ROLE OF SERUM COPEPTIN AND ISCHEMIA-MODIFIED ALBUMIN IN DETECTION OF CARDIAC AFFECTION IN NEONATAL SEPSIS

Eman Mohamed Elsayed [2], Omnia Ibrahim Hegazy [1], Nevin Mohamed Mamdouh [2] and Basma Mohamed Shehata [2]

[1] Department of Pediatrics, Dar-Esmail Hospital, Alexandria, Egypt.

[2] Department of Pediatrics, Faculty of Medicine, Ain-shams University, Cairo, Egypt.

Corresponding author:
Omnia Ibrahim Hegazy
Mobile: +2 01004654805
E-mail:
doctor.omniahegazy@gmail.com

ABSTRACT:

Background: *Neonatal sepsis is a serious condition with increased morbidity and mortality. Cardiac complications are common sequalae for neonatal sepsis with poor prognosis. Utilization of biomarkers for early detection of these cardiac complications helps in improving the prognosis.*

Aim of the work: *Detect the reliability of plasma copeptin and ischemia-modified albumin (IMA) as indicators of cardiac involvement in neonatal sepsis.*

Patients and methods: *The current study included 70 late preterm neonates divided into 3 groups; 30 neonates diagnosed with sepsis and cardiac affection (group 1), 20 neonates diagnosed with sepsis without cardiac affection (group 2) and 20 matched neonates free of sepsis and cardiac affection (group 3). All included neonates had a full history taking, general and local examination. In addition to measuring serum copeptin and IMA levels. Cardiac functions were assessed by transthoracic echocardiography and tissue doppler imaging.*

Results: *A significantly higher mean value of copeptin in group 1 (12.26 ± 4.06 ng/ml), followed by group 2 (4.25±1.56 ng/ml), then group 3 (2.17±0.79 ng/ml) (p<0.001). Also, IMA was significantly higher in group 1 (263.97±81.49 ng/ml), followed by group 2 (68.62±22.08 ng/ml), then group 3 (35.94±10.94 ng/ml) (p<0.001). There was a significant positive correlation between copeptin with IMA.*

Conclusion: *Serum Copeptin and IMA levels are good predictors for detection of cardiac complications in neonatal sepsis besides their role in sepsis detection itself.*

Keywords: *Neonatal, Sepsis, Cardiac, Copeptin, Ischemia-modified Albumin.*

INTRODUCTION:

Neonatal sepsis is a serious condition being responsible for 2.6 million newborns yearly and three-quarters of that number was reported to be in the first seven days postnatal[1].

Infections either bacterial, viral or fungal induce systemic response characterized by hemodynamic changes and clinical findings with subsequent high incidence of morbidity and mortality[2].

The heart is one of the organs affected by sepsis and echocardiographic studies showing right and left ventricular systolic and diastolic dysfunction in cases of sepsis and septic shock[3]. The global tissue hypo-perfusion and oxidative damage are the major causes of poor prognosis in patients with sepsis. These mechanisms cause multi-organ

failure, and this metabolic consequence eventually proceeds to death[4].

Myocardial dysfunction caused by sepsis, so-called "septic cardiomyopathy", is less reported in neonatology, and in case of neonatal sepsis with different terms of gestation in particular. So, there is a need for other parameters including biochemical parameters that would help in improving the prognosis with neonatal sepsis[5].

Cardiac dysfunction in neonates associated with sepsis is not studied as well as that of the adult patients, whose myocardial dysfunction is rather spread with the frequency of registration ranging from 10% to 70%[6].

Copeptin is the 39-amino-acid C-terminal portion of pre-provasopressin molecule which is cleaved in the hypothalamus to release copeptin in the posterior pituitary gland[7]. Copeptin levels are increased in cases with sepsis that could reach 30-fold increase in septic shock[8].

Ischemia-modified albumin (IMA) has been identified as an indicator of myocardial ischemia. Reduced blood flow, acidosis and superoxide-radical injury were also shown to be responsible for IMA formation[9].

These observations could be promising in use of these two markers for prognosis in cardiac condition in sepsis.

AIM OF THE WORK:

the current study was conducted to detect the reliability of plasma copeptin and ischemia-modified albumin as indicators of cardiac affection in neonatal sepsis.

PATIENTS AND METHODS:

Study design:

A cross sectional case control study that included 70 late preterm neonates (gestational age is $\geq$ 34weeks and < 37 weeks) at NICU, Children's Hospital, Ain Shams University, Cairo, Egypt starting from June 2022 till March 2023.

The neonates were distributed into three groups; group 1 (30 neonates diagnosed with sepsis having cardiac affection proved by echocardiographic findings), group 2 (20 neonates diagnosed with sepsis free of cardiac affection by echocardiographic findings) and group 3 (20 matched neonates free of sepsis and cardiac affection).

Studied neonates had the following **inclusion and exclusion criteria:** sepsis was confirmed clinically& laboratory using Tollner criteria[10] including clinical criteria of neonatal sepsis, e.g., poor feeding, hypoactivity, hypoperfusion, pallor or cyanosis, hypo or hyperthermia, apnea or respiratory distress& vomiting and laboratory findings in neonatal sepsis, e.g., rising C-reactive protein (CRP) level, positive blood or urine culture, PCR in viral infections. The cases with the following criteria were excluded congenital heart defects, genetic syndromes, congenital malformations, inborn errors of metabolism and conditions that increase level of serum copeptin & IMA such as history of perinatal asphyxia, maternal comorbidities like preeclampsia and DM, intrauterine growth restriction, acute kidney injury, intracranial hemorrhage& history of major surgical intervention[11,12].

Study tools:

A full history was obtained, general examination was performed, vital data were recorded with plotting of the anthropometric parameters on Fenton growth charts[13]. In addition to local cardiac examination for heart rate and rhythm, searching for murmur and signs of heart failure for all included neonates.

Serum Copeptin and serum Ischemia-modified Albumin levels were measured using commercially available ELISA kits (Cat.No E1129Hu for Copeptin and Cat.No E1172Hu for Ischemia-modified Albumin).

Blood samples of 2 ml were withdrawn into a specimen gel and clot activator tube from septic neonates (within 48 hours from suspecting the hemodynamic instability event) and from the control at matched gestation and postnatal ages.

