis but no difference was found at one year (p= 0.10) (Figure 1).

Table 3: Comparison of survival between ER and LR

Month on dialysis	Total.	ER.	LR.	*P*
	Cumulative survival probability			
0-1 Month	176 (0.951 ± 0.029)	53 (0.982 ± 0.029)	123 (0.939 ± 0.029)	0.19
0-3 Month	169(0.933 ± 0.019)	51(0.981 ± 0.020)	118(0.915 ± 0.025)	0.08
0-6th Month	142(0.811 ± 0.030)	46(0.920 ± 0.038)	96(0.768 ± 0.038)	0.02
0-12th Month	126(0.733 ± 0.034)	40 (0.816 ± 0.055)	86(0.699 ± 0.041)	0.10

In multivariate analysis factors associated to mortality were male sex (p=0.007), presence of diabetes (p=0.006) hospitalization (p=0,002) and pulmonary oedema at initiation (p=0.004) (Table 4)

Table 4: Associated factors to mortality in Univariate and multivariate analysis

Variables	Univariate Hasard ratio	IC (95%)	*P*	Multivariate Hasard ratio	OR (95% CI)	*p*
Timing of referral						
ER	Réf					
LR	1.791	[0.90-3.55]	0.09	1.22	[0.56-2.60]	0.62
Predialysis follow up	0.49	[0.25-0.96]	0.039	0.85	[0.31-2.39]	0.13
Dialysis initiation						
Planned	Réf					
Emegency	3.754	[0.95-14.84]	0.06	1.55	[0.56-4.30]	0.39
Pulmonary oedema at initiation	3.58	[1.72-7.43]	0.001	2.92	[1.40-6.09]	0.004
Hospitalization at initiation	0.349	[0.19-0.61]	0.000	0.34	[0.17-0.67]	0.002
Gender						
Female	Réf					
Male	1.64	[0.90-2.94]	0.10			
Comorbidity score						
Low	Réf					
Moderate	1.12	[0.55-2.27]	0.74			
High	1.63	[0.69-3.82]	0.26			
Very high	1.61	[0.61-4.26]	0.34			
Age category in years						
< 30	Réf					
30 - 40	0.54	[0.19-1.55]	0.25	0.62	[0.20;1.88]	0.40
40 - 50	0.75	[0.29-1.89]	0.54	1.16	[0.39;3.48]	0.79
50 - 60	0.53	[0.20-1.37]	0.19	0.49	[0.16;1.48]	0.21
60 - 70	0.94	[0.37-2.38]	0.90	1.00	[0.33;3.03]	0.99
70 years and +	0.86	[0.23-3.23]	0.82	0.73	[0.15;3.51]	0.69
Hypertension	1.0207	[0.57-1.83]	0.95			
Diabetes	1.6134	[0.92-2.84]	0.10	3.22	[1.41;7.37]	0.006
HIV	1.089	[0.38-3.13]	0.87			
Temporary catheter	2.88	[0.89-9.27]	0.077	2.67	[0.89-7.98]	0.08

DISCUSSION

Timing of referral and quality of nephrology care prior to dialysis are major determinants of outcome of patients with ESKD. The aim of our study was to assess the influence of the timing of nephrology referral on adverse outcomes and to identify associated factors to mortality in patients undergoing chronic HD in a tertiary hospital in Cameroon. Our results showed that patients starting dialysis were relatively young, with more than 2/3 referred late. There was no difference in major co morbidities and laboratory characteristics (eGFR and hemoglobin) at dialysis initiation between ER and LR. LR patients required more emergent dialysis and temporary central venous catheterization at initiation and during the first months on HD compared to ER. LR was not significantly associated with more hospitalizations and withdrawal during the first year of HD. There was a trend towards more deaths in LR compared to ER patients in between 0- 6 months of dialysis but not at one year. Male sex, presence of diabetes mellitus, initial hospitalization and pulmonary oedema were factors associated with mortality.

Late nephrology referral is a common problem in the world especially in developing countries. The present study confirm than LR remain a serious problem in our setting. The proportion of patients seen for the first time by a nephrologist less than 4 months before the start of RRT was extremely high (70.2%), compared to studies in developed countries [1,3,4] and was in the range of referral pattern in less developed countries[16,17]. This is a major cause of concern as this rate remains high despite efforts of awareness during the last 20 years.

Many studies have suggested that timing and quality of care before initiation of RRT may significantly affect initial morbidity in ESRD patients, especially the need of urgent dialysis on a temporary vascular access through reduced systemic infections [13,19,20]. In the present study, emergent dialysis was significantly high among LR patients compared to ER (96.21% vs 62.50%: p<0.001), and also the use of a temporary central venous catheter for the first dialysis (LR 96.9% vs ER 55.36%; p< 0.001). This tendency is similar with results of previous studies in the literature [9,13,21]. Schmidt et al. showed that the need for emergency HD was significantly high among LR patients compared with ER (22% versus 90%) [13], also Kim et al. in Korea had the same findings [6]. In the present study both groups were similar at the start of dialysis in term of mean eGFR (p= 0.88), mean haemoglobin (p= 0.19), rate of pulmonary

oedema and hospitalizations. Also emergent dialysis on a temporary catheter was high in ER patients. This is contrary to the findings of previous study, that shown that ER patients mostly start dialysis planned with a permanent vascular access An explanation of this results could be that despite the early contact with the nephrologist, the follow up of these patients was not regular in our setting due to many factors such as the timing of early referral (4 months) was a short period to evaluate and educate ESKD patients, especially the lack of found (absence of health insurance for the majority) and the silent course of the disease.

