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Original Article

Can Copeptin be an Indicator of Heart Failure in Children with Congenital Heart Disease?

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Abstract

Background: Heart failure (HF) remains to be an essential contributor to morbidity and mortality in children across the world. Congenital heart disease (CHD) represents one of the most frequent causes of heart failure in infants and pediatric age groups. This study was primarily to assess the role of plasma copeptin levels in early prediction of HF among infants and children with CHD, also detecting its relation to various clinical and echocardiographic findings among cases.

Methods: This case-control study was conducted on 64 children; divided into two equal groups; the cases group (32 CHD children presented with HF), the control group (32 healthy individuals' age- and sex- matched). All study participants underwent full history taking, clinical evaluation, routine laboratory, and radiological assessment, including echocardiography and plasma copeptin levels, upon admission.

Results: Plasma copeptin levels were significantly higher in HF-CHD cases than in the controls. Accordingly, these elevated copeptin levels may serve as a valuable biomarker for early prediction of HF in children with CHD. There was a positive significant correlation between copeptin levels and HR, RR, TR, PASP, and Tricuspid E/é ratio. Conversely, copeptin levels revealed a significant negative correlation with TAPSE/RVSP, LV fraction shortening, ejection fraction, and mitral S′ within. The ROC curve showed that copeptin levels at the cut-off point >5.30 ng/dL can predict HF in CHD, with a sensitivity of 93.8%, a specificity of 90.6%.

Conclusions: Plasma copeptin levels could be a promising diagnostic biomarker in early detection of HF in children with CHD.

Keywords: Plasma copeptin, Heart Failure, Congenital Heart Disease

INTRODUCTION

Heart failure (HF) in pediatrics is defined as a complex progressive clinical and pathophysiological syndrome characterize by the heart's incapacity to contract or expel blood to provide enough blood supply to the body's organs [1].

HF in pediatric is multifactorial, it could potentially be arising from cardiac dysfunction, volume overload, pressure overload, or a combination of them. Structural abnormality like congenital heart diseases (CHD) that

considered one of the most prevalent reasons of HF in pediatric age group with varying risks related to the kind of cardiac defect, or functional abnormalities such as cardiomyopathies [2]. Additional causes such as arrhythmias, toxins, collagen or vascular diseases, sepsis, metabolic syndromes, anemia, pulmonary diseases, malnutrition, malignancies, renal failure, and drugs [3].

The clinical presentation of HF among young children and infants are mostly feeding difficulties, dyspnea, rapid breathing, fast heart rate and excessive sweating; however, the main symptoms that older children and teenagers may suffer include easy fatigability, short rabid breathing, and activity and effort intolerance. Additionally, oliguria, pitting edema, abdominal pain and discomfort, maybe manifest [4].

To categorize the HF severity in children, the Ross modified classification, should be used which identifies four functional classes with progressive clinical features of severity from I to IV: Class I: Asymptomatic. Class II: In infants, mild tachypnea or diaphoresis during feeding; in older children, dyspnea on exertion. Class III: Marked tachypnea or diaphoresis with feeding in infants, prolonged feeding time with failure of growth, and older children experience marked dyspnea on activity. Class IV: Signs including resting excess sweating, increased respiratory rate, intercostal retractions, and grunting [5].

The pathophysiology of pediatric heart failure (PHF), regardless of the cause, involves initially injury of cardiomyocytes leads to a reduction in contractility followed by diminish output of the heart that is subsequently counteracted by two essential compensating system to certain physiological changes. First, sympathetic nervous system activation, that elevates the norepinephrine liberation and reduces its reuptake that induces peripheral blood vessels constriction. The second is triggering of neurohormonal reflexes as compensatory response, particularly the renin-angiotensin-aldosterone system (RAAS). This activation increases levels of angiotensin II in the bloodstream inducing a powerful vasoconstrictor that maintain blood supply to vital body parts. Additionally, aldosterone production promotes retention of salt and water [6]. Moreover, when cardiac output decreases and blood viscosity rises, it prompts the arginine vasopressin (AVP) release from the posterior lobe of the pituitary gland; also known as antidiuretic hormone, AVP exhibits both water-retaining and blood vessel-constricting properties[6].

The AVP has a short plasma half-life because of its attachment to platelets; it is rapidly cleared from the circulation. This AVP's plasma instability in cardiac patients influences its level accuracy [7].

Copeptin, is long peptide made up of a 39 amino acids-, produced alongside vasopressin and released in equal proportions. It is more stable and has a longer half-life than AVP. In adults, copeptin has been established as a biomarker for diagnosis and prognosis of HF [8, 9]. It rises in acute and chronic ventricular dysfunction and also could evaluate pulmonary arterial hypertension and evaluate the outcome and prognosis of right ventricular (RV) dysfunction [10].

