

ORIGINAL ARTICLE

Copeptin as a biomarker for prediction of prognosis of acute ischemic stroke and transient ischemic attack: a meta-analysis

Qian Xu^{1,2}, Yunfan Tian¹, Hao Peng^{1,2} and Hongmei Li^{1,2}

This meta-analysis aimed to investigate the predictive effect of copeptin as a biomarker for the prognosis of acute ischemic stroke and transient ischemic attack. Electronic databases including PubMed, Medline, EMBASE, Web of Science and Cochrane Central were searched for studies assessing the association of copeptin level on admission with prognosis of acute ischemic stroke and transient ischemic attack. The Newcastle–Ottawa Quality assessment scale for cohort study was used to evaluate quality. A total of 1976 acute ischemic stroke patients from 6 studies were included, and 59% of patients were male. Patients with poor outcomes and nonsurvivors had a higher copeptin level at admission ($P < 0.0001$). Copeptin combined with an admission National Institutes of Health Stroke Scale score significantly improved the discriminatory accuracy of functional outcome and mortality compared with the National Institutes of Health Stroke Scale alone. 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. In addition, copeptin improved the prognostic value of the ABCD2 (age, blood pressure, clinical features of transient ischemic attack, duration of symptoms and presence of diabetes mellitus) score for a recurrent cerebrovascular event in transient ischemic attack. Copeptin seems to be a promising independent biomarker for predicting the functional outcome and all-cause mortality within 3 months or 1 year after acute ischemic stroke, and it could also be a powerful tool for early risk stratification for patients with transient ischemic attack.

Hypertension Research (2017) 40, 465–471; doi:10.1038/hr.2016.165; published online 1 December 2016

Keywords: acute ischemic stroke; copeptin; prognosis; transient ischemic attack

INTRODUCTION

The average annual stroke incidence in seven Chinese cities was 215.6 per 100 000 during the period from 1986 to 1990,¹ and this was almost twice of that in Japan in 1985.² Another study from 1986 to 2000 reported that the incidence of stroke increased to 236.6 per 100 000, with the highest incidence of ~486 per 100 000 in the north and the lowest of 136 per 100 000 in the south.³ Stroke was the second leading cause of mortality in China and one of the leading causes of severe morbidity. Approximately 15–30% of stroke survivors are permanently disabled.⁴ Ischemic stroke was the most common type of stroke, accounting for 60–80% of all types of stroke.⁵ Age-standardized incidence rates of total stroke events and ischemic stroke events grew at a speed of 6.7% and 8.7%, respectively.⁶ The risk of stroke increases after a transient ischemic attack (TIA).⁷ An early estimate of the severity and prognosis of ischemic stroke and TIA is important in the routine practice of medicine. Therefore, reliable and rapid measurable blood biomarkers to predict the outcome after ischemic stroke and TIA are urgently needed and useful in clinical decision making.

Some studies found that arginine vasopressin was elevated in ischemic stroke patients, and the elevation was correlated with stroke severity.⁸ However, the clinical application of arginine vasopressin is limited because of a very short half-time (24 min) *in vivo*,⁹ and it is still unstable in isolated plasma even stored at -20°C .¹⁰ Furthermore, it is largely attached to platelets^{11,12} in plasma. Copeptin, the C-terminal portion of pro-vasopressin, is a neurohypophysis hormone that is a 39-amino acid glycopeptide released in an equimolar ratio to arginine vasopressin. The *ex vivo* stability of copeptin was shown in serum and plasma for at least 7 days at room temperature and 14 days at 4°C .¹³ Copeptin can be easily measured using automated assays with interlaboratory coefficient of variation $<20\%$ for values $>2.25\text{ pmol l}^{-1}$;¹⁴ therefore, it seems to be a sensitive surrogate for arginine vasopressin.¹² ABCD2 (age, blood pressure, clinical features of TIA, duration of symptoms and presence of diabetes mellitus)¹⁵ and ABCD3-I (ABCD2, dual TIA, imaging)⁷ are management models based on clinical data and have been used for predicting stroke recurrence after TIA. However, some studies revealed that the ABCD2

¹Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou, People's Republic of China and ²Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, School of Public Health, Soochow University, Suzhou, People's Republic of China
Correspondence: Dr H Li, Department of Epidemiology, School of Public Health, Medical College of Soochow University, 199 Renai Road, Industrial Park District, Suzhou 215123, People's Republic of China.
E-mail: lihongmei@suda.edu.cn

Received 31 May 2016; revised 25 August 2016; accepted 28 August 2016; published online 1 December 2016

score has limited ability to predict stroke risk after TIA.^{16,17} In addition, the limited availability of urgent MRI prevents the ABCD3-I score from being widely used.⁷ Katan *et al.*¹⁸ found that plasma copeptin provides additional prognostic information beyond the ABCD2 clinical risk score for risk stratification in patients with TIA. Some studies^{18,19} have demonstrated that copeptin independently predicts functional outcome and mortality in patients with ischemic stroke as well as recurrent cerebrovascular events in patients with TIA. However, most studies are conducted in a single center, and conclusions are not consistent. We performed a meta-analysis to assess the role of copeptin for risk stratification after acute ischemic stroke (AIS) and TIA, aiming to provide powerful evidence for clinical practice.

METHODS

This meta-analysis complied with the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines.²⁰

Literature retrieval

Studies were identified by searching electronic databases (PubMed, Medline, EMBASE, Web of Science and Cochrane Central) from inception, reviewing conference proceedings and contacting field experts. The last electronic search was undertaken on 10 December 2015, and search terms included stroke, ischemic stroke, transient ischemic stroke, copeptin, C-terminal pro-vasopressin, mortality, outcome and recurrent cerebrovascular events. Language was limited to English. We also tracked the reference lists of selected articles to identify more studies.

