Study of plasma copeptin level as a prognostic marker in respiratory failure patients admitted in the ICU at Benha University Hospital

Mahmoud M. Al Salahy[a], Mohammad A. Elmahdy[a], Tahany M. Gouda[a], Khaled M. Belal[b], Shiemaa M. Elnahas[a]

Background Arginine vasopressin (AVP), produced by hypothalamic neurons, is released during stress following different stimuli such as hypotension, hypoxia, hyperosmolarity, acidosis, and infections. Measurement of AVP levels has limitations because of its short half-life and instability. Copeptin, the carboxy-terminal part of the precursor (prepro-AVP), is a more stable peptide and mirrors AVP concentrations.

Aim The aim of this work was to study the usefulness of plasma copeptin as a predictor of prognosis and outcome of respiratory failure patients admitted in the ICU.

Patients and methods This prospective study was carried out on 45 patients (38 patients admitted at Benha University Hospital ICU and Chest Department and seven healthy patients). They were classified into three groups: group A (ICU patients) comprised 30 patients admitted with respiratory failure due to different chest diseases; group B (in-patients) comprised eight patients selected from those hospitalized at Chest Department because of respiratory failure and with no need for ICU admission as a positive control group; and group C comprised seven healthy patients included as a negative control group. All patients were submitted to full clinical history and physical examination at ICU admission, as well as available preadmission clinical data, pulmonary function tests, chest radiography if done, arterial blood gases, ECG, and clinical lab data; blood samples were taken and plasma was separated and copeptin level was measured by sandwich immunoluminometric assay.

Results There was a statistically significant difference among studied groups as regards plasma copeptin level, which was higher in ICU patients (group A) than in in-patients (group B) and healthy control patients (group C) ($P<0.001$). There was a statistically significant correlation between copeptin level and both Glasgow Coma Scale and Acute Physiology and Chronic Health Evaluation II (APACHE II) score ($P<0.001$). The relation with Glasgow Coma Scale was negative, whereas that with Acute Physiology and Chronic Health Evaluation II score was positive. There was a statistically significant positive correlation between mean copeptin level and patients' outcome, as its level was markedly higher in nonsurvivors (80.6+31.6) than in survivors (30.5+17.3) ($P<0.001$), substantiating it as a prognostic marker in critically ill patients. In ICU patients copeptin levels less than 55 pg/ml predict good prognosis and survival among ICU patients, with a sensitivity of 88.2% and a specificity of 84.6%.

Conclusion Elevated plasma copeptin levels reflect disease severity and predict short-term mortality. Copeptin concentrations are strongly related to hypoxia, as they increase markedly with low blood oxygen concentration. Elevated plasma copeptin levels predict long hospital and ICU stay. Plasma copeptin levels increased progressively with the development of complications in ICU patients.

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[a]Departments of Chest Diseases, [b]Clinical and Chemical Pathology, Benha University, Benha, Egypt

Correspondence to Tahany Mahmoud Ali Gouda, MD, Benha Elvilal Elzohor Blocks Elbanse, 12345, Egypt. Tel: +20 100 644 0624;
e-mail: ice_stifness@yahoo.com

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Introduction

The severity of a disease influences the consumption of costly healthcare resources including the need for intensive care admission and suitability for discharge. Therefore, there is a potential need for rapidly available biomarkers to predict the disease severity and finally outcome [1].

Arginine vasopressin (AVP) produced by hypothalamic neurons is stored and released from the posterior pituitary gland following different stimuli such as hypotension, hypoxia, hyperosmolarity, acidosis, and infections, and it is claimed to be a sensitive marker in these situations [2].

AVP has vasoconstrictor and antidiuretic properties and has the potency to restore vascular tone in vasodilatory hypotension [3]. It is derived from a larger precursor (prepro-AVP) along with two other peptides of unknown function – neurophysin II and copeptin, the carboxy-terminal part of the precursor [4].

Measurement of AVP levels has limitations because of its short half-life and instability. Copeptin is a more stable peptide, and its concentrations mirror that of

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AVP in individual stress response. In critically ill patients, copeptin values increased significantly with the severity of the disease [5].

Copeptin levels were found to be elevated in many conditions needing ICU admission such as septic shock and respiratory failure [6].In addition, it is found to be elevated in ICU patients when complications develop – e.g. ventilator-associated pneumonia [7].