As early diagnosis of PHF is challenging, different biomarkers are under study for helping in early prediction of PHF. Furthermore, the existing few biomarkers like troponins and natriuretic peptides (BNP and NT-proBNP) that have been used practically in adult HF diagnosis, however, these biomarkers are infrequently utilized in pediatric HF because the causes are different and are influenced by body size, sex, age, and kidney function. The current focus of PHF diagnosis researches is trying to discover HF-related biomarkers, that

are easy, straightforward, precise, and sensitive procedures to help in the HF diagnosis [11].

This study's objective was to assessthe levels of plasma copeptin in heart failure in infants and children with CHD, to determine its predictive significance in early diagnosis of HF in CHD and its relation to severity of heart failure and correlation of these levels to various echocardiographic and clinical data.

METHODS

Design and population: our case-control study was performed in the pediatric department cardiology unit at Children's Hospital of Zagazig University during the period from April 2022 to December 2023 after the approval from the Institutional Review Board had received (IRB#9751/18-9-2022). All participants' parents or other first-degree relatives wrote an informed consent. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research.

The study recruited a total 64 children, aged 2 months to 2 years, split into two groups: Cases group: included 32 children with CHD presented with manifestations of HF diagnosed and classified according to modified Ross classification and Control group: included 32 apparently healthy, age- and sex-matched children.

Patient Selection

Inclusion Criteria: Pediatric patients with manifestations of HF due to CHD, ages ranging from 2 months to 2 years. However, children with multiple congenital anomalies, renal or liver disease, diabetes mellitus, diabetes insipidus, central nervous system disease, sepsis, malignancies, and cardiac diseases other than CHD, or those who had undergone previous surgical correction of CHD, and neonates or patients aged more than two years were excluded from the study.

All selected children underwent full history taking: age, sex, recurrent chest infection, previous operations, previous hospital and ICU admissions, and anti-failure medications for cases. Complete systemic and general assessment that includes body weight, height, the body mass index (BMI), all anthropometric measurements, respiration rate (RR), pulse rate, blood oxygen saturation, body temperature, systemic blood pressure, and local examination of the heart. Routine laboratory tests comprising full blood picture, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver function tests and renal functions. X-rays chest, electrocardiogram (ECG) and echocardiography (echo) were carried out to all study contributors.

All heart failure (HF) children were evaluated clinically to identify symptoms and clinical signs of HF, such as increased heart rate and respiratory rate, dyspnea, cough, recurrent chest infection, hemoptysis, edema, non-tolerating feeding, and easy fatigability. According to the modified ROSS classification, that confirms the diagnosis of HF with categorization of its severity [5].

Echocardiography:

Echocardiography (echo) was performed to all study participants using the Philips EPIQ CVx system (USA) machine, using 2–3 MHz and 8 MHz transducers, patients were in the supine position and connected to the ECG tracing of the echo machine. Echocardiography was carried out and analyzed by a pediatric cardiologist, who wasn't aware of the clinical grouping and laboratory results to minimize interpretation bias. All measurements followed the standardized guidelines set by the American Society of Echocardiography [12].

Tran thoracic echocardiography (TTE); standard two-dimensional (2D) echo was performed to detect structure of the heart, type of cardiac anomaly and shunt direction. Furthermore, Echo is used to measure the diastolic and systolic cardiac functions, confirming the HF diagnosis in CHD group of after clinical suspicion has

been established by applying the modified Ross, and follow up treatment and outcome.TTE examination included (M mode) motion mode, (PW) pulsed wave Doppler, (CW) continuous wave Doppler, and color flow Doppler.

In long axis parasternal view, M mode is used to measure left ventricular end-diastolic dimension(LVEDD), LV end-systolic dimension(LVESD), LV end diastolic volume (LVEDV), interventricular septum (IVS)and LV posterior wall(LVPW) in end diastole, calculating the LV Ejection fraction(LV EF %) and LV fractional shortening(LV FS %).

LVEF serves as the principle measure systolic function of left ventricle, through the equation of LVEF= [SV/EDV] x 100, as, Stroke volume (SV) is obtained from the difference between end-diastolic volume (EDV) and end-systolic volume (ESV). [13]

Moreover, tricuspid regurgitation (TR) jet, systolic pulmonary artery pressures (sPAP) and pulmonary regurge (PR) were evaluated using CW Doppler echo, right ventricular (RV) diameter also detected. RV longitudinal systolic function measured by tricuspid annular plane systolic excursion (TAPSE) in the four-chamber apical view using M-mode with putting the cursor at the tricuspid annulus free wall. TAPSE mainly reflects the RV longitudinal myocardial contraction in normal hearts, where decreased values indicate RV longitudinal systolic dysfunction [14].

