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Original Article

Estimated glomerular filtration rate and functional status among older people: A systematic review

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ABSTRACT

Background: The association between chronic kidney disease (CKD) and functional status may change as a function of the equation used to estimate glomerular filtration rate (eGFR). We reviewed the predictive value of different eGFR equations in regard to frailty and disability outcomes.

Methods: We searched Pubmed from inception to March 2018 for studies investigating the association between eGFR and self-reported and/or objective measures of frailty or disability. Cross-sectional and longitudinal studies were separately analysed.

Results: We included 16 studies, one of which reporting both cross-sectional and longitudinal data. Three out of 7 cross-sectional studies compared different eGFR equations in regard to their association with functional status: two studies showed that cystatin C-based, but not creatinine-based eGFR may be associated with hand-grip strength or frailty; another study showed that two different creatinine-based eGFR equations may be similarly associated with disability. Four out of 10 longitudinal studies provided comparative data: two studies reported similar association with disability for different creatinine-based eGFR equations; one study showed that creatinine-based eGFR was not associated with frailty, but a not significant trend for association was observed with cystatin C-based eGFR; one study showed that cystatin C-based but not creatinine-based eGFR may predict incident mobility disability, while both methods may predict gait speed decline. High heterogeneity was observed in regard to confounders included in reviewed studies. None of them included the most recently published equations.

Conclusion: Available data do not support the superiority of one of the eGFR equations in terms of measuring or predicting functional decline.

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1. Introduction

Progressive aging of the population in industrialized countries is accompanied by an increase in the prevalence of chronic kidney disease (CKD) [1]. Recently, it has been estimated that the residual lifetime incidence of CKD among US people aged 65 or more is 42%, while the prevalence of CKD among older adults is projected to increase from 13.2% currently to 14.4% in 2020 and 16.7% in 2030 [2]. Thus, CKD has a relevant public health burden in the older population, resulting in an increased risk of end-stage renal disease (ESRD), morbidity and mortality [3].

Besides carrying negative prognostic implications in general and selected diseased populations, including older ones [4–8], CKD also has negative implications in terms of functional limitation and disability, including impaired physical function [9, 10], frailty [11, 12], and sarcopenia [13, 14]. Thus, early identification and management of CKD patients are paramount for planning interventions aimed at slowing the progression of kidney disease and associated comorbidities, but also to delay the onset of its functional complications.

Currently available creatinine-based measures of kidney function are plagued by some degree of inaccuracy and may provide discrepant estimates [15, 16]. Indeed, several studies showed the existence of a U-shaped relationship between creatinine-based eGFR and mortality in frail and older people [17–20]. Additionally, creatinine-based eGFR may systematically underestimate measured GFR at higher levels of kidney function [21], leading to systematic over-diagnosis of CKD in clinically healthy older people.

Efforts have been made to improve the estimating equations, especially in older patients. The Berlin Initiative Study (BIS) equations have been developed and tested in older people and have been proved to be accurate and precise in this population [22]. Nevertheless, the creatinine-based CKD-EPI (CKD-EPI$_{cre}$) remains the recommended equation also for older people [23], as the role and practical place of BIS equations have not been conclusively defined. Additionally, the potential usefulness of cystatin C-based equations is still to be clarified. Finally, given the mounting evidence about the disabling potential of CKD, individual equations should be tested not only as for their accuracy in predicting measured GFR as reference standard or traditional endpoints (e.g. mortality and end-stage renal disease (ESRD)), but also for their ability in predicting functional outcomes.

Therefore, greater focus should be on the comparison between the recommended CKD-EPI$_{cre}$ and other eGFR equations in predicting functional status. Improving knowledge on this issue may assist in designing CKD-related disability risk assessments and in tailoring interventions for older people. Thus, the purpose of this systematic literature review was to (i) identify all studies reporting on the relationship between eGFR and self-reported or objectively measured functional status among older people, and (ii) describe findings with regard to the difference between data obtained with CKD-EPI$_{cre}$ compared to other eGFR equations.

2. Methods

2.1. Data Sources and Searching

We conducted a systematic literature review in MEDLINE (via PubMed) from inception to March 2018, using the following syntax:

(Equation OR formula) AND (Berlin-Initiative-Study OR “CKD-EPI” OR “CKDEPI” OR Chronic Kidney Disease Epidemiology Collaboration OR Cockcroft-Gault OR MDRD4 OR (Modification of Diet in Renal Disease) OR (Cystatin C) OR “Cystatin C"[Mesh] OR “Glomerular Filtration Rate”[Mesh] OR Glomerular Filtration Rate OR BIS-1 OR “CKD-EPI” OR BIS-2 OR “Kidney Function Tests”[Mesh] OR Schwartz equation).

Only English language studies were selected for further evaluation. A manual search of reference lists of relevant papers and reviews was performed to identify additional articles.

2.2. Eligibility Criteria and Quality Assessment

Three assessors (MDR, PF, AC) independently screened title and abstract of the records retrieved from the medical literature. The following eligibility criteria were used to retrieve studies to be included in the review:

- Study design: Either cross-sectional or cohort (retrospective and prospective) studies were included. All study settings and design (cross sectional/longitudinal cohort) were included in further evaluation.
- Participants: studies not including people older than 65 years were excluded, while studies including also people younger than 65 were included for further evaluation.
- Reference assessment of eGFR: Creatinine-based CKD-EPI equation was considered as the reference assessment of eGFR on the basis of current recommendations [23].
- Comparators: We searched for studies comparing creatinine-based CKD-EPI to other equations in regards to their association with functional status. However, in order to obtain a comprehensive review, we also included papers investigating only one eGFR equation.
- Outcomes: physical functional status outcomes were considered. Studies including self-reported and/or objectively measured functional status were gathered and analysed.
- Measures for cross-sectional studies: β coefficients for continuous outcomes and ORs for binary outcomes. Measures for longitudinal studies: HRs for survival analyses, β coefficients for continuous outcomes and ORs for binary outcomes. Relative risk for eGFR value < 60 ml/min/1.73 m^2 was also extracted or calculated from data reported in retrieved longitudinal studies.

The full-text of the articles selected by at least one of the assessors was further evaluated. The same assessors extracted independently information from the selected studies, including study aims, population, eGFR equation(s) used, specification of outcomes and main findings. The list of confounders included in each study was also gathered. Additional details were collected as deemed necessary. Any disagreement was resolved through consensus building in the focus group. Data were grouped according to study design (cross-sectional and cohort studies).

