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Prognostication in End-Stage Renal Disease

Ana Farinha, MD

Nephrology Department – Centro Hospitalar de Setúbal, Setúbal, Portugal

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"Alice: How long is forever?
White Rabbit: "Sometimes, just one second."
Lewis Carrol, Alice's Adventures in Wonderland

When outpatient haemodialysis programmes began, strict criteria were developed to deliver a limited resource to those patients who would benefit the most. The goal was to rehabilitate – to enable patients disabled by end-stage renal disease (ESRD) to return to their normal activities, and not merely to extend life or postpone death. Dialysis is currently offered to many patients who would not have been considered suitable for this treatment a few decades ago. The "technological imperative" and access to advanced health technology has allowed patients to live with a disease that otherwise would be fatal. Although dialysis therapy may extend life, it is now increasingly clear that it often fails to restore health and that many patients suffer from distressing symptoms or disability prior to death. This translates into the challenge of recognizing patients who would benefit from renal replacement therapies (RRT), with a growing prevalence of older ESRD patients on dialysis.

In 2015, data from *Gabinete de Registos da Sociedade Portuguesa de Nefrologia*[1] reported 2335 incident patients on dialysis. Forty-four percent were aged between 65 and 80, and 19.5% were over 80 years old. Of prevalent patients (n=12265), 39.8% were aged between 65 and 80, and 19.5% were over 80 years old. Of haemodialysis patients, 1511 patients died: 82.9% were older than 65 and 42.2% were older than 80 years old. More than 8% of deaths occurred in the first 90 days. For the first time in Portugal, withdrawal numbers were presented (71 patients).

Elevated rates of death in the first 3 months and the dialysis withdrawal rates highlight the importance of prognosis and goals of care discussions. A realistic understanding of life expectancy and illness trajectory is critical for making decisions. Very optimistic expectations have caused ESRD patients to be overtreated[2]. Compared to other life-limiting illnesses, such as cancer or heart failure, patients on dialysis experience very high rates of hospitalization, ICU admission and use of intensive procedures during the final month of life. This would not necessarily reflect patient values or preferences.

It is important to be able to recognize predictors of poor outcome, so that ethical principles in medicine can be respected. The focus should be on *non maleficience* (*Primum non nocere* – the harms of dialysis may outweigh its benefits in elderly patients), *beneficience* and autonomy rather than paternalism. In 2010, Sara Davison reported that over 60% of patients regretted the decision to start dialysis. More than a half chose dialysis because of their doctor's or family's wish (13.9%)[3]. Several societies and renal associations now recommend that the decision to start dialysis should be based on a shared decision-making model[4-9]. This attitude has been also highlighted in the American Board of Internal Medicine´s Choosing Wisely campaign[10] and in Portugal by its directive on therapeutic options[11].

Clinicians should become familiar with prognostic tools and be comfortable and skillful in communicating this information. Shared decision making, to provide an integrated individual approach, should be incorporated into our nephrology practices. This article reviews the current data regarding prognostication in patients

with ESRD, emphasizing its multiple dimensions: life expectancy and causes of death, trajectory of illness, frailty, functional status and quality of life, comorbidities, predictors of prognosis and predicting tools.

LIFE EXPECTANCY AND CAUSES OF DEATH

The US Renal Data System has published the life expectancy for the general US population, dialysis and transplanted patients by age, gender and race. This report highlighted how much shorter the remaining expected lifetime is for people undergoing renal replacement therapy compared to the general population. It also documented that adjusted mortality rate of maintenance dialysis patients is nearly twice that of adults with cancer and more than twice that of adults with congestive heart failure or stroke[12].

Life expectancy also decreases significantly with age. Outcomes of three groups of patients with different ages on RRT were analyzed: ≥75 years old (group 1); 65-74 years (group 2) and <65 years (group 3). A 1-year survival rate of 53.5, 72.6 and 90.6% and a 5-year survival rate of 2.4, 18.8 and 61.4% in groups 1, 2 and 3 respectively was reported[13]. In this population, withdrawal from dialysis remained the most common cause of death in the elderly group (38%), followed by cardiovascular causes (24%) and infections (22%), which is common to many other reports[14-17].

