The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care

Luca De Nicola[1], Roberto Minutolo[1], Paolo Chiodini[2], Silvio Borrelli[1], Carmine Zoccali[3], Maurizio Postorino[3], Carmela Iodice[1], Felice Nappi[4], Giorgio Fuiano[5], Ciro Gallo[2], Giuseppe Conte[1] for the Italian Society of Nephrology Study Group 'TArget Blood pressure LEvels (TABLE) in CKD'[6]

[1]Nephrology Division, Second University of Napoli, Napoli, Italy; [2]Medical Statistics Unit-Department of Medicine and Public Health, Second University of Napoli, Napoli, Italy; [3]Nephrology Division at CNR-IBIM Hospital in Reggio Calabria, Reggio Calabria, Italy; [4]Nephrology Division at County Hospital in Nola, Nola, Italy and [5]Magna Graecia University in Catanzaro, Catanzaro, Italy

To define whether age modifies the prognosis of patients with chronic kidney disease (CKD) on nephrology care, we prospectively followed patients with CKD who have been receiving nephrology care in a clinic for 1 year or more. The incidence of end-stage renal disease (ESRD), defined by the occurrence of dialysis or transplant, or death without ESRD was estimated by a competing-risk approach, and interactions between age and risk factors tested in Cox models over a median follow-up period of 62.4 months. Of 1248 patients with stage III–V CKD, 481 were younger than 65, 410 were between 65 and 75, and 357 were over 75 years old. Within each age class, the mean estimated glomerular filtration rate (eGFR) was 31, 32, and 29 ml/min per 1.73 m^2, respectively. There were 394 ESRD events and 353 deaths. The risk of ESRD was higher than the risk of death without ESRD for ages <60 years, and independent of eGFR. The ESRD risk diminished with aging but still prevailed for eGFRs of 25–35 in patients between 65 and 75 years and with an eGFR below 15 in those up to 85 years old. Proteinuria significantly increased the risk of ESRD with advancing age. Surprisingly, the unfavorable effects of cardiovascular disease on ESRD and of diabetes on survival significantly decreased with increasing age. Male gender, higher phosphate, lower body mass index, and hemoglobin were age-independent predictors for ESRD, while cardiovascular disease, lower hemoglobin, higher proteinuria and uric acid, and ESRD also predicted death. Thus, in older patients on nephrology care, the risk of ESRD prevailed over mortality even when eGFR was not severely impaired. Proteinuria increases ESRD risk, while the predictive role of other modifiable risk factors was unchanged compared with younger patients.

Correspondence: *Luca De Nicola, Cattedra di Nefrologia - Dip. Gerontologia, Geriatria, Mal.Metabolismo, Seconda Università di Napoli, Piazza Miraglia, 80131 Napoli, Italia. E-mail: luca.denicola@unina2.it*

[6]See Supplementary Material for the complete list of TABLE Investigators.

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The prevalence of overt non-dialysis chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2, is markedly high at older ages.[1–3] Prevalence of CKD stages III–IV in people aged 70–79 and >80 years was found equal to 32% and 61% in the United States and 18% and 40% in Italy, respectively.[4] It is also estimated that the number of elderly patients with treated end-stage renal disease (ESRD) has almost doubled in the past 25 years.[2,3] More important, non-dialysis elderly patients have become prevalent also in nephrology clinics.[5–9] The latter epidemiological finding is critical for three reasons. First, nephrologists represent the main reference of care for patients with overt non-dialysis CKD. Second, the number of elderly patients referred to nephrologist has significantly grown in the past decade.[9] Third, patients followed in the nephrology setting are worldwide characterized by more advanced renal disease and higher burden of cardiovascular (CV) comorbidities as compared with unreferred patients.[5–7,10–14]

In spite of the changing epidemiology of non-dialysis CKD in nephrology clinics, no prognostic information has been so far provided in the elderly patients under nephrology care. This gap of knowledge is particularly important because many elderly patients, unreferred or newly referred to nephrology clinics, do not follow an inexorable course to ESRD as they die before.[6,8,15-17] It is also still unknown whether and how age influences the predictive role of other risk factors for ESRD and death in referred as well as unreferred patients.

