Author’s response to reviews

Title: Cerebral Microbleeds Shouldn’t Dictate Treatment of Acute Stroke: A retrospective cohort study evaluating risk of intracerebral hemorrhage

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Author’s response to reviews:

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Dr. Lou:

We are pleased to submit our revised manuscript entitled “Cerebral Microbleeds Shouldn’t Dictate Treatment of Acute Stroke: A retrospective cohort study evaluating risk of intracerebral hemorrhage" for consideration for publication in BMC Neurology. Symptomatic hemorrhagic conversion is the most feared complication of intravenous thrombolysis and the risk associated with cerebral microbleeds has varied in prior studies. In our cohort, we evaluate not only the presence of microbleeds in patients with acute stroke treated with tPA, but also the location and burden, as this likely provides important information regarding the risk of cerebral amyloid angiopathy.

In this manuscript, we show that a high number of cerebral microbleeds (>10) is associated with a higher risk for symptomatic hemorrhagic transformation. Nonetheless, it is also evident that the prevalence of this number of cerebral microbleeds is very low. Our findings indicate that the presence of single digit cerebral microbleeds should not contraindicate thrombolytic treatment.
We hope you find this revised manuscript appropriate for publication. Please find the answers to the reviewers’ comments below. Do not hesitate to contact us if we can be of any assistance. All authors significantly contributed in the design and writing of this manuscript. This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Sincerely,

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Response to Reviewers:

1. Please provide the exact image parameters for T2*-GRE MRI sequences, i.e. echo time, slice thickness etc.

We agree that this information would be beneficial to the reader and now include it within our methods section (lines 104-106).

2. As suggested by one of the reviewer's, for comprehensiveness, the discussion should probably mention and comment on a large IPD meta-analysis on the topic, see Stroke. 2017 Jul 18. PMID: 28720659
Thank you for the suggestion. We agree that this meta-analysis is important and should be included as it further emphasizes the importance of CMB burden for the risk of hemorrhagic transformation (lines 229-231 and 246-252).

3. A more transparent discussion on limitations of the current study is needed, especially re the small sample size, MRIs often performed after tPA was given etc. How could these limitations affect the reposted associations?

We agree that ours is a relatively small number of patients, which potentially could affect our power to find statistically significant associations. However, our cohort represents the 5-year experience of a relatively large comprehensive stroke center with a standardized protocol. It portrays a real life clinical application of the post-thrombolytic hemorrhage risk associated with CMBs to centers of similar size that do not perform MRI studies before thrombolytic treatment.

It is also true that performing MRIs following tPA may result in detecting microbleeds that were not present before:

Although MRIs were performed after tPA treatment, the incidence of new CMBs is low. On three series found by the authors, only up to 13% of patients may develop new CMBs. This 13% is from the following study. Jeon et al. studied the incidence of new CMBs within the first 7 days after acute ischemic stroke in a sample of 237 patients. These patients underwent an MRI within 24 hours of symptom onset and underwent a follow-up MRI in in a median time from symptom onset to follow-up GRE of 4 days (range, 1-7 days). Only 52/237 (22%) received thrombolytic therapy, which makes their sample different from ours. The rest received either anticoagulants or antiplatelets. At follow-up 30/237 (12.7%) patients had 56 new CMBs. [1] Kimura et al. studied 224 acute stroke patients treated with tPA who underwent MRI T2 within 24 hours of the ischemic stroke and after 24 hours from the event. A total of 72 (32%) had baseline CMBs. Only
11 (5%) had new CMBs. [2] Yan et al. studied 121 consecutive tPA treated acute ischemic stroke patients who underwent tPA. These patients underwent GRE MRI within 6 hours of symptom onset and follow-up GRE sequence 24 hours after tPA infusion. The study found that the only significant factor for finding new CMBs in the post-tPA MRI was having pre-tPA CMBs (OR 10.6, 95% CI 20.7-54.3; p=0.005). From 121 patients, 100% of which underwent MRI before and after tPA, 57/121 (47%) patients had CMBs in the initial MRI, and CMBs were found in 6 new patients (5%). [3]


However, if anything this would indicate an even lower rate of CMBs than we found, and does not change our overall findings that ICH rate is low without screening and consideration of CMB.

We address these limitations in our discussion (lines 269-280).

4. The readers will benefit from a more critical discussion of the literature cited. For example the meta-analyses cited (JAMA Neurol. 2016;73:675–683), was aggregate level, with very wide confidence intervals, and not accounted for different centers contributing data. Previous meta-
analyses on the topic were also aggregate level and only looked at CMBs presence in univariable models. These points will further strengthen the rational and aims for the current study.

We agree that this would strengthen the manuscript and now include it within our discussion (lines 242-252).

Thank you again for the opportunity to revise.