Inclusion and exclusion criteria

Studies that complied with the following criteria were included in this meta-analysis: (1) prospective studies had similar end point criteria and follow-up time of at least 3 months; (2) adult AIS or TIA patients were confirmed according to unified diagnostic criteria; (3) the original data included basic

information such as age, proportion of gender, smoking and hypertension, disease history such as diabetes, coronary heart disease, atrial fibrillation and family stroke history, and copeptin levels within 24 h after stroke or TIA onset; and (4) odds ratios (ORs) or hazard ratios (HRs) with their 95% confidence intervals (CIs) of copeptin were reported or could be obtained by other numerical calculation. If repeated reports from the same population were available, only the one with the largest database was included. Studies with poor quality or providing little information were excluded.

Data extraction

Two review authors independently screened the literature, evaluated the quality and extracted information of each study using a data abstraction form. Disagreements were ruled by a third reviewer. Data extraction of AIS patients included study characteristics (the first author's name, country where the study was performed, publication year, study type, multicenter or not, duration of follow-up, criterion of outcome assessment and number of patients), patient characteristics, baseline copeptin levels the area under receiver operating characteristic curves of copeptin and the National Institutes of Health Stroke Scale (NIHSS), the adjusted OR or HR and 95% CI and possible bias. Data extraction of TIA patients included study characteristics (the first author's name, country where the study was performed, publication year, study type, multicenter or not, duration of follow-up and number of patients) and ABCD2 score, the adjusted OR or HR and 95% CI and patient characteristics.

Quality assessment

The Newcastle–Ottawa Quality assessment scale for cohort studies²¹ was used to evaluate study quality because all the included studies were cohorts. Studies were assessed from three aspects: the selection of patients and controls, the comparability of the groups and the evaluation of the outcome. The total score of each study ranged from 0 to 9, and studies with a score of ≥ 6 were included.

Statistical analysis

The data of AIS patients were statistically analyzed using Stata10 (College Station, TX, USA), and the OR or HR was a statistic. The heterogeneity test between studies was evaluated using the Cochran's Q χ^2 test with the I^2 statistic. An I^2 of 25%, 50% and 75% represent mild, moderate and severe inconsistency, respectively. The P -values of >0.1 and $I^2 < 50\%$ were taken as indicators of the same scale of outcome, and ORs or HRs were pooled using a fixed effect model. $P \leq 0.1$ and $I^2 \geq 50\%$ were taken as indicators of heterogeneity between studies, and ORs or HRs were pooled using a random effects model.²² The source of heterogeneity and sensitivity analysis also needed to be conducted. After a logarithmic transformation of ORs or HRs and 95% CI, pooled ORs or HRs were calculated, and the forest plot was drawn using the metan program. The Z -test was used to assess the pooled ORs or HRs, and $P < 0.05$ was considered significant.

Reporting bias

Evidence of publication bias was assessed statistically and graphically by Begg's rank correlation test²³ and Egger's regression²⁴ examining a scatter plot of the log of the diagnostic relative risk vs. the inverse of the square root of the effective sample size. A graph shaped symmetrical inverted funnel indicates there is no publication bias.

RESULTS

A total of 75 records of AIS and 14 records of TIA were identified through a database search, and all were in English. Of all the records, 80 records were removed, including 54 duplicates, 6 articles with content inconformity and 20 without essential data based on the full-text of articles. Six records of AIS^{4,18,25–28} (1976 patients) were included in the meta-analysis, and 3 records (646 patients) of TIA^{7,19,29} were analyzed (Figure 1).

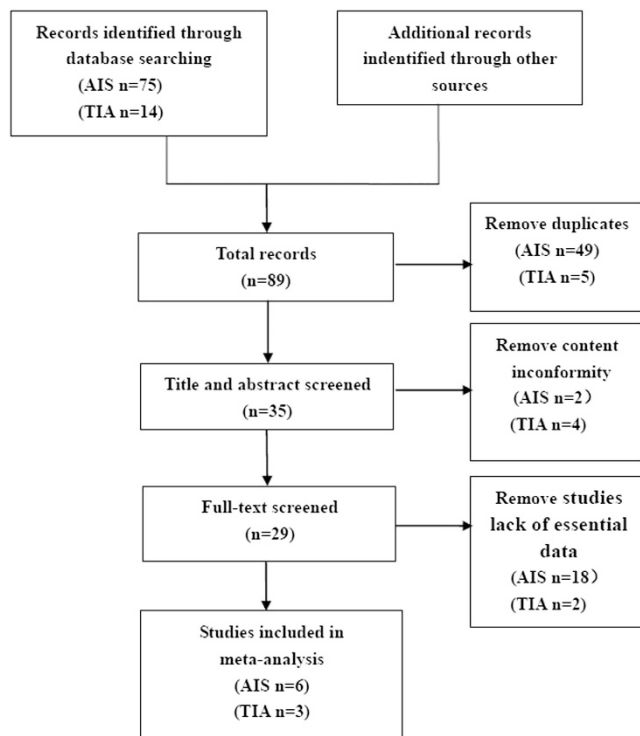


Figure 1 Flowchart of the study selection and exclusion process. AIS, acute ischemic stroke; TIA, transient ischemic attack.

