



ORIGINAL ARTICLE

A study to describe the health trajectory of patients with advanced renal disease who choose not to receive dialysis

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Abstract

Background: Some patients with end-stage renal failure (ESRF) are unlikely to benefit from dialysis and conservative management (CM) is offered as a positive alternative. Understanding the trajectory of illness by health care professionals may improve end-of-life care.

Methods: We aimed to describe the trajectory of functional status within our CM population through a prospective, observational study using the objective Timed Up and Go (TUG) test and subjective Barthel Index (BI) and health-related quality of life (HRQoL) [EuroQol 5D-5L (EQ-5D-5L)] measurements and correlating them with demographic and laboratory data and with sentinel events.

Results: There was a significant increase in TUG scores over the 6 months prior to death {2.24 [95% confidence interval (CI) 1.16–4.32], $P = 0.017$ } and a significant decrease in EQ-5D-5L [–0.19 (95% CI –0.33 to –0.06), $P = 0.006$]. The only significant associations with mortality were serum albumin [hazard ratio (HR) 0.81 (95% CI 0.67–0.97), $P = 0.024$] and male gender [HR 5.94 (95% CI 1.50–23.5), $P = 0.011$].

Conclusions: We have shown there is a significant decline in functional status in the last 6 months before death in the CM population. Of interest, there was a significant relationship of lower serum albumin with functional decline and risk of death. We hope that with improved insight into disease trajectories we can improve our ability to identify and respond to the changes in needs of these patients, facilitate complex and sensitive end-of-life discussions and improve end-of-life care.

Key words: chronic kidney disease, end-of-life care, end-stage renal disease, functional trajectories, palliative care

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Introduction

Over the past decade there has been increasing appreciation that there is a group of patients with end-stage renal disease (ESRD) for whom dialysis adds little to the prolongation of life but may have a significant negative impact on quality of life. These patients are often offered conservative management (CM) of ESRD; that is, management of ESRD without renal replacement therapy (RRT). CM management attempts to offer multidisciplinary team (MDT) holistic care to the patient, actively managing ESRD while also addressing symptoms, maximizing the patients' functional abilities to maintain independence and quality of life as much as possible and addressing end-of-life care. We have previously described our CM service [1]. The CM clinic is a weekly clinic staffed by a nephrologist, CM specialist nurse, social worker, anaemia nurse and dietician who provide 'one-stop' multidisciplinary care and assessment of patients' needs. In addition, there is a physiotherapy practitioner providing comprehensive physiotherapy assessment, therapy and collaboration with community services where appropriate. The physiotherapist aims to maximize a patient's independence through specialized assessment and therapy such as individually designed exercise programs. As symptom burden increases the physiotherapist can identify and support changing needs with interventions such as breathlessness and fatigue management and equipment provision. The CM specialist nurse also visits patients between clinic visits. The service has links with palliative care services when required.

An improved understanding of the trajectory of illness by health care professionals enables patient education and informed decision-making and therefore patient-centred care [2, 3]. It can help identify patients whose health is deteriorating and who may be at risk of dying and those who may require additional service provision and symptom management; it may also facilitate the sensitive end-of-life discussions needed to improve the quality of end-of-life care [4-7].

Within the CM population there is limited evidence to define illness trajectory, although it has been shown that there is a distinct functional decline in the last month before death in the CM population [8], in contrast to other trajectories of chronic illness [9]. However, the authors were concerned that the Karnofsky Performance Scale (KPS) may have limited sensitivity to change and may not record more subtle but significant changes. We aimed to describe the trajectory of functional status within our CM population through a prospective, observational study of patients attending the CM clinic using objective and subjective measurements of functional status. We further correlated these measurements of functional status with demographic and laboratory data and with sentinel events such as hospitalization.

Methods

This was a prospective, observational study over a period of 18 months. Previous clinic data showed the average time spent in the clinic before death was 17.8 months [1].

