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Predicting survival of older community-dwelling individuals according to five estimated glomerular filtration rate equations: The InChianti study

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Abstract

Aims—There is uncertainty about which estimated glomerular filtration rate eGFR equation to use in older people with respect to the prediction of prognosis. Our aim was: (i) to compare the discriminative capacity of eGFR estimated by different equations with respect to all-cause mortality; and (ii) to identify the eGFR threshold at which the risk of mortality starts to increase for each equation.

Methods—We used data from 828 community-dwelling older adults aged >65 years enrolled in the InCHIANTI study. The outcome measure was all-cause mortality at 9 years. GFR was estimated by five different equations: Chronic Kidney Disease Epidemiological Collaboration (creatinine equation [CKD-EPI_{cre}], and creatinine and cystatin C equation [CKD-EPI_{cre-cys}]), Berlin Initiative Study (BIS_{cre} and BIS_{cre-cys}) and full age spectrum. Sensitivity, specificity, areas under receiver operating curve (AUC) and C-statistics were used to compare their predictive capacity.

Results—The best mix of sensitivity, specificity, AUC and C-statistic value in predicting mortality was observed with BIS equations. BIS_{cre} (AUC 0.65, 95% CI 0.61–0.69) outperformed both CKD-EPI_{cre} (AUC 0.60, 95% CI 0.56–0.64; $P = 0.005$) and full age spectrum (AUC 0.63, 95% CI 0.59–0.67; $P = 0.002$) in terms of predictivity. Similarly, BIS_{cre-cys} (AUC 0.67, 95% CI 0.63–0.71) outperformed CKD-EPI_{cre-cys} (AUC 0.63, 95% CI 0.59–0.67; $P = 0.01$). AUC obtained with equations also including cystatin C were not significantly different compared with their

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Disclosure statement

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Supporting information

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creatinine-based counterparts. The risk of long-term mortality began to increase at under 65.6 mL/min/1.73 m² for CKD-EPI_{cre-cys}, 60.5 for CKD-EPI_{cre}, 60 for BIS_{cre-cys}, 56.3 for BIS_{cre} and 55.2 for full age spectrum.

Conclusions—The BIS equation discriminates the risk of all-cause mortality better than other equations in older community-dwelling individuals. The eGFR threshold under which mortality starts to increase could change as a function of the equation used.

Keywords

Berlin Initiative Study; Chronic Kidney Disease Epidemiological Collaboration; estimated glomerular filtration rate; full age spectrum; mortality

Introduction

Chronic kidney disease (CKD) is one of the leading chronic non-communicable diseases, especially among older people, in which it is a primary determinant of health status and prognosis.¹ Recognizing CKD prevents drug overdosage and adverse reactions, as well as contributing to predicting survival, especially in selected categories.² Indeed, dramatic differences in survival according to different levels of estimated glomerular filtration rate (eGFR) have been observed in patients having heart failure,³ coronary artery disease⁴ or diabetes⁵ as the main disease. In the same way, eGFR was found to accurately predict mortality in older people.⁶ Thus, eGFR seems to be an accurate measure of actual GFR, and an easily obtained and reliable source of information on the patient's health status. However, aging accounts for important changes in the relative weight of individual predictors of survival. In the case of eGFR, the result of the source equation might variously match GFR due to several age-related factors.⁷ Indeed, efforts have been made to improve the estimating equations in older people who are at special risk of CKD. The Berlin Initiative Study (BIS) equations have been developed and tested in an aged population, and have been proved to be accurate and precise in this population.⁸ Although the available evidence provided by external validation studies supports the use of the BIS equation in older adults,⁹ the CKD Epidemiological Collaboration (CKD-EPI) also remains the recommended equation for older adults.¹⁰ Additionally, the full age spectrum (FAS) creatinine-based equation has been very recently developed, and its prognostic value in older adults is yet to be evaluated.¹¹

Therefore, the aim of the present study was to compare the long-term discriminative capacity with respect to mortality of eGFR estimated by the CKD-EPI and BIS equations, either in the creatinine-based or in the creatinine/cystatin C-based forms, and by the FAS equation in a population of community-dwelling older people. Finally, we also investigated whether the eGFR threshold at which the risk of mortality starts to increase could change as a function of the equation used.

