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# Prognostic value of copeptin in patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

*Background:* Recently, copeptin has been identified as a plasma prognosis marker in acute ischemic stroke and intracerebral hemorrhage (ICH). This study investigated the prognostic value of copeptin in the patients with aneurysmal subarachnoid hemorrhage(aSAH).

*Methods:* In this retrospective study, 243 consecutive patients were included. Upon admission, plasma copeptin levels were measured by enzyme-linked immunosorbent assay. The end points were mortality and poor functional outcome (Glasgow Outcome Scale score of 1–3) after 3 months.

*Results:* In 243 patients, 112 (46.1%) were male and median age was 58 years (IQR 49–68). Median copeptin plasma levels were 21.0 pmol/l (IQR 13.2–31.2). Copeptin levels increased with increasing severity of aSAH as defined by the World Federation of Neurological Surgeons (WFNS) score. Patients with a poor outcome and nonsurvivors had significantly increased copeptin levels on admission ($P < .001$ *both*). In the multivariate analysis, for each 1 pmol/l increase of plasma concentration of copeptin, the adjusted risk of poor outcomes and mortality would be increased by and 6% (1.06 [1.02–1.10], $P < .001$) and 9% (1.09 [1.03–1.13], $P < .001$), respectively. Receiver operating characteristics to predict functional outcome and mortality demonstrated areas under the curve of copeptin of 0.74 (95% confidence interval [CI], 0.67–0.81) and 0.81 (95% CI, 0.74–0.87), which was comparable with the WFNS score($P > .05$) but superior to C-reactive protein and IL-6 ($P < .01$).

*Conclusions:* The data shows that copeptin levels may reliably predict short-term prognosis at its onset in aSAH patients.

## 1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating cerebrovascular event with long-term morbidity and mortality (Galea et al., 2018). The mechanisms contributing to brain injury and after in-hospital death aSAH remain unclear. Secondary cerebral insults (hypoxia, hypotension, and hyperglycemia) are common after SAH, including among patients with a good clinical grade. These insults after SAH are associated with worse outcome (Doerfler et al., 2018).

A growing understanding of the pathophysiology of aSAH has improved efforts to recognize biomarkers that can predict outcomes in these patients (Tamargo, 2012). Delayed cerebral ischemia (DCI) observed 4 to 14 days after SAH is the most important treatable determinant of poor outcome (Vergouwen et al., 2010a). Some serum markers which can predict DCI might be used as prognostic markers in SAH. However, Juvela found that (Juvela et al., 2012) elevated serum levels of C-reactive protein were predictive of poor outcome at 3 months after aneurysmal SAH but not of DCI. Similar results were reported in D-dimer (Juvela and Siironen, 2006).

Copeptin is a 39 amino-acid glycopeptide and is equivalent to the C-terminal part of pre-provasopressin (Morgenthaler et al., 2006). Copeptin was a surrogate marker for vasopressin release and might act as a marker for stress response (Morgenthaler et al., 2006). Copeptin has been proposed as a prognostic marker in many acute illness, such as intracerebral hemorrhage (ICH) (Zhang et al., 2012; Yu et al., 2014; Zweifel et al., 2010), ischemic stroke (De Marchis et al., 2013; Tu et al., 2013), acute myocardial infarction (Lattuca et al., 2019), traumatic brain injury (Choi et al., 2017), cardio-cerebrovascular patients (Sun et al., 2015) and heart failure with reduced ejection fraction (Pozsonyi et al., 2015).

Interestingly, one study reported that copeptin level was a useful, complementary tool to predict functional outcome and mortality after aSAH (Zhu et al., 2011), while Fung et al. (Fung et al., 2013) found that copeptin may indicate clinical severity of the initial bleeding and may therefore help in guiding treatment decisions in the setting of aSAH. This study also suggested that copeptin might also have prognostic

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value for clinical outcome in aSAH (Fung et al., 2013). This study investigated the ability of copeptin to predict the disease functional outcome and mortality in the Chinese patients with aSAH.

## 2. Study population

Between September 2016 and December 2017, all patients with aSAH confirmed by computerized tomography (CT) angiography with or without digital subtraction angiography who were admitted to Department of Emergency, Tianjin Huanhu Hospital were evaluated in the study. Patients with (1) admitted > 48 h after the onset of symptoms; (2) death appeared imminent on admission; (3) prior systemic diseases including neurological disease, liver or renal insufficiency, malignancy; (4) chronic heart or lung disease were also excluded.

