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NEPHROLOGY-REVIEW

# Dialysis or not in the very elderly ESRD patient

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## Introduction

Nephrology societies and dialysis registries are reporting a dramatic increase in the number of elderly patients who require dialysis. During the last decade the number of patients starting renal replacement therapy (RRT) has increased for all ages but the increase for patients over the age of 75 years has been particularly dramatic, with a 4.3-fold rise in the USA [1]. In view of this development, it is necessary to examine more closely the quality of the results (survival, selected technique, and morbidity) of kidney replacement therapy in this age group. Despite the fact that very old patients raise the most difficult problems with respect to indication and dialysis therapy management because of their multiple comorbidities and presumed short life expectancy, there are few studies devoted to very old end-stage renal disease (ESRD) patients and their conclusions are rather discordant. Some studies report very poor survival of very old patients on dialysis, whereas others report more favorable outcomes. Moreover, specific predictive factors that could help in deciding whether dialysis would offer pre-ESRD old patients substantial prolongation of life expectancy with an acceptable quality of life are lacking [2].

Below we discuss in more depth the reasons why, in general, dialysis should not be withheld from patients above 75 years of age. Let us first consider the title of this controversy: "The dilemma of renal replacement therapy in patients over 75 years." Is this actually a dilemma?

Basically, a dilemma is characterized by the need to choose between two evils, or in the present case between two possibilities. If the question is posed "should 75-year-old patients be started on dialysis: yes or no?" it is sensible to ask the question the other way round. What could be the reasons for not providing them with dialysis? Is the survival time too short? Is the quality of life that can be achieved unsatisfactory? Are there so many old people above 75 years of age and dialysis facilities are insufficient? Do financial constraints make age a matter of rationing? Good survival on dialysis for the very old is currently well documented. Shaefer and Röhrich showed that survival in very old patients after 12 months from the start of dialysis treatment was 70.5%, and after 24 months 50.3%, and after 60 months 18.5%. These results provide no rationale for withholding dialysis treatment, even when life expectancy of over 75-year-old dialysis patients is compared with that of younger dialysis patients. In fact 75-year-old dialysis patients have a life expectancy of only 36% of age-matched healthy controlled individuals. Therefore, the remaining life time is,

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using such calculations, proportionally higher than that of 40- to 60-year-old dialysis patients, as their life expectancy is only 16% that of healthy peers [3].

Let us examine whether quality of life is unsatisfactory in dialysis patients aged 75 years or more. A study performed recently in Berlin yielded amazing results: 75-year-old dialysis patients were not only very satisfied with their lives on dialysis, but also had less difficulty accepting the adjustments required for life while on dialysis than did younger patients. It is also interesting that 80% of the dialysis patients over 75 years old would recommend dialysis treatment to patients of the same age and only 12.5% would recommend that patients of the same age refuse dialysis treatment [4].

## Prognostic factors: the role of comorbid conditions

The decision to initiate dialysis is based exclusively on medical considerations in the best interest of the patients. The dialysis-related survival advantage might be substantially reduced by comorbidities—ischemic heart disease in particular. Comorbidity should be a major consideration when advising old patients for or against dialysis. The majority of 75-year-olds had one or more comorbid factors present at the time of starting renal replacement therapy (RRT). Hypertension and ischemic heart disease were found to be the most common comorbid factors (REF). Diabetes mellitus is another frequent comorbid condition, and peripheral vascular disease, malignant disease, and chronic pulmonary disease are often significant comorbid factors at the start of RRT. Most frequently survival-associated prognostic factors in old patients on dialysis are ethnicity, age, sex, social support, time and year of referral, use of erythropoietin, Karnofsky performance status, anthropometric measures, and body mass index [5]. Ethnicity was either defined as white or non-white. The small percentage of non-whites among the very old may be explained by three factors: (a) an overall decreased life span in the group due to a greater prevalence of diabetes mellitus and cardiovascular risk factors, (b) a decreased awareness of their disease and (c) limited access to nephrology services [6, 7]. The survival for the two sexes suggested a higher female mortality during the first 2 years of dialysis therapy and a lower mortality thereafter.