In 2003, we designed a multicenter prospective study to gain information on prognosis and risk factors in adult stage III–V CKD patients regularly attending Italian renal clinics.[5] In this cohort, we have recently quantified the predictive role

of uncontrolled (not-at-goal) risk factors.[18] In this study, we evaluate the specific effect of age on the competing risks of ESRD and death, and tested all the potential interactions between age and the main determinants of either outcome.

RESULTS

Characteristics of patients

In all, 1248 Caucasian patients were prospectively followed from 2003 to death or May 2011. Median age was 67 years (interquartile range: 58–76). Of these, 481 (38%) patients were <65 years old, 410 (33%) patients were between 65 and 75 years, and 357 (29%) patients were over 75 years. Table 1 describes the main features by age class at study visit. Median (interquartile range) length of follow-up in the clinic before the study visit was slightly shorter in very old patients; however, the number of visits in the year preceding the study start was not different among age classes. Aging was associated with higher prevalence of diabetes and CV disease (CVD). Nutritional status was adequate throughout the age classes, as documented by mean values of body mass index and serum albumin. Frequency of underlying nephropathy differed between the three groups, with hypertensive nephropathy being prevalent in older patients and glomerulonephritis in younger patients. Aging was also associated with higher systolic blood pressure, and lower hemoglobin (Hb) and 24 h proteinuria.

Therapeutic regimens at study visit by age are reported in Table 2. Aging was associated with a wider use of furosemide

Table 1 | Demographics and clinical features of patients at study visit by age class

	Overall (*n*=1248)	<65 years (*n*=481)	65–75 years (*n*=410)	>75 years (*n*=357)	*P*-value
Age (years)	67 ± 14	53 ± 10	71 ± 3	81 ± 5	
Male gender (%)	57.5	58.2	56.6	57.4	0.887
Nephrology care (years)	2.6 (1.4–5.8)	2.8 (1.7–6.1)	2.7 (1.3–5.5)	2.4 (1.4–4.9)	0.014
Nephrology visits (*n*)	4 (2–5)	4 (2–6)	3 (2–5)	4 (2–5)	0.182
BMI (kg/m^2)	27.3 ± 4.6	27.2 ± 5.2	28.0 ± 4.4	26.6 ± 3.9	0.0002
Albumin (g/dl)	3.9 ± 0.5	4.0 ± 0.5	3.9 ± 0.5	4.0 ± 0.5	0.268
Smokers (%)	10.0	12.3	8.5	8.7	0.111
Diabetes (%)	27.7	23.9	31.7	28.3	0.033
Previous CV event (%)	31.8	22.7	35.6	39.8	<0.0001
Renal disease (%)					<0.0001
Hypertension	24.0	13.9	31.2	29.4	
Diabetes	14.7	12.9	17.8	13.5	
GN	13.0	22.4	8.0	5.9	
IN/PKD	16.4	19.8	14.4	14.3	
Other/unknown	31.9	31.0	28.5	36.3	
Systolic BP (mm Hg)	140 ± 18	135 ± 18	142 ± 17	143 ± 18	<0.0001
eGFR (ml/min per 1.73 m^2)	31 ± 14	31 ± 15	32 ± 14	29 ± 13	0.042
CKD stages II/IV/V (%)	48.8/36.0/15.2	50.9/33.3/15.8	50.0/35.6/14.4	44.6/40.1/15.4	0.303
Phosphate (mg/dl)	3.9 ± 0.8	4.0 ± 0.8	3.8 ± 0.9	3.8 ± 0.8	0.020
Hemoglobin (g/dl)	12.6 ± 1.8	12.9 ± 1.9	12.5 ± 1.7	12.2 ± 1.7	<0.0001
Uric acid (mg/dl)	6.2 ± 1.7	6.3 ± 1.6	6.1 ± 1.7	6.1 ± 1.8	0.358
Cholesterol (mg/dl)	199 ± 40	203 ± 43	197 ± 38	195 ± 37	0.028
Proteinuria (g/24 h)	0.57 (0.17–1.28)	0.70 (0.28–1.5)	0.43 (0.13–1.28)	0.53 (0.15–0.96)	<0.0001

Abbreviations: BMI, body mass index; BP, systolic blood pressure; CV, cardiovascular; eGFR, glomerular filtration rate estimated by the 4-variable MDRD equation; GN, glomerulonephritis; IQR, interquartile range; IN, interstitial nephritis; nephrology visits, number of visits in the clinic in the last year before the study start; PKD, autosomal dominant polycystic kidney disease.
Values are mean (s.d.), median (IQR), or percent.

