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ORIGINAL ARTICLE

Structured clinical follow-up for CKD stage 5 may safely postpone dialysis

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Abstract
Background and objectives The optimal timing of dialysis initiation is still unclear. We aimed to ascertain whether a strict clinical follow-up can postpone need for dialysis in chronic kidney disease (CKD) stage 5 patients.
Design, setting, participants and measurements We reviewed records of all consecutive adult patients attending our conservative CKD stage 5 outpatient clinic from 2001 to 2010. Chronicity was defined as two consecutive estimated glomerular filtration rate (eGFR) measurements below 15 ml/min/1.73 m^2. Characteristics of subjects, including comorbidities, were assessed at baseline; blood pressure and serum markers of uremia were assessed both at first and last visit. GFR was estimated by the 4-variable Modification of Diet in Renal Disease (MDRD) formula.
Results In the 312 patients analyzed baseline eGFR was 9.7 ± 2.7 ml/min, which declined by 1.93 ± 4.56 ml/min after 15.6 ± 18.2 months. Age was inversely related to eGFR decline (r −0.27, p = 0.000). During conservative follow-up 55 subjects (18 %) died. In comparison with those eventually entering dialysis, deceased subjects were older and had a longer follow-up with no CKD progression. Multivariate analysis identified age, proteinuria and lower baseline K values as the only independent determinants of death. One hundred ninety-four subjects (66 %) started dialysis with an average eGFR of 6.1 ± 1.9 ml/min. During 35.8 ± 24.7 months of dialysis follow-up, 84 patients died. Multivariate analysis identified age as the main determinant of death (hazard ratio [HR] for every year 1.07, 95 % confidence interval [CI] 1.04–1.11, p 0.000). Patients starting dialysis with eGFR below the median, e.g. <5.7 ml/min, showed a better survival (HR for mortality 0.52, 95 % CI 0.30–0.89, p 0.016) than the other group.
Conclusions A well-organized nephrological outpatient clinic for conservative follow-up of CKD stage five patients can delay dialysis entry as long as 1 year. Starting dialysis with eGFR lower than 6 ml/min does not confer any increased risk of death in selected early-referral patients.

Keywords Survival · Chronic kidney disease · Dialysis · Progression of renal failure

Introduction

In accordance with guideline recommendations [1–3], a trend of increasing estimated glomerular filtration rate (eGFR) at the initiation of chronic dialysis has been observed over the past decade in the US [4, 5] and Europe [6]. Moreover, the median target eGFR selected by European nephrologists to start dialysis in uncomplicated patients has been 10 ml/min and even higher in the presence of signs and symptoms [7]. However, many reports have found increased mortality in those who started dialysis at higher eGFR [8–12]. According to some [11] but not all [12] studies, the paradox might be due to a higher number of coexisting comorbidities among patients who started dialysis early vs. late, or to the detrimental effect of dialysis initiation itself [13], or to the lead time bias, e.g. not taking into account the same starting point of chronic kidney disease (CKD) [14].

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The only prospective randomized trial aimed at shedding some light on the matter [15] suggests that starting dialysis treatment at low levels of eGFR may not be associated with further risk for uremic patients. However, due to many protocol violations, average eGFR at the time of initiation of dialysis was 9.8 ml/min in the late-start group, e.g. far above the targeted values. Thus, the optimal timing of dialysis initiation is still unclear. In clinical practice nephrologists have to find the right balance between the hazards of advanced uremia and of dialysis itself and in decision making it seems wise to rely more on clinical symptoms than on numerical criteria such as the eGFR [16].

Against this background, we reviewed the records of all consecutive patients attending our conservative CKD stage 5 outpatient clinic with the aim of ascertaining whether a strict clinical follow-up can prevent onset of uremic symptoms and, accordingly, may delay dialysis onset irrespective of eGFR value.