Diastolic function of both ventricles; trans-mitral and tricuspid inflow velocities could be obtained through using pulsed wave (PW) Doppler to detect: (E-wave)peak early filling velocity, (A-wave) peak atrial filling velocity, and E/A ratio, which is considered a marking of diastolic function, when the E/A reduced it refers to impaired relaxation and reduced diastolic filling [15].

Tissue Doppler echo was performed for detecting the myocardial velocities after activation of PW TDI mode in the same machine. TDI can record the peak systolic velocity (S), peak early diastolic velocity (E'), and peak late diastolic velocity (A') waves of both lateral mitral and tricuspid annuli,(E'/A' ratio) and (E/E' ratio). The E/E' ratio assess the filling pressures of LV non-invasively; and can detect the diastolic dysfunction [16]. TDI derived myocardial performance index (Tei index) is used to estimate the global ventricular function of both ventricles independent of geometric inference. It is defined as the ratio between isovolumic time and the (ET) ejection time.MPI = (IVCT + IVRT) / ET [17].

Test Principle: we measured plasma copeptin levels through the Enzyme-Linked Immunosorbent Assay (ELISA) kit usage.

The copeptin levels were calculated using the ELISA kit for Human copeptin (Shanghai Korian Biotech Co. Ltd., Shanghai, China).The intra-and inter-assay coefficients' of variation (CV) were < 10 and < 12% respectively.

Statistical analysis:

The collected data were computerized and statistical analysis was performed using the software SPSS program (Statistical Package for Social Science) version 27.0 (IBM, 2020). Frequencies and relative percentages were used to display the qualitative data.

Quantitative data were expressed as; for normally distributed variables data presented as mean ± SD (Standard deviation), yet for the non-normal distribution median and range were used. To determine the difference between quantitative variables, the Mann Whitney and independent T tests were utilized. To determine the correlation between quantitative variables, the Pearson's and Spearman's correlation coefficients are utilized.We used the receiver operating characteristic (ROC) curve analysis, to get the best cut-off values with the highest sensitivity and specificity for anticipation of outcome. In addition, the area under the ROC curve is employed for measuring the accuracy, positive predictive value (PPV) and negative predictive value (NPV) also calculated from ROC curve. A P value of <0.05 means statistically significant results yet, P value of <0.001 indicates highly significant results [18].

RESULTS:

The current research involved 64 children, displayed equally into two groups. The case group involved 32 children with CHD presented with manifestations of HF; their ages ranging from 2 to 24 months (median 16 months), and they presented as 20 females and 12 males. The control group of 32 healthy age- and sex-matched children, the same range of age, was represented as 16 females and 16 males. The groups did not show any statistically significant differences regarding age or sex distribution. In the present study, the CHD patients are grouped as16 patients with VSD (50% of the cases), 5 patients with large ASD (15.6%), 7 patients with atrioventricular septal defect (AVSD) (21.9%), and 4 patients with PDA (12.5%). Our HF patients received various anti-failure drugs: 96.5% were on Furosemide, 93.8% were on ACEI, 18.8% were on Spironolactone, 18.8% were on beta-blockers, and 12.5% were on Doputamin. The severity of HF in our cases was classified according to the Ross modified classification into 25% class II, 37.5% class III, and 37.5% class IV. The body weight, body mass index (BMI), and O_2 saturation were declined statistically significant across cases comparing to the control group. We had a statistically significantly rise in the heart beats, rate of respiration, systolic and diastolic blood pressure, and body temperature in HF-CHD cases than the controls(Table 1).

Regarding clinical manifestation, all HF cases (100%) manifested by sweating, 28 patients (87.5%) manifested by edema, 24 patients (75%) manifested by tachypnea and tachycardia, 24 patients (75%) manifested by irritability, 20 patients (62.5%) manifested by poor activity, and 18 patients (56.25%) manifested by vomiting. There was a significantly elevation in ESR and CRP levels but a statistically significant decrease of Hbvalues across cases in comparison with the controls. In our study there was a statistically significant rise in MR and LA/AO whereas the AR and AO diameter are statistically significant decreased in cases compared to controls (Table 2). TR, sPAP, and PR showed a statistically significant escalation, in contrary to a statistically significant diminish in RVD, TAPSE, and TAPSE/RVSP between the cases and controls (Table 2). There were no statistically significant differences among the studied groups in IVSD or LVPWD. While there was a statistically significant rise in LVEDD, LVESD, and LVEDV among cases, regarding LV systolic functions, our study reveals a statistically significant decline in FS & EF (mean 57.7±4.7) with ($P < 0.001$) among cases compared to the controls (Table2).