TRAJECTORY OF DISEASE

The concept of illness trajectories is an established issue brought from palliative medicine to describe a pattern of functional decline to death observed in individuals with various illnesses[18]. Models for the organ failure illness trajectory have included chronic pulmonary disease, heart failure, and, more recently, stroke and diabetes mellitus[19]. ESRD has never been a model for illness trajectory, but in most patients undergoing long-term dialysis it would resemble this pattern of organ failure[20]. Acute declines are common among dialysis patients experiencing hospitalizations for acute myocardial infarction, limb amputation, bactereamic episodes associated with central venous catheter infections, or hip fractures. These episodes or sentinel events generally affect a patient's functional status, from which some improvement may be observed; however, often slight but perceptible greater impairment in functional status occurs. On the other hand, a different functional trajectory has been described in 75 elderly patients with stage 5 chronic kidney disease (CKD) who were treated conservatively (without dialysis)[21]. They found a distinct trajectory in which functional status remained stable until the last month of life and then steeply declined, much more like what happens in cancer patients' trajectories.

FRAILTY

In geriatrics, the elderly are categorized based on estimated life expectancy, functional level, presence of frailty and cognitive impairment to guide decisions. In geriatric oncology, protocols that screen for elderly vulnerability, geriatric syndromes and comorbidities are used to evaluate the risks and benefits of cancer therapy. This approach recognizes the variable prognosis of older patients at any given (chronological) age, highlighting the importance of "functional age" to evaluate the benefit of a given therapy. Also in ESRD, geriatric syndromes such as frailty, functional disability (mobility, activities of daily living) or cognitive dysfunction are powerful predictors of adverse events such as mortality, hospitalization and nursing home placement[22].

COMORBIDITIES

It has been known for a long time that the mortality of CKD patients is closely linked to associated comorbidities. In 2004, Keith et al. showed that death was far more common than dialysis at all stages of CKD and that congestive heart failure, coronary artery disease, diabetes and anaemia were more prevalent in patients who died[23].

Chronic kidney disease cannot be considered in isolation: Fraser et. al. evaluated the impact of 11 comorbidities (hypertension, painful condition, anaemia, ischaemic heart disease, diabetes, thyroid disorder, cerebrovascular disease, respiratory condition, depression, peripheral vascular disease and heart failure) in people with CKD stage 3. They found that only 4% of these patients had no comorbidities and that greater multimorbidity (3 or more comorbidities) was independently associated with mortality[24]. The same effect has already been described for rates of survival in RRT

populations[25] where number of comorbidities decreased survival probability, specially for diabetes, peripheral vascular disease or ischaemic heart disease.

PREDICTING FACTORS

Assuming comorbidities as being associated with worse prognosis, interest has grown in defining which of them would represent a predicting factor for mortality. Because of ethical issues, no randomized clinical trials have been conducted to identify these factors or to access the benefit of RRT over conservative therapy (CT) in elderly CKD patients. On the other hand, a number of clinical observational studies have been published in the past decade to address this issue.

One of the first studies, published in 2003, analyzed 144 patients aged over 80 years old, referred to a renal unit. Patients who were not proposed for dialysis presented more social isolation, later nephrology referral, higher Karnofsky score and higher percentage of diabetes. Although patients on dialysis lived longer, poor nutritional status, later referral and functional dependence were identified as independent predictors of death within a year, and peripheral vascular disease was an independent predictor beyond a year[26].

In 2007, in one of the most cited studies, Murtagh evaluated patients older than 75 years. Except for age, there were no differences in baseline characteristics between the two groups (dialysis versus conservative treatment). Survival benefit would be lost in patients over 75 years old who presented a high comorbidity score, especially if the comorbidity included ischaemic heart disease[27].

