**Author’s response to reviews**

**Title:** SYSTOLIC BLOOD PRESSURE AS A PREDICTOR OF TRANSIENT ISCHEMIC ATTACK/MINOR STROKE IN EMERGENCY DEPARTMENT PATIENTS UNDER AGE 80: A PROSPECTIVE COHORT STUDY

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**Author’s response to reviews:**

Editor-in-Chief
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Dear Editor,

Thank you and the reviewers for taking the time to review our manuscript and for your helpful comments. Please find below a comprehensive point-by-point response to the comments and recommendations of the reviewers. The original comments and recommendations are presented in italics. Our response is in red font.

Sincerely,

Kristine Votova, PhD

Reviewer One comments

Reviewer 1:

1. I have previously reviewed an early version of this paper and the current version has addressed most of the concerns that were previously discussed.

One additional comment:

The authors used SBP and DBP as continuous variables and showed that in patients aged <60 and 60-79 years, SBP was associated with a significant increase in the odds of having TIA/MS by 18% and 23% per 10mmHg increase, respectively, after accounting for age and sex.

Given that in clinical practice, physicians are frequently faced with one single BP reading at ED. Therefore it might be worth also exploring SBP and DBP in categories - i.e. it would be interesting to know if there was an age-specific threshold for example.

We greatly appreciate this Reviewer’s feedback on an earlier version of this paper. With their comments we were able to greatly improve the presentation of our results. However we do not feel this new comment requires re-analysis.

What the Reviewer is asking for has partially been investigated with the conditional inferences trees at the beginning of the analysis. The trees were used as an exploratory tool and indicated there was a potential age-BP interaction for distinguishing TIA/MS from stroke mimics in the ED that was worth further exploration. We potentially could have, as the Reviewer suggests, categorized SBP and DBP and explored age to look for an age-specific threshold. However, based on how the results of this study are intended to be used by a clinician in the ED, we feel the suggested re-analysis is not warranted. For a clinician to be able to draw comparisons
between two patients of different ages with the same BP does not seem to the Authors as clinically useful as being able to understand how the predictive effect of BP diminished in older cohorts of patients.

Older age is a risk factor for TIA/MS, whereas BP is thought to vary between TIA/MS and stroke mimic patients in response to the TIA/MS process. Further, the conditional inference tree in Figure 2 shows the data split is first split by age. In the conditional inference tree framework the covariate significantly and most strongly associated with the response is chosen at each step. Thus age is a stronger predictor of TIA/MS than BP. Hence, our analysis as performed, looking at the effect of BP after fixing the stronger predictor (age) makes more sense than the reverse.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

1. The major criticism I have is the exposure (i.e. the single BP at ED triage), rather than using multiple BPs while the patient is in the ED. BPs can often vary over time even if they are not treated, and these data may be independently predictive, ie persistently elevated BP.

We acknowledge that BPs can vary over time and that their trend may be independently predictive of TIA/MS, however, that was not the focus of this study. As per our study protocol, stroke study nurses recorded a single BP reading in the ED when the patient was being enrolled into the study. While it would be interesting to investigate the effect of BP on TIA/MS diagnosis using multiple BP readings in the ED, this is not feasible in this study.

We feel the effects we report based on a single BP reading are still clinically useful. Many clinical prognostic/diagnostic scores such as the ABDC2 [Johnston 2007] score and Framingham [Wilson 1998] use a single BP measure. And, as Reviewer One points out, in clinical practice it is common for physicians in the ED to be faced with a single BP reading.

2. The authors make no mention of potential reasons that this phenomenon may occur (i.e. pathophys). While clearly this study did not study the causative nature of this, it would be useful for a clinical audience.

We have added a paragraph to the Discussion (paragraph 2).

3. The modeling appear robust, however, some journals favor the kitchen sink approach v. backward elimination which can produce variable results.

We validated the model selection procedure with bootstrap resampling to probe the variability of the resulting backward elimination model. Reduced models were found by backwards elimination of the full model (covariates: BP, age, BP*age, sex, hypertension, diabetes, and reported anxiety) ensuing BP was always included in the models. We report in the Results that “BP (by design), age, and sex were selected in all bootstrap samples, while the age-BP interaction was selected in 96.5% (systolic) and 94.5% (diastolic) of samples, suggesting these are all stables predictors”.
We have added a sentence to the Results to indicate the other potential variables (hypertension, diabetes, and anxiety) were selected each selected in less than 20.5% of the bootstrap models, providing further evidence that no important variables were excluded from the final reduced model with age, sex, and the age-BP interaction.

4. The sentence in the results that state that SVO BPs are higher than others should be reconsidered because it did not appear that this hypothesis was directly tested.

We did test the hypothesis that SVO BPs are higher than all other stroke etiologies, individually.

We described the testing procedure in the Statistical Analysis:

“Differences in BP between the diagnostic groups were analyzed by one-way ANOVA followed by Tukey’s honest significant difference test which adjusts for multiple comparisons”.

And the results demonstrating SVO BPs are higher are reported in the Results:

“When divided into groups based on TOAST criteria and including a stroke-mimic category, differences in SBP and DBP were seen across TOAST classifications (both p<0.001). Patients with SVO had higher SBP (175.0±3.2mmHg) than every other group: stroke-mimic (148.9±1.4mmHg, p<0.001), CE (154.4±2.4mmHg, p<0.001), cryptogenic (157.8±1.5mmHg, p<0.001), LAA (163.4±2.5mmHg, p=0.041), other (150.6±6.0mmHg, p=0.002), and competing etiologies (157.9±4.7mmHg, p=0.027)”.

We have changed the sentence in the Discussion to make it clear that we compared SVO to every other stroke etiology (and stroke mimics), not all other stroke etiologies combined.

5. If there are more data to study how changes in BP or variation may impact diagnosis, that would be good to add or as a separate study.

Although this analysis would be interesting to conduct, we would be challenged to do so given only two BP measures were recorded in this study, one in the ED and one at the TIA clinic. Further, we do not have data on medications or treatments given in the ED that could affect BP, so any investigation of changes in BP between the two time points would be seriously limited.

References
