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Predictivity of survival according to different equations for estimating renal function in community-dwelling elderly subjects

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Abstract

Background. Detection of subjects with early chronic kidney disease (CKD) is important because some will progress up to stage 5 CKD, and most are at high risk of cardiovascular morbidity and mortality. While validity and precision of estimated glomerular filtration rate (eGFR) equations in tracking true GFR have been repeatedly investigated, their prognostic performance for mortality has not been hitherto compared. This is especially relevant in an elderly population in whom the risk of death is far more common than progression.

Methods. We analysed data of participants in the InCHIANTI study, a community-based cohort study of older adults. Twenty-four-hour creatinine clearance (Ccr), Cockcroft–Gault (C-G) and Modification of Diet in Renal Disease (MDRD)-derived equations (six and four input variables) were calculated at enrolment (1998–2000), and all-cause mortality and cardiovascular mortality were prospectively ascertained by Cox regression over a 6-year follow-up.

Results. Of the 1270 participants, 942 (mean age 75 years) had complete data for this study. The mean renal function ranged from 77 ml/min/1.73 m^2 by Ccr to 64 ml/min/1.73 m^2 by C-G. Comparisons among equations using K/DOQI staging highlight relevant mismatches, with a prevalence of CKD ranging from 22% (MDRD-4) to 40% (C-G). Reduced renal function was a strong independent predictor of death. In a Cox model—adjusted for demographics, physical activity, comorbidities, proteinuria and inflammatory parameters—participants with Ccr 60–90 ml/min/1.73 m^2 and Ccr <60 ml/min/1.73 m^2 were, respectively, 1.70 (95% CI: 1.02–2.83) and 1.91 (95% CI: 1.11–3.29) times more likely to die over the follow-up compared to those with Ccr >90 ml/min/1.73 m^2. For the C-G, the group with values <60 ml/min/1.73 m^2 had a significant higher all-cause mortality compared to those with values >90 ml/min/1.73 m^2 (HR 2.59, 95% CI: 1.13–5.91). The classification based on the MDRD formulae did not provide any significant prognostic information. The adjusted risk of all-cause mortality followed a similar pattern when Ccr and estimating equations were introduced as continuous variables or dichotomized as higher or lower than 60 ml/min. C-G was the best prognostic indicator of cardiovascular mortality. Possibly, Ccr and C-G are better prognostic indicators than MDRD-derived equations because they incorporate a stronger effect of age.

Conclusions. In a South-European elderly population, the prevalence of CKD is high and varies widely according to the method adopted to estimate GFR. Researchers and clinicians who want to capture the prognostic information on mortality related to kidney function should use the Ccr or C-G formula and not MDRD equations. These results highlight the importance of strategies for early detection and clinical management of CKD in elderly subjects.

Keywords: Cockcroft–Gault formula; elderly; MDRD equations; mortality; population-based study

Introduction

The epidemiology of chronic kidney disease (CKD) is receiving growing attention across medical disciplines [1–6]. This global recognition parallels the growing evidence that mild to moderate renal dysfunction is associated with increased risks of all-cause mortality as well as cardiovascular morbidity and mortality [7–13]. CKD is predominantly a disease of older people [14–18], and age affects outcomes in CKD with older people more likely to die than to develop stage 5 CKD [19,20]. Thus, an accurate and feasible estimate of glomerular filtration rate (eGFR) is critical in the clinical evaluation of older subjects.

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Equations widely accepted in the medical community are the Cockcroft and Gault (C-G) formula [21] and the Modification of Diet in Renal Disease (MDRD) formulae [22]. The abbreviated MDRD formula [23] was recommended for classifying patients with CKD into stages established by the National Kidney Foundation kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) [1].

While predictive performance of these equations in estimating true GFR has been extensively exploited [24,25], their prognostic value for mortality has seldom been compared. If one goal of estimating renal function in clinical practice is to obtain estimates of death or cardiovascular risks due to early CKD, it seems logical to use the equation that provides the best prediction of these outcomes. This is especially relevant in an elderly population.

Thus, we examined the relationship between renal function estimated by different equations and all-cause and cardiovascular mortality over a 6-year follow-up among participants in the Invecchiare in Chianti (InCHIANTI) study.

Material and methods

The study participants consisted of men and women aged 65 and older who participated in the InCHIANTI study. The rationale, design and data collection have been described elsewhere [26]. Briefly, a representative sample of 1270 persons was randomly selected from an elderly population living in two small towns in the Chianti area, Tuscany, Italy. Of them, 942 had complete data for the analyses here presented. In comparison with subjects included in the study, those excluded were older and had greater comorbidities, as reported elsewhere [27].

