ORIGINAL ARTICLE

Nephrol Dial Transplant, 2023, **38**, 2494–2502
https://doi.org/10.1093/ndt/gfad091
Advance access publication date: 16 May 2023

Clinical and patient-reported trajectories at end-of-life in older patients with advanced CKD

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ABSTRACT

Background. We explore longitudinal trajectories of clinical indicators, patient-reported outcomes, and hospitalizations, in the years preceding death in a population of older patients with advanced chronic kidney disease (CKD).

Methods. The EQUAL study is a European observational prospective cohort study with an incident eGFR <20 ml/min per 1.73 m^2 and ≥65 years of age. The evolution of each clinical indicator was explored using generalized additive models during the 4 years preceding death.

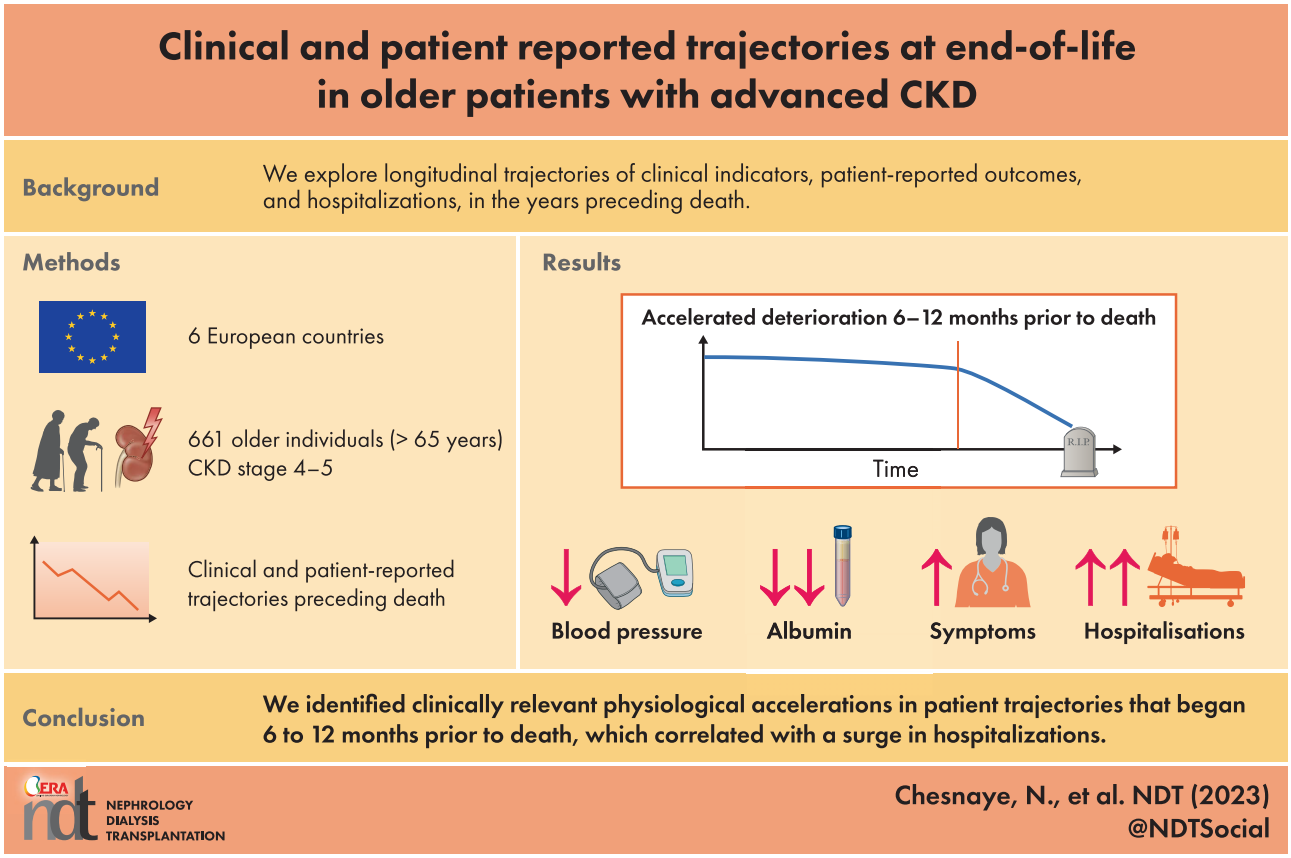
Results. We included 661 decedents with a median time to death of 2.0 years (IQR 0.9–3.2). During the years preceding death, eGFR, Subjective Global Assessment score, and blood pressure declined, with accelerations seen at 6 months preceding death. Serum hemoglobin, hematocrit, cholesterol, calcium, albumin, and sodium values declined slowly during follow-up, with accelerations observed between 6 and 12 months preceding death. Physical and mental quality of life declined linearly throughout follow-up. The number of reported symptoms was stable up to 2 years prior to death, with an acceleration observed at 1 year prior to death. The rate of hospitalization was stable at around one hospitalization per person year, increasing exponentially at 6 months preceding death.