Table 2 | Therapeutic features of patients at study visit by age class

	Overall (*n*=1248)	<65 years (*n*=481)	65–75 years (*n*=410)	>75 years (*n*=357)	*P*-value
NaCl intake <100 mmol/24 h (%)	20.6	19.0	21.6	21.8	0.620
Protein intake <0.8 g/kg per 24 h (%)	54.0	57.7	50.4	52.8	0.225
BP lowering drugs (average number per patient)	2.16 ± 1.13	2.08 ± 1.15	2.25 ± 1.11	2.19 ± 1.11	0.070
ACEi or ARB (%)	71.8	74.0	72.9	67.5	0.097
ACEi+ARB (%)	5.5	8.3	4.2	3.4	0.003
CCB (%)	46.8	44.1	51.7	44.8	0.051
BB (%)	18.8	23.1	18.5	13.2	0.001
Furosemide (%)	37.4	26.6	38.3	51.0	<0.0001
Statin (%)	22.0	23.5	25.6	15.7	0.002
ESA (%)	12.4	9.1	9.1	20.7	<0.0001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; ESA, erythropoiesis-stimulating agents; IQR, interquartile range.
Values are mean (s.d.), median (IQR), or percent.

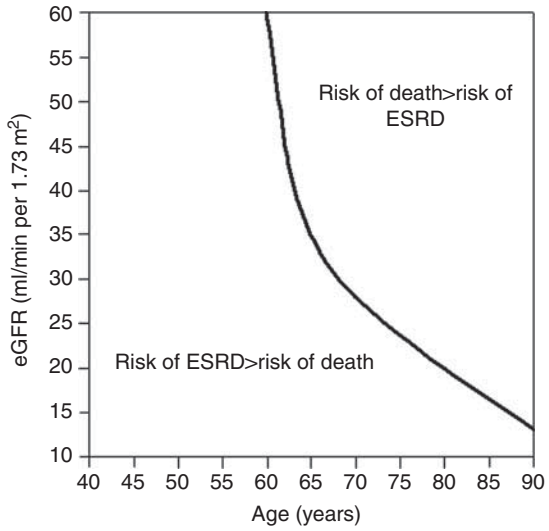

Figure 1 | Relationship between competing risks of end-stage renal disease (ESRD) and death without ESRD after 5 years by age and estimated glomerular filtration rate (eGFR). Boundary line identifies equal risks of ESRD and death: above the line, risk of death overcomes risk of ESRD, while the opposite occurs below the line.

Table 3 | Multivariable Cox model (HR and 95% CI) of determinants of ESRD

	HR (95% CI)	*P*-value
Age (years)	—	0.019
Male gender	1.32 (1.06–1.65)	0.015
BMI (kg/m^2)	0.97 (0.95–0.99)	0.007
Diabetes	1.17 (0.92–1.49)	0.212
CVD	—	0.010
Smoking	1.09 (0.78–1.51)	0.623
Systolic BP (5 mm Hg)	1 (0.97–1.03)	0.876
Cholesterol (mg/dl)	1.00 (1.00–1.00)	0.507
Uric acid (mg/dl)	0.95 (0.89–1.01)	0.080
Hemoglobin (g/dl)	0.93 (0.87–1.00)	0.043
Phosphate (mg/dl)	1.25 (1.10–1.42)	0.0008
Uprot (g/24 h)	—	0.037
CKD stage × Uprot	—	0.022
Age × Uprot	—	0.012
Age × CVD	—	0.020

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio; Uprot, 24 h proteinuria.
Model is stratified for CKD stage and center.
Restricted cubic splines were used for Uprot and for CKD stage*Uprot (see Statistical analysis).
The interaction between CKD stage and Uprot indicates that the predictive role of Uprot decreases from stage III to V. HRs of interactions of age with Uprot and CVD are depicted in Figures 2 and 3, respectively.
Only significant interactions with age were retained.

and epoietin, whereas the use of β-blockers, statins, and combined angiotensin-converting enzyme inhibitor-angiotensin II receptor blocker therapy was less frequent in elderly people. Adherence to dietary regimens did not differ by age class.