The study was described to each participant and all signed written, informed consent. The participants were evaluated at the study entry (1998–2000), at 3-year and 6-year follow-up visits. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee. After 6 years, we collected data on all-cause and cardiovascular mortality for the study entry cohort, using data from the Mortality General Registry maintained by the Tuscany Region and the death certificates that are deposited after the death at the Registry office of the Municipality of residence. We classified cardiovascular deaths with ICD-9-CM codes from 410 to 438.

Blood and urinary parameters

At the time of the home interview, participants were provided a plastic container and received detailed instructions for 24-h urine collection, including advice to take note of the start and end time. Subjects with incomplete times of collection were excluded. Blood samples were obtained after a 12-h fast and after the participants had been resting for at least 15 min. Aliquots of serum and 24-h urine samples were stored at −80°C and were not thawed until analysed. Serum urea nitrogen and serum albumin were measured using commercial kits. Urinary protein excretion was assessed on early morning spot sample by an automated urine test-strip analyser (Aution Max AX-4280, A. Menarini Diagnostics, Florence, Italy) with minimum detecting sensitivity of 5 mg/dl. Serum high sensitivity C-reactive protein (CRP) was measured in duplicate using an enzyme-linked immunoabsorbent assay (ELISA) and colorimetric competitive immunoassay that uses purified protein and polyclonal anti-CRP antibodies; the minimum detectable threshold was 0.03 mg/l, and the inter-assay coefficient of variation was 5%. Serum and urine creatinine were measured by using a compensated modified Jaffe method for Roche/Hitachi analyser (Roche Diagnostics GmbH, Mannheim, Germany). The method has been standardized against isotope dilution mass spectrometry (IDMS) starting with a primary calibrator, e.g. the standard reference material (SRM) 914. Making use of a standardized IDMS-traceable calibrated creatinine assay, we applied the re-expressed MDRD equations [28,29].

The following indexes of renal function were calculated:

- Twenty-four-hour Ccr: urinary creatinine (mg/dl)* urinary volume (ml)/serum creatinine (mg/dl)*length of collection (min).
- Cockcroft–Gault (C-G): (140−age)*weight*0.85(if female)/(serum creatinine*72).
- eGFR from the six-variable MDRD equation (MDRD-6): 161.5*(serum creatinineˆ−0.999)*(ageˆ −0.176)*0.762(if female)*(BUNˆ−0.170)*(albuminˆ 0.318).
- eGFR from the four-variable MDRD equation (MDRD-4): 175*(serum creatinineˆ−1.154)*(ageˆ−0.203)* 0.742(if female).

In MDRD equations, we did not apply the multiplier factor for blacks as all individuals were whites.

To make allowance for comparisons with MDRD formulae, Ccr and C-G results were adjusted for 1.73 body surface area (BSA) calculated according to the DuBois and Dubois formula [30]: BSA = 0.007184* (weightˆ0.425)*(heightˆ0.725) where weight (kg) and height (cm) were measured objectively.

Comorbidity and other variables

All participants were examined at home by an experienced clinician. Diseases were ascertained according to pre-established criteria that combine information from self-reported physician diagnoses, current pharmacological treatment, medical records, clinical examinations and previous blood tests. Diseases included in the current analysis were myocardial infarction, angina, chronic heart failure (CHF), stroke, diabetes and hypertension. Criteria for defining hypertension were previous positive history and/or a measured blood pressure >140/90 mmHg. Smoking history was determined from self-report and dichotomized in the analysis as ‘current smoking’ versus ‘ever smoked’ and ‘never smoked’. Physical activity in the year before the interview was coded as (1) sedentary, (2) moderate and (3) high. Alcohol intake (grams/day) was estimated by the European Prospective Investigation into Cancer and Nutrition food frequency questionnaire [31].

Statistical analysis

Variables are reported as mean values ± standard deviations (SD), medians and inter-quartile ranges or percentages. Comparisons between participants who died and those who remained alive were performed by age-adjusted linear regression models (ANCOVA) and Mantel–Hansel chi-square. Agreement between indexes of renal function was explored by scatter plots with lines drawn at the 90 and the 60 ml/min/1.73 m^2 values as well as by Pearson's correlations. The relationship between measures of renal function and all-cause and cardiovascular mortality was analysed by the Cox proportional hazard model. Potential confounders of the relationship between renal function and mortality were those significantly associated with preliminary univariate analysis. We included age and gender among the potential confounders for Ccr but not for MDRD and C-G, as those variables were already incorporated in the estimate equations. Moreover, we did not compute as potential confounders the cardiovascular events that have occurred after the first wave of InCHIANTI, e.g. after study entry, since they may be involved in the process by which reduced renal function may increase the risk of death. Ccr and different estimate equations were introduced in the model according to the K/DOQI staging [1] or as continuous variables or dichotomized for values above or below 60 ml/min/1.73 m^2.

Correlations were performed also to evaluate the relationship between age and different estimate equations. We tested non-linearity of this relationship using the quadratic term of the age.