Regarding diastolic functions, there were no statistically significant differences across the investigated groups in mitral E wave, D/T & E/A ratio, and tricuspid A wave, but there was a statistically significant rise in mitral A wave, tricuspid E wave, and E/A and a statistically significant decline in tricuspid D/T among cases compared to controls. (Table 3)

For tissue Doppler velocities, we found no statistically significant variations across the investigated groups regarding Mitral é, á, E/é or É/Á, however, a statistically significant decline in Mitral s was detected when comparing cases to controls. For the Tricuspid É/Á there weren't statistically significant differences across the investigated groups. Conversely, a statistically significant reduction in Tricuspid s, é, and á values in cases when compared to the controls, whereas the Tricuspid E/é ratio increased in the cases relative to the controls (Table 4).

The case group's plasma copeptin levels showed a statistically significantly increase more than those of the control group ($P < 0.001$) (Table 5).

Based on the updated ROSS classification, the severity of HF in CHD children had no statistically significant correlation to their copeptin levels. Copeptin did not exhibit a significant correlation with CRP levels, age, or the type of CHD. Copeptin and HR, RR, and diastolic and systolic blood pressure all had statistically significant positive relationships; temperature and ESR, but there were significant negative correlations with weight, height, BMI, and hemoglobin. Regarding the relationship between copeptin levels and different echocardiographic data, copeptin levels and TAPSE/RVSP ratio showed statistically significant negative

correlations, while copeptin levels represented statistically significant positive correlations with TR, (LA/AO), and PASP. Copeptin correlated statistically significantly positively with both LV end-systolic and LV end-diastolic diameters (LVEDD, LVESD), which indicates higher copeptin levels associated with LV dilation. However, we found the high levels of copeptin correlated significantly negative to the left ventricular fractional shortening (FS%) and ejection fraction (EF%), P < 0.001, suggesting higher copeptin levels correspond to worse left ventricular systolic function. We observed a strong positive correlation between copeptin levels and left atrial filling velocity during late diastole (LV A) and a negative correlation with LV E/A ratio and deceleration time. There was also a significant negative correlation with right ventricular DT. However, copeptin did not significantly correlate with RV E, RVA wave, or RV E/A ratios.

The present study detected a negative statistically significantly correlation between the copeptin levels and mitral (s). However, copeptin did not significantly correlate with mitral (é), mitral (á), mitral E/é ratio, or mitral É/Á ratio. Regarding the tricuspid valve, we revealed a statistically strong negative correlations between copeptin and tricuspid (s) and (á) whereas, a significant positive correlation with tricuspid E/é ratio. Furthermore, the RV myocardial performance index (MPI) had a remarkable positive correlation to the copeptin levels. However, copeptin levels did not significantly correlate with LV MPI. (Table 6)

ROC curve showed that Copeptin levels at cut off >5.3 (ng/dl) had sensitivity 93.2%, specificity 90.6 % and accuracy 92.2 % in prediction of congenital heart disease among the studied groups. (Table 7), (fig 1)

Table 1: Demographic data of the studied groups.

Variable		Cases (n=32)	Control (n=32)	MW/t	P
Weight: (kg)	**Mean ± SD**	6.98+-2.77	8.88+-3.65	2.35	**0.02***
Height: (cm)	**Mean ± SD**	64.5+-12.81	70.62+-13.8	1.84	0.07 NS
BMI: (Kg/m^2)	**Mean ± SD**	15.94+-2.16	17.05+-1.58	**2.36**	**0.02***
Herat Rate: (Beat/min)	**Mean ± SD**	148.8+-11.2	76.59±8.54	29.02	<0.001**
Respiratory Rate: (bath/min)	**Mean ± SD**	53.38±8.5	32.31±3.72	12.8	<0.001**
Systolic blood pressure: (mmHg)	**Mean ± SD**	124±6.78	104.87±5.1	12.7	0.001*
Diastolic blood pressure: (mmHg)	**Mean ± SD**	81.94±3.93	61.18±4.44	19.9	0.001*
O_2 Saturation: (%)	**Mean ± SD**	94.94±3.93	99.44±0.5	6.43	<0.001**
Temperature: (degree)	**Mean ± SD**	38.08±0.83	37±0	7.43	<0.001**

SD: Standard deviation, t: Independent t test, MW: Mann Whitney test,. *: Significant (p<0.05)),**: Highly significant (P<0.001) BMI :body mass index

Table 2: 2D left & right ventricular echo finding& 2D conventional LV systolic functions among the studied groups:

Variable		Cases (n=32)	Control (n=32)	MW/t	P
MR:(mmHg)	**Median Range**	24.5 12-87	21 15-32	2	0.04*
LA/AO: (%)	**Mean ± Sd**	1.54±.282	1.21±.074	6.402	.002**
TR: (mmHg)	**Mean ± Sd**	52.25±21.19	23.06±6.8	7.42	<0.001**
PASP: (mmHg)	**Mean ± Sd**	62.25±21.19	33.06±6.81	8.38	<0.001**
PR: (mmHg)	**Mean ± Sd**	22.06±7.04	10.6±2.66	8.59	<0.001**
RVD: (mm)	**Mean+-Sd**	17.43+-6.8	22.43+-4.84	3.39	0.001*
TAPSE: (mm)	**Mean ± Sd**	17.28±5.27	19.7±2.69	2.32	0.02*
TAPSE/RVSP:	**Mean+-Sd**	0.23+-0.19	0.61+-0.15	6.65	<0.001**

Variable		Cases (n=32)	Control (n=32)	MW/t	P
LVEDD: (mm)	Mean ± Sd	41.8±2.68	34.87±1.09	13.5	0.001**
LVESD: (mm)	Mean ± Sd	26.37±1.14	21.33±1.33	16.21	0.001**
LVEDV: (ml)	Median Range	50.35 44.35-56.35	23.5 20.5-26.5	2.1	0.04*
FS: (%)	Mean ± Sd	29.24±1.69	35.55±1.15	17.40	0.001*
EF: (%)	Mean ± Sd	57.7±4.7	71.06±3.39	13.02	0.001*

MR: mitral regurge, LA: Left atrium, AO: Aorta, TR: Tricuspid valve, PR: Pulmonary regurgitation, PASP: Pulmonary arterial systolic pressure, RVD: Right ventricular diameter, TAPSE: Tricuspid Annular Plane Systolic Excursion LVEED: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVEDV: Left ventricular end diastolic volume, FS: Fractional shortening , EF: Ejection fractiont: Independent t test MW: Mann Whitney test, NS: Non significant (P>0.05), *: Significant (p<0.05)),: Highly significant (P<0.001)**

Table 3: Conventional 2D diastolic function findings across the studied groups:

Variable			Cases (n=32)	Control (n=32)	t/MW	P
LV (Lateral mitral annulus inflow velocities)	LV E: (cm/s)	Mean ± Sd	110.27±34.94	101.96±8.97	1.30	0.20 NS
	LV A: (cm/s)	Mean ± Sd	78.71±21.07	62.84±6.02	4.10	<0.001 **
	LV E/A:	Mean ± Sd	1.52±0.68	1.62±0.18	0.806	0.42 NS
	LV D/T:	Mean ± Sd	132.75±38.62	150.37±39.71	1.80	0.08 NS
RV (Lateral tricuspid annulus inflow velocities)	RV E: (cm/s)	Mean ± Sd	97.55±20.43	83.96±18.16	2.81	0.007*
	RV A: (cm/s)	Mean ± Sd Range	53.96±24.08 29.7-111	51.88±8.23 41-63.5	0.46	0.65 NS
	RV E/A:	Mean ± Sd	2.15±0.91	1.62±0.25	3.19	0.002*
	RV D/T:	Mean ± Sd	109.93±21.93	157.87±45.00	5.42	<0.001**

LV: Left ventricle RV: Right ventricle SD: Standard deviation t: Independent t test MW: Mann Whitney test, NS: Non significant (P>0.05), *: Significant (p<0.05)

Table 4: Tissue Doppler (TDI) Mitral valve and Tricuspid valveannular velocities across the studied groups

Variable		Cases (n=32)	Control (n=32)	t/MW	P
Mitral S′:	Mean ± Sd	6.64±1.52	7.78±1.58	2.93	0.005*
Mitral é:	Mean ± Sd	14.58±4.16	14.8±2.73	0.25	0.80
Mitral á:	Median Range	6.75 4.23-20	7.3 4.57-13.9	1.02	0.31
Mitral E/ é:	Mean ± Sd	7.68±2.00	7.05±1.14	1.54	0.13
Mitral É/ Á:	Mean ± Sd	2.10±0.65	1.86±0.48	1.62	0.11
Tricuspid S′:	Median Range	7.2 3.4-16	11.3 . 7.79-15.5	2.53	0.01*
Tricuspid é:	Median Range	11.3 6.2-22.2	17.4 10.5-26.1	3.82	<0.001 **
Tricuspid á:	Median Range	6.91 2.6-17.5	10.2 6.7-15.1	2.96	0.003*
Tricuspid E/ é:	Median Range	10 3.9-16.7	4.5 3.4-6.9	4.42	<0.001**
Tricuspid É/ Á:	Mean ± Sd	1.78±0.58	1.75±0.30	0.22	0.83
LV-MPI:	Mean ± Sd	0.59±0.26	0.44±0.14	2.87	0.006*
RV-MPI:	Mean ± Sd	0.56±0.11	0.44±0.10	4.55	<0.001**

LV: Left ventricle, RV: Right ventricle, SD: Standard deviation, t: Independent t test, (P>0.05).*Significant (p<0.05),: Highly significant (P<0.001)**

Table 5: Plasma copeptin level across the studied groups.

