The potential of serum copeptin as a prognostic marker of mortality in patients with sepsis, severe sepsis, or septic shock

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Background
The present study sought to investigate the correlation of copeptin with the severity of septic status and to analyze the usefulness of copeptin as a predictor of mortality in patients with sepsis, severe sepsis, and septic shock.
Patients and methods
This prospective observational study was conducted in Alexandria Main University Hospital. The participants were 60 patients who had sepsis, severe sepsis, and septic shock consecutively admitted to the internal medicine ward and the ICU from October 2014 to August 2015. All patients were subjected to full history taking, clinical examination, as well as routine laboratory workup including serum Na^+, serum K^+, and serum lactate and imaging parameters. Serum copeptin was measured on the first or second day of admission. APACHE II scores were assigned on the basis of the most pessimistic clinical and laboratory data obtained during the first 24 h following admission. Patients were followed up for 10 days after admission, and the 10-day mortality rate was calculated. In addition, 20 age-matched and sex-matched healthy participants were enrolled as controls.
Results
Measured serum copeptin was significantly increased in groups I, II, and III in comparison with the control group ($P<0.001$). The value was increasing from sepsis to severe sepsis to septic shock. When patients were followed up for early mortality within 7–10 days, we found that the measured serum copeptin was higher in nonsurvivors than in survivors but without statistically significant difference. It was concluded according to the study of receiver operating characteristic curves that APACHE II score is more sensitive and specific than the serum copeptin when used as a prognostic tool to predict mortality in patients with severe sepsis and septic shock.
Conclusion
Our data demonstrate that serum copeptin levels increase progressively with the severity of sepsis and may be considered an independent predictor of mortality in severe sepsis and septic shock with superiority of APACHE II scoring.

Keywords:
argenine vasopressin, copeptin, mortality, sepsis, septic shock

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Introduction

Severe sepsis and septic shock are the most common causes of death in ICUs, with a mortality rate ranging from 30 to 70%. Most related deaths result from multiple organ dysfunction/failure occurring in advanced stages of septic shock [1]. The rapid progression of sepsis requires correspondingly swift adjustments in therapy, and accurate evaluation of disease severity is therefore important for predicting prognosis, preventing complications, and reducing mortality.

Hemodynamic instability associated with septic shock is characterized by a reduction in total peripheral vascular resistance and hypovolemia, with or without myocardial dysfunction. Numerous pathophysiological mechanisms have been postulated as contributing to cardiovascular failure in patients with severe sepsis and septic shock. Vascular tone loss and the subsequent decrease in arterial blood pressure and tissue perfusion were explained as the result of an altered balance of endogenous vasopressor/vasodilator mediators, qualitative and quantitative downregulation of endogenous vasoconstrictor hormone receptors, and inappropriately low levels of neuroendocrine stress hormones, such as arginine vasopressin (AVP) and cortisol [2,3]. AVP, also termed antidiuretic hormone, is a nonapeptide produced in the

magnocellular neurons of the hypothalamus. It is released into the blood by the neurohypophysis to induce water conservation through the kidneys. Its synthesis is mainly mediated by variations in blood volume or osmotic pressure, thereby contributing to the regulation of osmotic and cardiovascular homeostasis [4].

AVP is derived from a larger 164-amino-acid precursor peptide termed preprovasopressin, consisting of a signal peptide, AVP, neurophysin II, and copeptin. Copeptin (also known as the AVP-associated glycopeptide) is the 39-amino-acid C-terminal portion of the AVP precursor (provasopressin), cosecreted into blood by the hypothalamus in an equimolar ratio to AVP [5]. Copeptin has been shown to be a more stable peptide in the circulation and easier to determine than AVP, whose measurements have limitations because of its short half-life and instability. Therefore, copeptin is used as a useful surrogate for vasopressin measurement [6].

Copeptin concentrations in plasma increase as a response to physiological stress [7] and have been shown to have prognostic value in several disease entities, such as cardiovascular disease [8], head injury [9], pulmonary disease [10], and shock [11], but also in older people with nonspecific complaints [12]. Copeptin therefore could be a marker for adverse outcome in unselected patients admitted to a hospital, and its measurement could optimize both short-term and long-term risk stratification in an emergency department. The aim of the work was to determine the level of serum copeptin in patients with sepsis, severe sepsis, and septic shock and to correlate its level with the severity of sepsis and the outcome.

