Serum Copeptin Level as a Predictor Marker of Pediatric Heart Failure Outcomes

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Research Article

Abstract

Background: This study aimed to assess the role of copeptin as a diagnostic marker of heart failure (HF) and outcomes.

Method: We randomly recruited 76 cardiac patients aged 1 month to 15 years and 65 control healthy children matched in age and sex. Based on plasma copeptin level, the study population were sub-grouped into quartiles (Q).

Results: The mean age of cases and control was 40.52 ±34.35 months and 42.43 ±30.42 months respectively. Median copeptin level was higher among patients 16.80 (16.4) compared to control 8.00 (3.0), $P<0.01$. Copeptin level was not statistically significantly different in-between patients with different etiologies of HF, P =0.515. Total leukocytic count, platelets, serum sodium, inotropic score, and troponin were significantly correlated with copeptin quartile. Three-fourth of dead children were within the Q4, and 12.5 % were within the first one, P=0.214. Around 76.5% of patients who had multiorgan dysfunction were within the Q4 while 5.9% belonged to Q1, P=0.022. Of those who developed sepsis, 82.6% and 4.3% were located within Q4 and Q1, $P<0.01$. All patients who required mechanical ventilation were within Q4, P= 0.005.

Conclusion: Plasma level of copeptin is elevated in pediatric HF regardless its etiology and can be used as a predictor of poor outcomes.

What's Known

What's Known

Pediatrics heart failure is a serious condition that can lead to significant morbidity and mortality. Searching for novel biomarkers for earlier diagnosis and prediction of outcomes is mandatory. Copeptin has been studied in heart failure in adults but not in pediatrics.

What This Study Adds

Copeptin is a rapid test that can predict the outcomes of HF. It can help in early management. Future studies are needed to address the role of AVP antagonists in management of pediatric HF.

Introduction

Heart failure (HF) in children is a serious public health problem due to the higher hospital costs compared to adults and frequent needs for interventions. This can disturb the family structure and adversely affects parenteral economic productivity. This economic impact is magnified if the child died of HF due to loss of potentially productive years. (Hsu and Pearson 2009). HF is a progressive clinical and pathophysiological syndrome in which the heart fails to pump enough blood to meet the body demands and results in characteristic signs and symptoms as respiratory distress, growth failure, edema associated with circulatory and neurohormonal disturbances. (Park and Salamat 2020) The causes of HF in children are multifactorial and not limited to the presence of left ventricular dysfunction. It can be caused by pressure, volume overload or both, or due to congenital or acquired heart disease. Congenital heart diseases (CHDs) are the most common etiologies in infancy and viral myocardial dysfunction are common beyond infancy. Other causes of HF are metabolic, pulmonary diseases, anemia, collagen vascular diseases and drugs. (Hsu and Pearson 2009; Park and Salamat 2020)

Due to the non-characteristic signs and symptoms of HF, ongoing research exists to discover its most perfect markers. To date, only a few markers, troponins, and natriuretic peptides (BNP) have been approved to be useful in clinical practice. In adult HF these markers are important in diagnosis, titration of medical therapy, predicting outcome and the need for further interventions. However, these biomarkers are utilized less frequently in children due to the low prevalence of HF and the presence of different causes of HF. (Da Cruz, et al. 2014; Dickstein 2008)

Arginine vasopressin (AVP), also known as the antidiuretic hormone, is one of the key hormones of the hypothalamic-pituitary-adrenal (HPA) axis. It has a role in the regulating plasma osmolality and plays an important role in regulation of systemic vascular resistance and cardiac output. Several previous studies in HF in adults showed that AVP is a useful biomarker of HF However, AVP is very unstable in plasma due to short half-life and pulsatile release pattern, also, it is rapidly cleared from circulation and more than 99% of the circulating hormone is bound to platelets that can affect the reliability of its level.(Alehagen, et al. 2011; Schlendorf and Kasper 2011)

Copeptin, a peptide of 39 amino acids, is the C-terminal part of pro-AVP and is released together with AVP during processing of the precursor peptide. Copeptin is released in equimolar amounts to vasopressin and has been demonstrated to be a surrogate marker for vasopressin. It also has both structural and methodological advantages in clinical practice. Copeptin is more stable than vasopressin, and results may be available within 1 hour which represents an advantage to the clinician. Therefore, copeptin has replaced vasopressin in most recent clinical studies. (Alehagen, et al. 2011; Schlendorf and Kasper 2011) In adults, copeptin has been found to be a superior biomarker to the already established biomarkers BNP and N.Terminal-pro BNP (NT-proBNP) in HF patients. (Balling and Gustafsson 2014a) Furthermore, copeptin has been associated with HF mortality, length of hospital stays and adverse outcomes. Copeptin was shown to be a stronger predictor of mortality than either BNP or NT-proBNP. (Neuhold, et al. 2008)