Methods

Since 2001 we have adopted a structured and comprehensive approach to CKD stage 5 outpatients. The cornerstone of our approach is: (1) healthcare team management (doctors, nurses, dieticians) of patients, (2) at least monthly clinical and biochemical controls, (3) check of therapy compliance and, whenever possible, direct administration of drugs by the clinic staff, i.e. monthly intravenous iron and/or subcutaneous long-acting erythropoiesis-stimulating agents (ESAs), (4) control of main biochemical serum markers of uremia, e.g. hemoglobin (Hb), bicarbonate (HCO_3), potassium (K), phosphorus (P) and parathyroid hormone (PTH), according to current guidelines [17], and (5) counselling for standard low sodium, low protein diet (<0.8 g/kg body weight). Patients are trained by skilled dieticians to follow the diet. Indications for starting dialysis are based more on doctors' clinical judgment, e.g. uncontrollable fluid overload, hypertension, nausea, anorexia, pericarditis and/or biochemical metabolic derangement not corrected by therapy, than on eGFR values.

Before attending our dedicated clinic, subjects were mainly followed by internists and nephrologists, including ourselves, in "standard" outpatient clinics and referred for dialysis evaluation, ours being the only Nephrological Unit for the 320.000 inhabitants living in Florence south municipality and Chianti area.

To be eligible for the study, adult subjects (aged 18 years or older) were required to have at least two consecutive eGFR values $\leq$15 ml/min/1.73 m^2 to confirm chronic kidney damage. From computerized clinical records we selected baseline parameters, e.g. age, gender, underlying renal disease (European Dialysis and Transplant Association [EDTA] code), comorbidities (classified qualitatively—yes or no—as cardiovascular, diabetes or other), 24-h urinary protein excretion (proteinuria), and antihypertensive therapy (yes/no).

Blood Pressure (BP) and main biochemical serum markers of uremia were retrieved both at study entry and at the last follow-up. Missing data at study entry or at the last follow-up were computed as the most recent registered data for that patient within the following or the preceding 3 months.

Patients were censored at dialysis start, at death or at 31/12/2010. Patients transferred, lost to follow-up or preemptively transplanted were regarded as censored at the date of the last documented medical examination. Whenever subjects started dialysis, we tracked their subsequent vital status till the end of 2010. Causes of death were classified as cardiovascular, infection, cachexia, neoplasia or other.

Serum creatinine was measured using a compensated modified Jaffe method with a Roche/Hitachi analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The method is standardized against isotope dilution mass spectrometry (IDMS) starting with a primary calibrator, e.g. the standard reference material 914. Making use of a standardized IDMS-traceable calibrated creatinine assay, we applied the re-expressed 4-variable Modification of Diet in Renal Disease (MDRD) equation for eGFR [18]. Proteinuria and serum biochemical parameters were analyzed by standard methods.

Statistics

Data were retrieved and handled in compliance with Italian privacy regulations (Garante law n. 133 of 6 August 2008, and subsequent amendments). Data are expressed as mean $\pm$ standard deviation (SD), median and interquartile range (IQR) or as percent frequency, as appropriate. For continuous variables analysis of variance (ANOVA) was performed to compare groups and post hoc analysis by Bonferroni was applied for multiple comparisons; the Mann–Whitney U test was applied for categorical variables. Simple linear correlations were performed by calculating the Pearson product moment correlation coefficient. Cox proportional hazards regression modelling was applied with the primary end-point as death from all causes; covariates tested included demography, clinical and biochemical parameters as well as comorbidities and antihypertensive therapy. All analyses were performed using the SPSS statistical package.

Results

Of the 410 incident subjects who attended our CKD stage 5 clinic in the period 2001–2010, 312 met the criteria for inclusion (Fig. 1). Baseline characteristics of this cohort are reported in Table 1. We were able to retrieve all parameters in all subjects except for proteinuria (proteinuria data were available for 240 patients). Of the 312 cohort patients, two-thirds were males. Overall, subjects were elderly and 25 % were very elderly, i.e. aged >79 years. As expected in view of elderly age, the most frequent underlying renal disease was vascular. For blood pressure, therapeutic goals were reached in the majority of cases by prescribing at least one antihypertensive drug. All subjects had at least one comorbidity, in particular cardiovascular. Proteinuria was high, e.g. 2.3 ± 2.4 g/die on average, being in the nephrotic range in 25 % of subjects.

