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RESEARCH PAPER

The relevance of geriatric assessments on the association between chronic kidney disease stages and mortality among older people: a secondary analysis of a multicentre cohort study

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Abstract

Background: age-adapted definition of chronic kidney disease (CKD) does not take individual risk factors into account. We aimed at investigating whether functional impairments influence CKD stage at which mortality increases among older people.
Methods: our series consisted of 2,372 outpatients aged 75 years or more enrolled in a multicentre international prospective cohort study. The study outcome was 24-month mortality. Kidney function was assessed by estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). Geriatric assessments included handgrip strength, short physical performance battery (SPPB), cognitive impairment, dependency in basic activities of daily living (BADL) and risk of malnutrition. Analysis was carried out by Cox regression, before and after stratification by individual functional impairments. Survival trees including kidney function and functional impairments were also investigated, and their predictivity assessed by C-index.
Results: overall, mortality was found to increase starting from eGFR = 30–44.9 ml/min/1.73 m^2 (hazard ratio [HR] = 3.28, 95% confidence interval [CI] = 1.81–5.95) to ACR = 30–300 mg/g (HR = 1.96, 95%CI = 1.23–3.10). However, in survival trees, an increased risk of mortality was observed among patients with impaired handgrip and eGFR = 45–59.9 ml/min/1.73 m^2, as well as patients with ACR < 30 mg/g and impaired handgrip and SPPB. Survival tree leaf node membership had greater predictive accuracy (C-index = 0.81, 95%CI = 0.78–0.84 for the eGFR survival tree and C-index = 0.77, 95%CI = 0.71–0.81 for the ACR survival tree) in comparison with that of individual measures of kidney function.
Conclusions: physical performance helps to identify a proportion of patients at an increased risk of mortality despite a mild–moderate impairment in kidney function and improves predictive accuracy of individual measures of kidney function.

Keywords: older people, geriatric assessment, disability, physical performance, mortality, ACR, eGFR

Key Points

- Age-adapted chronic kidney disease (CKD) definition does not take individual risk factors into account
- Whether functional status affects estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) mortality risk thresholds among older people is not known
- Physical performance identifies patients with mild–moderate impairment in kidney function and increased mortality
- Focusing on geriatric assessment for optimal risk definition would be better than adapting CKD definition to age.
- Alternatively, an age adapted definition of CKD should take functional risk factors into account.

Introduction

Adapting chronic kidney disease (CKD) definition to age is a matter of debate [1, 2]. The threshold for defining CKD stage 3a has been suggested to be changed to estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2, to account for expected changes in eGFR with normal ageing, avoid overdiagnosis and provide CKD diagnostic and classification systems that are less discriminatory toward the ever-expanding older component of the global population [3]. Yet, Levey et al. stated against an age-calibrated CKD definition, arguing that it may require more categories, based on the combination of age, GFR and albuminuria [4]. In addition, CKD classifications may change because of age without considering health status, and age calibration would not change major treatment recommendations and would not take into consideration the covariate patterns in individual patients [4].

Although age calibration would reduce overdiagnosis of CKD in older people and avoid an overestimation of the CKD burden in the general population [5, 6], older age also poses other challenges, including a high prevalence of risk factors and the need for optimal risk assessment strategies [7]. Geriatric assessment is recognised as a relevant multidimensional instrument able to capture the numerous dimensions of health status of older people, and its use in primary care includes the assessment of functional, mental and nutritional status, mobility and balance [8]. Impaired physical performance [9], dependency in basic activities of daily living (BADL) [10], cognitive impairment [11] and malnutrition [12] are known to affect prognosis in older populations. In addition, aforementioned functional impairments may interact with kidney function to impact prognosis [13, 14]. Thus, the influence of a geriatric assessment on the association between CKD stages and mortality is worth studying.

We aimed to investigate the association between CKD stages and mortality to verify if an age-adapted definition of CKD may apply to a population aged 75 years and older. We also aimed to verify if functional impairments change the CKD stage at which the risk of mortality increases. Our main hypothesis was that impaired physical performance, disability, malnutrition and/or cognitive impairment affect the thresholds.

