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# Comparison of plasma copeptin and multiple biomarkers for assessing prognosis of patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

*Background:* Increased plasma copeptin concentrations are related to poor prognosis after aneurysmal subarachnoid hemorrhage (aSAH). The aim of this study was to assess prognostic significance of plasma copeptin detection compared with glial fibrillary astrocyte protein, myelin basic protein, S100B, phosphorylated axonal neurofilament subunit H, neuron-specific enolase, tau and ubiquitin carboxyl-terminal hydrolase L1 in aSAH.

*Methods:* We detected plasma concentrations of the aforementioned biomarkers in 105 healthy controls using ELISA. Their predictive ability for symptomatic cerebral vasospasm and 6-month poor outcome (Glasgow Outcome Scale score of 1–3) were compared.

*Results:* Plasma concentrations of the preceding biomarkers were highly correlated with World Federation of Neurological Surgeons subarachnoid hemorrhage scale (WFNS) scores as well as were significantly higher in patients with symptomatic cerebral vasospasm than in those without symptomatic cerebral vasospasm and in patients with poor outcome than in those with good outcome. In terms of area under receiver operating characteristic curve, their predictive value for symptomatic cerebral vasospasm and 6-month poor outcome was in the range of WFNS scores. Plasma copeptin concentration, but not plasma concentrations of other biomarkers, statistically significantly improved the predictive performance of WFNS scores.

*Conclusions:* Copeptin in plasma might have the potential to be a useful prognostic biomarker for aSAH.

## 1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) results in high case-fatality rate and loss of productive life-years [1–4]. The neurological status after the initial hemorrhage is an important prognostic factor for outcome [5,6]. World Federation of Neurological Surgeons subarachnoid hemorrhage scale (WFNS) is an accurate staging system for the prognostic prediction after aSAH [7,8]. Nevertheless, the neurological status can sometimes be evaluated very difficultly because of sedation or impaired consciousness. Hence, a biomarker, which reflects tissue damage and is measurable in blood, could be useful for clinical monitoring.

Myelin basic protein (MBP), glial fibrillary astrocyte protein (GFAP), the calcium-binding protein S100B, neuron-specific enolase (NSE), phosphorylated axonal neurofilament subunit H (pNF-H), tau protein and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) are some cell-type-specific proteins, which are mainly released from neurons and/or glia in the central nervous system after hemorrhagic injury [9–23]. Accumulating evidence has shown that levels of these biomarkers in peripheral blood can reflect extent of primary cerebral injury and are independently associated with prognosis after aSAH [16–23]. Alternatively, copeptin is a marker of endogenous vasopressin levels and its circulating levels are related to severity and clinical outcomes after aSAH [24–28]. It has been demonstrated that prognostic performances of plasma concentrations of the above-mentioned biomarkers were similar to that of Glasgow Coma Scale score in severe traumatic brain injury and resembled that of National Institute of Health Stroke Scale score in spontaneous intracerebral hemorrhage; and except plasma copeptin concentration, other biomarkers concentrations in plasma did not significantly improve prognostic predictive value of Glasgow Coma Scale score or National Institute of Health Stroke Scale score [29,30]. However, it is largely unclear that

*Abbreviations:* aSAH, aneurysmal subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons; GFAP, glial fibrillary astrocyte protein; MBP, myelin basic protein; NSE, neuron-specific enolase; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1

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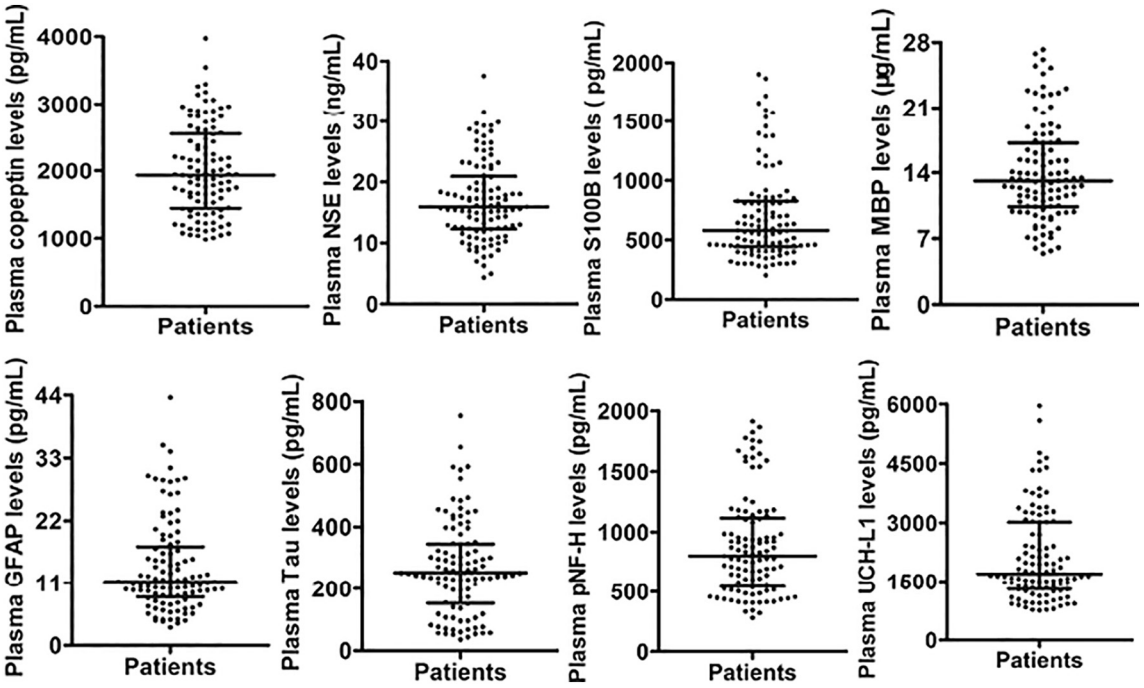


