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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