Table 1 Characteristics of included studies and baseline characteristics of included stroke patients

First author (year) and country	Design	Multicenter	Follow-up	Type of patients	Criteria	Outcome criteria	Patients, n	Male, %	Age, years	NIHSS or ABCD2 score on admission	quality
Zhang, ⁴ Changchun, China	Cohort study	No	1 Year	AIS	NIHSS	Good outcome: mRS: 0-2 Poor outcome: mRS: 3-6	245	58.0	73 (64-82)	6 (3-12)	8
Dong, ²⁵ Dalian, China	Cohort study	No	3 Months	AIS	NIHSS	Good outcome: mRS: 0-2 Poor outcome: mRS: 3-6	125	55.2	69 (61-85)	7 (3-12)	8
De Marchis, ²⁶ Germany, USA, Switzerland	Cohort study	Yes	3 Months	AIS	NIHSS	Good outcome: mRS: 0-2 Poor outcome: mRS: 3-6	783	61.9	71 (61-80)	6 (3-13)	8
Katan, ¹⁸ Switzerland	Cohort study	No	3 Months	AIS	NIHSS	Good outcome: mRS: 0-2 Poor outcome: mRS: 3-6	359	59.0	75 (63-83)	5 (2-10)	8
Wang, ²⁷ Xinxiang, China	Cohort study	No	1 Year	AIS	NIHSS	Did not provide	275	50.9	68 (60-79)	10 (6-15)	8
Tu, ²⁸ China	Cohort study	No	3 Months	AIS	NIHSS	Good outcome: mRS: 0-2 Poor outcome: mRS: 3-6	189	61.9	66 (58-75)	7 (5-12)	8
De Marchis, ⁷ Germany, Switzerland	Cohort study	Yes	3 Months	TIA	-	TIA or stroke	302	62.9	69 (59-78)	-	-
Katan, ¹⁹ Switzerland	Cohort study	No	3 Months	TIA	-	TIA or stroke	107	40	71 (60-79)	4 (3-5)	-
Purroy, ²⁹ Spain	Cohort study	No	7 Days, 3 months	TIA	-	Stroke	237	57.4	70.8	5.0 (1.5)	-

Abbreviations: ABCD2, age, blood pressure, clinical features of transient ischemic attack, duration of symptoms and presence of diabetes mellitus; AIS, acute ischemic stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Study characteristics and equality evaluation

Study characteristics, baseline characteristics of included stroke patients, NIHSS or ABCD2 score on admission and quality are shown in Table 1. All studies were prospective cohorts published since 2009 with follow-up ranging from 3 months to 1 year. AIS patients from all centers were confirmed in accordance with the unified WHO (World Health Organization) criteria. Functional outcomes of all studies were obtained at 90 days or 1 year according to the modified Rankin Scale score (scores range from 0 to 6, with higher scores indicating increasing severity). A standard definition of TIA was used to confirm patients in cohort studies, whereas functional outcomes of the three included studies were not completely the same.

A total of 1976 AIS patients were included, and 59% of patients were male. In the 6 studies, the median ages of patients were ~70 years. The distribution of risk factors for common cardiovascular diseases in all AIS patients was as follows: the proportion of smokers was 24.3, 21.5% were diagnosed with atrial fibrillation, 71.6% had a history of hypertension, diabetes patients accounted for 24.4, 24.5% had a family history of stroke and the proportions of patients with hypercholesterolemia and coronary heart disease were 36.7% and 23.0%, respectively. TIA patients were ~70 years old, and 40-60% of them were male.

Copeptin level

The outcomes of AIS patients were assessed based on the modified Rankin Scale score after follow-up blinded to copeptin levels. As shown in Table 2, all studies found that copeptin levels in patients with poor outcomes were significantly greater than those with good outcomes (all $P < 0.001$). Moreover, nonsurvivors had significantly higher baseline copeptin levels than survivors (all $P < 0.001$). In TIA patients, two studies found that patients with recurrent stroke had significantly higher baseline copeptin levels than no-stroke patients with P -values of 0.02 and 0.088. Katan *et al.*¹⁹ found re-event (TIA or Stroke) patients had significantly higher baseline copeptin levels than no re-event patients ($P = 0.0016$). However, De Marchis *et al.*⁷ reported a result with no significance ($P = 0.63$; Table 3).

Predictive value of copeptin, NIHSS and copeptin in combination with NIHSS for AIS outcome and all-cause mortality

NIHSS score (scores range from 0 to 42, and higher scores indicate more serious illness) was performed by one trained medical staff blinded to copeptin levels on admission. In most studies, the area under receiver operating characteristic curves of copeptin was similar to that of the NIHSS score for poor functional outcome and mortality. However, copeptin combined with NIHSS showed a significantly greater discriminatory ability than NIHSS alone ($P < 0.001$) for poor functional outcome and mortality of AIS (Table 4).

Predictive value of copeptin, ABCD2, ABCD3-I and copeptin in combination with ABCD2 or ABCD3-I for stroke

As shown in Table 5, copeptin combined with ABCD2 ($P < 0.05$) or ABCD3-I had a greater discriminatory ability than ABCD2 or ABCD3-I alone for re-stroke after TIA.

Overall effects of copeptin on poor outcome and all-cause mortality of AIS

Five studies^{4,18,25,26,28} reported the association of poor functional outcome with log copeptin. A total of 1787 AIS patients were included in this meta-analysis. As shown in Figure 2, the pooled OR of poor outcome was 2.56 (95% CI: 1.97-3.32) for a 10-fold copeptin increase, and the heterogeneity test results were $\chi^2 = 2.42$, $P = 0.659$, $I^2 = 0.0\%$.