Methods

This study uses data from the Screening for Chronic Kidney Disease among Older People across Europe (SCOPE) study

(European Grant Agreement No. 436849). Methods of the SCOPE study have been extensively described elsewhere [15]. A brief description of SCOPE methods is reported in Supplementary Table 1.

Overall, 2,461 patients were initially enrolled in the study, 77 patients were excluded from this analysis because of incomplete baseline kidney function data. Twelve patients were excluded because of missing follow-up, leaving a final sample of 2,372 patients for this analysis. In addition, 123 patients had missing data for albumin-to-creatinine ratio (ACR) and were excluded from the ACR analyses (Supplementary Figure 1).

Outcome

Overall mortality was the outcome of this study. Time from the day of study enrolment to last follow-up or death was considered as temporal function. For patients dying during the follow-up period, information about date, place and cause of death were collected from death certificates provided by relatives or caregivers. City or town registers were consulted to retrieve information about death, when neither relatives nor caregivers could be contacted.

Study variables

Baseline serum creatinine was measured by isotope dilution mass spectrometry traceable standard method, and estimated GFR (eGFR) was calculated by creatinine-based Berlin Initiative Study (BIS) equation, which was specifically developed in a population older than 70 years [16].

Physical performance was measured by Short Physical Performance Battery (SPPB) [17] and hand-grip strength [18]. The total SPPB score was calculated and an analytical variable was generated to identify people with SPPB score < 7 [17]. Grip strength was measured twice on each hand by North Coast hand dynamometer and the highest value obtained with the dominant hand was used for this study. During assessment, patients were seated with the wrist in a neutral position and the elbow flexed 90°. Hand grip strength was categorised by using sex-specific cut-offs (women <16 kg, men <27 kg), according to the EWSGOP2 criteria [19].

Disability was assessed by Katz Index [20], and dependency in one or more BADL was considered as a risk factor in the analysis. Cognitive impairment was defined as age- and education-adjusted Mini Mental State Examination (MMSE) score <24 [21]. Nutritional status was assessed using the Mini Nutritional Assessment (MNA) questionnaire [22]. A total MNA score < 24 was used to identify participants at risk of malnutrition.

Statistical analyses

Patient characteristics were reported using descriptive statistics. Statistical differences between survivors and dead were tested by using the Welch Two-Sample *t*-test for normally distributed continuous variables and Pearson's Chi-squared test for categorical variables. The distribution of each variable was also judged by visual inspection. Then, we estimated the mortality rate per 1,000 person-years in the whole population and among individuals carrying each individual risk factor. The person-days of follow-up computed from the day of the first outpatient visit to death or the end of the study. Kaplan–Meier curves were used to visualise the cumulative survival probability over the 2-year follow-up period. The association between kidney function and mortality was investigated by univariate and multivariable Cox proportional hazard (PH) regression models adjusted by age, sex, SPPB, Hand grip strength, MMSE, BADL and MNA. A further adjustment for country of origin was made to assess for interhospital and interregional differences. The fully adjusted model was also repeated after stratification by SPPB, handgrip, BADL dependency, risk of malnutrition and cognitive impairment. The PH assumptions were assessed through the inspection of Schoenfeld residual plots and by regressing Schoenfeld residuals against time to test for independence between time and residuals. Multicollinearity was investigated using the variance inflation factor (a value >3 was considered index of multicollinearity).

To further investigate the potential prognostic interplay between kidney function and functional status, we fitted two separate survival tree models based on eGFR or ACR and impairments in functional domains. A complete description of analytic method is reported in Supplementary Box 1.

Sensitivity analyses were also carried out in an attempt to verify whether the worst cases identified by geriatric assessment may affect the results obtained by the survival tree analysis. To this aim, the survival trees were re-analysed after excluding patients with SPPB = 0, Handgrip strength <19 in men and < 12 in women, MMSE<18, dependency in all BADLs or MNA < 13.5. Furthermore, we performed additional survival tree analyses after including CKD-EPI [23] instead of BIS eGFR equation, to verify the independence of study results from methods used to assess eGFR. The accuracy of the survival tree models produced by sensitivity analyses was also assessed as aforementioned.

