**Reviewer’s report**

**Title:** Clinical Benefit of Improved Prehospital Stroke Scales to Detect Stroke Patients with Large Vessel Occlusions: Results from a Conditional Probabilistic Model

**Version:** 0  **Date:** 19 Nov 2017

**Reviewer:** Henry Zhao

**Reviewer's report:**

The authors utilized a previously published model of conditional probability (published by the same group) which estimates the chances of good 3-month outcome if clinical triage is used for pre-hospital bypass to a comprehensive stroke center. The model takes into account only LVO and non-LVO infarcts, and primarily weighs the benefits of faster endovascular therapy for LVO, against the harms of slower thrombolysis if non-LVO infarcts are incorrectly bypassed. This is done primarily through comparing the outcome-versus-time curves for endovascular (using the meta-analysis trial data of Saver et al.) versus thrombolysis (using the undifferentiated ischemic stroke meta-analysis of Emberson et al.). This effectively results in the positive predictive value (which provides for the ratio of LVO to non-LVO infarcts) as the predominant parameter of concern.

In this study the authors used this model to look at the absolute difference in outcomes if a perfect diagnostic clinical tool were used instead of RACE. At a RACE score of ≥5 (which is the most used cutoff worldwide), this essentially compares a tool with PPV of ~50% (as published in de la Ossa et al.) against a theoretical tool with PPV of 100%. At transfer times up to 120 minutes, the authors found the absolute difference in outcomes was <5% at all RACE scores, and therefore concluded that a theoretical perfect tool would add little benefit.

There are several key flaws in this interpretation. The fact that the outcomes vary so little between a tool with PPV of 50% (50% LVO, 50% non-LVO) and one with a PPV of 100% (100% LVO, 0% non-LVO) can only be explained by two reasons: 1) The effect of thrombolysis for non-LVO infarcts is miniscule compared to the effect of endovascular for LVO in the model, or conversely 2) The effects of earlier endovascular treatment in the model are so small that PPV can be halved with negligible effect on absolute outcome. If reason 1) were the case, Figure 1A would show a plateau in decline of absolute outcomes from RACE 0 to 9, as LVO becomes progressively more likely with higher clinical severity. Instead, the results are consistent with reason 2), as Figure 1A and suppl Figure 1 show almost no change in absolute outcomes between a 15-minute transfer compared to a 120-minute transfer at a RACE of 9 (where the vast majority are likely to be LVO). This suggests that the model itself finds no significant benefit of earlier endovascular treatment, which would provide a better explanation of why a theoretically perfect tool has no significant benefit. This also puts into question the necessity of clinical triage in the first place, if a 120-minute transfer delay does not significantly change outcomes.
To confirm this, I would consequently suggest that the authors compare both the RACE scale and a theoretical perfect tool, to a theoretical tool with very low accuracy using their model to determine if a similar result occurs (i.e., very small effect in absolute outcomes).

Part of the explanation for relative insensitivity of the model to benefits of expedited endovascular treatment could lie in the data used for the time-delay curves by the authors. In the meta-analysis of endovascular trials by Saver et al., all except MR CLEAN used some form of penumbral selection. This consequent selection of patients with better collaterals would likely have resulted in less curve decay due to delayed treatment in comparison to contemporary practice (and therefore underestimated the benefits of earlier endovascular therapy). On the flipside, the use of thrombolysis outcome time-decay curves for undifferentiated ischemic stroke is of question. The false positive non-LVO infarcts by their intrinsic nature are likely to possess much higher clinical severity and may be of different subtypes (e.g., spontaneously recanalized LVOs, multifocal embolic infarcts) compared to an undifferentiated population. The relative efficacy of thrombolysis in this subgroup may therefore be significantly different to that in Emberson et al. The authors should acknowledge such limitations in data.

The authors also do not consider the other beneficial aspects of a theoretical tool with perfect diagnostic accuracy, such as greater sensitivity, avoidance of overburdening of the comprehensive stroke center (with not only non-LVO infarcts but intracerebral hemorrhage and stroke mimics) and avoidance of deskilling and deprioritizing of primary stroke centers due to less workload.

As such, the authors should address these major issues prior to recommendation for publication.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

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