Patients and methods

This study is an observational prospective study that was conducted in the Internal Medicine ward and the general ICU of Alexandria Main University Hospital, Faculty of Medicine, Alexandria University, from October 2014 to August 2015. It involved 60 patients (all above 20 years of age) divided into the following groups – 20 patients with sepsis, 20 patients with severe sepsis, and 20 patients with septic shock – according to the criteria of the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference and surviving sepsis campaign guidelines [13]. These guidelines defined the following:

(1) Sepsis (documented or suspected infection plus at least one of the following):
   (a) General variables: fever (core temperature>38.3°C), hypothermia (core temperature<36°C), elevated heart rate (>90 beats/min), tachypnea, altered mental status, substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-h period), and hyperglycemia.
   (b) Inflammatory variables: leukocytosis (white-cell count>12 000/mm^3), leukopenia (white-cell count<4000/mm^3), normal white-cell count with more than 10% immature forms, elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range), and elevated plasma procalcitonin (>2 SD above the upper limit of the normal range).
   (c) Hemodynamic variables: arterial hypotension (systolic pressure<90 mmHg; mean arterial pressure<70 mmHg; or decrease in systolic pressure of >40 mmHg in adults or to >2 SD below the lower limit of the normal range for age), elevated mixed venous oxygen saturation (>70%), and elevated cardiac index (>3.5 l/min/m^2 of body-surface area).
   (d) Organ-dysfunction variables: arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen<300), acute oliguria (urine output<0.5 ml/kg/h or 45 ml/h for at least 2 h), increase in creatinine level of >0.5 mg/dl (>44 μmol/l), coagulation abnormalities (international normalized ratio>1.5; or activated partial-thromboplastin time>60 s), paralytic ileus (absence of bowel sounds), thrombocytopenia (platelet count<100 000/mm^3), and hyperbilirubinemia [plasma total bilirubin>4 mg/dl (68 μmol/l)].
   (e) Tissue-perfusion variables: hyperlactatemia (lactate>1 mmol/l), decreased capillary refill, or mottling.
(2) Severe sepsis: (sepsis plus organ dysfunction).
(3) Septic shock: [sepsis plus either hypotension (refractory to intravenous fluids) or hyperlactatemia].

Exclusion criteria were age below 20 years, renal diseases, liver disease, heart failure, hypothalamic–pituitary–adrenal axis dysfunction, and patients on corticosteroid therapy and other types of shock.

All patients were subjected to full history taking, clinical examination with stress on vital signs, as well as routine laboratory workup including serum Na^+, serum K^+, and serum lactate and imaging parameters. Serum copeptin was measured on the first or second day of admission. Commonly used APACHE II scores were

assigned based on the most pessimistic clinical and laboratory data obtained during the first 24 h following admission. Patients were followed up for 10 days after admission, and the 10-day mortality rate was calculated. Clinical and demographic characteristics of all patients were recorded, including age, sex, comorbidities, vital signs, and results of auxiliary examinations. In addition, 20 age-matched and sex-matched healthy subjects with no history or clinical evidence of acute or chronic disease were enrolled as controls.

The ethical committee of Alexandria Faculty of Medicine approved the protocol of this study.

Blood sampling and processing

Samples were obtained from all patients and collected in sterile tubes, and then they were allowed to coagulate for 10–20 min at room temperature, followed by centrifugation for 20 min at ~2000–3000 rpm. Serum had been removed and stored at −20°C until the time of assay.

Copeptin assay

(1) Serum copeptin levels were measured with a new sandwich immunoassay by using Human copeptin ELISA kit in certain steps recommended by the manufacturer Glory Science Co. Ltd (Del Rio, Texas, USA).

Statistical analysis of the data [14]

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0 (IBM, New York, New York, USA) [15]. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level.

Tests

χ^2-test

χ^2-test was used for categorical variables, to compare between different groups.

Fisher's exact or Monte Carlo correction

This test was used as a correction for χ^2 when more than 20% of the cells have expected count less than 5.

Student's t-test

This test was used for normally quantitative variables, to compare between two studied groups.

F-test (analysis of variance)

This test was used for normally quantitative variables, to compare between more than two studied groups, and Post-hoc test (least significant difference) (Tukey) for pairwise comparisons.

Mann–Whitney test

This test was used for abnormally quantitative variables, to compare between two studied groups.

Kruskal–Wallis test

This test was used for abnormally quantitative variables, to compare between more than two studied groups.

Spearman's coefficient

This test was used to correlate between two abnormally quantitative variables.

