ORIGINAL ARTICLE

Plasma Copeptin as a Prognostic Marker in Children with Heart Failure

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ABSTRACT

Objective: To investigate the role of plasma copeptin in predicting mortality in children with heart failure (HF) in addition to poor outcomes, including sepsis, multiorgan dysfunction syndrome, need for mechanical ventilation, and duration of stay in the pediatric intensive care unit.

Methods: This diagnostic study included 76 children aged 1 month to 16 years who were hospitalized with congenital or acquired heart disease with HF, and an age- and gender-matched control group of 65 healthy children. Plasma copeptin level was evaluated within 24 hours of admission. Patient with HF were classified into quartiles according to copeptin levels.

Results: The median plasma copeptin level (pmol/L) was significantly higher in children with HF compared to the healthy children (16.8 vs 8.0; $P = 0.001$). Patients were classified into quartiles according to their plasma copeptin level as follows; Q1, plasma copeptin level < 7.60 pmol/L; Q2, plasma copeptin level 7.60-10.75 pmol/L; Q3, plasma copeptin level 10.76-17.70 pmol/L; Q4, plasma copeptin level >17.70 pmol/L. The Pediatric Risk of Mortality III (PRISM III) score and inotropic scores were significantly different among the quartiles of copeptin levels in HF ($P = 0.001$ and 0.003, respectively). A higher proportion of patients who developed sepsis and MODS were in the fourth quartile ($P = 0.001$ and 0.022, respectively). All mechanically ventilated children were also in the fourth quartile. Plasma copeptin level of 35.5 pmol/L had a sensitivity of 72% and a specificity of 92.5% to predict mortality in children with HF (AUC = 0.72, $P = 0.046$).

Conclusion: Plasma copeptin is a novel biomarker for the early prediction of mortality and poor outcomes in children with HF.

Keywords: *Arginine vasopressin, Brain natriuretic peptide, Congenital heart disease, Mortality, PICU*

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INTRODUCTION

Heart failure (HF) in children can result from various factors such as congenital heart diseases (CHDs), acquired heart diseases such as viral myocarditis, metabolic disorders, pulmonary diseases, anemia, collagen diseases, and certain medications [1]. HF involves disruptions in hemodynamics and neurohormonal regulation [2]. Few biomarkers can aid the diagnosis of HF in children with atypical symptoms [3]. Troponin and brain natriuretic peptide (BNP) have been approved to aid diagnosis of HF, but their use in children is limited [4]. Arginine vasopressin (AVP) is released in circulation to regulate plasma osmolality and regulate the systemic vascular resistance and cardiac output. However, AVP is not a reliable biomarker in HF due to its short half-life and pulsatile release resulting in fluctuating plasma levels. Additionally, more than 99% of the circulating AVP binds to platelets and is cleared from the bloodstream. Plasma copeptin, derived from the C-terminal portion of pro-AVP, is released in equal amounts as vasopressin and therefore may act as its surrogate marker. It offers enhanced stability compared to vasopressin, with serum concentrations measurable within an hour of symptom onset [5].

Among the established biomarkers such as BNP and N-terminal-pro-BNP, plasma copeptin has been widely investigated in the adult population [6, 7], and it has shown superiority as a diagnostic biomarker of HF in adults by its utility for predicting long-term clinical outcomes and all-cause mortality in heart failure [8, 9]. In addition, raised plasma copeptin level is involved in the diagnosis of pediatric conditions, including pneumonia, nocturnal enuresis, traumatic brain injury, and CHDs accompanied by pulmonary hypertension [10], and metabolic syndrome [11].

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The primary objective of this study was to investigate the role of plasma copeptin in predicting mortality in children with HF, and its relation with poor outcomes including sepsis, multiorgan dysfunction syndrome (MODS), the need for mechanical ventilation (MV), and the duration of stay in the pediatric intensive care unit (PICU).

METHODS

This diagnostic study was conducted in the pediatric intensive care unit (PICU) of Menoufia University Hospital, Menoufia, Egypt, from January 1, 2020, to February 28, 2021. The study was approved by the Institutional Review Board.