Overall median follow-up was 62.4 months; 394 ESRD events (all started dialysis) and 353 deaths (250 in the absence of ESRD) were observed. Overall death rates (per 100 patient-year) in the three classes of age (<65, 65–75, and >75) were equal to 1.7 (95% confidence interval (CI) 1.3–2.3), 6.1 (95% CI 5.1–7.4), and 14.5 (95% CI 12.6–16.7), respectively. Corresponding rates (per 100 patient-year) of ESRD by age were equal to 9.0 (95% CI 7.8–10.4), 7.3 (95% CI 6.1–8.8), and 7.9 (95% CI 6.4–9.8), whereas rates of death without ESRD were equal to 1.2 (95% CI 0.8–1.7), 5.2 (95% CI 4.2–6.5), and 12.6 (95% CI 10.7–14.9), respectively. Overall, risk of ESRD exceeded mortality ($P<0.0001$).

Figure 1 shows the complex nonlinear relationship between age and eGFR, and risk of first occurrence of ESRD or death without ESRD by 5 years of follow-up. Boundary line corresponds to equivalence of risks. The area above the line corresponds to pairs of values of age and eGFR for which the risk of death without ESRD overcomes risk of ESRD, the reverse being true in the area below. It appears that for eGFR >35 ml/min per 1.73 m^2, risk of death is greater in people >65 years; thereafter, the risk of ESRD increases with decreasing eGFR and overcomes risk of death without ESRD even in advanced age. Independent of eGFR, the risk of ESRD was higher than the risk of death for ages <60 years. Cumulative incidence curves of the competing risks over the entire length of follow-up for specific eGFR and age values are reported in the Supplementary Appendix (Supplementary Figure S1 online).

Results from multivariable analyses about age as modifier of determinants of ESRD are reported in Table 3. Male gender, lower body mass index, lower Hb, and higher phosphate levels increased the risk of ESRD independently of age. Conversely, age interacted significantly with proteinuria ($P=0.012$) and CVD ($P=0.20$). The complex interaction between age and proteinuria is depicted in Figure 2. Higher proteinuria significantly increased the risk of ESRD with advancing age; however, the predictive role of proteinuria diminished from stages III to V because of the contemporaneous interaction between CKD stage and proteinuria ($P=0.022$). A negative interaction between age and CVD was also disclosed; indeed, the unfavorable effect of CVD on the risk of ESRD decreased at older age and virtually disappeared in patients aged >75 years (Figure 3).

Results from multivariable analyses about age as risk modifier of overall death are reported in Table 4. CVD, ESRD, higher uric acid levels, and lower Hb increased the risk independently of age, whereas, as already reported in a previous paper,[18] association between proteinuria and death was nonlinear, with a decreased risk below 0.5 g/24 h and no substantial increments above 0.5 g/24 h (Table 4). A negative interaction between age and diabetes was observed ($P=0.002$) and is depicted in Figure 4. The unfavorable effect of diabetes on the risk of death decreased with aging and virtually disappeared in patients over 80 years.

Results from univariate analyses on ESRD and death are reported in the Supplementary Appendix online.

DISCUSSION

This is the first study evaluating the modifying effect of age on the competing risk of ESRD vs. death and on the

