

Copeptin combined with National Early Warning Score for predicting survival in elderly patients with acute and critical illness

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Research article

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Abstract

Purpose

Copeptin, reflecting vasopressin release, as well as the National Early Warning Score (NEWS), reflecting the severity of critical illness, might qualify for survival prediction in elderly patients with acute and critical illness. This prospective observational study aimed at assessing the predictive value of copeptin combined with NEWS on the prognosis of elderly patients with acute and critical illness.

Methods

We analyzed serum copeptin levels and the NEWS at admission to the emergency department (ED) in a prospective, single-center and observational study comprising 205 elderly patients with acute and critical illness. Death within 30 days after admission to the ED was the primary end point.

Results

The serum copeptin levels and the NEWS in the non-survivor patients group were higher than those in the survivor group [30.35 (14.20, 38.91) vs 17.53 (13.01, 25.20), $P = 0.001$ and 9.0 (7.0–10.0) vs 7.0 (6.0–8.0), $P = 0.001$]. Multivariate logistic regression analysis showed that Copeptin, NEWS and copeptin combined with NEWS were all independent risk factors for 30-day mortality in elderly patients with acute and critical illness. Copeptin, NEWS and copeptin combined with NEWS all performed well in predicting 30-day survival, with area under the ROC curve (AUC) values of 0.766 (95%CI, 0.702–0.822), 0.797 (95%CI, 0.744–0.877) and 0.854 (95%CI, 0.798–0.899) respectively. Using the Z test to compare the areas under the above three curves, copeptin combined with NEWS showed a higher predictive value for 30-day survival ($P < 0.05$). As we calculated, the optimal cut-off value of copeptin and NEWS using the Youden index were 19.78 pg/ml and 8.5 points respectively. Risk stratification analysis showed that patients with both higher copeptin levels and higher NEWS had the highest risk of death.

Conclusions

Copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with acute and critical illness, comparing to either factor individually.

1. Introduction

Vasopressin, also known as arginine vasopressin (AVP) or anti-diuretic hormone (ADH), plays a key role in many physiologic and pathologic processes, such as hypovolemia, hypoxia, acidosis, and changes in plasma osmolality. Copeptin, a 39-aminoacid glycopeptide, is a C-terminal part of the precursor pre-provasopressin (pre-proAVP), which secretes into the circulation from the posterior pituitary gland in

equimolar amounts with vasopressin [1, 2]. Vasopressin, which has a short half-life in blood, is bound to platelets to a great extent and biochemically instable. In contrast, copeptin is stable, easily measured and reliably mirrors biological functionality of vasopressin in both healthy and acutely ill individuals [2–5]. In recent years, many studies have found that copeptin exhibits early diagnosis, severity assessment and survival prognostic abilities in various patient cohorts, including acute coronary syndrome, decompensated heart failure, acute exacerbation of chronic obstructive disease, sepsis and trauma [5–11].

In fact, accurate diagnosis could be delayed in elderly patients with acute and critical illness in emergency department (ED) because of atypical signs and symptoms, which make early evaluation important. Back in 2012, the UK Royal College of Physicians developed the National Early Warning Score (NEWS), which has become a common tool for predicting deterioration in the emergency patients, and commonly used internationally [12, 13]. In this study, we observed whether copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness in ED, which was never reported previously.

2. Materials And Methods

2.1 Subjects and study design

We conducted a prospective observational study of consecutive patients admitted to the ED of a single academic tertiary hospital between January 2017 and November 2018. We included patients aged over 60 at admission to the ED who had NEWS of 5 points or more. The following patients were excluded: patients with immunodeficiency or autoimmune diseases; pregnant women; patients with end-stage renal disease and end-stage liver disease; patients with advanced malignant tumor; family members of patients to give up for further treatment; patients who disagreed to join this study; patients with poor compliance; patients could not be followed up. The study was approved by the ethical review board at Beijing Hospital. A written informed consent was obtained from all participants.

2.2 Baseline assessment and follow-up

On admission to the ED, patients' demographic data, medical/medication history and vital signs were recorded, and the NEWS were calculated. A separate blood tube for copeptin analysis was included in the standardized laboratory panel, routinely collected within few minutes from ED admission. Routine laboratory tests include complete blood count, creatinine, urea nitrogen, aminotransferase, procalcitonin, cardiac troponin I and N-terminal pro-B-type natriuretic peptide.