Quality assessment was carried out by the same assessors using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [24], a 14-item tool designed to aid appraisal of internal validity (potential risk of selection, information, or measurement bias, or confounding). Any disagreement in quality assessment was resolved through consensus.

3. Results

Fig. 1 shows information about the process of literature review and the reasons for inclusion and exclusion of identified citations. The electronic search strategy identified a total number of 5796 citations. Of these, 55 were considered as potentially eligible during title/abstract evaluation and included in full-text assessment. Fourteen primary studies [9, 11, 12, 25–35] and one systematic review/meta-analysis [36] were selected. The five studies included in the systematic review by Shen et al. [36] were analysed: one study was excluded because it did not include older people, while two other studies were excluded because kidney function was not estimated by eGFR. The remaining two studies [37, 38] were retrieved, leading to a total of 16 studies included in the analysis. One of the included studies reported both cross-sectional and prospective data [38]. The overall number of subjects included in reviewed studies was 45,381.

The equations used to calculate eGFR mentioned in this systematic

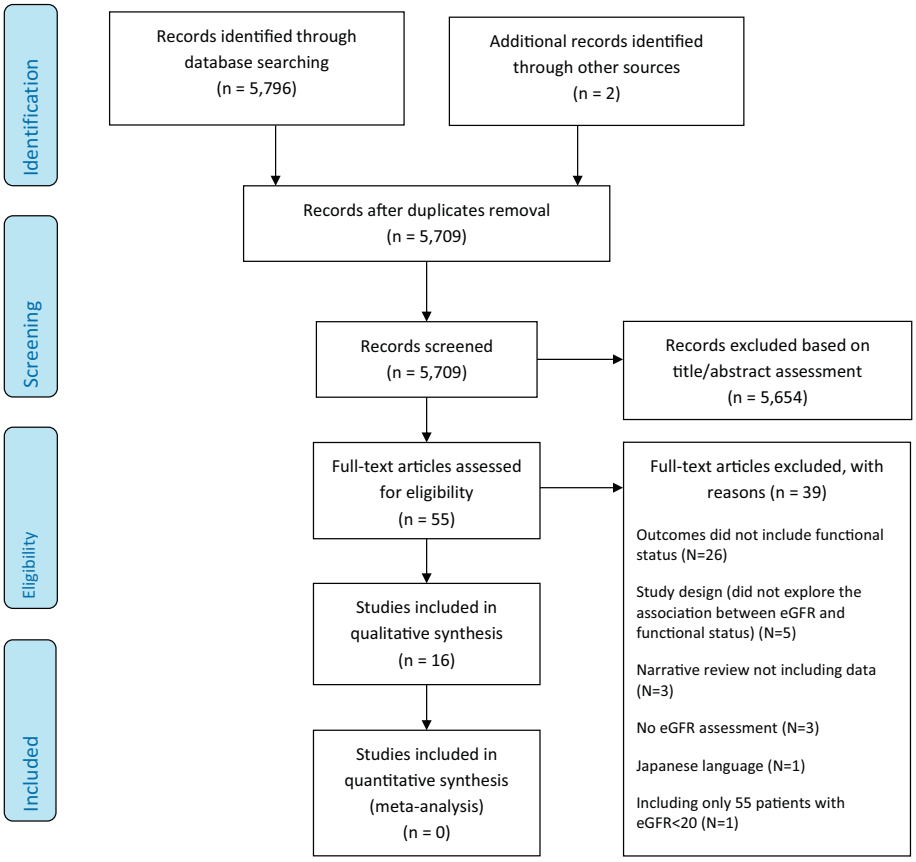

Fig. 1. PRISMA diagram.

Table 1
Equations for estimating GFR used in reviewed studies.

CG [39]	[(l40–age) × weight]/(72xScr) [×0.85 if female]
MDRD [40]	[186.3 × (Scr)$^{-1.154}$ × (age)$^{-0.203}$] [×0.742 if female] [×1.212 if black]
6-variables MDRD [40]	170 * [Scr] − 0.999 × age$^{-0.176}$ × BUN$^{-0.170}$ × serum albumin$^{0.318}$ [×0.762 in females] [×1.180 if black]
CKD-EPI$_{cre}$ [41]	Female (Scr ≤ 0.7) eGFR = 144 × (Scr/0.7)$^{-0.329}$ × (0.993)^{Age} (Scr > 0.7) eGFR = 144 × (Scr/0.7)$^{-1.209}$ × (0.993)^{Age} Male (Scr ≤ 0.9) eGFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)^{Age} (Scr > 0.9) eGFR = 141 × (Scr/0.9)$^{-1.209}$ × (0.993)^{Age}
CKD-EPI$_{cys}$ [42]	(Scys ≤ 0.8), eGFR = 133 × (Scys/0.8)$^{-0.499}$ × 0.996^{Age} [×0.932 if female] (Scys > 0.8), eGFR = 133 × (Scys/0.8)$^{-1.328}$ × 0.996^{Age} [×0.932 if female]
CRIC [44]	Study equation is only available for CRIC study internal use
BIS1 [22]	3736 × creatinine$^{-0.87}$ × age$^{-0.95}$ [×0.82 if female]
BIS2 [22]	767 × cystatin C$^{-0.61}$ × creatinine$^{-0.40}$ × age$^{-0.57}$ [×0.87 if female]
FAS [43]	107.3/(Scr/Q) for age = 2–40 years [107.3/(Scr/Q)] × 0.998$^{(Age-40)}$ for age > 40 years Q = mean or median Scr value for age−/sex-specific healthy populations

Scr: serum creatinine; BUN: blood urea nitrogen; Scys: serum cystatin C; CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiological Collaboration; CRIC, Chronic Renal Insufficiency Cohort; BIS: Berlin Initiative Study; FAS: Full Age Spectrum.

review are reported in Table 1 [22, 39–44]. Study outcomes assessed in retrieved studies are described in Table 2 [33, 45–51] [52].

3.1. Overview of Included cross-sectional studies

Among the 7 cross-sectional studies retrieved (Table 3), only three studies provided a comparison between different eGFR equations in regards to their association with functional status: Plantinga et al. [32] compared CKD-EPI$_{cre}$ and MDRD, while Tufan et al. [33] compared CKD-EPI$_{cre}$, CKD-EPI$_{cys}$ and MDRD, and Dalrymple et al. [38] compared CKD-EPI$_{cre}$ and CKD-EPI$_{cys}$. Other cross-sectional studies used only MDRD [29, 31], CKD-EPI$_{cre}$ [9], or CRIC [37] equations. Six studies involved community-dwelling individuals [29, 31–33, 37], while only one study included hospitalized patients [9]. The study by Plantinga et al. [32] also included people aged 18–65 years, but only results for subjects aged > 65 were included in the present analysis. The outcomes were self-reported in two out of six studies [29, 32], while one or more objective measures of functional status were used in the remaining five studies [9, 31, 33, 37, 38].