## 3. Clinical and radiological assessment

On arrival to the emergency department, sex, age, a detailed history of vascular risk factors, concomitant medication and Glasgow Coma Scale (GCS) score were taken. At admission, clinical severity was assessed (Zuo Z) using the World Federation of Neurological Surgeons (WFNS) score (Drake, 1988). The initial CT was classified according to the modified Fisher score (Fisher et al., 1980). All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. In addition, aneurysmal location and size, radiological characteristics (Intracerebral hemorrhage, intraventricular hemorrhage, hydrocephalus and cerebral vasospasm), delayed cerebral ischemia (DCI), rebleeding, aneurysm treatment (coiling or clipping) and were collected.

*Re*-bleeding was defined as a change of at least four points in the NIHSS score within the first 72 h after hospital admission together with an increase of intracranial bleeding on brain imaging (Llull et al., 2017). Transcranial Doppler (TCD) sonography was performed daily or every other day. Cerebral vasospasm was defined using TCD as flow velocity in the middle cerebral artery > 120 cm/s, with a concomitant Lindegaard Ratio above 3.0 (Duan et al., 2018). DCI was defined as (1) clinical deterioration (a new focal neurological deficit (at least increasing 2 points on the NIHSS score) or a decrease in the level of consciousness (at least reducing 2 points on the Glasgow Coma Scale), or both, lasting for at least 1 h, and/or (2) a new infarct on CT; other potential causes of clinical deterioration, such as hydrocephalus, rebleeding, or seizure, were rigorously excluded (Vergouwen et al., 2010b; Crobeddu et al., 2012).

## 4. Determination of copeptin in plasma

Fasting plasma samples were collected at 6:00 am on the first morning after the admission and within 48 h of stroke onset (within 0–6 h [$n$ = 66], 6–12 h [$n$ = 82], 12–24 h [$n$ = 48], and 24–48 h [$n$ = 47] from the symptom onset). The concentration of copeptin in plasma was analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Cusabio biotech co. ltd, Wuhan, Hubei Province, China) in accordance with the manufactures' instructions. Intra-assay and inter-assay coefficients of variation were 4.0%-8.0 and 5.0%–9.5%. The blood samples were run in duplicate. Researchers running ELISAs were blinded to all patient details. In addition, plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were also tested using standard laboratory methods.

## 5. End points

Participants were followed up until death or completion of 3-month after SAH. Their primary outcome was functional outcome at 3 months and their secondary outcomes were death (at 3-month or in-hospital). The functional outcome was defined by Glasgow outcome scale (GOS) score (1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery) (Jennett and Bond, 1975). GOS Scores were dichotomized in good and poor functional outcomes (GOS of 4–5 vs. GOS of 1–3). In addition, in the subgroup analysis, good outcome also be defined as truly back to normal life function. For follow-up, outcome assessment was performed by two trained medical students blinded to copeptin levels with a structured follow-up telephone interview with the patient or, if not possible, with the closest relative or family physician.

### 5.1. Statistical analysis

The results were expressed as medians [interquartile ranges (IQRs) for continuous variables or as percentages for categorical variables. The Mann-Whitney $U$ test (continuous variables) or Chi-Square (categorical variables) were used to tested the different between two groups. The bivariate correlations were tested by the Spearman's rank correlation.

The relation of copeptin with two endpoints were assessed by the logistic regression models. Crude models and multivariate models adjusted for all significant predictors in univariate analysis were used and reported as odds ratios (ORs) [95% confidence interval (CI)]. For a more detailed exploration of relationship between copeptin and two endpoints, the relation according to copeptin quartiles (the lowest quartile[Q1] as the reference) was also been used. In addition, the relation of elevated copeptin status (defined as ≥31.2 pmol/l[3rd quartile]) with endpoints was analyzed.

The accuracy of plasma levels of copeptin in two endpoints was analyzed with receiver operating characteristic (ROC) curves and area under the curve (AUC) analysis. The AUC summary equals the probability that the underlying classifier will score a randomly drawn positive sample higher than a randomly drawn negative sample. To test whether the copeptin level improves score performance, we considered the two nested logistic regression models with WFNS and copeptin as compared with WFNS only. Furthermore, care was taken to adjust for the optimistic bias of in-sample prediction error estimates using a fivefold cross-validation scheme.