The study included children aged 1 month to 16 years admitted in the PICU with HF due to congenital or acquired heart diseases. Children with other comorbidities such as malignancy, sepsis, metabolic syndrome, central nervous system disorders (such as meningoencephalitis, and stroke), diabetes insipidus, and diabetes mellitus, were excluded. Another group of age and sex matched healthy children who visited the outpatient clinics for minor conditions was considered as the control group. Written informed consent was obtained from the guardians of all participants.

A comprehensive patient history was recorded, and a thorough clinical examination was performed to determine the underlying cause of HF. Clinical signs of HF were evaluated, with the Pediatric Risk of Mortality III (PRISM III) score at admission to the PICU. The inotropic score, vital signs, and anthropometric measurements were also recorded. The diagnosis of HF was made based on clinical criteria, like difficulty in feeding, cyanosis, and diaphoresis in infants and young children and fatigue, shortness of breath, and exercise intolerance in older children. In addition, signs of HF such as tachypnea, tachycardia, congested neck veins, tender hepatomegaly, combined with radiological findings of cardiomegaly and plethoric lungs were also considered [12]. At the time of admission and after stabilization, echocardiography was performed by a cardiologist to assess the cardiac function and determine the etiology of HF, using a Philips ultrasound machine with 2–3 and 8-MHz probes. 2D, M mode, and Doppler were used to diagnose the type of CHD. By acquiring 2D images and using M mode, left ventricular systolic function was assessed via the Teichon method, including left ventricular end-diastolic and end-systolic diameters, ejection fraction (EF%), and fraction shortening (FS%).

Venous blood samples were obtained for routine investigations including hemoglobin, renal function, liver enzymes, C-reactive protein, serum electrolytes, and troponin levels. Blood samples for copeptin estimation were collected within 24 hours of admission, sera separated and stored at -20 to -80°C until laboratory analysis. Plasma copeptin level was measured using a commercially available immunoluminometric assay (B.R.A.H.M.S. LUMI test CT-proAVP, B.R.A.H.M.S. AG, Hennigsdorf, Berlin, Germany). The plasma copeptin concentration in each sample was determined by comparing the optical density of the sample with a standard curve. Patients with HF were classified into quartiles according to their plasma copeptin level. All participants were followed up until discharge from the PICU or death.

Using MedCalc version 14.8., the minimum required sample size was 62 patients with HF based on the assumptions of 70% discrimination for long-term clinical outcomes (composite of all-cause death and re-admission for HF) using plasma copeptin, at 80% power and 95% confidence interval [9].

Statistical analysis: Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26. Normality was assessed using visual inspection of Q-Q plot and histogram, further assessment was done using Shapiro-Wilk test. Continuous variables were described using mean and standard deviation or median with interquartile range (IQR), depending on their distribution pattern and compared between the children with and without HF using student's t test or Mann-Whitney test, respectively. Categorical variables were presented as numbers and percentages and compared using Chi-square test or Fisher's exact test. Kendall's tau-b correlation coefficient was used to assess the association between a numerical e.g; hemoglobin and an ordinal variable e.g; plasma copeptin quartiles. To determine the optimal cutoff level for plasma copeptin level for predicting mortality outcomes (death or survival), a receiver operating characteristic (ROC) curve was plotted. The other measures of diagnostic accuracy like sensitivity and specificity were also calculated. P value < 0.05 was regarded as statistically significant.

RESULTS

This study tested 152 children (76 each with and without HF) with a median (IQR) age of 36 (12, 60) months for the HF group and 36 (15, 60) months for the control (without HF) group. Parents of 11 participants withdrew their children from the control group after initial consent.

The most common etiology of HF was CHD (30/76) and toxic (28/76). The most frequent reason for admission to the PICU was pneumonia (n = 35; 46.05%), congestive

HF (n = 32; 42.11%), viral myocarditis (n = 5; 6.58%), and lupus with acute kidney injury (n = 4; 5.26%); none of them required renal dialysis. The median (IQR) ejection fraction (%) was 35 (30, 37). The echocardiographic findings were atrioventricular septal defect (n = 15; 19.73%), atrial and ventricular septal defect (n = 7; 9.21%), ventricular septal defect (n = 3; 3.94%), transposition of the great arteries (n = 4; 5.26%), tetralogy of Fallot (n = 3; 3.94%), and cardiomyopathy (n = 10; 13.16%). The median (IQR) plasma copeptin level (pmol/L) was significantly higher in children with HF compared to healthy children [16.8 (11.15, 27.93) vs 8 (7, 19); P = 0.001].