The combination of late referral (defined as referral to the nephrology unit less than 4 months before index date), the Karnofsky performance score (stratified in three functional classes—patients with normal activity >80, patients requiring assistance 50–70 and dependent patients, or requiring institutional or hospital care <40) and the body mass index (BMI) may provide a powerful discriminatory profile. According to a study, 1-year mortality was 15% in a low-risk group (old patients referred early, with BMI 22 kg/m$^2$, and Karnofsky score >40 at the time of dialysis initiation), and as high as 83% in a high-risk group (patients referred late, BMI 18 kg/m$^2$, and Karnofsky score <40) [5].

Late referral—an independent and a major determinant of poor dialysis outcome [8]—is more frequent in the very elderly. Although the relative risk of death conferred by late referral is similar in the very elderly and nonelderly, the higher frequency of late referral explains a large(r) proportion of the excess mortality seen in the very old. The interval between referral and first dialysis is significantly lower in patients >75 years (median interval 3.5 weeks) compared with patients <75 years (median 20.5 weeks). The difference in 1-year mortality between timely (>8 weeks) versus late (<8 weeks) referral, however, was as high in the very old (42% versus 16%) as in younger patients (34% versus 9%) [9]. Late referral is also frequently associated with starting dialysis on a central catheter, instead of a planned access. Mortality in very old patients starting dialysis using a fistula or synthetic graft was lower compared with those patients starting dialysis using a dialysis catheter (23.1% and 35.2%, respectively). Vascular access is a predictor of outcome and is age related. The prevalence of native fistulas among US hemodialysis patients was 35% in adult patients under age 45 years, 31% in patients aged 45–54 years, 26% in patients ages 65–74 years, and 23% among patients aged 75 years or older [10].

Cardiovascular disease (CVD) is a strong prognostic factor. Documented ischemic heart disease decreases the 5-year survival to only 5% from 70% at 2 years, compared with an almost unchanged 67% in patients without coronary disease. Similarly, left ventricular dysfunction (defined as clinical evidence of pulmonary oedema, not attributable to errors in fluid balance, and/or moderate to severe left ventricular dysfunction on echocardiography), is responsible

for decreasing the survival of a dialysed patient from 63% (at 2 years) to 14% (at 5 years) [11]. Finally, survival at 5 years was 10% in patients with peripheral vascular disease (defined as claudication with absent pulses, history of amputation or significant stenoses on vascular imaging), compared with the rest of the population (61%). The negative effect of peripheral vascular disease on overall survival becomes obvious after 18 months of dialysis therapy. Old patients on RRT almost always have clinically relevant CVD. In the study of Munshi et al. [12] in the very old (75 years and older), 53% had ischemic heart disease, 52% hypertension, 12% diabetes mellitus, and 17% peripheral vascular disease at dialysis initiation. However, CVD apparently accounted for 24% of overall death, and cerebrovascular causes for 5%. The main cause of death, unlike in younger patients, was withdrawal from dialysis, due to poor quality of life, attributable at least in part to severe cardiovascular morbidity [13].

Conditions severe enough to have an impact on survival in the general population also include: severe chronic obstructive airways disease, liver cirrhosis, and psychotic illness.

