End-stage renal disease versus death in a Portuguese cohort of elderly patients: an approach using competing event analysis

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ABSTRACT

Chronic kidney disease (CKD) is higher in elderly, but mortality outweighs the risk of end-stage renal disease (ESRD). Our aim was to identify prognostic markers for ESRD or death in elderly CKD, within a competing-risk analysis. This is a longitudinal study of consecutive newly referred patients with CKD ages 65 years, followed until the time of the first event (ESRD or death), using a competing-risk analysis. A modified Charlson Comorbidity Index (mCCI) was subdivided into subgroups (0-2, 3-4, ≥5). Patients were followed for hospitalizations that occurred prior to the outcomes. Among 416 patients, age 76±8 years, 52% male, median estimated glomerular filtration rate of 32 mL/min per 1.73 m^2, 50% had diabetes, and 67% cardiovascular disease. Over a median follow-up of 3.6 years, 36 patients progressed to ESRD (8.7%) and 103 died (24.8%). Older age (subdistribution HR (sHR)=1. 06; p<0.001), creatinine≥1.6 mg/dL (sHR=2.03, p=0.004), hemoglobin <11 g/dL (sHR=1.91, p=0.003), mCCI score≥5 (sHR=3.01, p<0.001) and having one or more hospitalizations (sHR=1.73, p<0.001) were associated with death before ESRD. The independent predictors for ESRD with competing risk of death were: lower age (sHR=0.94; p=0.009), creatinine≥1.6 mg/dL (sHR=3.26, p=0.006), hemoglobin <11 g/dL (sHR=2.15, p=0.027), peripheral vascular disease (sHR=3.45, p=0.001) and having one or more hospitalizations (sHR=1.56, p=0.031). Elderly referred patients with CKD are near threefold more likely to die than progress to ESRD. A competing-risk framework based on available clinical and laboratory data may discriminate between those outcomes and could be used as a decision-making tool.

Significance of this study

What is already known about this subject?

- Prevalence of chronic kidney disease (CKD) is rising worldwide, and the elderly represent the most rapidly growing segment of the end-stage renal disease (ESRD) population requiring renal replacement therapy.
- Mortality, mainly from cardiovascular disease, outweighs the risk of progression to ESRD in older patients with CKD.

What are the new findings?

- Our study includes the rigorous exploration of the first Portuguese CKD cohort that included patients aged 65 years over, newly referred to nephrology.
- We demonstrated that peripheral vascular disease was an independent predictor for ESRD, but was not associated with increased pre-ESRD mortality.
- We implemented a competing risk framework for the statistical analysis to examine risk factors based on available clinical and laboratory data, for ESRD and differentiating them from those that increase mortality.

How might these results change the focus of research or clinical practice?

- Identifying predictors of death and ESRD within a competing-risk approach may allow us to use them as a decision-making tool, enabling more targeted therapeutic intervention, in elderly patients with CKD.

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INTRODUCTION

The world's population is aging, and by demographic projections, in 2050, about 32% of the Portuguese population is projected to be aged 65 and over, meaningfully above the European Union average of 25.7%.[1]

Parallel to this, the prevalence of chronic kidney disease (CKD) is rising worldwide, and the elderly represent the most rapidly growing segment of the end-stage renal disease (ESRD) population requiring renal replacement therapy (RRT) in wealthier countries.[2 3] Portugal has the highest unadjusted incidence and prevalence of ESRD among European countries[4] and 67.7% of the incident dialysis patients, in 2015, were over 65 years with a mean age of prevalent patients of 66.7 years.[5]

Despite the growing number of older patients initiating dialysis, another problem stands out in this group: mortality, mainly from cardiovascular disease, outweighs the risk

of progression to ESRD.[6 7] One of the major challenges to clinicians caring for older patients with CKD is to identify each patient's risk for progressive CKD and likelihood for requiring RRT in relation to the competing risk of death. This may involve important clinical decisions, such as referrals and procedures for dialysis access placement or transplant decision or on the contrary the possibility to identify patients with higher comorbid conditions at high risk of early death for which conservative management may be the best option.