Previous studies on the association of the timing of referral to a nephrologist with mortality have demonstrated conflicting results. The present study found no significant difference in mortality between ER and LR patients after one year on dialysis (p=0.62), but between 0 to 6 months the cumulative survival of ER patients was significantly better than LRs (p=0.02). Our results are different to the general trend in the literature where LR has detrimental consequences on patient's outcome at one year. LR (<4 months) was associated with a 44% risk of death at one year after dialysis initiation in a study on 2195 patients from Kazmi et al. [22]. Similar results were found by Khan et al, Innes et al and Herget et al. [23–25] . The lack of association of LR with mortality in our study can be explain in one hand by the fact that in previous published studies, ER patients had significant higher e GFR at the initiation of HD compared with LR patients and this could explain the better outcome associated with ER [1,3,6,8,26] . In our study, there was no significant difference in the residual renal function at start of HD between the 2 groups; also morbidity was similar except emergent dialysis on catheter which might explain the difference with others studies. In the other hand the rate of patients referred early who started dialysis unplanned was relatively high (62.5% emergency dialysis and 55.36% on a temporary catheter) and also morbidity at the start of dialysis was similar in both group, meaning that dialysis initiation was suboptimal in ER patients. It has been shown that the benefit of ER are lost if dialysis is started suboptimal [14,27]. There is a need in our setting to look for factors that contribute to this suboptimal start of HD. These factors are patient's and physician's related, such as reservations on the part of patients and treating physician or acute deterioration, should be carefully considered [28]. Others studies in the literature have shown that LR had an effect on mortality only in the first months of dialysis and not after as in the present study [9,25,29]

This early survival benefit after initiation of HD can be due to the "depletion susceptibles" [30] . It is a survival bias driving by the fact that patients referred late who are vulnerable to the effect of suboptimal preparation for HD dies more, and with time after depletions of "susceptibles" the survival of the remaining patients is similar to the ER patients. Our finding is also similar with the study of Roubicek et al. that included 270 patients and LR defined as referral less than 4 months prior to dialysis initiation was not associated to death [12]. Schmidt et al. and Ellis et al. had the same conclusion [13,31].

Even if most studies favored ER to nephrologists, some did not find any significant advantage of ER.The difference among studies could be explained by many factors such as the lack of a consensual definition of ER/LR. The definition of the timing of ER is different in each study, most studies were retrospective and single centre and some excluded patients who died during the first 90 days leading to selection and confusion biases. Others influencing factors are the geographic location with difference in general medical management among countries, difference in HD technical conditions, in psychosocial conditions and medical characteristics of ESKD populations that are not equivalent from one country to another.

In this study, the factors statistically associated with higher mortality were male sex, presence of diabetes mellitus, pulmonary oedema and hospitalisation at initiation of HD. Studies have shown that non-elective presentation for RRT, cardiovascular disease and co morbidities were factors independently associated with early mortality [22,26].. Henrique Diegoli in Bresil and Kim et al. in Korea also described an association between Diabetes mellitus and higher one-year mortality rates [6,16]. DM is well known as an independent risk factor for increased mortality in dialysis patients [32–34]. We also found that mortality was high among men at one year. Gender differences have been described in CKD. Men are more affected by CKD and progresses rapidly compare to women, but on dialysis is it known that there is no difference in survival between both gender. [35]. One study in Israel found that ER was associated with better survival in women, but not in men [5]. The reasons for these differences are not clear and further investigations are necessary.

LIMITATIONS

This study has some limitations. The retrospective nature of data collection with potential confounding information, a limitation shared by most studies published on this issue. The follow up period was relatively short (12 months) and could influence the survival in ESKD patients. Despite these limitations and giving the paucity of data on the issue in sub-Saharan Africa, our results are informative and could serve as basis for further research on determinant of referral in our setting.

CONCLUSION

LR to the nephrologist remains a major problem in our setting, it generated greater initial morbidity, but one year outcome of HD patients was not associated with timing of referral. Mortality was more affected by co morbidity and initial morbidity. Further studies are needed to determine whether these results are linked with geographic influence, especially reason for suboptimal start of HD despite ER and determinant of referral in our setting.

DECLARATIONS

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Authors' contributions
MPH: Conception and design of the study, supervision of data collection, interpretation of data and drafting of the manuscript.
LT: Data collection and critical revision of the manuscript.
AFF: Data analysis and interpretation and critical revision of the manuscript.
FFK: Critical revision of the manuscript.
AMS: Critical revision of the manuscript
GA: Conception and design of the study, interpretation of data and critical revision of the manuscript.
All authors read and approved the final manuscript.

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