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The Stress Hormone Copeptin as a Prognostic Biomarker in Acute Illness

Raef Malak Botros, Maram Mohamed Maher, Rahma Khaled El Shaer, Hanan Mahmoud Ali*
Department of Internal Medicine & Endocrinology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
***Corresponding author**: Hanan Mahmoud Ali, **Mobile:** (+20)1222521314, **Email**: hanan.mahmoud29@yahoo.com

ABSTRACT

Background: Copeptin has been evaluated as biomarker for several illnesses such as cerebrovascular stroke, heart failure, showing a promising role mainly as a prognostic biomarker. Copeptin levels seem to be strongly related to short, mid, and long-term mortality in patients admitted to hospital showing that copeptin could be a valuable prognostic tool in the most frequent disease entities.

Objective: The aim of the current study was **t**o study the level of copeptin as a prognostic biomarker in acute illness.

Patients and Methods: This study included a total of 64 patients with acute deterioration of their chronic illness as chronic liver diseases (most of them were child C on Child-Pugh score), COPD (admitted with infective exacerbation), cerebrovascular stroke and Decompensate heart failure and 20 controls, attending at emergency room, Ain Shames University Hospital.

Results: Serum copeptin levels have positive correlation with longer duration of hospitalization, the higher the copeptin level the more length of hospital stay ($r= 0.264^{*}$ $p= 0.035$). There was highly statistically significant difference between copeptin level and survival rate, copeptin concentrations were significantly higher in non-survivors than in survivors (p=0.000).The mean of copeptin level among patient who died was 500) pmol/L with range of 70 to 750 pmol/L, while the mean of copeptin level among survivors was 60 pmol/L with range of 20-600 pmol/L.

Conclusion: It could be concluded that copeptin has a role in prognosis of mortality and morbidity of hospitalized patients and high copeptin level significantly associated with a longer hospital stay and a poor outcome of hospital admission.

Keywords: Copeptin, Acute illness, Prognostic biomarker.

INTRODUCTION

'Stress' may be defined as any situation which tends to disturb the equilibrium between a living organism and its environment. In day-to-day life there are many stressful situations such as stress of work pressure, examinations, psychosocial stress, and physical stresses due to trauma, surgery and various medical diseases. Copeptin is located in the C-terminal section of the arginine vasopressin (AVP) precursor (pro-AVP) and consists of 39 amino acid glycopeptides. Evidence demonstrated that copeptin is released from pro-AVP together and equivalent with AVP [(1)]. Why is copeptin a good prognostic tool in a variety of diseases? Vasopressin, together with corticotropin-releasing hormone, is the main secretagogue of the Hypothalamic–pituitary–adrenal axis to produce adrenocorticotropic hormone and cortisol. Serum cortisol levels have been reported to be proportionate to the degree of stress and, by mirroring the individual stress level, to predict outcome in sepsis and pneumonia [(2)]. Importantly, copeptin levels seem to mirror even more subtly moderate levels of stress than cortisol levels [(3)].

The prognostic role of copeptin has been reported in various types of acute illness, including hemorrhagic/septic shock, lower respiratory tract infection, heart failure, and acute myocardial infarction [(4)]; a higher copeptin level has been associated with all of these conditions and also predicts outcomes following heart failure and acute myocardial infarction.

Different studies have suggested that a higher copeptin level is an independent prognostic marker for unfavorable outcome and mortality in patients with acute ischemic stroke and intracranial hemorrhage [(5)].

The aim of the current study was **t**o study the level of copeptin as a prognostic biomarker in acute illness.

PATIENTS AND METHODS

This study included a total of 64 patients with chronic illness and 20 controls of both sexes and their age ranging between 18- 60 years, attending at emergency room, Ain Shames University Hospital.

The included subjects were divided into two groups; **Group I (**admitted to ward**)** consisted of 64 patients with chronic illness as chronic liver diseases, chest infection, cerebrovascular stroke, and heart failure. **Group II (control)** consisted of 20 apparently healthy individuals served as control.