The whole CM cohort was screened for recruitment, including existing CM patients as well as new patients referred for CM during the study period. Data were collected every 12 (± 3) weeks during individual clinic visits for up to seven successive measurements.

The functional outcome measures of interest were the Timed Up and Go (TUG) test, Barthel Index (BI) and EuroQol 5D (EQ-5D), which were selected on the grounds of reliability and validity, together with clinical relevance as objective measurements appropriate for the CM population.

The TUG test is recognized to have reliability (interrater and retest) and validity [10]. The TUG test is a short test for patients

to perform, rendering a continuous level measure of balance, mobility and chair-based function. The patients were timed and observed standing from a chair, walking 3 m, turning around and walking back to the chair and sitting down. Walking aids were used if required. The TUG test was chosen instead of the KPS since it allowed a more objective investigator measurement of the patients' functional mobility. The TUG test has been studied in CKD patients receiving palliative care and has been shown to have good interobserver reliability [11] and has also been used to monitor changes over time in other disease states [12].

The BI is a widely used self-reporting tool that provides ordinal level data as a functional measure. It uses a 10-point scale (eight activities of daily living and two mobility components), with a possible score of 100 [13, 14], and has been used in different settings without a reduction in reliability or validity. The BI has been shown to lack sensitivity to changes in high-level functioning patients [15].

The EQ-5D-5L has been widely used and recognized as a measure of health-related quality of life (HRQoL), and has been used within groups of CKD patients [16]. It is a measure consisting of five questions measuring five dimensions of health concepts encapsulating QoL on a visual analogue scale. The ordinal five-level scale of health states has been shown to be reliable and sensitive [17]. Patients were asked to complete the BI and the EQ-5D-5L forms on arrival at the clinic prior to physiotherapy assessment. Additional physiotherapy or other services were accessed for patients as needs arose throughout the study.

Blood samples are routinely assessed, including estimated glomerular filtration rate (eGFR), haemoglobin and albumin. Patients are also weighed routinely. The Stoke Co-morbidity Grade (SCG) was used to record comorbidity. This is an ordinal 3-point scale that has been previously validated in dialysis patients [18] and has been described as an independent prognostic tool in survival prediction of CM patients [1]. Sentinel events were defined as hospital admission, falls, acute episodes of illness or bereavement.

Patients were excluded if they lacked the mental capacity to provide informed consent.

Ethical permission was sought and obtained for the study. All patients were provided with a patient information sheet and signed a consent form.

Statistical analysis

This was a descriptive, observational study and therefore no formal power calculation was carried out.

Baseline demographics are summarized as mean (SD) for continuous variables and frequency (%) for categorical variables. Data are graphically represented as means \pm 95% confidence limits.

To analyse the three outcomes over time, longitudinal regression analysis with robust standard errors to take into account within-patient correlation was used. The time variable was re-ordered such that it corresponded to the number of months left alive for the patients who died and the number of months remaining in the study for those who remained alive. Tobit regression was used to model the TUG outcome, as this allowed the incomplete tests to be censored at an upper limit (8 min). Prior to analysis, a log transformation was performed on the TUG measurements due to the non-normal distribution. Quantile regression was used to model BI and EQ-5D. To investigate how each outcome changed over time, the initial regression model included only a time, group (died/alive) and time-by-group interaction term. These models were then adjusted for age, SCG, eGFR, haemoglobin and albumin.

A multivariable Cox regression model was used to estimate the adjusted hazard ratios. A stepwise model selection procedure using Akaike's Information Criteria was used to identify covariates to be included alongside log(TUG), BI and EQ-5D in the final model. For patients who chose to withdraw from the study and pursue dialysis, data were analysed up until the point of withdrawal.

All statistical analyses were conducted using Stata 13 (Stata-Corp, College Station, TX, USA).