The two groups were divided into quartiles according to their plasma copeptin level. Among children with HF, a higher proportion of children was found in third and fourth quartile. None of the children in the control group were in fourth quartile, P = 0.041; **Fig. 1**.

Plasma copeptin level did not show a statistically significant difference between children with different etiologies of HF, **Table I**. The other laboratory parameters were compared among children with HF as per the quartile of plasma copeptin level as shown in **Table II**. The median (IQR) plasma copeptin level was similar in children with (n = 35) and without pneumonia [14.7 (9.7, 29.1) and 18.2 (12.4, 24.6); P = 0.549]. Plasma copeptin level was higher in eight children who succumbed than those who survived [38.2 (14.5, 73.0) and 16.0 (11.2, 24.9); P = 0.046].

The distribution of children with HF for different clinical parameters as per quartiles of plasma copeptin level is shown in **Table III**. The median duration of stay in the PICU was 8 days; there was no statistically significant difference between the quartiles (P = 0.063). Using a plasma copeptin cutoff level of ≥ 35.5 pmol/L, the sensitivity was 72% and the specificity was 92.5% for predicting mortality in children with HF (AUC = 0.72, P = 0.046); **Fig.2**.

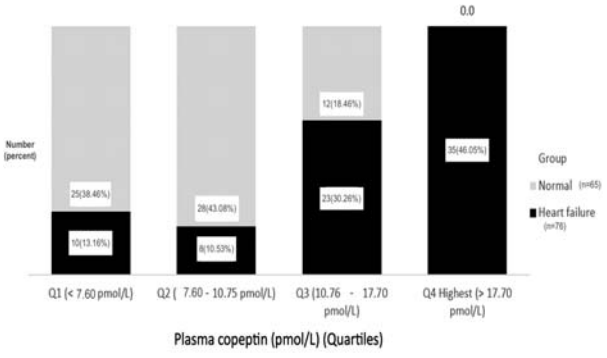

Fig. 1 Distribution of children with heart failure and controls as per quartiles of plasma copeptin level

DISCUSSION

This study explored the role of plasma copeptin as a diagnostic and prognostic biomarker in children with HF. Studies in adults have shown an elevated plasma copeptin level in patients with HF compared to healthy controls, mirroring the findings of this study [6, 7, 13]. This study reported significantly higher level of plasma copeptin in children with HF compared to healthy controls, regardless of the cause, which aligns with an earlier study in children [14]. In another study, the plasma copeptin level was significantly elevated in children with cardiomyopathy-induced HF compared to the control group [15].

Unlike some previous studies, the current study did not report higher plasma copeptin levels in pneumonia [16, 17]. Plasma copeptin level showed a significant positive correlation with PRISM III and the inotropic score, likely due to the activation of neurohormones, including AVP, in response to changes in plasma osmolality and blood volume. Elevated plasma copeptin levels indicate adverse hemodynamic conditions and an unfavorable prognosis in patients with HF [6], and in adults with HF [18].

Some studies in adults have shown that plasma copeptin and AVP are significantly increased in patients with sepsis and septic shock [19, 20]. Renal dysfunction is more prevalent in patients with HF when plasma copeptin level is elevated [21]. Plasma copeptin level increases as a neurohormonal response to hypovolemia, and loss of