In spite of the low baseline eGFR values, we maintained our cohort of 312 patients in conservative follow-up for an average 15.6 ± 18.2 months, median 9.1 [IQR 4.2–20.3]. During this period eGFR declined by an average 1.93 ± 4.56 ml/min. At univariate analysis, age was inversely related to both eGFR decline (r −0.27, p = 0.000) and proteinuria (r −0.16, p = 0.016).

Table 2 reports the main biochemical markers of uremia at the first and last ambulatory visit, according to the outcome. In comparison to those who eventually entered dialysis, patients who died during CKD follow-up were significantly older (Bonferroni p 0.000), had a significant longer follow-up (Bonferroni p 0.003) and significantly lower baseline K values (Bonferroni, p 0.001). Deceased patients had no CKD progression and stable clinical and biochemical parameters, all first-last comparisons being not significant. The most common causes of death were cardiovascular (47 %), neoplasia (15 %), and cachexia and/or infection (9 %).

Multivariate analysis (Table 3) identified age, proteinuria and lower baseline K values as the only independent determinants of death. Hb values were marginally significant. The other biochemical markers of uremia and clinical variables tested did not enter into the model.

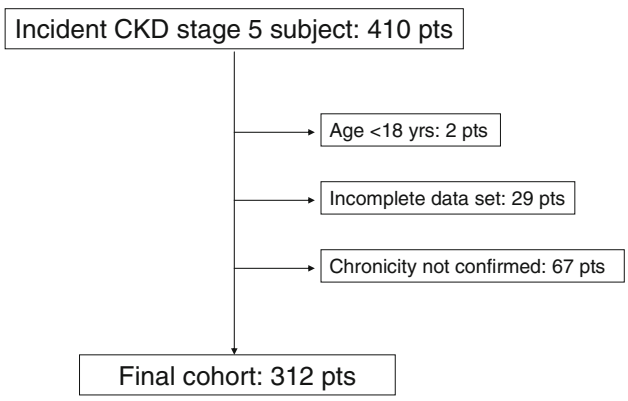

Fig. 1 Flowchart for enrolment of patients in the study

Table 1 Baseline characteristics of the 312 subjects recruited

Characteristics	Value
Age (years)	72 (62–79)
Male (%)	(64)
Systolic BP (mmHg)	150 (135–160)
Diastolic BP (mmHg)	80 (70–90)
Any antihypertensive treatment (%)	(85)
Renal Disease	
Vascular (%)	(25)
Glomerular (%)	(17)
Tubulo-interstitial or cystic (%)	(21)
Diabetes (%)	(19)
Undetermined (%)	(17)
Comorbidities	
Cardiovascular (%)	(67)
Diabetes (%)	(31)
Other (%)	(51)
Serum creatinine (mg/dl)	5.6 (4.9–6.7)
eGFR (ml/min/1.73 m^2)	9.5 (7.9–11.4)
Proteinuria (g/die)	1.4 (0.6–3.0)

Values are expressed as median [25–75 interquartile range] or (%), as appropriate

BP blood pressure, *eGFR* estimated glomerular filtration rate

After an average of 14 months of conservative follow-up (Table 2), 194 subjects started dialysis with an average eGFR 6.1 ± 1.9 ml/min. Dialysis modality was hemodialysis (HD) in 140 and peritoneal dialysis (PD) in 54 subjects. eGFR was 9.2 ± 2.7 ml/min in the former and 9.5 ± 3.1 ml/min in the latter group at baseline and 5.7 ± 1.8 ml/min and 6.6 ± 2.4 ml/min at dialysis start, respectively. All comparisons were not significant at ANOVA.

Table 4 shows clinical and biochemical parameters at dialysis start dichotomized for median eGFR. None of the parameters analyzed were significantly different among the two groups, except for a significantly higher percentage of diabetes in the higher eGFR group.