Methods

Data source

We used data from the “Invecchiare in Chianti” (InCHIANTI) study.¹² Participants were randomly selected from the populations of two town areas in the Chianti region: Greve in

Chianti and Bagno a Ripoli. The Italian National Institute of Research and Care on Aging ethical committee ratified the study protocol. Participants signed an informed consent including permission to carry out analysis on the biological specimens collected and stored. For those unable to fully consent because of cognitive or physical problems, surrogate consent was also obtained from a close relative. The eligible participants were interviewed at their homes by trained study researchers using a structured questionnaire aimed at investigating their health status, their physical and cognitive performance, and other factors possibly related to loss of independence in late life. The interview was followed by a physical examination at the study clinic. Participants were evaluated for the 3-year (2001–2003), 6-year (2004–2006) and 9-year follow-up visits (2007–2009). Mortality data of the original InChianti cohort were collected using data from the Mortality General Registry maintained by the Tuscany Region, and death certificates deposited immediately after death at the Registry office of the municipality of residence.

Sample selection

Overall, 1453 older adults were enrolled in the InChianti database. Of them, 514 individuals aged <65 years and 111 individuals with missing serum creatinine and/or cystatin C were excluded from the present study, leaving a final sample of 828 individuals having at least one visit over the follow-up period.

Laboratory assays

Blood samples obtained after the patient had fasted for 12 h and rested for at least 15 min were centrifuged and stored at -80°C until analyzed. Serum creatinine was measured by the modified Jaffé method standardized against gas chromatography (isotope dilution) mass spectrometry (Roche Diagnostics GmbH, Mannheim, Germany). Serum cystatin C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C kit; Dade Behring, Deerfield, IL, USA). eGFR was calculated using the CKD-EPI creatinine equation ($\text{CKD-EPI}_{\text{cre}}$), the CKD-EPI creatinine and cystatin C equation ($\text{CKD-EPI}_{\text{cre-cys}}$), the BIS creatinine equation (BIS_{cre}) and BIS creatinine and cystatin C equation ($\text{BIS}_{\text{cre-cys}}$), as well as the creatinine-based FAS equations (Table S1).^{8,11,13,14}

eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$) values were categorized as follows: >90 ; 89.9–60; 59.9–45; 44.9–30 and <30 .⁴

Study variables

Age, sex, body mass index and smoking habits were considered in the analysis. In order to obtain a deconfounded estimate of the eGFR–survival relationship, chronic conditions related to renal function and mortality were taken into account: hypertension, coronary artery disease, heart failure, stroke, peripheral arterial disease, diabetes, chronic obstructive pulmonary disease, cancer, anemia, femur fracture and osteoarthritis. These confounders were already included in studies investigating the predictivity of survival by eGFR.¹⁵ Diagnoses were defined using standard criteria that combined information from self-reported medical history, medication use, medical documents and a clinical medical examination. Anemia was defined as hemoglobin $<12 \text{ g/dL}$ in women and $<13 \text{ g/dL}$ in men.¹⁶ Given that

reduced muscle mass can significantly affect serum creatinine, a muscle cross-sectional area measured at 66% of tibial length was also considered a potential confounder.¹⁷

Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale.¹⁸ Cognitive status was assessed using the age- and education-adjusted Mini-Mental State Examination score.¹⁹ Self-reported degree of disability was rated using the number of lost basic activities of daily living.²⁰

Analytic approach

First, we analyzed the demographic and clinical characteristics of participants, and calculated the prevalence of selected risk factors. The baseline characteristics of the sample were reported as mean and standard deviation for continuous variables or the number of cases with percentage for categorical variables. Cox proportional hazard regression models were used to investigate the association between study variables and mortality. Crude hazard ratios and 95% confidence intervals were initially calculated for each variable. Therefore, in order to obtain an adjusted estimate of the association between eGFR groups and 9-year mortality, separate Cox regression models were built for each different kidney function estimating method. This latter analysis was adjusted for all potential confounders included in univariable analysis. Given that eGFR values are already adjusted for age and sex, these variables were not included in the fully adjusted models.

