



# Reply: “Methodological considerations in the analysis of multiphase CT angiography findings for outcome prediction in MCA M1 occlusion”

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Dear Editor,

We sincerely thank the author for their careful appraisal of our manuscript<sup>1</sup> and their insightful methodological observations.<sup>2</sup> We welcome this scholarly exchange as an opportunity to better articulate our analytical decisions.

The author raises a valid consideration regarding the omission of clinical confounders such as age, sex, comorbidities, and National Institutes of Health Stroke Scale from the regression model. The primary aim of our study was to evaluate the independent predictive value of imaging-based biomarkers obtainable at initial multiphase computed tomography angiography (mCTA) rather than to build a comprehensive outcome prediction model. We acknowledge that adjustment for age is standard practice in prognostic modeling. Although the age difference between groups was non-significant (63.0 vs. 69.5 years;  $P = 0.590$ ), this 6 year difference may have biological relevance. A meta-analysis of nine randomized controlled trials ( $n = 2,195$ ) showed that the benefit of mechanical thrombectomy was numerically greater in non-elderly patients [ $< 70$  years, odds ratio (OR): 2.70] than in elderly patients ( $\geq 70$  years, OR: 1.95) with large vessel occlusion stroke, suggesting age may modulate functional recovery.<sup>3</sup> Although we agree this is a valid suggestion, the non-significant age difference between groups ( $P = 0.590$ ) and the concern that including additional clinical variables would have further reduced the already constrained events-per-variable ratio led us to limit the model to imaging predictors.

A second consideration relates to the apparent discordance between the non-significant univariate  $P$  value for thrombus density ( $P = 0.053$ ) and its emergence as an independent predictor in multivariable logistic regression ( $P = 0.022$ ). Such a pattern is well described in multivariable prognostic modeling. In multivariable logistic regression, adjustment for correlated predictors—here, the actual thrombus length—can unmask associations that appear non-significant in univariate analysis, a phenomenon described as a suppressor or adjustment effect.<sup>4</sup> The borderline  $P = 0.053$  combined with significance in the adjusted model ( $P = 0.022$ ) is consistent with this effect rather than a spurious finding.

The third comment addressed the potential for overfitting arising from the number of predictors relative to the number of outcome events and requested clarification of the variable selection strategy. We acknowledge that the inclusion of seven independent variables corresponds to approximately 3.4 events per variable, which is below the commonly cited 10:1 guideline.<sup>5</sup> This limitation arises from our study design, which required sufficient collateral circulation to delineate thrombus margins on mCTA—a criterion that enriched the cohort with good-outcome cases, reducing the number of poor-outcome events available for modeling. The candidate variables were selected a priori based on established imaging biomarkers in the mCTA literature rather than through data-driven selection, which may mitigate concerns regarding overfitting in the context of a limited events-per-variable ratio.

Finally, with respect to thrombus density measurement, the author highlighted the potential limitations of absolute Hounsfield unit values and suggested that normalized met-

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rics may improve reproducibility. We agree with this observation. Absolute Hounsfield unit (HU) values are subject to scanner-dependent variability and hematocrit-related fluctuation. In the MR CLEAN cohort, relative thrombus density on CTA was independently associated with functional outcomes, whereas absolute density was not.<sup>6</sup> We used absolute HU values given our retrospective single-center design with uniformly standardized acquisition parameters. Future prospective multicenter studies should consider relative density metrics for improved cross-institutional comparability.

We thank the author for these constructive and expert remarks, which will help guide future prospective multicenter studies on this topic.

## Footnotes

## Conflict of interest disclosure

The authors declared no conflicts of interest.

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