Results

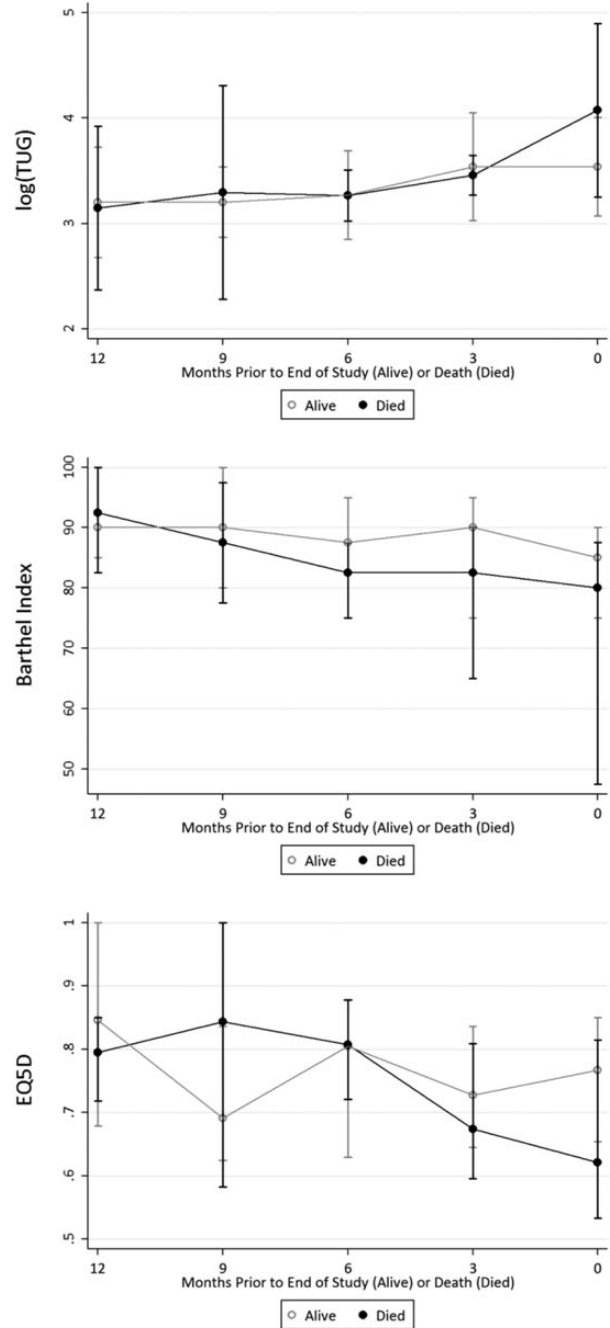
Sixty-two patients were screened and approached for recruitment. Twelve patients were excluded because they lacked the mental capacity and eight patients declined consent. One patient was excluded because the eGFR was >30 mL/min. A total of 41 patients were recruited, with an average age of 82.7 years (range 72–95). Twelve patients died and three patients withdrew throughout the course of the study. Of the withdrawn patients, two changed their treatment decision and opted for RRT and one patient's capacity to make decisions changed during the study and thus that patient was withdrawn. The 41 patients recruited into the study provided a total of 182 observations. Baseline demographics are summarized in Table 1. The median follow-up period was 11.3 months.

Figure 1 shows the trajectory of the TUG, BI and EQ-5D results prior to death or the end of the study. There was a steady increase in TUG scores in both patient groups, with a larger increase observed in the group that died. There was a significant increase in TUG scores over the 6 months prior to death [2.24 95% confidence interval (CI) 1.16–4.32], $P = 0.017$. For the BI there were no significant changes over time; full results are shown in the Supplementary data. When the changes over time of the variables measured were compared there was a moderately strong and statistically significant inverse correlation between log TUG and BI ($P < 0.001$) (Figure 2).