Then samples were centrifuged for 20 minutes at speed of 2000-3000 RPM, then serum samples were stored at -80°c till the time of analysis, using quantitative Human ELISA kit (ELISA; Enzyme-Linked Immunosorbent Assay) and values were reported as ng/ml.

Transthoracic echocardiography was performed using the portable cardiac ultrasound device model (Philips CX50 ultrasound system, Bothell, WA), the sonographic scan was performed with neonatal cardiac sector S12-4 MHz (CX50) transducer and the cardiac ultrasound unit device model (Vivid E95 ultrasound system, General Electric, Vingmed, Herten, Norway) with a 5 MHz (M5Sc) phased-array transducer. All echo echocardiographic measurements were carried out by the same specialized pediatric cardiologist.

The determination of cardiac dimensions was measured by M-mode and 2-Dimensional Echocardiography. Calculation of fractional shortening and ejection fraction were done according to the recommendations of the American Society of Echocardiography[14].

Transthoracic echocardiographic examination was performed during rests with no sedation while the neonates were in the left lateral position. Two dimensional multi frame B-mode (grey scale) pictures were acquired in the parasternal basal short-axis view, the apical four-chamber view, and the parasternal mid cavity short-axis view (at the level of the papillary muscle, and at the level of the mitral valve)[15].

EF was also obtained from volume data by Simpson's method:

The FS is derived from 2D imaging or M-mode tracings in the PSAX view at the level of the papillary muscles or from in the PLAX view at the tips of the mitral valve leaflets. Left ventricular end-systolic dimension (LVESD) is acquired at the end of the T-wave, whereas left ventricular end-diastolic dimension (LVEDD) is measured at the cardiac cycle's R-wave[16].

FS is calculated using the following equation:

$$FS = \frac{LVEDD - LVESD}{LVEDD} \times 100\%$$

LA: Ao ratio is measured on parasternal LAX using M-Mode. After placing the transducer perpendicular to the aortic valve, a cut is made in the left atrium at the level of the aortic valve. While the left atrium is measured at its maximal volume during the systole, the aortic valve is measured shortly before it opens, at the conclusion of the diastole. The LA/Ao ratio should be less than 1.5[17].

The measurement of the tricuspid and mitral annular plane systolic excursion (TAPSE) and (MAPSE) in the apical four chamber view will also be performed using the M-Mode.

LV and RV diastolic function were estimated by Pulsed Doppler Echocardiography through the measurement of mitral and tricuspid valves E/A ratio respectively[15]. Myocardial performance index (MPI) or Tei index, assessing both systolic and diastolic functions, is calculated from pulsed wave (PW) Doppler at the mitral and aortic valves simultaneously or using TDI tracing at the lateral mitral annulus and then index is derived from the following formula: Tei index = IVRT+ IVCT/ ET

(IVRT is isovolumetric relaxation time, IVCT is isovolumetric contraction time, and ET is the ejection time of LV)[15].

$$EF= \frac{EDV - ESV}{EDV} \times 100\%$$

Mitral and tricuspid valvular incompetence were detected to be present or not by using the Color Doppler Echocardiography[18].

Statistical analysis:

Study data were analyzed using Statistical Package for Social Sciences (SPSS) version 25 for Windows (IBM, SPSS Inc, Chicago, IL, USA). Categorical data were expressed number and percent. The Chi-Square test (Monte-carlo test) made the comparison between two or more groups with categorical data. The quantitative data were tested whether normal distributed or not by using Kolmogorov-Smirnov test and were expressed as median ± SD if was parametric or median (range) if non-parametric.

The one-way ANOVA test was used to compare three groups with quantitative variables that were regularly distributed, and the Kruskal Wallis test was employed if the data were abnormally distributed. ANOVA and the Kruskal Wallis test were followed by post-hoc Tukey or Bonferroni tests, respectively.

Correlation of numeric data was done by Pearson's or Spearman correlation (r). Receiver operator characteristic (ROC) curve was used to detect the best cutoff pint of quantitative variable in differentiating two classes of binary categorical outcome. The dependent and independent risk variables were examined using univariate and multivariate logistic regression analysis. P values <0.05 are considered significant.

Ethical consideration:

The study was carried out with permission from the Ain Shams University Faculty of Medicine's local ethics committee FMASU MS 387/2022. The study was performed in accordance with Helsinki Standards as declared in 2013[40]. Before the study subjects were involved, their parents or legal guardians gave their informed written agreement for them to participate in the study.

RESULTS:

The study included 70 neonates divided into three groups as mentioned before.

All groups were comparable as regards demographical data and perinatal history. Regarding prenatal risk factors, vaginitis had the highest prevalence among mothers. Regarding natal risk factors, PROM was the most common among the studied groups.

There were higher mean values of HR (beat per minute) and capillary refill time (seconds), with more frequent audible murmur, palpable liver and lower limb edema in group 1, followed by 2 and group 3. As well as a higher mean value of urine output in group 3, followed by 2 and group 1. While there is no difference between groups according to mean arterial blood pressure BP (mmHg) and mean airway pressure Paw (cm H2O). As regards arterial blood gases; there were lower PCO2 and HCO3 levels in group1 than group2 and group3. While there is no difference between groups according to PH.

Regarding the blood culture; klebsiella 30% and staphylococci 20% were predominant in group 1, while staphylococci 35%, streptococci 20% and E-coli 20% were predominant in group 2, with predominance of blood cultures with no growth in group 3. Otherwise, there was no difference between groups.

A significantly higher mean value of copeptin in group 1 (12.26 ± 4.06 ng/ml), followed by group 2 (4.25±1.56 ng/ml), then group 3 (2.17±0.79 ng/ml). Also, IMA was significantly higher in group 1 (263.97±81.49 ng/ml), followed by group 2 (68.62±22.08 ng/ml), then group 3 (35.94±10.94 ng/ml). There was a significant positive correlation between copeptin with IMA.

Table 1: Comparison between groups according to laboratory biomarkers.