Receiver operating characteristic curve

It was generated by plotting sensitivity (true positive) on *Y*-axis versus 1−specificity (false positive4) on *X*-axis at different cutoff values. The area under the receiver operating characteristic curve (ROC) curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area of about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests.

Results

The study included 60 patients (sepsis, n=20; severe sepsis, n=20; septic shock, n=20), as well as 20 healthy participants, and classified them into four groups (I, II, III, and IV), respectively.

There was no statistically significant difference between the four groups as regards the sex and age. Early mortality was significantly higher in the septic shock group in comparison with the severe sepsis group.

Measured APACHE II score % was significantly higher in the septic shock group versus the severe sepsis group (P<0.001).

There was no statistically significant difference between the four groups regarding measured serum K^+, but measured serum Na^+ was significantly decreased in the sepsis and severe sepsis groups versus the control group (P<0.001 and <0.006), respectively. There was no significant correlation between measured serum copeptin and measured serum sodium, nor measured serum potassium, in this study.

Measured blood urea and serum creatinine were significantly increased in the severe sepsis and septic shock groups versus control and sepsis groups ($P<0.001$).

Serum lactate was measured in 22 patients with severe sepsis and septic shock. There was a significant association between its levels and the severity of sepsis. The mean value in patients with severe sepsis was 3.82±1.45 mmol/l, whereas in those with septic shock it was 11.27±4.39 mmol/l (Table 1).

We found that the most common sources of infection in the patients depending on clinical examination, radiological studies, and laboratory investigations was respiratory tract infection in the form of pneumonia, which predominated in patients with severe sepsis and septic shock, and acute bronchitis, which predominated in patients with sepsis. In addition, the results of our study revealed that the Gram negative organisms were the most common causative organisms of infection, as Gram negative organisms infected 45% of patients with sepsis (*Escherichia coli* was most common), and 50 and 55% of patients with severe sepsis and septic shock, respectively (*Acinetobacter* was most common).

Table 2 shows the levels of serum copeptin in the studied groups; the levels ranged from 3.0 to 9.80 pmol/l with a mean of 6.67±2.16 pmol/l in the sepsis group, from 4.20 to 23.60 pmol/l with a mean of 10.45±5.15 pmol/l in the severe sepsis group, from 3.50 to 50.0 pmol/l with a mean of 16.84± 11.23 pmol/l in the septic shock group, and from 0.80 to 5.0 pmol/l with a mean of 1.93±1.18 pmol/l in the control group.

Measured serum copeptin was significantly increased in groups I, II, and III in comparison with control ($P<0.001$). The value was increasing from sepsis to severe sepsis to septic shock (Fig. 1).

Twenty-one survivals out of 40 cases of patients with severe sepsis and septic shock were observed within

Table 1 Demographic, clinical, and routine laboratory data of the patients with sepsis, severe sepsis, and septic shock

	Group I	Group II	Group III	Group IV	*P* value
	Sepsis	Severe sepsis	Septic shock	Control	
n	20	20	20	20	
Age (years) (mean±SD)	49.55±19.28	56.80±13.16	58.75±12.09	48.50±9.64	0.052
Male [*n* (%)]	13/20 (65)	9/20 (45)	11/20 (55)	8/20 (40)	0.399
Early Mortality	No	No	6	13	0.027*
Copeptin (pmol/l)	6.67±2.16	10.45±5.15	16.84±11.23	1.93±1.18	<0.001*
APACHE II (%)		58.19±15.75	76.86±10.49		<0.001*
Serum Na^+ (meq/l)	134.20±3.14	132.95±4.55	135.55 ±3.79	138.2±3.08	<0.001*
Serum K^+ (meq/l)	4.01±0.68	4.03±0.72	4.22±0.53	4.04±0.64	0.714
Blood urea (mg/dl)	26.15±10.24	117.50±86.22	125.70±67.16	20.35±5.82	<0.001*
Serum creatinine (mg/dl)	1.05±0.31	2.37±1.42	2.97±1.88	0.93±0.23	<0.001*
Serum lactate (mmol/l)	–	In 11 out of 20 (3.82±1.45)	In 11 out of 20 (3.82±1.45)	–	<0.001*
Gram positive (*n*)	5	8	7	–	
Gram negative (*n*)	9	10	11	–	
Acinetobacter(*n*)	2	4	3	–	
Escherichia coli (*n*)	4	1	2	–	

*Statistically significant at $P\leq0.05$.