Table 2 Copeptin levels in acute ischemic stroke (AIS) patients on admission onset

Study	Average copeptin (pmol l ⁻¹)	Copeptin in good outcome (pmol l ⁻¹)	Copeptin in poor outcome (pmol l ⁻¹)	Copeptin in survivors (pmol l ⁻¹)	Copeptin in nonsurvivors (pmol l ⁻¹)
Zhang <i>et al.</i> ⁴	12.4 (6.4–22.8)	10.3 (5.6–17.1)	21.9 (7.5–38.1)	10.6 (6.5–19.5)	36.2 (20.5–43.50)
Dong <i>et al.</i> ²⁵	15.8 (10.2–25.8)	12.9 (9.4–21.6)	27.3 (14.9–34.8)	15.1 (12.4–24.6)	32.4 (18.7–38.5)
De Marchis <i>et al.</i> ²⁶	14.2 (5.9–46.5)	9.6 (4.7–25.8)	32.2 (11.8–103.5)	11.7 (5.6–35.1)	58.8 (23.0–141.0)
Katan <i>et al.</i> ¹⁸	11.6 (5.6–21.2)	8.2 (4.5–14.5)	19.4 (8.7–36.6)	9.5 (5.3–19.1)	35.6(19.4–93.7)
Wang <i>et al.</i> ²⁷	16.1 (12.2–24.3)	—	—	14.3 (11.0–17.2)	32.1 (23.2–43.4)
Tu <i>et al.</i> ²⁸	—	12.5 (9.6–16.4)	24.6 (17.5–31.3)	14.6 (9.7–18.6)	28.9 (19.8–32.7)

Table 3 Copeptin levels in transient ischemic attack (TIA) patients on admission onset

Study (country)	Average copeptin (pmol l ⁻¹)	Copeptin in no re-events (pmol l ⁻¹)	Copeptin in re-events (pmol l ⁻¹)	Copeptin in no stroke (pmol l ⁻¹)	Copeptin in stroke (pmol l ⁻¹)
De Marchis <i>et al.</i> , ⁷ Germany, Switzerland	6.1 (2.8–14.6)	6.2 (2.8–14.2)	5.3 (1.9–29.4)	5.8 (2.8–13.7)	24.3 (8.7–63.8)
Katan <i>et al.</i> , ¹⁹ Switzerland	4.6 (2.8–10.1)	4.6 (2.8–7.8)	11.3 (9.1–24.8)	—	—
Purroy <i>et al.</i> , ²⁹ Spain	9.8 (6.5–17.8)	—	—	9.8 (6.4–17.0)	13.9 (8.2–34.1)

Table 4 The AUC for copeptin, NIHSS and copeptin in combination with NIHSS of outcome and all-cause mortality

Study	Outcome			Mortality		
	Copeptin	NIHSS	Copeptin and NIHSS	Copeptin	NIHSS	Copeptin and NIHSS
Zhang <i>et al.</i> ⁴	0.75 (0.70–0.80)	0.63 (0.58–0.69)	0.78 (0.72–0.83)	0.87 (0.82–0.93)	0.84 (0.77–0.90)	0.91 (0.85–0.94)
Dong <i>et al.</i> ²⁵	0.74 (0.62–0.84)	0.73 (0.66–0.78)	0.83 (0.76–0.90)	—	—	—
De Marchis <i>et al.</i> ²⁶	0.71 (0.67–0.75)	0.81 (0.78–0.84)	0.83 (0.80–0.86)	0.75 (0.71–0.80)	0.80 (0.77–0.84)	0.83 (0.79–0.86)
Katan <i>et al.</i> ¹⁸	0.73 (0.67–0.78)	0.75 (0.70–0.80)	0.79 (0.75–0.84)	0.82 (0.76–0.89)	0.85 (0.78–0.91)	0.89 (0.84–0.94)
Wang <i>et al.</i> ²⁷	—	—	—	0.88 (0.85–0.92)	0.90 (0.86–0.93)	0.94 (0.91–0.97)
Tu <i>et al.</i> ²⁸	0.84 (0.77–0.91)	0.73 (0.65–0.80)	—	0.85 (0.81–0.91)	0.66 (0.56–0.77)	—

Abbreviations: AUC, area under receiver operating characteristic curves; NIHSS, National Institutes of Health Stroke Scale.

No evidence of publication bias was found in this meta-analysis according to Begg's rank correlation Test ($P=0.221$) and Egger's regression ($P=0.149$).

Six studies^{4,18,25–28} including 1976 AIS patients reported an association between all-cause mortality and log copeptin. As displayed in Figure 3, the pooled OR from four studies^{18,25,27,28} of all-cause mortality was 4.16 (95% CI: 2.77–6.25) for 10-fold copeptin increase, and the heterogeneity test results were as follows: $\chi^2=0.40$, $P=0.940$, $I^2=0.0\%$. Furthermore, publication bias was not found in this meta-analysis (Begg's test: $P=0.308$; Egger's test: $P=0.317$). Another 2 studies^{4,26} reported HRs based on Cox's proportional hazards regression model, and copeptin level was significantly associated with mortality in AIS patients (HR=2.84; 95% CI: 1.97–4.10; Figure 4). The heterogeneity test results were as follows: $\chi^2=3.60$, $P=0.058$, $I^2=72.2\%$.