The patients were followed up till their discharge, or transfer, or death. For patients who transferred to ICU, their progress was also monitored till their discharge or death.

All participants were subjected to the following:

Full history taking, full clinical examination, investigations including: serum copeptin level, serum random free cortisol level, complete blood picture (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney function tests, serum

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sodium and potassium. APACHE II score: was calculated for the patients: PaO2 (depending on FiO2),temperature (rectal), mean arterial pressure, pH arterial, heart rate, respiratory rate, Glasgow Coma Scale.

Ethical approval:

The study was done after approval of ethical board of Ain Shams University and consent was taken from each participant in the study.

Statistical analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t- test, chi-square and linear correlation. It is hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables. Linear correlation coefficient was used for detection of correlation between two quantitative variables in one group. Pearson correlation coefficient(r). The significance of the test was determined according to the P value to be: Non-significant (NS) if $P > 0.05$. Significant (Sig) if $P < 0.05$. Highly significant (HS) if $P < 0.001$. Significant relations were graphically represented by Pie and Scatter Graphs.

RESULTS

In the present study there is a highly significance difference between studied groups as regarding serum cortisol level, being higher in-patient group than control group. In control group it was 15.5 nmol/L (10-18.5) with range 6.5-50 while in the patient group it was 20.25 nmol/L (15-42.5) with range (3-60) with (P=0.013) (Table 1).

In the present study there is a highly significance difference between studied groups as regarding serum copeptin level, being higher in patient group than control group. In control group median copeptin level was 8 pmol/L (10-5.5) with range (1.5-12) while it was in the patient group 60 pmol/L (32.5-150) with range (20-750) with (P=0.001) **(Table 1).**

Table (1): Comparison between control group and patients group regarding cortisol level and copeptin level.

		Control group No. = 20	Patients group No. = 64	Test value‡	P-value	Sig.
Cortisol level	Median (IQR) Range	15.5 (10 – 18.5) 6.5 – 50	20.25 (15 – 42.5) 3 – 60	-2.493	0.013	HS
Copeptin level	Median (IQR) Range	8 (10 – 5.5) 1.5 – 12	60 (32.5 – 150) 20 – 750	-3.217	0.001	HS

In the current study shows that the gender did not affect copeptin level so, there was no significance difference. (P=0.856) **(Table 2).**

Table (2): Relation between copeptin level and gender.

		Copeptin level		Test value	P-value	Sig.
		Median (IQR)	Range			
Gender	Females Males	60 (30 –100) 60 (30 –105)	15 – 500 20 – 750	0.182	0.856	NS

In the present study there is a highly significant difference between survivors and non-survivors as regarding copeptin levels (P= 0.000) (64 patients, 56 survivors and 8 non survivors), showed that non-surviving patients had a highly significant copeptin level than surviving patients, Median Copeptin level in survivors 60 pmol/L (30-81) with range 20-600 and copeptin levels in non survivors was 500 pmol/L (125-500) with range of 70-750 **(Table 3).**

Table (3): Relation between the copeptin level and fate of the patients (survivors and non survivors).

		Copeptin level		Test value	P-value	Sig.
		Median (IQR)	Range			
Fate	**Survivors** **Non survivors**	60 (30 – 81) 500 (125 – 500)	20 – 600 70 – 750	3.573	0.000	HS

In the current study there is a highly significant difference between survivors and non survivors in a different diseases for example cerebrovascular stroke, decompensated heart failure, COPD with acute exacerbation (P=0.000, P= 0.003, P=0.001) respectively **(Table 4).**

Table (4): Relation of copeptin level as a predictor for mortality with different diseases.

