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RESEARCH

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Copeptin as an inflammatory marker in diagnosis and prognosis of neonatal sepsis

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Abstract

Background Copeptin is an immediate biomarker of individual stress response; many life-threatening diseases are causing a high elevation of its concentration in plasma, such as myocardial infarction and cardiovascular shock. Moreover, copeptin is a promising marker in sepsis. We aimed to evaluate copeptin as a diagnostic and prognostic marker in neonatal sepsis for the early initiation of appropriate therapy and the prediction of mortality. A prospective case-control study involved 237 neonates (165 cases had neonatal sepsis, and 72 served as controls). Cases were admitted to the neonatal intensive care unit (NICU) and followed up for symptoms and signs of sepsis confirmed by laboratory data: complete blood count (CBC), c-reactive protein (CRP), and cultures. Serum copeptin level by the enzyme-linked immunosorbent assay (ELISA) was measured for all included neonates. We observed that the copeptin level was significantly higher in cases than control (3.51 ± 1.4, 1.61 ± 0.51 pmol/liter, respectively). The cut-off value of copeptin at which we can discriminate between cases and controls was above 2.065 pmol/liter. Among cases, copeptin was higher in early-onset sepsis (EOS) than late-onset sepsis (LOS) neonates, and there was a significant correlation between its level and all the following: age at admission, birth weight, gestational age, history of perinatal asphyxia, maternal chorioamnionitis, and premature rupture of membrane (PROM). Also, copeptin was strongly associated with CRP level and the poor prognosis of patients. Copeptin can predict the death of cases at a cut-off value above 2.995 pmol/liter.

Conclusion Serum copeptin level can be used as a diagnostic and prognostic marker in neonatal sepsis.

Keywords Serum copeptin, Neonatal sepsis, Stress, Diagnostic marker

1 Background

A bloodstream infection in newborn babies under 28 days old is referred to as neonatal sepsis. Particularly in middle- and low-income nations, it continues to be a major cause of illness and mortality in newborns. EOS and LOS are two categories of neonatal sepsis based on when symptoms first appear after birth [1]. A number of host factors, in addition to the particular microbiological reasons, raise the newborn's risk of sepsis. These variables, which affect cellular immunity, humoral immunity, and barrier function, are particularly pronounced in preterm infants. There is an increased risk of newborn sepsis, morbidity, and mortality in preterm and/or extremely low birth weight newborns due to immature immune defenses, environmental variables, and maternal factors. A genetic link might also exist [2]. A newborn who has an infection and develops sepsis can have inflammation throughout their body. This inflammation and blood clotting cause reduced blood flow to the baby's limbs and vital organs. It can lead to organ failure and even death [3]. An increased risk of neurocognitive sequelae, such as cognitive deficits, visual or hearing impairments, or potentially harmful outcomes like cerebral palsy in patients receiving antibiotic treatment, makes

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early identification crucial [4]. The C-terminal portion of pre-provasopressin is a 39-amino-acid glycopeptide called copeptin (pre-pro AVP). Arginine vasopressin, neurophysin II, copeptin, and a signal peptide make up the precursor protein known as pre-pro AVP. The transit of axons from the cell body to the axon terminals in the posterior pituitary gland separates these parts [5]. AVP transport proteins on the pathway from the hypothalamus to the pituitary gland include copeptin and neurophysin II. AVP, neurophysin II, and copeptin are all kept in the neurohypophyseal vesicles until they are secreted. Copeptin primary function in circulation is yet unknown; it plays a critical role in the proteolysis of pre-pro AVP [6]. After being released into the bloodstream, copeptin has no recognized biological function. However, copeptin may aid in the 3D folding of vasopressin when pre-provasopressin is processed during the axonal transport. In sepsis, copeptin is a promising marker. However, its role in newborn disorders is yet unclear [7]. AVP is a vasoactive neuropituitary hormone. It is a key hormone of the hypothalamic-pituitary-adrenal axis, and one of its principal functions is to regulate water and electrolyte balance. The key catalyst for the release of AVP is hyperosmolarity. Hypotension, hypoxia, acidosis, infection, insulin-induced hypoglycemia, pain, nausea, and vomiting, as well as several drugs and other common stressors, can all result in an increase in the blood levels of AVP [8]. In stressful situations, such as illness, the relationship between plasma osmolality and AVP is lost because AVP and corticotropin-releasing hormone (CRH) induce the production of cortisol and adrenocorticotropic hormone (ACTH). Because serum cortisol reflects stress levels, it can be used to forecast how various diseases will progress. Serum cortisol is proportional to stress levels. It is challenging to test cortisol as a free hormone since the circadian rhythm has a significant impact on it. Copeptin is a hormone that is more trustworthy for determining stress levels than cortisol because of these features of cortisol. It should be noted that even low to moderate levels of stress can cause the release of copeptin. In recent years, research on copeptin as a diagnostic and predictive biomarker in a variety of illnesses has increased [9]. Individuals with sepsis had higher AVP concentrations than individuals with illnesses without systemic inflammation, and both AVP and copeptin levels are elevated in sepsis and septic shock. The release of AVP can be brought on by a number of factors, including interleukin 1, tumor necrosis factor, acidosis, pain, hypoxia, and neuroendocrine stress. Patients with infections without systemic inflammation are less likely to develop severe sepsis than those with infections. Copeptin is a promising diagnostic for sepsis since it is an instantaneous indicator of a person's response to stress [10].