A preserved nutritional status is an important protective factor during the dialysis. In a recent study, Leavy et al. [14] found that albumin level and low BMI were the most powerful predictors of mortality. The incidence of malnutrition is widely held to be greater in the elderly, but this specific factor has not been extensively studied in old dialysis patients. Cianciaruso et al. [15] reported a prevalence of malnutrition of 27% in the 18- to 40-year-old age group, 31% in the 41- to 64-year-old group and 51% in the group aged 75 years or more. This increased prevalence of malnutrition in old hemodialysis (HD) patients is believed to be caused by a high incidence of concomitant illnesses that contribute to hypercatabolism, as well as by a reduced nutritional intake fueled by inadequate dialysis and socioeconomic and physiological factors. Male sex (hemodialysis patients), time on dialysis, weekly duration of dialysis, and protein catabolic rate (PCR)/ideal body weight appear as the most important predictors of malnutrition [16]. In contrast, survival was not different according to Kt/V urea, considered to be a marker of dialysis adequacy. In fact, the average value of this parameter in some old HD populations was close to the Dialysis Outcomes Quality Initiative recommendations and greater than the values previously reported in other studies of HD patients [17]. Finally, somewhat surprisingly, despite a high prevalence of protein and energy malnutrition, malnutrition and cachexia have rarely been reported as a direct cause of death. Therefore, it is possible that malnutrition may correlate with a reduced life span by favoring or accompanying such comorbid conditions as atherosclerotic cardiovascular disease, infections or sepsis.

Evaluating the prevalence of and risk factors for cognitive impairment is important because decreased cognitive function and an individual's quality of life increase resource utilization and result in suboptimal medical care. Cognitive impairment can range from mild cognitive impairment to dementia. Dementia is characterized by: (1) a decline from a previous higher level of cognitive functioning and (2) a behavioral disturbance caused by the cognitive decline that interferes with daily function and independence [18, 19]. In dialysis patients, cognitive impairment is more likely to be caused by vascular disease than by Alzheimer's disease because there is no evidence that kidney disease per se increases the risk for Alzheimer's disease [20]. The burden of dementia in dialysis patients has not been well assessed. Dementia is recorded as a cause of death on the Death Notification Form. In the 1999 US Renal Data System Annual Data Report [21], dementia was reported as the cause of death in less than 1% of dialysis patients. Dementia was listed as the cause of death in 0.8% of patients aged 65 years or older compared with 0.2% of patients aged 20–44 years. In these older patients, mortality attributed to dementia was 2.7 deaths/1,000 patient-years.

In a Tokyo-based study, the 1-year incidence of dementia in HD patients older than 65 years was 4.2% (Alzheimer's disease, 0.5% multi-infarct dementia, 3.7%). The 1-year incidence of multi-infarct dementia in HD patients older than 65 years was 7.4 times more than that in the elderly general population, suggesting that older HD patients might be at much greater risk for multi-infarct dementia. The investigators suggested that the high incidence may be related to the increased prevalence of atherosclerosis and other medical conditions, such as hypertension and diabetes, common in the HD population [22].

It is likely that very old ESRD patients on RRT may just represent the tip of an iceberg of the many

old patients with ESRD either not referred or not accepted for RRT. Does this imply indirectly that the very elderly with ESRD who are taken up for RRT are the ones with less comorbidity and, if all very old ESRD patients were selected, the prognosis would be much worse?

## Causes of death in the very old dialysis patient

The most frequent cause of death in old dialysis patients was due to withdrawal of dialysis, infectious complications (peritonitis, pneumonia, septicaemia, and endocarditis), and cardiovascular complications. Cardiovascular causes of death included acute vascular event, pulmonary oedema, severe right heart failure and pulmonary artery hypertension, myocardial infarction, complete hearth block, and major artery emboli.

A retrospective analysis of the survival of all over 75 years with chronic kidney disease (CKD) stage 5 attending dedicated multidisciplinary predialysis care clinics was performed. One- and two-year survival rates were 84% and 76% in the dialysis group ($n = 52$) and 68% and 47% in the conservative group ($n = 77$), respectively, with significantly different cumulative survival (log-rank 13.6, $P < 0.001$). However, this survival advantage was lost in those patients with high comorbidity scores, especially when the comorbidity included ischemic heart disease [22].

Dialysis in old patients: which method to use?