Statistical analysis was carried out by the use of a forestmodel (https://CRAN.R-project.org/package=forestmodel), rpart (https://CRAN.R-project.org/package=rpart), rms (https://CRAN.R-project.org/package=rms) and survminer (https://CRAN.R-project.org/package=survminer) packages of R software V4.0.

Results

Overall, the mean age of the participants was 80.4 ± 4.2 years, 388 (16.4%) were aged 85 and older and 1,326 (55.9%) were women. At the baseline, the mean SPPB score was 8.6 ± 3.0 and handgrip strength was 25.9 ± 13.0. The number of lost BADL was 0.2 ± 0.7, age-and education-adjusted MMSE score was 27.9 ± 2.7 and MNA score was 26.1 ± 2.6. The mean eGFR was 53.2 ± 14.8 ml/min/1.73 m^2, and ACR was 118.2 ± 499.8 mg/g. A complete

Table 1. General characteristics of the study population and age- and sex-adjusted Cox PH models of study risk factors and kidney function measures to overall 24-month mortality

	All $N = 2,372$	Survivors ($n = 2,252$)	Died ($n = 120$)	Mortality rate n/1,000 py (95%CI)	Age- and gender-adjusted HR (95%CI)
Age (years)					
75–84	1,984 (83.6)	1,904 (84.5)	83 (69.2)	22.3 (17.6–27.2)	1.0
85 or more	388 (16.4)	348 (15.5)	37 (30.8)	53.2 (36.1–70.4)	2.36 (1.60–3.47)
Sex (men)	1,046 (44.1)	968 (43.0)	78 (65.0)	40.4 (31.4–49.4)	2.40 (1.65–3.49)
SPPB<7	524 (22.1)	480 (21.3)	44 (37.0)	47.6 (33.5–61.7)	2.20 (1.49–3.26)
Hand grip strength <27 kg in men and < 16 kg in women	500 (21.1)	454 (20.2)	46 (38.3)	51.8 (36.8–66.8)	1.95 (1.33–2.88)
MMSE<24	183 (7.7)	170 (7.6)	13 (10.8)	40.1 (18.3–61.9)	1.36 (0.76–2.44)
Dependency in 1 or more BADL	334 (14.0)	301 (13.4)	33 (27.5)	54.0 (35.6–72.4)	2.26 (1.50–3.40)
MNA < 24	365 (15.4)	335 (14.9)	30 (25.0)	46.3 (29.7–62.9)	1.94 (1.28–2.95)
eGFR, ml/min/1.73 m^2					
60 or more	797 (33.6)	781 (34.7)	16 (13.3)	10.5 (5.4–15.7)	1.0
45–59.9	912 (38.4)	884 (39.2)	28 (23.3)	16.3 (10.3–22.4)	1.37 (0.74–2.54)
30–44.9	481 (20.3)	443 19.7)	38 (31.7)	43.6 (29.7–57.5)	3.25 (1.79–5.91)
<30	182 (7.7)	144 (6.4)	38 (31.7)	127.8 (87.2–168)	9.02 (4.91–16.55)
ACR, mg/g[a]					
<30	1,647 (69.4)	1,601 (74.8)	46 (41.8)	14.8 (10.6–19.1)	1.0
30–300	450 (19.0)	418 (19.5)	32 (29.1)	38.4 (25.1–51.7)	2.06 (1.30–3.27)
>300	152 (6.4)	120 (5.6)	32 (29.1)	126.9 (82.9–171)	6.88 (4.33–10.92)

Data are no. of cases (percentage) unless otherwise stated. SPPB, short physical performance battery; MMSE, mini mental state examination; BADL, basic activities of daily living; MNA, mini nutritional assessment; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; py, person-years [a]Data are limited to 2,249 participants because of missing ACR data in 123 patients.

description of baseline clinical and demographic characteristics of enrolled patients is reported in Supplementary Table 2.

