Author's response to reviews

Title: Estimation of Glomerular Filtration Rate from Serum Creatinine and Cystatin C in Octogenarians and Nonagenarians

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Dear Editor,

Thank you for your considerations and the comments of the reviewers on our manuscript.

We did our best to answer the remaining concerns of the reviewer. In particular, we understand the concerns with the standardization of cystatin C measurements. At the time of the study planning and execution there were no clear international recommendations about standardization of cystatin C measurements. The recommendation about this standardization has been made just very recently and it was not possible for us to incorporate it in the present study. We tried to deal with it using a formula proposed by Inker el al (AJKD 2011), but as pointed out by the reviewer this was not appropriate since it was calibrated using another assay (Siemens) instead of the one we used (Dako). As we could not find another way to overcome this limitation, we decided to maintain the cystatin C values without standardization and acknowledge it in the Discussion as a study limitation.

We send the revised version of the manuscript with modifications highlighted. In this letter are the point-by-point answers to the reviewer’s comments. Once again, thank you for your comments and your attention.

Sincerely,

Ricardo Sesso, MD

Reply to reviewer: Pierre Delanaye
1. The authors wrote they account for standardization of cystatin C using the formula proposed by Inker (AJKD, 2011): $1.13\times\text{Cystatin C} - 0.105$. This way to do is however still misleading. Indeed, in their letter, Inker calibrated the PENIA assay from Siemens. However, the authors measured cystatin C with another method (PETIA, Dako). The calibration to reference material is thus totally different because differences between PENIA and PETIA results might be very relevant (Clin Chim Acta, Volume 398, Issue 1-2, December 2008, Pages 118-124). For this reason, it could be better to focus on the performances of different creatinine-based equations. A potential solution could be to obtain a formula for calibration from the Dako Company.

Answer: We do understand and agree with the comments of the reviewer. At the time of the performance of the cystatin C measurements in this study there was no available way to precisely account for the standardization of the cystatin C with ERM-DA471/IFCC using the Dako assay, as recommended in very recent guidelines. We used of the formula proposed by Inker [AJKD 2011;58:678] as an attempt to deal with this shortcoming. However, as noted by the reviewer this formula is not appropriate as it was produced with measurements assayed by particle-enhanced immunonephelometry (Siemens) and we measured with another method (immunoturbidimetry, Dako). As we could not find another way to overcome this limitation, we opted to keep the cystatin C values without standardization. We confirmed that these are the values used in the presented analyses and results.

We added two sentences to the Discussion acknowledging this limitation due the lack of standardization in our results and recommending caution in the interpretation of these data (pg. 16).

2. The authors still overinterpret some results. In their conclusion “CKD-EPI_cr is better than BIS-cr at higher GFR levels”. Accuracy 30% is however not different. Precision is even clearly better for the BIS_cr. Only bias is better for CKD-EPI_cr.

Page 10: “There was a greater area under the curve of the CKD-Epi_cr-cys compared with the MDRD and the CKD-Epi_cr equations, although the level of statistical significance has been marginal, $p=0.06$ and $p=0.09$, respectively.” And “In general the net reclassification was favorable with the CKD-Epi_cr-cys equation as compared with the CKD-Epi_cys (NRI=6.7, $p=0.38$), BIS_cr (NRI=12.7, $p=0.18$) or the BIS_cr-cys (NRI=15.9, $p=0.08$) equations, basically due to a more often correct reclassification of those with mGFR $\leq 60$ ml/min/1.73m².” Once again, the differences are simply NOT significant.

Answer: We corrected our overinterpretation of some results as indicated by the reviewer in the Conclusion (pg.3, pg.17), and Results, pg 10, 2nd and 3rd parag.

Minor remarks:
1) Regarding the point 9 of our prior review. Please consider the KDIGO
guidelines “Guidelines 1.4.3.4 : “We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (µmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). We recommend that eGFR should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m² in adults using the units ml/min/1.73 m².”

Answer: We corrected the eGFR estimates and rounded to the nearest whole number (pg. 9, 1st parag., Table 2, pg 24 and 25).