Respiratory failure is the most common indication for ICU admission, and in many cases outcome is poor. Therefore, using copeptin as a prognostic marker in these patients can improve their outcome [8].

Aim

The aim was to study the usefulness of plasma copeptin as a predictor of prognosis and outcome of respiratory failure patients admitted in the ICU.

Patients and methods

Patients

This prospective study was carried out on 45 patients at Benha University Hospital ICU and Chest Department; they were classified into three groups as follows:

(1) Group A: this group comprised 30 patients admitted at the ICU with respiratory failure owing to different chest diseases.
(2) Group B: this group comprised eight patients selected from those hospitalized at the Chest Department owing to respiratory failure and improved on conservative treatment as a positive control group.
(3) Group C: this group comprised seven apparently healthy patients selected from patients' relatives as a negative control group.

Acute respiratory failure diagnosed according to Campbell [9]

The diagnosis of acute respiratory failure was made by the presence of clinical evidence suggestive of respiratory muscle fatigue (respiratory rate more than 25 breaths/min, use of accessory muscles of respiration and/or abdominal paradoxical movements) and arterial blood gases abnormalities: PaO_2 less than 8 kPa (60 mmHg) with or without a $PaCO_2$ greater than 6.5 kPa (49 mmHg) breathing room air at rest at sea level.

(1) Group A: according to the outcome of ICU patients, they were further divided into two groups:
   (a) Survivor group: 17 patients (15 male and two female with an age range between 40 and 90 years).
   In all, 14 patients were diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2016), two patients were diagnosed with acute exacerbation of bronchial asthma according to Global Initiative for Asthma (GINA) (2006), and one patient was diagnosed with community-acquired pneumonia according to American Thoracic Society (ATS) (2007).
   A total of nine patients were associated with comorbidities: five patients with hypertension, two patients with diabetes mellitus, one patient with both, and one patient with Parkinsonism.
   In all, nine patients had noninvasive ventilation on the first day of ICU admission [three of them were successful and six failed, where they had invasive mechanical ventilation (IMV) later] and eight patients had IMV on the first day of ICU admission.
   ICU complications in this group occurred in four patients: they vary to include nutritional insufficiency, renal impairment, ventilator-associated pneumonia, ventilator-associated tracheobronchitis, difficult weaning, and bed sores.
   The period of ICU stay in this group of patients ranged between 1 and 14 days. The period of hospital stay after discharge from ICU ranged between 3 and 18 days.
   (b) Nonsurvivor group: this group comprised 13 patients (eight male and five female with an age range between 40 and 80 years).
   A total of nine patients were diagnosed with AECOPD according to GOLD (2016), one patient with community-acquired pneumonia according to ATS (2007), one patient with aspiration pneumonia, one patient with interstitial pulmonary fibrosis according to ATS (2002), and one patient with malignant pleural effusion.
   Nine patients were associated with comorbidities: three patients with hypertension, three patients with diabetes mellitus, one patient with both, one patient with diabetes mellitus and hepatitis C, and one patient with brain tumor.

All patients had IMV in the first day, four of them were shifted to IMV because of failure of noninvasive ventilation.

Regarding the development of ICU complication in this group, nine patients of the 13 patients developed complications that vary to include the following: electrolyte imbalance, gastrointestinal bleeding, nutritional insufficiency, liver function impairment, renal impairment, ventilator-associated pneumonia, deep venous thrombosis, myocardial infarction, and bed sores.

The period of ICU stay in this group of patients ranged between 1 and 28 days.

(2) Group B: this group comprised eight hospitalized patients at the Chest Department because of respiratory failure and improved on conservative treatment. This group included four men and four women with the range of age between 44 and 70 years.

There were five patients diagnosed with AECOPD according to GOLD (2016), two patients were diagnosed with acute exacerbation of bronchial asthma according to GINA (2006), and one patient was diagnosed with community-acquired pneumonia according to ATS (2007).

Regarding comorbidities, four patients had comorbidities: three patients had hypertension and one patient had diabetes mellitus.

No complications developed at their hospital stay.

(3) Group C (negative controls): this group comprised seven apparently healthy patients, three men and four women, with an age range between 25 and 76 years.

The following patients were excluded:

(a) Pregnant women.
(b) Patients who died or those who were discharged within 24 h after admission to the ICU.
(c) Patients with renal insufficiency known before admission.
(d) Patients with cardiovascular disease known before admission.
(e) Patients already receiving an exogenous AVP infusion.