In our research, we aimed to assess the serum copeptin level as a diagnostic marker in neonatal sepsis, which would help us in the early initiation of appropriate therapy and estimate its value as a prognostic marker.

2 Methods

A prospective case-control study was carried out in the NICU from May 2022 to July 2023. The Medical Ethics Committee granted ethical permission for this trial, and each individual participant gave their agreement after receiving full disclosure. The study involved 237 neonates admitted to the NICU. They were followed up for signs of sepsis in the form of: poor feeding, lethargy, respiratory problems (such as tachypnea, apnea, grunting, cyanosis, and retraction), temperature instability (such as hyperthermia and hypothermia), gastrointestinal problems (such as vomiting, abdominal distension, diarrhea, and abnormal gastric residual), and central nervous system symptoms (such as convulsion, hypotonia, and irritability). Additionally, comprehensive prenatal histories were gathered to identify maternal risk factors such as PROM, meconium-stained amniotic fluid, chorioamnionitis, fever, and urinary tract infection (UTI). Moreover, neonates with congenital anomalies were excluded from the study. Laboratory data were detected to confirm the sepsis as follows: CBC, CRP, blood culture, and other cultures such as sputum and urine cultures. Regarding the previous data, patients were classified into 2 groups: Group A: Cases (sepsis group), which included 165 neonates and divided into two groups (early and late-onset sepsis groups). Group B: Controls (non-sepsis group), that included 72 neonates.

2.1 Early onset sepsis group (EOS)

Neonates who presented with sepsis within the first 72 h of life were considered EOS instances according to the following standards: (i) At least two clinical indications of sepsis must be present (i.e., unstable body temperature, irritability or lethargy, feeding problems, poor capillary refill > 2 s, apnea, tachycardia, and/or tachypnea). (ii) Increased CRP > 20 mg/l. (iii) The attending physician's choice to administer intravenous antibiotics for at least 7 days of treatment. (iv) The recovery of microorganisms that cause disease in blood cultures. All three of the aforementioned criteria have to be met in newborns with negative blood cultures but clinical diagnoses of EOS [11].

2.2 Late onset sepsis group (LOS)

Neonates who showed signs of sepsis between 4 and 90 days after birth, and acquired it from their surroundings and is more likely in preterm infants, particularly those with prolonged hospitalization, using IV catheters, or

both. Additionally, ventilatory support and neurological harm, including intraventricular hemorrhage with effects on growth and neurodevelopment, have all been linked to LOS [12].

2.3 Control group

They were neonates with gestational age 37.04 ± 0.8 weeks, without evidence of neonatal infection; there were no signs of sepsis with normal CBC, negative CRP, and negative cultures. Some of them were admitted to the NICU with physiological jaundice, and others from a neonatal outpatient clinic.