Effects of copeptin on recurrent events of TIA

We could not estimate the pooled OR value of copeptin because of different study endpoints of TIA patients. De Marchis *et al.*⁷ reported that after adjusting for the ABCD2 score, a 10-fold increase in copeptin levels was associated with an OR for stroke of 3.39 (95% CI: 1.28–8.96; $P=0.01$) after a 3-month follow-up of TIA patients. Katan *et al.*¹⁹ stated in their study that measurement of plasma copeptin in TIA patients provided additional prognostic information

beyond the ABCD2 score alone. Purroy *et al.*²⁹ found that copeptin levels of ≥ 13.8 pmol l⁻¹ was an independent predictor of SR (stroke recurrence) at the 7-day follow-up in TIA patients.

DISCUSSION

Our findings suggest that copeptin significantly increased in poor functional outcome patients and nonsurvivors, and a high level of copeptin was associated with an increased risk of all-cause death and poor outcome for AIS patients. Overall, the risks of all-cause death and poor outcome increased 316% and 156%, respectively, with a 10-fold copeptin increase. In addition, copeptin combined with the admission NIHSS score improved the accuracy of outcome and mortality prognosis than the NIHSS score alone. These findings supported the hypothesis that copeptin is a novel and independent biomarker for predicting functional outcome and all-cause mortality within 3 months or 1 year after AIS. Furthermore, copeptin improved the prognostic value of the ABCD2 score for a recurrent cerebrovascular event in TIA patients. The mechanisms of copeptin release after patients sustained AIS have already been proposed. First, copeptin is argued to be an immediate and rapid biomarker of stress response because copeptin is a substantial part of the endocrine stress response.³⁰ Second, cerebral edema after stroke is a main reason for copeptin release that develops very early after onset of cerebral ischemia and may be a major factor in early disability after AIS.³¹ Therefore, it is not surprising that the body

Table 5 The AUC for copeptin, ABCD2, ABCD3-I and copeptin in combination with ABCD2 or ABCD3-I of stroke

Study (country)	ABCD2	ABCD3-I	Copeptin	ABCD2 and copeptin	ABCD3-I and copeptin
De Marchis <i>et al.</i> , ⁷ Germany, Switzerland	0.60 (0.46–0.74)	0.61 (0.43–0.79)	0.70 (0.53–0.87)	0.74 (0.60–0.88)	0.75 (0.62–0.89)
Katan <i>et al.</i> , ¹⁹ Switzerland	0.43 (0.29–0.57)	0.61 (0.43–0.79)	0.73 (0.55–0.92)	0.77 (0.60–0.94)	0.75 (0.62–0.89)
Purroy <i>et al.</i> , ²⁹ Spain	0.54 (0.37–0.72)	0.67 (0.48–0.87)	0.63 (0.48–0.78)	—	0.65 (0.45–0.86)

Abbreviations: ABCD2, age, blood pressure, clinical features of transient ischemic attack, duration of symptoms and presence of diabetes mellitus; ABCD3-I, ABCD2, dual TIA, imaging; AUC, area under receiver operating characteristic curves; NIHSS, National Institutes of Health Stroke Scale.

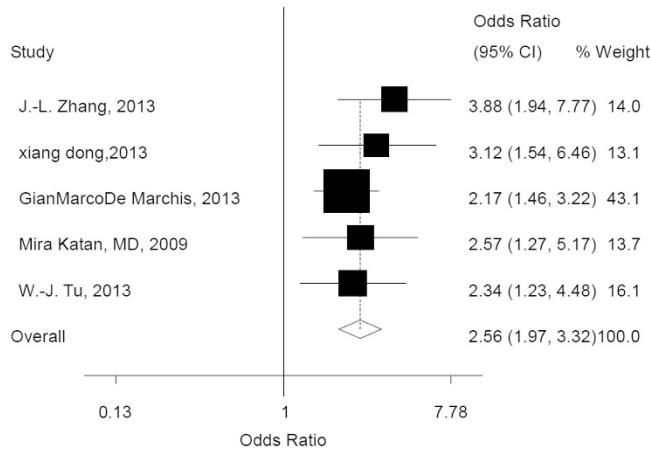


Figure 2 The pooled estimate of odds ratio (OR) with 95% confidence interval (CI) of poor outcome by log copeptin level.

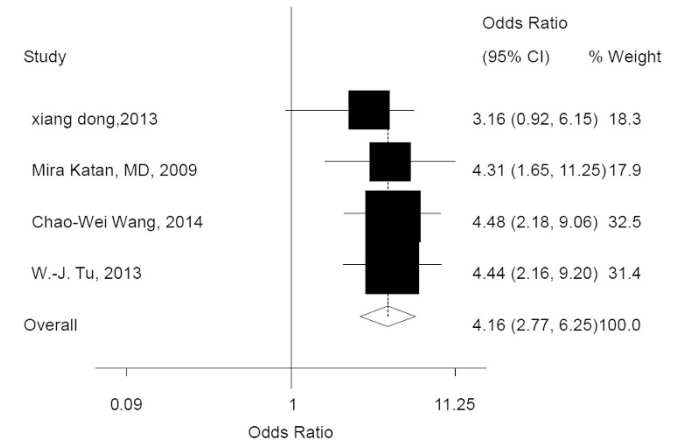


Figure 3 The pooled estimate of odds ratio (OR) with 95% confidence interval (CI) of all-cause mortality by log copeptin level.

responds to acute and life-threatening diseases, including traumatic brain injury,³² hemorrhagic shock³³ or cerebral hemorrhage,³⁴ by a rapid copeptin release. Previous studies have reported the prognostic role of copeptin in various types of cardiovascular disorders. Pozsonyi *et al.*³⁵ identified copeptin as a predictor of mortality (adjusted HR = 2.168, 95% CI: 1.740–2.700 for 1 s.d. increase) among heart failure patients with reduced ejection fraction. A systematic review also suggested that elevation in copeptin carried a similar risk of all-cause mortality to an elevation in troponin (odds ratio 5.84 vs. 6.74, respectively, $P = 0.67$) in acute myocardial infarction³⁶.