Patients had been followed up in the ICU until the end points which are:

(1) Patient's condition improved and was discharged to the Chest Department.
(2) Patient died.
(3) After 1 month on the ventilator.

Methods

On admission to ICU, the following tests were carried out for all patients:

(1) Full medical history from the patient (if possible) or his relatives, including age, occupation, special habits of medical importance (smoking, drugs), previous ICU admission, history of previous intubation and/or ventilatory support, comorbidities (hypertension, diabetes, hepatic, and so on), sites of medical advice the patient had sought, and possible investigations they had done before ICU admission.
(2) Full clinical examination, both general and local, was also performed.
(3) Arterial blood gases analysis
(4) Radiology: plain chest X ray (postero-anterior or antero-posterior view) and computed tomography of chest if done according to the circumstances.
(5) Pulmonary function test if the patient is able to do it.
(6) Other laboratory investigations:
(a) Serum electrolytes (Na, K).
(b) Complete blood count.
(c) Liver function tests (aspartate aminotransferase, total bilirubin, and serum albumin).
(d) Kidney function tests (serum creatinine and blood urea).
(7) ECG

Assessment of Acute Physiology and Chronic Health Evaluation II (APACHE II) Score within 24 h of admission [10]

(1) Acute physiology score: the largest component of the APACHE II score is a severity-of-disease classification system that is derived from 12 clinical measurements that are obtained within 24 h after admission to the ICU [except Glasgow Coma Scale (GCS) which was assessed on admission]: an integer score from 0 to 71 is calculated based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The required data were collected to generate the acute physiology score component of the APACHE II score; if a variable has not been measured, it is assigned 0 points. All variables were measured in this study.
(2) Age adjustment: different points (from 1 to 6) were added for patients older than 44 years of age as follows: 45–54 years=two points, 55–64 years=three points, 65–74 years=five points, up to75 years=six points.

(3) Chronic health adjustment: an additional five points were added for all patients included in this study for chronic health adjustment.

The GCS was developed by Teasdale *et al.* [11] as a method for assessing depth and duration of impaired consciousness and is one of the most widespread clinical scores in medicine. The GCS has become a standard method of assessing unconsciousness and coma in the setting of trauma and traumatic brain injury. The importance of the GCS in the ICU, with the exception of neurointensive care, is probably its inclusion in more complex scoring systems as in the APACHE II score [12].

Measurement of copeptin levels

Approximately 2.5–5 ml of blood samples were taken from patients in test tubes containing EDTA as an anticoagulant, centrifugation of samples for 15 min at 1000 *g* within 30 min of collection was done, and samples were stored in aliquots at −20°C to −80°C until the time of measurement.

For determination of copeptin plasma concentration samples, a new sandwich immunoluminometric assay was used. Briefly, the EDTA plasma samples were incubated with antibodies diluted in 10–20 ml of standard assay buffer under agitation (170–300 rpm) at room temperature (18–24°C) for 2 h. The polyclonal antibodies used were directed against the amino acid sequence 132–164 of prepro-vasopressin. The test tubes were then washed four times with 1 ml of LUMI test wash solution and bound chemoluminescence was measured for 1 s per tube with a LB952T Luminometer (Berthold, Wildbad, Germany).

The analytical detection limit of the assay is 1.7 pmol/l and inter-laboratory coefficient of variation is less than 20% for values higher than 2.25 pmol/l.

Samples were taken from all patients on admission to hospital.

Statistical analysis

The collected data were tabulated and analyzed using statistical package for the social sciences version 16 software (SPSS; SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages, whereas quantitative data were expressed as mean±SD, median, interquartile range (IQR), and range. Fisher's exact test, Student's *t*-test, Mann–Whitney *U*-test, analysis of variance, Krauskal–Wallis test, and Spearman's correlation coefficient (ρ) were used as tests of significance. Significant analysis of variance and Krauskal–Wallis were followed by Bonferroni and Bonferroni-adjusted Mann–Whitney *U*-test, respectively, to detect significant pairs. Receiver operating characteristic (ROC) curve was used to determine cutoff value of Copeptin with optimum sensitivity and specificity in prediction of good prognosis among ICU patients with respiratory failure. The accepted level of significance in this work was stated at 0.05 ($P<0.05$ was considered significant, $P>0.05$ was insignificant, $P<0.001$ was highly significant).