Among comparative studies, Plantinga et al. [32] showed that MDRD-based stage 3-4 CKD is associated with higher prevalence of disability into ability to work, type or amount of work performed, walking or difficulties in basic activity of daily living (BADL), instrumental activities of living (IADL), leisure and social activities, lower extremity mobility, and general physical activity. However, after adjusting for potential confounders most of these associations were no longer significant, so that only disability in type or amount of work and leisure-time activities resulted to be more prevalent in CKD compared to no-CKD subjects. Similarly, a significantly increased adjusted prevalence of disability in leisure-time activities among patients with stage 3-4 CKD was observed when using CKD-EPI$_{cre}$ equation [32]. On the other hand, Tufan et al. showed that CKD-EPI$_{cys}$ was significantly correlated to reduced hand grip strength, while MDRD and CKD-EPI$_{cre}$ were not [33]. Finally, Dalrymple et al. [38] showed that CKD-EPI$_{cys}$ < 45 ml/min/1.73 m^2 was significantly associated with frailty, while CKD-EPI$_{cre}$ was not.

Non comparative cross-sectional studies provided consistent results across different outcome measures [9, 29, 31, 37]: MDRD was found

Table 2
Summary of outcomes reported in reviewed studies.

Outcome(s)	Description
Self-reported	
Working, walking and cognition	Self-reported limitation in listed tasks
Leisure and social activities	Self-reported limitation in listed tasks
Lower extremity mobility	Self-reported limitation in listed tasks
General physical activity	Self-reported limitation in listed tasks
Walking or climbing stairs	Self-reported limitation in listed tasks
Basic activities of daily living (BADL) [49]	Rating dependency in bathing, dressing, toileting, transferring, continence, eating
Instrumental activities of daily living (IADL) [50]	Rating dependency in ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, managing medications, managing money
Short Form-36 (SF36) physical function scale (PFS) [51]	SF36 is a 36-item questionnaire which measures Quality of Life across eight domains, including: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. The Physical function scale is calculated as average score of items 3 to 12.
Functional Independence Measurement (FIM) [52]	The FIM is an 18-item, 7-level functional assessment designed to evaluate the amount of assistance required by a person with a disability to perform basic life activities safely and effectively.
Objectively measured or mixed	
400-m walk time	Time taken to walk a distance of 400 m
Lower extremity performance score [45, 46]	Modified version of the lower extremity performance test used in the Established Populations for Epidemiologic Studies of the Elderly (EPESE), including five repeated chair stands, semi-tandem, full tandem, and single-leg standing balance tests, a 6-min walking test to determine usual gait speed, and a narrow walk test of balance.
Hand grip strength	Isokinetic dynamometer
Sarcopenic hand grip strength (HGS) [33]	Hand grip strength < 29 kg when BMI < 24 kg/m^2, < 30 kg when BMI = 24.1–28 kg/m^2, < 32 kg when BMI > 28 kg/m^2
Knee extension strength	Isokinetic dynamometer
Walking (gait) speed	Gait speed in m/s measured on a 4-or 6-m path at usual pace.
SPPB [45]	The short physical performance battery (SPPB) is a group of measures that combines the results of walking speed, chair stand and balance tests.
Frailty [47]	Frailty if defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss, weakness (handgrip strength), self-reported exhaustion or poor endurance, slowness (walking speed), and low physical activity (kilocalories expended per week).
Rankin scale [48]	Measures the degree of disability or dependence in the daily activities of people with stroke or other neurological disabilities. The 6 levels of rating are: no symptoms; no significant disability despite symptoms; slight disability; moderate disability; moderately severe disability; severe disability; dead.

associated with 400-m walk time, lower extremity performance, grip strength, knee extension [31]; eGFR decline ≥ 25% (based on MDRD equation) during the 10 years preceding functional assessment was found associated with impaired SF36™ physical performance scale [29]; CKD-EPI$_{cre}$ was found associated with Short Physical Performance Battery (SPPB) total score, balance and muscle strength sub-scores, but not walking speed [9]; Chronic Renal Insufficiency Cohort (CRIC) equation was found associated with SPPB total score and frailty [37] (Table 3).

Overall, the quality of cross-sectional studies was fair (Table S1). Sample size justification was reported by Lin et al. [29], while Lattanzio et al. [9] and Plantinga et al. [32] reported different levels of kidney function as related to the outcomes. Confounders included age, gender and comorbidities (especially cardiovascular disease, diabetes, cancer, and anemia) in the majority of studies [9, 29, 32, 37]. Results obtained by Odden et al. [31] and Tufan et al. [33] were not adjusted for comorbidity, while the study by Lattanzio et al. [9] also included cognitive status and cumulative comorbidity as potential confounders. Selected studies also adjusted their analysis by serum albumin [9, 33].

3.2. Overview of included cohort studies

Among the 10 cohort studies (Table 4), only one study was retrospective, while the remaining nine had a prospective design. Pedone et al. [12] provided a comparison between Cockcroft-Gault (CG) and MDRD, while Bowling et al. [26] compared MDRD and CKD-EPI$_{cre}$ in regard to their association with functional status. Dalrymple et al. [38] and Liu et al. [30] compared the ability of CKD-EPI$_{cys}$ and CKD-EPI$_{cre}$ in predicting incident frailty and mobility disability or change in gait speed, respectively. Among the remaining cohort studies, two used MDRD [11, 28], one used the 6-variables MDRD [25], and three used CKD-EPI$_{cre}$ [27, 34, 35]. Seven out of ten studies involved community-dwelling individuals [11, 12, 26–28, 30, 38], while the remaining three were carried out in the hospital setting [25, 34, 35]. The outcomes were self-reported in five studies [12, 26–28, 30] and objectively measured or rated by study researchers in the remaining ones [11, 25, 34, 35, 38].