Of note, many studies that addressed the role of copeptin in different pediatric diseases like pneumonia (Wrotek, et al. 2015), nocturnal enuresis (Nalbantoğlu, et al. 2013), traumatic brain injury (Lin, et al. 2013), CHD with pulmonary hypertension(Gaheen, et al. 2021), and metabolic syndrome (Tuli, et al. 2021). The aim of this study was to assess the utility of copeptin as a diagnostic marker of HF due to different etiologies in pediatric patients and its possible relation to different outcomes.

Methods

This study was performed at Pediatric Intensive Care Unit (PICU), Pediatric Department, Minoufia University Hospital, during the period from Jan 2018 to June 2020. The minimum sample size was calculated based on a previous study aimed to assess whether the relationship of serum copeptin at admission with clinical outcomes. Yoshikawa, et al. (2019) concluded that copeptin was a useful marker for predicting outcomes in patients with HF. Based on his findings, the minimal required sample size was 62 patients with HF assuming a significance level of 95% and statistical power of 80% with the assumption of the copeptin discrimination for the long-term clinical outcome (composite of all causes deaths and readmission for heart failure) was 70%. In total, 76 of 538 pediatric patients admitted with acute HF with different etiologies were selected randomly using the simple random generator. All children aged from 1 month to 16 years, admitted with a diagnosis of HF either of congenital or acquired etiologies were eligible for inclusion. Children with any chronic condition other than cardiac diseases, malignancy, metabolic syndrome, central nervous system (CNS) disorders, diabetes insipidus and diabetes mellitus were excluded.   HF was diagnosed both clinically by signs of HF as tachypnea, tachycardia, and enlarged tender liver, and radiologically, by chest X ray showing cardiomegaly, plethoric lungs. Then assessing cardiac function and diagnosis of etiology by echocardiography. A total of 65 normal children matched in age and sex were included to identify the normal level of

copeptin. The study was approved by the Ethical Committee of the Faculty of Medicine, Minoufia University. Informed written consent was signed by all caregivers of included children.

All children were subjected to detailed history taking, thorough clinical examination to determine the primary cause of HF either congenital or acquired causes, clinical signs of HF, ROSS classification of heart failure(Ross 2012), PRISM (Pollack, et al. 1988) score at PICU admission, inotropic score, vital signs were recorded appropriately, anthropometric measures. Routine investigations were performed as complete blood count (CBC), renal functions (blood urea, serum creatinine), liver enzymes (alanine transaminase ALT, aspartate transaminase AST), C reactive protein (CRP), blood electrolytes (serum sodium, potassium and calcium), and cardiac troponin.

Echocardiography:

Two pediatric cardiologists blindly performed cardiac examination using Philips's ultrasound machine with 2-3 MHZ and 8MHZ probes. Two-dimensional, M mode and Doppler were used for diagnosis of type of congenital heart defect and other causes. Left ventricular systolic functions was measured by acquiring parasternal long axis view in 2D, and M mode was used to measure LVEDD and LVESD, EF% &FS% were measured using Teichon method. If there was any disagreement in diagnosis, consultant opinion was sought.

Plasma level of copeptin

Two ml of venous blood were withdrawn under aseptic condition and allowed to clot for 30 minutes before centrifugation for 15 minutes. Serum was separated into separate tubes and frozen at -20 to -80 degrees Celsius till the assay was performed after all samples were collected from all patients and controls. The kit assay Human Copeptin level in the sample, use Purified Human Copeptin antibody to coat microtiter plate add Copeptin to wells, Combined Copeptin antibody which with enzyme-labeled, become antibody — antigen — enzyme—antibody complex, after washing Completely, Add substrate, the substrate becomes blue color At Horse-radish peroxidase(HRP) enzyme —catalyzed, reaction is terminated by the addition of a sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 nm. The concentration of Copeptin in the samples is then determined by comparing the O.D. of the samples to the standard curve. Based on Copeptin level patients with heart diseases were divided into quartiles.