We performed all analyses using SAS (version 8.2, SAS Institute, Inc., Cary, NC, USA) assuming a statistical significance level set at $P < 0.05$.

Results

Characteristics of the study population at enrolment according to vital status at the end of the follow-up are reported in Table 1. Only 1.6% males and 1.3% females had serum creatinine values >1.5 mg/dl. Mean levels of renal function ranged from 77 ml/min/1.73 m^2 by Ccr and 64 ml/min/1.73 m^2 by MDRD-6 and C-G, with MDRD-4 values lying in between. Percentages of comorbidities are in line with figures found in the elderly Italian population [32]. Spot protein urinary excretion was absent in the overwhelming majority of this cohort and very mild when detectable; only 17 subjects had values ≥20 mg/dl.

After a 6-year follow-up, 171 of the 942 participants enrolled at baseline had died, with an annual mortality rate of ∼3%. Compared to participants who were still alive at the end of the follow-up, those who died had significantly higher serum levels of creatinine, glucose and CRP and significantly lower total cholesterol serum levels. Those who died were older and more likely to be male, sedentary and to be affected by hypertension, stroke and CHF. Interestingly enough, proteinuria did not predict mortality (Table 1).

Renal function was categorized according to K/DOQI staging [1]. Due to their limited number (4, 7, 9 and 11 subjects for MDRD-4, MDRD-6, C-G and Ccr, respectively), the participants with eGFR <30 ml/min/1.73 m^2 were

Table 1. Characteristics of the study population

	All participants ($n = 942$)	Not dead ($n = 771$)	Dead ($n = 171$)	P*
Age (years)	74.69 ± 6.74	73.43 ± 5.98	80.35 ± 7.07	<0.0001
Sex female (%)	54.88	57.07	45.03	0.0042
Weight (kg)	69.11 ± 12.37	69.68 ± 12.18	66.49 ± 12.91	0.3484
Height (cm)	158.57±9.45	159.07 ± 9.36	156.34 ± 9.55	0.6176
Alcohol intake (g/day)	0.85 ± 0.35	0.85 ± 0.35	0.85 ± 0.35	0.7149
Smoking status[a] (%)	14.01	14.01	14.04	0.6648
Physical activity (%)				
Sedentary	17.52	13.49	35.67	<0.0001
Moderate	76.96	80.54	60.82	
High	5.52	5.97	3.51	
Hypertension (%)	47.88	46.17	55.56	0.0264
Stroke (%)	4.14	3.24	8.19	0.0019
Angina (%)	4.46	4.02	6.43	0.1186
Myocardial infarction (%)	4.78	4.40	6.40	0.2621
Chronic heart failure (%)	4.25	2.59	11.70	<0.0001
Diabetes mellitus (%)	10.83	10.12	14.04	0.1316
Serum creatinine (mg/dl)	0.92 ± 0.20	0.91 ± 0.18	0.98 ± 0.26	0.0015
eGFR MDRD-4 (ml/min/1.73 m^2)	71.42 ± 15.64	72.0 ± 15.12	68.81 ± 17.62	0.5844
eGFR MDRD-6 (ml/min/1.73 m^2)	64.14 ± 13.40	64.84 ± 12.87	60.99 ± 15.22	0.9045
Cockcroft–Gault (ml/min/1.73 m^2)	64.65 ± 15.72	66.40 ± 14.89	56.74 ± 16.97	0.9726
Ccr (ml/min/1.73 m^2)	77.16 ± 23.60	79.72 ± 22.80	65.64 ± 23.80	0.0017
Proteinuria (%)	5.73	5.32	7.60	0.2451
C-reactive protein-high sensitivity (μg/ml)	4.94± 9.02	4.38 ± 6.72	7.46 ± 15.40	0.0008
Total cholesterol (mg/dl)	219.0 ± 39.02	221.12 ± 38.66	209.39 ± 39.31	0.0084
Blood glucose (mg/dl)	96.21 ± 26.37	94.97 ± 22.52	101.78 ± 38.93	0.0012

Values are percentages for dichotomous (yes/no) variables and mean ± SD for continuous variables.
*Age-adjusted.
[a]Current smoking versus ever smoked or never smoked.