Our aim was to characterize elderly patients with CKD who were newly referred to our outpatient department to determine the independent predictors of ESRD or death through a competing-risk analysis. Furthermore, we sought to identify potential variables that may indicate a higher likelihood of death before ESRD or of attaining first ESRD status.

METHODS

Study design and population

This longitudinal retrospective study included consecutive patients aged ≥65 years with CKD (non-dialyzed and non-transplanted), newly referred to our outpatient Nephrology department in Hospital de Santo António, CHUP, between January 1, 2012 and December 31, 2012, followed until the occurrence of the first event (ESRD or death) or until the end of the study (April 30, 2016). Hospital de Santo António is a tertiary-care hospital affiliated with the Abel Salazar Institute of Biomedical Sciences, University of Porto, which serves a diverse population of 500,000 inhabitants in the North region of country.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of CHP.

The diagnosis of CKD was done by the KDIGO 2012 criteria.[8] ESRD was defined as the need for RRT initiation or transplantation.

Baseline data included gender, age, weight, height, body mass index (BMI), CKD stage, proteinuria level, medication use, and associated comorbid conditions, such as diabetes, dyslipidemia, hypertension, smoking status, and cardiovascular disease (coronary artery disease, peripheral artery disease, and cerebrovascular accident). Coronary artery disease was defined as a previous myocardial infarction, angina pectoris, coronary artery bypass grafting, or coronary stent implantation. Peripheral artery disease was defined as the presence of intermittent claudication or with the need of peripheral revascularization or amputation.

Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology (CKD-EPI) 2009 creatinine equation.[9] Etiological diagnosis of CKD was based on the patient's history, proteinuria, kidney ultrasound, and kidney biopsy, when available. Data blood and urine routine measurements were collected: hemoglobin, platelet, serum albumin, urea nitrogen, creatinine, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, intact parathyroid hormone (PTH), glucose, hemoglobin A1c, uric acid, lipid profile, iron, unsaturated iron binding capacity, ferritin, urinary sediment, and urine protein-to-creatinine ratio in spot urine sample.

Cognitive status was evaluated and screened using the Mini Mental State Examination,[10] and classified as cognitive impairment if the score was 23 or lower.

Functional dependency was defined as the requiring of assistance in the activities of daily living and classified as totally dependent, partially dependent, and autonomous.

A modified version of the Charlson Comorbidity Index (mCCI),[11 12] that is, by excluding subject's age and presence or absence of kidney disease, was calculated to assess severity of comorbidities and subdivided into three subgroups (0–2, 3–4, and ≥5).

During the follow-up, number and reasons for hospitalizations were registered, all-cause hospitalization and cardiovascular-related hospitalization, defined as hospitalization secondary to cardiovascular events (coronary artery disease, congestive heart failure, stroke or transient ischemic attack, peripheral artery disease). The cause of death was categorized as cardiovascular (defined as death due to cardiac, cerebrovascular, atherosclerotic or other vascular causes), malignancy, infection, other, and unknown causes.

Statistical analysis

Baseline characteristics for the all sample and by primary outcomes of interest are presented as medians with IQRs for continuous non-normally distributed variables and as proportions for categorical variables. Subgroups were compared using the χ^2 for categorical and Mann-Whitney test for continuous variables.

Unadjusted incidence rates for progression of ESRD (defined as renal failure requiring RRT or transplant) and all-cause mortality before any RRT (pre-ESRD death) were calculated per 100 person-years.

Hospitalization rate was calculated as the number of hospital admissions, divided by years at risk, expressed as hospitalizations per patient-year, using Poisson regression.

Survival analysis was performed and the two outcomes of interest were progression of ESRD and all-cause mortality before any RRT (pre-ESRD death). These two events were considered as competing risks. Patients without any of these outcomes were censored at the date of their last recorded visit or at the end of the study period.

