Author's response to reviews

Title: Estimation of glomerular filtration rate by a radial basis function neural network in patients with type-2 diabetes mellitus

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Version: 3 Date: 27 April 2013

Author's response to reviews: see over
Dear Dr. Henderson,

We have carefully reviewed the comments provided by you and the Referees of our manuscript, “Estimation of glomerular filtration rate by a radial basis function neural network in patients with type-2 diabetes mellitus” (MS# 2429087568207330). We wish to thank you all for the many thoughtful and helpful comments.

As requested, we have provided point-by-point responses to these comments and the locations where changes were made in the revised manuscript. All of our changes were made with use of the “Track Changes” feature of MS-Word.

We hope that our revised manuscript is suitable for publication and we look forward to hearing from you.

Sincerely,

Professor Lou Tanqi
**Editorial points:**
1. Authors Contributions

Can you please remove the authors' contributions from the Title page. This section should appear after the Conflict of Interest section. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

**Author response:** As requested, we have provided this information in the “Conflict of Interest” section.

2. Figures

Figure 1 has been submitted as more than one page. We ask that if a figure consists of separate pages, then a single composite illustration file should be submitted which contains all parts of the figure on a single page. If this is not possible, we recommend that page 1 be submitted as figure 1, page 2 as figure 2, and page 3 as figure 3, etc. Please remember to change any references to the figures in the manuscript file after any changes.

**Author response:** As requested, we have merged the figures into a single file.

3. Formatting

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

**Author response:** As requested, we have reviewed our manuscript to ensure that it follows the guidelines given at www.biomedcentral.com/info/ifora/medicine_journals.

**Referee 1:**

Title: Estimation of glomerular filtration rate by a radial basis function neural network in patients with type-2 diabetes mellitus
Version: 1 Date: 2 November 2012
Reviewer: Kearkiat Praditpornsilpa

**Reviewer's report:**

The study evaluated the validation of MDRD eGFR equation and GFR estimation by a radial basis function (RBF) network by comparing with measured GFR by isotope dynamic imaging in DM type 2 CKD patients. There are critical issues should be concerned:

Major compulsory revision
1. The measured GFR as gold standard for GFR measurement (99mTc-DTPA renal dynamic imaging) used in this study is an operator dependent measurement, The measured GFR that should be used in this study should be either inulin clearance, renal isotope clearance or plasma isotope clearance.

**Author response:** In China, $^{99m}$Tc-DTPA plasma clearance and $^{99m}$Tc-DTPA dynamic
imaging have been widely used as standard methods for evaluation of kidney function and estimation of GFR. $^{99m}$Tc-DTPA dynamic renal dynamic imaging yields accurate results that are nearly the same as those from measurements of inulin clearance. For example, Rehling et al. [1986] showed that a regression line between the values measured by these different methods did not differ from the line of identity. Additional studies support this conclusion [Li et al., 2007]. Renal imaging also demonstrated good agreement with plasma isotope clearance, such as plasma clearance of $^{51}$Cr-EDTA [Rehling et al., 1986]. The conventional multiple samples method with $^{51}$Cr-EDTA tend to overestimate true renal clearance at low GFR values, but $^{99m}$Tc-DTPA dynamic imaging did not have this problem because $^{99m}$Tc-DTPA accumulates in the bladder with a high signal-to-noise ratio [Carlsen et al., 2004].


We revised the Measurements section of the Methods, and added these additional references in Discussion section.

2. The radial basis function (RBF) network GFR calculation has not been well described and it is impossible for the reader to evaluate the validation of the study results.

**Author response:** As requested, we have thoroughly revised the RBF network section of the Methods and provided more details on this method.

3. The creatinine assay in this study was not standardized to reference serum creatine such as SRM 967 material. The non standardized serum creatine cause uncertain of the study results.

**Author response:** We forgot to say in our text that SRM967 (standard reference material released by NIST for serum creatinine calibration) was routinely used for calibration in our clinical practices. We have modified the Measurements section of the Methods accordingly.

4. The conclusions of the studies are contradict with the results.

**Author response:** Our results indicate that our RBF network provided better precision and accuracy than estimation by the traditional MDRD equations, but that eGFR estimated by the RBF neural network tended to be higher than the sGFR. We have revised text in the Conclusions section of the Abstract and in the last paragraph in the Discussion to clarify our conclusions.
Referee 2:
Title: Estimation of glomerular filtration rate by a radial basis function neural network in patients with type-2 diabetes mellitus
Version: 2 Date: 18 January 2013
Reviewer: Boriana Deliyska

Reviewer's report:
Diabetes mellitus is the most common cause of chronic kidney disease (CKD) all over the world. The estimation of glomerular filtration rate (GFR) is of basic necessities for staging of CKD.
For this reason the theme of the article is up to date. The article is written in comprehensible academic medical English language.
The authors propose an original methodology for assessing GFR, which is currently slightly known and discussed in medical literature. They are appropriate and well described.
The aim of this study is not well defined as a separate part of the abstract.

Author response: As requested, we have revised the Background section of the Abstract, and made sure that we clearly identified “the context and purpose of the study” (as requested in the “Instructions to Authors”).