Multivariable analysis suggested an increase in the TUG score and a decrease in the BI following a sentinel event; however, this failed to reach significance (Supplementary data). There was a significant association of serum albumin with the TUG score [0.90 (95% CI 0.84–0.97), $P = 0.005$] and BI [1.80 (95% CI 0.19–3.42), $P = 0.029$]. The only significant associations with mortality were serum albumin [hazard ratio (HR) 0.81 (95% CI 0.67–0.97), $P = 0.024$] and male gender [HR 5.94 (95% CI 1.50–23.5), $P = 0.011$], both of

which were associated with an increased risk of mortality. Male gender was associated with an approximately 6-fold increased risk of mortality. Each decrease of 1 g/dL of serum albumin was associated with a 19% increased risk of death (95% CI 3–33%) (Table 2).

There was also a significant decrease in the EQ-5D over the 6 months prior to death [−0.19 (95% CI −0.33 to −0.06), $P = 0.006$],



| Month | 12 | 9 | 6 | 3 | 0 |
|--------------|----|----|----|----|----|
| Alive (n=29) | 17 | 19 | 22 | 25 | 29 |
| Died (n=12) | 4 | 4 | 8 | 10 | 12 |

Table 1. Baseline demographics of recruited subjects

| | Total | Alive | Died | P-value |
|-----------------------|------------|------------|-----------------|---------|
| n | 41 | 29 | 12 | |
| Gender | | | | |
| Male | 18 (44%) | 10 (34%) | 8 (67%) | |
| Female | 23 (56%) | 19 (66%) | 4 (33%) | 0.087 |
| Age, mean (SD), years | 82.7 (5.7) | 82.1 (5.8) | 83.9 (5.6) | 0.372 |
| eGFR | 14.3 (4.2) | 13 (10–16) | 11.5 (9.5–16.5) | 0.177 |
| Comorbidity | | | | |
| 0 | 6 (15%) | 5 (17%) | 1 (8%) | |
| 1 | 27 (66%) | 21 (72%) | 6 (50%) | |
| 2 | 8 (20%) | 3 (10%) | 5 (42%) | 0.079 |
| Outcome | | | | |
| Alive | 26 (63%) | | | |
| Died | 12 (29%) | | | |
| Withdrew | 3 (7%) | | | |

Fig. 1. Trajectory of the TUG score, BI and EQ-5D. The number of observations at each time point in each group has been tabulated.

however, there was no trend in the EQ-5D over the study period in patients who remained alive (Figure 1). The EQ-5D has five dimensions. In a *post hoc* analysis we explored the relationship between the mobility dimension of the EQ-5D, which is patient-reported, the TUG, which is investigator measured, and serum albumin. The results are shown in Figure 3 and suggest that both serum albumin and TUG were associated with EQ-5D patient-reported mobility.

There was no relationship between eGFR, SCG, haemoglobin and mortality or TUG, BI and EQ-5D (see Supplementary data).

Discussion

The primary objective of this study was to observationally define the trajectory of the functional status of patients with advanced renal disease who choose not to dialyse. We have shown that the TUG score increased while the EQ-5D decreased in the last 6 months of life. Prior to 6 months before death, these variables remain statistically stable. This suggests that both mobility and HRQoL decrease in the last 6 months of life but are preserved prior to that point. This study did not determine the cause for the decreasing TUG scores; however, we believe it is likely to be multifactorial due to increased frailty, declining cardiovascular

health, musculoskeletal disease and duration of uraemia. Understanding a trajectory of disease has a number of benefits for patients and their caregivers. First, it allows the patient to be aware of how their illness is likely to progress in the future. Knowing their functional capacity, including mobility and HRQoL, is likely to be maintained until the final months of life may be useful for many patients and their families and health care professionals. In this group of patients where functional capacity has been stable for some time but starts to deteriorate, a further steady decline leading to death may be expected and appropriate measures and plans put in place in a timely manner. This also highlights the importance in involving the MDT in the assessment of patients.