Regression models taking competing risks into account were carried out to analyze the independent effect of covariates on each of two competing endpoints. This analysis was performed considering two types of hazards: cause-specific hazard and subdistribution hazard. Proportional cause-specific hazard regression models were performed using the standard Cox (cause-specific hazard regression model), censoring all patients without the event of interest. If a patient initiated dialysis, then the endpoint of mortality was censored. If a patient died, then the outcome of dialysis initiation was censored. An alternative model proposed by Fine and Gray[13] was the approach used in the current study to model the subdistribution hazard.

An exploratory analysis was performed to examine the unadjusted effect of the potential predictors of ESRD progression and patient death by fitting univariable models. The cause-specific HR and the subdistribution HR for ESRD or for patient death before any RRT were then estimated in multivariable analyses. The covariates were selected on the basis of univariate analysis and because of their potential

biological plausibility to predict progression of ESRD and/or death.

The variables included in the univariate competing-risk model were baseline age, gender, baseline serum creatinine (<1.6 or ≥1.6 mg/dL, the median value for this sample), serum hemoglobin (<11 or ≥11 g/dL),[14] BMI (<18.5, 18.5–24.9, 25–29.9, or ≥30), estimated GFR (eGFR) (continuous or categorized as <60 or ≥60 mL/min), tobacco use (never, former, or current), dyslipidemia, hypertension, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, number of antihypertensive drugs, referral from primary care versus another hospital appointment, CKD etiology (diabetes vs others), cognitive status, functional dependency, mCCI score at baseline, and the occurrence of hospitalizations during the follow-up period. For both outcomes, the occurrence of hospitalizations during the follow-up period was used as a time-varying covariate.

Statistical analyses were performed using SPSS V.22.0 and STATA V.13.0 software packages. A significance level of 0.05 was considered.

RESULTS

Baseline characteristics

Among 416 patients newly referred, 52% were male, with a mean age of 76 years, and 36% of them aged 80 years or more. Their baseline characteristics are summarized in table 1.

Fifty per cent of the patients were referred by primary care physicians. At baseline, they had a median eGFR of 32 mL/min per 1.73 m^2. The most frequent etiologies of renal disease were ischemic nephropathy (38%), diabetic nephropathy (25.5%) and unknown causes (13.5%).

Most of the patients were non-smokers (74%) and 22% were obese (BMI >30 kg/m^2). About 50% were diabetic, and 96% presented hypertension, of which 50% were receiving more than two antihypertensive drugs, renin–angiotensin blockade in 33% of them; 63% of the patients had a systolic blood pressure >130 mm Hg. Dyslipidemia was present in 85% of the patients, 60% were under lipid-lowering medication. An active or previous malignancy was present in 15% of the patients. Cardiovascular disease was present in 67% of the patients, including coronary artery disease in 25%, peripheral vascular disease in 19% and cerebrovascular disease in 23% of the patients.

Regarding functional dependency, 5% of the patients were totally dependent and 38% were partially dependent. Cognitive impairment was present in 11% of the patients.

Most patients had a hemoglobin level ≥11 g/dL (71%), with no iron deficiency (ferritin level ≥100 ng/mL: 75%; transferrin saturation ≥20%: 62%).

Intact PTH was elevated in 81% of the patients, despite good control of calcium–phosphorus levels.

Follow-up and outcomes

During a median follow-up of 3.6 years (min–max: 0.02–4.3 years), 36 patients progressed to ESRD (8.7%) and 103 patients died (24.8%) prior to ESRD, giving an ESRD rate of 2.7/100 patient-years and a mortality rate of 7.8/100 patient-years, respectively. Figure 1 shows the cumulative incidences of events, considering competing risks.

The leading causes of death prior to ESRD were cardiovascular (35%), infection (29%), malignancy (21%), other causes (8%), and unknown (7%).

Concerning the 36 patients who initiated RRT, all of them hemodialysis, 18 patients started treatment with an arteriovenous fistula and 18 patients with a venous catheter. It should be mentioned that eight patients of overall cohort (1.9%) that underwent fistula died without receiving dialysis.