**Fig. 1.** Graph depicting plasma copeptin, neuron-specific enolase (NSE), S100B, glial fibrillary astrocyte protein (GFAP), myelin basic protein (MBP), tau protein, phosphorylated axonal neurofilament subunit H (pNF-H) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) concentrations after aneurysmal subarachnoid hemorrhage.

**Table 1**
Comparisons of plasma biomarkers in terms of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage.

| Variables | Symptomatic cerebral vasospasm | | | No symptomatic cerebral vasospasm | | | *P* value |
|---|---|---|---|---|---|---|---|
| | Median | Range | Interquartile range | Median | Range | Interquartile range | |
| Copeptin (pg/ml) | 2612.5 | 1040.8–3544.8 | 2156.0–2942.9 | 1720.5 | 984.8–3973.9 | 1322.1–1981.4 | < 0.001 |
| NSE (ng/ml) | 22.6 | 6.2–37.6 | 15.2–26.8 | 15.2 | 4.3–31.7 | 10.9–17.4 | < 0.001 |
| S100B (pg/ml) | 877.1 | 300.9–1900.9 | 613.8–1376.2 | 495.0 | 202.9–910.8 | 408.7–633.7 | < 0.001 |
| MBP (μg/ml) | 17.0 | 6.1–27.3 | 12.7–22.6 | 12.2 | 5.4–26.2 | 9.9–13.9 | < 0.001 |
| GFAP (pg/ml) | 21.1 | 4.2–43.6 | 10.1–28.9 | 10.4 | 3.2–20.1 | 7.3–13.1 | < 0.001 |
| Tau (pg/ml) | 349.3 | 117.9–754.5 | 236.2–450.8 | 235.0 | 35.7–493.4 | 95.3–283.5 | < 0.001 |
| pNF-H (pg/ml) | 1171.8 | 280.3–1913.6 | 779.8–1620.7 | 696.4 | 320.7–1183.7 | 505.8–898.0 | < 0.001 |
| UCH-L1 (pg/ml) | 3034.2 | 768.3–5579.7 | 1952.2–3754.3 | 1530.7 | 752.2–5952.3 | 1154.0–1900.5 | < 0.001 |

Intergroup comparisons were conducted using the Mann-Whitney *U* test. NSE indicates neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.

which one, among these biomarkers including copeptin, MBP, GFAP, S100B, NSE, pNF-H, tau and UCH-L1, has advantage over others in prognostic prediction in aSAH.

## 2. Methods

### 2.1. Study population

Between February 2013 and February 2016, we prospectively collected patients with first-ever non-traumatic SAH in the Department of Neurosurgery, Hangzhou First People's Hospital, China. Alternatively, we required that those patients should be admitted within 24 h after onset of stroke, with intracranial aneurysms confirmed by computerized tomography angiography or digital subtraction angiography, which were treated within the 48 h after admission. Moreover, we excluded such patients with rebleeding after admission, < 18 y, prior head trauma, prior neurological disease, prior use of antiplatelet or anticoagulant medication, or other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart disease, and chronic lung disease. This study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The medical ethics committee at our hospital approved the study and the relatives wrote informed consent to participate in this study.

### 2.2. Data collection

Clinical severity of patients was assessed according to the World Federation of Neurological Surgeons subarachnoid hemorrhage scale (WFNS) [7]. Radiological severity of patients was estimated in accordance with the Fisher scale [31]. Symptomatic cerebral vasospasm was defined as the development of new focal neurological signs, deterioration in level of consciousness, or the appearance of new infarction on CT when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (e.g., hydrocephalus, seizures, metabolic derangement, infection, or oversedation) had been excluded [32,33]. Patients were followed up until death or completion of 6 months after stroke. A poor outcome was defined as a Glasgow outcome scale score 1–3 at 6 month [34].

### 2.3. Laboratory examinations

Venous blood samples of patients, which were obtained as soon as possible after admission, were taken from sterile EDTA test tubes, centrifuged and immediately stored at − 80 °C until the final analysis.