The comparative study by Pedone et al. [12] showed that both CG and MDRD equations were able to predict the loss of at least 1 BADL during a 6-years follow-up period among community-dwelling older people. Bowling et al. [26] showed that both CKD-EPI$_{cre}$ and MDRD were similarly associated with incident BADL and IADL dependency during a 2-year follow-up. At variance, despite the observed increased relative risk for CKD-EPI$_{cre}$ < 60 ml/min/1.73 m^2, creatinine-based eGFR did not predict incident frailty after adjusting for potential confounders in the study by Dalrymple et al., while a not significant trend for increased risk was observed with CKD-EPI$_{cys}$ [38]. Finally, Liu et al. showed that CKD-EPI$_{cys}$ but not CKD-EPI$_{cre}$ may predict incident mobility disability, while both equations may predict gait speed decline [30].

Non comparative studies showed that MDRD equation could predict IADL and BADL decline, as well as difficulty in walking or climbing stairs [11, 28]. The 6-variable MDRD equation could predict motor, but not total Functional Impairment Measurement (FIM) score at discharge among older patients with hip fracture in the only study with retrospective design [25]. CKD-EPI$_{cre}$ was found associated with IADL and BADL decline, self-reported difficulty in walking or climbing stairs, and gait speed decline in community-dwelling individuals [27, 30]. The relative risk for incident stroke disability was also increased among hospitalized patients with CKD-EPIcre eGFR < 60 ml/min/1.73 m^2, but such an association was no longer significant in multivariable analysis [34, 35] (Table 4).

None of the cohort studies reported sample size justification. The exposure variable was assessed more than once over time only in the studies by Adunsky et al. [25] and Dalrymple et al. [38]. Relative risk or data for its calculation were available for eight out of ten cohort studies reviewed. Subjects lost to follow up were not reported in five out of eight studies [12, 25, 30, 34, 35] (Table S1). Age, gender, cardiovascular comorbidities and diabetes were the most frequently included

Table 3
Summary of findings from retrieved cross-sectional studies.

Study	N	Age	Design and setting	Outcome(s)	eGFR method	Main results
Odden [31]	3043	74	Cross-sectional Community-dwelling	400-m walk time Lower extremity performance score Grip strength Knee extension strength	MDRD	Among patients with eGFR < 60 ml/min/1.73 m^2 - 400-m walking time: β = 19.7, 95%CI = 9.2–30.1 - Lower extremity performance: β = −0.18, 95%CI = −0.26- -0.10 - Grip strength: β = −1.9, 95%CI = −3.0- -0.7 - Knee extension: β = −10.2, 95%CI = −14.7- -5.6 Among patients with eGFR ≥ 60 ml/min/1.73 m^2 - 400-m walking time: β = −3.5, 95%CI = −7.0–0.0 - Lower extremity performance: β = 0.04, 95%CI = 0.02–0.07 - Grip strength: β = 0.9, 95%CI = 0.5–1.3 - Knee extension: β = 3.8, 95%CI = 2.2–5.5
Lin [29]	2544	67	Cross-sectional Community-dwelling	SF36 physical function scale (PFS)	MDRD	Association between former eGFR decline ≥25% and actual PFS - Linear analysis: β = −3.5, 95%CI = −5.4, −1.5 - Logistic regression analysis considering PFS ≤ 65 as outcome variable: OR = 1.37, 95%CI = 1.04–1.81 (not significant after adjusting for BMI: OR 1.15; 95% CI 0.90–1.47).
Plantinga [32]	16,011	≥65	Cross-sectional Community-dwelling	Self-reported limitations in: • Working, walking, and cognition; • BADL; • IADL; • Leisure and social activities; • Lower extremity mobility; • General physical activity	MDRD $CKD\text{-}EPI_{cre}$	Stage 3–4 CKD compared to no CKD Using MDRD: - Adjusted prevalence of disability in type or amount of work performed (43.7 (95%CI = 39.0–48.4) vs 39.0 (95%CI = 35.5–42.4), $p < .05$) - Adjusted prevalence of disability in leisure time activities (21.5 (95%CI = 18.5–24.6) vs 17.4 (95%CI = 15.5–19.3), $p < .05$) Using CKD-EPIcre: - Adjusted prevalence of disability in leisure time activities (21.7 (95%CI = 18.5–24.9) vs 17.4 (95%CI = 15.5–19.2), $p < .05$)
Lattanzio [9]	486	80.1	Cross-sectional Hospital	SPPB, either global score or its individual components (muscle strength, balance, and walking speed)	$CKD\text{-}EPI_{cre}$	Linear association between eGFR and: - SPPB total score (B = 0.49, 95%CI = 0.18–0.66) - Balance (B = 0.30, 95%CI = 0.10–0.49) - Muscle strength (B = 0.06, 95%CI = 0.01–0.10) - Walking speed (B = −0.04, 95%CI = −0.09–0.11) Compared to patients with eGFR > 60: - eGFR = 30.0–44.9, adjusted mean difference − 1.28 (95%CI = −2.37- -0.18) for SPPB total score, and − 0.63 (95%CI = −1.12- -0.14) for balance score; - eGFR < 30, adjusted mean difference − 2.26 (95%CI = −3.60- -0.93) for total SPPB score, −0.76 (95%CI = −1.30- -0.22) for muscle strength score, and − 1.03 (95%CI = −1.63 to −0.43).
Dalrymple [38]	4150	≥65	Cross-sectional Community-dwelling	Frailty (slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss)	$CKD\text{-}EPI_{cre}$ $CKD\text{-}EPI_{cys}$	$CKD\text{-}EPI_{cre}$ ≥ 90: reference - 76–89 OR = 0.48 (95%CI 0.42–0.73) - 60–75 OR = 0.59 (95%CI 0.39–0.89) - 45–59 OR = 0.69 (95%CI 0.45–1.07) - 15–44 OR = 0.83 (95%CI 0.49–1.41) $CKD\text{-}EPI_{cys}$ ≥ 90: reference - 76–89 OR = 0.77 (95%CI 0.48–1.31) - 60–75 OR = 1.05 (95%CI 0.64–1.72) - 45–59 OR = 1.47 (95%CI 0.89–2.43) - 15–44 OR = 2.44 (95%CI 1.43–4.19)
Reese [37]	1111	65.0	Cross-sectional Community-dwelling	SPPB; Frailty (slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss)	CRIC	For SPPB - eGFR 30–59: β = −0.51, 95%CI = −0.80 - -0.22; - eGFR 15–29: β = −0.61, 95%CI = −1.03 - -0.19; - eGFR < 15: β = −1.75, 95%CI = −2.33 - -1.16. For frailty - eGFR 30–59: OR = 1.45, 95%CI = 1.05–1.99; - eGFR 15–29: OR = 2.02, 95%CI = 1.29–3.16; - eGFR < 15: OR = 4.83, 95%CI = 2.60–8.98.