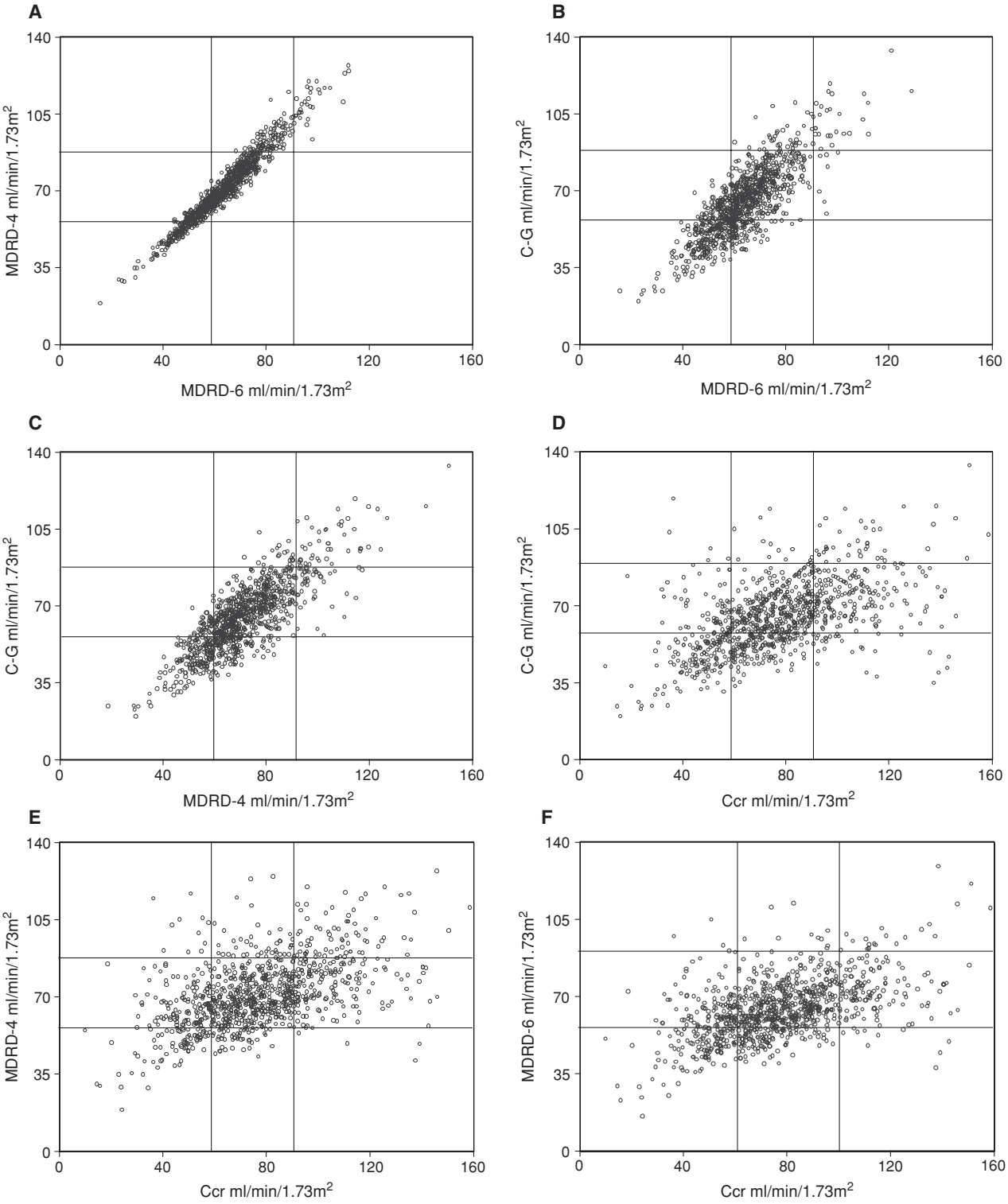

Fig. 1. Scatter plots comparing (**A**) MDRD-6 versus MDRD-4; (**B**) MDRD-6 versus C-G; (**C**) MDRD-4 versus C-G; (**D**) Ccr versus C-G; (**E**) Ccr versus MDRD-4 and (**F**) Ccr versus MDRD-6. Each point represents one subject. Continuous lines are drawn at 60 and 90 ml/min/1.73 m^2.

included in the eGFR <60 ml/min/1.73 m^2 group. Scatter plots between various indexes of renal function are shown in Figure 1. The lines drawn at 60 and 90 ml/min/ 1.73 m^2 disclosed substantial mismatches. As a consequence of this, the prevalence of an eGFR <60 ml/min/1.73 m^2 varied widely depending on the equation used: from 22% (MDRD-4) to 40% (C-G) (Figure 2). Correlation coefficients (not shown in Figure 1) indicate good agreement

between the two MDRD formulae ($r = 0.97$). Correlations between MDRD-4 or MDRD-6 and C-G were lower ($r = 0.82$ for both comparisons) and even worst when estimate equations were compared with Ccr (r values between 0.51 and 0.53); all these comparisons were highly significant ($P < 0.0001$).