Table 2 Serum copeptin in patients with sepsis, severe sepsis, and septic shock

	Group I sepsis (*n*=20)	Group II severe sepsis (*n*=20)	Group III septic shock (*n*=20)	Group IV control (*n*=20)	$^{KW}\chi^2$	*P*
Copeptin (pmol/l)						
Minimum–maximum	3.0–9.80	4.20–23.60	3.50–50.0	0.80–5.0	52.782*	<0.001*
Mean±SD	6.67±2.16	10.45±5.15	16.84±11.23	1.93±1.18		
Median	7.10	9.30	16.25	1.60		
P_{cont}	<0.001*	<0.001*	<0.001*			
Significant difference between groups		P_1=0.004*, P_2<0.001*, P_3=0.050*				

$^{KW}\chi^2$: χ^2 for Kruskal–Wallis test, significant difference between groups was done using Mann–Whitney test. P_{cont}, *P* value for comparing between control and each of the other groups. P_1, *P* value for comparing between sepsis and severe sepsis. P_2, *P* value for comparing between sepsis and septic shock. P_3, *P* value for comparing between severe sepsis and septic shock. *Statistically significant at $P\leq0.05$.

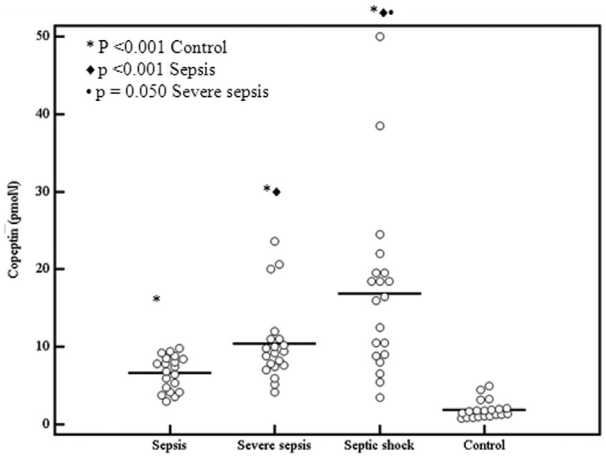
the first 10 days of admission. In survivors, the level of serum copeptin ranged from 4.20 to 24.50 pmol/l with a mean of 11.04±5.66 pmol/l, whereas in nonsurvivors the level of serum copeptin ranged from 3.50 to 50.0 pmol/l with a mean of 16.53±11.46 pmol/l.

The measured serum copeptin was higher in nonsurvivors than in survivors without a statistically significant difference (Table 3 and Fig. 2).

ROC in Fig. 3 and data of analysis in Table 4 show that the area under the curve (AUC) for copeptin to predict ten days' mortality, in patients of severe sepsis and septic shock patients, was 0.660, with a sensitivity of 57.89% and a specificity of 76.19%, when the cutoff point of copeptin serum level was more than 11 pmol/l. There was no significant difference (P=0.083).

However, when APACHE II score was used as a prognostic tool to predict mortality with a cutoff point of more than 78.3%, it was noticed that the AUC of APACH II score was 0.850, which was higher than that of copeptin, with a sensitivity of 63.16% and a specificity of 100.0%. There was a significant difference (P>0.001).

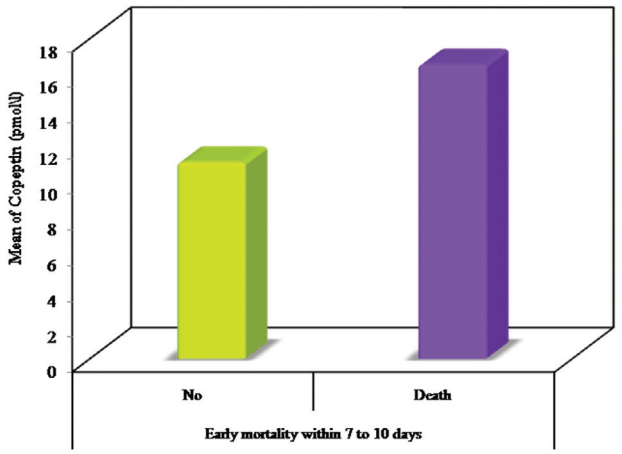
Figure 1



Serum copeptin in patients with sepsis severe sepsis and septic shock.

