Author's response to reviews

Title: Association of hypertension with physical factors of wrist pulse waves using a computational approach: a pilot study

Authors:

Bum Ju Lee (jupiter-lee@hanmail.net)
Young Ju Jeon (jyj92@kiom.re.kr)
Boncho Ku (secondmoon@kiom.re.kr)
Jaeuk U. Kim (jaeukkim@kiom.re.kr)
Jang-Han Bae (fcbest11@kiom.re.kr)
Jong Yeol Kim (bjlee@kiom.re.kr)

Version: 4
Date: 18 June 2015

Author's response to reviews:

Response to the reviewer's comments

To the reviewers and editor:

We appreciate the valuable comments we have received regarding our manuscript titled “Association of hypertension with physical factors of wrist pulse waves using a computational approach: a pilot study”. We have revised our manuscript in accordance with the reviewers’ comments, and our revisions are listed below.

Reviewer 1

Reviewer's report:

A clinical trial about wrist pulse measurement was conducted to explore the association of hypertension with pulse factors. Pulse wave detector device developed by Korea Institute of Oriental Medicine (KIOM) was used for measurement. For statistical calculation, logistic regression, Bayes algorithm, wrapper, and AUROC were used. Five-fold cross validation was conducted for calculating predictive powers. Hypertension is a very popular disease and a very important medical risk factor to the various diseases including CVA, and so evaluating and managing blood pressure are essential to the whole ages. Despite of the many useful and convenient methods to measure BP, wrist pulse measurement has also clinical values of importance in TKM or TCM point of view.

In spite of important subject, well-designed trial, and interesting approach like ML, there are some issues to discuss and revise.

Major Compulsory Revisions

1. In result, authors suggest useful predictors of hypertension based on the high association like p-value under 0.05. But it is known that p-value is influenced by sample size very well, so, AUC should be the standard of judgment if authors
discuss predictions. In general, AUC greater than 0.7 means fair predictability. So, I think only L-PPI and R-PPI can be suggested as good predictors.

Answer:

We agree with the reviewer's comment. Thus, in the Abstract and Conclusion sections, we suggested L-PPI and R-PPI as the best predictors.

2. I think Table 4 has some mistakes or ambiguity. I recommend specificity rather than 1-specificity. Moreover, in general, sensitivity and specificity have strict definition about disease and non-disease, so sensitivity and specificity should be expressed in the assumption that hypertension is a disease to predict. If so, 2nd, 4th, 6th, 8th lines will be deleted. Likewise, the sentence “The sensitivity and 1-specificity values were much higher for… in our study” delivers ambiguous meanings.

Answer:

In our case we have two classes (normotension and hypertension), and therefore, a 2x2 confusion matrix (namely, contingency table) was generated. In Table 4, for the Wrapper: NB method in the left wrist, the sensitivity (true positive rate) of class normotension was 0.778, and the sensitivity of class hypertension was 0.154. The specificity (true negative rate) of normotension was 0.154, and the specificity of hypertension was 0.977. However, we wanted to present more prediction performances in the two classes. Therefore, we presented the sensitivity and 1-specificity in all two classes as a convenient explanation. Furthermore, if we remove the 2nd, 4th, 6th, and 8th lines in Table 4, we cannot describe the precision and F-measure values in the two classes, respectively. The F-measure is defined as a harmonic mean between precision and recall, and it is used as an important criterion for prediction or classification results. Many researchers in prediction and classification fields believe that the maximization of both recall and precision values should be considered for a good prediction model and as a major issue of prediction algorithms. Therefore, we presented the sensitivity and 1-specificity in Table 4. Moreover, to avoid ambiguous meanings, the sentence “The sensitivity and 1-specificity values were much higher for normotensive subjects than for hypertensive subjects in our study” was removed.

3. In clinical view, the most important investigation of this study is the difference between left and right physical factors. There must be discussion about that. If there is no proper evidence or previous study to refer, authors can say so, at least.

Answer:

As suggested by the reviewer, we have added content regarding the difference between left and right physical factors or arm dominance to the Discussion section.

Minor Essential Revisions

1. Detail descriptions of parameters are necessary (e.g. L-Sum-30p, L-Asys-HR75, L-PSD-w1, etc)
Answer:

We have revised Figure 1 with detail descriptions of parameters such as L-Asys-HR75, and L-PSD-w1, Sum-30p, Sum-30p-PPI, Sum-1.12v, and Sum-1.12v-PPI, according to the reviewer’s comment. In addition, detail explanations of the variables are described in Figure 1.