Finally, to study the ability of copeptin for mortality prediction, we calculated Kaplan–Meier survival curves and stratified patients by copeptin levels (elevated vs. normal). Elevated copeptin status was defined as ≥31.2 pmol/l(3rd quartile). The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and the ROCR package (Version 1.0–2), which is available from the CRAN repository (http://cran.r-project.org/). All testing was two tailed, and $p$ values < .05 were considered to indicate statistical significance.

## 6. Ethics

This study was approved by and conducted in accordance with the ethical standards of the Institutional Review Board (IRB) of the Tianjin Huanhu Hospital. Patient consent for procedures, data collection and review were obtained based on the guidance of Declaration of Helsinki and institutional guidelines.

## 7. Results

### 7.1. Study population characteristics

During the study period, 304 patients with suspected aSAH were admitted, 272 (89.5%) patients fulfilled the inclusion criteria, and 243 individuals (79.9%) were finally included in the analysis. However, these 243 patients were similar in terms of baseline characteristics [age ($P$ = .18), gender ($P$ = .89), WFNS ($P$ = .12) and BMI ($P$ = .44)] compared to the overall cohort. In those patients, 112 (46.1%) were male and median age was 58 years (IQR 49–68). Median WFNS at admission was 2 (IQR 1–4) and median aneurysmal size was 7.2 (IQR 5.8–10.2). Cystic aneurysm accounted for 77.8% (189/243) among all patients. A

**Table 1**
The characteristics for 243 aSAH patients characteristics.

| N | 243 |
|---|---|
| Sex-male | 112(46.1) |
| Age, years | 58(49–69) |
| BMI, kg/m2 | 26.5(24.8–28.3) |
| WFNS Score | 2(1–4) |
| Modified Fisher score | 3(1–3) |
| Aneurysmal location | |
| Posterior communication artery | 62(25.5) |
| Anterior communication artery | 31(12.8) |
| Internal carotid artery | 51(21.0) |
| Cerebral artery | 81(33.3) |
| Vertebral artery | 18(7.4) |
| Aneurysmal size, mm | 7.2(5.8–10.2) |
| Rebleeding | 16(6.6) |
| Acute hydrocephalus | 72(29.6) |
| Intracerebral hemorrhage | 35(14.4) |
| Intraventricular hemorrhage | 48(19.8) |
| Angiographic vasospasm | 81(33.3) |
| External ventricular drain | 74(30.4) |
| DCI | 61(25.1) |
| Seizure | 31(12.8) |
| Treatment | |
| Clipping | 114(46.9) |
| Endovascular coiling | 131(53.9) |
| Time from onset to blood collected, min | 10.5(6.5–17.0) |
| C-reactive protein level, mg/l | 5.5(3.4–11.2) |
| IL-6, pg/ml | 8.6(7.1–10.3) |
| Copeptin, pmol/l | 21.0(13.2–31.2) |

Numerical variables were presented as median (IQR) and categorical variables were expressed as counts (percentage).
WFNS, World Federation of Neurological Surgeons; BMI, Body Mass Index; DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage.

total of 114 patients underwent clipping of aneurysm; 131, endovascular coiling; 2, clipping and endovascular coiling. Alternatively, an external ventricular drain was performed for 74 (30.4%) patients. Also, 72 (29.6%) patients with acute hydrocephalus, 81 (33.3%) patients with symptomatic cerebral vasospasm and 61(25.1%) patients with DCI were observed. Median copeptin plasma levels were 21.0 pmol/l (IQR 13.2–31.2). Table 1 presented the demographic, clinical, laboratory and radiological data of the patients.

### 7.2. Copeptin concentrations and other variables in aSAH patients

Copeptin levels increased with increasing severity of aSAH as defined by the WFNS score, Fig. 1. There was a modest correlation between levels of plasma copeptin and WFNS score ($r = 0.434$, $P < .001$). Interesting, copeptin concentrations in patients with a WFNS score of 0 to 3 points ($n = 176$) were 17.2 (IQR, 12.2–25.6) pmol/l and in patients with a WFNS score > 3 points ($n = 76$) were 29.6 (IQR, 21.1–45.9) pmol/l. There were also modest correlations between copeptin and CRP ($r = 0.184$, $P = .004$) and IL-6($r = 205$, $P = .001$). There were no correlations between copeptin and sex ($P = .15$), age ($P = .11$) and BMI($P = .32$).