After an average 35.8 ± 24.7 months of follow-up 84 out of 194 patients (43 %) died, 38 among the 97 subjects starting dialysis with eGFR values below the median and 46 among the 97 starting dialysis with eGFR values above the median. The two groups had a comparable lead time, e.g. conservative plus dialysis follow-up. Death prevalence was similar in HD and PD, being 43.6 and 42.6 %, respectively. Fifty-three percent of patients died of cardiovascular disease, 21 % of cachexia and/or infection, and 13 % of neoplasia.

Table 2 Main markers of uremia at the first and last outpatient visit, according to outcome

	Still in FU	Death	Dialysis	Other[a]
n (%)	41 (13)	55 (18)	194 (62)	22 (7)
Age at baseline (years)	72.3 ± 14	78.8 ± 7.2	66.4 ± 14.5	64.5 ± 13.0
FU (months)	16.7 ± 1.6	23.9 ± 27.8	13.9 ± 15.6	10.0 ± 11.6
eGFR (ml/min 1.73 m^2)				
First	11.2 ± 2.9	9.5 ± 2.0	9.4 ± 2.7	9.5 ± 2.8
Last	10.9 ± 3.9	9.8 ± 4.9	6.1 ± 1.9	9.0 ± 1.8
Systolic BP (mmHg)				
First	146 ± 27	145 ± 22	149 ± 19	147 ± 19
Last	148 ± 23	143 ± 21	151 ± 21	149 ± 24
Diastolic BP (mmHg)				
First	78 ± 11	78 ± 11	82 ± 11	79 ± 12
Last	76 ± 11	76 ± 11	81 ± 10	80 ± 9
Hb (g/dl)				
First	11.3 ± 1.3	10.8 ± 1.2	10.9 ± 1.7	10.3 ± 1.7
Last	11.6 ± 1.5	11.0 ± 1.5	10.7 ± 1.5	11.0 ± 1.4
HCO_3 (mmol/l)				
First	22.6 ± 5.6	23.0 ± 4.6	21.0 ± 4.3	21.0 ± 4.1
Last	23.3 ± 4.7	22.0 ± 4.2	22.0 ± 4.4	21.0 ± 3.6
K (mmol/l)				
First	4.8 ± 0.5	4.4 ± 0.7	4.9 ± 0.8	4.6 ± 0.9
Last	4.5 ± 0.7	4.7 ± 0.8	4.9 ± 0.8	4.9 ± 0.5
P (mg/dl)				
First	4.5 ± 1.1	4.9 ± 1.2	5.2 ± 1.3	5.3 ± 1.2
Last	4.5 ± 1.1	5.0 ± 1.6	6.1 ± 1.7	5.6 ± 1.7
PTH (pg/ml)				
First	269 ± 228	230 ± 244	266 ± 221	292 ± 267
Last	289 ± 363	204 ± 121	321 ± 382	256 ± 155

First–last: clinical and biochemical data retrieved at first and last outpatient visit. For statistics see text

FU follow-up, *eGFR* estimated glomerular filtration rate, *BP* blood pressure, *Hb* hemoglobin, HCO_3 bicarbonate, *K* potassium, *P* phosphorus, *PTH* parathyroid hormone

[a] 8 pre-emptive transplant, 14 lost to follow up or transferred

Table 3 Final Cox proportional hazards analysis for death in conservative CKD stage 5 subjects

	Wald	Sig.	Exp(B)	95 % CI for Exp(B)	
				Lower	Upper
Age	18.3	0.000	1.156	1.081	1.235
Proteinuria	11.5	0.001	1.472	1.177	1.841
K	4.9	0.027	0.555	0.329	0.935
Hb	2.8	0.094	1.28	0.96	1.72

CKD chronic kidney disease, *CI* confidence interval, *K* potassium, *Hb* hemoglobin