Laboratory biomarkers	Group 1 (n=30)	Group 2 (n=20)	Group 3 (n=20)	Test value	P-value	Sig.
Copeptin (ng/ml)						
Mean±SD	12.26±4.06	4.25±1.56	2.17±0.79	26.071	<0.001	HS
Range	0.866-23.66	0.74-18.68	0.295-7.283			
IMA (ng/ml)						
Mean±SD	263.97±81.49	68.62±22.08	35.94±10.94	23.5	<0.001	HS
Range	22.3-638.6	16.72-170.2	13.9-76.69			

Table 2: Left and right ventricular function detected by echocardiography.

Echo findings	Group 1 (n=30)	Group 2 (n=20)	Group 3 (n=20)	Test value	P-value	Sig.
Left ventricular function						
LVES-D (cm)						
Mean±SD	0.76±0.10	0.78±0.11	0.99±0.30	9.366	<0.001	HS
Range	0.58-0.91	0.6-0.96	0.5-1.5			
LVED-D (cm)						
Mean±SD	1.62±0.14	1.65±0.17	1.90±0.57	3.868	0.026	S
Range	1.3-1.87	1.34-1.98	1.07-3.1			
IVS-D (cm)						
Mean±SD	0.39±0.07	0.37±0.06	0.37±0.07	1.037	0.583	NS
Range	0.16-0.5	0.25-0.46	0.27-0.49			
LA /Ao R						
Mean±SD	1.29±0.20	1.26±0.14	1.24±0.14	0.995	0.361	NS
Range	1.09-1.73	0.96-1.5	0.92-1.47			
FS (%)						
Mean±SD	30.17±6.93	34.95±4.80	35.40±5.35	2.695	0.032	S
Range	19-45	25-41	28-46			
EF (%)						
Mean±SD	59.93±11.89	64.45±9.51	68.25±7.50	4.137	0.020	S
Range	35-81	42-77	54-80			
MAPSE (mm)						
Mean±SD	3.70±0.82	5.59±0.70	5.85±0.74	60.024	<0.001	HS
Range	2.56-4.97	4.3-7.14	4.82-7.8			
LV Tei Index						
Mean±SD	0.55±0.12	0.50±0.11	0.46±0.13	2.875	0.041	S
Range	0.4-0.86	0.34-0.72	0.21-0.7			
Mitral E/A R						
Mean±SD	0.90±0.32	0.99±0.32	1.15±0.34	3.569	0.034	S
Range	0.3-1.5	0.33-1.55	0.52-1.81			
Mitral regurge						
No	22 (73.3%)	18 (90.0%)	19 (95.0%)			
Mild	6 (20.0%)	2 (10.0%)	1 (5.0%)	5.721	0.221	NS
Moderate	2 (6.7%)	0 (0.0%)	0 (0.0%)			
Right ventricular function						
PASP (mmhg)						
Mean±SD	32.13±6.19	25.70±3.64	23.60±3.35	21.364	<0.001	HS
Range	22-43	18-32	17-30			
TAPSE (mm)						
Mean±SD	7.66±1.82	9.17±1.06	9.72±1.20	13.381	<0.001	HS
Range	5.2-10.9	7.8-11.6	8.1-12.4			
RV Tei Index						
Mean±SD	0.57±0.16	0.46±0.13	0.46±0.12	5.962	0.004	S
Range	0.41-0.95	0.28-0.73	0.26-0.64			

Tricuspid E/A R						
Mean±SD	0.90±0.28	0.97±0.25	1.00±0.34	2.695	0.024	S
Range	0.28-1.4	0.31-1.46	0.4-1.9			
Tricuspid regurge						
No	17 (56.7%)	17 (85.0%)	18 (90.0%)	9.667	0.046	S
Mild	7 (23.3%)	2 (10.0%)	2 (10.0%)			
Moderate	6 (20.0%)	1 (5.0%)	0 (0.0%)			

As shown in Table (2), there were higher mean values of PASP (mmhg), LV Tei Index, RV Tei Index, more frequent Mitral regurge and Tricuspid regurge in group 1, followed by 2 and group 3. Also, higher mean values of LVES-D (cm), LVED-D (cm), FS (%), EF (%), MAPSE (mm), TAPSE (mm), Mitral E/A R and Tricuspid E/A R in group 3, followed by 2 and group 1.

Table 3: Correlation between Copeptin (ng/ml) and IMA (ng/ml) with different parameters in Group 1 and group 2.

Group 1	Group 1				Group 2			
	Copeptin (ng/ml)		IMA (ng/ml)		Copeptin (ng/ml)		IMA (ng/ml)	
	r-value	p-value	r-value	p-	r-value	p-value	r-value	p-value
Copeptin (ng/ml)			0.457	0.011*			-0.267	0.255
IMA (ng/ml)	0.457	0.011*			-0.267	0.255		
GA (wks)	-0.127	0.505	-0.181	0.339	-0.002	0.995	-0.165	0.486
Birth Weight (kg)	-0.058	0.759	-0.094	0.620	0.273	0.245	-0.272	0.246
Apgar Score 1min.	0.194	0.365	0.237	0.264	-0.349	0.497	0.381	0.456
Apgar Score 5min.	0.176	0.412	0.154	0.472	-0.631	0.180	0.755	0.082
HR (beat per minute)	0.113	0.551	-0.027	0.888	0.164	0.490	0.110	0.645
BP (mmHg)	0.183	0.333	0.327	0.077	-0.149	0.531	0.039	0.870
Paw (cm H2O)	-0.364	0.245	-0.591	0.043*	-0.960	0.182	0.958	0.185
Capillary refill time	-0.011	0.955	0.003	0.989	0.478	0.033*	-0.624	0.003*
Urine Output	0.084	0.657	-0.047	0.805	-0.305	0.191	-0.289	0.217
CRP (mg/L)	-0.253	0.177	-0.210	0.266	0.150	0.528	-0.025	0.916
LVES-D (cm)	-0.054	0.820	-0.040	0.867	0.151	0.526	0.250	0.288
LVED-D (cm)	0.092	0.699	0.305	0.190	0.120	0.614	-0.356	0.123
IVS-D (cm)	-0.202	0.332	-0.156	0.444	-0.275	0.240	-0.094	0.694
LA /Ao R	-0.171	0.408	-0.109	0.576	-0.394	0.086	0.235	0.320
PASP (mmhg)	-0.046	0.808	-0.120	0.526	-0.189	0.424	-0.002	0.992
FS (%)	-0.399	0.060	-0.073	0.686	-0.212	0.369	0.075	0.755
EF (%)	-0.067	0.726	-0.143	0.452	-0.399	0.081	0.484	0.031*
TAPSE (mm)	0.148	0.435	0.229	0.224	0.642	0.002*	-0.208	0.378
MAPSE (mm)	0.071	0.711	0.157	0.408	-0.377	0.101	0.285	0.223
RV Tei Index	0.064	0.737	-0.111	0.560	-0.027	0.909	-0.001	0.997
LV Tei Index	0.232	0.270	0.278	0.188	-0.105	0.650	-0.339	0.198
Tricuspid E/A R	0.194	0.445	0.078	0.718	0.269	0.303	-0.268	0.304
Mitral E/A R	0.167	0.481	0.036	0.881	0.169	0.477	-0.078	0.743
Tricuspid regurge	-0.074	0.696	-0.061	0.749	-0.295	0.207	0.079	0.741
Mitral regurge	0.207	0.272	-0.174	0.359	0.037	0.876	0.264	0.260

