

Effect of Early Nephrology Referral on the Mortality of Dialysis Patients in Israel

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ABSTRACT: **Background:** Late nephrology referral, before initiation of dialysis treatment, is associated with adverse outcome.

Objectives: To investigate the implications of late nephrology referral on mortality among dialysis patients in Israel.

Methods: We retrospectively analyzed 200 incident dialysis patients. Patients were defined as late referrals if they started dialysis less than 3 months after their first nephrology consultation. Survival rates and risk factors for mortality were analyzed

Results: The early referral (ER) group comprised 118 patients (59%) and the late referral (LR) group 82 patients (41%). The mortality rate was 44.5% (53 patients) in the ER and 68% (n=56) in the LR group. The 4 year survival rate was 41.1% in the ER and 18.7% in the LR group ($P < 0.0001$). The mortality rate increased with late nephrology referral (HR 1.873, 95%CI 1.133–3.094), with age (HR 1.043 for each year, 95%CI 1.018–1.068), with diabetes (HR 2.399, CI 1.369-4.202), and with serum albumin level (HR 0.359 for an increase of each 1 g/dl, 95%CI 0.242–0.533). The median survival time was higher for the ER group in women, in patients younger than 70, and in diabetic patients. A trend for longer survival time was found in non-diabetic patients. Survival time was not increased in early referred patients older than 70 and in male patients.

Conclusions: Late nephrology referral is associated with an overall higher mortality rate in dialysis patients. The survival advantage of early referral may have a different significance in specific subgroups. The timing of nephrology referral should be considered as a modifiable risk factor for mortality in patients with end-stage renal disease.

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The mortality rate of dialysis patients older than 65 is ten times higher as compared to people of the same age without kidney disease. Unadjusted mortality rate in prevalent hemodialysis patients in the United States is 283 per 1000 patient-years [1]. Adjusted survival rates for the first 5 years of dialysis in the USA are 0.74, 0.61, 0.51, 0.42 and 0.35. Unadjusted survival rates in Israel are 0.86, 0.71, 0.6, 0.49 and 0.4 [2]. The term late nephrology referral means that patient management and clinical outcomes could have been improved by earlier contact with specialist care. Patients in whom the interval between the first nephrology consultation and the initiation of RRT is less than 1 to 6 months are considered LR. An increasing number of studies suggest that patients whose referral to a nephrologist for pre-dialysis medical care was late, as compared to those referred early in their disease course, have an enhanced mortality risk once dialysis is initiated. LR has also been associated with choice of RRT modality, type of dialysis access, rate of hospitalizations, quality of life, and utilization of renoprotective medications and biochemical markers related to kidney disease [3-17].

The rate of late referral varies between countries, with rates ranging from 10.5% to 83% [18,19]. Our aim was to investigate the implications of late nephrology referral on the survival of dialysis patients in a large dialysis unit in Israel.

PATIENTS AND METHODS

All consecutive patients who entered the hemodialysis program in our center between 1 January 2006 and 31 December 2009 were studied retrospectively. Patients with acute renal failure or advanced malignancy at presentation were excluded. Patients were classified as early referrals or late referrals depending on whether they began hemodialysis < 3 or > 3 months after their first nephrology clinic consultation.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 18. Normality of the data was tested by the Kolmogorov-Smirnov test. As some of the variables were not normally distributed, the Mann-Whitney U test was used to analyze differences between the two groups.

RRT = renal replacement therapy
LR = late referral

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End-stage renal disease is a complex condition that impacts on patient life expectancy and quality of life. This condition is associated with substantial medical resource utilization and high costs. Despite the introduction of renal replacement therapy more than half a century ago, the mortality rate remains high.

Student's *t*-tests were used for differences between groups. Fisher's exact test was used to determine the relation between categorical variables. Survival time was calculated from the date of the first dialysis until death or 31 December 2011. Kaplan-Meier survival function was performed to compare overall survival rates between the two groups. We used Cox proportional hazards regression to test the presence, strength and independence of the association between timing of referral and mortality. We also analyzed other risk factors for mortality.

RESULTS

The ER group comprised 118 patients (59%) and the LR group 82 (41%). The median follow-up time was 3.1 years. The ER and LR groups were similar in mean age (ER 69.3 years, LR 71.4 years, $P = 0.29$), gender distribution (ER males 60.2%, LR males 50%, $P = 0.19$), prevalence of diabetes (ER 59%, LR 61%, $P = 0.88$), mean hemoglobin level at the start of dialysis (ER 10.7 g/dl, LR 10.2 g/dl, $P = 0.08$) and mean serum albumin at the start of dialysis (ER 3.4 g/dl, LR 3.1 g/dl, $P = 0.088$) [Table 1].