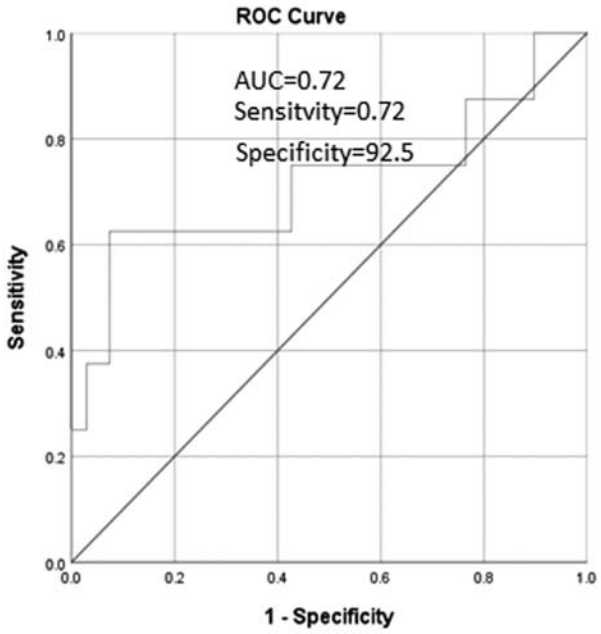

Fig 2. Receiver operating characteristic curve to determine plasma copeptin level to predict mortality in children with heart failure

Table I Plasma Copeptin Level in Children With Heart Failure due to Varying Etiology (*n* = 76)

Etiology of heart failure	*Plasma copeptin level (pmol/L)*[a]	*Quartile wise distribution, n (%)*			
		Q1 (n = 10)	*Q2 (n = 8)*	*Q3 (n = 23)*	*Q4 (n = 35)*
Toxic (*n* = 28)	15.15 (9.73, 19.05)	3 (10.7)	5 (18)	9 (32)	11 (39.3)
Congenital heart diseases (*n* = 30)	18.30 (10.75, 33.60)	6 (20)	1 (3.3)	7 (23.7)	16 (53.3)
Cardiomyopathy (*n* = 10)	14.80 (12.88, 22.03)	0	1 (10)	5 (50)	4 (40)
Myocarditis (*n* = 5)	25.50 (11.20, 31.50)	0	1 (20)	1 (20)	3 (60)
Hypertension (*n* = 3)	17.10 (6.60, 19.10)	1 (33.3)	0	1 (33.3)	1 (33.3)

Data expressed as [a] median (IQR); P value = 0.90
Plasma copeptin level (pmol/L) Q1 < 7.60, Q2 7.60 – 10.75, Q3 10.76 – 17.70, Q4 >17.70

Table II Laboratory Findings in Children With Heart Failure Based on Plasma Copeptin Level

Variables	*Total*	*Plasma copeptin (pmol/L) (Quartiles)*				*CC*	*P value*
	(n = 76)	*Q1 (n = 10)*	*Q2 (n = 8)*	*Q3 (n = 23)*	*Q4 (n = 35)*		
Hemoglobin (g/L)	12 (11, 13)	12.5 (11.2, 13.3)	12 (10.5, 12.4)	12 (11.5, 13)	12 (10.4, 13)	-0.7	0.440
Creatinine (mg/dL)	0.8 (0.7, 1)	0.8 (0.7, 0.8)	0.9 (0.7, 2.5)	0.9 (0.7, 1)	0.8 (0.7, 1)	-0.1	0.868
CRP (mg/L)	12 (5, 24)	12 (9, 18)	12 (6, 21)	12 (4, 18)	18 (8, 36)	0.1	0.084
AST (U/L)	40 (33, 45)	39 (35, 46)	33.5 (30, 46)	40 (33, 45)	40 (34, 50)	0.1	0.338
ALT (U/L)	30 (25, 37)	31 (30, 38)	24.5 (21, 32)	30 (25, 36)	30 (25, 38)	0.1	0.876
K (mEq/L)	4.5 (4, 5)	4.9 (4.5, 5)	4.4 (3.6, 5.6)	4.6 (4.2, 5)	4.2 (4, 4.8)	-0.1	0.164
Ca (mg/dL)	8.6 (8, 9)	9 (8.4, 9.5)	8.6 (8.1, 8.9)	8.5 (8, 9)	8.5 (8, 9)	-0.1	0.410
Na (mEq/L) [a]	139.4 (5.4)	141.4 (3.8)	138.3 (6.3)	139.3 (4.6)	139.2 (6)	-0.1	0.344
PRISM III	15 (12, 20)	14 (10, 17)	14 (11, 18)	12 (11,15)	20 (15, 25)	0.4	0.001
Inotropic score [a]	6.1 (1.3)	5.6 (0.84)	5.6 (0.71)	5.4 (0.9)	6.6 (1.65)	0.3	0.003
Troponin (ng/mL)	4.5 (3, 6)	4.3 (3.6, 7.1)	4.4 (3.4, 5.8)	3.6 (3, 4.6)	5 (3, 9)	0.1	0.237