Patients follow up

Patients were managed with follow up of disease course, occurrence of other morbidities as sepsis (systemic inflammatory reaction (SIRS) in the presence of suspected or proven infection), multi-organ dysfunctions (MODS), need for mechanical ventilation (MV) and its duration, duration of PICU stay, and mortality.

Study outcome

The primary outcome of this study was to evaluate the level of plasma copeptin in children with HF of different etiologies. Secondly, we correlated different clinical, echocardiographic and hemodynamic characteristics with plasma copeptin levels. Finally, we assessed the role of plasma copeptin in predicting HF outcomes.

Statistical analysis

Statistical analysis Continuous variables were presented as mean ± standard deviation (SD) or median ± inter-quartile range (IQR) and were compared with Student's t-test or by Mann-Whitney U test (if not normally distributed).

Categorical variables were expressed as rate or proportion and compared by the Chi-square test or the Fisher's exact test. Kendall's coefficient of rank correlation

tau-sub-b was used to test the association between ordinal and continuous variables(Khamis 2008). Copeptin level was expressed as median with inter-quartile range (IQR) [25th−75th percentile] and the non-parametric Wilcoxon rank-sum test was adopted for group comparisons.

Results

This study was conducted on two groups; patients group included 76 pediatric patients with HF of different etiologies, their mean age was 40.52 ±34.35 months, 39.47% of them were males. The control group included 65 healthy children with a mean age of 42.43 ±30.42 months, and 40.0% of them were males. there was no statistically significant difference between the two groups as regards age and sex, P>0.05.

The median plasma level of Copeptin was significantly higher among patients with HF compared to normal children 16.80 (16.4) vs 8.00 (3.0), P =0.043. There were 5 main etiologies of HF in the patient group, CHDs 30 (39.47%), toxic myocarditis 28(36.84%), cardiomyopathy 10 (13.16%), viral myocarditis 5 (6.58%) and hypertensive HF 3 (3.95%). Regarding Ross classification, about four-fifth (78.95) of patients with HF were class 3, while 21.05% were class 4. The most common cause of PICU admission was pneumonia (46.05%), followed by congenital heart (42.11%). The median PRISM score, inotropic scores, and ejection fraction of patients were 15.0(7.5), 6.0(0), and 34.50 (7.0) respectively. Table 1.

The studied groups (cases and control) were divided into quartiles according to their plasma copeptin level, where the lowest quartile with copeptin level below 7.6 Pmol/L, the second quartile with copeptin level 7.7-10.75 Pmol/L, the third quartile with copeptin level 10.76- 17.70 Pmol/L and the highest quartile with copeptin level above 17.70 Pmol/L. Patients with HF were more located in the third (30.3%) and fourth quartile (46.1%), while 38.5% and 43.1% of normal children were located within the first and second quartile respectively, none of the control were located in the fourth quartile, P<0.05. Figure 1

Statistical analysis revealed that plasma copeptin level was not different between patients with different etiologies of HF (P =0.919), patients with viral myocarditis had the highest plasma copeptin level median 25.50 (11.80- 28.20), while patients with cardiomyopathy had the lowest median copeptin level 14.8 (13.0-21.9), this difference was not statistical significance P=0.919.

Among the studied patients with HF, CBC showed that the mean hemoglobin, median WBCs, platelets level were 11.7±1.5, 9.7 (4.0), and 220 (77.5) respectively. The biochemical profile showed that the median creatinine, AST, and ALT, were 12(19), 40(12.0), and 30(11.8) respectively. Regarding blood electrolytes the median potassium and calcium was 4.5(1.0) and 8.6 (1.0) respectively, while the mean sodium was 139.4±5.4. The median PRISM score was15.0(7.6), and the median inotropic score was 6.0(0.0). Finally, cardiac and inflammatory markers showed that the median troponin and CRP were 4.5(3.0) and 0.8(0.3) respectively. Of these variables the median WBCs, PRISM, and inotropic score had significant positive correlation with the copeptin quartile correlation coefficient was (0.2,0.4, and 0.3) respectively, P<0.05. On the other hand, platelets count had a significantly negative correlation with copeptin quartiles, correlation coefficient =-0.2, P<0.05. Table 3