Over one-half ($n=109$, 54.5%) of all patients died during the follow-up period, 53 (44.5%) in the ER group and 56 (68%) in the LR group. The overall 4 year survival was 41.1% in the ER group compared to 18.7% in the LR group ($P < 0.0001$). The median survival time was 3.23 and 1.26 years for the ER and LR groups respectively, $P = 0.001$ [Figure 1].

Univariate analysis showed that the mortality rate increased with the following factors: age (hazard ratio for each year 1.03, 95% confidence interval 1.02–1.05), late referral (HR 1.95, CI 1.33–2.85), diabetes (HR 1.56, CI 1.04–2.34), albumin level (HR for an increase of each 1 g/dl 0.38, CI 0.26–0.55), and hemoglobin level (HR for an increase of each 1 g/dl, 0.87, CI 0.77–0.99). We did not find increased mortality in association with gender.

On multivariate analysis for all the above variables we found that mortality rate increased with late nephrology referral (HR 1.873, CI 1.133–3.094); mortality rate also increased with age (HR 1.043 for each year, CI 1.018–1.068), diabetes (HR 2.399, CI 1.369–4.202), and serum albumin level (HR 0.359 for an increase of each 1 g/dl, CI 0.242–0.533) [Table 2].

ER = early referral
HR = hazard ratio

Table 1. Patient characteristics at start of dialysis

	Early referral (%)	Late referral (%)	<i>P</i> value
No. of patients	118 (59)	82 (41)	
Age (yr)	69.3	71.4	0.29
Gender: male	71 (60.2)	41 (50)	0.19
Diabetes mellitus	69 (59)	50 (61)	0.88
Hemoglobin (g/dl)	10.7	10.3	0.08
Albumin (g/dl)	3.4	3.1	0.088

Survival analysis was also performed for subgroups according to age, gender and the presence of diabetes [Table 3]. The median survival time (in years) for patients younger than 70 years was 4.482 in the ER group and 1.959 in the LR group ($P = 0.003$), for patients older than 70 years 1.912 in the ER group and 1.230 in the LR group ($P = 0.17$), for female gender 4.978 in the ER group and 1.263 in the LR group ($P = 0.006$), for male gender 2.833 in the ER group and 1.392 in the LR group ($P = 0.087$), for patients with diabetes 2.811 in the ER group and

Figure 1. Kaplan-Meier survival curve

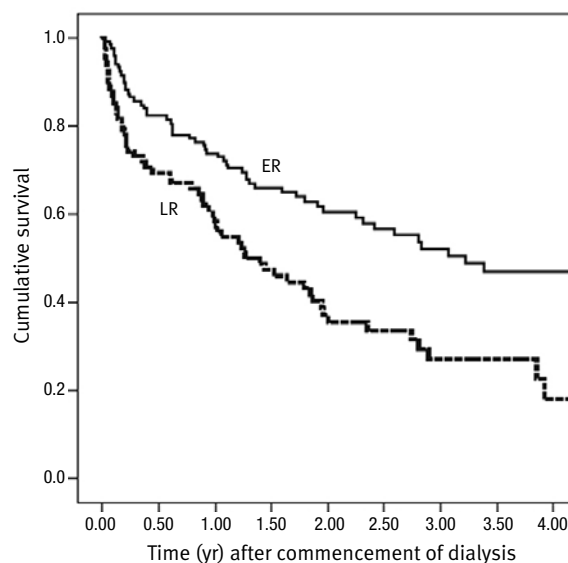


Table 2. Hazard ratio for mortality in Cox regression multivariate analysis

	Hazard ratio	95%	Confidence interval
Late referral	1.873	1.133	3.094
Age (yr)*	1.043	1.018	1.068
Diabetes	2.399	1.369	4.202
Albumin**	0.359	0.242	0.533

*HR calculated for increment in units of 1 year

**HR calculated for increment in serum albumin in units of 1 g/dl

Table 3. Relation between time of referral and survival, by subgroup

	ER median survival time (yr)	LR median survival time (yr)	<i>P</i> value
Age < 70 yr	4.482	1.959	0.003
Age ≥ 70 yr	1.912	1.230	0.17
Male	2.833	1.392	0.087
Female	4.978	1.263	0.006
Diabetes	2.811	1.008	0.005
No diabetes	4.978	1.789	0.06

1.008 in the LR group ($P = 0.005$), and for non-diabetic patients 4.978 in the ER group and 1.789 in the LR group ($P = 0.06$).

DISCUSSION

We studied 200 consecutive incident patients on dialysis treatment. The median follow-up time was 3.1 years. Overall, late nephrology referral occurred in 41% of the patients and was found to be associated with higher short- and long-term mortality when compared to patients who were referred early to a nephrology specialist. Our findings are in accordance with previous published results [2-14].

