Reviewer’s report

Title: Reference intervals for serum cystatin C and serum creatinine in an adult sub-Saharan African population

Version: 0 Date: 04 Dec 2018

Reviewer: Hans Pottel

Reviewer's report:

This article wants to establish reference intervals for serum creatinine and serum cystatin C in a Cameroonian adult population.

1. It has been shown, for Caucasians, that creatinine is different between males and females. Therefore, when establishing reference intervals, the authors should present RIs separately for males and females, for both biomarkers. As this is clearly presented in Table 2, I wonder why they did not present these results in the abstract? I would recommend to present RIs separately for males and females already in the abstract!!

2. Is the modified Jaffe kinetic method equivalent to the gold standard IDMS method? Is the cystatin C assay calibrated against the international certified standard? Please specify!

3. Table 3 and 4 should be split up into males/females. I know that it will reduce the sample size, but the differences between males and females are too important and do not allow pooling of the data.

4. The differences between genders are more important than between ethnicities. As the male/female ratio is inversed between Sudanese and Semi-Bantu samples, with much more males in the Sudanese sample compared to the Semi-Bantu sample, this may explain the results of Table 4, where the median creatinine is much higher for the Sudanese sample compared to the other ethnicities. This is because males have higher creatinine values than females. The authors should present medians and RIs for the different ethnicities separately for males and females. Only in case they do not find significant differences, the data can be pooled. E.g. the authors can perform two-way anova for creatinine as continuous variable, using gender and ethnicity as the categories.

5. It has also been seen in Caucasians that creatinine and cystatin C start to rise with age, after the age of 65 years. There can be referred to relevant articles (see below).
6. Page 8 lines 1-5: the difference between Sudanese and Bantu or Semi-Bantu can be due to the different male/female ratio. Please check whether the difference is due to this or due to the different ethnicity. Provide RIs for each ethnicity separately for males and females.

7. It would be interesting to compare the results of this Cameroonian population with known reference intervals of Caucasians. The authors should consider referring to two important articles (not mentioned here) concerning reference intervals for serum creatinine, especially the article of Pottel et al, CCA 2008; 396: 48-55 who presents median values and RIs for all ages/sexes and describes that serum creatinine increases with age (see also Ceriotti et al, Clin Chem 2008; 54:559-566). For cystatin C, they may refer to Pottel et al, NDT 2017; 32: 497-507 where he describes the rationale for normalizing cystatin C with the median value of 0.82mg/L. It is also shown that cystatin C increases with age, after the age of 70 years.

8. Correlation between biomarkers has been reported before, see e.g. Pottel et al 2017; Data in Brief vol 14: 763-772. In this article, cystatin C reference intervals are presented according to age decades. Appropriate scaling of the biomarkers resulted in Pearson correlation coefficients as high as 0.85-0.90.

9. Other important references to be considered in the discussion are: Bukabau J. et al Plos One 2018; 13(3): e0193384, where mean Scr-values are presented for a healthy Congolese population.

10. Discussion: it is not because the minimum of 120 subjects is recommended by the IFCC that you should pool the data when it is clear that there important differences between males and females. It is more important to present the data separately than to fulfill the IFCC requirements in this case. Only the 90% CIs on the limits will be wider.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

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I am able to assess the statistics

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