Table (3) shows that there was a positive correlation between Copeptin (ng/ml) and IMA (ng/ml). As well as a negative correlation between IMA (ng/ml) and MAP (Paw) (cm H2O). Furthermore, in group 2, there was a positive correlation between Copeptin (ng/ml) with Capillary refill time (seconds) and TAPSE. Also, a negative correlation between IMA (ng/ml) with Capillary refill time (seconds) and EF (%). The rest had insignificant correlations.
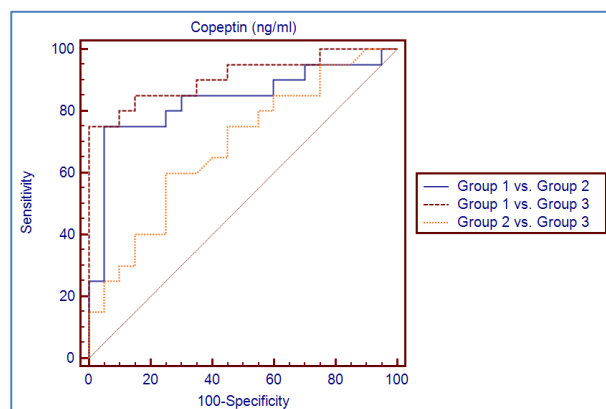

Figure (1)

Table 4:

Groups	Cut-off	Sens.	Spec.	PPV	NPV	AUC (95% C.I.)
Group 1 vs. Group 2	>8.17	73.3%	95%	95.7%	65.2%	0.835 (0.684 to 0.933)
Group 1 vs. Group 3	>5.21	73.3%	90%	91.7%	69.2%	0.910 (0.776 to 0.977)
Group 2 vs. Group 3	>1.83	60%	75%	70.6%	65.2%	0.685 (0.519 to 0.822)

Sens.: Sensitivity, Spec.: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, AUD: Area Under the Curve.

Figure (1) and Table (4): Receiver-operating characteristic (ROC) curve for detection of cardiac affection, using the Copeptin (ng/ml).

The best cut off value for discrimination between septic neonates with and without cardiac involvement using Copeptin was >8.17 ng/ml with sensitiv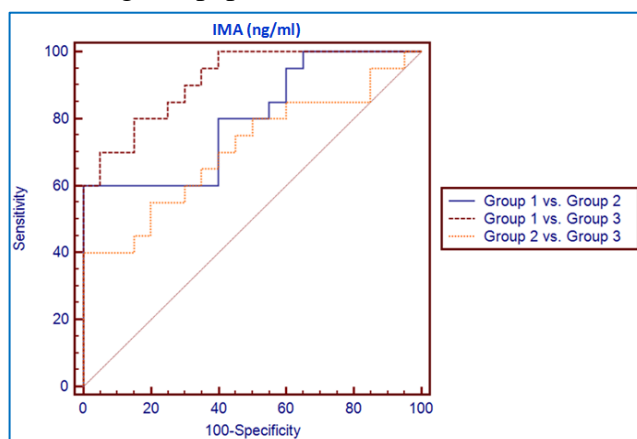ity 73.3% and specificity 95%. Also, the best cut off value for discrimination between septic vs. aseptic neonates using Copeptin was >1.83 ng/ml with sensitivity 60% and specificity 75%.

Figure (2)

Table 5:

Groups	Cut-off	Sens.	Spec.	PPV	NPV	AUC (95% C.I.)
Group 1 vs. Group 2	>170.2	66.7%	100%	100%	66.7%	0.800 (0.644 to 0.909)
Group 1 vs. Group 3	>63.8	76.7%	95%	95.8%	73.1%	0.915 (0.783 to 0.980)
Group 2 vs. Group 3	>38.4	60%	70%	66.7%	63.6%	0.710 (0.545 to 0.842)

Figure (2) and Table (5): Receiver-operating characteristic (ROC) curve for detection of cardiac affection, using the IMA (ng/ml).

The best cut off value for discrimination between septic neonates with and without cardiac involvement using IMA was >170.2 ng/ml with sensitivity 66.7% and specificity 100%. Also, the best cut off value for discrimination between septic vs. aseptic neonates using IMA was >38.4 ng/ml with sensitivity 60% and specificity 70%.

DISCUSSION:

Our cross-sectional study included 70 patients classified as mentioned before. Regarding the initial diagnosis on admission; the most common causes of admission were congenital pneumonia 40% and RDS 23.3% in group 1, while pneumonia 25% and congenital pneumonia 25% were predominant in group 2, with predominance of TTN 45% and neonatal jaundice 40% in group 3. From a total of 30 neonates with early onset sepsis (EOS) in both septic groups; pneumonias represented 100% with absent meningitis, also from a total of 20 neonates with late onset sepsis (LOS) in both septic groups; pneumonias represented 45% and meningitis 15%.

Camargo et al. classified EOS according to the site of infection; primary bloodstream infections were 76.1%, pneumonias 15.2% and meningitis 8.7%. Contrarily, *Berardi et al.* studying LOS; meningitis was 43.7% and pneumonia 30.7%[19, 20].

