Copeptin in Intracerebral hemorrhage

Copeptin has been identified as a biomarker of disease severity and is associated with mortality risk in several common diseases. This study sought to determine the association between circulating copeptin level and mortality risk in patients with intracerebral hemorrhage. PubMed, Web of Science, and Wanfang Medicine Database were searched for studies assessing the association between circulating copeptin level and mortality risk in patients with intracerebral hemorrhage. The pooled hazard ratio (HR) of mortality was calculated and presented with 95 % confidence interval (95 % CI). Data from 1332 intracerebral hemorrhage patients were derived from 9 studies. Meta-analysis showed that intracerebral hemorrhage patients with poor prognosis had much higher copeptin levels than those survivors (standardized mean difference = 1.68, 95 % CI 1.26-2.11, P < 0.00001). Meta-analysis of 8 studies with HRs showed that high circulating copeptin level was associated with higher risk of mortality in patients with intracerebral hemorrhage (HR = 2.42, 95 % CI 1.60-3.65, P < 0.0001). Meta-analysis of 6 studies with adjusted HRs showed that high circulating copeptin level was independently associated with higher risk of mortality in patients with intracerebral hemorrhage (HR = 1.67, 95 % CI 1.26-2.22, P = 0.0003). Our study suggests that there is an obvious association between circulating copeptin level and mortality in patients with intracerebral hemorrhage. High circulating copeptin level is independently associated with higher risk of mortality in patients with intracerebral hemorrhage [1)].

Yu et al., measured plasma concentrations of these biomarkers in 118 healthy controls and in 118 acute patients with a comparison analysis for their prediction of 6-month mortality and unfavorable outcome (modified Rankin Scale score>2).

Plasma concentrations of these biomarkers were statistically significantly higher in all patients than in healthy controls, in non-survivors than in survivors and in patients with unfavorable outcome than with favorable outcome. Areas under receiver operating characteristic curves of plasma concentrations of these biomarkers were similar to those of the National Institute of Health Stroke Scale score for prognostic prediction. Plasma copeptin concentration statistically significantly improved the prognostic predictive value of the National Institute of Health Stroke Scale score, but other biomarkers did not.

CONCLUSIONS: Copeptin may help in the prediction of long-term clinical outcomes after intracerebral hemorrhage [2)].

Higher plasma copeptin concentrations have been associated with poor clinical outcomes after intracerebral hemorrhage.

Comparing plasma concentrations of copeptin and other biomarkers like myelin basic protein, glial fibrillary astrocyte protein, S100B, neuron-specific enolase, phosphorylated axonal neurofilament subunit H, tau and ubiquitin carboxyl-terminal hydrolase L1 for analysis of their prognostic prediction in 118 healthy controls and in 118 acute patients with a comparison analysis for their prediction of 6-month mortality and unfavorable outcome (modified Rankin Scale score>2), showed that plasma concentrations of these biomarkers were statistically significantly higher in all patients than in healthy controls, in non-survivors than in survivors and in patients with unfavorable outcome than with favorable outcome. Areas under receiver operating characteristic curves of plasma concentrations of

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Copeptin may help in the prediction of long-term clinical outcomes after intracerebral hemorrhage [3].

Fifty healthy controls and 89 patients with acute spontaneous basal ganglia hemorrhage were recruited in this study. Plasma copeptin concentrations on admission measured by enzyme-linked immunosorbent assay were considerably high in patients than healthy controls. A multivariate analysis identified plasma copeptin level as an independent predictor for 1-year mortality, 1-year unfavorable outcome (modified Rankin Scale score>2) and early neurological deterioration. A receiver operating characteristic curve showed that the predictive value of plasma copeptin concentration was similar to that of National Institutes of Health Stroke Scale scores for long-term poor outcome and early neurological deterioration. However, copeptin did not obviously improve the predictive values of National Institutes of Health Stroke Scale scores. Thus, increased plasma copeptin level is an independent prognostic marker of 1-year mortality, 1-year unfavorable outcome and early neurological deterioration after ICH [4].