Functional decline as a risk of deteriorating health and a risk of dying is well known in the general population and used within the Gold Standards Framework prognostic indicator guidance and Supportive and Palliative Care Indicators Tool (<http://www.spict.org.uk/front-page/> and <http://www.goldstandardsframework.org.uk/cd-content/uploads/files/General%20Files/Prognostic%20Indicator%20Guidance%20October%202011.pdf>). Previous studies looking at functional status in ESRF have shown that on starting dialysis, nursing home residents suffer a significant functional decline that was an independent risk factor of mortality [19]. A previous trajectory study of functional status in the CM population showed this remained stable until the final weeks before death [8]. The KPS was used as a functional measure. The authors suggested further trajectory studies with other functional outcome measures, which we have attempted to do. Selecting the TUG and BI, we aimed to give a more detailed observation of illness trajectory. In particular, by using the TUG test, we attempted to objectively measure mobility. If our results and those of Murtagh *et al.* are considered together, it could be hypothesised that a decreasing TUG (mobility) score may, from 6 months before death, subsequently cause a decrease in KPS at 1 month before death. Further studies may test the relationship between the TUG and KPS.

As shown in Figure 2, changes in the TUG score were associated with changes in BI. While a statistical association does not necessarily prove causation, it would be reasonable that this result suggests that as mobility decreases, ADLs become more difficult. Consequently, maintaining mobility in this group of patients should enable them to maintain their independence and QoL for longer.

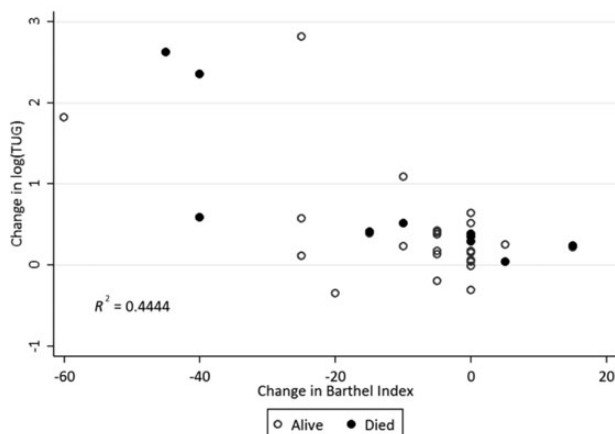


Fig. 2. Scatter plot of the overall change in the TUG score versus the change in BI for patients with more than one measurement ($n = 35$).

Table 2. Multivariable analysis of the TUG score

| | Unadjusted | | | Adjusted | | |
|----------------|------------|-------------|---------|----------|-------------|---------|
| | Estimate | 95% CI | P-value | Estimate | 95% CI | P-value |
| Alive | | | | | | |
| 6 versus 0 | 1.30 | (0.99–1.70) | 0.060 | 1.14 | (0.85–1.54) | 0.373 |
| 12 versus 6 | 1.07 | (0.87–1.32) | 0.505 | 0.99 | (0.77–1.26) | 0.907 |
| Died | | | | | | |
| 6 versus 0 | 2.24 | (1.16–4.32) | 0.017 | 1.09 | (0.51–2.34) | 0.821 |
| 12 versus 6 | 1.18 | (0.75–1.85) | 0.462 | 1.25 | (0.68–2.30) | 0.459 |
| Age | | | | 1.02 | (0.98–1.07) | 0.316 |
| Gender | | | | 1.12 | (0.69–1.84) | 0.638 |
| Stoke Comorb | | | | | | |
| 1 | | | | 1.44 | (0.80–2.59) | 0.217 |
| 2 | | | | 2.14 | (0.94–4.84) | 0.069 |
| Sentinel event | | | | 1.48 | (0.87–2.52) | 0.148 |
| eGFR | | | | 1.00 | (0.96–1.05) | 0.916 |
| Haemoglobin | | | | 0.96 | (0.80–1.15) | 0.654 |
| Albumin | | | | 0.90 | (0.84–0.97) | 0.005 |