Hospitalizations

During the follow-up period, 222 patients (53%) were hospitalized for any reason, with a global hospitalization rate of 0.38 per patient-year. Stratifying for the competing events, the hospitalization rate was 1.27 per patient-year in the patients with ESRD, and 1.06 hospitalizations per patient-year in the patients who died before ESRD.

Cardiovascular-related hospitalization accounted for almost 40% of the hospitalization events during the same period. The global cardiovascular hospitalization rate was 0.15 hospitalizations per patient-year, being 0.56 cardiovascular hospitalizations per patient-year in the patients with ESRD and 0.39 hospitalizations per patient-year in the patients who died before ESRD.

Competing-risk analysis of death and ESRD

The Cox proportional hazards model indicated that baseline younger age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, peripheral vascular disease diagnosis, and the occurrence of one or more hospitalizations (all-cause hospitalizations) during the follow-up were associated with higher risk of ESRD (table 2). Diabetes mellitus (vs other CKD etiologies) and mCCI score at baseline were not associated with higher risk of ESRD.

Older age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5, and the occurrence of hospitalizations during the follow-up were associated with death before ESRD.

Conversely, subhazard ratios estimated from competing-risk regression necessarily discriminated between endpoints. Significant risk factors for ESRD included younger age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, peripheral vascular disease, and the occurrence of one or more hospitalizations during the follow-up (table 3).

Risk factors for pre-ESRD death included older age, creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5, and the occurrence of one or more hospitalizations during the follow-up. By adjusting for these competing risks, we show that peripheral vascular disease increases the cumulative incidence of ESRD, but is not associated with increased pre-ESRD mortality. Similarly, a mCCI score ≥5 increased the hazard for pre-ESRD death, but not for RRT initiation.

DISCUSSION

In our cohort, newly referred patients aged over 65 years with CKD were near threefold more likely to die than progress to ESRD. These results were consistent with those found in previous studies confirming that elderly CKD are