Patients were followed-up for 22.3 ± 4.9 months; the median survival time was 23 [IQR, 22–24] months. During follow-up period, 120 (5.1%) patients died with an incidence of mortality of 25.3/1,000 person-years, and increasing rates across eGFR and ACR stages (Table 1). Kaplan–Meier curves showing survival in relation to study risk factors are reported in Supplementary Figure 2. Older age, sex, BADL dependency, impaired handgrip and SPPB and MNA < 24 were significantly associated with 24-month mortality in the age-and sex-adjusted models (Table 1). After adjusting for potential confounders, eGFR and ACR showed a graded association with overall mortality which was statistically significant for eGFR<45 ml/min/1.73 m^2 and ACR > 30 mg/g (Table 2). In the adjusted eGFR model, male sex also qualified as significant predictor, SPPB and BADL were not significantly associated with the outcome. In the adjusted ACR model, age, male sex and impaired handgrip were significant predictors, whereas ADL dependency was not significantly associated with the outcome. Results were unchanged after further adjusting for country of origin (Supplementary Table 3), and PH assumptions confirmed (Supplementary Table 4 and Supplementary Figure 3).

When stratifying the eGFR analysis by SPPB, the risk of mortality increased significantly for eGFR<45 ml/min/1.73 m^2 in both participants with impaired or preserved physical performance, BADL dependency and risk of malnutrition. In cognitively impaired participants, an association between eGFR and mortality was observed only for eGFR<30 ml/min/1.73 m^2, whereas the risk of mortality was found to increase significantly starting from eGFR = 30–44.9 ml/min/1.73m^2 among participants without cognitive impairment (Supplement Figure 4). When stratifying ACR analysis, a graded association between ACR and mortality could not be observed among cognitively impaired patients (Supplementary Figure 5).

Survival tree analysis including eGFR and functional impairments showed that the lowest mortality was observed among patients with eGFR≥45 ml/min/1.73 m^2 and preserved handgrip strength and was considered as reference in the Cox regression analysis (Supplementary Figure 6A). Similar mortality was observed among those with impaired handgrip and eGFR≥60 ml/min/1.73 m^2. Interestingly, the node at which the risk of mortality started to increase was that including patients with impaired handgrip and eGFR = 45–59.9 ml/min/1.73 m^2 (Table 3). Among patients with eGFR<45 ml/min/1.73 m^2, a graded increase in risk was observed, with highest mortality observed among patients with eGFR<30 ml/min/1.73 m^2, with or without BADL dependency. Patients with eGFR = 30–44.9 ml/min/1.73 m^2 showed intermediate mortality, with a graded increase in risk associated to the co-occurrence of handgrip or SPPB impairment (Table 3). Cognitive impairment and risk of malnutrition were not loaded into survival tree nodes.

Survival tree including ACR and functional impairments is reported in Supplementary Figure 6B. The lowest mortality rate was observed among patients with ACR < 30 mg/g and preserved handgrip. The risk of mortality was found to increase among patients with ACR = 30–300 mg/g

Table 2. Fully adjusted Cox regression models of kidney function measures to 24-month overall mortality

	Fully adjusted HR (95%CI)
eGFR model	
Age (years)	
75–84	1.0
85 or more	1.31 (0.86–1.99)
Sex (men)	2.23 (1.51–3.31)
SPPB<7	1.31 (0.84–2.03)
Hand grip strength	1.49 (0.99–2.25)
<27 kg in men and < 16 kg in women	
MMSE<24	1.21 (0.65–2.26)
Dependency in 1 or more BADL	1.53 (0.97–2.41)
MNA < 24	1.29 (0.83–2.03)
eGFR, ml/min/1.73 m^2	
60 or more	1.0
45–59.9	1.42 (0.77–2.63)
0–44.9	3.28 (1.81–5.95)
<30	7.82 (4.23–14.45)
ACR model[a]	
Age (years)	
75–84	1.0
85 or more	1.63 (1.05–2.52)
Sex (men)	2.38 (1.56–3.61)
SPPB<7	1.31 (0.82–2.10)
Hand grip strength	1.71 (1.11–2.63)
<27 kg in men and < 16 kg in women	
MMSE<24	1.06 (0.57–1.98)
Dependency in 1 or more BADL	1.52 (0.94–2.45)
MNA < 24	1.42 (0.89–2.27)
Albumin-to-creatinine ratio (ACR) mg/g	
<30	1.0
30–300	1.96 (1.23–3.10)
>300	5.51 (3.41–8.90)