Conclusions. We identified clinically relevant physiological accelerations in patient trajectories that began ~6 to 12 months prior to death, which are likely multifactorial in nature, but correlate with a surge in hospitalizations. Further research should focus on how to effectively use this knowledge to inform patient and family expectations, to benefit the planning of (end-of-life) care, and to establish clinical alert systems.

Keywords: chronic kidney disease, end-of-life, mortality

Received: December 19, 2022; Editorial decision: April 6, 2023

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- People suffering from CKD have a considerably higher mortality risk than the general population, and a large body of literature exists on the various clinical and demographic factors affecting mortality risk. Clinically relevant physiological changes may start months or years leading up to death, but can only be detected using longitudinal information in decedents.

What this study adds?

- This is the first European study to explore the evolution of both clinical parameters and PROMs in the years preceding death in advanced CKD decedents. Distinct accelerations in trajectories were detected for cardiovascular and nutritional indicators, as well as for hemoglobin and albumin, marking the metabolic and physiological changes that occur as death nears.

What impact this may have on practice or policy?

- The trajectories reported in this large multi-national prospective cohort study will usefully inform patient and family expectations, benefit the planning of (end-of-life) care, and help establish clinical alert systems to optimize timely intervention.

INTRODUCTION

Chronic kidney disease (CKD) is one of the most prevalent non-communicable diseases worldwide, affecting >840 million adults [1]. People suffering from CKD have a considerably higher mortality risk than the general population, especially those who are older and in the more advanced stages of the disease [2]. A large body of literature exists on the various clinical and demographic factors affecting mortality risk in the CKD population [3]. Typically, evidence is derived from the association between the risk factor and the time to death in the CKD population at large. As this type of analysis is performed in both survivors and decedents, and often uses a single risk factor measurement (at baseline), it precludes investigation into how risk factors evolve longitudinally in the proximity of death. Clinically relevant physiological changes may start months or even years leading up to death, and can only be detected using longitudinal information specifically in decedents. The nature of the physiological changes preceding death may yield valuable information depending on when they occur (i.e. leaving sufficient time for intervention), and whether they are modifiable.

The "terminal decline" framework is commonly used in gerontological and palliative care research to provide insights into mortality-related processes, such as functional decline, that occur during the final years of life [4, 5]. The terminal decline

hypothesis postulates that the last years of life encompass two phases; a "pre-terminal" phase characterized by a stable functional decline, followed by the "terminal" phase of accelerated decline (i.e. terminal drop) as death nears. This method uses a death-anchored approach (i.e. time to death) to model follow-up time, which may better characterize late-life health changes compared with chronological age [6]. Exploring the evolution of these processes in CKD decedents, as well as establishing the tipping points for the transition from the pre-terminal to the terminal-phase, may benefit the planning of (end-of-life) care, and the development of alert systems to optimize timely intervention, as well as help inform patient and family expectations.

Previous research using the terminal decline framework in CKD has focused on symptom burden and functional status in conservatively managed stage 5 CKD patients [7, 8], showing a steep increase in symptom burden and a steep decline in functional status in the months preceding death. However, evidence on the evolution of other clinical indicators prior to death in the advanced CKD population as a whole is scarce. Physiological trajectories related to renal-, cardiovascular-, and other biochemical processes, as well as trajectories concerning quality of life and symptom burden may yield valuable information pertinent to the planning of care. Therefore, the current study aims to explore longitudinal trajectories of clinical indicators, symptom burden, quality of life, and hospitalizations, in the years preceding death in a population of older patients with advanced CKD.

MATERIALS AND METHODS

Study design and population

The European QUALity Study on treatment in advanced CKD (EQUAL) is an ongoing observational multicenter cohort study including CKD patients of 65 years of age and older, with an incident eGFR <20 ml/min/1.73 m^2 not on dialysis, receiving routine medical care in Germany, Italy, the Netherlands, Poland, Sweden, and the UK. Participants were excluded if the drop in eGFR resulted from an acute event or if they had previously received dialysis or a kidney transplant. For the current study, decedents were selected from the EQUAL cohort by including all participants that had died between April 2012 and January 2022. Approval was obtained from the medical ethical committees in each country. Informed consent was obtained from all participants. A full description of the study has been published elsewhere [9].