The survival benefit of early nephrology referral can be attributed to several factors: preparation of a vascular access (fistula or graft) and avoidance of central venous catheters, management of traditional and non-traditional cardiovascular risk factors, and maintenance of adequate nutritional status. These factors are related to mortality rates in dialysis patients. The highest mortality rate among hemodialysis patients is within the first months of treatment. The most prevalent and powerful predictors of early mortality are the presence of a CVC as the initial dialysis access and low serum albumin level at the beginning of dialysis treatment [20]. In our study albumin level was not significantly higher in the ER group, but higher albumin level was associated with a better survival rate. All our LR patients started dialysis with a CVC, but after 7 months of dialysis there was no difference in the percentage of CVC use between the groups. In the course of dialysis treatment there can be a switch in vascular access from CVC to shunt and from shunt to CVC. The use of a CVC as the initial dialysis access could be associated with increased mortality in the LR group in the short term, but for the long term the presence of a CVC is no longer related to the timing of nephrology referral. Most of the clinical studies analyzed only the short-term (3–12 months) mortality rate. We found that not only short-term but also long-term higher mortality rates were associated with late referral. Cardiovascular disease is the most common cause of death in hemodialysis patients at any given time. It is presumed that the benefits of early referral and appropriate pre-dialysis nephrology care can be attributed to attenuation of these complications by, for example, treating hypertension, anemia, and chronic kidney disease-mineral bone disorder. It is not clear whether other factors contribute to the long-term effect on mortality [14]. We could not determine the exact causes of mortality in our patients because of the lack of reliable data from autopsies. Prospective data are needed for further analysis in this regard.

In the subgroup analysis, we found that patients younger than 70, diabetic patients, and women are more likely to benefit from early referral in terms of survival.

A lack of survival benefit from early referral for older dialysis patients was also reported by Winkelmayer et al. [21]. It was suggested that the high burden of comorbidities in older patients may explain this finding. When compared to the general population, there is excess mortality in CKD and ESRD patients. This gap in mortality rates decreases with age and is less prominent in the older population [22]. It appears that the relative contribution of CKD to mortality rates in older patients may be attenuated by the presence of other medical conditions. In the past few years, the most rapidly expanding group of incident dialysis patients comprises patients aged 75 and above [1,2]. It is possible that this group of patients has different characteristics from the general dialysis population. More data on this issue are needed.

We also found that diabetes mellitus is associated with a higher risk of mortality in dialysis patients. For the diabetic patients, LR was associated with a higher mortality rate when compared to ER. For non-diabetic dialysis patients, the survival benefit associated with ER was only of borderline significance. It has been reported repeatedly that diabetes is associated with increased mortality in the ESRD population [22-24]. However, there are only a few reports on the beneficial effect of early nephrology referral on diabetic patients specifically [7].

In subgroup analysis by gender, we found that ER was associated with better survival in women. For men, the better survival rate for the ER group did not reach statistical significance. The effect of timing of nephrology referral on survival in women has not been previously reported. Gender differences in kidney disease epidemiology, progression and outcomes have been described. The rate of progression of CKD is slower in women than in men. Risk factors for CKD progression may have a different impact in women as compared to men. However, once dialysis is started women and men have the same survival rates, so the survival advantage of women in the general population is nullified [25]. The reasons for these differences are not clear and many hypotheses exist. This issue should be investigated further.

Our results, especially the subgroup analyses, should be interpreted with caution because of the limitations related to the retrospective nature of our study and the relatively small number in our patient groups.

Late referral was frequent in our study population. A combination of patient and health system characteristics is associated with late referral of patients with CKD [18,19]. Factors that depend on the patient are a rapid progression of the renal disease (occurring in only a minority of cases), asymptomatic occurrence of CKD until very advanced stages, lack of awareness about CKD and its consequences, and patient fear of dialysis. All these factors can be addressed with patient education. Factors that depend on the health system are specific for each

CVC = central venous catheter

CKD = chronic kidney disease
ESRD = end-stage renal disease

country. In Israel, economic obstacles or lack of medical insurance are of negligible importance. Primary physicians' referral patterns and nephrology service availability seem to play a role. More detailed data regarding the causes for late referral in Israel are needed. Life expectancy of patients on dialysis is disappointingly short. Since many predictors of survival are not modifiable, it is important to address those predictors that are modifiable, such as early nephrology referral.

The ideal timing of nephrology referral is not simple to determine. Data from clinical trials show that the benefit from early referral is influenced by the length of the nephrology care [6-7,11]. Nonetheless, even short-term pre-dialysis nephrology care, up to 3 months before dialysis is started, is of significant benefit, as shown in our study.

