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Proenkephalin A as Potential Prognostic Biomarker in Acute Ischemic Stroke

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Gruber et al conclude in their recent study that proenkephalin A (PENK-A) plasma levels may not provide an independent prognostic value in patients with acute ischemic stroke.[1] This conclusion is in contrast to previous studies that reported independent prognostic value in ischaemic[2] or hemorrhagic[3] stroke. This discrepancy deserves further evaluation.

Notably, Gruber et al reported a significant association of PENK-A plasma levels with unfavorable functional outcome (odds ratio: 10.67) as well as mortality (hazard ratio: 8.61) in univariate analysis, in the same dimension, as reported (hazard ratio for mortality: 8.65) in our previous study.[2] The significant association, however, was lost in the recent study after multivariate adjustment which included Charlson index as well as heart failure and NIHSS (National Institutes of Health Stroke Scale) as separate factors. Importantly, heart failure and cerebral vascular disease are already included in the Charlson index, suggesting multicollinearity that may affect the reported association. Collinearity increases the estimate of standard error of regression coefficients, causing wider confidence intervals and increasing the chance to reject the significant test statistic.[4] It would be, also, of great interest to include the results of alternative models in a more exhaustive stepwise analysis. This would allow to know at which level and in the presence of which variables, the effect of PENK-A gets insignificant.

Further, the final multivariate model on mortality prediction (Table 3) contains 8 predictors in a data set with just 39 outcome events. This is less than the minimum of 10 events per variable, which is recommended for a logistic regression. These aspects suggest a relevant over adjustment in this multivariate model, which may have resulted in inadequate attenuation of the associations.[5]

Additionally, the assessment of PENK-A was conducted by Gruber et al using the identical monoclonal sandwich immunoassay similar to our previous study,[2] describing the same accuracy limits, mean values, and reference range in healthy controls. The current study, however, reported consistently higher PENK levels in the entire cohort (19% higher mean level in comparable subsets) compared to the previous report. It is unclear if this is a true difference in PENK plasma levels between the populations in both studies or whether the difference could simply be due to the unit transversion in the recent study as the results are reported in pg/mL, while the method description for the assay indicates pmol/L.

Finally, PENK-A has emerged in recent studies to be associated with impaired kidney function and to carry prognostic significance in the context of acute kidney injury.[6,7] The role of renal injury was not addressed in the study by Gruber at al nor in our previous study. Latent renal injury may play a relevant role in the setting of acute stroke as volume control and urinary tract infections are of major concern in the acute phase of stroke.

Biomarkers are biological measurements (often but not exclusively lab assessments from blood samples) that are intended to be easy and reliable measurements to provide meaningful diagnostic or prognostic information on a given clinical condition to inform the clinical decision-making. Despite a great need for biomarkers in the field of stroke and substantial research efforts, biomarkers for the detection or evaluation of stroke are still not available in routine clinical work.[8] Further studies with larger cohorts of stroke patients are warranted to clarify if PENK-A may have a role as a potential

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biomarker, not only with statistical but with clinical significance in patients with acute stroke.

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