In this study 8 patients (10.5%) died, 17 patients (22.4%) developed MODS, 23 patients (30.2%) had sepsis and 10 patients (13.2%) required MV. The median duration of PICU stay was 8.00 (3.0) days. Regarding mortality, 75% of dead children were within the Q4 group, and 12.5 % were within the Q1 group, however, this difference was not

statistically significant, *P*=0.214. On the other hand, 76.5% of patients who had MODS belonged to the Q4 group while 5.9% belonged to Q1 group, this difference was statistically significant P=0.022. Of those who developed sepsis, 82.6% and 4.3% belonged to the Q4 and Q1 respectively this difference was statistically significant (P<0.01). There was a noticed statistically significant difference regarding need for MV. All patients who required MV were of Q4 group, while none of the other three groups needed M, P= 0.005. the median duration for MV was 5.5(1.25) days. Patients in the Q4 group had the longest PICU stay 9.00(4.0) days, while patients in the Q1 group had the shortest PICU stay 7.5(1.0) days but the difference was not statistically significant (p=0.063).

Discussion

Plasma copeptin level has been studied in HF in adults frequently, but to the best of our knowledge, this is the first study in pediatrics on plasma copeptin level in HF. In this study, we included patients with HF of different etiologies not only CHDs to study the diagnostic and prognostic role of plasma copeptin level.

In the current study, we found that the median plasma copeptin level was significantly higher in patients with HF than in controls. As HF is characterized by activation of several neurohormones, one of which is AVP that is produced by hypothalamus in response to changes in plasma osmolality and blood volume, this can lead to cardiomyocyte hypertrophy due to activation of V1A receptors, this contributes to left ventricular remodelling and failure. Copeptin is released in equimolar amounts to AVP and is more stable, so it is an ideal surrogate biomarker for AVP. (Zhong, et al. 2017) A similar finding was reported by Hage, et al. (2015), they concluded that plasma copeptin level was significantly higher among patients with HF and preserved ejection fraction ≥45% compared to healthy control. Furthermore, plasma copeptin level was a strong discriminator between dypnea induced by HF from which induced by an acute exacerbation of the chronic obstructive pulmonary disease. (Winther, et al. 2017)

In this study, we found a significant association between copeptin and PRISM score and s inotropic score, this may be attributed to more hemodynamic instability in these patients causing more AVP production. A similar finding was reported by Nickel, et al. (2011) that copeptin provides additional information to clinical risk scores in adults with HF as the Katz Index of Independence in Activities of Daily Living and the Charlson Comorbidity Index reported a significantly higher proportion of catecholamine use in patients with high copeptin than in patients with low copeptin.   AVP was found to be a major contributor to hyponatremia, that was associated with poor prognosis in HF patients in previous studies.(Neuhold, et al. 2008)

Indeed, HF in pediatrics is associated with increased morbidities and mortality, so finding a noninvasive biomarker for early identifying patients at risk and early intervention with close follow up is an important target in critical care management. We found that plasma copeptin level was higher among patients who died (75% of the dead patients were in the highest copeptin quartile), however, this difference was not statistically significant. Adult studies revealed similar findings,Maisel, et al. (2011) found that adult patients   with acute HF with elevated copeptin concentration have increased 90-day mortality and that copeptin was an important predictor of 90-day mortality and provide additional prognostic information over clinical predictors. Also in a meta-analysis by Zhong, et al. (2017) that incorporated ten prospective cohort studies comprising 4473 adults' patients with HF, found thatthe risk of mortality in HF patients with high copeptin (Relative risk (RR) was 2.64 (95% CI, 2.09–3.32). This finding urges the need for larger multicenter studies to assess the role of copeptin in predicting mortality among pediatric patients with HF.

In the current work, patients with high copeptin level were exposed to more worse outcomes, we found that copeptin level was significantly higher in patients who needed MV, similar to our results Yoshikawa, et al. (2019) found that patients in the higher copeptin group had a higher incidence of noninvasive positive pressure ventilation (NIPPV) use