All my comments listed below are in category Minor Essential Revisions
Because of the specificity of methodology used in this study is appropriate a more detailed description of RBF in “Materials and methods”.

Author response: As requested, we have thoroughly revised the RBF network section of the Methods and provided more details on this method (also see our response to Referee #1, comment #2, above).

The authors present a precise displaying of the data in “Materials and methods”, but there is not a clear explanation about the merging of patient groups with CKD stages I and II and IV and V.

Author response: As requested, we revised the Patients section of the Methods to clarify this issue. Patients were placed into 3 groups based on CKD stage: Stage I/II (GFR ≥ 60 mL/min/1.73 m²), Stage III(GFR = 30-59 mL/min/1.73 m²), and Stage IV/V (GFR < 30 mL/min/1.73 m²), as described in the K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (Ref. 2). Stage I/II patients had mild CKD, Stage III patients had moderate CKD, and Stage IV/V patients had severe CKD or renal failure.

The number of patients (207) included in the study is sufficient for statistical analysis.
There is a good attempt for assessment of the precision of different methods for estimation of GFR.
The manuscript adhere to the relevant standards for reporting and data deposition.
The discussion and conclusions are well balanced and adequately supported by the data The authors left open the question about the accuracy of the method for determining GFR using multivariate RBF, which would have a positive role for further research in this direction.
The title and abstract convey what has been found. The references include 28 papers, more of them from the last five years. The writing is acceptable. The work was supported by the National Natural Science Foundation of China (Grant No. 81070612), the China Postdoctoral Science Foundation (Grant No. 201104335), the Guangdong Science and Technology Plan (Grant No. 2011B031800084), and the Fundamental Research Funds for the Central Universities (Grant No. 11ykpy38)

Referee 3:
Title: Estimation of glomerular filtration rate by a radial basis function neural network in patients with type-2 diabetes mellitus
Version: 2 Date: 19 January 2013
Reviewer: Mladen Knotek

Reviewer's report:
This paper deals with important question of assessing GFR in a simple and reliable manner. Paper is well written.
1. Major compulsory revisions
I suggest inclusion of results of their first publication (ref. 20, which is a conference report). In this case, the present paper would present the reader with both ANN development and external validation results.

Author response: As requested by this Referee (and by Referee #1 and Referee #2), we thoroughly revised the RBF network section of the Methods. We have also added text to the Discussion (penultimate paragraph), which notes that use of more similar training and study groups would provide better external validation and may provide improved results.

2. Discretionary revision
Did the authors try to improve GFR prediction by RBFNN by inclusion additional variables, such as age and gender?

Author response: In a recent publication (Liu et al., 2013), we reported the performance of a genetic algorithm back propagation (GABP) network to estimate GFR. This GAPB network had similar features to the RBF network but had six input variables: serum creatinine, serum urea nitrogen, age, height, weight and gender.


We believe that discussion of the details of this other model is outside the scope of this manuscript.

Referee 4:
Title: Estimation of glomerular filtration rate by a radial basis function neural network in
patients with type-2 diabetes mellitus

Version: 2 Date: 4 February 2013
Reviewer: James Tattersall

Reviewer's report:
This paper describes a study to compare various methods for estimating GFR in 207 Chinese patients with CKD and type-2 diabetes. One of these methods is a novel neural network model, previously trained on an independent dataset of 307 CKD patients. The results of each prediction method was compared with a ‘standard’ GFR measured using the (99m) Tc-DTPA renal dynamic imaging method. The paper is nicely written. The study population is well-defined and includes approximately equal proportions of patients with stages 1-2, 3 and 4-5.

The methods used in the study were adequate to validate the ability of the neural network model to predict the GFR measured by the (99m) Tc-DTPA renal dynamic imaging method in an independent set of patients. The results of the study show that the neural network model cannot predict GFR well enough to be clinically useful. The standard deviation of error was -25 to +47 ml/minute/1.73m2.

My main concern with the paper is that it assumes that the (99m) Tc-DTPA renal dynamic imaging is a valid reference method for GFR. This method is not recommended for GFR measurement and has not been validated for this purpose, to my knowledge. The method is designed to measure the proportional contribution of each kidney (split-function), not absolute GFR. Where the GFR calculated by (99m) Tc-DTPA renal dynamic imaging has been compared to an accepted ‘gold-standard’, the agreement has been rather poor. In one study in Chinese patients, the agreement between GFR calculated by (99m) Tc-DTPA renal dynamic imaging agreed with an accepted standard method (plasma clearance of (99m) Tc-DTPA) less well than the MDRD prediction [reference Ma YC, Zuo L et al]. The modified Gates method used in the study to return GFR from (99m) Tc-DTPA renal dynamic imaging, was originally calibrated by comparison with measured creatinine clearance, not GFR.

Author response: As noted in our response to Referee #1, (99m)Tc-DTPA plasma clearance and (99m)Tc-DTPA dynamic imaging have been widely used as standard methods for evaluation of kidney function and estimation of GFR in China. (99m)Tc-DTPA dynamic renal dynamic imaging yields accurate results that are nearly the same as those from measurements of inulin clearance. For example, Rehling et al. [1986] showed that a regression line between the values measured by these different methods did not differ from the line of identity. Renal imaging also demonstrated good agreement with plasma isotope clearance, such as plasma clearance of 51Cr-EDTA [Rehling et al., 1986]. The conventional multiple samples method with 51Cr-EDTA tend to overestimate true renal clearance at low GFR values, but (99m)Tc-DTPA dynamic imaging did not have this problem because (99m)Tc-DTPA accumulates in the bladder with a high signal-to-noise ratio [Carlsen et al., 2004].

Although the outcome of a previous study reported by Ma et al. [Nephrol Dial Transplant 2007 22:417-23] indicated that GFR estimated by (99m)Tc-DTPA dynamic renal imaging was
not better than the modified abbreviated MDRD equation, these authors suggested that the Gates method can be improved by using proper reference GFR, more adequate background subtraction, and soft-tissue attenuation correction.

We noted this limitation and briefly discussed the conclusions of Ma et al. in the penultimate paragraph of the Discussion.

Specific points:
1) The methods section (page 7) states that 207 consecutive patients with type 2 diabetes attending the Third Affiliated Hospital of Sun Yet-sen University (Guangzhou, China) were enrolled in the study. The paper should state how many patients refused consent or dropped out of the study.

Author response: The data were retrieved from routine clinical practice records, so no patients refused consent. Furthermore, the study was cross-sectional, so there were no problems relating to withdrawal.

2) The methods section states that the stage of CKD was determined according to the KDOQI guidelines. This guideline states that GFR should be estimated from serum creatinine using the MDRD or Cockcroft and Gault method. The serum creatinine measurement should be calibrated against an international standard. Which method was used in the study? Which international standard was used? If MDRD method was used, was it the 4-variable or 6-variable method? In table 4, neither of the MDRD methods used in the study (4- or 6-variable) resulted in the same number of patients classified in each stage of CKD as the original classification (KDOQI method). This suggests the original classification was made using the Cockcroft and Gault method. Is this correct?

Author response: CKD was staged according to the National Kidney Foundation (NKF) – KDOQI clinical practice guidelines based on the GFR value, but GFR was measured by 99mTc-DTPA dynamic imaging (sGFR in this study) instead of the MDRD or Cockcroft and Gault equations proposed by NKF. We have deleted Table 4 to prevent from causing confusion.

3) The methods section (page 8) states that an enzymatic method was used to calculate serum creatinine. How was this method calibrated with the international standard?

Author response: As noted in our response to Referee #1 comment #3, we routinely used SRM967 (a standard reference material released by NIST for serum creatinine calibration) to calibrate the serum creatine measurements. We revised the text accordingly.

4) The methods section should state the inputs used for by the neural network model.

Author response: As requested by this Referee and the other 3 Referees, we expanded the RBF network section of the Methods.

5) The methods section should provide more information on the modified gates method and on the DTPA renal dynamic imaging. As described in the literature, Gates’ method estimates GFR not corrected for surface area. How were the results normalized to surface area in the
study?

**Author response:** After image acquisition, the patient’s weight and height were used to estimate body surface area (BSA). Then, sGFR was calculated according to Gate’s algorithm. This procedure is described by Li et al. [2007].

\[
\text{BSA} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}
\]

\[
\text{GFR (mL/min/1.73 m}^2) = (631.633 \times \text{renal uptake percentage} - 2.040) \times 1.73/\text{BSA}
\]

We modified the *Measurements* section of the *Methods* accordingly, and added this new reference.


6) The results show that the neural network model predicted a higher GFR than calculated using the DTPA renal dynamic imaging. The paper should discuss the reason for this. In theory there should have been no bias as the neural network model was trained using the same method of GFR measurement. Presumably there were significant differences between the subjects in the training and study groups.

**Author response:** The RBF network model predicted a higher GFR than calculated using $^{99m}$Tc-DTPA renal dynamic imaging. As noted above (Referee #3, comment #1) and in our revised Discussion, this bias might due to differences in the training and study groups.

Silveiro et al. [Ref. #6] demonstrated that the CKD-EPI and MDRD equations significantly underestimated GFR in patients with type-2 diabetes. In that study, standard GFR was measured by the $^{51}$Cr-EDTA single-injection method. Although our standard GFR was measured by $^{99m}$Tc-DTPA renal dynamic imaging, it is possible that the RBF network developed by CKD (non-diabetic) patients would have bias when the same network is used in diabetes patients with CKD. As noted in our revised Discussion, ideally, an RBF network specifically developed for type 2 diabetic patients (training group) would provide better external validation and may provide improved results in our future study.

7) The discussion section (page 15) states “Our results suggest that an RBF model based on a single measurement (SCr) can provide precise and accurate estimates of GFR.” The results of the study does not support this statement. The results show that the model was very imprecise at predicting at GFR measured using DTPA dynamic imaging. The ability of the model to predict true GFR was not tested as no ‘standard’ method was used.

**Author response:** As noted in our response to Referee #1 comment #4, we have revised text in the Conclusions section of the Abstract and in the last paragraph in the Discussion to clarify our conclusions.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests