Title: Would artificial neural networks implemented in clinical wards help nephrologists in predicting epoetin responsiveness?

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Author's response to reviews: see over
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Dear Editorial Team,

Ref: Submission of the revised original paper (MS # 1775992960105250)
"Would artificial neural networks implemented in clinical wards help nephrologists in predicting epoetin responsiveness?"

Thank you very much for the helpful comments. We have revised the text as requested with the hope that the present version meets your approval. Each point of the reviewers’ suggestions has been commented on in the following paragraphs (changes to the original text are highlighted in red in the attached file):

Reviewer 1: Ken Farrington

Discretionary revisions:

1. The reasons of choosing linear regressions to calculate the epoetin dose required to obtain the target haemoglobin of 11.5 g/dl are now included in the methods section:

“The choice of using suboptimal tools like linear regressions to estimate the ideal epoetin dose was made considering that (i) the small number of observations reduced the statistical options at our disposal and (ii) an epoetin dose approximating the ideal one was necessary to build the models”

2. Thank you very much for the pertinent comment; as you state linear regressions tolerate missing data less well than ANNs. However in the present study only subsets of complete data have been used to build both ANNs and linear regressions.

3. The fact that patients with intercurrent illnesses susceptible to influence epoetin responsiveness have not been excluded from the study is now discussed in the text.

“Of note, a large intra- and inter-individual variability in the requirements of erythropoietin (17.5 ± 19.2 and 35.3 ± 34.0 % respectively), to be referred at least in part to the inclusion in the study even of patients with intercurrent illnesses susceptible to influence the haemoglobin value, making the prediction of the ideal dose particularly difficult, was found in our database”

4. We agree that the haemoglobin level one month after the adaptation in the epoetin dose does not exhaustively represents the haemoglobin trend; however in the study only data about erroneous lack of epoetin dose increase have been collected and used to calculate the sensitivity, specificity and the predictive values of both nephrologists and ANNs. The methods section has been further clarified.

“Respecting statistical and modeling exigencies the haemoglobin measured one month after the adaptation in the dose has been considered as the follow-up haemoglobin.”

Reviewer 2: Roger W Jelliffe

Discretionary Revisions:

1. In order to facilitate the understanding of the neural network structure the methods section concerning ANNs has been further clarified and extended and a figure showing a schematic representation of the ANNs applied in the study has been added to the manuscript (Figure 1).
“ANNs are composed of one input layer (collecting input variables expected to be predictive), one output layer (collecting the predictions, known in training and unknown in testing and validation cases) and one or more hidden layers (performing a weighted sum of the inputs and passing the resulting value through a non-linear function to the output layer). Individual weights are progressively adapted, using for instance a back-propagation algorithm, to minimize the difference between calculated and expected outputs; the weights assuring the best results then being used to test and compare the performance of the ANNs (see Figure 1 for a schematic representation). “

2. A further study analysing the usefulness and the efficacy of individualized models based on each subject’s own data has been planned. The discussion section has been completed accordingly.

“The next step will be to include in the electronic documentation of the dialysis patients in use in our centres individualized models automatically warning the nephrologists about the need and modality of adaptations in the epoetin dose. ”

Reviewer 3: Bengt Rippe

Revisions:

None requested.

Being at your disposal for further revisions we hope that we have answered all the questions which were raised by the reviewers and that our manuscript will now be accepted for publication in BMC Nephrology.

We look forward to hearing from you

Yours sincerely

Luca Gabutti