Data collection

Clinical data were collected on demographics, primary kidney disease, laboratory data, medication, nutritional status, lifestyle, symptoms, health-related quality of life (HRQOL), hospitalizations, and comorbid conditions. Study visits and data collection were scheduled at 3- to 6-month intervals, and participants were followed for 4 years or until kidney transplantation, death, refusal for further participation, and loss to follow-up. eGFR was calculated from serum creatinine level standardized to isotope dilution mass spectrometry using the CKD-EPI equation. Albumin-creatinine ratio was also determined following routine 24-hour urine collection or a single sample if 24-hour urinary collection was unavailable. Primary kidney disease was classified using the codes of the European Renal Association [10]. HRQOL and symptoms was collected through self-administered paper questionnaires. HRQOL was measured using the SF36, a 36-item questionnaire measuring HRQOL on eight domains, resulting in an overall Physical Component Summary and a Mental Component Summary score. Nutritional status was assessed using the 7-point Subjective Global Assessment (SGA) scale [11]. The uremic symptoms burden was measured using the Dialysis Symptom Index which comprises 30 symptoms [12], adapted to include items on bleeding, weight loss, and loss of strength. We report the total number of symptoms ranging from 0 to 33.

Statistical analysis

The evolution of each clinical indicator over time was explored using generalized additive models (GAM). Follow-up time was anchored at death, and inverted either up to 4 years in the past or up to the date of the first study visit. GAMs do not assume any specific functional form and can be used to reveal non-linear time effects using splines [13]. We used thin-plate regression splines, which place a knot at each unique time value, thus avoiding having to choose an appropriate number and placement of knots [14]. The smoothing parameter (i.e. amount of "wiggliness") was also determined by the model using restricted maximum likelihood [15]. A random intercept was included to capture the variation in baseline values between individuals, and a random slope for time to capture variability in individual's trajectories.

To test the terminal decline hypothesis, for each clinical indicator we tested whether a non-linear term provided a significantly better fit than a simple linear model. If this was the case, we attempted to find a change point, defined as a statistically significant acceleration—or deceleration—in trajectory. We calculated the first derivative (rate of change) across the full length of the trajectory. Taking the (model-based) rate of change at $t = -4$ years as the comparison value, statistical significance was met where the 95% confidence interval of the rate of change—at any point in time—did not include the value for the rate of change at $t = -4$ years [16]. In case multiple change points were identified, we selected the point in time closest to death. The analyses were stratified by sex and diabetes. The effect of dialysis status on trajectories was explored (i) through a dialysis-time interaction term, and (ii) by censoring at dialysis. The rate of hospitalization (per person year) at any given time during follow-up was estimated non-parametrically by the hazard function and smoothed using B-splines. Missing measurements were dealt with through pairwise deletion. All analyses were performed in R v.4.0.2 (R Core Team, Vienna, Austria).

RESULTS

Participant characteristics at inclusion

Table 1 describes the characteristics of the 661 decedents and 1075 survivors at inclusion in the EQUAL cohort. Compared with survivors, decedents were older, more likely to be male, widowed, current- or ex-smokers, suffer from hypertension as the primary cause of kidney disease, and have a higher systolic blood pressure. Decedents had a poorer nutritional status, lower levels of serum albumin, potassium, sodium, hemoglobin, and cholesterol, but higher levels of uric acid and parathyroid hormone. Furthermore, they suffered more often from pre-existing comorbidities, especially cardiovascular comorbidities, and reported both lower mental and physical HRQOL scores at inclusion. The proportion of missing values is provided in Table S1, and over time in Figure S8.

Table 1: Clinical characteristics at inclusion for decedents and survivors in the European QUALity Study on treatment in advanced CKD (EQUAL). Continuous variables are expressed as mean (SD) except for ACR, which is presented as median [interquartile range (IQR)]. Categorical variables are expressed as *n* (%). BMI, body mass index; Hb, hemoglobin; PO4, phosphate; ACR, albumin-creatinine ratio; PTH, parathyroid hormone.

	Survivors (*n* = 1075)	Decedents (*n* = 661)
Demographics		
Age	75.3 (6.5)	77.9 (6.7)
Men	674 (62.7)	460 (69.6)
Primary kidney disease		
Glomerular disease	117 (11.1)	42 (6.4)
Tubulo-interstitial disease	108 (10.2)	38 (5.8)
Diabetes	211 (20.0)	140 (21.5)
Hypertension	359 (34.0)	254 (39.0)
Miscellaneous renal disorders	261 (24.7)	178 (27.3)
Marital status		
Married	575 (66.6)	315 (60.8)
Divorced	60 (7.0)	40 (7.7)
Widowed	187 (21.7)	146 (28.2)
Never married	41 (4.8)	17 (3.3)
Education level		
Low education	255 (29.5)	171 (32.9)
Intermediate education	471 (54.5)	276 (53.2)
High education	138 (16.0)	72 (13.9)
Smoking status		
Current smoker	61 (7.0)	59 (11.4)
Ex-smoker	467 (53.9)	281 (54.5)
Never	338 (39.0)	176 (34.1)
Physical		
Weight (kg)	79.7 (16.4)	80.2 (18.7)
Height (cm)	167.4 (10.1)	168.0 (9.6)
BMI (kg/m^2)	28.5 (5.1)	28.3 (5.7)
Waist (cm)	103.3 (13.8)	104.4 (14.9)
SGA	6.0 (1.0)	5.8 (1.0)
Systolic blood pressure (mmHg)	141.5 (20.4)	144.6 (24.4)
Diastolic blood pressure (mmHg)	74.3 (11.0)	73.2 (11.6)
Pulse pressure (mmHg)	67.3 (18.5)	71.4 (21.8)
Heart rate (bpm)	71.4 (12.3)	70.4 (12.6)
Blood chemistry		
Albumin (g/dl)	38.1 (5.8)	37.1 (6.0)
Calcium (mmol/l)	2.3 (0.2)	2.3 (0.2)
PO4 (mmol/l)	1.3 (0.3)	1.3 (0.3)
Potassium (mmol/l)	4.7 (0.6)	4.6 (0.6)
Sodium (mmol/l)	140.2 (3.2)	139.8 (3.6)
Urea (mg/dl)	20.9 (9.2)	21.1 (8.2)
Bicarbonate (mmol/l)	23.2 (3.8)	22.9 (4.2)
Uric acid (µmol/l)	416.7 (131.0)	433.7 (153.8)
PTH (pmol/l)	18.5 (16.3)	20.6 (17.1)
Hb (mmol/l)	7.3 (0.9)	7.1 (1.0)
Ht (%)	35.7 (4.4)	35.1 (4.6)
Cholesterol (mmol/l)	4.6 (1.3)	4.4 (1.3)
Renal		
eGFR (ml/min/1.73 m^2)	17.5 (5.8)	17.0 (5.1)
ACR (median [IQR])	29.6 [4.3, 137.0]	45.6 [7.3, 178.9]
Creatinine (µmol/l)	291.8 (101.3)	294.3 (92.6)
Comorbidities		
Charlson comorbidity score	6.81 (1.82)	7.65 (1.87)
Diabetes	423 (40.6)	293 (45.5)
Chronic heart failure	141 (14.0)	158 (25.2)
Cerebrovascular disease	139 (13.5)	119 (18.6)
Peripheral vascular disease	152 (14.8)	136 (21.6)
Myocardial infarction	157 (15.1)	137 (21.3)
Angina pectoris	129 (12.6)	117 (18.5)
Left ventricular hypertrophy	205 (22.5)	160 (27.0)
Atrial fibrillation	151 (14.6)	156 (24.6)
Hypertension	905 (89.3)	558 (88.7)
Pulmonary	143 (13.9)	121 (19.0)
Psychiatric	60 (5.8)	53 (8.3)
Malignancy	205 (19.9)	146 (23.0)
Patient-reported outcomes		
Mental health score	68.3 (22.7)	62.7 (22.3)
Physical health score	53.3 (23.4)	44.5 (20.3)
Symptom burden	12.3 (6.5)	13.0 (6.1)

Longitudinal follow-up preceding death

During the maximum of 4 years of follow-up preceding death, we included 3212 visits in 661 decedents covering a total of 1314 patient follow-up years, with a median of 5 (IQR 3–7) measurements per patient, and a median follow-up time of 2.0 years (IQR 0.9–3.2). Patients were treated on dialysis 26% (337 years) of the total follow-up time, and 201 (31%) patients died while on dialysis. Figure 1 provides the population average trajectories for various clinical indicators in decedents during the 4 years preceding death. The causes of death are provided for decedents in Figure S1.