Table 1 Baseline clinical characteristics of patients divided by outcomes

	Total, n=416	Alive without ESRD, n=277	ESRD, n=36	Dead without ESRD, n=103	p Value
Age (years)	71 (71–83)	76 (70–82)	74 (71–80)	81 (75–86)	0.017*
Age ≥80 years, n (%)	149 (36)	87 (31)	7 (19)	55 (53)	<0.001*
Male, n (%)	218 (52)	139 (50)	21 (58)	58 (56)	0.430
eGFR EPI (mL/min/1.73 m^2)	32 (23–42)	33 (25–44)	24 (16–38)	28 (22–34)	<0.001*
CKD stage, n(%)					
Stage 1	6 (2.0)	4 (1.0)	0 (0.0)	2 (2.0)	
Stage 2	34 (8.0)	30 (11)	1 (3.0)	2 (2.0)	0.004*
Stage 3a	46 (11)	45 (16)	1 (3.0)	0 (0.0)	
Stage 3b	139 (33)	101 (37)	7 (19)	31 (30)	
Stage 4	158 (38)	88 (32)	11 (31)	59 (57)	
Stage 5	34 (8.0)	9 (3.0)	16 (44)	9 (9.0)	
Referral, n(%)					
Primary care	206 (50)	123 (44)	21 (58)	50 (49)	0.013*
Hospital appointment	194 (47)	148 (53)	14 (39)	44 (43)	
Other	16 (3.8)	6 (2.2)	1 (2.8)	9 (8.7)	
Primary renal disease, n (%)					
Ischemic nephropathy	158 (38)	105 (38)	13 (36)	40 (39)	
Diabetic nephropathy	106 (26)	63 (23)	15 (42)	28 (27)	0.222
Glomerulonephritis	16 (3.8)	10 (3.6)	1 (2.8)	5 (4.9)	
Other/unknown	136 (33)	99 (36)	7 (19)	30 (29)	
BMI (kg/m^2)	27 (24–30)	27 (24–31)	26 (24–30)	26 (23–29)	0.112
Cognitive impairment, n (%)	47 (11.3)	30 (10.8)	3 (8.3)	14 (13.6)	0.632
Totally dependent	24 (5.8)	15 (5.4)	2 (5.6)	7 (6.8)	
Partially dependent	156 (38)	96 (35)	17 (47)	43 (42)	0.430
Autonomous	236 (57)	166 (60)	17 (47)	53 (52)	
mCCI, n (%)					
0–2	184 (44.2)	148 (53.4)	12 (33.3)	24 (23.3)	<0.001*
3–4	127 (30.5)	84 (30.3)	12 (33.3)	31 (30.1)	
>5	105 (25.2)	45 (16.2)	12 (33.3)	48 (46.6)	
Diabetes, n (%)	207 (50)	133 (48)	52 (61)	49 (51)	0.330
Former/current smoking, n (%)	110 (27)	66 (24)	11 (31)	33 (32)	0.246
SBP (mm Hg)	140 (125–155)	141 (127–158)	138 (120–159)	132 (121–150)	0.037*
DBP (mm Hg)	70 (63–80)	71 (64–80)	77 (60–81)	68 (60–76)	0.017*
Antihypertensive ≥2, n (%)	207 (50)	140 (51)	18 (50)	49 (48)	0.876
Renin–angiotensin blockade	137 (33)	88 (32)	16 (44)	33 (32)	0.306
Diuretics	295 (71)	196 (71)	30 (83)	69 (67)	0.177
Dyslipidemia, n (%)	354 (85)	238 (86)	30 (83)	86 (84)	0.801
Lipid-lowering medication, n (%)	248 (60)	168 (61)	22 (61)	58 (56)	0.712
Antiplatelet medication, n (%)	203 (49)	135 (39)	14 (52)	54 (49)	0.376
Cardiovascular diseases, n (%)	277 (67)	172 (62)	22 (61)	65 (63)	0.739
Peripheral vascular disease, n (%)	78 (19)	43 (16)	15 (42)	20 (19)	0.001
Albumin <3.5 g/dL, n (%)	40 (11)	24 (10)	5 (15)	11 (12)	0.667
Uric acid (mg/dL)	7.3 (5.6–9.8)	7.2 (5.4–9.6)	7.4 (5.9–9.3)	7.7 (6.2–11.3)	0.367
Total cholesterol (mg/dL)	176 (147–205)	179 (150–205)	175 (142–207)	168 (142–204)	0.355
HDL (mg/dL)	47 (38–57)	48 (39–57)	48 (36–59)	45 (37–58)	0.720
LDL (mg/dL)	98 (75–123)	99 (79–121)	95 (71–118)	95 (74–132)	0.673
Hemoglobin (g/dL)	11.9 (10.6–13.6)	12.0 (10.9–13.4)	11.3 (10.6–13.1)	11.6 (10.1–13.1)	0.086
TSAT (%)	21(14–28)	21(15–28)	21(15–33)	21(14–28)	0.642
Ferritin (ng/mL)	160 (80–337)	150 (77–344)	151 (70–256)	181 (90–363)	0.407

Continued

Table 1 Continued

	Total, n=416	Alive without ESRD, n=277	ESRD, n=36	Dead without ESRD, n=103	p Value
iPTH (pg/mL)	100 (61–155)	98 (61–161)	115 (69–140)	99 (61–156)	0.446
Calcium (mg/dL)	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.3 (2.2–2.5)	0.158
Phosphate (mg/dL)	1.1 (0.99–1.25)	1.1 (0.99–1.24)	1.1 (0.90–1.17)	1.2 (1.00–1.33)	0.292
uPCr (g/g)	0.25 (0.1–1.0)	0.28 (0.11–1.11)	0.19 (0.07–0.47)	0.19 (0.10–0.85)	0.147

Note: Data expressed as medians and IQRs or n (%) when appropriate. Comparisons between continuous variables were done using a non-parametric test (Kruskal-Wallis); associations between categorical variables were analyzed using the χ^2 test; *p<0.05.
BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high density lipoprotein; iPTH, intact parathyroid hormone; LDL, low density lipoprotein; mCCI, modified Charlson Comorbidity Index; SBP, systolic blood pressure; TSAT, transferrin saturation; uPCr, urinary protein-to-creatinine ratio.