Several studies^{4,18,26,27} have suggested that the lower copeptin group had less risk of mortality by dividing AIS patients into three or four groups according to copeptin levels and comparing their survival time using the product-limit method (Kaplan–Meier curve) after follow-up. Increased copeptin can predict complications after AIS within 3 months, and it is also a dependent indicator of mortality,²⁶ poor functional outcome and early neurologic deterioration of cerebral hemorrhage within 1 year.³⁷ Subgroup analysis for patients undergoing brain MRI demonstrated that copeptin levels were positively correlated with stroke lesion size.⁴

The results of TIA patients mentioned above could not be pooled because of different study end points. Purroy *et al.*²⁹ established a cutoff point of 13.8 pmol l⁻¹ for copeptin with a great predictive negative value (97.4%), and they found copeptin levels of ≥ 13.8 pmol l⁻¹ (HR = 3.9; 95% CI: 1.01–14.4; $P = 0.039$) were independent predictors of stroke recurrence at the 7-day follow-up in TIA patients. De Marchis *et al.*^{7,26} reported that in TIA patients, a 10-fold increase in copeptin level was significantly associated with an adjusted OR of 3.39 (95% CI: 1.28–8.96) for ischemic stroke within 3 months, although they did not find a significant association between copeptin and the composite end point (i.e., ischemic stroke or recurrent TIA) within 3 months.

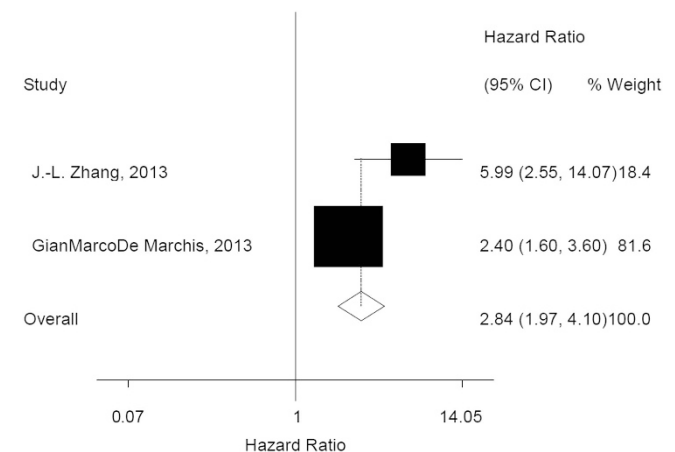


Figure 4 The pooled estimate of hazard ratio (HR) with 95% confidence interval (CI) of all-cause mortality by log copeptin level.

In the past few years, several predictive models for disability and mortality in stroke patients have been generated, validated and evaluated in terms of accuracy, with values of $\sim 80\%$ in most models, and many of the models agree on common predictor variables including age,^{38,39} severity of stroke³⁸ and admission systolic blood pressure.⁴⁰ The NIHSS is a credible, effective and comprehensive standardized stroke scale that is widely used in predicting stroke severity and prognosis. However, the use of NIHSS implies special training, and there remains a notable interobserver variability.⁴¹ In addition, left hemispheric stroke syndromes show greater NIHSS scores than right hemispheric syndromes.⁴² Our study endorsed that the prognostic value of copeptin alone was similar to the NIHSS score, and copeptin combined with NIHSS improved the prognosis value of

NHSS score alone, and this could help clinicians in refining the risk stratification for patients with AIS. Copeptin is a blood marker adding additional information beyond the ABCD2 score for the risk of subsequent stroke.⁷ As shown in Table 5, copeptin combined with ABCD2 significantly improved the prognostic value of ABCD2 scores alone that could be a powerful tool for early risk stratification for patients with TIA.

Bustamante *et al.* considered that the OR or the C-statistic seemed to not adequately represent whether a biomarker added a predictive value over clinical models.⁴³ One way to quantify the predictive probabilities is the net reclassification improvement (NRI) index that evaluates the net number of patients who are correctly reclassified among various groups at risk, when biomarkers are added to the model.⁴³ Because of the absence of relevant data collection, we were not able to test the NRI of copeptin over clinical information in our meta-analysis. However, a large multicenter and prospective study including 783 AIS patients recently published showed that the combination of copeptin with validated clinical variables, both the NIHSS and age, led to a NRI of 11.8% for poor functional outcome and 37.2% for mortality.²⁶ Copeptin combined with ABCD2 score moved 36.4% of TIA patients who experienced a subsequent stroke to a higher risk category and 18.2% to a lower risk category compared with the ABCD2 score alone.⁷ The addition of copeptin to a model including age and vascular risk factors corresponded to a relative increase of NRI of 32% ($P < 0.0001$) in TIA patients.⁴⁴ Therefore, more

similar well-designed cohort studies with sufficient sample sizes should be conducted to test the predictive value of copeptin through NRI analysis. This further research is an important step before clinical use.