In order to verify whether the eGFR threshold at which the risk of death increases changes as a function of the eGFR equation used, splines evaluating the relationship between the different estimates of kidney function and mortality were also investigated.

Cubic smoothing spline methods were used to assign an automatically defined number of knots to each predictor value, while the regression is fitted by penalized least squares. For small data vectors ($n < 50$), a knot is placed at every distinct data point. For larger datasets, a suitable fine grid of knots is chosen, usually fewer than the number of unique values of the predicted variable. Knots are placed at equally spaced data points, and the number of knots is chosen judiciously to keep the computation time manageable. In the present analysis, the number of knots selected by the algorithm was 131 with FAS, 132 with CKD-EPI_{cre} and BIS_{cre}, and 140 with CKD-EPI_{cre-cys} and BIS_{cre-cys}.

Finally, areas under receiver operating characteristic curves, sensitivity, specificity and C-statistic derived from the crude model were used to assess how accurately individual eGFR equations predict all-cause mortality.

Statistical analysis was carried out by SPSS Statistical Software Package for Win V23.0 (SPSS, Chicago, IL, USA), and the smooth.spline function from the “stat” library of R 3.3 statistical package for Linux (R Foundation for Statistical Computing, Vienna, Austria). Receiver operating characteristic curve comparisons were carried out using MedCalc for Win (MedCalc, Ostend, Belgium). Statistical significance was set at $P = 0.05$. Multiple comparisons were carried out using the Bonferroni correction.

Results

The general characteristics of the individuals studied are reported in Table 1. Average eGFR values obtained using the CKD-EPI equations ($\text{CKD-EPI}_{\text{cre}} = 72.0 \pm 13.4$, and $\text{CKD-EPI}_{\text{cre-cys}} = 72.7 \pm 16.0 \text{ mL/min/1.73 m}^2$) were higher than those obtained with the BIS ($\text{BIS}_{\text{cre}} = 62.5 \pm 12.0$, and $\text{BIS}_{\text{cre-cys}} = 65.3 \pm 13.5 \text{ mL/min/1.73 m}^2$) and FAS ($63.0 \pm 13.5 \text{ mL/min/1.73 m}^2$) equations.

Older age, male sex, hypertension, heart failure, stroke, anemia, chronic obstructive pulmonary disease and peripheral arterial disease were significantly associated with the outcome in crude analysis, as were cognitive performance, depressive symptoms score and the number of lost basic activities of daily living (Table 1).

Decreasing eGFR values were associated with increased mortality regardless of the equation used (Table 2), and Kaplan–Meier curves showed a graded relationship between kidney function and 9-year mortality (Fig. 1). The association between eGFR categories and mortality was confirmed after adjusting for all potential confounders included in the analysis (Table 2). In fully adjusted models, heart failure, peripheral arterial disease, chronic obstructive pulmonary disease, anemia, number of lost basic activities of daily living and muscle area were also associated with mortality (Table S2).

The best mix of sensitivity, specificity, AUC and C-statistic value was observed with BIS equations, followed by FAS and CKD-EPI equations. CKD-EPI equations had lower sensitivity, but higher specificity in predicting mortality compared with BIS and FAS equations (Table 3). The magnitude of differences, though statistically significant, was unlikely to reach primary clinical significance. AUC for $\text{CKD-EPI}_{\text{cre}}$ and FAS were significantly lower than that observed for BIS_{cre} ($P = 0.005$ and $P = 0.002$, respectively), and AUC for $\text{CKD-EPI}_{\text{cre-cys}}$ was significantly lower than that observed for $\text{BIS}_{\text{cre-cys}}$ ($P = 0.01$). The use of equations including both creatinine and cystatin C was not associated with a significant improvement of prognostic accuracy (BIS_{cre} vs $\text{BIS}_{\text{cre-cys}}$: $P = 0.450$; $\text{CKD-EPI}_{\text{cre}}$ vs $\text{CKD-EPI}_{\text{cre-cys}}$: $P = 0.200$; Table 3).