### 7.3. Relationship between copeptin and short-term outcome

In our study, 59 patients (24.3%) experienced a poor outcome in the 3-month follow-up. Plasma copeptin levels in those patients were nearly 2 times greater as compared with patients who with good outcomes [30.7 (IQR, 21.8–45.9) pmol/l vs. 19.0 (13.1–25.3) pmol/l, $P < .001$; Fig. 2.). In logistic regression analysis, we calculated the odds ratio (OR) of copeptin levels as compared with the WFNS and other risk factors. As a continuous variable, for each 1 ng/ml increase of plasma concentration of copeptin, the unadjusted and adjusted risk of poor outcomes would be increased by 10% (with the OR of 1.10 [95%

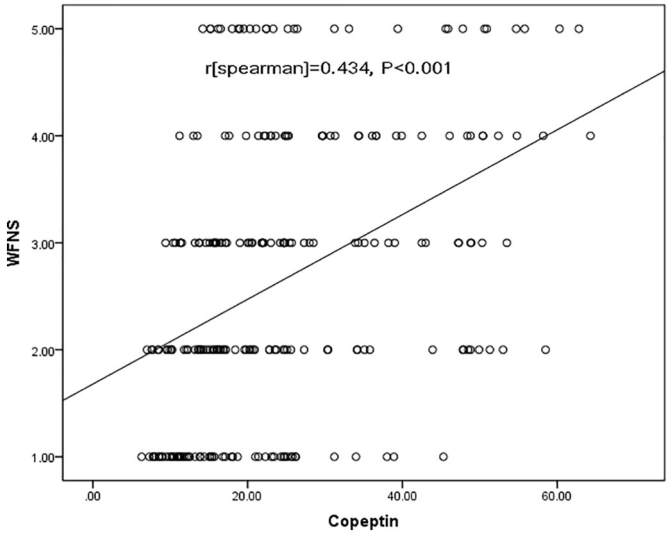


**Fig. 1.** The relationship between copeptin and WFNS score at admission after aSAH. WFNS = World Federation of Neurological Surgeons. aSAH = aneurysmal subarachnoid hemorrhage.

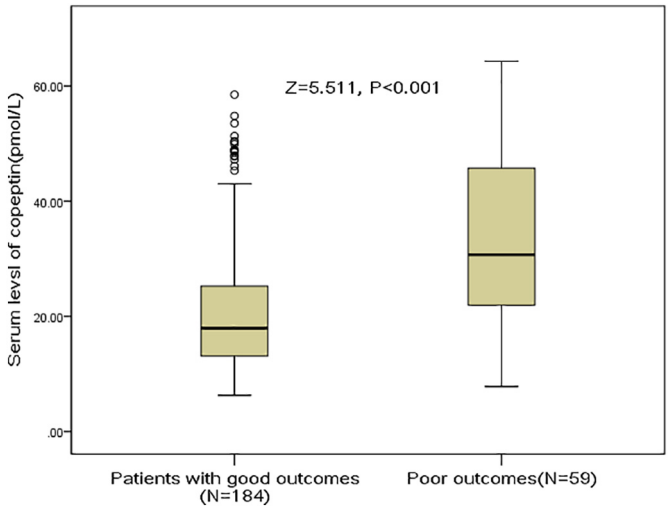


**Fig. 2.** Copeptin levels in aSAH patients with poor and good functional outcome. Mann–Whitney U Test. All data are medians and interquartile ranges (IQR). aSAH = aneurysmal subarachnoid hemorrhage.

