Author’s response to reviews

Title: The GFR estimated by different new and old equations as a predictor of important outcomes in elderly patients

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Author’s response to reviews: see over
Point to point Answer

Reviewer: Masaru Horio
Reviewer’s report:

1) Page 5, calibration of creatinine value
Show the measurement method of creatinine (Jaffe or enzyme).
Show how to calibrate the creatinine value using IDMS.

We added more information in the methods section.

2) Page 9
More events occurring at higher eGFR by CKDEPIcyst.
Please comment about the reasons in Discussion.

We added a paragraph on Cystatin C and Creatinine in the discussion and a paragraph on the finding of more events at higher eGFR based on cystatin C. However we don’t want to make assumptions of draw conclusion based on this finding except that more research into this topic is needed.

3) Page 11 line 3
“The BIS equation predicted a higher rate of renal deaths.”
Is this correct?

No and we like to thank the reviewer for correcting this error.

Minor
4) Fig-2
Data of CKDEPIcreat >90 is missing.

Here again we would like to thank the reviewer because indeed some data was missing. We added the missing data in the figure.

Reviewer 2:

Major Compulsory Revisions:
- The authors make one major assumption, namely that the definition of CKD is an eGFR < 60 mL/min/1.73 m2 regardless of age. This needs to be discussed carefully. Firstly, KDIGO and KDOQI define CKD stage II as a measured GFR less than 90 mL/min/1.73 m2, and CKD stage III is defined as a GFR of less than 60. This is NOT the definition of CKD as a whole. Secondly, elderly patients have similarities with infants with regards to GFR. Because of the gradual recruitment of nephrons in a similar fashion as the in-utero formation, GFR does not reach its final level until 18-24 months of age. Nobody would consider a newborn with a physiological GFR of 10 mL/min/1.73 m2 as having CKD. Similarly, GFR
deteriorates over the life span and an 80-year old may well have a physiological 
GFR of 50 mL/min/1.73 m² that is considered normal. Ideally, age-independent 
z-scores should be used to define CKD. Suggested reading: Pediatr Nephrol. 
2013 Jul;28(7):991-4. and Kidney Int. 2011 Sep;80(6):567-8. This entire aspect is 
completely ignored and needs to be included in the introduction and the 
discussion.

We agree with the reviewer that the cutoff of 60 ml/min for the definition of CKD is 
debatable. However we do not fully agree that decline in eGFR with age is a physiological 
process as it is in children. In an earlier publication in Age Aging (Van Pottelbergh, G., 
disease in a Flemish primary care morbidity register. Age and ageing, 41 (2), 231-3.) we 
focused on this discussion and we wrote the following paragraph:

“The large increase in the prevalence of CKD with ageing is mainly due to an increase in the 
number of patients with stage 3 CKD. Even in the group of patients older than 80 years, the 
number of patients with stages 4 and 5 CKD remained limited to 5–7%. Therefore, many of 
these patients have CKD but 

few have severe CKD. Until the age of 90, around half of all people exhibit a relatively good 
eGFR of 60 ml/min or more. This result shows that not all older kidneys have suffered large 
amounts of ageing-related damage. These findings suggest that there is no such thing as a 
general and large decline in the eGFR due to age-related kidney changes or damage. This 
theory is supported by the data reported by the Baltimore longitudinal study on ageing, 
which found no decline in eGFR with ageing in one-third of the patients.”

We added in the strengths and limitations section a few lines on the possible limitations of 
the cutoff we used to define CKD because we feel that adding the full discussion regarding 
fysiological vs pathological age related decline into the paper will make this paper less 
focused.

- Clarify that the CKD-EPIcreaticyst, CKD-EPIcyst, and BIS equations include 
cystatin C, which is an independent marker of cardiovascular morbidity and 
mortality. This may confound the results.

First, the full equations are given in the methods section. Second, we added some more 
information regarding the background of these equations in the introduction. Third we 
added more on the creatinine and cystatine C differences in the discussion and added the 
following sentence in the discussion: “It’s not surprising that differences are observed since 
some of these equations uses serum creatinine other cystatine c and some both to calculate 
the GFR.”

- Include a short paragraph on the strengths and weaknesses of both cystatin C 
and serum creatinine, particularly in view of the elderly population studied.

We added such a paragraph
- Include short statements about the strengths and weaknesses of the formulae used for the study. Include the appropriate literature (the authors may wish to review Clin Chem Lab Med. 2012 Dec;50(12):2081-91 for a possible format as a table.)

We added more concerning the background of all the equations in the introduction, (third paragraph)

Minor essential revisions:
- Provide the total imprecision of both the IDMS traceable creatinine and the cystatin C measurements.
- It seems that standardized calibrators for cystatin C were not used, but rather the commercially available standards were adjusted. How was this done?

We added more information on cystatin and creatinine measurements in the methods section.

- How was normal distribution assessed? Provide the details.

Generally we analyze normal distribution by looking and plotting the raw data. However in this article we used mainly survival statistics.

- Provide details about missing data and how these were handled.

There were very few missing data and no persons missed to follow up. We added this information at the beginning of the results section.