The modality of RRT used in very old ESRD population was equally distributed between hospital hemodialysis and peritoneal dialysis (PD) [23]. A few large studies have been published comparing the effect of PD and HD on patients' survival. Vonesh et al. [24] found that patients with baseline congestive heart failure (CHF) had similar survival rates on both modalities, except for the subgroup of diabetics, which had a lower mortality on HD than on PD (RR = 0.80, $P < 0.0001$). In PD, along with age, residual renal function (RRF) and membrane function remain important factors in patient survival, and plasma albumin loses its predictive power. The relationship of comorbidity to plasma albumin was expected, although the lack of a dose-dependent effect was surprising. Patients with moderate and severe grades had similar plasma albumin at the start and throughout their time on treatment. Yet again, the effect of informative censoring may be masking a true difference. There are many determinants of low plasma albumin in PD patients, including age, comorbidity, acute and chronic inflammation, high solute transport, and undernutrition [11].

Obesity, hypoalbuminaemia, anaemia, malignancy, and smoking on the other hand reduce the preference for PD. As shown in the study by Winkelmayer et al. [25] but in contrast to the Choice study [26], old patients with congestive heart failure were more likely to start on PD. Previous to data reported by Stack et al. [27], congestive heart failure was considered a good indication for PD as it offers a gentler, continuous ultrafiltration. Some clinicians favor PD for diabetic patients [26] whereas others do not; potential advantages of PD include that neither vascular access nor systemic anticoagulation is needed and that fluid removal is more gradual. Both of these advantages are useful in patients with polyvascular disease. In a recent prospective study involving 1,041 incident dialysis patients, Jaar et al. [28] found that, among those with cardiovascular disease (including arrhythmias, cerebrovascular and peripheral vascular disease, congestive heart failure, and coronary artery disease) risk of death after 2.4 years of therapy was significantly greater in those undergoing PD than in those undergoing HD; on the other hand, there was no difference in survival between PD-treated and HD-treated patients without previous cardiovascular disease.

After controlling for all other factors, older age remained a strong independent predictor for choosing PD. This is unusual since, except for countries such as Canada, the UK, and Scandinavian countries [29], PD is more often prescribed for autonomous young patients [30, 31].

PD is a common treatment option in French old patients. PD was chosen significantly more often than planned HD for the oldest (>85 years) compared with the youngest (75–79 years) patients: odds ratio 2.1 (95% confidence interval, 1.5–2.8), in those with congestive heart failure 1.8 (1.5–2.3), and severe behavioural disorder: 2.2 (0.3–0.8) and smokers: 0.4 (0.2–0.9). Two-year survival rates were 58%, 52% and 39% in patients aged 75–79 years, 80–84 years, and >85 years, respectively. Compared with planned HD, unplanned HD was associated with a risk of mortality

50% higher, and PD with a risk 30% higher, independent of patient case mix. In contrast, the stable 1-year survival of 46% observed in the dialysis patients aged 80 years and older in the USA from 1996 to 2003 [2], was well below the values of 67.3% and 60.5% found in those aged 80–84 years and older than 85 years, respectively [32].

## Conclusion

Age discrimination does not appear to be a major factor. It is true that much of the prognostic data are not favorable for the old, but for patients over 75 years with CKD stage 5 who are referred to nephrology care early and who follow a planned management pathway, those choosing to follow a dialysis pathway have a survival advantage. It is not clear whether this survival advantage derives from dialysis itself or from selection of patients into this management pathway, but nevertheless, comorbidity and ischemic heart disease in particular appear to substantially reduce this survival advantage. Future prospective survival studies should measure equilibrated glomerular filtration rate in both dialysis and conservative groups regularly in order to compare survival at different levels of disease severity, and additional work is needed to explore the determinants of the dialysis decision, from both nephrology and patient perspectives. For those patients with high comorbidity including ischemic heart disease, conservative management does not imply withdrawal from care, but rather active disease management and detailed supportive care right until end of life; nevertheless HD remains the best choice for old patients with comorbidities.

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