2.4 Copeptin measurement

Blood was drawn into EDTA plasma tubes for copeptin analysis, immediately centrifuged at 4 °C for 10 min at 4000 rpm, and then kept at 80 °C until analysis. The Brahms Copeptin pro AVP KRYPTOR assay (Short KRYPTOR), the Brahms CT-pro AVP Shot Line blot immunoassay (LIA assay), and the Cloud Clone CT-pro AVP ELISA assay (short ELISA) were used to test copeptin in duplicates. The Cloud Clone is an example of an research use only (RUO), and the first two assays are CE-registered; both rely heavily on ELISA technology [13].

2.5 Statistical analysis

With the use of the IBM SPSS software package version 20.0, data was input into the computer and analyzed. IBM Corp., Armonk, New York Numbers and percentages were used to describe qualitative data. The normality of the distribution was examined using the Kolmogorov-Smirnov test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR) were used to characterize quantitative data. At the 5% level, the significance of the results was determined. The tests used were:

1. Chi-square test (to compare between groups using categorical data)
2. Student *t* test (to compare two groups under study for normally distributed quantitative variables)

- R values were between 0 and 0.3, either positive or negative, denoting a weak correlation; between 0.3 and 0.6, denoting a moderate connection; and between 0.6 and 1, denoting a significant association.
- *P* values of 0.05 or less were regarded as statistically significant. Some information was graphically represented using straightforward graphs.
- An ROC curve was employed to establish the best copeptin marker cut-off for predicting neonatal sepsis and risk of mortality.

3 Results

237 neonates were involved in our research; 69.6% of them had confirmed sepsis and 30.4% didn't. Among the sepsis group, 57.6% had early-onset sepsis and a late-onset in 42.4% of cases.

3.1 Clinical and laboratory data for the sepsis group

47.3% were female and 52.7% were males; the mean gestational age was 36.84 ±2.7 weeks (the range was 28–40); the mean age at the time of admission was 3.16 ± 5.36 days (the range was 1–24); the mean birth weight was 2.54 ± 0.47 kg (the range was 1–3.2); and the mean duration of stay in the NICU was 15.56 ± 5.97 days. Regarding the mode of delivery, 76.4% were cesarean sections, and 23.6% were normal vaginal deliveries. There was a history of PROM in 32.7%, complicated delivery in 23.6%, and chorioamnionitis in 12.7%. Additionally, 70% had poor activity, while no one reported jaundice. According to the moro reflex, only 25.5% showed good reflex, and according to the suckling reflex, only 10.9% had good reflex. Also, there were 10.9% with bradycardia, 14.5% with tachycardia, and 52.7% with prolonged capillary refilling time (CRT). Moreover, there were 10.9% with apnea and 90.9% with respiratory distress. Additionally, 50.9% had poor feeding, 49.1% had vomiting, 38.2% had distention, 32.7% had petechial, and 43.6% had bleeding. However, 59.1% had irritability, 38.2% had lethargy, and 9.1% had seizures. Descriptive data for the sepsis group are demonstrated in Table 1. The mean heart rate was 144.78 ± 15.05 beats per minute (the range was 90–175). The mean respiratory rate was 59.6 ± 7.82 (the range was 36–72), hypothermia was in 7.3%, and hyperthermia was in 5.5%. Hypotension and septic shock were in 15% and needed treatment with catecholamines. As regard to CBC, the mean total leukocyte count (TLC) was 11.33 ± 7.8 × 109/L, the mean hemoglobin was 11.48 ± 2.68 g/dl, and the mean platelet count was 180.87 ± 129.03 × 109/L. Regarding the results of CRP, blood, urine, sputum cultures, and sensitivity, the data are demonstrated in Table 2. In early-onset sepsis, Staphylococcus aureus was the commonest organism in blood culture, but Escherichia coli was the commonest in urine culture. While in late-onset sepsis, the most commonly detected bacteria was Klebsiella species in both blood and urine cultures. Regarding the outcome, 124 patients (75.2%) improved, and 41 patients (24.8%) died. The mortality rate was higher in early-onset sepsis (30.5%) than late-onset sepsis (17.1%).