The analysis of the relationship between eGFR and mortality showed that the threshold at which the risk of long-term mortality increases varies remarkably as a function of the equation used, ranging from 60 to $65.6 \text{ mL/min/1.73 m}^2$ for creatinine–cystatin C-based equations, and from 55.2 to $60.5 \text{ mL/min/1.73 m}^2$ for creatinine-based equations (Fig. 2).

Discussion

The present data suggest that in older community-dwelling individuals the CKD-EPI, BIS and FAS eGFR equations differed marginally as predictors of survival, and neither cystatin C-based equations nor the recently developed FAS equation had better predictive capacity.

Although all eGFR equations had comparable prognostic accuracy, some differences between them are worthy of comment. Indeed, the BIS equations had the best sensitivity, but still not >60% and with worse specificity than the other formulas. The GFR estimated by the BIS equation was lower than the GFR estimated by the other equations, and this might help

to explain this finding. The different shapes of the eGFR–mortality relationship of the tested equations implies that clinicians and epidemiologists should take into consideration equation-specific thresholds of risk in prognostic assessment and longitudinal studies. Accordingly, it might be reductive to consider a given eGFR value indicative of worse prognosis in older adults without considering the estimating equation used. It should also be observed that the increase in risk for declining eGFR is very gradual and, nevertheless, shows some differences between equations. Indeed, the highest cut-off for increasing the risk of death was observed for equations including both creatinine and cystatin C, followed by creatinine-based eGFR.

Adding cystatin C to GFR equations did not improve predictivity. Cystatin C is a proxy for the metabolically active cell mass, and is considered to be less influenced by sarcopenia compared with serum creatinine. Circulating cystatin C was found to independently predict long-term all-cause, cardiovascular, cancer and non-cardiovascular mortalities in a general population aged >40 years with normal kidney function.²¹ Additionally, the predictive value of cystatin C in terms of all-cause mortality, cardiovascular mortality and total adverse vascular events was recently confirmed in people with suspected or established coronary artery disease.²² Nevertheless, studies comparing the predictive value of creatinine- and cystatin C-based eGFR equations reported conflicting results. Indeed, predictivity of all-cause mortality was found to be far from optimum, with AUC ranging between 0.604 and 0.606, using CKD-EPI_{cre}, CKD-EPI_{cys} and CKD-EPI_{cre-cys} in older women participating in the Calcium Intake Fracture Outcome Study,²³ whereas CKD-EPI_{cys} and CKD-EPI_{cre-cys} equations were found to better predict mortality compared with CKD-EPI_{cre} and BIS_{cre-cys} in older men enrolled in the Osteoporotic Fractures in Men Study.²⁴ Differences in study populations could account for the observed differences with our findings, which were obtained in a population including both sexes. Additionally, cystatin C levels are variously affected by dysthyroidisms, corticosteroid therapy and selected cancers.²⁵ Furthermore, in older patients with chronic kidney disease, GFR estimation was found to improve when fat-free mass was considered.²⁶

The observed lack of improvement in prognostic accuracy with cystatin C-based eGFR suggests that it might be less cost-effective in older people compared with other populations. Indeed, cystatin C measurement might be cost-effective in selected conditions, such as screening for CKD among: (i) adults with eGFR_{cr} 60–74 mL/min/1.73 m² without albuminuria; (ii) diabetes patients; and (iii) people with conditions affecting muscle mass, which might lead to a bias in creatinine-based estimation of GFR.²⁷ Furthermore, according to the National Institute for Health and Care Excellence Guidelines, eGFR measurement using cystatin C was found to be cost-effective in young adults where it can help to reduce the number of false positives, but not in individuals aged ≥ 75 years.²⁸ The present findings are in keeping with these data, and suggest not using cystatin C-based estimation of GFR for prognostic stratification among older community-dwelling individuals.