Table 4 Parameters for eGFR above and below the median

	eGFR <5.7 ml/min (n = 97)	eGFR ≥5.7 ml/min (n = 97)	Statistics[a]
Age (years)[b]	66.7 ± 13.5	66.3 ± 15.3	ns
Cardiovascular comorbidities (%)[b]	65	70	ns
Diabetes (%)[b]	22	39	0.004
Other comorbidities (%)[b]	49	42	ns
Antihypertensives (yes %)[b]	81	80	ns
eGFR (ml/min)[c]	4.77 ± 0.69	7.49 ± 1.72	–
Systolic BP (mmHg)[c]	150 ± 20	153 ± 22	ns
Diastolic BP (mmHg)[c]	82 ± 11	80 ± 10	ns
Hb (g/dl)[c]	11.0 ± 1.4	10.8 ± 1.5	ns
HCO3 (mmol/l)[c]	21.5 ± 4.8	21.5 ± 4	ns
K (mmol/l)[c]	4.9 ± 0.7	4.8 ± 0.9	ns
P (mg/dl)[c]	6.3 ± 1.8	5.9 ± 1.4	ns
PTH (pg/ml)[c]	357 ± 450	280 ± 298	ns
CDK FU (months)	15.1 ± 16.4	12.5 ± 14.6	ns
Dialysis FU (months)	34.6 ± 24.2	36.9 ± 25.2	ns
Lead time (months)[d]	49.7 ± 33.1	49.4 ± 31.5	ns

eGFR estimated glomerular filtration rate, *BP* blood pressure, *Hb* hemoglobin, HCO_3 bicarbonate, *K* potassium, *P* phosphorus, *PTH* parathyroid hormone, *CDK* chronic kidney disease, *FU* follow-up

[a] ANOVA for continuos variables, Mann–Whitney U test for categorical variables

[b] Determined at baseline

[c] Determined at dialysis start

[d] Lead time = CKD + dialysis follow-up

Multivariate Cox analysis identified age as the main determinant of death (HR for every year 1.07, 95 % confidence interval [CI] 1.04–1.11, p 0.000). Also, dichotomized eGFR (Fig. 2) explained mortality with significantly better survival observed in those starting dialysis with eGFR below 5.7 ml/min (hazard ratio [HR] for mortality 0.52, 95 % CI 0.30–0.89, p 0.016). Blood pressure and biochemical parameters at the time of dialysis initiation did not enter into the model.

Discussion

The main finding of this study is that a careful clinical monitoring of CKD stage 5 patients allowed us to postpone the start of dialysis until eGFR values were much lower than those recommended. This delay took place safely in that: (1) during the time of conservative follow-up we were able to dissociate CKD progression assessed by eGFR from clinical and biochemical markers of uremia, (2) for the