than the low copeptin group. Also, we found that patients with high copeptin level are more liable to develop sepsis, MODS and longer PICU stay. In the same vein, Egyptian researchers conducted a similar study at the pediatric department, Tanta University on patients with congenital heart failure. They concluded that copeptin had sensitivity and specificity of 90% and 80% respectively in predicting poor outcomes among patients with congenital heart disease . (Gaheen, et al. 2021) In a study by Urganci, et al. (2020) to assess copeptin levels in pediatric cardiac surgery, they found that patients with high copeptin levels had higher PICU stay and elevated copeptin level was positively correlated with prolonged stays due to requirements of longer duration of mechanical ventilation and more inotropic support, also they had more incidence of minor complications.   In agreement with our results, several studies in adults had shown that copeptin level significantly increased in patients with sepsis and septic shock, and both AVP and copeptin were reported as severity markers for sepsis and septic shock (Jochberger, et al. 2009; Urganci, et al. 2020) Also, copeptin had been studied as a biomarker in sepsis-related deaths and found to be higher in patients with sepsis and septic shock, All these can be attributed to hemodynamic instability in patients with sepsis and septic shock that can affect the release of copeptin (Palmiere and Augsburger 2014) Further evidence of associated MODS was reported by Balling and Gustafsson (2014b). They concluded that renal impairment was prevalent in patients with HF and high plasma copeptin levels.

Strength and limitations:

To the best of our knowledge this is the first study that addressed the copeptin level among pediatric patients with HF and correlate its level with different outcomes. Second, the relatively large sample of patients with HF recruited provided robust evidence and increased the power of the outcomes. However, the main limitation was the short follow up duration. In addition, we measured copeptin level once, we could not correlate copeptin level with time or changes in other laboratory and clinical findings. Also, we did not take into consideration volume status, fluid balance, renal functions and medications as diuretics as they can affect copeptin level.

Conclusion:

Plasma copeptin level was statistically significantly higher in patients with HF than in controls and had a significant association with various outcomes. Patients in the highest quartile group based on copeptin level had the highest incidence of mortality, however, this was not statistically significant. Copeptin level was statistically higher in patients who developed sepsis, MODS and who were mechanically ventilated. This finding should guide future research on the role of AVP antagonists as a line of therapy of HF in pediatrics, as elevated copeptin may identify patients with an activated AVP system. These patients are most likely to benefit from AVP antagonists. Further studies on a larger pediatric HF cohort with longer follow up are recommended to determine the prognostic value of copeptin in conjunction with other biomarkers and to determine an optimal cut-off level.

Abbreviations

2D	:	Two Dimensional.
ALT	:	Alanine Aminotransferase
ASD	:	Atrial Septal Defect
AST	:	Aspartate Aminotransferase
AVSD	:	Atrio Ventricular Septal Defect
Ca	:	Calcium
CBC	:	Complete Blood Count.
CHDs	:	Congenital Heart Diseases
CI	:	Confidence Interval
EF	:	Ejection Fraction.
FS	:	Fraction of Shortening.
IQR	:	Inter Quartile Range.
K	:	Potassium
LVEDD	:	Left Ventricular End Diastolic Diameter.
LVESD	:	Left Ventricular End Systolic Diameter.
M MODE	:	Motion Mode
MHZ	:	MegaHertZ.
Na	:	Sodium
NIPPV	:	Noninvasive positive pressure ventilation
Pmol /L	:	Picomol per litre
Q1	:	Quartile 1
Q2	:	Quartile 2
Q3	:	Quartile 3
Q4	:	Quartile 4
RAS	:	Reticular Activating System
SD	:	Standard Deviation.
SIRS	:	Systemic Inflammatory Reaction Syndrome.
TGA	:	Transposition of Great Arteries
U Test	:	ManWitney test
VSD	:	Ventricular Septal Defect.
WBCs	:	White Blood Cells

Declarations

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Tables

Table 1 patient characteristics

Variable	Heart failure group (n=76) (Cases)	Normal group (n=65) (control)	Test of significance
Age (months) median (IQR)	36.00 (48.0)	36.00 (42.0)	0.531
Sex (%) Male (n=56)	30 (39.5)	26 (40.00)	0.949
Copeptin level Pmol\l median (IQR)	16.80 (16.4)	8.00 (3.0)	0.001*
Weight (kg)	14.00 (7.25)	15.00(7.00)	0.001*
Primary diagnosis (%) Renal Failure	9 (11.8)		
Sepsis	2 (2.6)		
Down Syndrome with congenital heart	9 (11.8)		
Pneumonia	35 (46.1)		
Congenital heart	32 (42.1)		
Cardiomyopathy	10 (13.2)		
Myocarditis	3 (4.0)		
Lupus	1 (1.3)		
Type of heart failure (%) Toxic	28 (36.8)		
Congenital heart	30 (39.5)		
Cardiomyopathy	10 (13.2)		
Myocarditis	5 (6.6)		
Hypertensive	3 (4.0)		
Ross classification (%) Class 3	1. (79.0)		
Class 4	6 (21.1)		
PRISM median (IQR)	15.00 (7.5)		
Inotropic score	6.0 (0.0)		
Ejection fraction % median (IQR)	34.5 (7.0)		
Echo findings (%) No Congenital heart	35 (46.05)		
AVSD	15 (19.74)		
VSD	3 (3.95)		
VSD+ASD	7 (9.21)		
Fallot	5 (6.58)		
TGA	4 (5.26)		
Cardiomyopathy	7 (9.21)		