(*continued on next page*)

Table 3 (*continued*)

Study	N	Age	Design and setting	Outcome(s)	eGFR method	Main results
Tufan [33]	209	67.8	Cross-sectional Community-dwelling	Hand grip strength (HGS). Sarcopenic HGS was defined as (< 29 kg when BMI < 24 kg/m^2, < 30 when BMI = 24.1–28 kg/m^2, and < 32 kg when BMI > 28 kg/m^2)	MDRD $CKDEPI_{cre}$ $CKDEPI_{cys}$	Only $CKDEPI_{cys}$ < 60 was significantly associated with sarcopenic HGS (OR = 2.40, 95%CI = 1.04–5.40).

MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; CRIC, Chronic Renal Insufficiency Cohort.

confounders in cohort studies [11, 12, 28, 30, 34, 35, 38]. Other potential confounders considered in cohort studies were serum albumin [25, 27, 28, 38], hemoglobin [25, 27, 28, 38], lipids [27, 38], smoking habits and alcohol consumption [27, 30, 34, 35]. Few studies also included cognitive status [25, 26, 28], depression [28] and physical activity [28, 30] among potential confounders.

4. Discussion

Our systematic review shows that eGFR is associated with different phenotypes of functional impairment in most of the studies included in the analysis. However, selected differences among studies deserve mention. Indeed, two comparative cross-sectional studies showed that $CKD\text{-}EPI_{cys}$, but not MDRD and/or $CKD\text{-}EPI_{cre}$ was associated with hand grip strength or frailty [33, 38]. Additionally, one comparative cohort study showed $CKD\text{-}EPI_{cre}$ may not predict incident frailty, while a not significant trend for increased risk could be observed with $CKD\text{-}EPI_{cys}$ [38]. Finally, $CKD\text{-}EPI_{cre}$ was not associated with incident stroke disability [34, 35]. Thus there is consistent uncertainty, if changes in kidney function estimated with different equations may predict phenotypes of functional decline with different accuracy.

While the potential superiority of cystatin C-based equations in predicting functional status needs to be further investigated in comparative studies, the small evidence currently available suggests that sarcopenia may represent an important confounder in the association between eGFR and functional phenotypes. Indeed, normal or even high eGFR based on a calculation using serum creatinine may at least partly reflect inflammation, frailty and/or muscle loss with consequent reduced creatinine production rather than normal kidney function [53, 54]. This incongruence affirms the need for new approaches to estimate kidney function in elderly individuals. Ideally, a new formula should not only extrapolate age-associated declining muscle mass but also reflect functional decline.

eGFR has been considered a key prognostic and classificatory indicator in public health campaigns, whereas serum creatinine is an unreliable marker of renal function [55]. Equations have been developed by incorporating demographic and clinical variables as surrogates for unmeasured physiological factors, such as creatine generation and tubular secretion, that contribute – apart from filtration function – to serum creatinine concentration [22, 40–42]. Estimating equations seems to be reasonably accurate in detecting changes in kidney function over time [56]. However, the distinctive lack of data comparing the predictive value of different eGFR equation in regard to functional status observed in the present study is a relevant issue because the accuracy in predicting outcomes may change as a function of the equation used. Indeed, disagreement between eGFR equations has been consistently reported [15, 16, 57–60], with age, gender, weight, and study setting representing important sources of discrepancy between equations [15]. Thus, results obtained with different equations may be difficult to interpret. As an example, a U-shaped relationship between eGFR and mortality has been observed by using MDRD [17], $CKD\text{-}EPI_{cre}$ [18, 20], and BIS_{cre} [61], but not with cystatin-C-based CKD-EPI equation [20]. This evidence further suggests that eGFR may not only reflect kidney function, but rather muscle loss, which may contribute to a low serum creatinine concentration [61]. Such hypothesis is also sustained by the observation that both low serum creatinine and low 24 h urine creatinine are associated with adverse outcomes [62], while cystatin C is less influenced by body composition [63]. Nevertheless, only two longitudinal study [30, 38] and two cross-sectional studies [33, 38] compared the predictive value of creatinine- and cystatin C-based eGFR in regard to functional status.

Current evidence suggests that filtration markers other than serum creatinine and not affected by muscle loss (i.e. cystatin C, beta-trace protein and beta2-microglobulin) [64] may better predict negative outcomes, but their usefulness in predicting functional decline is still to be investigated. Despite $CKD\text{-}EPI_{cre}$ remains recommended as a reference equation [23], it may not perform better than other equations in predicting outcomes in older populations [58, 65]. The cross-sectional association between MDRD or $CKD\text{-}EPI_{cre}$ and disabilities was no longer significant after adjusting for potential confounders [32]. On the other hand, $CKD\text{-}EPI_{cys}$, but not $CKD\text{-}EPI_{cre}$ was found cross-sectionally associated with frailty [38]. In cohort studies, CG, MDRD and $CKD\text{-}EPI_{cre}$ showed similar associations with incident disability [12, 26]. However, when comparing $CKD\text{-}EPI_{cre}$ and $CKD\text{-}EPI_{cys}$ in regard to their ability to predict incident frailty or mobility disability, only the latter equation showed a near significant trend for increased risk [30, 38]. Thus, available studies are not sufficient to build a meta-analysis of comparative studies. Additionally, it is worth noting that we could not find any study including the most recent equations addressing the issue of estimating kidney function among older people. The BIS equations have been specifically developed in an older population and published in 2012 [22]. It showed a reduced rate of misclassification of CKD stages [22, 56], which was confirmed in two external validation studies in older patients [66, 67]. In our review, three cross-sectional studies and five longitudinal studies were published after 2012, but none of them included BIS equation for kidney function assessment. Furthermore, the Full Age Spectrum (FAS) equation has been published in 2016, and it has been mathematically obtained by requiring continuity during the pediatric–adult and adult–old age transition to improve validity across the full age spectrum [68]. Thus, it seems sensible to suggest for including BIS and FAS equations in future studies investigating the relationship between kidney function and functional impairment.