Variable		Cases (n=32)	Control (n=32)	MW	P
Copeptin:	**Median** **Range**	13.41 5.25-26.52	2.16 1.06-7.14	6.72	<0.001 **

MW: Mann Whitney test **: Highly significant (p<0.001)
There were statistically significant rise in plasma copeptin levels in the case group

Table 6:Correlation between copeptin levels and various clinical data, Mitral valve tissue Doppler data, and Tricuspid tissue doppler data among the studied cases group

Variable	Copeptin (n=32)		Variable	Copeptin (n=32)	
	r	P		r	P
HR:(Beat/min)	0.742	<0.001**	**LV A:**	0.467	<0.001**
RR:(breath/min)	0.605	0.001*	**LV E/A:**	-0.272	0.029*
O2 Saturation: (%)	0.284	0.115	**RV E/A:**	0.188	0.138
Hb:(gm/dl)	-0.457	0.001*	**Mitral s:**	-0.360	0.004*
ESR: (mm/Hl))	0.560	<0.001**	**Mitral é:**	-0.103	0.420
LA/AO: (%)	0.453	<0.001**	**Mitral á:**	-0.152	0.231
LVEDD:	0.650	<0.001**	**Mitral E/ é:**	-0.038	0.765
TR: (mmHg)	0.397	0.001*	**Tricuspid s:**	-0.330	0.008*
PASP: (mmHg)	0.505	0.001*	**Tricuspid é:**	-0.388	0.002*
TAPSE: (mm)	-0.216	0.234	**Tricuspid á:**	-0.367	0.003*
TAPSE/RVSP:	-0.412	<0.001**	**Tricuspid E/ é:**	0.398	<0.001**
FS: (%)	-0.634	0.001*	**LV-MPI:**	0.101	0.427
EF: (%)	-0.542	0.001*	**RV-MPI:**	0.368	0.003*

RR: respiratory rate, HR: heart rate, Hb: haemoglobin, ESR erythrocyte sedimentation rate. LA: Left atrium, AO: Aorta, TR: Tricuspid valve, PASP: Pulmonary arterial systolic pressure, TAPSE: Tricuspid Annular Plane Systolic Excursion LVEED: Left ventricular end-diastolic diameter, FS: Fractional shortening, EF: Ejection fraction, t: Independent t test, r: Correlatoin coefficient (P>0.05)*: Significant (p<0.05): Highly significant (P<0.001)**

Table 7: Validity of serum copeptin in prediction of heart failure among patients with congenital heart disease

Cut off	AUC (CI 95%)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
>5.30(ng/dl)	0.98 (0.97-1)	93.8%	90.6%	90.9%	93.5%	92.2%	<0.001**

AUC: Area under curve, CI: Confidence interval, PPV: +ve predicted value, NPV: -vepredicted value, **: Highly Significant (P<0.001).

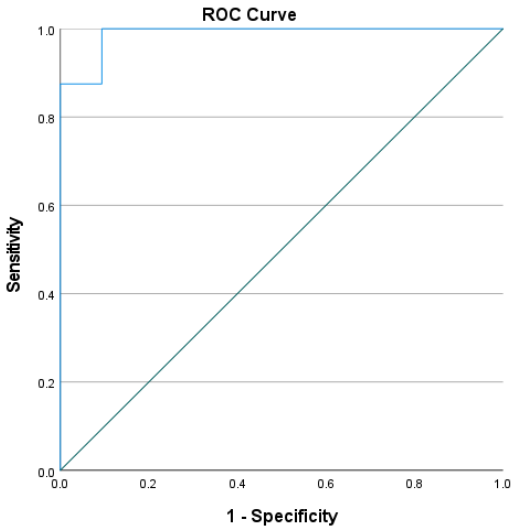

Figure (1): Roc curve for Validity of copeptinin prediction of CHD among the studied groups.

DISCUSSION

HF in pediatrics is linked to higher morbidity and mortality rates. Therefore, identifying a noninvasive biomarker for the early detection of at-risk patients, along with timely intervention and careful monitoring, presents a significant challenge in critical care. Currently, diagnosis of HF is focused on sensitive, straight forward and targeted recent techniques utilizing HF-concerning biological markers [19].

However, frequent studies had investigated the plasma copeptin'spredictive role in adults' HF, still the predictive value of plasma copeptin in early diagnosis of pediatrics' HF under research and assessment.

The current study revealed a statistically significant drop in weight and BMI in the cases as opposed to the control group, in accordance with El-Amrousy et al. [20].