CONCLUSIONS

Survival time in dialysis patients was independently associated with time of nephrology referral. Our results show a significantly higher mortality rate up to 4 years after the initiation of dialysis in late referred patients with CKD, compared to patients who had received early referral. The survival advantage of early referral may vary in specific subgroups. The timing of nephrology referral should be considered a modifiable risk factor for mortality in the setting of ESRD.

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References

1. USRDS 2012 annual data report. www.usrds.org
2. Renal Replacement Therapy in Israel 1990-2010. www.health.gov.il/publicationsfiles/RRT1990_2010.pdf
3. Hommel K, Madsen M, Kamper AL. The importance of early referral for the treatment of chronic kidney disease: a Danish nationwide cohort study. *BMC Nephrol* 2012; 13: 108.
4. Hasegawa T, Bragg-Gresham JL, Yamazaki S, et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. *Clin J Am Soc Nephrol* 2009; 4: 595-602.
5. Kessler M, Frimat L, Panescu V, et al. Impact of nephrology referral on early and midterm outcomes in ESRD: EPide'miologie de l'Insuffisance REnale chronique terminale en Lorraine (EPIREL): results of a 2-year prospective community-based study. *Am J Kidney Dis* 2003; 42: 474-85.
6. Stack AG. Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 2003; 41: 301-18.
7. Tseng CL, Kern EFO, Miller DR, et al. Survival benefit of nephrologic care in patients with diabetes mellitus and chronic kidney disease. *Arch Intern Med* 2008; 168: 55-62.
8. Kinchen KS, Sadler J, Flnk N, et al. The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 2002; 137: 479-86.
9. Goncalves EAP, Andreoli MCC, Watanabe R, et al. Effect of temporary catheter and late referral on hospitalization and mortality during the first year of hemodialysis treatment. *Artif Organs* 2004; 28: 1043-9.
10. Nakamura S, Nakata H, Yoshihara F. Effect of early nephrology referral on the initiation of hemodialysis and survival in patients with chronic kidney disease and cardiovascular diseases. *Circ J* 2007; 71: 511-16.
11. Roderick P, Jones C, Drey N, et al. Late referral for end stage renal disease: a region-wide survey in the south west of England. *Nephrol Dial Transplant* 2002; 17: 1252-9.
12. Jungers P, Massy ZA, Nguyen-Khoa T, et al. Longer duration of predialysis nephrological care is associated with improved long term survival of dialysis patients. *Nephrol Dial Transplant* 2001; 16: 2357-64.
13. Herget-Rosenthal S, Quellmann T, Linden C, et al. How does late nephrological co-management impact chronic kidney disease? An observational study. *Int J Clin Pract* 2010; 13: 1784-92.
14. Smart NA, Titus TT. Outcomes of early versus late referral in chronic kidney disease: a systematic review. *Am J Med* 2011; 124: 1073-80.
15. Roubicek C, Brunet P, Huiart L, et al. Timing of nephrology referral: influence on mortality and morbidity. *Am J Kidney Dis* 2000; 36: 35-41.
16. Lhotta K, Zoble M, Mayer G, et al. Late referral defined by renal function: association with morbidity and mortality. *J Nephrol* 2003; 16: 855-61.
17. Goransson LG, Bergrem H. Consequences of late referral of patients with end-stage renal disease. *J Intern Med* 2001; 250: 154-9.
18. Navaneethan SD, Aloudat S, Singh S. A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease. *BMC Nephrol* 2008; 9: 3.
19. Sprangers B, Evenepoel P, Vanrenterghem Y. Late referral of patients with chronic kidney disease: no time to waste. *Mayo Clin Proc* 2006; 81 (11): 1487-94.
20. Lukowsky LR, Kheifets L, Arah OA, et al. Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *Am J Nephrol* 2012; 35: 548-58.
21. Winkelmayer WC, Liu J, Chertow GM, et al. Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med* 2011; 171: 1371-8.
22. Villar E, Remontet L, Labeuw M, et al. Effect of age, gender, and diabetes on excess death in end stage renal failure. *J Am Soc Nephrol* 2007; 18: 2125-34.
23. Sattr A, Argyropoulos C, Weissfeld L, et al. All cause and cause specific mortality associated with diabetes in prevalent hemodialysis patients. *BMC Nephrol* 2012; 13: 130.
24. Van Dijk PC, Jager JC, Stengel B, et al. Renal replacement therapy for diabetic end stage renal disease: data from 10 registries in Europe (1991-2000). *Kidney Int* 2005; 67: 1489-99.
25. Carrero JJ. Gender differences in chronic kidney disease: underpinnings and therapeutic implications. *Kidney Blood Press Res* 2010; 33: 383-92.