far less likely to develop kidney failure than to die, especially from cardiovascular disease, even with higher CKD stage.[6 7 15 16]

However, our results differ from others, also from patients with CKD referred for nephrologist care,[17 18] who have been showed to have either similar or even higher risk of ESRD compared with death. We can speculate about the reasons for these differences, namely our patients were older, with a higher burden of comorbidity and frailty. In fact, 25% of our patients have a severe mCCI score (CCI ≥5), 43% have some degree of functional dependency and 11% had a cognitive impairment.

Our cohort fits the frailty phenotype associated with CKD and geriatric syndrome,[19 20] in contrast with other elderly CKD European cohorts newly referred to nephrologists,[16] that despite older than our patients, had a good health status, reflecting a selection bias in referring patients for nephrology care, not found in our group.

To better understand the chances associated with the competing risks between mortality and ESRD, in elderly patients with CKD, where the supply of conservative management is weighed against the benefits and costs of RRT, we have applied a competing-risks model[13] that looks at the cumulative incidence of ESRD or death before ESRD while also taking into consideration competing risk of the alternate outcome. We believe that such approach better identifies prognostic factors for a particular event in the presence of competing risks and provide an important tool for better decision-making.[21]

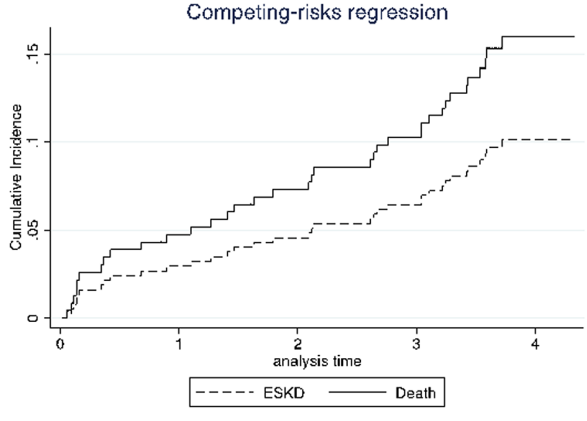

Figure 1 Cumulative incidence rates for the competing endpoints of end-stage renal disease or death.

In the competing-risk framework, patients who are younger, with creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, had previous peripheral vascular disease and one or more hospitalizations during the follow-up, are more likely to reach ESRD. Those who are older, with creatinine higher than 1.6 mg/dL, hemoglobin lower than 11 g/dL, mCCI score ≥5 and one or more hospitalizations during the follow-up, are more likely to die.

Our findings confirm that renal function at baseline was an important predictor for both ESRD and mortality[6 22–25] although this association was stronger for ESRD than for death, still reinforce the importance of early nephrology referral. In fact, in our cohort a shorter time between referral and ESRD was also associated with RRT initiation by catheter as primary access.

We found, as others,[26] that anemia (hemoglobin <11 g/dL) was a predictor of mortality and ESRD, undoubtedly related with adverse cardiovascular effects and the potential role of hypoxia on CKD progression, particularly important in this elderly population. This highlights the importance of anemia treatment although the target hemoglobin is still a matter of debate.[14 27]

The occurrence of one or more hospitalizations was common in our cohort and it was associated with both outcomes (ESRD and death). The increased risk for mortality among patients with hospitalization is consistent with other studies, assuming that the majority of those hospitalizations were cardiovascular-related,[28 29] or associated with an infection event, also known a risk factor for increased cardiovascular events and mortality in patients with CKD.[30]

The occurrence of hospitalizations events during the follow-up was also associated with ESRD. In our group the global and cardiovascular hospitalization rate was higher in patients with ESRD, than in the patients who died before RRT initiation. These findings are consistent with other studies,[29 31 32] as cardiovascular admissions may have served as a marker for patients who had more progressive ischemic nephropathy, or more important, related to a superimposed acute kidney injury (AKI) episode on the underlying CKD.[29 33] AKI episodes, frequent in elderly population, may accelerate progression of renal disease.[34 35]