Trajectories of renal function preceding death

eGFR and creatinine levels worsened steadily during 4 years of follow-up, with a slight acceleration in decline seen at 6 months preceding death. ACR increased linearly throughout follow-up (Fig. 1).

Trajectories of nutritional indicators preceding death

Both body weight and BMI declined slowly during follow-up, accelerating slightly at just over a year prior to death. SGA on the other hand declined steadily during follow-up, followed by a sharp drop at 6 months preceding death (Fig. 1).

Trajectories of cardiovascular indicators preceding death

Both diastolic and systolic blood pressure declined slowly during follow-up, accelerating at ∼6 months preceding death, with a steeper drop observed for systolic blood pressure. Conversely, heart rate increased slowly during follow-up, accelerating sharply at ∼6 months preceding death (Fig. 1).

Trajectories of blood chemistry preceding death

Serum hemoglobin, hematocrit, cholesterol, calcium, albumin, and sodium values declined slowly during follow-up, with accelerations observed between 6 and 12 months preceding death. The decline in serum albumin accelerated particularly steeply at 6 months. Potassium declined steadily, and started increasing at 11 months prior to death. Urea increased throughout follow-up, accelerating at 0.7 years prior to death. Phosphate levels increased during follow-up, with acceleration starting at 2.6 years prior to death. Uric acid decreased- and PTH increased linearly