In general, our results support copeptin's potential clinical value, although several questions should be answered. First, we used all-cause mortality instead of cause-specific mortality that may have different associations with copeptin because it was arduous to classify death in practice. Second, all included studies lacked repeated and continuous measurements of baseline serum copeptin. In our opinion, future studies of copeptin should address this action to find the best moment for copeptin measurement and its critical values. Even with the above-mentioned limitations, our study also has some strengths that deserve to be mentioned. Our meta-analysis was mainly based on the same categorical studies that were performed with a high level of precision and low heterogeneity. Moreover, all involved studies adequately adjusted for potential confounders, avoiding the likelihood that other confounders influenced the association of copeptin with the outcome and mortality. Therefore, these included prospective studies have provided useful evidence concerning the potential influence of increased copeptin on AIS or TIA patients.

In conclusion, our study suggests that the elevation of plasma copeptin level in stroke patients indicates that they need further evaluation to determine early therapeutic interventions and aggressiveness in care to improve the prognosis. In addition, most current studies focused on the risk of log copeptin, and further trials should determine threshold or normal ranges of copeptin.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are deeply appreciative of the participants in this study and thank all staff for their support and assistance. This study was supported by the National Natural Science Foundation of China (Grant No. 81102189) and a Project

Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

- Cheng XM, Ziegler DK, Lai YH, Li SC, Jiang GX, Du XL, Wang WZ, Wu SP, Bao SG, Bao QJ. Stroke in China, 1986 through 1990. *Stroke* 1995; **26**: 1990–1994.
- Fukuyama K, Kimura Y, Wakugami K, Muratani H. Incidence and long-term prognosis of initial stroke and acute myocardial infarction in Okinawa, Japan. *Hypertens Res* 2000; **23**: 127–135.
- Yang QD, Niu Q, Zhou YH, Liu YH, Xu HW, Gu WP, Tian FF, Xie YQ, Zhang L, Xia J. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. *Cerebrovasc Dis* 2004; **17**: 303–313.
- Zhang JL, Yin CH, Zhang Y, Zhao LB, Fu HJ, Feng JC. Plasma copeptin and long-term outcomes in acute ischemic stroke. *Acta Neurol Scand* 2013; **128**: 372–380.
- Zhang GH, He ML. Association between blood pressure variability and risk of stroke (Chinese). *Chin J Neuromed* 2014; **13**: 749–752.
- Yong H, Foody J, Linong J, Dong Z, Wang Y, Ma L, Meng HJ, Shiff S, Dayi H. A systematic literature review of risk factors for stroke in China. *Cardiol Rev* 2013; **21**: 77–93.
- De Marchis GM, Weck A, Audebert H, Benik S, Foerch C, Buhl D, Schuetz P, Jung S, Seiler M, Morgenthaler NG, Mattle HP, Mueller B, Christ-Crain M, Arnold M, Katan M. Copeptin for the prediction of recurrent cerebrovascular events after transient ischemic attack: results from the CoRisk study. *Stroke* 2014; **45**: 2918–2923.
- Barreca T, Gandolfo C, Corsini G, Del Sette M, Cataldi A, Rolandi E, Franceschini R. Evaluation of the secretory pattern of plasma arginine vasopressin in stroke patients. *Cerebrovasc Dis* 2001; **11**: 113–118.
- Baummann G, Dingman JF. Distribution, blood transport, and degradation of antidiuretic hormone in man. *J Clin Invest* 1976; **57**: 1109–1116.
- Robertson GL, Mahr EA, Athar S, Sinha T. Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *J Clin Invest* 1973; **52**: 2340–2352.
- Preibisz JJ, Sealey JE, Laragh JH, Cody RJ, Weksler BB. Plasma and platelet vasopressin in essential hypertension and congestive heart failure. *Hypertension* 1983; **5** (2 Pt 2): 1129–1138.
- Gunbakmaz O, Celik A, Inanc MT, Duran M, Karakaya E, Tulmac M, Akpek M, Sarli B, Ergin A, Topsisakal R. Copeptin level and copeptin response to percutaneous balloon mitral valvuloplasty in mitral stenosis. *Cardiology* 2011; **120**: 221–226.
- Morgenthaler NG, Struck J, Alonso C, Christ-Crain M, Müller B, Bergmann A. Measurement of the very stable vasopressin precursor copeptin as alternative to vasopressin in the clinical routine. *Exp Clin Endocrinol Diabetes* 2006; **114** (S1): P16_203.
- Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem* 2006; **52**: 112–119.
- Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; **369**: 283–292.
- Purroy F, Jimenez Caballero PE, Gorospe A, Torres MJ, Alvarez-Sabin J, Santamarina E, Martinez-Sanchez P, Canovas D, Freijo MM, Egado JA, Giron JM, Ramirez-Moreno JM, Alonso A, Rodriguez-Campello A, Casado I, Delgado-Medeiros R, Marti-Fabregas J, Fuentes B, Silva Y, Quesada H, Cardona P, Morales A, de la Ossa N, Garcia-Pastor A, Arenillas JF, Segura T, Jimenez C, Masjuan J. Prediction of early stroke recurrence in transient ischemic attack patients from the PROMAPA study: a comparison of prognostic risk scores. *Cerebrovasc Dis* 2012; **33**: 182–189.
- Hill MD. 2012 - Review: a dichotomized ABCD2 score has limited ability to predict stroke risk less than or equal to 90 days after TIA. *ACP J Club* 2013; **158**: 1–1.
- Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C, Bingisser R, Muller K, Meckel S, Gass A, Kappos L, Steck AJ, Engelter ST, Muller B, Christ-Crain M. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. *Ann Neurol* 2009; **66**: 799–808.
- Katan M, Nigro N, Fluri F, Schuetz P, Morgenthaler NG, Jax F, Meckel S, Gass A, Bingisser R, Steck A, Kappos L, Engelter S, Muller B, Christ-Crain M. Stress hormones predict cerebrovascular re-events after transient ischemic attacks. *Neurology* 2011; **76**: 563–566.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336–341.
- Wells G, Shea B, O'Connell D, Peterson D, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.
- Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
- Dong X, Tao DB, Wang YX, Cao H, Xu YS, Wang QY. Plasma copeptin levels in Chinese patients with acute ischemic stroke: a preliminary study. *Neural Sci* 2013; **34**: 1591–1595.