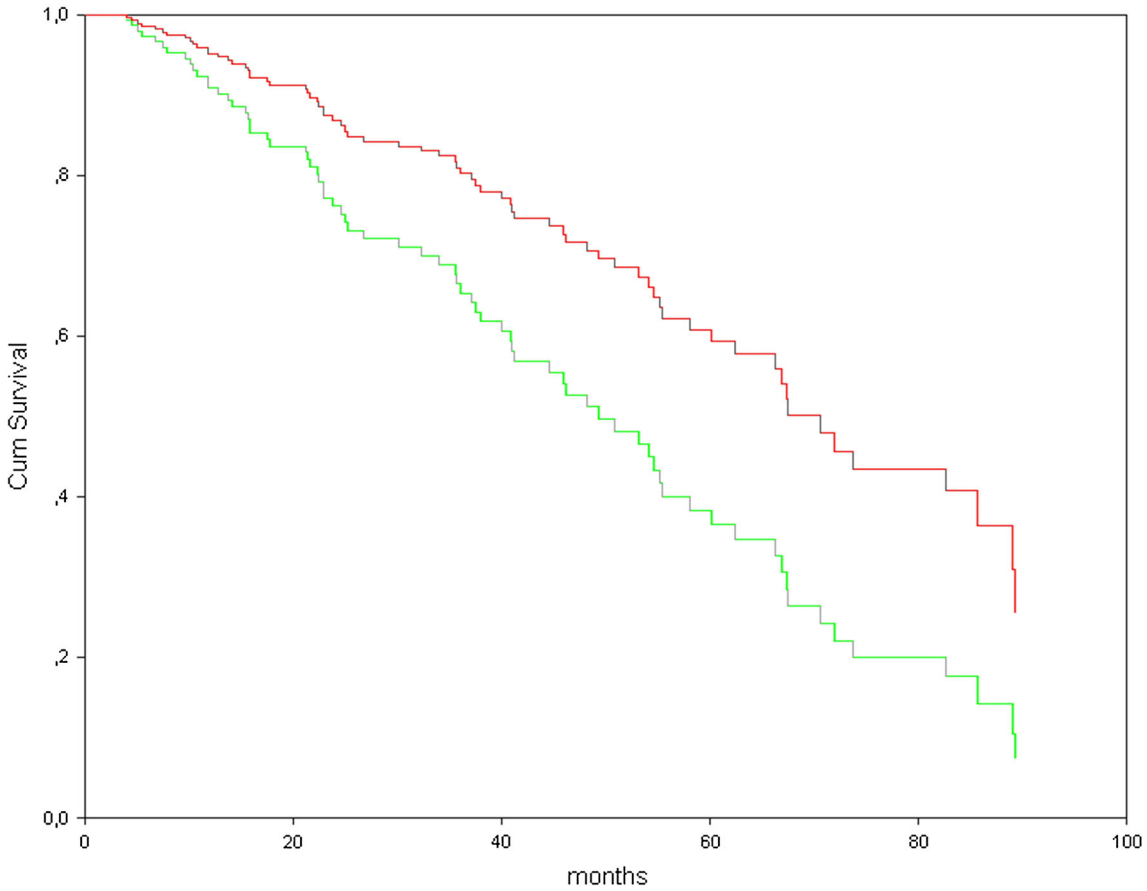

Fig. 2 Cumulative survival function for subjects starting dialysis with eGFR below or above median values. *eGFR* estimated glomerular filtration rate. *Red line* <the median (5.7 ml/min); *green line* >the median (5.7 ml/min)

same lead time, we found a better survival in patients starting dialysis with lower eGFR.

At CKD stage 5, nephrologists should evaluate the benefits, risks and disadvantages of beginning renal replacement therapy. According to European Best Practice Guidelines (EBPG) guidelines "To ensure that dialysis is started before the GFR is <6 ml/min/1.73 m2, clinics should aim to start at 8–10 ml/min/1.73 m^2" [3]. In our cohort, the average eGFR at first attendance at the outpatient CKD stage 5 clinic was 9.7 ml/min, which is the value that would indicate the need to prepare for dialysis. Despite this, we maintained our patients in conservative follow-up for more than 1 year, e.g. 16 months on average. Benefits of pre-dialysis care and educational intervention have been recognized in the literature [19–21]. In a prospective randomized study, Brunori et al. [22] obtained similar results utilizing a vegan diet in non diabetic subjects aged >70 years. Our retrospective study included also diabetics and patients younger than 70 years. But what matters more here, we did not go through extreme diets, limiting counseling to a balanced low protein diet, certainly more palatable and less expensive than Brunori's very low protein diet supplemented with amino acids.

Overall, 56 % (109/194) of our patients started dialysis with eGFR values equal to or lower than 6 ml/min. This prevalence is 2–3 times higher than that reported in 2003 in Europe [6] and in the French renal epidemiology and information network (REIN) registry from 2002 to 2006 [11]. Starting dialysis at such a low eGFR did not undermine control of hypertension, anemia, acidosis, hyperkalemia, hyperphosphoremia or hyperparathyroidism (Table 2) and this holds true also when the population was dichotomized according to whether eGFR at dialysis start was below or above the median (Table 4). That is to say, the subgroup of patients starting dialysis with an average 4.8 ml/min eGFR had the same metabolic control as the subgroup starting dialysis with an average 7.5 ml/min eGFR.