We demonstrated that peripheral vascular disease was an independent predictor for ESRD, but was not associated with increased pre-ESRD mortality. These findings extend

Table 2 Risk factors associated with death and ESRD (Cox regression analysis)

	ESRD		Death	
	csHR (95% CI)	p Value	csHR (95% CI)	p Value
Baseline				
Age, years	0.95 (0.91 to 1.00)	0.049	1.04 (1.01 to 1.07)	0.004
Creatinine (>1.6 vs <1.6 mg/dL)	3.64 (1.58 to 8.38)	0.002	2.27 (1.44 to 3.57)	<0.001
Hb (<11.0 vs >11.0 g/dL)	2.72 (1.35 to 5.49)	0.005	2.20 (1.49 to 3.26)	<0.001
CCI score				
(3–4 vs 1–2)	0.55 (0.22 to 1.39)	0.205	1.35 (0.80 to 2.29)	0.258
(≥5 vs 1–2)	0.80 (0.33 to 1.96)	0.626	2.82 (1.70 to 4.67)	<0.001
Peripheral vascular disease (yes vs no)	3.60 (1.70 to 7.60)	0.001	1.03 (0.64 to 1.68)	0.890
DM vs other CKD etiologies	1.75 (0.85 to 3.58)	0.127	1.02 (0.67 to 1.55)	0.930
During the follow-up				
Hospitalizations (yes vs no)	1.72 (1.17 to 2.52)	0.006	1.84 (1.44 to 2.36)	<0.001

Note: Values given as csHR (95% CI) for risk factors associated with ESRD and death prior to ESRD.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; csHR, cause-specific HR; DM, diabetes mellitus; ESRD, end-stage renal disease; Hb, hemoglobin.

the association between vascular disease and CKD progression founded in other studies,[31 36 37] given that peripheral vascular disease is the result of an atherosclerotic process similar to that one seen in cardiovascular disease. As we know, atherosclerosis is a potentially important mechanism of kidney disease in older persons[38 39] and increases the susceptibility for AKI and CKD progression.[40] A study in European cohort,[41] also using a competing risks modeling approach, showed that the endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine, considered one of the strongest markers of atherosclerosis, was an independent predictor of progression to dialysis and death in patients with CKD.

A reduced ankle–brachial index reflects peripheral arterial disease, and some studies demonstrated that this atherosclerotic disease marker predicted accelerated renal function decline, in general population,[42] and also in peritoneal dialysis patients.[43]

Given that finding, our study suggests that the presence of peripheral arterial disease, although reflecting an atherosclerotic systemic process also involving the kidneys, may be a potential marker for renal function decline in patients with CKD, through other mechanisms, in addition to the traditional association of CKD with vascular damage.

The higher burden of CV risk factors, and prevalent vascular disease, present in our cohort, and the association between peripheral vascular disease and ESRD that we found, may partially explain the highest incidence of ESRD of Portuguese population among European countries,[4] because data from the PREVADIAB Study[44] have shown that the prevalence of CKD stages 3–5 was 6.1%, which is similar to that in other Western countries. The reasons for this disparity are still a matter of debate. Although socioeconomic and political factors still play a part in RRT rates around the world, other important factors are genetics, birth weight, dietary habits, and diabetes prevalence. Another important issue is the age pattern at beginning of RRT. In countries with lower RRT incidence, the median age at start of RRT appears to be lower, suggesting that countries with higher RRT incidence, like Portugal, start older patients in RRT and this may contribute to differences in RRT epidemiology between countries.[45] In this respect, there is an urgent need for concrete evidence on the relative benefit of conservative treatment versus RRT

Table 3 Risk factors associated with death and ESRD (Fine and Gray model[13])