**Table 2**
Multivariate analysis of factors predicting the 3-month poor outcomes among 243 patients with aSAH[a].

| Factors | OR | 95%CI | P |
|---|---|---|---|
| Age > 60 | 1.88 | 1.19–3.02 | 0.013 |
| WFNS score on admission | 1.64 | 1.24–2.17 | 0.001 |
| Modified Fisher score on admission | 3.82 | 2.05–5.16 | 0.003 |
| Intraventricular hemorrhage | 2.67 | 1.48–4.02 | 0.015 |
| DCI | 2.41 | 1.65–3.18 | 0.009 |
| IL-6 | 1.19 | 1.05–1.35 | 0.006 |
| Copeptin | 1.05 | 1.02–1.09 | < 0.001 |

WFNS, World Federation of Neurological Surgeons; BMI, Body Mass Index; DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage.
[a] adjusted for age, sex, BMI, WFNS, Modified Fisher score, aneurysmal location and size, Intraventricular hemorrhage, rebleeding, acute hydrocephalus, angiographic vasospasm, DCI, seizure, treatment, serum levels of CRP, IL-6 and copeptin.

**Table 3**
The accuracy of plasma levels of copeptin in poor outcome was analyzed with ROC curves and AUC analysis at different cut-off value.

| Cut-off[a] | Patients (above /below the cutoff) | Sensitivity | Specificity | AUC (95%CI) |
|---|---|---|---|---|
| 24.0 | 98/145 | 70.5 | 69.6 | 0.74(0.67–0.81) |
| 13.2 | 184/61 | 94.9 | 25.0 | 0.61(0.53–0.68) |
| 21.0 | 121/122 | 76.3 | 58.7 | 0.68(0.60–0.75) |
| 31.2 | 60/183 | 47.5 | 82.6 | 0.65(0.57–0.74) |

ROC, Receiver operating characteristic; AUC, Area under the curve; CI, confidence interval.

[a] The cut-off value of 24.0 pmol/l was defined according to ROC curves. 13.2, 21.0 and 31.2 pmol/l were defined according to interquartile ranges (Q1, Q2 and Q3).

CI 1.06–1.14], $P < .001$) and 6% (1.06 [1.02–1.10], P < .001), respectively. In addition, age > 60, WFNS, DCI, Modified Fisher score, intraventricular hemorrhage and IL-6 remained significant predictors unlike other factors (all $P < .05$) (Table 2).

The poor outcomes distribution across the copeptin quartiles ranged between 7.7% (first quartile) to 52.0% (four quartile). Compared with the first quartile of copeptin, the 4th quartile OR for poor outcomes was 6.12 (95% CI, 2.76–12.28; $P < .001$). For the 2nd and 3rd quartiles, it was1.49 (95% CI, 0.83–3.94; $P = .42$) and 3.15 (95% CI, 1.86–5.16; $P = .011$), respectively. Furthermore, elevated plasma level of copeptin (> 31.2 pmol/l) was also associated with poor outcomes and the unadjusted and adjusted risk increased by 329% (with the OR of 4.29 [95% CI 2.27–8.12], P < .001) and 237% (3.37 [2.03–5.05], $P = .002$), respectively.

Based on the ROC curve, the optimal cutoff value of plasma level of copeptin as an indicator for predicting poor outcome was projected to be 24.0 pmol/l, which yielded a sensitivity of 70.5% and a specificity of 69.6%, Table 3. With an AUC of 0.74 (95% CI, 0.67–0.81), copeptin showed a significantly greater discriminatory ability to predict poor outcomes as compared with age(AUC, 0.59; 95% CI, 0.51–0.65; $P < .01$), CRP (AUC, 0.62; 95% CI, 0.53–0.70; P < .01), IL-6 (AUC, 0.63; 95% CI, 0.54–0.71; P < .01) and in the range of WFNS score (AUC, 0.72; 95% CI, 0.65–0.79; $P = .16$), Fig. 3 Interestingly, copeptin