		Copeptin level Median (IQR)	Test value	P-value	Sig.
Cerebrovascular Stroke	**Survivors** **Non survivors**	47.5 (30 – 60) 500(150– 500)	3.812	0.000	HS
Decompensated heart failure	**Survivors** **Non survivors**	45 (20 – 60) 500(150– 500)	3.017	0.003	HS
COPD with exacerbation	**Survivors** **Non survivors**	40 (30 – 60) 500(150–500)	3.421	0.001	HS

In the present study there is no significant correlation between the fate of the studied patients (survivors, non survivors) and serum cortisol level (P=0.752) **(Table 5).**

Table (5): Relation of cortisol level with fate of the studied patients:

		Cortisol level		Test value	P-value	Sig.
		Median (IQR)	Range			
Fate	**Survivors** **Non survivors**	20.25 (15 – 42.5) 19.8 (15 – 39)	3 – 60 8 – 47	0.316	0.752	NS

In the present study there is a positive correlation between copeptin levels the duration of hospital staying (r 0.264, P =0.035) so, the more copeptin level the more length of hospital stay also there is a positive correlation with WBCs (r 0.631, P=0.000), ESR (r 0.434, P=0.000) and CRP(r 0.279, P=0.025) and a negative correlation between copeptin and Hb (r -0.471, P=0.000), platelets (r -0.476, P=0.000) **(Table 6).**

Table (6): Correlation of copeptin levels with the other studied parameters:

	Copeptin level	
	R	P-value
Hospital stay in days	0.264*	0.035
Total leucocytic count	0.631**	0.000
Hemoglobin	-0.471**	0.000
Platelets	-0.476**	0.000
ESR	0.434**	0.000
CRP	0.279*	0.025

DISCUSSION

In the current study we found that the gender did affect copeptin level as there was no significance difference (P = 0.856), between them. These results were in contrary with **Bhandari *et al.* [6],** who found that the median copeptin levels were significantly higher in the male volunteers compared with the females (P<0.001) These conflicting results may be explained as the study of **Bhandari *et al.* [6]**, was done on healthy individual and ours was done on patients in late stages of the variable diseases with many complications. Also, there are multiple important variables which could influence the serum copeptin levels such as body mass index, serum and urine osmolality, serum sodium and cholesterol levels.

In current study there was a positive correlation between the duration of hospital staying and copeptin levels (r 0.264, P =0.035) so, the more length of hospital stays the more copeptin level. These results were in agreement with **Stolz *et al.*[7]** who found that the higher levels of serum copeptin on hospital admission was associated with a prolonged hospital stay (p = 0.002) and long-term complications (p < 0.0001).

In present study there was highly statistically significant difference between copeptin level and survival rate (p=0.000). The median of copeptin level among patient who died was 500 with range of (70 to 750pmol/L), while the median of copeptin level among survivors 60 pmol/L with range of (20-600 pmol/L). These results were in agreement with **Nickel *et al.* [8]** who found that the serum copeptin concentrations were significantly higher in non-survivors than in survivors. So copeptin was predictive of mortality and elevated levels were associated with an increased mortality.

Also, these result came in line with **Konstantin *et al.* [9]** who found that the patients who died within 30 days after ICU admission had significantly higher serum copeptin levels as

compared to patients that survived (77.6 IQR 30.7–179.3 pmol/L versus 45.6 IQR 19.6–109.6 pmol/L; p = 0.025) respectively.

In present study there was no statistically significant difference between cortisol level and survival rate (p= 0.752). These results was in contrary with **Ramalho *et al.*** [10] who found that the majority (75%) of patients who died had an elevated cortisol level greater than 690 nmol/L, compared to only 17% of patients who survived (P= 0.0001). This contrary may be due to serial cortisol levels show large variations during the day because single cortisol assessments are strongly affected by the acute context of the measurement situation (time of day, and other circumstances such as distress for blood sampling). .In the present study, serum cortisol levels were measured at the time of presentation, that is, at different times during the day, which could limit the predictive accuracy of a single cortisol value on presentation to the hospital. A standardized cortisol value determined at the same time of day in all patients would most probably have had an even higher prognostic accuracy. It is also possible that serial measurements over the course of the disease may add prognostic information and show differences in the values of free cortisol.

CONCLUSION

It could be concluded that copeptin has a role in prognosis of mortality and morbidity of hospitalized patients and high copeptin level significantly associated with a longer hospital stay and a poor outcome of hospital admission.

Conflict of interest:

The authors declare no conflict of interests.

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