[a]Data are limited to 2,249 participants because of missing ACR data in 123 patients

and BADL independency, followed by patients with ACR < 30 mg/g and impaired handgrip and SPPB, patients with ACR = 30–300 mg/g and BADL dependency, and those with ACR ≥ 300 mg/g independent of other functional impairments (Table 3). Even in this case, cognitive impairment and risk of malnutrition were not loaded into survival tree nodes**.** The accuracy obtained by eGFR survival tree node membership and, to a lesser extent that of ACR survival tree node membership was significantly higher than that obtained considering individual risk factors included in the analysis (Table 4). In addition, performance measures remain stable after bootstrap resampling (Table 5) and the calibration slope of both models was near-optimal.

After excluding patients with complete dependency in BADLs, SPPB = 0, and severe impairment of handgrip, cognitive or nutritional status, the survival across tree nodes was substantially unchanged, as was the accuracy of the leaf nodes in predicting 24-month mortality (Supplementary Figures 7 and 8). After using CKD-EPI equation instead of BIS equation to estimate GFR, the resulting survival tree remained unchanged as well (Supplementary Figure 9, Supplementary Tables 5 and 6).

Discussion

This study shows that even if the CKD definition of an eGFR<45 ml/min/1.73 m^2 may reliably apply to most people aged 75 or more, a clinically relevant prognostic interplay exists between impaired physical performance and less severe stages of CKD. In addition, physical performance and disability improve the accuracy of eGFR and ACR in predicting prognosis.

Among older people, mortality risk starts to increase for lower eGFR values compared with the adult population [6, 24], and substantial evidence showed that mortality starts to increase for eGFR values < 45 ml/min/1.73 m^2 in older populations [25–27]. For this reason, an age-adapted definition of CKD has been proposed [28]. Main advantages of such adaptation would be to account for age-related decline in eGFR, consistency with evidence regarding the prognostic role of eGFR, and to avoid overdiagnosis of CKD among older people [28]. Nevertheless, the age-adapted approach does not take into consideration the risk factors relevant to older people, including physical performance, frailty, disability, risk of malnutrition and cognitive impairment.

The most interesting results from survival tree analyses regard participants with eGFR = 45–59.9 ml/min/1.73 m^2 and impaired handgrip, where a significant increase in mortality was observed. This finding suggests that low mortality risk could not be generalised to the entire older patient population with stage 3a CKD, and a simple measure of physical performance helps to identify patients with moderate CKD carrying a slightly but significantly increased risk of mortality. Being a major determinant of muscle strength, sarcopenia is likely contributing to explain this complex scenario. Sarcopenia is highly prevalent in patients with CKD [29], and it was previously found to be an independent predictor of mortality in different older populations [30–32]. In addition, low muscle mass influences serum creatinine levels, leading to overestimation of kidney function [33], which may account for the observed increased risk of mortality starting from eGFR = 45–59.9 ml/min/1.73 m^2. Conversely, the assessment of physical performance and disability may capture several other dimensions strictly linked to both kidney function and ageing, including inflammation, oxidative stress and endocrine disorders [34], that are likely able to reveal the subclinical risk.