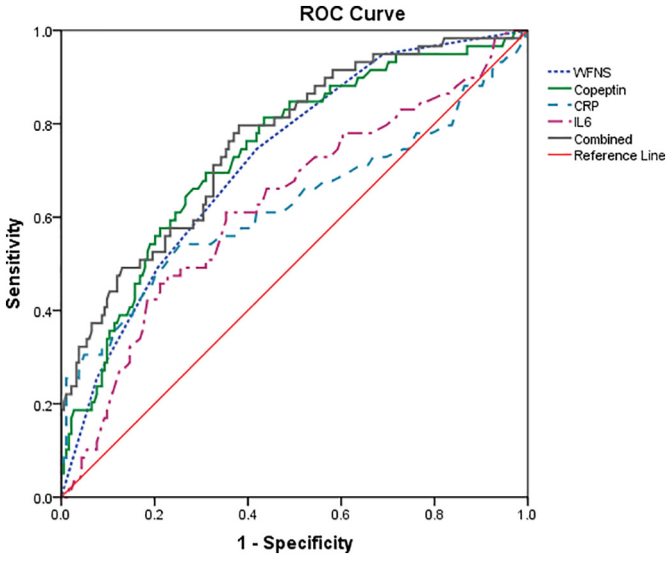


**Fig. 3.** Receiver operator characteristic curve demonstrating sensitivity as a function of 1 specificity for predicting the poor outcome based on the logistic model incorporating 2 biomarkers (copeptin/WFNS) and the relative contribution of each biomarker alone. CRP = C-reactive protein; WFNS = World Federation of Neurological Surgeons. aSAH = aneurysmal subarachnoid hemorrhage.

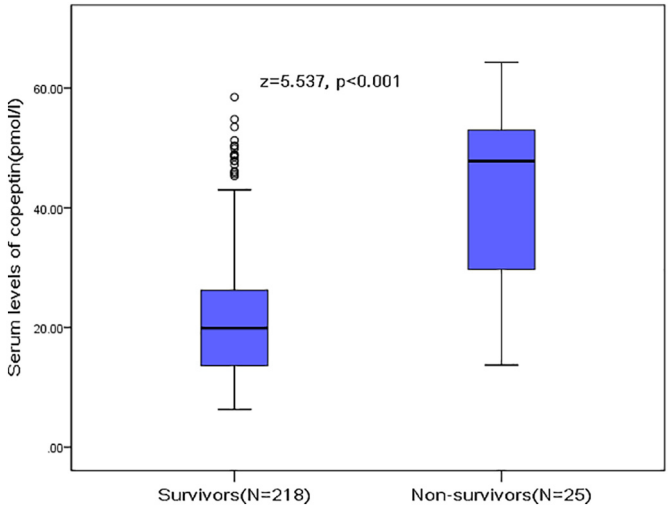


**Fig. 4.** Copeptin levels in survivors and non-survivors of aSAH. Mann–Whitney *U* Test. All data are medians and interquartile ranges (IQR). aSAH = aneurysmal subarachnoid hemorrhage.

improved the WFNS score (AUC of the combined model, 0.77; 95% CI, 0.69–0.83; $P = .003$). This improvement was stable in an internal 5-fold cross validation that resulted in an average AUC (standard error) of 0.72 (0.041) for the WFNS and 0.77 (0.036) for the combined model, corresponding to a difference of 0.05 (0.005). In addition, a model containing known risk factors plus copeptin compared with a model containing known risk factors without copeptin showed a greater discriminatory ability ($P = .006$).

### 7.4. Copeptin and death within 3 months

Copeptin levels in 25 patients who died were > 2 times greater as compared with patients who survived (19.9[IQR, 13.6–26.2] vs. 47.8 [IQR, 23.1–53.9]pmol/l; $P < .001$; see Fig. 4). As a continuous variable, for each 1 ng/ml increase of plasma concentration of copeptin, the unadjusted and adjusted risk of mortality would be increased by 14% (with the OR of 1.14[95% CI 1.06–1.20], P < .001) and 9% (1.09 [1.03–1.13], P < .001), respectively. Receiver operating characteristic curves demonstrated the greatest discriminatory accuracies for copeptin level (AUC, 0.81; 95% CI, 0.74–0.87) and the WFNS score (AUC, 0.80; 95% CI, 0.73–0.86). The combination of copeptin level and the WFNS score had a higher discriminatory accuracy (AUC, 0.84; 95% CI, 0.79–0.90) than the WFNS score alone ($P = .017$).

The time to death was analyzed by Kaplan–Meier survival curves based on copeptin levels (elevated vs. normal). Patients in normal levels (copeptin ≤ 31.2 pmol/l) had a minimal risk for death, in contrast with patients with copeptin levels in elevated levels (> 31.2 pmol/l) ($P < .001$) (Fig. 5). Furthermore, elevated plasma level of copeptin (> 31.2 pmol/l) were an independent predictor for mortality with an unadjusted OR of 5.05 (95% CI, 2.14–10.12) and an adjusted OR of 4.13(95%CI, 1.75–7.12).