3.2 Evaluation of serum copeptin level

Through measuring the serum level of copeptin, we found that it was higher in cases than control (3.51 ± 1.4, 1.61 ± 0.51 pmol/liter, respectively), *P* value < 0.001. The cut-off

Table 1 Descriptive data of the patients group

	Patients (Sepsis group) (n = 165)	
	No.	**%**
Gender		
Female	78	47.3
Male	87	52.7
Consanguinity		
Negative	123	74.5
Positive	42	25.5
Maternal risk factors		
UTI	30	18.2
Chorioamnionitis	21	12.7
Fever	57	34.5
PROM	54	32.7
Mode of delivery	No.	%
CS	126	76.4
NVD	39	23.6
Complicated delivery		
Prenatal asphyxia	27	16.4
Intra ventricular hemorrhage	12	7.3
Previous history of NICU admission	12	7.3
Moro reflex		
Poor	54	32.7
Weak	18	10.9
Fair	51	30.9
Good	42	25.5
Sucking reflex		
Poor	39	23.6
Weak	75	45.5
Fair	33	20
Good	18	10.9
Symptoms and signs		
Cardiac		
Bradycardia	18	10.9
Tachycardia	24	14.5
Prolonged CRT	87	52.7
Respiratory		
Apnea	18	10.9
RD	150	90.9
Abdominal		
Poor feeding	84	50.9
Vomiting	81	49.1
Distention	63	38.2
Jaundice	0	0.0
Petechial	54	32.7
Bleeding	72	43.7
Neurological		
Irritability	15	9.1
Lethargy	63	38.2
Seizures	15	9.1

Table 2 Distribution of group A according to CRP and culture

	Group A (n = 165)	
	No.	**%**
CRP		
Range	8–171	
Mean value	53.47 ± 37.89	
Blood culture	No.	%
Accinetobacter	10	6
E.coli	6	3.6
Enterobacter	12	7.2
G. – Ve bacilli	11	6.6
Klebsiella	62	37.5
Pseudomonas	12	7.2
S. aureus	52	31.5
No growth	0	0.0
Septum culture		
Accinetobacter	6	3.6
Candida	21	12.7
E.coli	19	11.5
G. – Ve bacilli	15	9.1
G. + Ve cocci	5	3
Klebsiella	41	24.8
MRSA	17	10.3
Pseudomonas	12	7.2
No growth	29	17.5
Urine culture		
Candida	12	7.2
Pseudomonas	22	13.3
No growth	131	79.4

value of copeptin at which we can discriminate between cases and controls was above 2.065 pmol/liter, with an area under curve (AUC) of 0.950, a sensitivity of 89.1%, and a specificity of 91.7% (Fig. 1). Among cases, copeptin was higher in cases with early-onset than late-onset sepsis (4.12 ± 1.5, 3.05 ± 0.52 pmol/liter, respectively). (P value < 0.02). There was no significant correlation between copeptin and the gender of the cases (P value < 0.54). Also, there was no association with consanguinity (P value < 0.86). Among the early-onset sepsis cases, we found a significant correlation between copeptin level and cases with a history of maternal chorioamnionitis (P value < 0.04) and cases with prolonged rupture of membrane (P value < 0.01) than others. Moreover, there is no correlation with cases with a history of maternal UTI or fever. Additionally, copeptin significantly inversely correlated with each of the following, age at admission (P value < 0.02), birth weight (P value < 0.04), and gestational age (P value < 0.01). But there was no association with mode of delivery (P value < 0.332). Moreover, we detected a positive correlation with neonates who were