In the present study, the best accuracy in predicting prognosis was obtained with BIS equations. Being tailored to older adults, BIS was expected to provide the best mix of sensitivity and specificity among creatinine-based equations. However, the difference compared with the other formulas was small, and in general in the present study, the

discriminative capacity of eGFR was no more than fair. The most likely explanation to this negative finding is that studies emphasizing the prognostic properties of eGFR equations have been carried out in populations with specific conditions, such as coronary artery disease or congestive heart failure patients, in which the risk of CKD is high. Furthermore, CKD affects the course of the main disease in those populations. On the contrary, in an older community-dwelling population, CKD is less prevalent and its prognostic implications are expected to be less evident, also due to the presence of several competing risk factors. Thus, although estimation of renal function remains mandatory to evaluate the health status, the impact of CKD on survival largely changes across populations with different demographic and clinical characteristics.

Limitations of the present study deserve to be mentioned. Measured GFR was not available in our study. Thus, it seems sensible to consider the prognostic capacity as a property of the estimating equation only in part related to its validity and was strictly dependent on the studied population. It should also be observed that CKD definition includes both GFR and albuminuria,²⁹ and albuminuria was found to have autonomous prognostic capacity in selected populations; for example, chronic obstructive pulmonary disease patients.³⁰ Accordingly, considering also the albuminuria in the multivariable predictive model might have improved the definition of the prognostic capacity of eGFR equations. However, eGFR can be easily derived from routine blood analysis, whereas albuminuria cannot be considered a routine analysis and was not available in the InChianti database. Finally, we could provide a good sense, but not a formal analysis of the cost/effectiveness of the use of cystatin C in estimating renal function.

In conclusion, our study adds to the present knowledge by showing that eGFR estimated through the BIS equation or the most recent FAS only marginally improved the discriminative capacity of CKD-EPI with respect to mortality in older community-dwelling adults. The same conclusion applies to cystatin C-based equations. However, the overall predictive performance of eGFR in older home-dwelling people, whichever is the calculating equation, is relatively poor. Furthermore, the threshold of eGFR under which the risk for mortality starts to increase changes as a function of the equation used; this should be taken into account in prognostic stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Bansal N, Katz R, De Boer IH, et al. Development and validation of a model to predict 5-year risk of death without ESRD among older adults with CKD. *Clin J Am Soc Nephrol*. 2015; 10:363–371. [PubMed: 25710804]

2. Corsonello A, Pedone C, Corica F, et al. Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med.* 2005; 165:790–795. [PubMed: 15824299]
3. Lofman I, Szummer K, Hagerman I, Dahlstrom U, Lund LH, Jernberg T. Prevalence and prognostic impact of kidney disease on heart failure patients. *Open Heart.* 2016; 3:e000324. [PubMed: 26848393]
4. Fu S, Liu Y, Zhu B, et al. Prognostic abilities of different calculation formulas for the glomerular filtration rate in elderly Chinese patients with coronary artery disease. *Clin Interv Aging.* 2013; 8:229–237. [PubMed: 23450793]
5. Tsai CW, Grams ME, Inker LA, Coresh J, Selvin E. Cystatin C- and creatinine-based estimated glomerular filtration rate, vascular disease, and mortality in persons with diabetes in the U. S Diabetes Care. 2014; 37:1002–1008. [PubMed: 24271191]
6. Mandelli S, Riva E, Tettamanti M, Detoma P, Giacomini A, Lucca U. Mortality prediction in the oldest old with five different equations to estimate glomerular filtration rate: the health and anemia population-based study. *PLoS ONE.* 2015; 10:e0136039. [PubMed: 26317988]
7. Fan L, Levey AS, Gudnason V, et al. Comparing GFR estimating equations using cystatin C and creatinine in elderly individuals. *J Am Soc Nephrol.* 2015; 26:1982–1989. [PubMed: 25527647]
8. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med.* 2012; 157:471–481. [PubMed: 23027318]
9. Koppe L, Klich A, Dubourg L, Ecochard R, Hadj-Aissa A. Performance of creatinine-based equations compared in older patients. *J Nephrol.* 2013; 26:716–723. [PubMed: 23843047]
10. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA.* 2015; 313:837–846. [PubMed: 25710660]
11. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant.* 2016; 31:798–806. [PubMed: 26932693]
12. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc.* 2000; 48:1618–1625. [PubMed: 11129752]
13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009; 150:604–612. [PubMed: 19414839]
14. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012; 367:20–29. [PubMed: 22762315]
15. Pizzarelli F, Lauretani F, Bandinelli S, et al. Predictivity of survival according to different equations for estimating renal function in community-dwelling elderly subjects. *Nephrol Dial Transplant.* 2009; 24:1197–1205. [PubMed: 18988669]
16. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Curr Opin Hematol.* 2005; 12:123–128. [PubMed: 15725902]
17. Rittweger J, Beller G, Ehrig J, et al. Bone-muscle strength indices for the human lower leg. *Bone.* 2000; 27:319–326. [PubMed: 10913929]
18. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977; 1:385–401.
19. Folstein MF, Folstein SE, McHugh PR. “Minimental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
20. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: a standardized measure of biological and psychosocial function. *JAMA.* 1963; 185:914–919. [PubMed: 14044222]
21. Wu CK, Lin JW, Caffrey JL, Chang MH, Hwang JJ, Lin YS. Cystatin C and long-term mortality among subjects with normal creatinine-based estimated glomerular filtration rates: NHANES III (Third National Health and nutrition examination survey). *J Am Coll Cardiol.* 2010; 56:1930–1936. [PubMed: 21109116]
22. Yang S, Song L, Zhao L, Dong P, Lai L, Wang H. Predictive value of cystatin C in people with suspected or established coronary artery disease: a meta-analysis. *Atherosclerosis.* 2017; 263:60–67. [PubMed: 28599259]