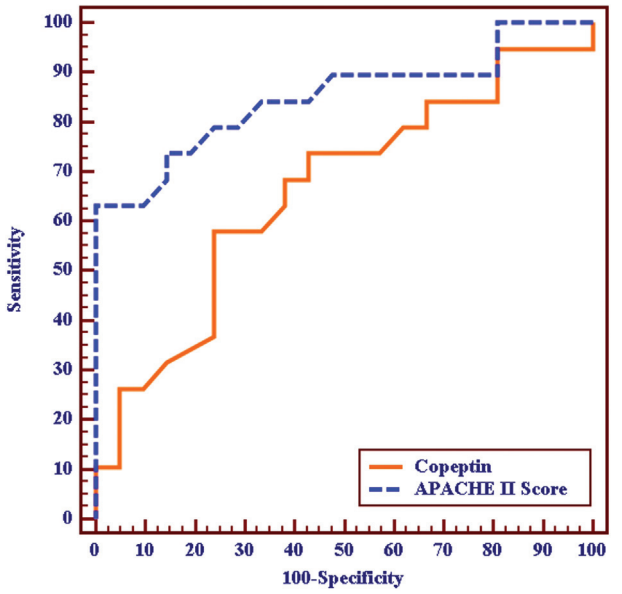
It was concluded according to the study of ROC curves that APACHE II score is more sensitive and specific than the serum copeptin level, with a specificity of 100.0%, and of more powerful positive predictive value,

Figure 2



Relation between early mortality within 7–10 days with copeptin in severe sepsis and septic shock groups.

Figure 3



Receiver operating characteristic curves for copeptin and APACHE II score to predict mortality in patients with severe sepsis and septic shock.

Table 3 Relation between early mortality within 7–10 days with copeptin in severe sepsis and septic shock groups

	Early mortality within 7–10 days		*Z*	*P*
	No (*n*=21)	Death (*n*=19)		
Copeptin (pmol/l)				
Min.imum–maximum	4.20–24.50	3.50–50.0	1.734	0.083
Mean±SD	11.04±5.66	16.53±11.46		
Median	9.20	12.50		

Z, *Z* for Mann–Whitney test.

Table 4 Agreement (sensitivity, specificity, and accuracy) for copeptin and APACHE II score (in severe sepsis and septic shock)

	Cutoff	AUC	*P*	Sensitivity	Specificity	PPV	NPV
Copeptin	>11	0.660	0.083	57.89	76.19	68.7	66.7
APACHE II score	>78.3	0.850*	<0.001*	63.16	100.00	100.0	75.0

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value. *Statistically significant at $P \leq 0.05$.

when used as a prognostic tool to predict mortality in patients with severe sepsis and septic shock. Therefore, there was no significant effect on AUCs of adding copeptin to the fully adjusted model of mortality for the entire observation period.

Discussion

Regarding the demographic data, in our study there was no significant association between the age and sex and the severity of sepsis, but regarding comorbid disease there was a significant association between patients with diabetes and hypertension and the severity of sepsis.

Zhang *et al*. [16] performed a study on 461 patients that metal of the specified inclusion criteria of severe sepsis. They found that there were no significant differences in age, sex, and correlative diseases among patients (which included sterile systemic inflammatory response system, sepsis, severe sepsis, septic shock groups) and healthy blood donors (control group).

In the current study, serum copeptin was increased in patients with sepsis, severe sepsis, and septic shock, with significant elevation from sepsis to severe sepsis to septic shock, and thus copeptin concentrations provide an accurate reflection of sepsis severity.

In the acute stage of sepsis, there is an increase in vasopressin levels by 20–200-fold to supraphysiologic levels; this response is induced by viral and bacterial products such as bacterial lipopolysaccharides, which cause release of acute phase cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α. Furthermore, endotoxin stimulates the release of vasopressin into hypophyseal portal blood [6]. Another cause that increases vasopressin levels is hypotension, which is caused by decreased cardiac output [17].

AVP secretion can be induced by several other factors such as acidosis, pain, hypoxia, increased serum osmolarity, or neuroendocrine stress, all of which are more likely to occur in patients with severe sepsis and septic shock than in those with infection but no systemic inflammation [18].

AVP secretion, in septic shock, can be more than 30-fold higher than in healthy individuals and more than six-fold higher than in patients with systemic inflammation not related to infection. Septic shock is characterized by hypovolemia, decreased vascular resistance with or without myocardial dysfunction, and the most potent stimulus for release and synthesis of vasopressin, which is hypotension. This early increase in vasopressin release is modulated by nitric oxide, which is induced by activation of nitric oxide synthase [19].