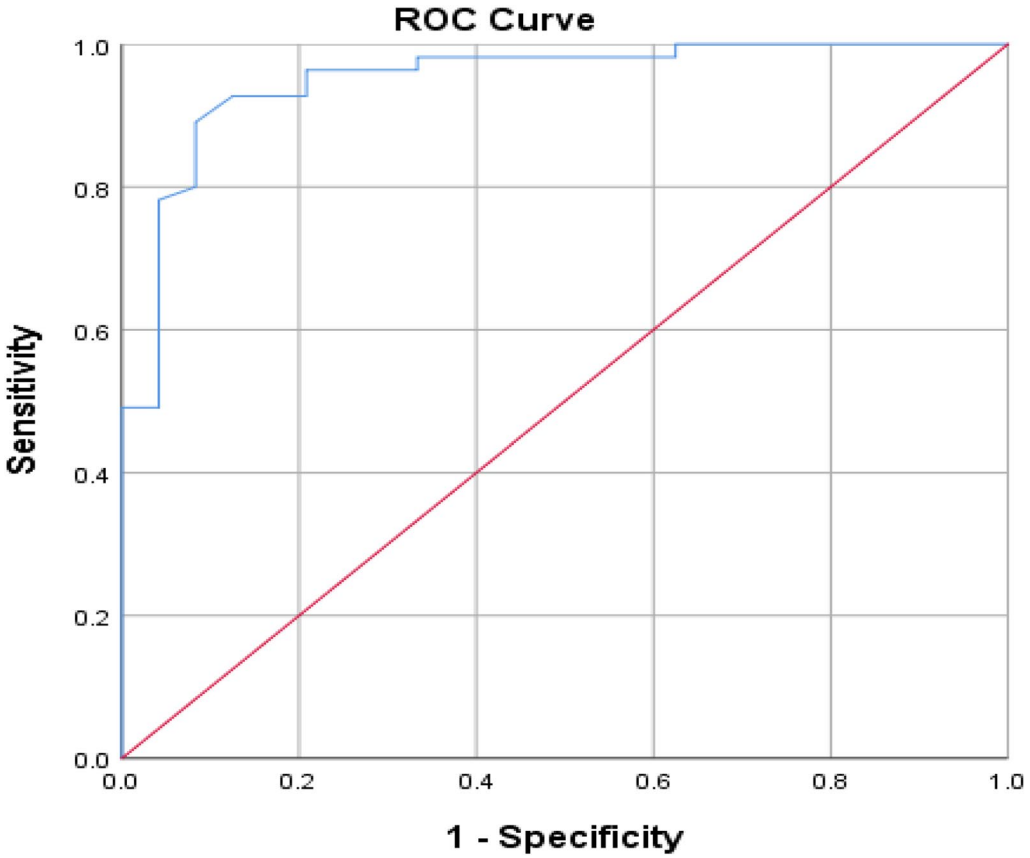

Fig. 1 Roc curve analysis for the use of serum copeptin level to discriminate between cases and controls

exposed to perinatal asphyxia (*P* value < 0.001), and neonates with interventricular hemorrhage (*P* value < 0.03). Additionally, a significant positive correlation existed between copeptin and CRP (*P* value < 0.002) (Fig. 2). But there was no correlation with all the following: TLC (*P* value < 0.949), Hb (*P* value < 0.424), and PLT (*P* value < 0.330). Finally, copeptin was significantly higher in cases who achieved a bad prognosis (mortality) than others (*P* value < 0.001). Roc curve analysis revealed that copeptin can predict the death of cases at a cutoff value above 2.995 pmol/liter with an AUC of 0.719, sensitivity of 77.3%, and specificity of 66.7% (Fig. 3).

4 Discussion

The hypothalami-pituitary axis generates stress hormones, including arginine-vasopressin (AVP), during the stress reaction. Depending on which receptors the AVP binds to, it can have a number of different consequences. Copeptin, the C-terminal portion of the precursor for vasopressin (AVP), and AVP are both produced at equal levels from the same precursor. Copeptin completely mimics the presence of AVP due to its molecular stability and other benefits over AVP, and it has gradually become recognized in clinical practice as a trustworthy marker of vasopressinergic activity in response to osmotic and hemodynamic stimuli [14]. Copeptin's prognostic potential has also been gradually demonstrated in a number of acute disorders where the AVP system's activity is predominantly associated with stress, as well as in psychologically stressful situations. Additionally, organic stressors cause an increase in copeptin levels that is nonspecific, unrelated to plasma osmolality, but proportional to their magnitude. Copeptin suggests the severity of the disease even in critical settings [15]. Our study found a pronounced positive correlation between serum copeptin and neonatal sepsis. Additionally, compared to cases of late-onset sepsis, early-onset sepsis cases had considerably greater copeptin levels. This is backed up by research from Katan et al. [16], Struck et al. [17], and Morgenthaler et al. [18], who found that sepsis, ischemia, and physical stress all result in elevated copeptin concentrations (5- to 100-fold). Also, Benzing et al. [19] and Palmier and Augsburger [20] recorded similar results. In contrast, Schlapbach et al. [21] reported a non-significant correlation between copeptin and neonatal sepsis. In addition, we recorded that copeptin can be used as a