Follow-up was performed for 30 days or until death, whichever occurred first. Patients alive at day 30 were classified as survivors; all others were classified as non-survivors. No patient was lost to follow-up.

2.3 Copeptin measurements

Venous blood samples were collected at the time of admission, centrifuged, and serum samples were stored at -80°C . Copeptin concentrations were analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Beijing Solarbio Science & Technology Co., Ltd, Beijing, China) in accordance with the manufactures' instructions.

2.4 Statistical analysis

Normally distributed continuous variables were described using mean \pm standard deviation (SD), non-normally distributed continuous variables as median and interquartile range (IQR). Categorical variables were described as frequency or percentage and tested by Chi-squared test. The relation of predictors with survival was investigated using logistic regression models. The prognostic values of copeptin, NEWS and copeptin combined with NEWS on the outcome were evaluated by (Receiver Operating Characteristic) ROC curve which compared by Z-test, and the Youden index was used to identify the optimal cut-off points for risk stratification. The area under the ROC curve (AUC) values were reported with corresponding 95% (confidence intervals) CIs. All tests were 2-tailed; $P \leq 0.05$ was defined as significant. Data were analyzed using statistical softwares (SPSS, Ver. 23.0; MedCalc, Ver. 18.0).

3. Results

3.1 Baseline characteristics

A total of 205 patients were included in the study, 128 patients with cardiovascular critical illness, 39 patients with respiratory critical illness, 26 patients with sepsis (except for severe pneumonia), 12 patients with other critical illness (including gastrointestinal bleeding, rhabdomyolysis, organophosphorus poisoning and anaphylactic shock). Within 30 days after admission, 159 patients (77.6%) alive at day 30 were classified as survivors, 46 patients (22.4%) were classified as non-survivors. Baseline characteristics—serum copeptin levels and the NEWS were compared between survivor group and non-survivor group (Table 1). The serum copeptin levels and the NEWS in the non-survivor group were higher than those in the survivor group (30.35 (14.20, 38.91), 17.53 (13.01, 25.20), $P = 0.001$; 9.0 (7.0–10.0), 7.0 (6.0–8.0), $P = 0.001$)).

Table 1
Clinical and demographic baseline characteristics of the study population

Non-survivors (n = 46)	Survivors (n = 159)	P-value
Age (years)	80.5(73.8–86.0)	79.0(72.3–85.8) 0.051
Male Gender, n (%)	23 (50.0)	91 (57.2) 0.404
cTnl (ng/ml)	0.230(0.028–0.845)	0.049(0.013–0.287) 0.006
NT-proBNP (pg/ml)	12395(3000.9-29136.6)	4819(1364.3-13416.0) 0.001
CRE (umol/L)	110.5(75.5-145.3)	92.5(75.0-149.0) 0.001
ALT (U/L)	30.0(13.0-136.3)	24.0(17.3–45.3) 0.348
AST (U/L)	39.5(17.5–114.0)	23.0(15.0–38.0) 0.016
MBP (mmHg)	68(56–95)	96(80–106) 0.017
PLT ($\times 10^9$ /L)	187(151.5-251.3)	165(140.3-224.3) 0.768
PCT (ng/ml)	3.26(0.85–27.84)	0.31(0.05–3.98) 0.001
NEWS (points)	9.0(7.0–10.0)	7.0(6.0–8.0) 0.001
Copeptin (pg/ml)	30.35(14.20-38.91)	17.53(13.01–25.20) 0.001
Values were given as numbers (%) or median (IQR).		
cTNI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRE, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MBP, mean arterial pressure; PLT, platelet; PCT, procalcitonin.		

3.2 Copeptin, NEWS and copeptin combined with NEWS were all independent risk factors for 30-day mortality in elderly patients with critical illness

Multivariate logistic regression analyses were performed using variables including copeptin, NEWS, MBP, ALT, AST, CRE, cTNI and NT-proBNP, showed that copeptin and NEWS were both independent predictors of 30-day survival in elderly patients with critical illness (Table 2). In further analysis, copeptin combined with NEWS was also an independent predictor of 30-day survival in elderly patients with critical illness.