2. The last paragraphs of introduction and result are thought to be more suitable in the discussion.

Answer:

As suggested by the reviewer, we have moved the last paragraph of the Introduction into the Discussion. However, we believe it is suitable to join the last paragraph of the Results to the previous paragraph in the Results.

3. Multicollinearity should be checked after LR or NB feature selections. Probably some variables could be associated with one another.

Answer:

We agree with the reviewer’s comment. We believe that our models may have multicollinearity. To avoid the multicollinearity among variables, we have added new models by Lasso (Least Absolute Shrinkage Selection Operator). In the “Statistical analysis and prediction configuration” section, Results section, and Tables 4 and 5, content regarding LASSO have been added, and two references have been added.

Added references:


Discretionary Revisions

1. A graphical example of AUROC in NB or LR may be very helpful to understand, if possible.

Answer:

We agree with reviewer’s comment that the AUROC curve in a graphical example may be helpful for clarity. However, an individual variable may be presented as a graph, but combined variables are difficult to present on the same graph. Therefore, we have presented the AUC values in tables.

Finally, our manuscript has been revised by a native English speaker again.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
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.

Reviewer 2
Reviewer’s report
Major Compulsory Revisions

1. It is well known that pulse pressure in hypertensive is higher than in normotensive. PPI corresponds to pulse pressure. What is new?

Answer:
The focus of this study is to find new physical factors associated with disease (hypertension) using a pulse wave detector device rather than hypertension prediction using a pulse wave detector device. In view of lacking quantifiable physical factors from pulse wave in traditional Korean medicine, we believe that this study is important for the quantification and objectification of pulse characteristics described in the pulse diagnosis literature of traditional and complementary medicine. Therefore, the main purpose of this study was to examine the association between hypertension and physical factors of wrist pulse waves. An additional purpose was to predict hypertension using physical factors because we wanted to determine the degree of agreement between diagnosis accuracies using physical factors from the pulse wave and using a sphygmomanometer (the gold standard).

The reviewer’s comment is correct. The pulse pressure in hypertensive subjects is higher than in normotensive subjects, and PPI is the difference between systolic and diastolic pressures, as already described in the Discussion section. However, we believe that this study is a valuable attempt to reveal an association between hypertension and several physical factors suggested by us, even though the association of the factors was weaker than PPI. PPI is only one of the physical factors used in this study. As suggested by the reviewer’s comment, we have modified the objectives of this study in the Abstract and Discussion. The modified contents in the Abstract are as follows:

"The objectives of this pilot study were to examine the association between hypertension and physical factors of wrist pulse waves to avoid subjective diagnoses in Traditional Chinese Medicine (TCM) and Traditional Korean Medicine (TKM). An additional objective was to assess the predictive power of individual and combined physical factors in order to identify the degree of agreement between diagnosis accuracies using physical factors and using a sphygmomanometer in the prediction of hypertension."

2. In almost all prediction models, increase in the number of independent variables enhances the predictive power. Is it one of the characteristics of the pulse that the predictive powers of combined physical factors were higher than those of the only PPI? The authors should formulate hypotheses, even though they couldn’t be evincible, about relationships between the combined physical factors and hypertension.
We agree with reviewer's comment that an "increase in the number of independent variables enhances the predictive power". In general, greater numbers of features (variables) exhibiting significant differences lead to better predictive power. However, we cannot guarantee that prediction model using only the significant features (with p values < 0.05) or using all variables always performs better than that using a subset combination of significant and less significant features. Therefore, the most important factor is the selection and combination of the features of each group, namely, how to combine the variables. For example, in a very well-known paper, Guyon and Elisseeff suggest that "a variable that is completely useless by itself can provide a significant predictive power improvement when taken with others" and that "noise reduction and consequently better class separation may be obtained by adding variables that are presumably redundant" [I. Guyon, A. Elisseeff, An introduction to variable and feature selection, J. Mach. Learn. Res. 3 (2003) 1157–1182.].

In the classification and prediction, machine learning, data mining, and variable subset selection fields, it is established that a good combination of variables or an optimal variable subset by a variable-selection technique reduces model complexity, improves predictive power, and reduces multicollinearity. Therefore, we do not believe that one of the characteristics of the pulse was that the predictive powers of combined physical factors were higher than those of the only PPI, and it is difficult to suggest any hypothesis because we attempted to find the optimal variable subset by a variable selection technique and showed the difference in predictive power between the best predictor and combined variables.