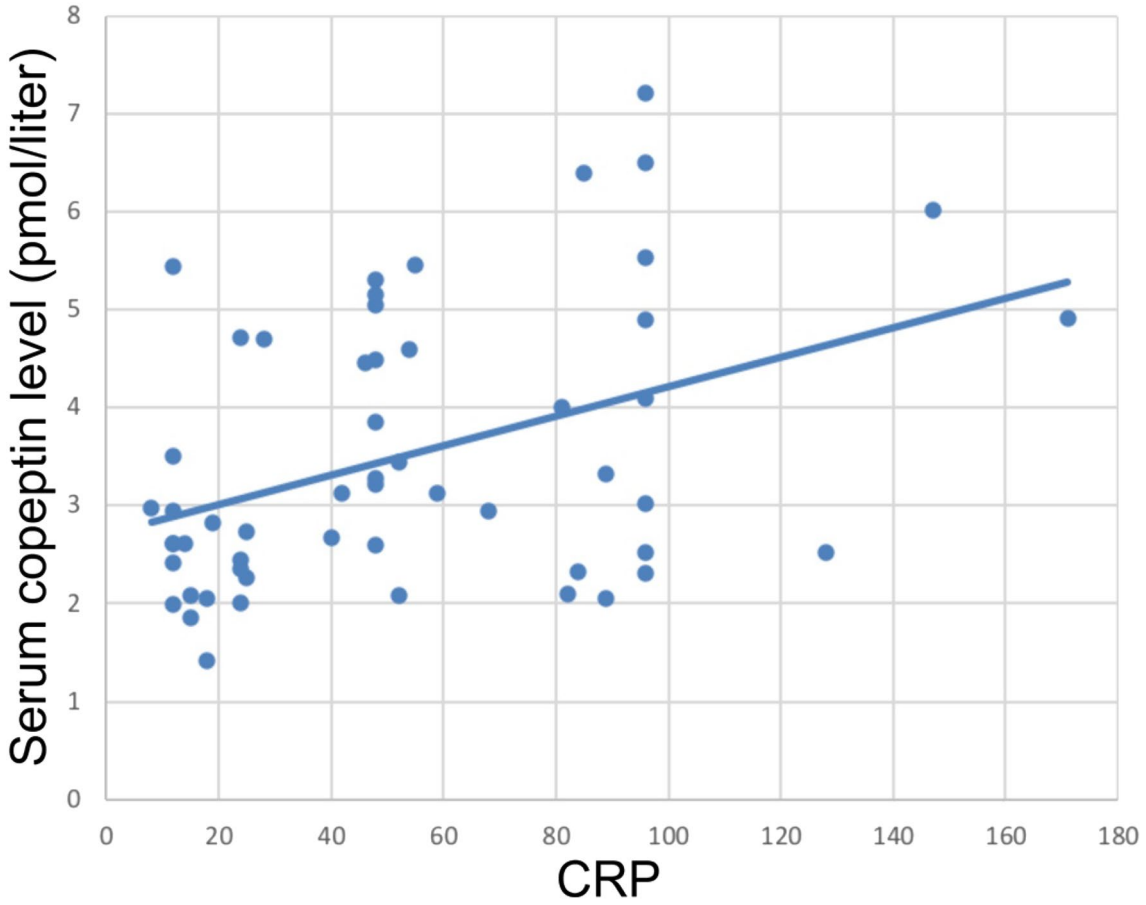

Fig. 2 Correlation between serum copeptin level and CRP

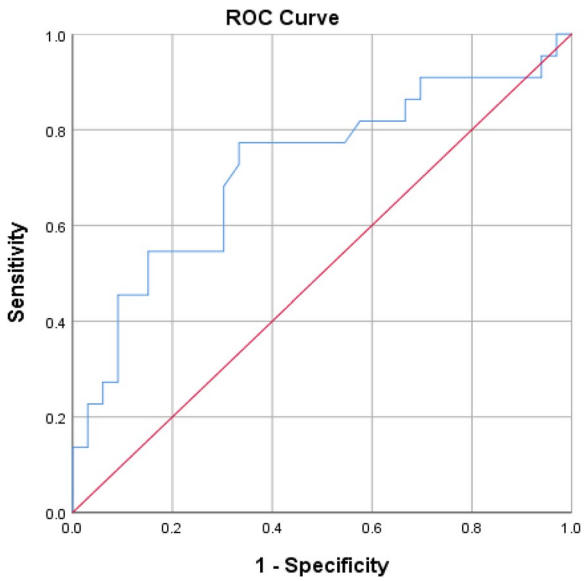

Fig. 3 Roc curve analysis for the use of serum copeptin level to predict death

predictor of neonatal sepsis; the cut-off value of copeptin that can discriminate between cases and controls was above 2.065 pmol/liter with an AUC of 0.950 and sensitivity of 89.1%. Similarly, the ROC curve analysis of Saleh et al. [22] showed that the AUC for copeptin was 0.960, which demonstrated a high sensitivity of 94% for sepsis diagnosis. Moreover, we reported that copeptin levels in neonates with a history of maternal chorioamnionitis, PROM, and complicated delivery (perinatal asphyxia and interventricular hemorrhage) were significantly higher than others. Also, Schlapbach et al. [21] reported equivalent outcomes. Chorioamnionitis and PROM are currently utilized as key risk factors for identifying children at risk of early-onset neonatal sepsis since they are linked to postpartum maternal infections and possibly fatal fetal problems [23, 24]. In addition, we documented that copeptin was higher in cases of prematurity, low birth weight, and early admission to the NICU. Also, Benzing j et al. [19] mentioned that copeptin was inversely correlated with gestational age. Another study [25] noted that low birth weight, preterm birth, maternal infection, and instrumental delivery were the conditions that

caused neonatal sepsis most commonly. We also discovered a significant positive correlation between copeptin and CRP. Also, Palmiere and Augsburger [20] reported similar results. Acute-phase protein CRP is produced by the liver in reaction to inflammation. Early in the course of sepsis, normal plasma CRP concentrations greatly increase. Copeptin may also be a biomarker for increased stress and inflammation. This explains the positive correlation between copeptin and CRP in sepsis [26]. While, another study [27] found no link between both. Moreover, we found that high copeptin levels in neonatal sepsis were directly linked to higher mortality. Copeptin can be used as a predictor of death at a cut-off value above 2.995 pmol/liter with an AUC of 0.719 and a level of sensitivity of 77.3%. Also, Saleh et al. [22] documented similar results (the ROC revealed that the AUC for copeptin was 0.705 with sensitivities of 58% for mortality