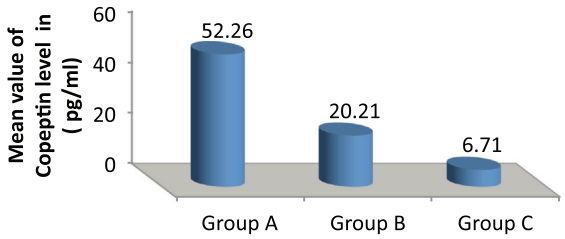
Results

ICU patients (Group A) were 30 patients and in-patient group with pulmonary diseases)Group B (were eight, whereas healthy control patients)Group C(were seven.

In all, 66.7% of all studied patients were male, whereas 33.7% were female, with an age range between 25 and 90 years.

There were statistically significant differences among studied groups as regards serum copeptin level, which was higher in ICU patients (group A) than in in-patients (group B) and healthy control patients (group C) ($P<0.001$); in addition, it was higher in in-patients than in healthy control patients ($P<0.001$) (Table 1 and Fig. 1).

Figure 1



Comparison of the studied groups regarding serum copeptin level

Table 1 Comparison of the studied groups regarding serum copeptin level (pg/ml)

Groups	Number of patients	Copeptin (mean±SD)	Kruskal–Wallis test	*P*
Group A (ICU patients)	30	52.26±34.888	20.1	<0.001
Group B (in-patients)	8	20.21±10.745		
Group C (healthy controls)	7	6.71±3.258		
Total	45	39.47±34.230		

Table 2 Copeptin level according to development of complications in ICU patients (group A)

Variable	Number of patients	Copeptin (mean±SD)	^{MW}U-test	*P*
ICU complications				
No	17	31.40±22.35540	22.5	<0.001
Yes	13	79.53±29.20079		

^{MW}U, Mann–Whitney *U*-test.

Table 3 Copeptin level according to outcome (survival) in ICU patients (group A)

Groups	Number of patients	Copeptin (mean±SD)	^{MW}U-test	*P*
Survivors	17	30.55±17.360	22.0	<0.001
Nonsurvivors	13	80.64±31.611		

^{MW}U, Mann–Whitney *U*-test.

There was a statistically significant positive correlation between copeptin level and ICU complications, as it was higher in patients who developed complications than in those with no complications ($P<0.001$) (Table 2).

There was a statistically significant positive correlation between copeptin level and outcome of patients, as its levels were markedly higher in nonsurvivors than in survivors ($P<0.001$) (Table 3 and Fig. 2).

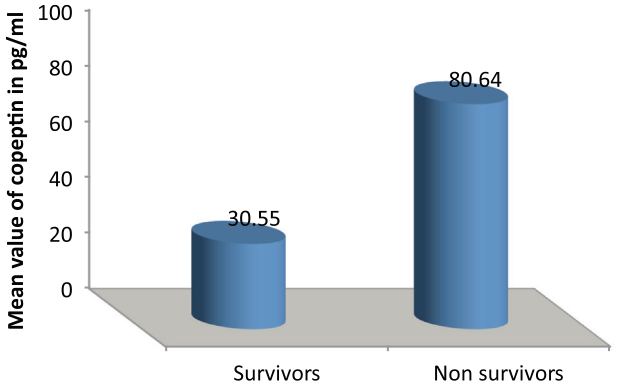
There was a statistically significant correlation between copeptin level and both GCS and APACHE II score ($P<0.001$) and shows no correlation with other clinical data; the relation with GCS was negative, whereas with APACHE score it was positive (Table 4).

There was a statistically significant correlation between copeptin level and PaO_2 and SaO_2 ($P=0.007$ and 0.002, respectively). Relation to other parameters was nonsignificant (Table 5 and Fig. 3).

There was a positive statistically significant correlation between copeptin level and duration of stay both in ICU ($P=0.01$) and hospital ($P=0.02$) (Table 6).

Copeptin level less than 55 pg/ml predicts good prognosis and survival among ICU patients with sensitivity of 88.2%, specificity of 84.6%, positive predicted value of 88.2%, and negative predicted value of 84.6%, with an accuracy of 90%, area under curve (AUC) of 0.9, and *P* less than 0.001 (Table 7).

Figure 2



Copeptin level according to outcome in group A (ICU patients)

Table 4 Correlation between copeptin level and clinical data in group A (ICU patients)

	Copeptin	
	r	*P*
Age	0.23	0.22
GCS	–0.642	<0.001
HR	0.02	0.91
RR	0.268	0.15
TEMP	0.14	0.45
MAP	0.249	0.18
APATCHE II	0.642	<0.001

APATCHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Score; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; TEMP, temperature.