23. Lim WH, Lewis JR, Wong G, et al. Comparison of estimated glomerular filtration rate by the chronic kidney disease epidemiology collaboration (CKD-EPI) equations with and without cystatin C for predicting clinical outcomes in elderly women. *PLoS ONE*. 2014; 9:e106734. [PubMed: 25265151]
24. Canales MT, Blackwell T, Ishani A, et al. Estimated GFR and mortality in older men: are all eGFR formulae equal. *Am J Nephrol*. 2016; 43:325–333. [PubMed: 27166079]
25. Chew JS, Saleem M, Florkowski CM, George PM. Cystatin C--a paradigm of evidence based laboratory medicine. *Clin Biochem Rev*. 2008; 29:47–62. [PubMed: 18787643]
26. Macdonald J, Marcora S, Jibani M, et al. GFR estimation using cystatin C is not independent of body composition. *Am J Kidney Dis*. 2006; 48:712–719. [PubMed: 17059990]
27. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis*. 2013; 62:595–603. [PubMed: 23701892]
28. Chronic Kidney Disease. NICE Clinical Guidelines, No. 182. National Clinical Guideline Centre (UK); London: National Institute for Health and Care Excellence (UK); 2014. Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care. (Partial Update)
29. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014; 63:713–735. [PubMed: 24647050]
30. Ford ES. Urinary albumin-creatinine ratio, estimated glomerular filtration rate, and all-cause mortality among US adults with obstructive lung function. *Chest*. 2015; 147:56–67. [PubMed: 25079336]

Figure 1.

Kaplan–Meier curves showing the relationship between different measures of kidney function and 9-year mortality. BIS_{cre}, Berlin Initiative Study creatinine equation; BIS_{cre-cys}, Berlin Initiative Study creatinine and cystatin C equation; CKD-EPI_{cre}, Chronic Kidney Disease Epidemiological Collaboration creatinine equation; CKD-EPI_{cre-cys}, Chronic Kidney Disease Epidemiological Collaboration creatinine and cystatin C equation; FAS, full age spectrum.

Figure 2.

Hazard ratio splines showing the relationship between different measures of kidney function and mortality. Arrows indicate the thresholds at which the risk of long-term mortality starts to progressively increase or decrease. BIS_{cre}, Berlin Initiative Study creatinine equation; BIS_{cre-cys}, Berlin Initiative Study creatinine and cystatin C equation; CKD-EPI_{cre}, Chronic Kidney Disease Epidemiological Collaboration creatinine equation; CKD-EPI_{cre-cys}, Chronic Kidney Disease Epidemiological Collaboration creatinine and cystatin C equation; FAS, full age spectrum.

