OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00118
Title: Leukoaraiosis is Associated with Clinical Symptom Severity, Functional Outcome and Recurrent Stroke in Patients with Intracerebral Hemorrhage
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COMMENTS TO AUTHORS
The authors present an investigation of the role of leukoaraiosis (LA) in acute (i.e., upon admission) symptoms and prognosis of intracerebral hemorrhage (ICH) within a fairly large (n=357) longitudinal sample. While the authors argue that the specific questions tested have not been conclusively addressed previously, there is little rationale provided for the value or novelty of these questions in the context of prior literature. Moreover, it is unclear how the questions relate to each other, and no clear hypotheses are provided, giving the impression of an arbitrary set of unrelated statistical tests. However, the underlying research appears to be sound, and it is likely that the impact of the manuscript could be substantially improved by more clearly explaining the rationale and interpreting results in that context. Specific comments and suggestions for improvement follow:

1) While the first paragraph of the Introduction clearly explains the overall rationale for "early detection of patients at high risk of poor prognosis", the remainder of the section fails to make a case for LA being a critical element to explore. In particular, the second paragraph is largely a series of prior observations with no unifying thread demonstrating a knowledge gap. It is unclear what questions will be pursued to address the overall goal expressed in the first paragraph. It is recommended to elaborate and/or better integrate the background information to clarify the goal, rationale, and hypotheses.

2) A minor point, but it may be useful to explicitly state that LA is equivalent to what the neuroimaging field typically calls white matter hyperintensities (WMH). This could substantially broaden the audience.

3) While the DWI parameters are included, none of the measures appear to be based on DWI. How was DWI used? If this sequence was not used, it should be removed. If it was, please include the b-value used. Also, if measures were extracted from the DWI, it would be valuable to address the poor resolution (5mm thick, 1mm gap).

4) The Fazekas scale is typically a 3-point scale, and I have been unable to find a manuscript using a 6-point scale (including those cited herein). Is it simply the sum of the scores for periventricular and deep white matter? The derivation of these scores is a critical point to describe explicitly.

5) Given the effects observed when using the Fazekas scale as a continuous measure, combined with the likely underlying distribution of scores, it is unclear why no further subdivision (e.g., 0 vs. 1-2 vs. 3-4 vs 5-6) was tested. It seems this would provide more complete characterization of the relationship between LA and outcomes.

6) The descriptions of some statistical tests, linear regression in particular, are unclear. Were variables "excluded by the model" based on selection methods (e.g., forward/backward selection)?


or some other basis (e.g., high bivariate correlation, conceptual overlap)? Were "confounding factors" included in the model regardless of weight, covaried separately, or tested for inclusion but ultimately excluded? It is generally difficult to follow the logic of the selected tests relative to goals or hypotheses.

7) Overall, because it is unclear how the statistical tests relate to gaps in knowledge being addressed, it is also unclear how the authors interpret the results. Given prior literature, is it remarkable that LA contributes to the prediction of symptom severity at admission above and beyond the contribution of hematoma volume? If so, what is the implication of this for clinical practice or future research? Are there attributes of this sample or method that created a lack of association between LA and hematoma volume when prior studies found such a relationship? Does this discrepancy influence (for better or worse) the generalizability of results?

In summary, there is likely substantial new knowledge provided by this study. However, limitations in the description of measures, statistical tests, and interpretations within the context of prior literature substantial reduce the impact and accessibility of this manuscript.