When in the Cox model renal function was categorized according to K/DOQI staging, participants with Ccr 60–90 ml/min/1.73 m^2 and with Ccr <60 ml/min/1.73 m^2 were more likely to die during follow-up than those with Ccr >90 ml/min/1.73 m^2 (Table 2, Figure 3A). For the C-G, the group with Ccr <60 ml/min/1.73 m^2 had significantly higher mortality compared to the reference group (Table 2, Figure 3B). *Per contra*, both MDRD-4 and MDRD-6 formulae did not provide any significant prognostic information (Table 2). When in the Cox model indexes of renal function were introduced as continuous variables, the adjusted risk of death was highly significant for Ccr (HR 1.01, CI: 1.00–1.02, $P < 0.02$) and even more so for C-G (Table 3). C-G was also the best predictor when renal function was dichotomized as higher or lower than 60 ml/min/1.73 m^2 (Table 3). Once again both MDRD equations were not associated with death neither when introduced as continuous variable nor when dichotomized as higher or lower than 60 ml/min/1.73 m^2. Stroke, CHF, level of physical activity, CRP and cholesterol were independent predictors of all-cause mortality in the many Cox models tested.

During the 6-year follow-up, death from cardiovascular causes occurred in 67 subjects, e.g. 7.1% of the baseline cohort. The adjusted hazard ratio for cardiovascular deaths increased inversely with renal function when it was estimated by C-G (Table 4), whereas both MDRD formulae did not provide any significant prognostic information.

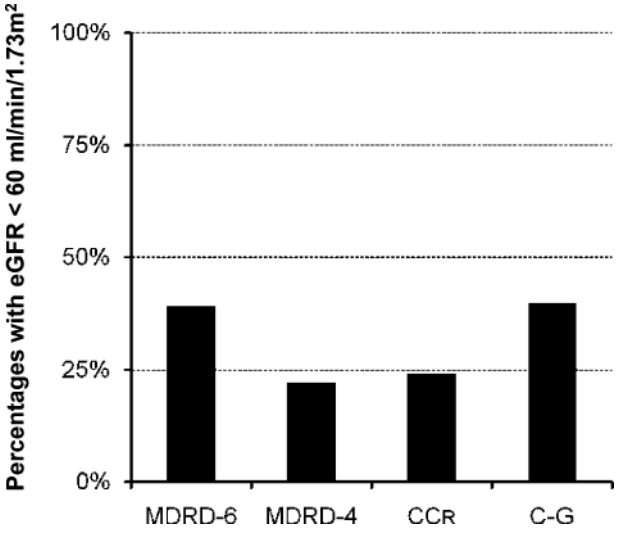

Fig. 2. Prevalence of CKD, defined as renal function <60 ml/min, according to Ccr and each estimate equation.

Table 2. Cox model for all-cause mortality with K/DOQI staging estimated by different methods

	HR	95% CI	*P*
eGFR MDRD-4			
<60 ($n = 207$)	1.18	0.67–2.07	0.57
≥60 <90 ($n = 633$)	1.03	0.62–1.72	0.91
≥90 ($n = 102$)	–		
eGFR MDRD-6			
<60 ($n = 367$)	1.58	0.64–3.91	0.33
≥60 <90 ($n = 539$)	1.22	0.49–3.03	0.66
≥90 ($n = 36$)	–		
Cockcroft–Gault			
<60 ($n = 374$)	2.59	1.13–5.91	0.02
≥60 <90 ($n = 513$)	1.03	0.44–2.38	0.95
≥90 ($n = 55$)	–		
Ccr			
<60 ($n = 226$)	1.91	1.11–3.29	0.02
≥60 <90 ($n = 462$)	1.70	1.02–2.83	0.04
≥90 ($n = 254$)	–		

HR = hazard ratio, for adjustment see the text; CI = confidence interval; eGFR = estimated glomerular filtration rate; Ccr = creatinine clearance; MDRD = Modification of Diet in Renal Disease.
Reference: renal function ≥90 ml/min/1.73 m^2.