Regarding vital signs and clinical examination, we revealed a statistically significant elevation in temperature, heart rate, respiratory rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in the HF cases in compared to the control group. Furthermore, a statistically significantly decrease was detected in O_2 saturation in CHD children with HF in comparison with healthy controls; these results were in consistence with Alkhaligi et al. [21] and El-Amrousy et al. [20].

We found Hb level was significantly decreased in CHD- HF group in contrast to the control group; nevertheless, a statistically significant rise in CRP and ESR, which was in consistence with El-Amrousy et al. [20] However, contrary to Alkhaligi et al. [21], they didn't find any remarkable variations in Hb and CRP between children and the controls.

In our study, we found that there was a statistically significant elevation in plasma copeptin level in HF-CHD group, ranging from 5.25 to 26.5 ng/dl with a median of 13.4 ng/dl, compared to the control group, which ranged from 1.06 to 7.14 ng/dl with a median of 2.16 ng/dl. This suggesting that copeptin levels may be utilized as prognostic indicator for the diagnosis of heart failure.

Similarly, El-Amrousy et al. [20] demonstrated that children with HF had elevated plasma copeptin levels than the control group, and they got higher in relation to bad prognoses. Moreover, Gaheen et al. [10] were in accordance, and Karaki et al. [22] also reported that plasma copeptin increased in HF children due to cardiomyopathy than control group.

In the current research, LVEF % and LVFS % were statistically significantly decreased among heart failure cases in comparison with the control group, although systolic function remained preserved. El-Amrousy et al. [20] and Karaki et al. [22] were in confirmation with our result.

Regarding own results, we detected a statistically considerable increase in Tricuspid regurgitation (TR), PASP, right ventricular diameter (RVD), and pulmonary regurgitation (PR) in cases than control group. In concordance with Gaheen et al. [10] reported the same findings. Among the cases, there was a statistically significant decline in TAPSE and the TAPSE/RVSP (right ventricular systolic pressure) ratio in comparison with control group, which came in contrast to Karaki et al., who reported that it was non-significant [22]. TAPSE is a reliable and reproducible echocardiographic measurement; it is used to assess longitudinal RV systolic function that considered closely related to the ejection fraction of RV, so the reduced TAPSE and TAPSE/RVSP ratio are indicative of impaired RV systolic function [23].

Concerning to diastolic functions in our research, we detected no statistically significant differences in mitral E/A, LV, D/T, and tricuspid A wave between the two groups, while the mitral A wave, tricuspid E wave, and E/A were a statistically significantly higher in HF-CHD cases than control group. In concordance with Karan et al. [22] reported that there was a statistically significant increase in mitral A velocity. In contrast with El-Amrousy et al. [20] demonstrated the HF cases had a significantly diminished mitral E/A ratio than control group, indicating compromised LV systolic and diastolic functions.

Regarding Tissue Doppler imaging (TDI) findings of the trans-annular mitral valve and tricuspid valve tissue velocities, we did not notice any statistically remarkable differences in Mitral É, Á, E/ É, and É/Á between the two studied groups, but there was a statistically significant decline in Mitral S among cases in comparison with controls. In contrast with El-Amrousy et al. [20] and Karaki et al. [22], we found Mitral E/A was decreased significantly among HF patients and controls. Additionally, the Tricuspid É/Á didn't' detect any recognizable differences among the participants' groups; however, the case group determined a statistically significant rise in Tricuspid E/É relative to the control group, while they reported a significant reduction in Tricuspid é, S′, and á compared to controls. Conversely, to our results, Gaheen et al. [10] reported a statistically significant decrease in Tricuspid É/Á and Tricuspid E/é among the studied groups.

Regarding Tissue Doppler derived MPI, the present investigation indicated a statistically significant increase in LVMPI & RVMPI among cases in comparison with control.

Receiver Operating Characteristic (ROC) curve analysis was utilized for estimating plasma copeptin's predictive value for heart failure in children with CHD. Results showed that a copeptin levels exceeding 5.3 ng/dl demonstrated high diagnostic accuracy, with 93.8% sensitivity, 90.6% specificity, and 92.2% overall accuracy in predicting heart failure among CHD children in the study groups. In accordance with our research findings, El Amrousy et al. [20] reported that copeptin levels was a significant predictor for Heart failure cases, at a cut-off value of copeptin ≥ 19.5 pmol/L according to ROC curve analysis, with 75% sensitivity and 93% specificity in predicting adverse outcomes for acute heart failure children. In another study, Karaki et al. [22] discovered that individuals with copeptin levels above the median of 25 pg/mL were more likely to experience adverse outcomes, as indicated by Kaplan-Meier survival analysis ($p = 0.024$). Plasma copeptin was discovered to be a very reliable indicator of outcomes, with an AUC of 0.861 (95% CI, 0.634-1.089). At the cutoff value of 25 pg /mL, copeptin demonstrated 86% sensitivity and 60% specificity in predicting outcomes Karaki et al. [22]. In a separate study on copeptin levels in CHD children experienced pulmonary hypertension(PH), Gaheen et al. [10] reported that higher copeptin levels in those cases with a detected copeptin cut-off value of 24.2 ng/ml yielding 90% sensitivity and 80%

specificity. Additionally, they found that copeptin has increased levels correlated to the PH severity, and these higher levels can predict opposite consequences [10].