Discussion

Respiratory failure is the most common indication for ICU admission, and in many cases outcome is poor. Therefore, using copeptin as a prognostic marker in these patients can improve their outcome [8].

This prospective study was carried out on 45 patients (38 patients admitted at Benha University Hospital ICU and Chest Department and seven healthy patients). They were classified into three groups: group A (ICU patients) comprised 30 patients admitted with respiratory failure due to different chest diseases; group B (in-patients) comprised eight patients selected from those hospitalized at Chest Department owing to respiratory failure and with no need for ICU admission as a positive control group; group C comprised seven healthy patients included as a negative control group.

In this work, there was a statistically significant difference among studied groups as regards serum

copeptin levels, which were higher in ICU patients (group A, mean: 52.26 pg/ml) than in in-patients (group B, mean: 20.21 pg/ml) and in healthy control patients (group C, mean: 6.71 pg/ml) ($P<0.001$); also, it was higher in in-patients than in healthy control patients ($P<0.001$) (Table 1 and Fig. 1).

In a study conducted by Müller *et al.* [6] to reveal circulating levels of copeptin in patients with lower respiratory tract infections (LRTI) (community-acquired pneumonia, AECOPD, exacerbation of asthma), copeptin levels were also significantly higher in patients with LRTI as compared with controls ($P<0.001$), and this supports the results of this study as the most common cause of respiratory failure in ICU patients was AECOPD (76.7%) followed by pneumonia (10%) and acute exacerbation of bronchial asthma (6.7%).

These results in Table 1 and Fig. 1 were also in agreement with results of Jochberger *et al.* [13] in his study on AVP and copeptin concentration in critically ill patients in a tertiary university teaching hospital ICU in Germany where the mean copeptin plasma concentrations were significantly higher in critically ill patients of the ICU (87±77 pmol/l) in comparison with healthy controls (6±3 pmol/l) ($P<0.001$).

In agreement with Morgenthaler *et al.* [14] who showed that in 60 ICU patients with sepsis, severe sepsis, or septic shock copeptin concentrations were significantly increased ($P>0.001$) compared with those of healthy individuals. Mean (range) values in the sepsis patients were 79.5 (10.6–228.0) pmol/l, 20-fold higher than those in healthy individuals.

The present work showed that there was a statistically significant positive correlation between copeptin levels and ICU complications, as they were higher in patients who developed complications, especially variant angina pectoris, myocardial infarction, and unstable hemodynamics, than in those with no complications ($P<0.001$) (Table 2), which points to that fact that copeptin levels could be used as a predictor of development of complications in ICU patients.

These results were in agreement with Seligman *et al.* [7], who studied copeptin as a novel prognostic biomarker in ventilator-associated pneumonia and showed that copeptin levels increased progressively with the severity of sepsis, being increased from sepsis to severe sepsis to septic shock both on the first day (41.2, 64.8, 84.2 pmol/l, respectively; $P=0.001$) and on fourth day (25.3, 68.7, 91.8 pmol/l, respectively; $P=0.009$) and levels were also independent predictors of mortality in these patients.

Also Omelyanenko *et al.* [15] found that copeptin values on ICU admission correlated significantly with need for vasopressors in unstable haemodynamically patients ($r=0.54$; $P=0.02$, respectively) and showed higher concentrations in patients requiring vasopressors compared with those with stable hemodynamics (74.8 vs. 47.6 pg/ml, $P=0.03$, respectively).

The present study showed a statistically significant positive correlation between mean copeptin level and patients outcome, as its levels were markedly higher in nonsurvivors (80.6+31.6) than in survivors

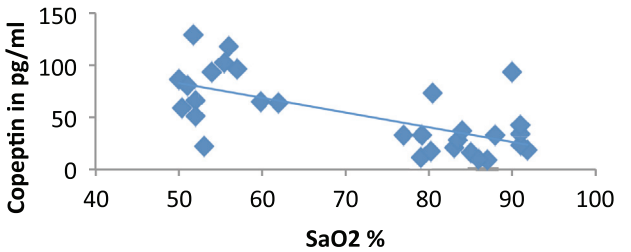
Table 5 Correlation between copeptin level and arterial blood gases and acid base status in ICU patients (group A)