AVSD Atrioventricular septal defects, ASD Atrial Septal Defect , VSD ventricular septal defect, TGA transposition of great arteries, IQR: interquartile range.

Table 2: Copeptin level of children with different etiologies of heart failure

Type of Heart Failure	Copeptin level (pmol/L) median (IQR)	P	Copeptin (Quartiles)				P
			Q1	Q2	Q3	Q4	
Toxic (n=28)	15.2 (19.2)	0.919	3 (10.7)	5(17.9)	9(32.1)	11(39.3)	0.551
Congenital heart (n=30)	18.3 (22.6)		6(20.0)	1(3.3)	7(23.7)	16(53.3)	
Cardiomyopathy (n=10)	14.8 (8.9)		0(0)	1(10.0)	5(50.0)	4(40.0)	
Myocarditis (n=5)	25.5 (16.4)		0(0)	1(20.0)	1(20.0)	3(60.0)	
Hypertensive (n=3)	17.10(38.6)		1(33.3)	0(0)	1(33.3)	1(33.3)	

Q1: copeptin level below 7.6 Pmol/L, Q2: copeptin level 7.7-10.75 Pmol/L, Q3: copeptin level 10.76-17.70 Pmol/L Q4: copeptin level more than 17.70 Pmol/L.

Table 3: Sociodemographic and laboratory findings among patients based on their copeptin level

| Variables	Total (76)	Copeptin (pmol/L) (Quartiles)				CC	P
		Q1	Q2	Q3	Q4		
Hemoglobin (gm/L)	11.7±1.5	12.3±1.3	11.5±1.6	11.9±1.1	11.5±1.8	-0.7	0.44
WBCs (x10^3/mm^3)	9.7[4.0]	9.0[3.4]	10.5[5.5]	9.0[2.0]	11.0[6.0]	0.2	0.027
Platelets (x10^3/mm^3)	220[77.5]	255.0[77.5]	260.0[101.8]	210.0[90.0]	200.0[60.0]	-0.2	0.009
Creatinine (mg/dl]	0.8[0.3]	0.8[0.2]	0.9[1.8]	0.9[0.3]	0.8[0.3]	-0.1	0.868
CRP (mg/L]	12[19.0]	12.0[9.5]	12.0[14.75]	12.0[14.0]	18.0[28.00	0.1	0.084
AST (U/L]	40[12.0]	39.0[11.0]	33.5[15.5]	40.0[12.0]	40.0[16.0]	0.1	0.338
ALT (U/L]	30.0[11.8]	31.0[8.0]	24.5[14.75]	30.0[11.0]	30.0[13.0]	0.1	0.876
K (mEq/L]	4.5[1.0]	4.9[0.5]	4.4[2.1]	4.6[0.8]	4.2[0.8]	-0.1	0.164
Ca(mg/dl]	8.6[1]	9.0[1.1]	8.6[0.8]	8.5[1.0]	8.5[1.0]	-0.1	0.410
Na (mEq/L]	139.4±5.4	141.4±3.8	138.3±6.3	139.3±4.6	139.2±6.0	-0.1	0.344
PRISM	15.0[7.6]	14.0[7.0]	14.0[6.5]	12.0[4.0]	20.0[10.1]	0.4	0.001
Inotropic score	6.0[0]	6.0[0.0]	6.0[0.0]	6.0[0.0]	6.0[0.0]	0.3	0.003
Troponin (ng/ml]	4.5[3.0]	4.3[3.5]	4.4[2.3]	3.6[1.6]	5.0[6.0]	0.1	0.237

Q1: copeptin level below 7.6 Pmol/L, Q2: copeptin level 7.7-10.75 Pmol/L, Q3: copeptin level 10.76-17.70 Pmol/L Q4: copeptin level more than 17.70 Pmol/L; CC: Correlation Coefficient; AT:Alanin transaminase, AST: aspartate transaminase, Na: sodium, Ca: Calcium, K: potassium.