The major strengths of the present study are the careful study selection and the assessment of their quality, both of which contribute to provide a reliable overview of the evidence in this research field. Additionally, most of the retrieved studies involve community-dwelling older people, which likely enhance the generalizability of our results. As for limitations, more than one-third of reviewed studies are cross-sectional, which limits the exploration of the causal relationship between eGFR and functional status. Another important limitation is the frequent use of self-reported outcome measures. Indeed, the outcome was self-reported in two out of seven cross-sectional studies, and in five out of ten cohort studies. Finally, a high heterogeneity was observed in confounding variables included in retrieved studies. Future studies are expected to bridge these gaps by using both objective and subjective outcome measures in order to increase the strength of evidence. From this point of view, the Screening for Chronic Kidney Disease among Older People across Europe (SCOPE) project, a large prospective multicenter cohort study, represents an important ongoing effort towards

Table 4
Summary of findings from retrieved cohort studies.

Study	N	Age	Design and setting	Outcome(s)	eGFR method	Main results
Fried [11]	2135	73.5	Prospective F.U.: Up to 54 months Community-dwelling	Difficulty in walking 1/4 mile or climbing 10 steps on two consecutive reports 6 months apart.	MDRD	Relative risk not available eGFR < 60: HR = 1.30 (95%CI = 1.08–1.56)
Bowling [26]	357	77.4	Prospective F.U.: 2 yrs. Community-dwelling	IADL decline BADL decline	MDRD CKD-EPI$_{cre}$	Using MDRD equation - - Relative risk for eGFR < 60 was 2.05, 95%CI = 1.80–2.30 for IADL decline and 2.89, 95%CI = 2.63–3.15 for BADL decline. - eGFR < 60: OR = 1.83 (95%CI = 1.06–3.17) for IADL decline; OR = 2.46 (95%CI = 1.19–5.12) for BADL decline. - eGFR < 45: OR = 3.12 (95%CI = 1.38–7.06) for IADL decline; OR = 3.78 (95%CI = 1.36–9.77) for BADL decline. Using CKD-EPI$_{cre}$ equation – - Relative risk for eGFR < 60 was 2.49, 95%CI = 2.30–2.68 for IADL decline and 2.42, 95%CI = 2.19–2.64 for BADL decline. - eGFR < 60 was significantly associated with IADL decline (unadjusted OR = 3.40, 95% CI = 2.00–5.77) and BADL decline (unadjusted OR = 2.56; 95% CI = 1.29–5.08). These associations were similar after multivariable adjustment (data not shown).
Adunsky [25]	499	83.6	Retrospective cohort Hospital Hip fracture patients	FIM at discharge after hospital rehabilitation	6-variables MDRD	Relative risk not available eGFR was significantly associated with motor FIM (β = 0.028, p = .022) but not total FIM (β = 0.072, p = .101).
Feng [28]	1186	65.6	Prospective F.U.: 4 yrs. Community- dwelling	IADL decline (total and cognitive)	MDRD	eGFR < 60: IADL decline - - Relative risk for eGFR < 60 = 2.91, 95%CI = 2.60–3.22 - OR = 1.99, 95%CI = 1.16–3.41 IADL cognitive decline - - Relative risk not available - OR = 2.06, 95%CI = 1.07–3.94 for cognitive IADL decline
Pedone [12]	666	73.1	Prospective F.U: 6 yrs. Community-dwelling	Loss of independency in ≥1 BADL	CG MDRD	eGFR < 60: - Relative risk for CG < 60 = 1.90 (95%CI = 1.11–3.26) - HR = 4.40 (95%CI = 2.80–6.94) for CG - Relative risk for MDRD < 60 = 1.72 (95%CI = 1.09–2.70) - HR = 3.19 (95%CI = 2.12–4.79) for MDRD
Dalrymple [38]	4150	≥65	Prospective Community-dwelling	Frailty (slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss)	CKD-EPI$_{cre}$ CKD-EPI$_{cys}$	CKD-EPI$_{cre}$ ≥ 90: reference - Relative risk for eGFR$_{cre}$ < 60 = 1.30, 95%CI = 1.07–1.53 - 76–89 IRR = 0.60 (95%CI 0.37–0.97) - 60–75 IRR = 0.86 (95%CI 0.54–1.37) - 45–59 IRR = 0.67 (95%CI 0.40–1.12) - 15–44 IRR = 1.08 (95%CI 0.58–2.01) CKD-EPI$_{cys}$ ≥ 90: reference - Relative risk for eGFR$_{cys}$ < 60 = 1.55, 95%CI = 1.39–1.71 - 76–89 IRR = 1.51 (95%CI 0.80–2.86) - 60–75 IRR = 1.62 (95%CI 0.88–2.99) - 45–59 IRR = 1.77 (95%CI 0.89–3.13) - 15–44 IRR = 1.87 (95%CI 0.95–3.69)
Chin [27]	984	≥65	Prospective F.U.: 59.4 ± 6.9 months Community-dwelling	IADL decline BADL decline	CKD-EPI$_{cre}$	eGFR≥ 60: reference For IADL decline – - Relative risk for eGFR < 60 = 2.36, 95%CI = 1.63–3.09 - eGFR 45–59: OR = 1.41, 95%CI = 0.82–2.44 - eGFR < 45: OR = 3.0, 95%CI = 1.57–5.74 For BADL decline - - Relative risk for eGFR < 60 = 2.24, 95%CI = 1.81–2.67 - eGFR 45–59: OR = 0.64, 95%CI = 0.20–2.00 - eGFR < 45: OR = 2.94, 95%CI = 0.99–8.73

(*continued on next page*)

Table 4 (*continued*)

Study	N	Age	Design and setting	Outcome(s)	eGFR method	Main results
Liu [30]	1226	68.0	Prospective F.U.: 6.6 yrs. Community-dwelling	Self-reported inability to walk 1/2 mile and/or climb a flight of stairs Gait speed decline	CKD-EPI$_{cre}$ CKD-EPI$_{cys}$	eGFR$_{cre}$ < 60: For mobility disability - Relative risk for eGFR < 60 = 1.26, 95%CI = 0.86–1.67 - OR = 1.03, 95%CI = 0.64–1.62 For gait speed decline - - Relative risk not available - β = 0.07, SE = 0.03, p = .0004 eGFR$_{cys}$ < 60: For mobility disability - - Relative risk for eGFR < 60 = 2.08, 95%CI = 1.33–2.83 - OR = 1.55, 95%CI = 1.05–2.31 For gait speed decline - Relative risk not available - β = 0.07, SE = 0.02, p = .0022
Wang [34]	8865	69.5	Prospective F.U.: 1 yr Hospital (stroke registry)	Stroke disability (Rankin scale)	CKD-EPI$_{cre}$	eGFR ≥ 90: reference - Relative risk for eGFR < 60 = 1.49, 95%CI = 1.37–1.61 - eGFR < 45: OR = 1.26, 95%CI = 0.95–1.67 - eGFR 45–59: OR = 1.00, 95%CI = 0.81–1.23 - eGFR 60–89: OR = 0.93, 95%CI = 0.83–1.05
Yang [35]	1909	66.5	Prospective F.U.: 90 days Hospital (stroke registry)	Stroke disability (Rankin scale)	CKD-EPI$_{cre}$	eGFR ≥ 90: reference - Relative risk for eGFR < 60 = 1.50, 95%CI = 1.31–1.68 - eGFR 15–44: OR = 1.35, 95%CI = 0.83–2.19 - eGFR 45–59: OR = 1.09, 95%CI = 0.75–1.59 - eGFR 60–89: OR = 0.87, 95%CI = 0.67–1.14