In assessing the state of adaptation of the neonatal body at birth by Apgar score during the 1st and 5th minutes, there was higher mean value of Apgar score in aseptic than septic groups. Indicating that after delivery, general

condition in neonates with sepsis was worse than the aseptic group. In agreement with our findings, *Koloskova and Kretsu* reported that Apgar score in the group of myocardial dysfunction in neonates with sepsis, with similar range of gestational age, was lower than in the healthy group (during the 1st and 5th minutes, respectively)[21].

As regards general examination and vital signs, the first group had higher level of heart rate and more prevalent audible murmur than the other two groups, indicating the severity of sepsis. They also had higher rates of hepatomegaly, lower limb edema, prolonged capillary refill time and oliguria maybe secondary to cardiac affection on top of sepsis. *Camargo et al.* while studying complications of neonatal sepsis among similar gestational age group, found there were tachycardia in 6.5% of cases, hypotension in 21.7% and oliguria 8.6%[21]. Behairy et al found that hepatomegaly was present in more in than 60%[22]. Similarly, Fahmey & Mostafa found that septic babies had a prolonged capillary refill time than healthy ones, they also found that septic cases had lower mean blood pressure than aseptic ones [23], which goes against our findings.

As regards to blood culture in our study, staphylococci 26% were predominant in septic groups followed by klebsiella 18% and E-coli 18%, while there was no growth in most of blood cultures in aseptic group. Our findings matched those of *Elshimi et al.* reporting that the most common isolated micro-organisms were gram-positive microbes (coagulase negative staphylococci in 66.7%) followed by gram-negative microbes (klebsiella 25%) and fungi (8.3%)[24]. In a study done by *Fahmey & Mostafa* as regards the microorganisms identified in septic blood cultures; Klebsiella

pneumoniae was the most common organism (43%) followed by coagulase-negative Staphylococci CONS (20%)[23].

As regards echocardiographic findings in cases and control; LVESD and LVEDD were lower in septic compared to aseptic neonates, this may be related to hemodynamic alteration and profound hypovolemia due to sepsis, which can induce myocardial depression and dysfunction. This went with the findings of the studies by *Abdel Hakeem et al.* and *Tomerak et al.* Contrarily, Alazharani demonstrated that there was increase in LVESD with normal range of LVEDD among septic group. While *AboElnour et al.* found an increase in LVEDD with normal range of LVESD among septic group[25-28].

Regarding LV function by echocardiographic findings; fractional shortening (FS, measuring LV systolic function) was lower in in septic than non-septic neonates. This is consistent with the Alazharani's stud [27]. On the other hand, *Fahmey et al.* found no difference in FS% between the septic neonates and their control group[18].

Furthermore, the LV's ejection fraction EF% which measures its systolic function, was lower in septic than aseptic neonates. Our results were supported by Alazharani's study[27]. These were against *Awany et al.* reporting no difference between septic and healthy neonates regarding EF[29].

The systemic inflammatory response in neonatal sepsis can also lead to microvascular dysfunction. The inflammation causes endothelial dysfunction and microvascular leakage, leading to decreased tissue perfusion and oxygen delivery to the myocardium. Reduced oxygen supply to the myocardium can further impair its contractile function and contribute to decreased EF[25].

Preterm septic group showed lower MAPSE in comparison to aseptic group reflecting the impairment of longitudinal myocardial functions of left ventricle. This was supported in the study of *Alzahrani et al.*[27].

One of the key mechanisms contributing to decreased left ventricular function is the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6). These cytokines can have direct negative effects on myocardial contractility and relaxation, leading to decreased fractional shortening and MAPSE[18].

In addition, the inflammatory response leads to synthesize of reactive oxygen species (ROS) and nitric oxide (NO) within the myocardium. Excessive ROS production can cause oxidative stress, leading to cellular damage and dysfunction. Nitric oxide, on the other hand, can impair myocardial contractility by inhibiting the intracellular calcium handling process within the cardiomyocytes. Disrupted calcium signaling impairs the myocardial contractile apparatus, which is essential for proper myocardial contraction[25].

The LV Tei index " MPI " increased in the septic neonates compared to aseptic group. The higher myocardial performance index (MPI) indicates impaired diastolic function of LV in septic patients' group. The investigations by *Awany et al.* which discovered a rise in the LV tei index, are consistent with this[30]. The Alazharani's study, in contrast, found no difference in LV tei index between septic and aseptic neonates[27].

Regarding mitral inflow: preterm septic patients' group had lower E/A ratio across mitral valve compared to aseptic group, indicating left ventricular diastolic dysfunction. This finding was also reported by *Fahmey et al.*[18].

Another factor contributing to decreased left ventricular diastolic function in neonatal sepsis is the disruption of the normal balance between myocardial relaxation and stiffness.

Inflammation and oxidative stress can lead to alterations in the extracellular matrix of the myocardium, causing fibrosis and increased myocardial stiffness. The increased stiffness of the myocardium impairs its ability to relax fully during diastole, resulting in impaired left ventricular filling[18].

Regarding right ventricular function detected by echocardiographic findings in our study; pulmonary artery pressure was substantially higher in septic than aseptic neonates. Also, septic patients' group had higher left atrial diameter compared to healthy group. Additionally, Abdel *Hakeem et al.* revealed that the septic group had greater pulmonary artery pressure than the healthy group, validating our findings[25].

Preterm septic group showed lower TAPSE in comparison to aseptic group reflecting the impairment of longitudinal myocardial functions of right ventricle. This was supported in the study of *Alzahrani et al.*[27].

In our investigation, septic neonates had a greater RV tei index than aseptic neonates. The higher MPI compared to control group indicates impaired global diastolic function of RV in septic patients' group. *Awany et al.* also demonstrated that, supporting our results[29].

Decreased right ventricular diastolic function could be associated to endothelial dysfunction and can lead to vasoconstriction and increased pulmonary artery pressure. Elevated pulmonary artery pressure indicates increased resistance to blood flow in the pulmonary circulation, which can negatively impact left ventricular diastolic function. The increased afterload imposed on the left ventricle can impair its ability to relax and fill adequately during diastole[18].