Copeptin levels was found to have statistically significant positive correlations to several clinical and laboratory parameters. Specifically, copeptin levels correlated significantly positively with heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature, and ESR level.

These correlations suggest that copeptin may be a valuable marker for estimating the severity of cardiovascular stress in affected individuals [24]. In concordance with Alkhaligi et al., they reported that copeptin levels were positively correlated HR, temperature, and systolic and diastolic blood pressure [21], in contrast to Karaki et al. [22] and El-Amrousy et al. [20].

Concerning to our research the plasma copeptin established no statistically considerable relation to the degree of HF severity according to Ross classes, whereas Karaki et al. and El Amrousy identified a strong relation between the copeptin and HF classes [22, 20].

Moreover, the current research identified that copeptin has a substantially positive relationship with both LVEDD and LVESD, suggesting that elevated copeptin levels was linked to left ventricular enlargement. However, copeptin levels had a significant negative relation with the LV EF%, LV FS%, and the TDI mitral valve's systolic velocity(S′ wave),in concordance with El Amrousy and Karaki et al., who demonstrated that copeptin correlated negatively with FS% and EF% [20, 22]. This suggests that higher copeptin levels may present with more progressive HF [25]. Additionally, the vasopressin action of vasoconstriction and water retention may affect the myocardium directly, leading to LV hypertrophy and dilatation, resulting in adverse effects on myocardial contractility [20].

In concordance with Karaki et al. [22], the current investigation revealed statistically positive correlations between copeptin and left atrial to aortic root ratio, TR jet velocity, and systolic PAP. However, the plasma copeptin was linked negatively to the RV diameter, TAPSE, and TAPSE/RVSP ratio. In addition, Gaheen et al. found that copeptin stated a valuable relationship between copeptin and mean pulmonary artery pressure [10], which may explain the direct pathological effect of copeptin on increased pulmonary pressure in those cases [26].

Moreover, a high copeptin levels had a strong negative relation with the Mitral E/A ratio, indicating its relation to advanced HF. On the other hand, copeptin showed no significant correlation with the mitral E/é ratio, mitral É/Á ratio, early diastolic mitral inflow velocity (é), or late diastolic mitral inflow velocity (á). However, copeptin did not seem to be correlated with diastolic function parameters or left ventricular filling pressures as determined by mitral inflow Doppler.

In converse to our results, Gaheen et al. discovered that high copeptin levels a correlate in an adverse manner with the RV diastolic functions [10].

There were statistically significant negative correlations between copeptin levels and Tricuspid annular systolic (S′) velocity and RV diastolic functions, such as early diastolic (é) and late diastolic (á) velocities. Whereas the copeptin recognized a remarkable positive correlation with the tricuspid E/é ratio, which all may contribute to chronic pulmonary pressure raising, stimulating RV hypertrophy, which declines RV compliance and diastolic function [27].Furthermore, copeptin levels indicated a significant positive correlation with the RV myocardial performance index.

CONCLUSIONS

According to the current study, plasma copeptin represents a reliable and promising early diagnostic biomarker for heart failure in children having CHD, with levels exceeding 5.3 ng/dL, can accurately distinguish CHD cases with heart failure with high accuracy.

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Limitations:

The study's relatively small sample size was one of its drawbacks; and thus, investigations that are more multicenter are still required for verifying these results.

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Author contributions

ALL authors confirm contribution to the paper as follows: S. A. S. S. , N. A. K. , M. L.M. R. contributed to the study conception and design, material preparation, data collection and analysis. S. A. S. S. and M. L.M. R. recruited patients and performed the clinical examination. N. A. K. and E.S. H. performed the laboratory part of the study. S. A. S. S, M. L.M. R. and E.S.H participated in reviewing the results, performed the statistical analysis of the data. All authors wrote the paper, reviewed, and approved the final version of the manuscript the manuscript. Marwa L. M. Rashad submitted the final manuscript.

Data availability

Data sets recorded and analyzed during the present study are accessible from the corresponding author upon reasonable request.

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Ethics Approval and Consent to participate:

Zagazig University's Research Ethical Committee of the Faculty of Medicine (International Review Board) (ZU-IRB) gave their endorsement of the study. The research adhered to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies comprising human participants. (Approval code: 9751-18-9-2022). All participants' parents or other first-degree relatives gave their written informed consent.

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