Table 1

General characteristics of study sample and association of study variables with 9-year mortality in age- and sex-adjusted Cox regression analysis

	All <i>n</i> = 828	Deceased <i>n</i> = 271	Crude HR (95% CI)
Age (years)	74.4 ± 6.9	79.7 ± 7.1	1.15 (1.13–1.17)
Sex (female)	473 (57.1)	139 (51.3)	0.61 (0.48–0.77)
BMI (kg/m ²)	27.4 ± 4.0	26.9 ± 4.1	1.0 (0.97–1.04)
Smoking habits			
Non-smoker	499 (60.3)	154 (46.8)	1.0
Ex-smoker	218 (26.3)	76 (28.0)	1.19 (0.86–1.64)
Smoker	111 (13.4)	41 (15.1)	1.83 (1.26–2.65)
Hypertension	521 (62.9)	186 (68.6)	1.31 (1.0–1.70)
Heart failure	35 (4.2)	25 (9.2)	2.97 (1.96–4.51)
Coronary artery disease	63 (7.6)	24 (8.9)	1.09 (0.72–1.68)
Stroke	37 (4.5)	24 (8.9)	2.30 (1.49–3.55)
Peripheral arterial disease	97 (11.7)	63 (23.2)	2.08 (1.55–2.79)
Chronic obstructive pulmonary disease	57 (6.9)	37 (13.7)	1.75 (1.20–2.54)
Diabetes	101 (12.2)	40 (14.8)	1.41 (1.0–1.99)
Anemia	91 (11.0)	58 (21.4)	1.70 (1.25–2.30)
Femur fracture	21 (2.5)	8 (3.0)	1.33 (0.66–2.70)
Osteoarthritis	94 (11.4)	39 (14.4)	1.46 (1.03–2.06)
Cancer	50 (6.0)	17 (6.3)	1.44 (0.87–2.36)
No. lost BADL at baseline	0.2 ± 0.7	0.6 ± 1.2	1.39 (1.26–1.54)
MMSE score	25.1 ± 3.2	24.2 ± 4.6	0.94 (0.91–0.97)
CES-D score	12.8 ± 8.7	14.4 ± 8.7	1.01 (1.0–1.03)
Muscle area (mm ³)	6206 ± 1266	5817 ± 1239	1.0 (1.0–1.0)
Muscle area (mm ³ < median value) [‡]	406 (49.0)	160 (59.0)	1.43 (1.08–1.90)

[‡]Median value = 6107 mm³. Data are mean ± SD or number of cases (percentage). BADL, basic activities of daily living; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression scale; MMSE, Mini-Mental State Examination.

Table 2

Prevalence of different estimated glomerular filtration rate categories in the study population, and their crude and fully adjusted association with 9-year mortality