According to tissue Doppler analysis, the right ventricle's diastolic function represented by the tricuspid E/A ratio, was found to be considerably poorer in the examined neonates with sepsis than in the aseptic group indicating right ventricular diastolic dysfunction. This is consistent with the study by *Abdel Hakeem et al.* which showed that the tricuspid E/A ratio was lower in cases than in control[25].

The pathophysiology behind decreased right ventricular function in neonatal sepsis involves the interplay of several mechanisms. Inflammation and the release of pro-inflammatory cytokines can directly impact myocardial contractility and relaxation of the right ventricle. The increased pulmonary artery pressure due to pulmonary vasoconstriction and vascular changes can increase the afterload on the right ventricle, leading to decreased contractility and impaired systolic function[30].

Furthermore, sepsis-induced endothelial dysfunction and microvascular leakage can cause fluid shifts and tissue edema, including in the right ventricle. Right ventricular edema can further compromise its function by increasing myocardial stiffness and impairing relaxation[31]. Tricuspid regurge was more frequent among neonates in septic group than control group.

Regarding Copeptin (ng/ml), it was higher in group 1 (12.26±4.06), followed by group 2 (4.25±1.56), then group 3 (2.17±0.79). *Abd El-Hai et al.* studied copeptin level in neonates with dilated cardiomyopathy to healthy controls; they detected that copeptin levels were higher in the patients' group with means of (32.26 ±21.9) and (8.97±1.04), respectively[32]. Gonchar et al. also reported that serum copeptin levels were higher among patients with post-hypoxic myocardial damage than healthy controls[33].

On the other hand, *Schlapbach et al.* reported no difference when comparing copeptin concentrations between neonates with sepsis and controls[34].

According to *Benzing et al.* there is no relationship between copeptin levels and the method of delivery; nevertheless, copeptin

levels rise in cases of chorioamnionitis, reduced placental perfusion, low birth weight and gestational age, and higher respiratory support requirements (indicating that Copeptin is a highly sensitive marker of perinatal stress)[35].

In addition, regarding correlation of Copeptin with cardiac function on our study, Copeptin levels were positively correlated with Mitral regurge and Tricuspid regurge incidences, while its levels were negatively correlated with ejection fraction percentages; however, they weren't significant.

In a study by *El Amrousy et al.* copeptin level was directly correlated with degree of heart failure, age, heart rate and respiratory rate and inverse correlation with left ventricular fraction shortening and diastolic function[36].

Also, a meta-analysis study done by *Yan et al.* on a total of 13 studies till May 2016 concluded that a higher level of plasma copeptin is linked to a higher risk of cardiac failure[37].

Using ROC curve, the best cut off value of Copeptin >8.17 (ng/ml) for discrimination between septic neonates with and without cardiac affection groups with sensitivity 73.3% and specificity 95%. Furthermore, we found that Copeptin can also differentiate between septic and healthy neonates. This can be done using ROC curve where the best cut off value using Copeptin (ng/ml) to detect sepsis is >1.83 with sensitivity 60% and specificity 75%.

Copeptin at a cut-off point ≥ 19.5 pmol/L showed sensitivity of 75% and a specificity of 93% in predicting adverse outcome in children with HF as shown by *El Amrousy et al.* who also showed that copeptin level directly correlated with the degree of HF[36].

Furthermore, regarding ischemia-modified albumin (IMA) (ng/ml) in our study, there was higher mean value of IMA in group 1 (263.97±81.49), followed by group 2 (68.62±22.08), then group 3 (35.94±10.94).

Similar results by *Azzab et al.* who reported that IMA level was higher among sepsis group compared to control group (82.7 vs 24.4 ng/ml respectively)[38], and by Abdel-Aty et al finding a difference between sepsis group and control group as regards mean serum IMA level (103.7± 31.82 versus 85.36 ± 14.07 ng/ ml) with positive predictive value 80% and negative predictive value 65%[24]. In addition, *Yerlikaya et al.* reported that the serum IMA levels increase in the septic cases in comparison to healthy controls[12].

Regarding IMA relation with cardiac involvement; *Goncher et al.,* also reported similar findings, they found that serum IMA levels were higher among the study patients (post-hypoxic myocardial damage) than healthy controls. We also found positive correlation between IMA with the linear size of LV, namely LVES-D and LVED-D, however, they were not significant. Similar, yet more significant results were reported by *Goncher et al.* reported that IMA showed a direct relationship with LVES-D and LVED-D[33].

Furthermore, we found that there was negative correlation between gestational age and birth weight with Copeptin and IMA, however, it wasn't significant. In a study by *Elraggal et al.* on preterm neonates diagnosed antenatally with IUGR, the IMA level was higher in the cases group compared to the other group. At a cut-off point of >50 IMA had an AUC of 0.850, a sensitivity of 92.5% and a specificity of 67.5% for prediction of IUGR[39]. On the other side, *Azzab et al.* reported that there was no difference between full term and preterm neonates with sepsis in IMA level[38].

While, regarding ROC curve for the neonates with sepsis and echo findings group, and the neonates with sepsis and echo free group, the area under the curve was 0.800. The best cut off value for discrimination between group 1 vs. group 2 using IMA (ng/ml) to detect cardiac affection was

>170.2 with sensitivity 66.7% and specificity 100%.

Furthermore, Regarding ROC curve in the neonates with sepsis group, vs the healthy control group, the area under the curve was 0.710. The best cut off value for discrimination between Group 2 vs. Group 3 using IMA (ng/ml) to detect sepsis was >38.4 with sensitivity 60% and specificity 70%.

In agreement with our findings, *Azzab et al.* reported in their study that the area under the curve (AUC) for IMA was 0.804 and best cutoff value of IMA level for detection of neonatal sepsis is >30 ng/ml[38].

Despite the obtained results, the study had some limitations such as the small included sample size and the cross-sectional nature of the study. Echocardiogram is operator dependent and the study was performed by a single specialized cardiologist. Also, the two studied biomarkers have indefinite half-life to be depended on.

Conclusion:

Neonates with sepsis may have notable alterations in their cardiovascular status; yet echocardiography provides a dependable and practical means of assessing the heart's function throughout this phase. We concluded that serum IMA and Copeptin levels are good predictors of sepsis. Furthermore, they were found to differentiate between septic neonates with and without cardiac affection. Further studies are needed to confirm their reliability.