Table 2
Regression analysis of copeptin and NEWS in elderly patients with critical illness

	B	SE	Wald	P-value	Exp(B)	95%CI Exp(B)	
						Lower	Upper
copeptin	0.047	0.014	11.491	0.001	1.049	1.020	1.078
NEWS	0.569	0.106	28.704	0.001	1.767	1.435	2.175
constant	-6.677	0.925	52.057	0.001	0.001	—	

3.3 Copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness

Copeptin, NEWS and copeptin combined with NEWS all showed a good performance for predicting 30-day survival in elderly patients with critical illness, with the AUC values of 0.766 (95%CI, 0.702–0.822), 0.797 (95%CI, 0.744–0.877) and 0.854 (95%CI, 0.798–0.899) (Fig. 1, Table 3). Using Z-test to compare the above three curves, copeptin combined with NEWS performed a higher predictive value for 30-day survival ($P < 0.05$) (Table 4). The optimal cut-off values of copeptin and NEWS for Risk stratification were calculated by Youden index, were 19.78 pg/ml and 8.5 points, respectively. Risk stratification analyses showed that patients with higher copeptin levels and higher NEWS points had the highest risk of death (Fig. 2). Copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness.

Table 3
The area under the ROC curve of copeptin, NEWS and copeptin combined with NEWS

	AUC	SE	Sensitivity(%)	Specificity(%)	P-value	Cut-off value	95%CI	
							Lower	Upper
copeptin	0.766	0.046	69.6	81.8	0.001	19.78	0.702	0.822
NEWS	0.797	0.040	59.0	90.0	0.002	8.5	0.744	0.877
Copeptin combined with NEWS	0.854	0.033	83.0	72.0	0.001		0.798	0.899

Table 4
The comparison of the AUC of copeptin, NEWS and copeptin combined with NEWS

Index	SE	Z	P-value	95%CI Exp(B)	
				Lower	Upper
copeptin/NEWS	0.059	0.654	0.512	-0.077	0.155
copeptin/combine	0.043	2.024	0.043	0.003	0.173
NEWS/ combine	0.022	2.263	0.024	0.007	0.092

4. Discussion

Hypothalamic–pituitary–adrenal (HPA) axis is an important part of the neuroendocrine system that responds to stressors which disrupt the homeostatic balance [14]. AVP is one of the key hormones of the HPA axis, and copeptin, a peptide consisting of 39 amino acids, is released together with AVP during processing of the precursor peptide [15, 16]. In contrast to the biochemically instable AVP, which has a short half-life in blood and is bound to a great extent to platelets, copeptin is a stable protein in the circulation and reliably mirrors biologically functional vasopressin in both healthy and acutely ill patients [17–20].

Of note, the spectrum of diseases underlying non-specific complaints is extremely broad in the ED. When the diagnosis is unclear, risk stratification and early prognostication become challenging correspondingly, but are still of particularly importance. The Basel Non-specific Complaints (BANC) study [21] was a delayed type cross-sectional diagnostic study with a prospective 30-day follow-up showed that sensitive risk stratification tools were needed to identify whether the patients with nonspecific complaints presenting to the ED had potentially adverse health outcomes.

Copeptin is triggered by many diseases, not limited to one single organ system. Its non-specificity, with respect to a precise diagnostic role, is its strength as a more generalized marker for acute critical illness [22]. In a prospective observational single-center study including 225 critically ill patients admitted to a medical ICU [23], non-survivors within 30 days after ICU admittance showed significantly higher circulating copeptin levels as compared to survivors. Circulating levels of copeptin at ICU admission independently predict 30-day mortality in patients admitted to a medical ICU. In our study, we confirmed the value of copeptin as a short-term prognostic biomarker in elderly patients with critical illness. The serum copeptin levels were significantly higher in non-survivors as compared with survivors. Multivariate logistic regression analysis showed that copeptin was an independent risk factor for 30-day mortality in elderly patients with critical illness. Therefore, copeptin may well be a clinically useful non-specific prognostic marker reflecting disease severity and survival.