Similar conclusions have been reached in larger studies with larger periods of observation thereafter. In a cohort of 844 patients, those who were managed conservatively were older (77.7 vs. 58.5 years old) with higher comorbidities. Even so, when corrected for age, high comorbidity and diabetes, the survival advantage from renal replacement therapy was ~4 months, which was not statistically significant[28].

An important study gave more clues to difference in time of survival between patients undergoing dialysis and on conservative treatment. Comparing the median survival of 202 patients who choose RRT or conservative treatment (CT), RRT patients had a median survival of 37.8 months, including the first 90 days versus 13.9 months for CT patients, but CT patients were older (median age 83.0 vs. 75.0, $p<0.000001$) and most of the survival advantage was lived as a hospital inpatient.[29].

More recently, an interesting study with 8341 patients from Taiwan older than 70 years demonstrated a survival advantage for CT patients compared to dialysis-treated patients, even if in the first group they were older, with shorter follow-up and more comorbidities[30]. These led the authors to associate dialysis *per se* to an increased mortality risk in patients over 70 years old.

This year (2016), a Spanish study (perhaps with a more similar population to the Portuguese one) showed no dialysis versus CT survival advantage for patients older than 80 years, with CT patients once more presenting a higher comorbidity index. Besides age, time of follow-up and baseline eGFR were also predictors of prognosis[31].

PROGNOSTIC TOOLS

After identifying common predicting factors of worse prognosis, a new challenge has been born: to built algorithms or prognostic tools to identify patients who might not benefit from renal replacement therapies. One of the first mathematical models used to predict mortality in ESRD patients was published by Beddhu et al. in 2000. It uses the Charleston Comorbidity Index and emphasizes the importance of comorbidities on mortality risk in these patients[32].

Other scores with a higher number of patients have been developed for specific populations such as Spain (n=5738 patients)[33], France (n=2500 patients)[34] or Canada n=16205 patients[35] but these models have not been validated for other populations, although they used similar predicting factors.

In 2009, a geriatrician used the Comprehensive Geriatric Assessment (CGA), a multidimensional diagnostic process intended to determine an elderly person's medical, functional and psychosocial capacity and problems, and reported the efficacy of the Multidimensional Prognostic Index (MPI), calculated from information collected by a standardized CGA, in predicting mortality risk in older patients hospitalized with CKD. The CGA included 6 standardized scales: Activities of Daily Living

(ADL), Instrumental Activities of Daily Living (IADL), Short Portable Mental Status Questionnaire (SPM SQ), Mini Nutritional Assessment (MNA), Exton-Smith score (ESS) and Cumulative Index Rating Scale (CIRS), as well as information on medication history and cohabitation, for a total of 63 items. Higher MPI values were significantly associated with higher 1-year mortality in older patients with CKD. Although it is an holistic model validated for dialysis patients, it is very complex and time-consuming, which renders it accessible to expert geriatricians only[36].

A new era began in 2010, when a study was published in which only five factors were selected to predict mortality for prevalent haemodialysis patients[37]: age, dementia, peripheral vascular disease, albuminaemia as a surrogate for malnutrition, and the "surprise" question. This question ("Would you be surprised if this patient died in the next 12 months?") has long been used in palliative care to recognize poor prognosis and improve end-of-life care, and has been validated for dialysis patients in a study published in 2008[38]. This study became popular because of its simplicity, and was the basis for the creation of a web calculator (application available at www.touchcalc.com) which allowed predicting survival at 6, 12 and 18 months, and which brought attention to prognostication.

Last year, three new scores were developed. Using data from prevalent patients registered in the US Renal Data System, Thamer et al. developed a score to predict mortality at 3 and 6 months. It applied 7 demographic, clinical, laboratorial and functional variables: age, cancer, heart failure history, time of hospitalization in previous year, albumin level, needs for assistance in daily living and residence in a nursing home, but it has been not validated for populations other than the US one[39].