### 7.5. Subgroup analysis

In our study, 162 patients (66.7%) experienced a good outcome (defined as truly back to normal life function). Plasma copeptin levels in those patients were lower as compared with patients who with poor outcomes [20.5(13.9–26.5)pmol/l vs. 30.1 (IQR, 21.3–44.7)pmol/l; $P < .001$). In logistic regression analysis, we calculated the odds ratio (OR) of copeptin levels as compared with the WFNS and other risk factors. As a continuous variable, for each 1 ng/ml increase of plasma concentration of copeptin, the unadjusted and adjusted risk of poor outcomes would be increased by 9% (with the OR of 1.09 [95% CI

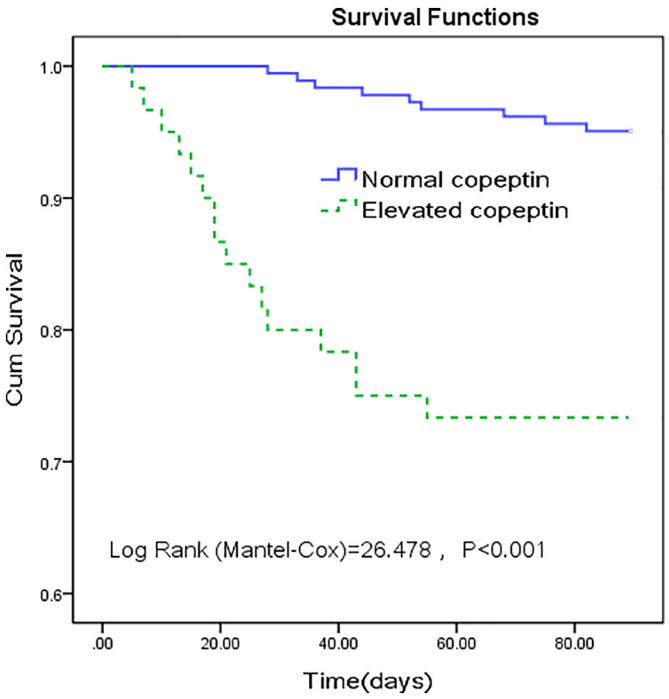


**Fig. 5.** Kaplan–Meier survival curves for copeptin levels (elevated vs. normal).

1.05–1.12], $P < .001$) and 5% (1.05 [1.02–1.09], $P < .001$), respectively. Furthermore, elevated plasma level of copeptin( > 31.2 pmol/l) was also associated with poor outcomes and the unadjusted and adjusted risk increased by 295% (with the OR of 3.95 [95% CI 2.04–7.49], $P < .001$) and 204% (3.04 [1.62–4.83], $P = .005$), respectively.

## 8. Discussion

Previous studies have shown associations between plasma copeptin concentration and functional outcome and mortality after aSAH (Zhu et al., 2011; Fung et al., 2013), which had been confirmed by our study. In this prospective, observational study, we showed that copeptin is a strong, and independent prognostic marker for functional outcome and death in patients with aSAH. The major advance in this work is that the prognostic accuracy of copeptin is superior to that of other commonly measured markers and in the range of the commonly used clinical WFNS score. Importantly, copeptin can improve the prognostic accuracy of the WFNS score significantly.

Consistent with our findings, Zheng et al., (Zheng et al., 2017) suggested that copeptin in plasma might have the potential to be a useful prognostic biomarker for aSAH. In patients with ischemic stroke, copeptin had been presented as a useful independent prognostic marker of all-cause or CVD mortality (Tu et al., 2017a). In a meta-analysis, the authors found that copeptin was a promising independent biomarker for predicting the functional outcome and all-cause mortality, and elevation in plasma copeptin level carried a higher risk of all-cause mortality (odds ratio = 4.16; 95% CI: 2.77–6.25) and poor functional outcome (odds ratio = 2.56; 95% CI: 1.97–3.32) after acute ischemic stroke (Xu et al., 2017). Furthermore, other studies had demonstrated that serum copeptin levels might be considered an independent predictor of mortality in severe sepsis and septic shock (Assaad et al., 2016), long-term mortality in a selected population of patients suspected for an Acute Coronary Syndrome (Morawiec et al., 2018), and intermediate-term mortality in patients with both coronary artery and renal disease (Engelbertz et al., 2016).