3. In this study areas of pulse power spectrum density were used as predictive independent variables. Why don't you consider that relationships between BP and area of PSD may not cause-and-effect but effect-and-effect from the same cause?

Answer:

We apologize for the incorrectly described text, "We suggested new physical factors related to the sum of the area on the particular region of pulse waves and the area of power spectrum density in both wrists". We only suggested new physical factors related to the sum of the area on the particular region of pulse waves, not the area of the power spectrum density. Therefore, we have modified the sentence.

The power spectrum density on the pulse wave has been widely studied. The time domain and frequency domain have strengths and weaknesses. The time domain is widely and popularly used for the quantifying the pulse condition; furthermore, the power spectrum density from the frequency domain is popularly studied in this field. Therefore, PSD was included as only one of several variables in this study. In this pilot study, we do not yet know the clinical significance and meaning of the relationship between BP and PSD. Therefore, we do not address the cause-effect or effect-and-effect relationship, and we believe the relationship is premature in this pilot study.
4. I can't agree with the authors’ opinion that pulse strength implies the degree of the blood vessel resistance against the pressing force to the radial artery. Do the authors claim that pulse strength is one of inverse indicators of vascular compliance?

Answer:
The term “pulse strength” remains hotly disputed by many Oriental medicine researchers. To avoid the equivocal meaning and disputation of the term, we have deleted the term “pulse strength” throughout the manuscript and have revised the sentences that included the pulse strength.

5. When BP in a wrist is compared with that in the other wrist, the author should also describe the dominance of the arm. It is well known that BP in a dominant arm is higher than that in the other arm. I wonder whether or not the differences result from the dominance of the arm.

Answer:
We agree with the reviewer's comment. BP was strongly associated with the arm dominance. However, when we designed this study, we did not consider the effect of right- or left-handed subjects. Therefore, we cannot explain the association between the BP difference between the right and left arms and the arm dominance. We may assume that the reason the association of physical factors from the right wrist was higher than that from the left wrist is the majority of right-handed persons in the Korean population.

We have added text regarding arm dominance to the Discussion section. The added contents are as follows:
"Certain investigators have reported the arm dominance according to the gender and the right and left arms. Rogers et al. [39] argued that in women, "the pulses should be a little stronger on the right wrist, but pulses in men should be stronger on the left". King et al. [40] examined the differences in depth, overall and relative pulse force, width, and rhythm at three sites between healthy male and female participants. They reported that the pulse force of men was stronger than that of women. Furthermore, they reported that the mean systolic and diastolic BPs were significantly lower in women than in men and that the mean SBP was significantly higher in the right wrist than the left wrist in both men and women. King et al. [41] documented that, out of three possible states with regard to the dominant side (right, left, and neither), the right-hand side was generally stronger than the left and neither sides in men and women. Furthermore, they mentioned that the difference in systolic pressure and pulse amplitude in the right arm was higher than that in the left arm in the cohort study. These findings are consistent with our results, which indicated that the right wrist had a higher association with BP compared with the left wrist in women. It is important to consider the association between BP and arm dominance. However, we did not consider the effect of right- or left-handedness in this study. We may assume the reason that the association of physical factors from the right wrist was higher than that from the left wrist is the majority of right-handed persons in the Korean population. Further study is necessary to reveal an association between differences in right
and left BPs and the dominance of the arm.”

6. I cannot accurately understand what meant Sum-30p, Sum-30p-PPI, Sum-1.12v and Sum-1.12v-PPI. Addition of drawings in more detail may make readers help to understand definitions of the factors.

   Answer:

As suggested by the reviewer, we have modified Figure 1 to accurately explain the Sum-30p, Sum-30p-PPI, Sum-1.12v, and Sum-1.12v-PPI variables. Detailed explanations of the variables are described in Figure 1.

   Discretionary Revisions

Discussion is too long. Please describe the only information directly related to results of this study.

   Answer:

We have revised the Discussion section according to the reviewer's comment. Therefore, some paragraphs have been summarized and deleted in our manuscript.

Level of interest: An article of limited interest
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.”

We greatly appreciate your thoughtful comments that helped improve the manuscript.