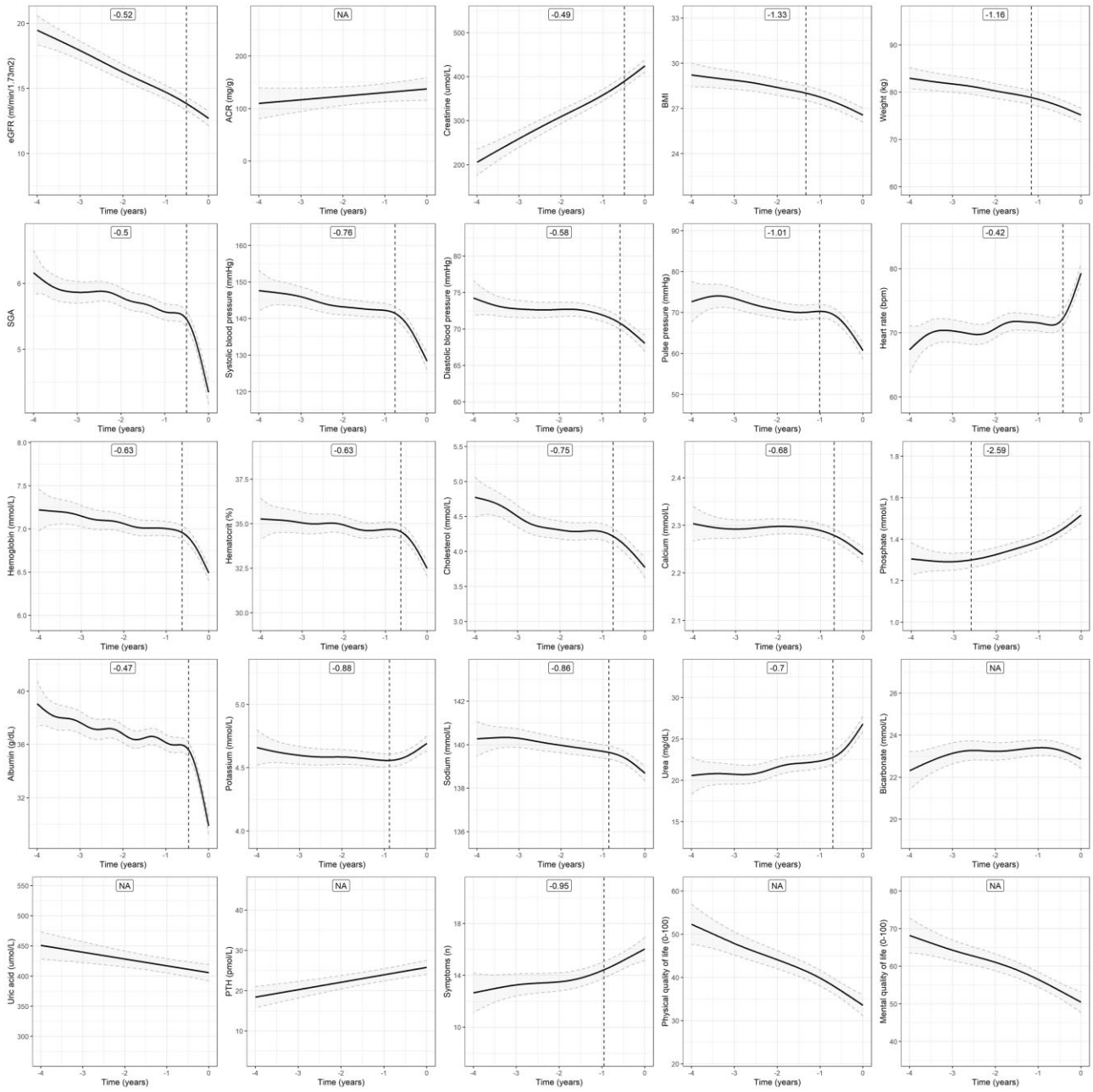


Figure 1: Trajectories of clinical indicators in decedents with 95% confidence intervals. The y-axes for all plots were scaled to +1 and −1 standard deviations from the mean to allow for comparisons across indicators. The estimated change points are provided in years and depicted by dotted lines.

throughout follow-up. No discernable pattern was observed for serum bicarbonate (Fig. 1).

Trajectories of patient-reported outcomes preceding death

Both physical and mental quality of life declined linearly throughout follow-up. The number of reported symptoms was stable up to ∼2 years prior to death, with an increase observed at 1 year prior to death (Fig. 1).

Subgroup analyses

Figure S2 provides the trajectories for clinical indicators in decedents during the 4 years preceding death stratified by sex, Figure S3 by dialysis status, and Figure S4 by diabetes. Patterns were mostly similar by sub-groups, with a few notable exceptions. Compared with men, trajectories for cholesterol in women were more stable during follow-up, but dropped more steeply during the final year of life. Women reported overall lower quality of life scores and a higher number of symptoms. Symptom burden and physical quality of life were more stable in women during follow-up, but accelerated prior to death. Censoring at dialysis initiation provided results similar to the main findings (Figure S5).

Hospitalizations

Figure 2 provides the rate of hospitalizations during the 4 years preceding death. The reasons for hospitalization are provided in

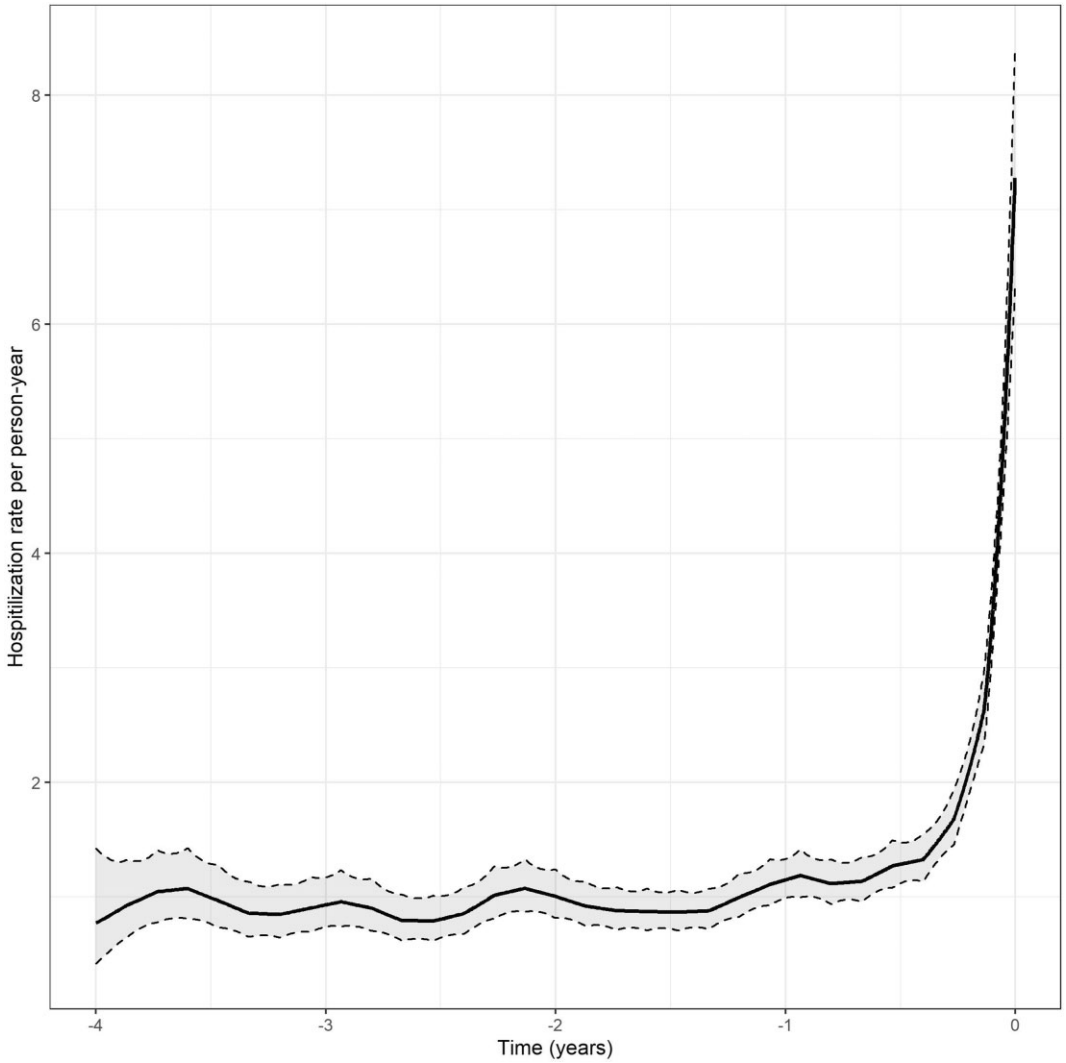


Figure 2: The rate of hospitalization in the 4 years preceding death.

Figure S6. The rate of hospitalization was stable at around one hospitalization per person year, increasing exponentially at ∼6 months preceding death.

Sensitivity analyses

Results were similar in the subgroup of patients ($n = 433$) with at least three measurements and at least 1 year of pre-mortality follow-up (Figure S7).

DISCUSSION

This is the first multi-national study to explore the evolution of both clinical parameters and PROMs in the years preceding death in a European population of stage 4 and 5 CKD decedents. Although this descriptive study is unable to prove causation, we hope it will contribute to our limited understanding of the biological dying process in CKD, which in turn will aid the planning of (end-of-life) care, as well as help inform patient and family expectations. Using the terminal decline framework, we identified tipping points for the transition from the pre-terminal to the terminal-phase, observed mostly between 1 year and 6 months prior to death, which coincided with an acceleration in hospitalization rate. Distinct accelerations in clinical trajectories were detected for cardiovascular and nutritional health indicators, as well as for serum hemoglobin and albumin, marking the metabolic and physiological changes that occur as death nears. The identification of these tipping points may provide valuable prognostic information; however, more research is required to determine how this longitudinal information could best be included into prognostic models.

The longitudinal evolution of serum albumin was characterized by a steady decline, followed by a marked drop at 6 months prior to death. Whereas low serum albumin is a well-established predictor of mortality, disease progression, and other adverse outcomes in CKD patients [17, 18], we are unaware of any previous work describing the distinct acceleration found at the 6-month mark preceding death. Interestingly, serum albumin has also been identified as a biomarker of dying in cancer patients in the last months of life [19]. As administration of albumin in patients with hypoalbuminemia seems to have no effect on improving outcomes, serum albumin should be viewed as a marker of an

underlying disease and not as a directly modifiable factor [20]. Impaired serum albumin homeostasis and its accelerating decline is likely multifactorial in nature, reflecting a worsening systemic inflammatory state, metabolic acidosis, hepatic dysfunction, and protein energy wasting [21–23]. The SGA, which measures protein energy wasting, followed a similar pattern of decline, indicative of a common biological process of dying, with both indicators dropping a full standard deviation between the 6-month mark and death.

Other biochemical markers such as hemoglobin, cholesterol, calcium, urea, potassium, and sodium, followed a similar pattern of acceleration into death, and may also be attributed to a worsening systemic inflammatory state and organ dysfunction. Phosphate levels are determined by two main opposing forces; renal function and protein intake. Assuming that protein intake decreases as death nears (i.e. loss of appetite), the increase seen in serum phosphate would only be explained by decreasing renal function. Unexpectedly, however, the linear decline in eGFR was not mirrored by the steadily increasing levels of serum phosphate. This discrepancy suggests an overestimation of eGFR, perhaps as the result of decreasing muscle mass in the proximity of death (as reflected by the SGA).

Patient-reported outcomes correlate well with hard outcomes such as dialysis initiation and mortality in CKD, but little is known about how they evolve in the final years of life [24]. Murtagh *et al.* surveyed CKD stage 5 patients managed without dialysis on a monthly basis, and found that patients reported a significant increase in symptoms and health-related concerns in the 2 months preceding death [7]. According to the authors, this particular CKD population has a similar or greater symptom burden compared with advanced cancer patients during their final month of life [25]. De Goeij *et al.* (PREPARE-2 study) studied the course of symptoms and HRQOL every 6 months during pre-dialysis care, finding that symptom burden increases, and both physical and mental HRQOL decreases during pre-dialysis care, with the sharpest change occurring in the last 6 to 12 months before reaching the composite endpoint of death, dialysis, or transplantation [26]. Although our results show a steady decline in both physical and mental HRQOL, with no distinct acceleration, symptom burden accelerated around 1 year prior to death.

We identified distinct accelerations in cardiovascular trajectories occurring at ∼6 months preceding death. In the UK general population, accelerations in systolic blood pressure have been described in the last 2 years of life, which were not accounted for by changes in antihypertensive treatment [27, 28]. Drops in mean systolic blood pressure—from peak values to death—ranged from −8.5 mm Hg for decedents aged 60 to 69 years to −22.0 mm Hg for those dying at 90 years or older [27]. In our older population of advanced CKD stage patients, we found accelerations in systolic and diastolic blood pressure occurring between 6 and 12 months prior to death, characterized by a terminal drop of ∼ −15 mmHg in mean systolic blood pressure. It has been suggested that this drop in blood pressure is likely a marker for comorbidity that could be explained by underlying poor functional status (and should not be a reason to avoid treating hypertension) [29–31]. In addition to blood pressure, we also identified a—to our knowledge, previously unseen—terminal increase in heart rate occurring a few months prior to death. A potential explanation could be deconditioning due to recurring acute illness and hospitalization, resulting in a more tachycardic profile on modest exertion, or a compensatory mechanism for the decrease observed in blood pressure.

Our study's key strengths include the prospective collection of extensive clinical data across six European countries, a long follow-up period, and a large cohort of advanced stage CKD decedents. The use of GAMs enabled us to objectively identify tipping points in patient trajectories, without needing to pre-specify when this could have occurred. We also acknowledge that our study is subject to several limitations. We were unable to investigate whether trajectories depend on the cause of death, as the statistical power was lacking to perform a stratified analysis. Patient visits were scheduled at 3–6-month intervals according to protocol. This temporal granularity may have been insufficient to capture sudden changes in biochemical trajectories (i.e. occurring in the last days or weeks of life). The necessity of having to select an arbitrary point in time (selected at 4 years prior to death) to be used as a comparison value, hindered our ability to objectively identify tipping points (i.e. statistically significant accelerations) in clinical trajectories, as the selection of a different reference point may have resulted in different tipping point estimations. Along the same lines, further work should focus on how to distinguish reversible acute deterioration in trajectory from a terminal drop leading to death. Last, more than half of the longitudinal PROMs questionnaires were missing during follow-up, although this is to be expected given the population's health and age. This may have introduced a "healthy" responder bias to our PROM results, although the proportion of missing values did not increase substantially until 2 weeks preceding death.

In summary, we describe the evolution of clinical indicators, symptom burden, quality of life, and hospitalizations, in the years preceding death, in a cohort of older patients with advanced CKD. We identify clinically relevant physiological accelerations in patient trajectories that begin ∼6 months prior to death and are likely multifactorial in nature, but correlate with an increase in hospitalization rate. The trajectories reported in this large multinational prospective cohort study will usefully inform patient and family expectations, benefit the planning of (end-of-life) care, and help establish clinical alert systems.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We would like to thank all the participants and health professionals participating in the EQUAL study.

FUNDING

Main funding was received from the European Renal Association (ERA) and contributions from the Swedish Medical Association (SLS), the Stockholm County Council ALF Medicine and Center for Innovative research (CIMED), the Italian Society of Nephrology (SIN-Reni), the Dutch Kidney Foundation (SB 142), the Young Investigators grant in Germany, and the National Institute for Health Research in the United Kingdom.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due the privacy of individuals that participated in the study. The

data will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

M.E. reports no conflict of interest in relation to this publication. Outside this work, M.E. reports payment for advisory boards and lectures by Astellas pharma, Vifor Pharma, and Astra Zeneca, and institutional grants from Astra Zeneca and Astellas pharma. C.W. had no conflict in respect to the present research. Outside this research, honoraria for consultancy and lecturing were received from Amicus, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli-Lilly, GILEAD, GSK, MSD, Sanofi-Genzyme, and Takeda.

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Received: December 19, 2022; Editorial decision: April 6, 2023