Reviewer’s report

Title: Creatinine-or cystatin C-based equations to estimate glomerular filtration in the general population: impact on the epidemiology of chronic kidney disease

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Reviewer: Martin Flamant

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In this study, Delanay et al. compare 4 GFR-estimating equations based on creatinine and/or cystatin C plasma concentrations. This issue had aroused considerable interest since recent publications showed that GFR estimates based on the combination of creatinine and cystatin C displayed the best performances of all estimates, at least in total population. A very large number of volunteers have been included in this study, which clearly demonstrates that GFR estimation differs significantly depending on the equation used, hence leading to different epidemiological analysis. This work thus answers the question raised in the title in a convincing manner, with however no possibility to assess which equation gives the best performances in the absence of a reference measurement of GFR.

A few methodological questions appear upon reading this manuscript: exclusion of patients older that 50 yo is surprising as it does not correspond the any particular pre-defined threshold. The lack of information regarding ethnicity is also a matter of concern. It would have made more sense to either collect the information or exclude patients of African origin.

The method to measure plasma creatinine concentration is also an issue; as the different equations have been established with different measurement methods, relative performances might have differed with an enzymatic dosage of creatinine.

As the main message of this work is to highlight the epidemiological consequences of the method used to estimate GFR, it would have been of great interest to simultaneously measure plasma creatinine concentration with an enzymatic method. Indeed, the method used to measure creatinine is probably as important as the equation itself in terms of epidemiological consequences.

Another matter of concern is related to part of the discussion. This study provides information on the differential modelling of age, sex, and plasma creatinine/cystatin C concentrations in the equations rather than on their respective performances. The authors outline this limitation several times in the manuscript, but try to overcome this intrinsic methodological issue by interpreting their results in the light of a thorough discussion of the literature. Evaluating GFR estimation equations without a gold standard measurement, by comparing them with each other is questionable: in the absence of a reference value, one cannot draw conclusion about the superiority of one method compared to another.

However, this review of the literature, which is very extensive and interesting, is
particularly difficult in this field because of the heterogeneity of the studies, and the evolution of the performances of the equations, mainly MDRD, since creatinine is now frequently measured enzymatically. Because of this limitation, the discussion concerning the comparison of the equations should maybe emphasize more the potential epidemiological differences of the equations rather than their performances.

One particularly interesting result that could be further developed is the difference in prevalence of diabetes mellitus is subjects whose CKD is defined by equations based on cystatin C or equations based on creatinine. What is the opinion of the authors concerning this finding? It would be interesting to analyse separately the subgroup of diabetic patients. Indeed, if the difference of the GFR estimates between cystatin-derived equations and creatinine-derived equations is not the same in diabetic patients versus non diabetics subjects, this may question the specificity of the cystatin C dosage in this subpopulation.

One indirect way of addressing the issue of the respective performances of the equations would have been to have data regarding metabolic complications of CKD, and how they correlate with the estimated level of GFR.

In conclusion, this large-scale study describes very well the relative differences of creatinine and/or cystatin C-derived GFR estimating equations, and their potential epidemiological consequences. An attempt to go further and compare the respective performances of the equations is made through an extensive discussion, even though the study itself, because of its design, is unable to bring new results concerning the superiority of one equation over the others.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests