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Letter to the Editor

Before Elevated Serum NOX4 is Considered a Biomarker for Spontaneous Intracerebral Haemorrhage, Appropriately Designed Trials are Required

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Letter to the Editor

We read with interest the article by Wu *et al*. on a prospective observational study of the usefulness of serum NOX4 activity as a biomarker of intracerebral haemorrhage (ICH) severity, early neurologic deterioration (END), and outcome in patients with spontaneous ICH (Sich) [1]. Serum NOX4 activity was elevated in patients with Sich compared to healthy controls and was associated with poor prognosis as assessed by the Glasgow Outcome Scale (GOS) [1]. It was concluded that elevated NOX4 activity could be a biomarker of ICH severity, END and outcome in the early stages of Sich [1]. The study is noteworthy, but several points should be discussed.

The first point is that the study did not include a disease control group [1]. To recommend NOX4 as an outcome biomarker for Sich, it is essential to study disease controls to prove that NOX4 is specifically elevated in sic patients and not in other patients with cerebral lesions. Specificity is one of the criteria that an outcome biomarker must fulfil. It is known that NOX4 can be elevated in various other central nervous system (CNS) diseases (e.g. Parkinson's disease, Alzheimer's disease, traumatic brain injury), which excludes NOX4 as an outcome biomarker for Sich [2].

The second point is that ischemic stroke was an exclusion criterion, but it was not explained how ischemic stroke with secondary haemorrhage in the initial phase was excluded by cerebral CT scan only [1]. Detection of ischemic stroke on CCT with haemorrhage is not easy and not always possible. Cerebral magnetic resonance imaging (MRI) is better suited to assess whether the haemorrhage was primary or secondary.

The third point is that NOX4 was measured in the serum, but the haemorrhage occurred in a different compartment. The measurement of NOX4 in cerebrospinal fluid (CSF) would be more appropriate than the measurement in serum. Was NOX4 measured in the CSF of any of the included patients?

The fourth point is that the current medication was not included in the analysis. Since various medications can affect NOX4 activity [3], it would have been important to exclude patients who regularly took medications that affect serum NOX4 levels.

The fifth point is that the study was conducted during the pandemic (August 2020 to May 2022) [1]. As ICH has been reported as a complication of SARS-CoV-2 infection (SC2I) [4], it would have been imperative to exclude patients who tested positive for SARS-CoV-2 by PCR or who had recently experienced SC2I.

The sixth point is that NOX4 may also be elevated in patients who cannot be successfully weaned from mechanical ventilation [5]. How many of the included patients had to be intubated and mechanically ventilated in the initial phase of ICH? In how many of them was the increased NOX4 concentration due to mechanical ventilation and not to ICH?

The seventh point is that the functional outcome was assessed by telephone interviews and not on site [1]. Telephone interviews have several disadvantages. It cannot be ensured that the person answering is really the patient, that the answers given are true and that the questions are understood correctly.

To summarize, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and corroborate the study's message. Appropriately designed studies are needed before elevated serum NOX4 levels are recommended as a biomarker for the outcome of spontaneous intracerebral haemorrhage.

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