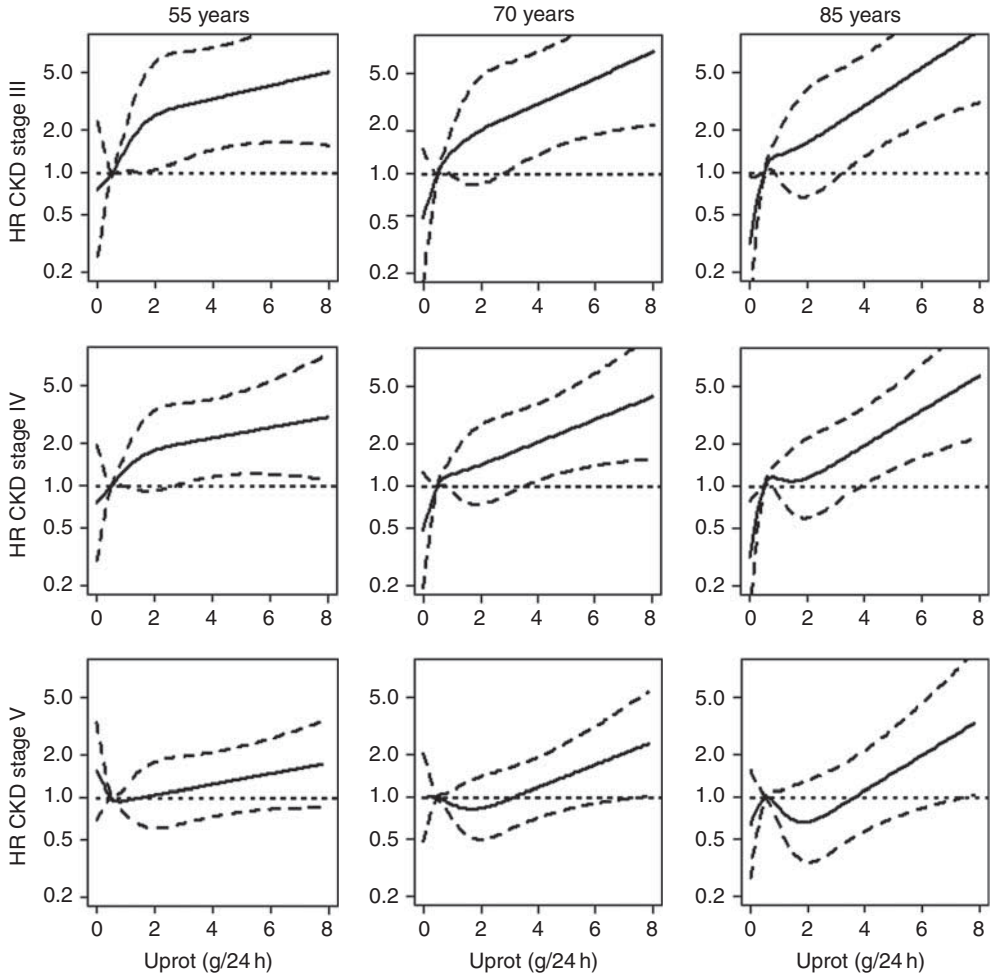

Figure 2 | Adjusted hazard ratio (solid line) and 95% confidence intervals (dashed lines) of the interaction between age and proteinuria in the prediction of end-stage renal disease (ESRD) by chronic kidney disease (CKD) stage (reference level of proteinuria, 0.5 g/24 h). Hazard ratios were estimated at three specific age values to properly describe the interaction effect. The horizontal dotted line represents hazard ratio = 1.

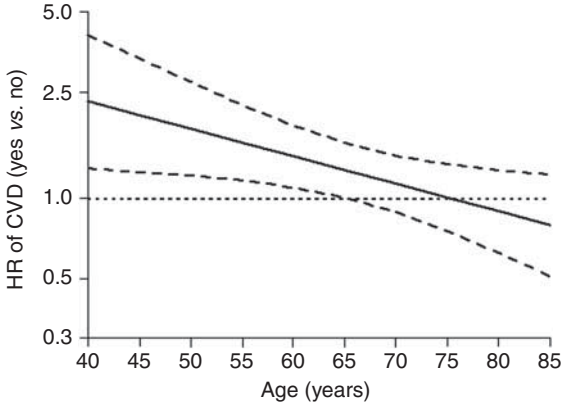

Figure 3 | Adjusted hazard ratio (solid line) and 95% confidence intervals (dashed line) of cardiovascular disease by age value in the prediction of end-stage renal disease (ESRD). The horizontal dotted line represents hazard ratio = 1.

predictive role of the main risk factors in a cohort of patients with non-dialysis CKD under stable nephrology care.