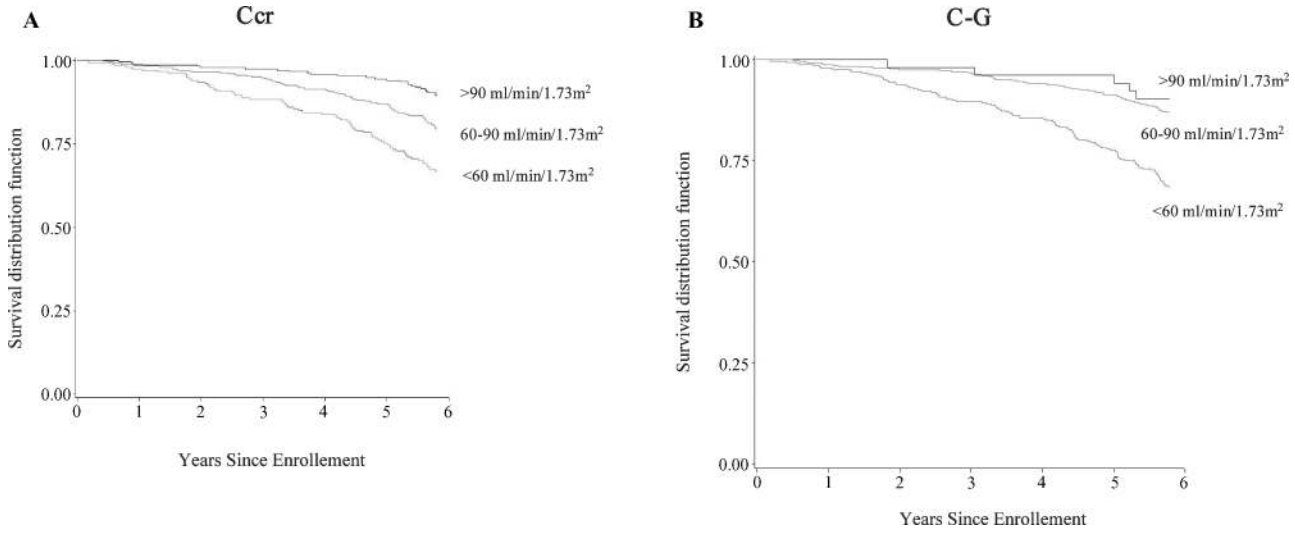

Fig. 3. Cox's survival curves during the 6-year follow-up according to renal function strata for Ccr (**A**) and C-G (**B**).

Table 3. Full Cox model for 6-year all-cause mortality with renal function estimated by the C-G equation

	HR	95% CI	*P*
C-G dichotomized			
C-G (<60 versus >60ml/min/1.73 m^2)	2.52	1.83–3.49	<0.0001
Stroke (yes versus no)	1.41	1.13–1.75	0.002
CHF (yes versus no)	1.35	1.14–1.60	0.001
Physical activity (low versus moderate versus high)	1.43	1. 22–1.58	0.001
CRP (μg/ml)	1.01	1.00–1.02	0.005
Cholesterol (mg/dl)	0.99	0.99–1.00	0.006
C-G continuous			
C-G (each ml/min/1.73 m^2 reduction)	1.03	1.02–1.04	<0.0001
Stroke (yes versus no)	1.38	1.11–1.72	0.004
CHF (yes versus no)	1.32	1.12–1.57	0.001
Physical activity (low versus moderate versus high)	1.40	1.17–1.56	0.002
CRP (μg/ml)	1.01	1.00–1.02	0.009
Cholesterol (mg/dl)	0.99	0.99–1.00	0.014

HR = hazard ratio; CI = confidence interval; CHF = chronic heart failure; C-G = Cockcroft–Gault; CRP = C-reactive protein.

Table 4. Full Cox model for 6-year cardiovascular mortality with renal function estimated by the C-G equation

	HR	95% CI	*P*
C-G dichotomized			
C-G (<60 versus >60 ml/min/1.73 m^2)	2.85	1.67–4.85	<.0001
Stroke (yes versus no)	1.50	1.08–2.07	0.016
CHF (yes versus no)	1.59	1.23–2.05	0.001
Physical activity (low versus moderate versus high)	1.56	1. 28–1.73	0.001
C-G continuous			
C-G (each ml/min/1.73 m^2 reduction)	1.04	1.03–1.06	<.0001
Stroke (yes versus no)	1.45	1.04–2.01	0.027
CHF (yes versus no)	1.55	1.20–2.00	0.001
Physical activity (low versus moderate versus high)	1.50	1.18–1.70	0.006

HR = hazard ratio; CI = confidence interval; CHF = chronic heart failure; C-G = Cockcroft–Gault.

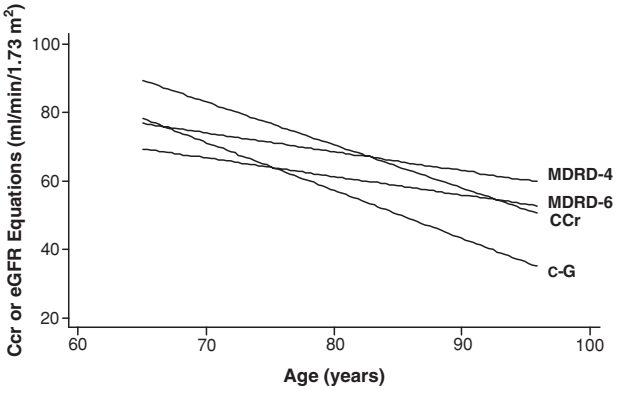

Fig. 4. Correlations between Ccr or estimate renal function equations and age. For details see the text.

Although not significant in preliminary univariate analysis, we forced proteinuria into the many Cox models tested but results did not change.