	Copeptin	
	r	*P*
pH	–0.236	0.21
PaO_2	–0.480	0.007
$PaCO_2$	0.016	0.93
HCO_3	0.092	0.62
SaO_2	–0.547	0.002

Table 6 Correlation between copeptin level and ICU and hospital stay in days

	Copeptin	
	r	*P*
ICU stay	0.462	0.01
Hospital stay	0.504	0.02

Figure 3



Correlation between copeptin level and SaO_2 in ICU patients (group A)

Table 7 Copeptin sensitivity, specificity, and accuracy as regards prediction of good prognosis among ICU patients with respiratory failure

Copeptin	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	95% CI	*P*
≤55.0 (pg/ml)	88.2	84.6	88.2	84.6	90	0.9	0.77–1.0	<0.001

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

(30.5+17.3) ($P<0.001$) (Table 3 and Fig. 2), substantiating it as a prognostic marker in critically ill patients.

The result of this study was in agreement with Stolz *et al.* [16], who found that circulating levels in nonsurvivors (42.00 pmol/l; IQR: 13.50–103.20 pmol/l; $n=5$) tended to be higher than in survivors (12.60 pmol/l; IQR: 5.49–27.05 pmol/l; $n=162$; $P=0.06$).

In this study, a highly statistically significant correlation was found between copeptin level and both GCS and APACHE II score ($P<0.001$). The relation with GCS was negative, whereas with APACHE II score it was positive. Lower GCS and high APACHE II score indicate severe patient condition with subsequent bad prognosis [17,18] (Table 4).

Regarding the present work, there was a statistically significant correlation between copeptin levels and PaO_2 and SaO_2 ($P=0.007$ and 0.002, respectively). The lower the oxygen concentration the higher the levels of copeptin (Table 5 and Fig. 3).

In one of the early studies on the relation between copeptin and hypoxia, Anderson *et al.* [19] in his research on anesthetized dogs, it was found that lowering the pressure of oxygen from 80 to 34 mmHg was accompanied by antidiuresis, and plasma AVP increased from 0.06 to 7.5 pmol/l ($P<0.05$). In addition, the results are supported by those of Ostergaard *et al.* [20] who found that when Sprague–Dawley rats plasma levels of copeptin were measured under control (normoxic) conditions and after acute exposure to 10% oxygen (5 min), they showed an almost sevenfold increase in plasma copeptin levels. Hence, plasma copeptin is a strong and sensitive marker of acute exposure to severe hypoxia.

This work showed that there was a positive statistically significant correlation between copeptin levels and duration of stay both in ICU ($r=0.462$, $P=0.01$) and hospital ($r=0.504$, $P=0.02$) (Table 6).

These results were matched with those obtained by Stolz *et al.* [16] in his study of prognostic markers in patients with AECOPD where they revealed that copeptin levels correlated significantly with length of hospital stay ($r=0.320$, $P=0.001$) and length of ICU stay ($r=0.272$, $P=0.001$).

In addition, the study found that in ICU patients copeptin levels less than 55 pg/ml predict good prognosis and survival among ICU patients with sensitivity of 88.2%, specificity of 84.6%, positive predicted value of 88.2% and negative predicted value of 84.6%, an accuracy of 90%, AUC of 0.9, and P less than 0.001 (Table 7).

These results were in agreement with the previous study conducted by Müller *et al.* [6], who found copeptin levels on admission to be significantly higher in patients who died as compared with levels in survivors [70.0 (28.8–149.0) vs. 24.3 (10.8–43.8) pmol/l, $P<0.001$]. The area under ROC curve for survival was 0.75.

In addition, Kolditz *et al.* [21] found copeptin to be the only biomarker significantly elevated in patients with adverse short-term outcome ($P<0.003$). They found after ROC curve analysis that copeptin predicted ICU admission or death within 7 days in patients with community-acquired pneumonia (AUC: 0.81, cutoff 35 pmol/l, sensitivity 78%, specificity 79%) and persistent clinical instability after 72 h (AUC: 0.74).

Conclusion

Elevated plasma copeptin levels reflect disease severity and predict short-term mortality. Plasma copeptin levels increase because of sepsis in LRTIs. Copeptin concentrations are strongly related to hypoxia as they increase markedly with low blood oxygen concentration. Elevated plasma copeptin levels predict long hospital and ICU stay and are associated with development of complications in ICU patients.

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Conflicts of interest

There are no conflicts of interest.

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