	ESRD		Death	
	sHR (95% CI)	p Value	sHR (95% CI)	p Value
Baseline				
Age, years	0.94 (0.89 to 0.98)	0.009	1.06 (1.03 to 1.09)	<0.001
Creatinine (>1.6 vs <1.6 mg/dL)	3.26 (1.40 to 7.60)	0.006	2.03 (1.25 to 3.29)	0.004
Peripheral vascular disease (yes vs no)	3.45 (1.68 to 7.10)	0.001	0.82 (0.49 to 1.34)	0.435
CCI score				
(3–4 vs 1–2)	0.57 (0.24 to 1.35)	0.202	1.53 (0.87 to 2.69)	0.137
(≥5 vs 1–2)	0.54 (0.23 to 1.28)	0.164	3.01 (1.75 to 5.19)	<0.001
Hb (<11.0 vs >11.0 g/dL)	2.15 (1.09 to 4.24)	0.027	1.91 (1.25 to 2.92)	0.003
DM vs other CKD etiologies	1.72 (0.84 to 3.53)	0.139	0.84 (0.54 to 1.32)	0.447
During the follow-up				
Hospitalizations (yes vs no)	1.56 (1.04 to 2.35)	0.031	1.73 (1.33 to 2.25)	<0.001

Note: Values given as sHR (95% CI) for risk factors associated with ESRD and death prior to ESRD.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease.; Hb, hemoglobin; sHR, subdistribution HR.

in the elderly as well as on the optimal timing of RRT initiation.

Finally, we found that mCCI score ≥5 was an independent predictor for pre-ESRD death, but not for RRT initiation. The CCI has been widely used and validated in patients with ESRD and seemed to be significantly more predictive for mortality than other comorbidity scoring systems[46 47] This is evidenced by studies demonstrating that elderly patients with CKD are likely to have a higher burden of comorbidity and frailty, which are markers of worst survival.[46]

Old age alone should not be used as an absolute barrier to treatment when considering the benefits of dialysis in elderly patients with CKD.[48] However, in the elderly patients with CKD with a high burden of comorbidity, conservative management may be a therapeutic option, as dialysis is unlikely to prolong or improve quality of life.[49–51]

Also, considering the likelihood of death prior to ESRD makes preparation for RRT, as the placement of an arteriovenous access unnecessary and potentially harmful.[52]

The strengths of our study include the rigorous exploration of the first Portuguese CKD cohort that included patients aged 65 years over, newly referred to nephrology, reflecting current clinical practice. We implemented a competing-risk framework for the statistical analysis to examine risk factors based on available clinical and laboratory data, for ESRD and differentiating them from those that increase mortality, which is an important tool to guide clinical decision process.

The effect of peripheral vascular disease as an independent predictor for ESRD in our cohort, although it deserves more research, reinforces the importance of strategic targeting vascular risk screening and reduction in this population.

There are certain limitations to our research. First, this is a single-center retrospective study. Second, due to the overall small number of patients who initiated RRT (n=36), it is not possible to identify the risk factors for progression within each CKD stage. In the stages 3 and 4, only 8 and 11 patients progressed to dialysis, respectively. Thus, we do not have sufficient number of events for performing a reliable survival analysis using mortality as a competing event.

Third, defining ESRD as the RRT initiation has the disadvantage of being dependent on local clinical practice. Fourth, proteinuria could not be included in the multivariable models due to the percentage of missings and, therefore, we could not analyze the effect of proteinuria on the risk of ESRD or death. Finally, because this cohort only comprised patients attending nephrology outpatient clinic, which can introduce a bias of referral, the results may not be generalizable to a non-referred population.

CONCLUSION

In summary, we found that newly referred older patients with CKD are substantially more likely to die than to reach ESRD. By using a competing-risk approach based on available clinical and laboratory data, we could identify risk factors predictors of CKD progression and distinguishing them from those that increase mortality, which may allow us to use them as a decision-making tool to guide clinical decision process.

Contributors JS, IF and JM were involved in research design, writing and in data collection. IB, LL, PO and AC were involved in editing.

Competing interests None declared.

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