Correlations between indexes of renal function and quadratic term of age were not significant; therefore we assumed linear associations. Linear correlations between formulae and age are presented in Figure 4. Slopes for Ccr, C-G, MDRD-6 and MDRD-4 resulted −1.26, −1.40, −0.54 and −0.55, respectively. That is to say that, for every year exceeding 65, the loss of renal function detected by Ccr and C-G was double that estimated by MDRD.

Discussion

In this study, we evaluated whether eGFR equations and calculated Ccr from 24-h urine collections in an elderly European population provide similar informations. We found that K/DOQI staging, and therefore the CKD prevalence, varied widely according to the assessment method adopted to estimate GFR. The main result of our study is that graded reduction in renal function, assessed by both Ccr and C-G but not by MDRD-derived equations, was a highly significant independent predictor of all-cause mortality as well as cardiovascular mortality after adjustment for major confounding baseline clinical characteristics, including proteinuria.

Inferences from epidemiologic studies are often difficult to extrapolate to the general population, due to the lack of detailed descriptions of the underlying reference population. This is particularly problematic in studying chronic diseases because chronically ill patients may be more or less likely to participate in screening programmes [33]. In contrast, the data reported here are from a population sample randomly selected from a well-defined reference population, with an extremely high participation rate. Moreover, our reference population is representative of the Italian population, with both percentages of elderly subjects being in the region of 20% [32]. The mean age for our community-based cohort was 75 years. It has been recently shown that, at variance with younger subjects, patients ≥75 years were far more likely to die than to progress to stage 5 CKD, age being an important effect modifier in CKD [19,20]. This not only might imply the need to develop separate risk scores for different clinical outcomes [20] but also underlines the critical need to identify the renal function estimate equation that provides the best prediction of these outcomes.

Accurate GFR measurements using inulin or iothalamate infusions are impractical for large-scale application, while Ccr is made complex by the need of obtaining accurate 24-h urine collection. To minimize this last limitation, we instructed subjects to take note of the start and end time of urine collection to allow for computation of the length of collection. The safeguard adopted probably minimizes the source of error deriving from inaccurate urine collection, but does not preserve from other critical factors such as creatinine metabolism and renal handling.

In the last decades, several equations to estimate GFR have been developed. The C-G equation has been validated against Ccr [21], whereas MDRD equations have been validated against iothalamate clearance [22]. Hence, C-G

and MDRD are two distinct variables, the former being an estimate of Ccr, the latter of GFR. Although these equations are very attractive due to their simplicity and ease of use, their prediction is highly influenced by factors that influence creatinine metabolism [24]. Scr is produced by muscle catabolism and, therefore, is strongly influenced by muscle mass. Formulae use age, sex, race and weight to estimate muscle mass and to improve the prediction of renal function. This approach is based on the assumption that the elderly, women, whites, leaner and smaller subjects have lower muscle mass and, therefore, produce less creatinine.

Unfortunately, while most of the estimating equations show a very good fit in the population where they were estimated, their performance in other population with different characteristics is usually much lower and they may even produce biased results [34–44]. For example, studies of eGFR equations in healthy potential kidney donors reported underestimation of GFR by 29% for the MDRD equation and 27% for C-G [41], a less negative bias when using the C-G formula in comparison to the MDRD equation [42] or the opposite [37]. Moreover, also racial differences may well impact on equation performance. For instance, MDRD-4 in China and Japan yielded conflicting results with underestimation or overestimation of the measured GFR, respectively [43,44]. The InCHIANTI study population is a Caucasian cohort representative of the general Italian elderly population with more participants having 'normal' creatinine and low prevalence of proteinuria and of comorbidities. *Per contra*, the participants of the MDRD study were blacks (12%), younger, heavier and had serum creatinine 2.5 times higher than in InCHIANTI [22]. Similarly, the C-G formula was developed from a primarily male (209 of 236) Canadian inpatient population [21]. Hence, it comes as no surprise how in our population K/DOQI CKD staging differed according to the method adopted to estimate renal function and how, more importantly, the prevalence of CKD ranged from 22% by MDRD-4 to almost double, 40%, by C-G. In other elderly populations, one can find quite different figures. The US NHANES population over 70s had a CKD prevalence of 38% by MDRD-4 [16]. In Jerusalem community, people aged 70 years and older had a CKD prevalence of 34% by MDRD-4 and 51% by C-G [17]. UK subjects over 80s recruited from residential care homes had a CKD prevalence ranging from 83% to 97% according to whether MDRD-4 or C-G was adopted [18]. These widespread differences may reflect true differences in population or may be due to different selection criteria. Moreover, the use of a single serum creatinine value may have led to an overestimation of the prevalence of CKD in some of these surveys, including ours. It has actually been estimated that 29% of subjects initially categorized as stage 3 CKD would no longer fall into this category upon having a second test after 3 months or more [45]. Therefore, we acknowledge the lack of estimation of chronicity as the main limitation of our study.