Furthermore, copeptin predicted heart disease and death, specifically in diabetes patients (Enhörning et al., 2015). High circulating copeptin level was independently associated with higher risk of mortality in patients with intracerebral hemorrhage (Zhang et al., 2017). One study demonstrated copeptin to be useful prognostic markers of stroke recurrence and cerebrovascular events in ischemic stroke patients (Zeng et al., 2016) and other study reported that a higher serum copeptin level was a predictor of both severity at admission and stroke recurrence at 1-year in stroke patients (Tang et al., 2017).

For assessment of the severity of aneurysmal subarachnoid hemorrhage (aSAH), the WFNS grade is the current gold standard (Drake, 1988). In addition, The WFNS is used to predict 3-month outcome. However, it has some limitations. The use of the WFNS implies special training and there remains a notable interobserver variability. In addition, some study found that the WFNS grading scale failed to predict significant differences in outcome between some of its grades (Lagares et al., 2001). In this context, readily measurable biomarkers, such as copeptin, are additionally helpful in predicting the severity level and outcome of patients with aSAH.

Whether copeptin release is SAH specific or reflects a general stress response remains unclear. The mechanism of copeptin's roles on poor outcome needs further demonstration. Frist, copeptin is co-synthesized with arginine vasopressin in the hypothalamus and is released into the portal circulation of the neurohypophysis. Arginine vasopressin contributes to the regulation of osmotic and cardiovascular homeostasis (Itoi et al., 2004; Asfar et al., 2006). Second, arginine vasopressin activates the hypothalamo – pituitary – adrenal axis through potentiation of corticotrophin – releasing – hormone -induced adrenocorticotropic hormone secretion and thus reflects the individual stress response at a hypothalamic level (Itoi et al., 1998; Katan et al., 2008). Therefore, it has been hypothesized that the close and reproducible relation of copeptin levels to the degree of activation of the stress axis is the basis of its unique usefulness as a prognostic biomarker (Katan et al., 2009). Third, vasopressin plays a role in brain edema formation as blocking of vasopressin receptors attenuates brain edema in ischemic and traumatic mice models (Molnar et al., 2008; Trabold et al., 2008). Some authors have reported that arginine vasopressin may play a role in the development of cerebral vasospasm (Cach et al., 1989) and ischemic brain edema (Shuaib et al., 2002). Lastly, delayed cerebral vasospasm is a well-recognized contributor to poor outcome (Bederson et al., 2009). One study found that higher plasma copeptin level was associated with cerebrovasospasm (Zhu et al., 2011).

Some limitations in this study should be acknowledged. First, data derived from a single-center and with a small sample size ($N = 243$). Second, cerebrospinal fluid samples from aSAH were not available. In addition, without serial measurement of the circulating copeptin levels, this study yielded no data regarding when and how long copeptin is elevated in these patients. Third, we assessed all-cause mortality because classification of death in clinical practice can sometimes be difficult and unreliable (Zhang et al., 2013). Fourth, some important comorbidities are missing which might confound the association of copeptin with outcome after stroke (e.g. kidney disease, heart failure). Thus, the loss of those factors could possibly lead to selection bias. Lastly, any causal relationship could not be proved due to the cross-sectional study design (Tu et al., 2017b). Further studies should investigate whether copeptin can help physicians tailor the therapy in view of the relative risk and allocate resources accordingly and whether this strategy might affect outcome.

## 9. Conclusions

The data shows that copeptin levels may reliably predict short-term prognosis at its onset in aSAH patients. Because it plays an important role at multiple stages of aSAH progression, copeptin is worthy of further research as a possible therapeutic target. If it is possible to elucidate the causal relationship, more intensive efforts could be directed towards the cause, thus hopefully improve the prognosis of these stroke patients.

## Declaration

*Ethics, consent and permissions*

Written informed consents were obtained from all patients; and, this study conformed to the principles of the Declaration of Helsinki was approved by the investigational review board of the Tianjin Huanhu Hospital.

*A consent for publication*

Not applicable.

*Data availability*

Please contact author for data requests.

*Disclosure of potential conflicts of interest*

None.

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