Reviewer's report

Title: Futile Reperfusion and Predicted Therapeutic Benefits after Successful Endovascular Treatment According to Initial Stroke Severity

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Reviewer: Babak S. Jahromi

Reviewer's report:

This paper presents what sounds like two contradictory conclusions, which the authors report as "novel" in their discussion: increasing "benefit" but also increasing "futility" of reperfusion, with increasing NIHSS. However, this is fundamentally a problem of using two different comparison populations, and poor choice of wording. Specifically, the authors find that "futile reperfusion", defined by the proportion of patients with successful EVT (TICI 2B-3) who have a worse outcome (mRS=3-6), increases with increasing NIHSS. Multiple studies have shown worse outcomes after stroke with increasing age and increasing presenting NIHSS, with or without intervention (for example, see Figure 3 in the meta-review by the HERMES collaboration in Lancet 2016), so there's nothing new or surprising about increased "futile reperfusion" (aka worse outcomes) with increasing NIHSS at time of presentation.

In contrast, the authors define "benefit" of EVT as a relative reduction in proportion of poor outcomes (mRS=3-6) when comparing patients with successful EVT (TICI=2b-3) versus patients not selected for EVT, stratified by NIHSS. This is a different question, across different comparison groups. Not surprisingly, they find that the higher the NIHSS, the worse the non-EVT patients do, relative to patients with successful EVT. Again, there is nothing new or surprising to this analysis: increasing NIHSS leads to increasing poor outcomes, which is much more pronounced in those who aren't able to undergo EVT.

Given the numerous publications, across multiple countries/sites, using randomized data to show benefit of EVT across all ages/NIHSS, the data in this paper (retrospective, non-randomized, without uniform patient selection via ASPECTS, CTP, DWI-mismatch, etc) is less applicable to current practice, especially when making claims regarding "predicted therapeutic benefits after successful EVT". The paper would be more useful to simply focus on what are predictors of worse outcome (aka "futile reperfusion") in patients who've already been selected for EVT, and omit discussion of "therapeutic benefit" of EVT - the latter simply confuses the message of the paper. I recommend focus on data in Table 1 and Table 2, which suggest that on multivariate analysis increasing age and NIHSS and decreasing premorbid antithrombotic use are associated with worse outcomes after EVT despite TICI 2b-3. Finally, the authors state that "negative association of pre-stroke antithrombotics with futile reperfusion as not been reported previously", which is not absolutely correct: subgroup analysis of MR CLEAN found "futile reperfusion" (mRS=3-6 after TICI 2b-3) in 53% of patients with antithrombotics versus 62% of patients without antithrombotics (Int J Stroke Vol 12, Issue 4, pages 368-376, 2017).
Lastly, from a semantic point of view, the use of the phrase "futile" is unfortunate here, since it implies reperfusion is of decreasing benefit with increasing age/NIHSS - which we know is not true (see prior RCT's showing benefit of EVT across all age and NIHSS subgroups). True "futility" of reperfusion across age/NIHSS strata can only be determined if the authors had compared their patients selected for EVT who achieved TICI-2b-3, versus patients selected for EVT who did not achieve TICI2b-3, across age/NIHSS strata (ideally with matched pairs or propensity scoring). So, a better way of phrasing the topic is to simply state "worse outcomes" (mRS 3-6) despite TICI 2b-3 reperfusion, and not necessarily "futility" of opening an occluded vessel - for example, achieving an mRS of 3 (e.g. ability to walk without assistance!) after successful reperfusion in someone initially presenting with NIHSS>20 and an ICA T-occlusion, would generally not be felt to be "futile".

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

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?  
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No

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