- 26 De Marchis GM, Katan M, Weck A, Fluri F, Foerch C, Findling O, Schuetz P, Buhl D, El-Koussy M, Gensicke H, Seiler M, Morgenthaler N, Mattle HP, Mueller B, Christ-Crain M, Arnold M. Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study. *Neurology* 2013; **80**: 1278–1286.
- 27 Wang CW, Wang JL, Zhang Y, Li Q, Guo SX, Ji SB. Plasma levels of copeptin predict 1-year mortality in patients with acute ischemic stroke. *Neuroreport* 2014; **25**: 1447–1452.
- 28 Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. *J. Neuroendocrinol* 2013; **25**: 771–778.
- 29 Purroy F, Suárez-Luis I, Cambray S, Farré J, Benabdelhak I, Mauri-Capdevila G, Sanahuja J, Quílez A, Begué R, Gil MI, Molina-Seguin J, Torreguitart N. The determination of copeptin levels helps management decisions among transient ischaemic attack patients. *Acta Neurol Scand* 2015; **134**: 140–147.
- 30 Katan M, Morgenthaler N, Widmer I, Puder JJ, König C, Müller B, Christ-Crain M. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. *Neuro Endocrinol Lett* 2008; **29**: 341–346.
- 31 Shuaib A, Xu Wang C, Yang T, Noor R. Effects of nonpeptide V(1) vasopressin receptor antagonist SR-49059 on infarction volume and recovery of function in a focal embolic stroke model. *Stroke* 2002; **33**: 3033–3037.
- 32 Dong X-Q, Yu W-H, Zhang Z-Y, Du Q, Yang D-B, Shen Y-F, Wang H, Zhu Q, Che Z-H, Liu Q-J. Comparison of the performances of copeptin and multiple biomarkers in long-term prognosis of severe traumatic brain injury. *Peptides* 2014; **60**: 13–17.
- 33 Morgenthaler NG, Müller B, Struck J, Bergmann A, Redl H, Christ-Crain M. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. *Shock* 2007; **28**: 219–226.
- 34 Zweifel C, Katan M, Schuetz P, Siegemund M, Morgenthaler NG, Merlo A, Mueller B, Christ-Crain M. Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage. *BMC Neurol* 2010; **10**: 34.
- 35 Pozsonyi Z, Forhecz Z, Gombos T, Karadi I, Janoskuti L, Prohaszka Z. Copeptin (C-terminal pro arginine-vasopressin) is an independent long-term prognostic marker in heart failure with reduced ejection fraction. *Heart Lung Circ* 2015; **24**: 359–367.
- 36 Lipinski MJ, Escarcega RO, D'Ascenzo F, Magalhaes MA, Baker NC, Torguson R, Chen F, Epstein SE, Miro O, Llorens P, Giannitsis E, Lotze U, Lefebvre S, Sebbane M, Cristol JP, Chenevier-Gobeaux C, Meune C, Eggers KM, Charpentier S, Twerenbold R, Mueller C, Biondi-Zoccai G, Waksman R. A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction. *Am J Cardiol* 2014; **113**: 1581–1591.
- 37 Zhang X, Lu XM, Huang LF, Ye H. Copeptin is associated with one-year mortality and functional outcome in patients with acute spontaneous basal ganglia hemorrhage. *Peptides* 2012; **33**: 336–341.
- 38 Ntaios G, Faouzi M, Ferrari J, Lang W, Vemmos K, Michel P. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. *Neurology* 2012; **78**: 1916–1922.
- 39 Strbian D, Seiffge DJ, Breuer L, Numminen H, Michel P, Meretoja A, Coote S, Bordet R, Obach V, Weder B. Validation of the DRAGON score in 12 stroke centers in anterior and posterior circulation. *Stroke* 2013; **44**: 2718–2721.
- 40 Koton S, Eizenberg Y, Tanne D, Grossman E. Trends in admission blood pressure and stroke outcome in patients with acute stroke and transient ischemic attack in a National Acute Stroke registry. *J Hypertens* 2016; **34**: 316–322.
- 41 Josephson SA, Hills NK, Johnston SC. NIH Stroke Scale reliability in ratings from a large sample of clinicians. *Cerebrovasc Dis* 2006; **22**: 389–395.
- 42 Sato S, Toyoda K, Uehara T, Toratani N, Yokota C, Moriwaki H, Naritomi H, Minematsu K. Baseline NIH Stroke Scale Score predicting outcome in anterior and posterior circulation strokes. *Neurology* 2008; **70**: 2371–2377.
- 43 Bustamante A, Garcia-Berrococo T, Lombart V, Simats A, Giral D, Montaner J. Neuroendocrine hormones as prognostic biomarkers in the setting of acute stroke: overcoming the major hurdles. *Expert Rev Neurother* 2014; **14**: 1391–1403.
- 44 Greisenegger S, Segal HC, Burgess AI, Poole DL, Mehta Z, Rothwell PM. Copeptin and long-term risk of recurrent vascular events after transient ischemic attack and ischemic stroke: population-based study. *Stroke* 2015; **46**: 3117–3123.