Back in 2012, the UK Royal College of Physicians developed the National Early Warning Score (NEWS), a simple and easy to use tool at the bedside, which has become a common tool for predicting deterioration

in acute critical illness patients [12, 13]. NEWS can be used to standardize the assessment of acute-illness severity not only when acute ill patients present to the hospital or as a surveillance system for all patients in hospitals, but potentially also in the pre-hospital assessment [24]. Through its use, clinical staff has a better indication whether a patient is more at risk, which make it possible to timely intervene and stabilize a patient before further deterioration occurs. Thus far the NEWS is the most sensitive Early Warning Score available [25].

A retrospective cohort study by Pirneskoski J et al. [26] including 35800 patients, showed that pre-hospital NEWS score had a good specificity and sensitivity for prediction of death within 1 day of emergency medical services dispatch. Another retrospective observational cohort study [27] with 81,520 consecutive ED patients concluded that the NEWS could predict in-hospital mortality within 24 h, 48 h, 7 days, and 30 days for patients arriving at the ED. In our study, median NEWS points were significantly higher in non-survivors as compared with survivors. Multivariate logistic regression analysis showed that NEWS was independent risk factors for 30-day mortality in elderly patients with critical illness. NEWS showed a good performance for predicting 30-day survival in elderly patients with critical illness, the same with copeptin.

As has been mentioned above, copeptin and NEWS both showed a good performance for predicting 30-day survival in elderly patients with critical illness. However, it was never reported whether copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness comparing to both factors independently.

From our multivariate logistic regression analysis, copeptin combined with NEWS were also an independent risk factor for 30-day mortality in elderly patients with critical illness. In the further study, we concluded that copeptin combined with NEWS performed a much higher predictive value for 30-day survival using the Z test to compare the areas under the ROC curves. Importantly, we also calculated the optimal cut-off value of copeptin and NEWS using the Youden index. Risk stratification analysis showed that the high-risk group with both higher copeptin levels and higher NEWS points had the highest risk of death. Therefore, our study concluded that copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness.

5. Conclusions

Copeptin combined with NEWS have a stronger predictive power on the prognosis of elderly patients with critical illness.

Declarations

Ethics approval and consent to participate

The study protocol was approved by Beijing Hospital Ethics Committee. A written informed legal consent to participate was obtained at the time of enrollment from all the patients, or from a family member if the

patient was unable to provide consent due to his/her medical condition.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FW and X CZ designed the trial and obtained institutional approval and research funding. FW and WA supervised the conduct of the trial and data collection. WA undertook recruitment of patients and managed the data. FW, WA and X CZ provided statistical advice on study design and analyzed the data. FW drafted the manuscript, and all authors contributed substantially to its revision. All authors have read and approved the manuscript.

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References

1. Morgenthaler NG. Copeptin: a biomarker of cardiovascular and renal function. *Congest Heart Fail.* 2010;16(Suppl 1):37–44.
2. Bolignano D, Cabassi A, Fiaccadori E, et al. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clin Chem Lab Med.* 2014;52(10):1447–56.
3. Jochberger S, Morgenthaler NG, Mayr VD, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. *J Clin Endocrinol Metab.* 2006;91(11):4381–6.
4. Morgenthaler NG, Struck J, Alonso C, et al. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem.* 2006;52(1):112–9.