The most relevant clinical consequence of the present finding would be the need of assessing physical performance to clarify whether patients with stage 3a CKD can be truly labelled as carrying a low or moderately increased mortality risk. Given that among 912 (38.4%) patients belonging to stage 3a CKD, 172 (18.8%) carry such a risk profile in our study population, geriatric assessments may help to identify a significant proportion of patients at risk. Furthermore, the prognostic interplay of physical performance and eGFR = 30–44.9 ml/min/1.73 m^2, as well as that of BADL dependency and eGFR<30 ml/min/1.73 m^2 also contribute to improve predictive accuracy of leaf node membership with respect to eGFR alone or other individual risk factors. Thus,

Table 3. Age- and sex-adjusted Cox regression analysis of leaf node membership to 24-month mortality

Survival tree with eGFR	Absolute risk	Relative risk (95%CI)	Age- and sex-adjusted HR (95%CI)
Node 3 (eGFR ≥45 and normal handgrip)	0.02	1.0	1.0
Node 5 (eGFR ≥60 and impaired handgrip)	0.01	0.61 (0.10–1.97)	0.60 (0.14–2.53)
Node 6 (eGFR 45–59.9 and impaired handgrip)	0.06	2.53 (1.20–4.87)	2.36 (1.15–4.86)
Node 10 (eGFR 30–44.9, SPPB 7–12 and normal handgrip)	0.05	2.03 (1.04–3.72)	1.75 (0.91–3.35)
Node 11 (eGFR 30–44.9, SPPB 7–12 and impaired handgrip)	0.13	5.64 (2.37–11.4)	4.34 (1.88–10.0)
Node 12 (eGFR 30–44.9 and SPPB 0–6)	0.12	5.33 (3.01–9.15)	5.39 (2.95–9.84)
Node 14 (eGFR <30 and no BADL dependency)	0.17	7.46 (4.48–12.3)	6.86 (3.96–11.9)
Node 15 (eGFR <30 and BADL dependency)	0.33	14.51 (8.08–24.6)	14.63 (7.71–27.78)
Survival tree with ACR			
Node 4 (ACR < 30 and normal handgrip)	0.02	1.0	1.0
Node 6 (ACR < 30, impaired handgrip and SPPB 7–12)	0.04	2.01 (0.87–4.15)	1.73 (0.78–3.82)
Node 7 (ACR < 30, impaired handgrip and SPPB 0–6)	0.09	4.45 (2.11–8.61)	4.29 (2.04–9.00)
Node 9 (ACR 30–300 and no BADL dependency)	0.06	2.68 (1.52–4.65)	2.16 (1.21–3.84)
Node 10 (ACR 30–300 and BADL dependency)	0.15	7.15 (3.53–13.42)	5.87 (2.88–12.01)
Node 11 (ACR ≥300)	0.21	10.11 (6.27–16.43)	9.02 (5.37–15.11)

Table 4. Accuracy of leaf node memberships obtained by survival trees in comparison to individual study risk factors

	C-index (95%CI)	*P* value*	*P* value**
BADL dependency	0.68 (0.62–0.73)	<0.001	<0.001
Cognitive impairment	0.66 (0.61–0.72)	<0.001	<0.001
Handgrip	0.67 (0.62–0.72)	<0.001	<0.001
SPPB	0.69 (0.63–0.74)	<0.001	0.005
MNA	0.68 (0.62–0.73)	<0.001	0.001
GFR < 60	0.69 (0.64–0.74)	<0.001	0.001
GFR < 45	0.74 (0.69–0.79)	0.006	0.07
GFR < 30	0.73 (0.68–0.78)	0.003	0.05
ACR > 30	0.72 (0.67–0.77)	0.01	0.01
ACR > 300	0.72 (0.67–0.78)	0.009	0.05
Leaf node membership eGFR survival tree	0.81 (0.78–0.84)		
Leaf node membership ACR survival tree	0.77 (0.71–0.81)		

*P values refer to the comparisons between leaf node membership from eGFR survival tree and individual study risk factors. **P values refer to the comparisons between leaf node membership from ACR survival tree and individual study risk factors.