F.U., follow-up; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiological Collaboration; CG, Cockcroft-Gault.

achieving this goal (ClinicalTrial.govNCT02691546).

5. Conclusions

Low eGFR is significantly associated with impaired functional status among older people. However, our findings do not allow to draw a definitive conclusion on which eGFR equation may better predict self-reported and/or objectively measured functional decline. Further studies based on longitudinal design and including both self-reported and objective outcome measures, as well as eGFR assessment by equations specifically developed in older people, and cystatin-based ones may be very informative and helpful to define CKD-related disability risk assessment among older people.

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Declarations of Interest

None.

Competing Interests

All Authors declare to have no competing interests with this manuscript.

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Authors' contributions

Andrea Corsonello, Regina Roller-Wirnsberger and Fabrizia Lattanzio conceived the study and participated in manuscript writing and revising.

Andrea Corsonello, Mirko Di Rosa and Paolo Fabbietti carried out literature search.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.05.030.

References

[1] Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int 2007;72:92–9.
[2] Hoerger TJ, Simpson SA, Yarnoff BO, Pavkov ME, Rios Burrows N, Saydah SH, et al. The future burden of CKD in the United States: a simulation model for the CDC CKD initiative. Am J Kidney Dis 2015;65:403–11.
[3] Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int 2011;79:1331–40.
[4] McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004–9.
[5] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[6] Corsonello A, Pedone C, Lattanzio F, Cherubini A, Onder G, Corica F, et al. Chronic kidney disease and 1-year survival in elderly patients discharged from acute care hospitals: a comparison of three glomerular filtration rate equations. Nephrol Dial Transplant 2011;26:360–4.
[7] Oh SW, Kim S, Na KY, Kim KW, Chae DW, Chin HJ. Glomerular filtration rate and proteinuria: association with mortality and renal progression in a prospective cohort of a community-based elderly population. PLoS One 2014;9:e94120.
[8] Malmgren L, McGuigan FE, Berglundh S, Westman K, Christensson A, Akesson K. Declining estimated glomerular filtration rate and its association with mortality and comorbidity over 10 years in elderly women. Nephron 2015;130:245–55.
[9] Lattanzio F, Corsonello A, Abbatecola AM, Volpato S, Pedone C, Pranno L, et al. Relationship between renal function and physical performance in elderly hospitalized patients. Rejuvenation Res 2012;15:545–52.
[10] Roshanravan B, Khatri M, Robinson-Cohen C, Levin G, Patel KV, de Boer IH, et al. A prospective study of frailty in nephrology-referred patients with CKD. Am J Kidney Dis 2012;60:912–21.
[11] Fried LF, Lee JS, Shlipak M, Chertow GM, Green C, Ding J, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. J Am Geriatr Soc 2006;54:750–6.
[12] Pedone C, Corsonello A, Bandinelli S, Pizzarelli F, Ferrucci L, Incalzi RA. Relationship between renal function and functional decline: role of the estimating equation. J Am Med Dir Assoc 2012;13. (84.e11-4).
[13] Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc 2011;12:403–9.
[14] Foley RN, Wang C, Ishani A, Collins AJ, Murray AM. Kidney function and sarcopenia in the United States general population: NHANES III. Am J Nephrol 2007;27:279–86.
[15] Pedone C, Corsonello A, Incalzi RA, Investigators G. Estimating renal function in older people: a comparison of three formulas. Age Ageing 2006;35:121–6.
[16] Corsonello A, Pedone C, Lattanzio F, Semeraro R, D'Andria F, Gigante M, et al. Agreement between equations estimating glomerular filtration rate in elderly nursing home residents and in hospitalised patients: implications for drug dosing. Age Ageing 2011;40:583–9.
[17] Cox HJ, Bhandari S, Rigby AS, Kilpatrick ES. Mortality at low and high estimated glomerular filtration rate values: a 'U' shaped curve. Nephron Clin Pract 2008;110:c67–72.
[18] Peters R, Beckett N, Poulter R, Burch L, Narkiewicz K, Fagard R, et al. Kidney function in the very elderly with hypertension: data from the hypertension in the very elderly (HYVET) trial. Age Ageing 2013;42:253–8.
[19] Tonelli M, Klarenbach SW, Lloyd AM, James MT, Bello AK, Manns BJ, et al. Higher estimated glomerular filtration rates may be associated with increased risk of adverse outcomes, especially with concomitant proteinuria. Kidney Int 2011;80:1306–14.
[20] Shastri S, Katz R, Rifkin DE, Fried LF, Odden MC, Peralta CA, et al. Kidney function and mortality in octogenarians: cardiovascular health study all stars. J Am Geriatr Soc 2012;60:1201–7.
[21] Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, Nelson RG, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol 2007;18:2749–57.
[22] Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med 2012;157:471–81.
[23] 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;313:837–46.
[24] National Heart Lung and Blood Institute. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies - NHLBI. NIH. National Institutes of Health; 2014https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.
[25] Adunsky A, Mizrahi EH, Kaplan A, Purits E, Waitzman A, Arad M. Elevated blood urea, independent of glomerular filtration rate (GFR), confers increased risk of adverse functional outcome in elderly hip fracture patients. Arch Gerontol Geriatr 2011;53:e174–8.
[26] Bowling CB, Sawyer P, Campbell RC, Ahmed A, Allman RM. Impact of chronic kidney disease on activities of daily living in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2011;66:689–94.
[27] Chin HJ, Ahn SY, Ryu J, Kim S, Na KY, Kim KW, et al. Renal function and decline in functional capacity in older adults. Age Ageing 2014;43:833–8.
[28] Feng L, Yap KB, Yeoh LY, Ng TP. Kidney function and cognitive and functional decline in elderly adults: findings from the Singapore longitudinal aging study. J Am Geriatr Soc 2012;60:1208–14.
[29] Lin J, Curhan GC. Kidney function decline and physical function in women. Nephrol Dial Transplant 2008;23:2827–33.
[30] Liu CK, Lyass A, Massaro JM, D'Agostino Sr. RB, Fox CS, Murabito JM. Chronic kidney disease defined by cystatin C predicts mobility disability and changes in gait speed: the Framingham Offspring Study. J Gerontol A Biol Sci Med Sci 2014;69:301–7.
[31] Odden MC, Chertow GM, Fried LF, Newman AB, Connelly S, Angleman S, et al. Cystatin C and measures of physical function in elderly adults: the Health, Aging, and Body Composition (HABC) Study. Am J Epidemiol 2006;164:1180–9.
[32] Plantinga LC, Johansen K, Crews DC, Shahinian VB, Robinson BM, Saran R, et al. Association of CKD with disability in the United States. Am J Kidney Dis 2011;57:212–27.
[33] Tufan A, Tufan F, Akpinar TS, Ilhan B, Bahat G, Karan MA. Low glomerular filtration rate as an associated risk factor for sarcopenic muscle strength: Is creatinine or cystatin C-based estimation more relevant? Aging Male 2016:1–5.
[34] Wang X, Wang Y, Wang C, Zhao X, Xian Y, Wang D, et al. Association between