Over a period of 10 years, recommendations on the clinical management of CKD stage 5 have changed. We cannot exclude that this has affected some of our patients; however, our overall approach to treatment has remained

essentially unchanged as far antihypertensives, diuretics, recombinant human erythropoietin doses, phosphate binders, calcium, and vitamin D supplements as well as sodium bicarbonate are concerned. As a matter of fact, the clinical control of uremia-related metabolic derangement represented a significant advantage from the stand point of safety. Indeed, the 43 % unadjusted 3-year mortality rate since the start of dialysis of our study is in line with the 30 % 2-year mortality found among European subjects starting dialysis with eGFR <8 ml/min [10]. On these grounds, we note the significantly better survival of the patients starting dialysis with eGFR values below in comparison to above the median cohort (Fig. 2). Far from being surprising, this result is in line with the literature. The overwhelming majority of studies addressing survival versus eGFR at dialysis initiation have found a survival advantage for late dialysis initiation [8–14]. Our study adds the novel notion that this holds true also for eGFR values as low as 5–6 ml/min. It is relevant that, at variance with some previous studies, our results were fully adjusted not only for comorbidities but also for the so-called lead time bias [14] since our whole cohort was followed up from the same starting point of CKD. Interestingly, baseline plasma K levels were significantly lower in the deceased group in comparison to the dialysis group, and emerged as an independent predictor of death in the Cox model, e.g. the lower the baseline K plasma levels the higher the mortality. We would be tempted to attribute this intriguing result to an excessive use of diuretics in our CKD stage 5 frail and elderly population, but we have not enough data to substantiate this hypothesis.

Baseline proteinuria was high in the majority of our CKD stage 5 subjects, being in the nephrotic range in 25 % of them. This is not the case in our background aged population, since in the inCHIANTI study spot urinary protein excretion was absent in the overwhelming majority of the cohort and very mild when detectable [23]. In our conservative managed subjects proteinuria was a powerful and independent predictor of death. End-stage renal disease (ESRD) and death are competing risk events. In US veteran patients O'Hare et al. [24] demonstrated that age is a major effect modifier among patients with CKD stage 3–5. Specifically, in patients 65–84 years old with CKD stage 5 the risk of ESRD exceeded the risk of death. In accordance with O'Hare et al.'s data, 62 % of our patients progressed to ESRD and only 18 % died. The latter was a very old cohort, the average age at death being 81 years. In this cohort eGFR did not progress during the average 2-year follow-up, but instead it slightly improved as did all the markers of uremia (Table 2). In other words, our elderly subjects with CKD stage 5 died prevalently of cardiovascular or neoplastic events with no CKD progression or metabolic derangement. This reinforces the thesis that in very old patients with high comorbidity the survival advantage conferred by renal replacement therapy over conservative management is likely to be small [25]. That age is inversely related to eGFR decline both in the general population and in CKD subjects has been repeatedly demonstrated in the literature [17, 23]. The inverse relation between age and proteinuria is in line with the much higher prevalence of non-proteinuric nephropathies, e.g. atherosclerosis, in the elderly than in the young. Finally, we wish to point out the good number (n = 8) of pre-emptive transplantations performed. This is due to both our structured approach and Tuscany's transplant policy.

There are a number of drawbacks in our study, namely its retrospective nature and lack of a refined assessment of patient frailty, including nutrition-inflammation status. Caution is thus warranted in the interpretation of our results. Moreover, this is a single-center study with a single model of CKD care. Therefore the generalizability of our results remains an open question. Strengths of our study are the good quality of parameters retrieved directly and not reworked to adjust for case mix, as often happens in large registry studies; moreover, at variance with previous studies on the prognosis of CKD subjects, we performed analyses from the same starting point of CKD progression, thus avoiding lead time bias, and followed our patients even after they started dialysis.

In conclusion, a well-organized nephrological outpatient clinic for conservative follow-up of CKD stage 5 subjects can postpone the need to start dialysis for up to 1 year or more. Delaying the dialysis initiation does not jeopardize patients and starting dialysis at eGFR lower than 6 ml/min does not confer an increased risk of death in selected early-referral patients. The subgroup of very old subjects tends to progress very slowly. In decision making as to whether or not start dialysis, clinical symptoms are of greater relevance than eGFR.

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Conflict of interest The authors declare no conflict of interest.

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