Based on the French National Renal Epidemiology and Information Network (REIN) registry, Couchoud et al. improved their previous prognostic score[40] to develop a prognostic screening algorithm for older patients (>75 years old) to stratify three groups of early mortality risk. It used fifteen characteristics, including age, gender, specific comorbidities, albumin level and mobility[41]. It has been validated for the French population where clinical patterns may be more similar to Portuguese ones.

The most complete predictive mortality risk score is that published by Floege et al. It has been validated for incident and prevalent patients and for all ages with a mortality risk score for all-cause mortality at 90 days, 1 and 2-year. It was based on a European haemodialysis cohort from 14 different countries from >300 facilities where fourteen parameters were included (such as age, clinical and laboratorial ones or vascular access). The score derived from a retrospective population was then externally and prospectively validated using similar-size data from the Dialysis Outcomes and Practice Patterns Survey (DOPPS)[42].

FUNCTIONAL STATUS AND QUALITY OF LIFE

If dialysis does not offer a survival advantage in the elderly, it would be expected to improve functional status and quality of life. In 2009, the first two studies focusing on this issue were published in the New England Journal of Medicine. In one study, among 3702 nursing home patients who start dialysis (mean age 73.4±10.9 years old), there was a substantial and sustained decline in functional status and at 12 months almost 75% died. A similar conclusion was stated in the smaller study with independent living patients older than 80 years after starting dialysis.

Patients with chronic kidney disease also have a very high burden of symptoms, sometimes worse than those associated with some cancers[43] which impacts on QoL. Symptoms in end-stage renal disease are under-recognized. Fatigue/tiredness, pruritus, constipation, anorexia, pain, sleep disturbance, anxiety, dyspnea, nausea, restlessness and depression are frequently reported in some studies[44]. It is often assumed that ERSD symptom will improve after dialysis initiation, but very little is known about the impact of dialysis on symptom control[45]. The only study which compared patients´ symptoms in those who are managed with or without dialysis found little or no differences[46].

CONCLUSION

Medical and technological advances may allow people to live longer but still with a great burden of comorbidities. Patients with end-stage renal disease have a high mortality, sometimes worse than that associated with some cancers. Prognostication is a complex issue to all nephrologists who manage ESRD patients because of its multidimensional perspective. Decisions are always difficult but pros and cons must be evaluated to ensure dignity and quality of life. Expectations should

be realistic, not leading to overtreatment. Late perception of lack of benefit contributes to the high amount of dialysis withdrawal, which presents a very different trajectory from that of not starting dialysis. Presenting prognosis to an end-stage renal disease patient is part of the commitment of any nephrologist. It poses the challenge of talking about survival, quality of life and control of symptoms. Dialysis may prolong life but not restore heath, so survival advantage may be lost in elderly patients with more comorbidities. Quality of life and control of symptoms do not always differ greatly between patients who choose to dialyse versus patients who choose a conservative pathway. Predicting survival is impossible but estimating based on different tools may be useful. Current studies have some limitations: study design, descriptions of conservative care models or active management regimens rarely being reported; the timings from comparison between the two groups are often different; worse baseline characteristics (patients who opt for conservative treatment tend to be older, with more comorbidities), but they still have some common findings: age and comorbidities represent a risk for survival. In selected cases, conservative management may represent an equivalent choice to dialysis in terms of prognosis and quality of life. Even so, it is recognized that further studies are required to evaluate if the existing tools are applicable to our population.

Determining prognosis for individual patients should, however, be a clinical skill that must be developed. Prognosis discussions should not be withheld because of reluctance to discuss it, lack of confidence in predicting prognosis, fear of abolishing hope or discomfort with such discussions. In most cases, it would help patients and doctors to manage the challenge of chronic kidney disease.

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Correspondence to:
Ana Farinha
Nephrology Department – Centro Hospitalar de Setúbal
Rua Camilo Castelo Branco, 2910-446 Setúbal, Portugal
E-mail: alpfarinha@gmail.com