prediction). Another study [28] reported that individuals with sepsis and septic shock who did not survive had much higher copeptin levels than those who did. Also, Jiang et al. [26] recorded higher levels of serum copeptin in severely ill patients who had multiple organ failures and non-surviving sepsis patients. On the other hand, we didn't observe any association between copeptin and all sex, consanguinity, or mode of delivery. Another study [19] reported that infants born vaginally had considerably greater copeptin levels than infants born via cesarean section. However, the concentration of copeptin did not change between males and females.

5 Conclusions

Copeptin is a very sensitive indicator of neonatal sepsis; it was elevated significantly in sepsis patients compared to others. Factors that affected copeptin levels in these patients were age at admission, birth weight, gestational age, history of perinatal asphyxia, maternal chorioamnionitis and PROM. Also, copeptin level was strongly linked to CRP value. Moreover, Copeptin was a predictor of death in neonatal sepsis; it raised significantly in patients with poor prognosis. Finally, copeptin can be considered as a diagnostic and prognostic marker in neonatal sepsis.

Abbreviations

NICU	Neonatal intensive care unit
CBC	Complete blood count
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
PROM	Prolonged rupture of membranes
EOS	Early onset sepsis
LOS	Late onset sepsis
AVP	Arginine vasopressin
UTI	Urinary tract infection
LIA assay	Line blot immunoassay
RUO	Research use only
CRT	Capillary refilling time
TLC	Total leukocyte count
AUC	Area under curve

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Author contributions
YA and RM analyzed and interpreted the patient data. SS supervised data collection and analysis. AG helped in data analysis. JB collected the data. All authors have read and approved the manuscript.

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Availability of data and material
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by Ethics Committee of Beni-Suef University, Faculty of medicine. Also, written consent was obtained from the care givers of the participating children.

Consent for publication
Not applicable.

Competing interest
The authors declare that they have no conflict of interest.

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