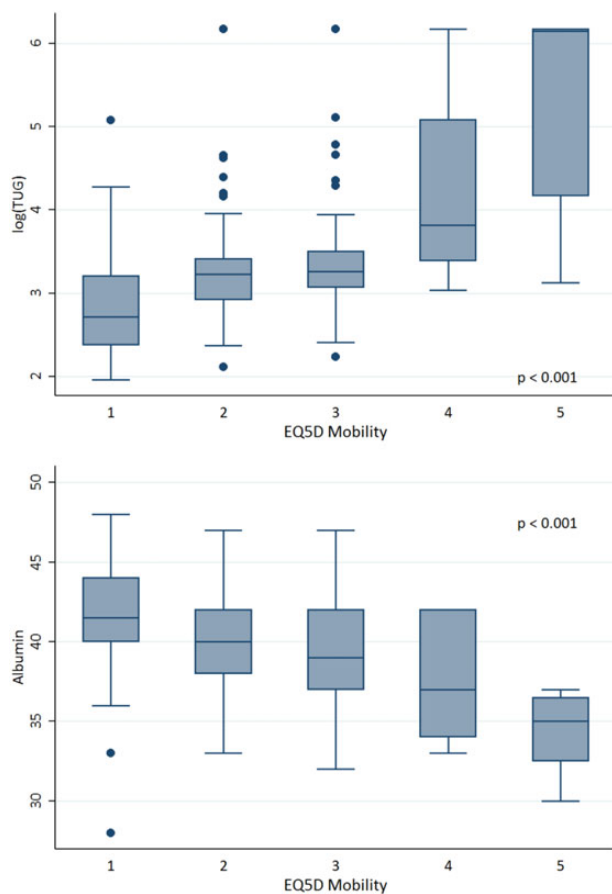


Fig. 3. Relationship between EQ-5D mobility, TUG score and serum albumin (g/dL).

In a *post hoc* multivariable analysis we analysed the relationship between the outcomes of interest and all the clinical variables measured. In this analysis we were able to show that the TUG, EQ-5D and BI were all associated with serum albumin; a lower serum albumin was associated with a higher TUG score and a lower EQ-5D and BI. Furthermore, there was a significant relationship between lower serum albumin and the risk of death. Consequently, lower serum albumin may potentially be used to identify patients likely to have lower functional capacity and be at increased risk of death. Similar associations have been shown in dialysis populations [20, 21]. Although a larger study [22] confirmed the association between serum albumin and mortality in ESRD CM patients, patients' functional status was not measured in this other study. Further prospective studies are required to determine the clinical utility of monitoring serum albumin in this way. This study did not address the mechanisms by which low serum albumin is associated with poorer functional status and increased mortality risk. It is known that serum albumin may be affected by chronic inflammation and proteinuria, but these were not measured as part of the study's protocol. Of interest, the only other significant association in this *post hoc* multivariable analysis was gender, with male gender being associated with an almost 6-fold increased risk of mortality. The cause of this is unclear and may be associated with the limitations of this study.

There are several limitations to this study. The numbers studied are small and it was a single-centre study where there was physiotherapy assessment and treatment available. More accurate trajectories could be determined by larger studies across

different centres. The trajectories obtained in this study may not be applicable to settings where physiotherapy services are not routinely available. The population we studied was elderly with significant comorbidity burden. We would caution against extrapolating these results to other ESRD CM patients who may have a different disease trajectory.

In this study we have showed there is a significant decline in functional status in the last 6 months before death in patients with ESRF who chose not to undergo dialysis, which can be measured objectively using the TUG test and subjectively using the EQ-5D. This is in contrast to a previously described trajectory of a sharp functional decline in the last few weeks of life in a similar patient population. Of interest, there was a significant relationship with lower serum albumin, functional decline and risk of death.

We hope through improved insight into the disease trajectories of our CM population and the impact this has on their QoL and symptom burden that we can improve our ability to identify and respond to the changing needs of these patients, facilitate complex and sensitive end-of-life discussions and consequently improve end of life care and support for the patients and caregivers.

Supplementary data

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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Conflict of interest statement

None declared.

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