In our cohort, the rate of combined end point of ESRD and death without ESRD more than doubled in patients over 75 as compared with younger patients, and this risk excess went along with a steep increase of death. Age modified the risks of the two competing end points depending on the eGFR level (Figure 1 and Supplementary Figure S1 online). Indeed, while the risk for ESRD overcame death risk independently from eGFR up to 60 years of age, the risk of death without ESRD tended to prevail at older age strata. However, ESRD still represented the more frequent outcome not only in elderly patients with kidney failure (stage V), but also in those with less severe kidney disease, as it was the case in patients in the 65–75 years stratum with eGFR in the 20–35 ml/min per 1.73 m^2 range. These findings complement the analysis by O'Hare *et al*,[16] who compared the crude incidence rates of ESRD and death in a large cohort of US Veterans with CKD stages III–V. In that cohort, the incidence of death was fivefold greater than that of ESRD, and the eGFR thresholds marking a greater ESRD risk vs. mortality were much lower than ours. In particular, in middle-aged patients

Table 4 | Multivariable Cox model (HR and 95% CI) of determinants of death

	HR (95% CI)	*P*-value
Age (years)	—	<0.0001
Male gender	1.10 (0.87–1.40)	0.378
BMI (kg/m^2)	0.99 (0.97–1.02)	0.651
Diabetes	—	0.0004
CVD	1.35 (1.08–1.68)	0.010
Smoking	1.20 (0.83–1.72)	0.329
Systolic BP (5 mm Hg)	0.97 (0.94–1.00)	0.079
Cholesterol (mg/dl)	1.00 (1.00–1.00)	0.367
Uric acid (mg/dl)	1.07 (1.00–1.13)	0.037
Hemoglobin (g/dl)	0.94 (0.87–0.99)	0.014
Phosphate (mg/dl)	1.01 (0.87–1.18)	0.985
Proteinuria (g/24 h)		0.007
0.0 vs. 0.5	0.65 (0.46–0.91)	
1.0 vs. 0.5	1.13 (0.98–1.30)	
3.0 vs. 0.5	1.19 (0.84–1.69)	
ESRD	1.52 (1.11–2.09)	0.010
Age × diabetes	—	0.002

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HR, hazard ratio.
Model is stratified for CKD stage and center. ESRD was entered as a time-dependent variable. Restricted cubic splines were used for proteinuria, see Statistical analysis. HR of the interaction of age with diabetes is depicted in Figure 4. HRs for proteinuria are derived from restricted cubic splines and estimated for specific values.
Only significant interactions with age were retained.

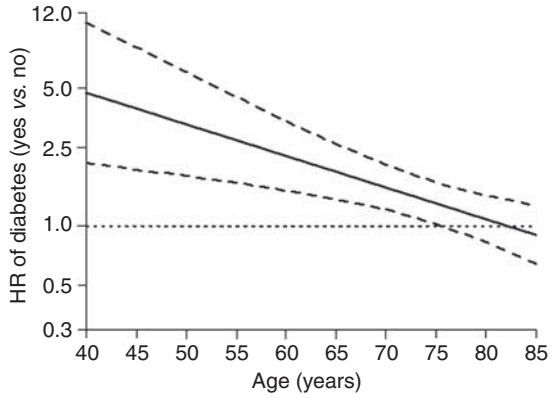

Figure 4 | Adjusted hazard ratio (solid line) and 95% confidence intervals (dashed lines) of diabetes by age value in the prediction of death. The horizontal dotted line represents hazard ratio = 1.

(45–65 years) rates of ESRD overcame mortality only if eGFR was <30 ml/min per 1.73 m^2, and the same occurred for patients aged 65–75 years exclusively when eGFR was <15 ml/min per 1.73 m^2.