To gain insight into the validity of the prediction provided by the different assessment methods, we examined how well the different formulae predict mortality. Mortality is an important reference parameter, especially considering the growing evidence of association between renal damage and increased morbidity and mortality [7–13]. Our analysis was adjusted for a wide panel of potential confounders, including traditional risk factors identified in the Framingham Heart study and non-traditional factors. As far as we know, measurements of sophisticated parameters, such as high-sensitivity CRP associated with measured renal function by 24-h creatinine clearance, are unique features of this cohort compared to other population-based studies.

In spite of the low mortality in our population, creatinine clearance measured with a 24-h urine collection or estimated with the C-G formula was a significant and independent predictor of all-cause as well as cardiovascular mortality, while MDRD-derived equations were not. This conclusion holds true either when renal function estimates were categorized according to K/DOQI CKD staging, or dichotomized as lower or higher than 60 ml/min/1.73 m^2, or when challenged in the Cox model as continuous variables. We analysed estimate equations in different ways because of their established inaccuracies for values >60 ml/min/1.73 m^2 [46,47]. Actually K/DOQI classification brings about an inherent potential limitation in 'defining different segments of a continuous distribution as separate stages of a disease process' [48].

Our results are in line with those recently achieved in different clinical settings. Perkovich *et al*. in subjects with cerebrovascular disease found that C-G is a better predictor of major clinical events than serum creatinine or MDRD-4 [49]. That MDRD-4 cannot be the gold standard worldwide is reinforced by data from Israel, where Maaravi *et al*. found that in an elderly general population the new Mayo Clinic equation was a stronger predictor of mortality than MDRD or C-G [17].

The way Ccr and estimate formulae describe the decline in GFR by age might explain the different performance. According to our data, slopes of Ccr and C-G against age are much steeper than those of MDRD. Similar results have been already described by Cirillo *et al*. in Italian individuals without CKD [50]. It is tempting to speculate that calculated or estimated creatinine clearance is a better prognostic indicator than eGFR by MDRD because it incorporates a stronger effect of age. However, estimating equations C-G and MDRD already incorporate age in the formula and this might beset validity of their correlation with age.

The limitations related to the measurements and interpretation of CKD tests are actively being addressed. International organizations have developed a process to standardize the serum creatinine assay to a high-quality reference standard with the goal of implementing assay standardization in all clinical laboratories [51]. This may attenuate the dispute on the performance of various eGFR equations. Until that time, researchers and clinicians who want to capture the link between CKD and all-cause as well as cardiovascular mortality should measure 24-h creatinine clearance or estimate it by the C-G formula. MDRD equations do not predict mortality. This holds true at least in a general elderly population with characteristics similar to InCHIANTI.

According to our and other reports, there appears to be little question that the prevalence of CKD is high in elderly people and is strongly associated with risk of death. These results may impact on designing and implementing strategies for early detection and clinical management of CKD in elderly subjects.

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Prevalence and risk factors associated with chronic kidney disease in an adult population from southern China

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Abstract

Background. Population-based studies evaluating the prevalence of kidney damage in different communities have been limited in developing countries. We conducted a population-based screening study in the southern Chinese city of Guangzhou that aimed to identify the prevalence and associated risk factors of chronic kidney disease (CKD) in southern Chinese populations.

Methods. We interviewed 6311 residents (>20 years) from six districts of Guangzhou from July 2006 to June 2007 and tested for haematuria, albuminuria and reduced renal function. Associations between age, gender, smoking, diabetes mellitus, hypertension, hyperuricaemia and kidney damage were examined.

Results. There were 6311 subjects enrolled in this study. After adjustment for age and gender, the prevalence of albuminuria, haematuria and reduced estimated glomerular filtration rate (eGFR) was 6.6% [95% confidence interval (CI): 5.5–7.6%], 3.8% (95% CI: 3.4%, 4.3%) and 3.2% (95% CI: 2.4%, 3.3%), respectively. Approximately 12.1% (95% CI: 11.3%, 12.9%) of the sample population had at least one indicator of kidney damage. Age, diabetes mellitus, hypertension, central obesity, hyperlipidaemia and use of nephrotoxic medications were independently associated with albuminuria; hyperuricaemia, age, gender, hypertension and use of nephrotoxic medications were independently associated with reduced eGFR, and female gender was independently associated with haematuria.

Conclusions. In the general adult population from southern China, 12.1% has either proteinuria, haematuria and/or reduced eGFR, indicating the presence of kidney damage, with an awareness of only 9.6%. The high prevalence and low awareness of CKD in this population suggest an urgent need for CKD prevention programmes in China.

Keywords: chronic kidney disease; epidemiology; screening

Introduction

The prevalence of chronic kidney disease (CKD) is increasing rapidly worldwide, and is now recognized as a global public health problem. In addition, end-stage renal disease

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