Conflict of Interest:

Authors declare no conflicts of interest.

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REFERENCES:

1. **Jemal B, Abebe T, Zemedkun A, Basu B, Mola S, Neme D, et al.** Determinants of neonatal mortality in the neonatal intensive care unit of Dilla University Referral Hospital, Southern Ethiopia; 2019–2020; A matched, case–control study. Heliyon. 2022;8(9):e10389.

2. **Nyenga AM, Mukuku O, Wembonyama SO.** Neonatal sepsis: A review of the literature. Theory and Clinical Practice in Pediatrics. 2021;3:94-101.

3. **Giesinger RE, McNamara PJ, editors**. Hemodynamic instability in the critically ill neonate: an approach to cardiovascular support based on disease pathophysiology2016: Elsevier.

4. **Cetin M, Oray NC, Bayram B, Calan OG.** The prognostic value of ischemia-modified albumin in patients with sepsis. Nigerian Journal of Clinical Practice. 2021;24(5):680-4.

5. **Hawiger J.** Heartfelt sepsis: microvascular injury due to genomic storm. Kardiologia Polska (Polish Heart Journal). 2018;76(8):1203-16.

6. **Kretsu N, Koloskova O, Bilous T.** Markers of myocardial dysfunction in neonates with sepsis of various gestational age. Acta Medica International. 2021;8(2):132-7.

7. **Saleh NY, Aboelghar HM, Garib MI, Rizk MS, Mahmoud AA.** Pediatric sepsis diagnostic and prognostic biomarkers: pancreatic stone protein, copeptin, and apolipoprotein AV. Pediatric Research. 2023:1-8.

8. **Rey C, García-Cendón C, Martínez-Camblor P, López-Herce J, Concha-Torre A, Medina A, et al.** High levels of atrial natriuretic peptide and copeptin and mortality risk. Anales de Pediatría (English Edition). 2016;85(6):284-90.

9. **Reddy CB, Cyriac C, Desle HB.** Role of "Ischemia Modified Albumin"(IMA) in acute coronary syndromes. Indian heart journal. 2014;66(6):656-62.

10. **Töllner U.** Early diagnosis of septicemia in the newborn: clinical studies and sepsis score. European journal of pediatrics. 1982;138:331-7.

11. **Keller T, Tzikas S, Zeller T, Czyz E, Lillpopp L, Ojeda FM et al.** Copeptin improves early diagnosis of acute myocardial infarction. *Journal of the American College of Cardiology.* 2010;55(19):2096-2106.

12. **Yerlikaya FH, Kurban S, Mehmetoglu I, Annagur A, Altunhan H, Erbay E, et al.** Serum ischemia-modified albumin levels at diagnosis and during treatment of late-onset

neonatal sepsis. The Journal of Maternal-Fetal & Neonatal Medicine. 2014; 27(17): 1723-7.

13. **Fenton TR, Kim JH.** A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC pediatrics. 2013;13(1):1-13.

14. **Groves AM, Singh Y, Dempsey E, Molnar Z, Austin T, El-Khuffash A et al.** Introduction to neonatologist-performed echocardiography. Pediatric Research. 2018; 84(1):1-12.

15. **Tissot C, Sekarski N, Singh Y.** Echocardiographic Evaluation of Left Ventricular Function and Hemodynamic Status. Point-of-Care Ultrasound for the Neonatal and Pediatric Intensivist: A Practical Guide on the Use of POCUS: Springer; 2023. p. 57-70.

16. **Bokiniec R, Własienko P, Szymkiewicz-Dangel J& Borszewska-Kornacka MK.** Echocardiographic analysis of left ventricular function in term and preterm neonates at week 40 of postconceptional life. Kardiologia Polska (Polish Heart Journal). 2019;77(4), 445-450.

17. **Arlettaz R.** Echocardiographic evaluation of patent ductus arteriosus in preterm infants. Frontiers in pediatrics. 2017;5:147.

18. **Fahmey SS, Hodeib M, Refaat K, Mohammed W.** Evaluation of myocardial function in neonatal sepsis using tissue Doppler imaging. The Journal of Maternal-Fetal & Neonatal Medicine. 2020; 33(22): 3752-6.

19. **Berardi A, Sforza F, Baroni L, Spada C, Ambretti S, Biasucci G, et al.** Epidemiology and complications of late-onset sepsis: an Italian area-based study. PloS one. 2019;14(11):e0225407.

20. **Camargo JFd, Caldas JPdS, Marba STM.** Early neonatal sepsis: prevalence, complications and outcomes in newborns with 35 weeks of gestational age or more. Revista Paulista de Pediatria. 2021;40.

21. **Koloskova OK, Kretsu NM.** Diagnostics of septic myocardial dysfunction in neonates. Modern Pediatrics Ukraine. 2022(5 (125)):19-25.

22. **Behairy AOG, Abdulhameed AA, Hamed MM, Abdelmotaleb DS.** Fibroblast Growth Factor 19 As A Predictor for Gastrointestinal-Liver Dysfunction in Neonatal Sepsis. Benha Medical Journal. 2023;40(2):474-84.

23. **Fahmey SS, Mostafa N.** Pentraxin 3 as a novel diagnostic marker in neonatal sepsis.

Journal of neonatal-perinatal medicine. 2019;12(4):437-42.

24. **El Shimi MS, Abou Shady NM, Hamed GM, Shedeed NS.** Significance of neutrophilic CD64 as an early marker for detection of neonatal sepsis and prediction of disease outcome. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30(14):1709-14.

25. **AbdeL Hakeem AM, Abdelmotalep MM, Eldahshan TA-K.** Assessment of Cardiac Functions in Neonatal Sepsis. Al-Azhar International Medical Journal. 2021;2(12):46-50.

26. **AboElnour SI, Al Gameel AL, Hammad NM.** Frequency of Myocardial Dysfunction in Neonatal Sepsis: A Single Center Experience. Pediatric Sciences Journal. 2024;4(1):34-41.

27. **Alzahrani AK.** Cardiac function affection in infants with neonatal sepsis. J Clin Trials. 2017;7(1):2167-0870.