When comparing the two studies, the different settings must be taken into account. Besides the obvious difference in gender (US Veterans were predominantly males, while in our cohort females were 41%), all our patients had been followed in a nephrology clinic for at least 1 year before enrolment, with four visits in the last year also in older patients, while, as reported recently,[19] more than one-third of old Veterans do not receive nephrology care before dialysis, and among those receiving predialysis care, 26% are seen by a nephrologist only 3 months before starting dialysis. This difference is crucial because prolonging the chronicity criterion for CKD definition from 3 to 12 months excludes a substantial number of patients, about 30% on average, with acute and transitory renal dysfunction rather than true CKD, and, moreover, it is associated with higher rates of ESRD and lower mortality.[20] The relevance of length and intensity of nephrology care on prognosis of CKD in elderly is further supported by the observation that death still represents the most frequent outcome in old people newly referred to nephrologist.[6,8] We cannot exclude that nephrology care may play a role *per se*; indeed, a recent study in a cohort of elderly diabetic CKD patients pointed out that mortality rates abate when patients are treated by nephrologists rather than other specialists.[21]

The effect of age on the fate of CKD patients does not represent the only critical issue in contemporary geriatric nephrology research, and in clinical practice as well; attention in fact has been recently drawn on the gaps of knowledge on age-related differences in the mechanisms and pathways that contribute to progression to ESRD and mortality.[2] This information is essential to better delineate risk profile, and preliminary to the identification of therapeutic goals, in elderly patients.[8,16,22] In this study, we originally assessed the effect of age on the role of the main recognized determinants of either outcome. Indeed, no previous study has systematically evaluated the interaction of age with other risk factors in the prediction of death and ESRD. We found that in the early stages of CKD, the presence of higher proteinuria significantly increased the risk of ESRD in older patients (Figure 2). The explanation is not readily apparent; we can only hypothesize that the kidney of elderly patients is more vulnerable to the 'nephrotoxic' effects of proteinuria due to the greater degree of renal fibrosis and ischemia.[23–25] To our knowledge, only one study has evaluated the impact of overt proteinuria by age on ESRD in tertiary nephrology care.[7] Authors found that overt proteinuria is associated with ESRD also in elderly patients; however, their analysis is limited by the low number of risk factors included in the Cox analysis, the inconsistent definition of overt proteinuria, and, more importantly, by the retrospective design and the small sample size.

Findings of our study therefore extend to the risk of ESRD, the major predictive role of proteinuria in elderly that has been previously evidenced for the mortality risk in the setting of general population or unreferred patients where death represents the most frequent outcome.[14,26] Overall our data lend support to the proposal of new trials specifically addressing the question as to whether a more intensive therapy with anti-renin–angiotensin system drugs may improve the cardiorenal prognosis in old proteinuric patients.[27]

In this study, age emerged also as a modifier of the prognosis dictated by CV disease and diabetes. Indeed, likely as a result of survival bias, the risk associated with these two

main comorbidities was attenuated in elderly CKD patients. Conversely, age did not affect the risk for ESRD associated with a series of modifiable risk factors, including body mass index and serum phosphate, or the risk of death associated with serum uric acid and proteinuria, and the risk for both outcomes associated with anemia. These results underscore that in outpatient nephrology clinics, the prognostic role of the above-mentioned risk factors holds true also at advanced age.

This study has strengths and limitations. Strengths are the well-characterized study cohort composed by patients under stable nephrology care, the long follow-up with the evaluation of the ideal hard end points for nephrology studies, and the systematic assessment of the commonly reported risk factors as continuous variables. On the other hand, results cannot be generalized to unreferred patients or to ethnic groups other than Caucasians. A further limitation is that the analysis of risk factors is based on a single data collection; therefore, we cannot exclude effects due to changes over time of the examined factors that we are unable to assess. Finally, even though we included in the survival analysis several determinants of outcome, the potential confounding of residual (unmeasured) factors cannot be excluded.

In conclusion, in non-dialysis CKD patients on stable nephrology care, (I) aging reduces the risk of ESRD vs. death, but the effect is remarkably minor as compared with previous analyses in patients extracted from general population where mortality predominates; (II) the predictive role of risk factors is selectively influenced by age, with the effect of proteinuria on the risk of ESRD being more pronounced at older age; on the other hand, the significant prognostic role of a number of modifiable determinants of outcome, such as body mass index, serum phosphate, and Hb for ESRD, and Hb, uric acid, and proteinuria for mortality, persists in older patients.

These findings may help nephrologists in recognizing which outcome is most important to the elderly CKD patients they regularly see (also to predict future renal replacement requirements), and at identifying the potential areas of further therapeutic improvement in this large and high-risk population.