Sharshar *et al*. [20] observed a negative correlation between AVP plasma concentrations and the time after shock onset. Almost all of their patients presented with elevated AVP plasma concentration during the first 36 h of septic shock.

In addition, the presence of certain conditions and complications that may occur in septic shock such as ventilator-associated pneumonia, a major complication in critically ill patients undergoing mechanical ventilation, causes significant elevation of copeptin [21].

After the initial increase of vasopressin levels in septic shock, vasopressin levels then decline rapidly. Many mechanisms were proposed for a possible sepsis-associated dysfunction of the AVP system including autonomic dysfunction of the afferent pathways and inadequate AVP production with consequent depletion of neurohypophyseal stores [22]. This is mostly caused by persistent systemic inflammation, which may result in tissue hypoxia, cell damage, and downregulation of vasopressin receptors. Furthermore, inhibitory effects of high plasma catecholamine concentrations and analgosedative drugs on AVP secretion have been observed [23]. In addition, it was found that fluid resuscitation and a mean central venous pressure of 10 +4 mmHg may have abolished stimulation of AVP secretion [24]. Patients who had received exogenous AVP or hydrocortisone during the management exhibited more pronounced decrease in copeptin levels during the observation period than patients without such a therapy [25].

In this present study, the level of serum copeptin was higher in septic shock patients than the level in patients with sepsis and severe sepsis, as most samples that had

been collected from septic shock patients were in the early days of admission to ICU and after the diagnosis of septic shock had been established. The exclusion criteria were patients receiving hydrocortisone or exogenous vasopressin during the management. So our patients were treated only by fluid resuscitation and intravenous vasopressors, and most of our patient were elderly and had multiple organ dysfunction with very grave laboratory variables, taken together, these may explain the elevation of serum copeptin in the early stage of septic shock.

When patients had been followed up for early mortality within the first 10 days of admission, it was noticed that there was a positive correlation between severity of sepsis and mortality; the nonsurvivors in patients with severe sepsis were six out of 20 cases, whereas in patients with septic shock the nonsurvivors were 13 out of 20 cases.

In addition, serum copeptin was higher in nonsurvivors among patients with severe sepsis and septic shock, but without statistical significance. In addition, copeptin concentration could independently predict the survival of critically ill patients with severe sepsis and septic shock but with a sensitivity and a specificity that is lower than those for APACHE II.

Our study was in agreement with many studies. Morgenthaler *et al*. [26] reported that patients with sepsis had significantly higher copeptin levels when compared with the healthy control group and that serum copeptin levels checked at the time of coming to the hospital increased in direct proportion to the seriousness of the infection. When the patients who died were compared with those who survived in the patient group, the patients who died had significantly higher serum copeptin levels.

In another prospective study [27] that included patients with sepsis who were treated in the ICU of Dalian Medical University First Hospital, in China, between May 2012 and December 2012, serum copeptin concentration could independently predict the survival of critically ill patients with hemorrhagic and septic shock. Plasma copeptin concentrations increased significantly with higher APACHE II scores in that study, reflecting the severity of sepsis. This study showed that plasma copeptin could be used to evaluate the severity of sepsis. In addition, the finding that elevated copeptin concentration at 72 h after admission was associated with increased mortality suggests that this parameter could be used to predict sepsis-related patient death.

Hyponatremia is the most common fluid and electrolyte disturbance occurring in asymptomatic and critically ill patients. It is frequently under-recognized and under-treated and is often associated with increased morbidity and mortality [28]. Hyponatremia may result from increased vasopressin release, thus resulting in increased water retention. Copeptin, as a surrogate marker of the unstable AVP, may also reflect changes in volume regulation and osmoregulation and thus it is considered as one of the important diagnostic markers in the approach to hyponatremia. In the present study, there was no significant correlation between measured serum copeptin and measured serum sodium; it may be because most of our patients had near normal serum sodium levels or underwent electrolytes correction during the management.

Conclusion

Copeptin constitutes a novel and promising biomarker during the acute phase for disease severity and prognosis in critically ill patients. Its concentration can distinguish between sepsis and other causes of critical illness.

Copeptin concentrations provide an accurate reflection of sepsis severity and can independently predict the survival of critically ill patients with severe sepsis and septic shock.

Future studies are needed to delineate whether copeptin measurements are cost-effective, add significantly to clinical judgment, and can be used for stratification of therapy, particularly early management of sepsis.

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Conflicts of interest

There are no conflicts of interest.

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