Table 4: Different outcomes of heart failure based on the copeptin level

Studied outcomes		Total	Copeptin (pmol/L) (Quartiles]				P
			Q1	Q2	Q3	Q4	
Fate (%]	died	8(10.5]	1(12.5]	1(12.5]	0(0.0]	6(75.0]	0.214
	survived	68(89.5]	9(13.2]	7(10.3]	23(33.8]	29(42.6]	
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
Mechanical Ventilation (%]		10(13.2]	0(0.0]	0(0.0]	0(0.0]	10(100.0]	0.005
PICU stay		8.0[3.0]	7.5[1.0]	8.0[1.8]	8.0[2.0]	9.0[4.0]	0.063

Q1: copeptin level below 7.6 Pmol/L, Q2: copeptin level 7.7-10.75 Pmol/L, Q3: copeptin level 10.76-17.70 Pmol/L Q4: copeptin level more than 17.70 Pmol/L, MODS: Multi-organ dysfunction

Figures
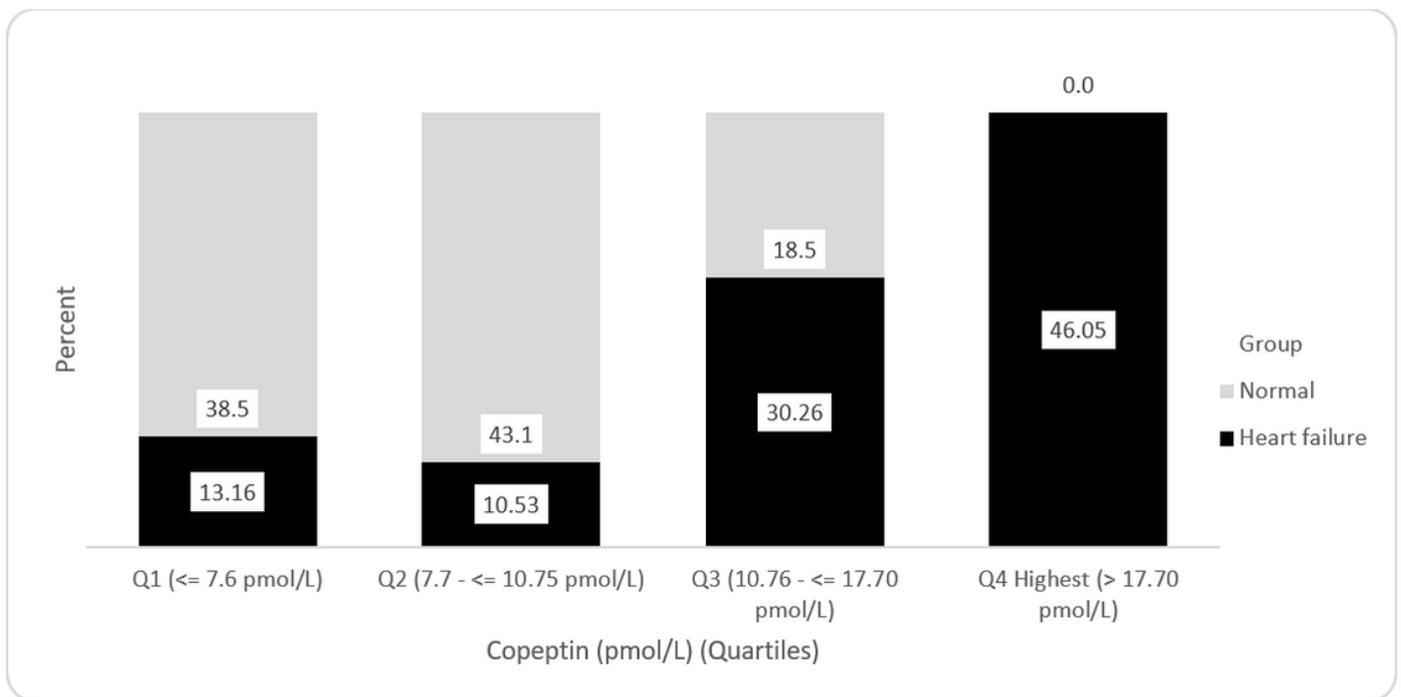
Figure 1

Study population classified according to their Copeptin level