Data expressed as median (IQR) or [a]mean (SD)
Plasma copeptin level (pmol/L) Q1 < 7.60, Q2 7.60 – 10.75, Q3 10.76 – 17.70, Q4 >17.70
ALT Alanine aminotransferase, AST Aspartate aminotransferase, Na Sodium, Ca Calcium, CC Correlation coefficient, CRP C-reactive protein, K Potassium, PRISM Pediatric Risk of Mortality

Table III Plasma Copeptin Level in Children with Heart Failure Based on Outcome

Outcomes		*Plasma copeptin (pmol/L)*				*P value*
	Total (n = 76)	*Q1 (n = 10)*	*Q2 (n = 8)*	*Q3 (n = 23)*	*Q4 (n = 35)*	
Mortality	8 (10.5)	1 (12.5)	1 (12.5)	0 (0.0)	6 (75)	0.214
MODS	17 (22.4)	1 (5.9)	2 (11.8)	1 (5.9)	13 (76.5)	0.022
Sepsis	23 (30.2)	1 (4.3)	1 (4.3)	2 (8.7)	19 (82.6)	0.001
MV	10 (13.2)	0 (0.0)	0 (0.0)	0 (0.0)	10 (100)	0.005
PICU stay (days)[a]	8 (7, 10)	7.5 (7, 8)	8 (7.25, 9)	8 (7, 9)	9 (7, 11)	0.063

Data expressed in n (%) or [a] median (IQR)
Plasma copeptin level (pmol/L) Q1 < 7.60, Q2 7.60 – 10.75, Q3 10.76 – 17.70, Q4 >17.70
MODS Multiorgan dysfunction syndrome, MV Mechanical ventilation, PICU Pediatric intensive care unit.

WHAT THIS STUDY ADDS?

- Plasma copeptin is a novel biomarker in children with heart failure that predicted poor outcomes and mortality.

vascular tone, which are the mechanisms of sepsis development [19,22]. However, in this study, since the samples for plasma copeptin estimation were extracted before the development of sepsis and MODS, we did not report any association of sepsis or MODS with higher plasma copeptin levels.

We observed that plasma copeptin level was significantly higher in children who required mechanical ventilation (MV) than in those who did not, consistent with the results of an earlier study [9]. Elevated plasma copeptin level after cardiac surgery was associated with a prolonged stay in the intensive care unit, a longer duration of MV, an increased requirement for inotropic support, and a higher incidence of complications [23].

Higher plasma copeptin levels were seen in those who succumbed in this study, as seen earlier [24]. The prognostic value of plasma copeptin in predicting poor outcomes in children with CHDs and pulmonary hypertension is also supported [25].

This study had some limitations including a short duration of follow-up. Further, plasma copeptin levels were measured only once; serial assessment of copeptin levels and its association with other clinical and laboratory findings was not studied. Confounders like volume status, fluid balance, renal function, and medications, such as diuretics, which can influence plasma copeptin levels were not adjusted. This study evaluated plasma copeptin to predict mortality and poor outcome, rather than its diagnostic ability in children with HF and did not compare plasma copeptin with other routinely used biomarkers such as troponin and pro-BNP.

We conclude significantly higher plasma copeptin level in children with HF than in those without HF that was strongly associated with mortality and poor outcomes such as sepsis, MODS, and prolonged duration of MV.

Contributors: AAA: Conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript; AAK: Conceptualized and designed the study, designed the data collection instruments; MHA: Collected data and drafted the initial manuscript; RMG: Analyzed data, reviewed and revised the manuscript; AN: Participated in study design, review and finalization of the manuscript.

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