Table 5. Performance measures of Cox regression model including eGFR or ACR survival tree leaf node membership before and after 1,000-fold bootstrap resampling procedure

eGFR model	Pre-bootstrap sample	Post-bootstrap sample
C statistic	0.81 (0.78–0.84)	0.78 (0.76–0.80)
Somer's Dxy	0.62 (0.56–0.68)	0.56 (0.52–0.60)
Calibration slope	1.00 (0.81–1.15)	0.84 (0.68–1.04)
ACR model		
C statistic	0.77 (0.71–0.81)	0.75 (0.71–0.78)
Somer's Dxy	0.54 (0.42–0.62)	0.50 (0.42–0.56)
Calibration slope	1.00 (0.82–1.14)	0.86 (0.66–1.08)

the assessment of physical performance and disability can be useful in the assessment of older patients with any CKD stage. Although nephrologists and geriatricians recognised the relevance of geriatric assessment in older CKD patients [35], current evidence regarding its use in primary care (i.e. the presumable setting for community-dwelling older people with mild-to-moderate CKD) is mixed and barriers to implementation still need to be overcome and warrant further investigations [36].

Similarly, a prognostic interplay of physical performance and disability was observed with ACR. A relevant prognostic role of proteinuria among older people, even greater than that of eGFR, was consistently reported in several different populations [37–41]. Findings from survival tree analysis add to current knowledge by demonstrating that physical performance and disability may help to improve predictive properties of albuminuria among people aged 75 or more. Indeed, although the independent association between ACR > 300 mg/g and mortality would be expected in keeping with previous observations [42], a relevant prognostic interplay between BADL dependency and ACR = 30–300 mg/g could be observed. Most interestingly, the prognostic interplay of handgrip strength, SPPB and ACR < 30 mg/g suggests that prognosis stratification among normoalbuminuric patients may be improved by combining laboratory and geriatric assessments. The cross-sectional

association between proteinuria and frailty is in agreement with this view [43, 44]. The frailty conceptual framework describes a condition of increased vulnerability to stressors due to declining function of homeostatic mechanisms and consequent increased risk of adverse health outcomes, where impairment in physical performance plays a key role [45, 46]. This evidence may be relevant in our findings of increased mortality risk in relation to physical impairment among normoalbuminuric patients. Indeed, it is worth noting that a non-significant trend of increased mortality along with an increase in ACR was previously observed among patients with ACR < 30 [39], and even low-grade albuminuria was found associated with frailty [44].

The apparent lack of prognostic interplay of kidney function with cognitive impairment and risk of malnutrition does not mean that these conditions should not be considered as important prognostic factors, rather that impaired physical performance and disability might exert a more relevant prognostic influence in our study population**.**

Limitations of our study deserve to be recognised. Although we were able to add an internal validation of our predictive model, the lack of an external validation remains a relevant limitation of this study. Given the observational design, confounding by indication is a relevant limitation. However, sensitivity analyses confirmed our main results. In addition, the results of the stratified analyses might lack in precision of estimates due to the relatively small size in selected subgroups of patients, especially those with cognitive impairment. Furthermore, including only baseline eGFR and ACR measurements, our results do not reflect changes in kidney function during follow-up. Finally, using a limited set of potential predictors, we cannot rule out the effect of residual confounding. However, we aimed at investigating the prognostic interplay of selected functional impairments, eGFR and ACR rather than searching for the most relevant risk factors.

The main strengths of our study are the inclusion of a real-world population of older outpatients enrolled by using a limited set of inclusion/exclusion criteria and the systematic use of geriatric assessment to explore relevant health dimensions in older outpatients. Second, the good internal validity and high reproducibility of survival trees in sensitivity analyses, as well as the good level of the predictive accuracy estimates, add further significance to study findings.

In conclusions, although an age-adapted definition of CKD seems to work well in prognostic stratification of people aged 75 and older, physical performance helps to identify a significant proportion of patients at increased risk of mortality, despite a moderate impairment in kidney function. These findings strengthen the need to focus on strategies for optimal risk assessment [7] rather than adapting CKD definition to age. Alternatively, an age-adapted definition of CKD should take the individual functional status into account. Finally, the assessment of physical performance and disability significantly improves accuracy of measures of kidney function in predicting 24-month mortality and could therefore be of value in routine clinical evaluations of older people with CKD.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Aging* online.

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