estimated glomerular filtration rate and clinical outcomes in patients with acute ischaemic stroke: Results from China National Stroke Registry. Age Ageing 2014;43:839–45.
[35] Yang J, Arima H, Zhou J, Zhao Y, Li Q, Wu G, et al. Effects of low estimated glomerular filtration rate on outcomes after stroke: a hospital-based stroke registry in China. Eur J Neurol 2014;21:1143–5.
[36] Shen Z, Ruan Q, Yu Z, Sun Z. Chronic kidney disease-related physical frailty and cognitive impairment: a systemic review. Geriatr Gerontol Int 2017 Apr;17(4):529–44.
[37] Reese PP, Cappola AR, Shults J, Townsend RR, Gadegbeku CA, Anderson C, et al. Physical performance and frailty in chronic kidney disease. Am J Nephrol 2013;38:307–15.
[38] Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. Clin J Am Soc Nephrol 2013;8:2091–9.
[39] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[40] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 1999;130:461–70.
[41] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[42] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.
[43] Pottel H, Delanaye P, Schaeffner E, Dubourg L, Eriksen BO, Melsom T, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrol Dial Transplant 2017;32:497–507.
[44] Anderson AH, Yang W, Hsu CY, Joffe MM, Leonard MB, Xie D, et al. Estimating GFR among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis 2012;60:250–61.
[45] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.
[46] Simonsick EM, Newman AB, Nevitt MC, Kritchevsky SB, Ferrucci L, Guralnik JM, et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. J Gerontol A Biol Sci Med Sci 2001;56:M644–9.
[47] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.
[48] Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200–15.
[49] 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;185:914–9.
[50] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.
[51] Ware Jr. JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I Conceptual framework and item selection. Med Care 1992;30:473–83.
[52] Hamilton BB, Granger CV, Sherwin FS, Zeilezny M, Tashman JS. Uniform national data system for medical rehabilitation. In: Führer MJ, editor. Rehabilitation outcomes: Analysis and measurement fpp. Baltimore: Paul H. Brooks; 1987. p. 137–47.
[53] Shastri S, Sarnak MJ. Chronic kidney disease: high eGFR and mortality: high true GFR or a marker of frailty? Nat Rev Nephrol 2011;7:680–2.
[54] Montesanto A, De Rango F, Berardelli M, et al. Glomerular filtration rate in the elderly and in the oldest old: correlation with frailty and mortality. Age (Dordr) 2014 Jun;36(3):9641.
[55] Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–83.
[56] Delanaye P, Mariat C. The applicability of eGFR equations to different populations. Nat Rev Nephrol 2013;9:513–22.
[57] Pattaro C, Riegler P, Stifter G, Modenese M, Minelli C, Pramstaller PP. Estimating the glomerular filtration rate in the general population using different equations: effects on classification and association. Nephron Clin Pract 2013;123:102–11.
[58] Mandelli S, Riva E, Tettamanti M, Detoma P, Giacomin 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.
[59] Corsonello A, Pedone C, Bandinelli S, Ferrucci L, Antonelli Incalzi R. Agreement between chronic kidney disease epidemiological collaboration and berlin initiative study equations for estimating glomerular filtration rate in older people: the invecchiare in chianti (aging in chianti region) study. Geriatr Gerontol Int 2017 Oct;17(10):1559–67.
[60] Pedone C, Semeraro R, Chiurco D, D'Andria F, Gigante M, Coppola A, et al. Reliability of equations to estimate glomerular filtration rate in the very old. Aging Clin Exp Res 2008;20:496–502.
[61] Montesanto A, De Rango F, Berardelli M, Mari V, Lattanzio F, Passarino G, et al. Glomerular filtration rate in the elderly and in the oldest old: correlation with frailty and mortality. Age (Dordr) 2014;36:9641.
[62] Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the heart and soul study. Circulation 2010;121:1295–303.
[63] Ferguson TW, Komenda P, Tangri N. Cystatin C as a biomarker for estimating glomerular filtration rate. Curr Opin Nephrol Hypertens 2015;24:295–300.
[64] Foster MC, Inker LA, Levey AS, Selvin E, Eckfeldt J, Juraschek SP, et al. Novel filtration markers as predictors of all-cause and cardiovascular mortality in US adults. Am J Kidney Dis 2013;62:42–51.
[65] Corsonello A, Pedone C, Bandinelli S, Ferrucci L, Antonelli Incalzi R. Predicting survival of older community-dwelling individuals according to five estimated glomerular filtration rate equations: The InChianti study. Geriatr Gerontol Int 2018 Apr;18(4):607–14.
[66] Koppe L, Klich A, Dubourg L, Ecochard R, Hadj-Aissa A. Performance of creatinine-based equations compared in older patients. J Nephrol 2013;26:716–23.
[67] Alshaer IM, Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, et al. External validation of the Berlin equations for estimation of GFR in the elderly. Am J Kidney Dis 2014;63:862–5.
[68] Pottel H, Hoste L, Dubourg L, Ebert N, Schaeffner E, Eriksen BO, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016;31:798–806.