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Letter to the Editor

There is Currently no Evidence that Neuroglobin is a Suitable Biomarker for the Outcome of Ischemic Stroke

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Letter to the Editor

We were interested to read the article by Ramli *et al.* on a cross-sectional cohort study on the association between serum neuroglobin (Ngb) and outcome of acute ischemic stroke (AIS) in 42 stroke patients ^[1]. It was found that Ngb levels were higher in patients with a modified Rankin Scale (mRS) of 3 to 6 than in patients with an mRS of 0 to 2 and that they were high in patients with high NIHSS, low Barthel Index and low Montreal Cognitive Assessment (MoCA) ^[1]. High serum Ngb levels were found to be associated with poor AIS outcome ^[1]. The study is noteworthy, but several points should be discussed.

The first point is that we disagree with the conclusion that Ngb can indeed be used as a predictor of the outcome of AIS ^[1]. Several arguments can be made for this assumption. First, Ngb is a non-specific prognostic biomarker and may be elevated not only in AIS but also in several other diseases, such as traumatic brain injury, Alzheimer's disease, glaucoma and certain cancers ^[2]. Second, Ngb has been measured in serum but not in CSF, suggesting that serum levels may not reflect neuronal damage (e.g., ischemia) due to disruption of the blood-brain barrier or metabolization of the protein as well as CSF levels ^[3]. A study examining the relationship between CSF and serum Ngb may be useful in this regard. Third, the outcome of AIS depends not only on the protective effect of a single protein (Ngb) - Ngb blocks mitochondrial apoptosis, increases oxidative phosphorylation and ATP production, binds oxygen and scavenges reactive oxygen species ^[4] - but also on numerous other factors. These include the latency period between the onset of AIS and the start of thrombolysis/thrombectomy, the type of treatment (thrombolysis/thrombectomy versus antiplatelet blockers or anticoagulants), the type of hospital care (stroke unit versus normal neurology or internal medicine department), the availability of early rehabilitation, the size of the stroke volume, the type of vascular collateralization, and the number and severity of complications.

The second point relates to the study design. The group size was small, only one center was involved, no control group was included, test-to-test reliability was not measured, and different causes for the Ngb increase were not sufficiently excluded. To assess whether Ngb could indeed be a biomarker for the outcome of AIS, a prospective randomized controlled trial (RCT) would be helpful. RCTs are valuable to confirm the clinical utility and generalizability of identified biomarkers ^[5].

The third point is that it is not clear why the two patients with excessively elevated Ngb were excluded from the study. What was the suspected cause of the excessive increase? Was it the methodology of the determination or the disease? Since "extreme" values were not an exclusion criterion, these two patients should be included in the analysis.

Overall, the study does not provide sufficient evidence that Ngb can be considered a reliable predictor of AIS outcome.

Declarations

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