5. Szinnai G, Morgenthaler NG, Berneis K, et al. Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. *J Clin Endocrinol Metab.* 2007;92(10):3973–8.
6. Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. *Circulation.* 2007;115(16):2103–10.
7. Hyun-Jung C, Chul KM, Sun SD, et al. Serum Copeptin Levels Predict Clinical Outcomes After Successful Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction. *Ann Lab Med.* 2018;38(6):538–44.
8. Molvin J, Jujic A, Bachus E, et al. Cardiovascular biomarkers predict post-discharge re-hospitalization risk and mortality among Swedish heart failure patients. *ESC Heart Fail.* 2019;6(5):992–9.
9. Stolz D, Christ-Crain M, Morgenthaler NG, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. *Chest.* 2007;131(4):1058–67.
10. Morgenthaler NG, Müller B, Struck J, et al. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. *Shock.* 2007;28(2):219–26.
11. Zhang ZY, Zhang LX, Dong XQ, et al. Comparison of the performances of copeptin and multiple biomarkers in long-term prognosis of severe traumatic brain injury. *Peptides.* 2014;60:13–7.
12. Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. *Resuscitation.* 2015;90:111–5.
13. Kivipuro M, Tirkkonen J, Kontula T, et al. National early warning score (NEWS) in a Finnish multidisciplinary emergency department and direct vs. late admission to intensive care. *Resuscitation.* 2018;128:164–9.
14. Kumar V, Sharma A. Is neuroimmunomodulation a future therapeutic approach for sepsis? [J]. *Int Immunopharmacol.* 2010;10(1):9–17.
15. Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: Implications for stress adaptation. *Regul Pept.* 2000;96(1–2):23–9.
16. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. *Peptides.* 2005;26(12):2500–4.
17. Morgenthaler NG, Struck J, Jochberger S, et al. Copeptin: clinical use of a new biomarker. *Trends Endocrinol Metab.* 2008;19(2):43–9.
18. Bolignano D, Cabassi A, Fiaccadori E, et al. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clin Chem Lab Med.* 2014;52(10):1447–56.
19. Jochberger S, Morgenthaler NG, Mayr VD, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. *J Clin Endocrinol Metab.* 2006;91(11):4381–6.
20. Szinnai G, Morgenthaler NG, Berneis K, et al. Changes in plasma copeptin, the c-terminal portion of arginine vasopressin during water deprivation and excess in healthy subjects. *J Clin Endocrinol Metab.* 2007;92(10):3973–8.

21. Nemeč M, Koller MT, Nickel CH, et al. Patients presenting to the emergency department with non-specific complaints: the Basel Non-specific Complaints (BANC) study. *Acad Emerg Med.* 2010;17(3):284–92.
22. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. *BMC Med.* 2012;10:7.
23. Krychtiuk KA, Honeder MC, Max L, et al. Copeptin Predicts Mortality in Critically Ill Patients. *Plos One.* 2017;12(1):e0170436.
24. Alam N, Hobbelenk EL, Van Tienhoven AJ, et al. The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. *Resuscitation.* 2014;85(5):587–94.
25. Smith GB, Prytherch DR, Meredith P, et al. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation.* 2013;84(4):465–70.
26. Pirneskoski J, Kuisma M, Olkkola KT, et al. Prehospital National Early Warning Score predicts early mortality. *Acta Anaesthesiol Scand.* 2019;63(5):676–83.
27. Lee SB, Kim DH, Kim T, et al. Triage in Emergency Department Early Warning Score (TREWS) is predicting in-hospital mortality in the emergency department. *Am J Emerg Med.* 2020;38(2):203–10.

Figures

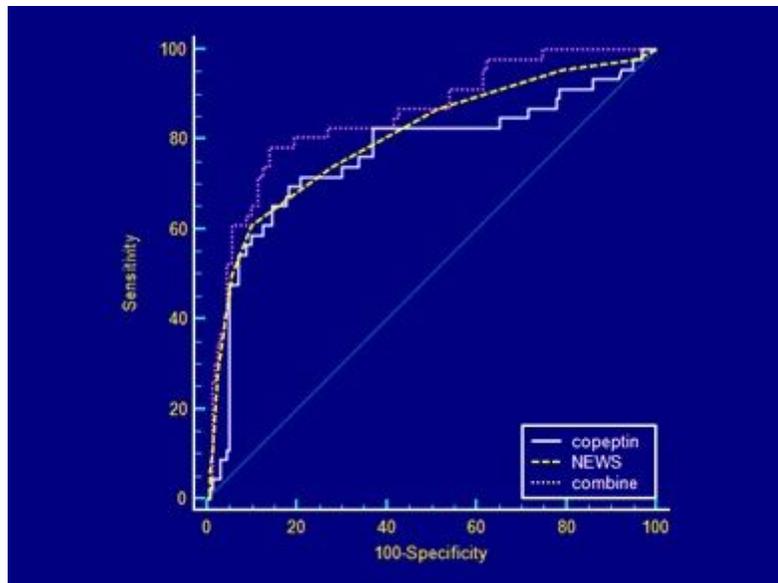


Figure 1

The ROC curve of copeptin, NEWS and copeptin combined with NEWS



Figure 2

Risk stratification according to the optimal cut-off values of copeptin and NEWS