Author's response to reviews

Title: Performance of Cockroft-Gault, MDRD, and CKD-EPI in estimating prevalence of renal function and predicting survival in the oldest old

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Author's response to reviews: see over
Response to editor and reviewers

Editor

*Editor comment*
Clarify the authorization details for the mortality or cause of death data access. Please clarify whether you obtained approval from a data protection committee or if this data is publicly available. A statement to this effect must appear in the Methods section of the manuscript.

*Response*
We obtained informed consent from every participant from the Leiden 85-plus Study to get their vital status and cause of death data. We added this to the method section.

*Changes in manuscript, page 6-7,*
We obtained informed consent from all participants from the Leiden 85-plus Study (study 2) to obtain their data on mortality and cause of death, which was approved by the Medical Ethical Committee of the Leiden University Medical Center (LUMC). Deaths that occurred between the start of the study (1 September 1997) and end of follow-up (1 February 2009), were obtained from the municipal registry. Cause of death was obtained from Statistics Netherlands. Only the primary cause of death on the death certificate was used in our analyses.

Reviewer 1

*Reviewer comment*
The information is still spare among the elderly between 65 to 84 years from this study. In Table 1, there are only 62 elderly persons with age of 61 to 85 years.

*Response*
We agree with the reviewer that it would be of great interest to analyze the older persons aged 65-84 years. Since there were only a small number of subjects in this age category (62) and all subjects were still alive, it was unfortunately not possible to calculate reliable estimates of CKD prevalence and mortality in this age category.

Reviewer: 2 (F. Pizarelli)

*Major points*

*Reviewer comment*
Knowledge of renal function decline with age has been investigated earlier.

*Response*
We agree with the reviewer that many studies have been performed addressing the decline in renal function with advancing age. However, the question for prevalence estimation and validation of the various eGFRs in the oldest old subjects is still an unanswered question. Moreover, we were especially interested if we could determine the best measure of renal function in very old people using the three different formulae.

*Reviewer comment*
Study 1 has few insufficiencies.
Response
Unfortunately, study 1 was done with a low number of included subjects of all age categories. This cohort was originally established in an affiliated hospital to set reference values for laboratory measurements. Since we were especially interested in calculating renal function in the oldest old age category we used participants from our Leiden 85-plus Study with sufficient numbers of very old participants.

Reviewer comment
Specify the creatinine determination of Study 2

Response
Creatinine was measured according to the Jaffe method using a Hitachi 747, Tokyo, Japan. We added this information to the manuscript.

Reviewer comment
Text of manuscript can be made more fluent.

Response
We made our manuscript more fluent. Changes in the manuscript in response to reviewers are indicated in red in the text. Grammatical and fluency changes are not highlighted.

Minor points

Reviewer comment
State C-G and MDRD clearly through the manuscript

Response
We now state clearly throughout the manuscript that C-G is an estimate of creatinine clearance and MDRD is an estimate of glomerular filtration rate.

Reviewer comment
Even reference 18 of the manuscript showed C-G was progressively lower than MDRD with increasing age.

Response
We checked reference 18 again and revised the sentence on page 11: "Our results are in line with earlier studies with older individuals (all mean age <85 years)[16,17], and also comparable with another community based study with younger participants (mean age of 75 years)[18]."

Reviewer comment
Check the manuscript for typing or grammar errors

Response
We corrected the manuscript for typing and grammar errors.

Reviewer: 3 (Hung-Bin Tsai)

Major revisions
Reviewer comment
Please explain the 496 subjects from your results. I could only catch the information of the lost 12 subjects from Table 2. Three parts of your article mentioned about 90% as follows: In abstract line 18, renal dysfunction (stage 1-3) at age 85 years was highest for C-G(90%), Page 8 Results line 23, Using this formula, in 496 subjects (90%), a creatinine clearance lower than 60 ml/min was found, and Page 11 Discussion line 4, prevalence of renal dysfunction (CKD stage 1-3) at age 85 years was highest for C-G (90%).

Response
A total number of 562 subjects aged 85 years was included in the Leiden 85-plus study (=study 2). For 12 subjects weight was not available to calculate Cockroft-Gault clearance. In 562 minus 12 = 550 subjects creatinine clearance was calculated. Of them 54 subjects had renal function > 60 ml/min; therefore 550-54=496 subjects had creatinine clearance < 60 ml/min. The percentage of the total subjects with < 60/ml/min is calculated as 496/550= 90%. We used this percentage consequently throughout the manuscript. For clarity we have added the denominator for the percentage calculations in the results section.

Reviewer comment
For stage 1-3 CKD patients using CKD-EPI formula, creatinine is not the only criteria for diagnosis. We will use proteinuria criteria as well. However, your study didn't have urine protein data. In daily clinical practice, severe proteinuria could also predict stroke, acute myocardial infarction, and dementia, so called diseases related to vascular endothelial dysfunction. It seems that your conclusion recommended MDRD formula to predict mortality best. However, CKD-EPI provided more information for clinical practice and predict hospital mortality and length of stay (LOS). Since your mortality data was between 1 Sept. 1997 and 1 Feb. 2009, the casual relationship between the three CKD criteria and death is very difficult to explain.

Response
Unfortunately, in both study cohorts, we did not have 24-hour urine collections for the measurement of creatinine clearance or proteinuria. Therefore the predictive value of proteinuria at old age could not be investigated. Furthermore, we found at very old age (85 years) that the MDRD equation predicted mortality best since subjects with MDRD < 45 ml/min/1.73m² and even with MDRD < 30 ml/min/1.73m² had higher mortality risks than eGFR calculated by C-G or CKD-EPI formulae. Also a large British cohort study of people 75 years and older showed this increased mortality risk with MDRD formula (reference 15 of the manuscript). However, data about the predictive value of CKD-EPI in very old subjects are scarce.

Reviewer comment
Clarify the viewpoint stated on P12, line 7-10: " Whereas based on these results, implementation of CKD-EPI formula would raise the number of older individuals with CKD on the basis of eGFR estimated with the MDRD formula, with as a consequence more hospitalizations, costs and also other therapeutic implications."

Response
For the oldest old subjects, based on our results, implementation of the CKD-EPI formula would raise the prevalence of CKD in this age category, whereas introduction of the CKD-
EPI formula would reduce the prevalence of CKD in subjects <70 years. This is an interesting and important finding and in line with a large study of over a half million British people of all ages. Our concern is that implementation of the CKD-EPI formula for general practitioners would raise the number of very old individuals unnecessarily referred to the hospitals. We clarified our viewpoints by including the suggested references in the discussion.