MATERIALS AND METHODS

TABLE prospective observational study was performed in 25 outpatient nephrology clinics scattered throughout Italy. Study design and methods have been detailed previously.[5,18]

Patients

All the consecutive patients attending the centers during a 9-month period in 2003 were eligible if they had diagnosis of CKD, eGFR <60 ml/min per 1.73. m^2 (no substitutive treatment), and first visit dating back more than 1 year before the study start. Patients with acute kidney injury during the 6 months preceding the study visit were excluded.

All patients gave informed consent to the protocol that was approved by the local Ethical Committee.

Data collection

At the study visit, information was collected on demographic, clinical and laboratory data, and medical history, including previous CV event. The 24-h urine collection was also required, and eventually repeated if the value of measured creatinine excretion rate was outside the 60–140% range of the value calculated according to Dwyer and Kenler.[28] GFR was estimated by the 4-variable Modification of Diet in Renal Disease study equation. Outcome measures were ESRD (defined by occurrence of dialysis or renal transplant) and death (without ESRD and overall). For this study, follow-up expiration date was 31 May 2011.

Statistical analysis

Continuous variables were reported as mean and standard deviation (s.d.) or median and interquartile range according to their distribution, as assessed by the Shapiro–Wilk test. Categorical variables were reported as percentage. Age was analyzed as a continuous variable, but it was categorized into three classes (<65, 65–75, and over 75 years) only for descriptive purposes. Differences in characteristics of the three age strata were tested by means of one-way analysis of variance or Kruskal–Wallis (according to their distribution) and Pearson's χ^2 test for continuous and categorical variables, respectively. Median follow-up was estimated by the inverse Kaplan–Meier approach.[29] CIs of rates of ESRD and overall death were calculated assuming a Poisson distribution. Risks of ESRD vs. death without ESRD in the whole cohort were compared according to Kochar *et al.*[30]

The prognostic role of age and eGFR was investigated using as outcome either ESRD or death without ESRD, the question being 'Which of the two events, ESRD or death, is more likely to occur as first event at specific combinations of age and eGFR?' As, as first event, ESRD and death without ESRD are mutually exclusive events, we used the competing-risk approach[31] by fitting a separate model for either outcome according to Fine and Gray.[32] Therefore, in this analysis, only ESRD was considered for patients who eventually experienced both events (ESRD and death). Age and eGFR were entered as continuous covariates. Nonlinear association of the covariates with outcomes was first evaluated by restricted cubic splines according to Harrell *et al.*[33] Four knots were defined '*a priori*' for age (55, 65, 75, and 85 years) and for eGFR (15, 30, 40, and 50 ml/min per 1.73 m^2). Evidence of nonlinearity, as assessed by likelihood ratio test,[33] was found for the association between eGFR and ESRD; therefore, in the final models age entered as a linear term, while restricted cubic splines was used for eGFR. The coefficients for covariates derived from the two models and the predicted cumulative incidence of the two outcomes at 5 years of follow-up were finally used to estimate the pairs of values of age and eGFR, where the cumulative incidence of ESRD exceeded the cumulative incidence of death without ESRD.

We further investigated the modifying role of age on determinants of ESRD and, alternatively, of overall death (i.e. irrespective of ESRD), the question being 'Does age modulate the risk of determinants on ESRD (or death)?' Two multivariable Cox proportional-hazard models, for ESRD and death, stratified by CKD stage and center, were therefore used to estimate hazard ratios and 95% CI. Interactions between age and all the other covariates were tested in turn and the significant ones ($P<0.05$) were retained in the final models. Consistently with previous findings,[18] the interaction between CKD stage and proteinuria was forced into the model when predicting ESRD, and the nonlinear association between proteinuria and either outcome was taken into account by using restricted cubic splines with four knots placed *a priori* at clinically relevant values (0, 0.5, 1, and 3 g/24 h of proteinuria). When evaluating overall survival, ESRD was included as time-dependent covariate; when

evaluating time to ESRD, dead subjects were censored at the date of death.

Data were analyzed using SAS version 9.2 (SAS, Cary, NC) and R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria) software packages.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Relationship between competing risks of ESRD and death before ESRD over the whole extent of follow-up and by specific values of eGFR and age.

Table S1. Results of univariate Cox regression models on ESRD and death.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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