28. **Tomerak RH, El-Badawy AA, Hussein G, Kamel NRM, Razak ARA.** Echocardiogram done early in neonatal sepsis: what does it add? Journal of Investigative Medicine. 2012;60(4):680-4.

29. **Awany M, Tolba O, Al-Biltagi M, Al-Asy H, El-Mahdy H.** Cardiac functions by tissue doppler and speckle tracking echocardiography in neonatal sepsis and its correlation with sepsis markers and cardiac troponin-T. J Pediatr Neonatal Care. 2016;5(3):00184.

30. **Wynn JL, Wong HR.** Pathophysiology of neonatal sepsis. Fetal and Neonatal Physiology. 2017:1536.

31. **Schwinger RHG.** Pathophysiology of heart failure. Cardiovascular diagnosis and therapy. 2021;11(1):263.

32. **Abd El Hai AM, Abdellatif A, Ali AAL, Sameer HA.** Assessment the Value of Serum Copeptin Level in Dilated Cardiomyopathy in Pediatrics. Zagazig University Medical Journal. 2021;27(3):516-27.

33. **Gonchar M, Ivanova Y, Kondratova I.** A possible role of troponin I, copeptin and ischemia-modified albumin in prognosis of the development of post-hypoxic myocardial damage in newborns. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). 2020;9(1):e090134-e.

34. **Schlapbach LJ, Frey S, Bigler S, Manh-Nhi C, Aebi C, Nelle M, et al.** Copeptin concentration in cord blood in infants with early-onset sepsis, chorioamnionitis and

perinatal asphyxia. BMC pediatrics. 2011;11:1-8.

35. **Benzing J, Wellmann S, Achini F, Letzner J, Burkhardt T, Beinder E, et al.** Plasma copeptin in preterm infants: a highly sensitive marker of fetal and neonatal stress. The Journal of Clinical Endocrinology & Metabolism. 2011;96(6):E982-E5.

36. **El Amrousy D, Abdelhai D, Nassar M.** Predictive value of plasma copeptin level in children with acute heart failure. Pediatric Cardiology. 2022;43(8):1737-42.

37. **Yan JJ, Lu Y, Kuai ZP, Yong YH.** Predictive value of plasma copeptin level for the risk and mortality of heart failure: a meta-analysis. Journal of cellular and molecular medicine. 2017;21(9):1815-25.

38. **Azzab HS, Abdelrahman IN, Abdelnaim AA.** ASSESSMENT OF THE ROLE OF SERUM ISCHEMIA MODIFIED ALBUMIN IN THE EARLY DIAGNOSIS OF NEONATAL SEPSIS. Al-Azhar Journal of Pediatrics. 2015;18(1):1348-59.

39. **Elraggal N, Abdelghani A, Nawara M, Erian M, Shehata BM.** Ischemia-Modified Albumin in Cord Blood of Preterm Infants: A Novel Indicator for Intrauterine Growth Restriction-A Prospective Case Control Study. The Egyptian Journal of Hospital Medicine. 2023;90(2):2161-9.

40. **Association WM.** World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.

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دور الكوببتين والألبومين المعدل بنقص التروية فى الكشف عن تأثر القلب لدى الأطفال حديثى الولادة المصابين بتسمم الدم

إيمان محمد السيد 2، أمنية إبراهيم حجازى1، نيفين محمد ممدوح 2، بسمة محمد شحاتة2

قسم الأطفال ـ مستشفى دار إسماعيل ـ الإسكندرية 1
قسم الأطفال ـ كلية الطب جامعة عين شمس ـ القاهرة 2

المقدمة: يعد تسمم الدم لدى حديثى الولادة حالة خطيرة تسبب ارتفاع معدلات المرض والوفاة. يعد تأثر القلب من المضاعفات المعتادة لتسمم الدم وهو ذو إنذار سيئ. استخدام الدلالات الحيوية للكشف المبكر عن تأثر القلب قد يساهم في تحسين مسار المرض.

الهدف من الدراسة: اكتشاف موثوقية الكوببتين والألبومين المعدل بنقص التروية كمؤشرات على تأثر القلب نتيجة تسمم الدم لدى حديثى الولادة.

المرضى وأساليب البحث: شملت الدراسة 70 طفل مبتسر غير مكتمل النمو تم تصنيفهم إلى ثلاث مجموعات؛ حيث تضمنت المجموعة الأولى 30 طفل حديث الولادة مصاب بتسمم الدم ولديه نتائج إيجابية بالموجات الصوتية على القلب، وتضمنت المجموعة الثانية 20 طفل حديث الولادة مصاب بتسمم الدم دون نتائج إيجابية بالموجات الصوتية على القلب، بينما تضمنت المجموعة الثالثة 20 طفل متطابق من حديثى الولادة الذين لا يعانون من تسمم الدم أو نتائج الموجات الصوتية على القلب. تم أخذ التاريخ المرضى تفصيلاً والفحص الشامل للجسم. كما تم قياس مستوى الكوببتين ومستوى الألبومين المعدل بنقص التروية فى الدم. تم استخدام الموجات الصوتية على القلب وتصوير دوبلر لتقييم وظائف القلب لدى الولدان الذين تمت دراستهم.

النتائج: أسفرت نتائج الدراسة فيما يتعلق بمستوى الكوببتين (نانوجرام/مل)؛ كان أعلى بكثير فى المجموعة الأولى (12.26 ± 4.06)، تليها المجموعة الثانية (4.25 ± 1.56)، ثم المجموعة الثالثة (2.17 ± 0.79). علاوة على ذلك، فيما يتعلق بقيمة الألبومين المعدل بنقص التروية (نانوجرام/مل) فى دراستنا؛ كانت هناك قيمة أعلى بكثير بالمجموعة الأولى (263.97 ± 81.49)، تليها المجموعة الثانية (68.62 ± 22.08)، ثم المجموعة الثالثة (35.94 ± 10.94).

الاستنتاج: وعليه استنتجنا أن مستويات الكوببتين والألبومين المعدل بنقص التروية في الدم تعد مؤشرات جيدة للتمييز بين حديثى الولادة المصابين بتسمم الدم أولئك الذين يعانون من خلل بوظائف القلب والذين لا يعانون منها. وذلك علاوة على دورهم فى الكشف عن تسمم الدم ذاته.

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