	All (n = 828)	Deceased (n = 271)	Crude HR (95% CI)	Adjusted HR (95% CI) [†]
Creatinine-based eGFR (mL/min/1.73 m ²)				
CKD-EPI _{cre}				
90	68 (8.2)	10 (3.7)	1.0	1.0
60–89.9	601 (72.6)	181 (66.8)	2.24 (1.18–4.23)	1.63 (0.84–3.17)
45–59.9	142 (17.1)	66 (24.4)	3.85 (1.98–7.50)	2.50 (1.21–5.15)
30–44.9	11 (1.3)	9 (3.3)	16.2 (6.57–40.1)	5.44 (1.10–27.7)
<30	6 (0.7)	5 (1.8)	15.1 (5.15–44.4)	7.42 (1.79–30.6)
BIS1 _{cre}				
90	17 (2.1)	1 (0.4)	1.0	1.0
60–89.9	461 (55.7)	107 (39.5)	4.74 (0.66–34.0)	4.27 (0.56–32.5)
45–59.9	306 (37.0)	128 (47.2)	9.36 (1.31–67.0)	7.63 (1.0–58.3)
30–44.9	38 (4.6)	30 (11.1)	29.6 (4.02–217.0)	13.1 (1.59–108.2)
<30	6 (0.7)	5 (1.8)	43.1 (5.02–370.3)	25.3 (2.36–271.9)
FAS				
90	24 (2.9)	3 (1.1)	1.0	1.0
60–89.9	448 (54.1)	110 (40.6)	2.21 (0.70–6.97)	1.74 (0.52–5.79)
45–59.9	301 (36.4)	120 (44.3)	4.08 (1.29–12.8)	3.31 (0.98–11.1)
30–44.9	47 (5.7)	31 (11.4)	9.62 (2.94–31.5)	4.51 (1.22–16.6)
<30	8 (1.0)	7 (2.6)	23.6 (6.08–91.8)	10.3 (1.85–57.9)
Creatinine/cystatin C-based eGFR (mL/min/1.73 m ²)				
CKD-EPI _{cre-cys}				
90	123 (14.9)	23 (8.5)	1.0	1.0
60–89.9	540 (65.2)	158 (58.3)	1.79 (1.15–2.77)	1.89 (1.12–3.19)
45–59.9	132 (15.9)	62 (22.9)	3.20 (1.98–5.18)	2.29 (1.22–4.27)
30–44.9	23 (2.8)	19 (7.0)	9.56 (5.18–17.6)	5.57 (2.46–12.6)
<30	10 (1.2)	9 (3.3)	16.9 (7.77–36.9)	8.94 (2.28–35.0)
BIS2 _{cre-cys}				
90	31 (3.7)	5 (1.8)	1.0	1.0
60–89.9	509 (61.5)	115 (42.4)	1.52 (0.62–3.73)	2.01 (0.62–6.49)
45–59.9	238 (28.7)	113 (41.7)	3.58 (1.46–8.76)	4.52 (1.38–14.8)
30–44.9	40 (4.8)	29 (10.7)	8.31 (3.21–21.5)	5.59 (1.54–20.4)
<30	10 (1.2)	9 (3.3)	19.3 (6.43–57.9)	13.4 (2.38–75.7)

[†]Adjusted for body mass index (BMI), smoking habits, hypertension, heart failure, coronary artery disease, stroke, peripheral arterial disease, chronic obstructive pulmonary disease, diabetes, anemia, femur fracture, osteoarthritis, cancer, Mini-Mental State Examination, basic activities of daily living, Center for Epidemiological Studies-Depression scale, and muscle area ST 66% tibia < median value. BIS_{cre}, Berlin Initiative Study creatinine equation; BIS_{cre-cys}, Berlin Initiative Study creatinine and cystatin C equation; CKD-EPI_{cre}, Chronic Kidney Disease Epidemiological Collaboration creatinine equation; CKD-EPI_{cre-cys}, Chronic Kidney Disease Epidemiological Collaboration creatinine and cystatin C equation; FAS, full age spectrum. Data are number of cases (percentage).

Table 3Accuracy of estimated glomerular filtration rate <60 mL/min/1.73 m² in predicting mortality

	Sensitivity	Specificity	AUC (95%CI)	C index (95%CI)
CKD-EPI _{cre}	0.29	0.86	0.60 (0.56–0.64)	0.61 (0.57–0.65)
BIS _{cre}	0.60	0.67	0.65 (0.61–0.69)	0.66 (0.62–0.69)
FAS	0.58	0.65	0.63 (0.59–0.67)	0.64 (0.61–0.68)
CKD-EPI _{cre-cys}	0.33	0.87	0.63 (0.59–0.67)	0.66 (0.63–0.69)
BIS _{cre-cys}	0.56	0.76	0.67 (0.63–0.71)	0.68 (0.65–0.72)

BIS_{cre}, Berlin Initiative Study creatinine equation; BIS_{cre-cys}, Berlin Initiative Study creatinine and cystatin C equation; CKD-EPI_{cre}, Chronic Kidney Disease Epidemiological Collaboration creatinine equation; CKD-EPI_{cre-cys}, Chronic Kidney Disease Epidemiological Collaboration creatinine and cystatin C equation; FAS, full age spectrum.