Thirty healthy controls and 86 patients with acute ICH were included. Plasma samples were obtained on admission and at days 1, 2, 3, 5, and 7 after ICH. Its concentration was measured by enzyme-linked immunosorbent assay. After ICH, plasma copeptin level in patients increased during the 6-h period immediately, peaked in 24h, decreased gradually thereafter, and was substantially higher than that in healthy controls during the 7-day period. A multivariate analysis showed plasma copeptin level was an independent predictor for 1-week mortality (odds ratio, 1.013; 95% confidence interval (CI), 1.003-1.023; P=0.009) and positively associated with hematoma volume (t=6.616, P<0.001). A receiver operating characteristic curve identified that a baseline plasma copeptin level >577.5pg/mL predicted 1-week mortality with 87.5% sensitivity and 72.2% specificity (area under curve (AUC), 0.873; 95% CI, 0.784-0.935). The AUC of the copeptin concentration was similar to those of Glasgow Coma Scale (GCS) scores and hematoma volumes (P=0.136 and 0.280). However, copeptin did not statistically significantly improve the AUCs of GCS scores and hematoma volumes (P=0.206 and 0.333). Hence, increased plasma copeptin level is associated with hematoma volume and an independent prognostic marker of mortality after ICH [5].

In 40 consecutive patients who were admitted to the hospital within 72 hours after a spontaneous ICH, the plasma copeptin level was measured with a sandwich immunoassay upon admission. The prognostic value of copeptin to predict 30 day mortality and functional outcome after 90 days was assessed. A favorable outcome was defined as a Barthel score above 85 and a score below 3 on the Modified Rankin Scale.

Copeptin correlated positively with hematoma volume ($r = 0.32$, $p < 0.05$) and negatively with the Glasgow Coma Scale (GCS) on admission ($r = -0.35$, $p < 0.05$). Copeptin levels were higher in patients who died within 30 days than in 30-day survivors (179.0 pmol/l (IQR 33.7- 566.0) vs. 12.9 pmol/l (IQR 5.2 - 42.8), $p = 0.003$). Copeptin levels were also higher in patients with an unfavorable functional

outcome at 90 days compared to patients with a favorable outcome (32.4 pmol/l (IQR 9.5-97.8) vs. 11.9 pmol/l (IQR 3.2-19.8), p = 0.04). For the prediction of death, receiver-operating-characteristics analysis revealed an area under the curve (AUC) for copeptin of 0.88 (95%CI 0.75-1.00). The predictive value of the copeptin concentration was thus similar to that of GCS (AUC 0.82 (95%CI 0.59-1.00) p = 0.53), of the ICH Score (AUC 0.89, (95%CI 0.76-1.00), p = 0.94) and the ICH Grading Scale (AUC 0.86 (95%CI 0.69-1.00), p = 0.81).

Copeptin is a new prognostic marker in patients with an ICH. If this finding can be confirmed in larger studies, copeptin might be an additional valuable tool for risk stratification and decision-making in the acute phase of ICH [6].

1)
Zhang R, Liu J, Zhang Y, Liu Q, Li T, Cheng L. Association Between Circulating Copeptin Level and Mortality Risk in Patients with Intracerebral Hemorrhage: a Systemic Review and Meta-Analysis. Mol Neurobiol. 2017 Jan;54(1):169-174. doi: 10.1007/s12035-015-9626-z. Epub 2016 Jan 5. Review. PubMed PMID: 26732599.
2), 3)
Yu WH, Wang WH, Dong XQ, Du Q, Yang DB, Shen YF, Wang H, Zhang ZY, Zhu Q, Che ZH, Liu QJ, Jiang L, Du YF. Prognostic significance of plasma copeptin detection compared with multiple biomarkers in intracerebral hemorrhage. Clin Chim Acta. 2014 Jun 10;433:174-8. doi: 10.1016/j.cca.2014.03.014. Epub 2014 Mar 20. PubMed PMID: 24657424.
4)
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 Feb;33(2):336-41. doi: 10.1016/j.peptides.2012.01.011. Epub 2012 Jan 24. PubMed PMID: 22286033.
5)
Dong XQ, Huang M, Yu WH, Zhang ZY, Zhu Q, Che ZH, Du Q, Wang H. Change in plasma copeptin level after acute spontaneous basal ganglia hemorrhage. Peptides. 2011 Feb;32(2):253-7. doi: 10.1016/j.peptides.2010.11.021. Epub 2010 Nov 30. PubMed PMID: 21126545.
6)
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 May 26;10:34. doi: 10.1186/1471-2377-10-34. PubMed PMID: 20504314; PubMed Central PMCID: PMC2889932.