Neonates with sepsis and cardiovascular dysfunction

Abstract

Background: Neonatal sepsis (NS) is a common cause of morbidity and mortality in newborns. Cardiovascular dysfunction (CVD), including biventricular impairment, altered vascular tone, and elevated pulmonary arterial pressure (PAP), is a frequent complication. **Aim:** To evaluate CVD in neonates with NS admitted to the NICU at Benha University Hospital. **Subjects and Methods:** This prospective observational research included neonates with NS in the NICU between July 2024 and December 2024, alongside an age- and sex-matched control group. All participants underwent functional echocardiography (f-Echo) for cardiac assessment. **Results:** In both NS and control groups, 50% were male. Birth weight ranged from 2.2–3.5 kg (mean 2.9 ± 0.3 kg). Thrombocytopenia was observed in 63.3% of NS cases, leukocytosis in 16.7%, and 36.7% exhibited significant neutrophil shift. Echocardiography demonstrated notable CVD in NS patients, which improved significantly following sepsis resolution (MAPSE) mitral annular plane systolic excursion, (TAPSE) tricuspid annular plane systolic excursion (1.71, 1.81) after resolution of sepsis (1.99, 2.11). There is significant association between (f-Echo) parameters and mortality, ejection fraction 64% in survivors 53% in non survivors. **Conclusion:** NS is associated with marked CVD, detectable and monitorable via f-Echo, highlighting the importance of cardiac evaluation in septic neonates.

Keywords: Neonatal sepsis; Targeted neonatal echocardiography; Myocardial dysfunction; inflammatory response syndrome.

1-Introduction:

Neonatal sepsis constitutes a critical form of invasive infection observed in newborns, wherein pathogenic microorganisms infiltrate the bloodstream, an environment that is typically sterile. The term "invasive disease" specifically denotes the pathological transgression of bacteria into normally aseptic compartments of the body, like the circulatory system, posing a profound risk to neonatal health [(1)].

The pathogenesis of sepsis-related myocardial dysfunction is multifactorial, involving impaired myocardial perfusion, direct myocardial suppression, and mitochondrial derangements.

Echocardiography emerges as a cornerstone in the non-invasive assessment of cardiac structure and function. Its capacity to be employed at the bedside offers immediate, real-time hemodynamic evaluation, making it an indispensable tool in neonatal intensive care. Through echocardiographic imaging, clinicians are able to delineate the cardiovascular profile of each neonate and tailor therapeutic approaches to address the specific underlying physio pathological abnormalities [(2)].

[fECHO], a specialized extension of point-of-care ultrasound [POCUS], has become increasingly integrated into the clinical protocols of intensive care units. fECHO serves not merely as a diagnostic modality, but as a dynamic bedside technique that empowers clinicians to address targeted clinical questions swiftly. This approach facilitates timely interventions and enhances procedural safety, particularly in the context of hemodynamic instability or when performing invasive procedures within the ICU setting [(3)].

In the Neonatal Intensive Care Unit [NICU], the role of fECHO is complementary rather than substitutive. It does not seek to replace the comprehensive cardiovascular evaluation conducted by pediatric cardiologists. Rather, fECHO offers neonatologists a practical and immediate tool for refining diagnostic accuracy and guiding clinical management, ultimately improving neonatal outcomes through individualized care strategies [(4)].

2- Subjects &Methods:

This investigation was designed as prospective observational research aimed at elucidating cardiovascular alterations in neonates with sepsis. A total of 45 neonates diagnosed with NS and admitted to the neonatal intensive care unit at Benha University Hospital during the period from July 2024 to December 2024."constituted the case group. An equal number of healthy, age- and sex-matched neonates were enrolled as the control group to serve as a baseline comparator. To minimize confounding factors, neonates with congenital heart disease (CHD), infants of diabetic mothers (IDM), those who had experienced perinatal asphyxia, and neonates with

chromosomal anomalies or known metabolic disorders were systematically excluded from the research.

Diagnostic Criteria for Neonatal Sepsis:

The diagnosis of NS was established based on a combination of clinical and laboratory criteria. Clinically, neonates were considered septic if they exhibited at least two of the following signs: feeding intolerance, temperature instability, apnea, diminished reflexes, or delayed capillary refill exceeding two seconds. Their number was 27 cases. Laboratory confirmation required the presence of at least two of the following abnormalities: leukopenia (<5,000/mm³), leukocytosis (>20,000/mm³), thrombocytopenia (<100,000/mm³), and elevated C-reactive protein (CRP >10 mg/dL). Blood cultures were also obtained to detect and identify the causative bacterial pathogens. The cases had positive blood culture and lab were 18 cases. A detailed patient history was collected, and a comprehensive clinical examination was performed, including assessment of complete blood count, CRP, and blood culture with sensitivity.

Echocardiographic Assessment:

f-Echo was conducted for all research participants. In the case group, echocardiographic evaluation was repeated following clinical resolution of sepsis to monitor changes in cardiac function. Cardiac dimensions were quantified using M-mode and two-dimensional (2D) echocardiography. Left ventricular (LV) systolic performance was assessed using fractional shortening (FS%) and ejection fraction (EF), in accordance with the guidelines of the American Society of Echocardiography [(5)]. Additional parameters, including the Tei index and mitral annular plane systolic excursion (MAPSE), were measured to evaluate LV function comprehensively. Right ventricular (RV) performance was estimated by measuring tricuspid annular plane systolic excursion (TAPSE) and calculating the RV Tei index [(6,7)]. M-mode imaging facilitated precise measurement of both TAPSE at the tricuspid annulus and MAPSE at the lateral mitral annulus and basal septal region in the apical four-chamber view.

Statistical Analysis:

Collected data were systematically organized, tabulated, and analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation (SD) with range, while categorical data were presented as frequencies and percentages. Comparisons between the case and control groups were performed using the independent t-test for continuous variables and the chi-square (χ^2) test for categorical variables. Pearson correlation analysis was conducted to explore relationships between the Tei index and other echocardiographic parameters, providing insights into the interdependence of cardiac functional measures in the context of NS.

Ethical consideration:

Ethical approval and consent to participate this research was conducted in full compliance with the ethical principles outlined in the declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Benha University. Prior to participation, all participants or their legal guardians provided written informed consent after receiving a comprehensive explanation of the research's objectives, procedures, potential benefits, and associated risks.)

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4-Results:

Regarding anthropometric measures, the data shows that all measured parameters were significantly diminished in the cases as opposed to controls. **Table1**

The result shows that wide distribution of klebsiella and MRSA methicillin resistant staph aureus between cases. **Fig 1**

Regarding vital signs and mortality, the results indicate that while heart rate (HR) exhibited comparability between survivors and non-survivors other vital signs exhibited more substantial differences. **Table 2**

Table 3 reveals a strong association between the occurrence of serious complications and neonatal death. **Table 3**.

Table 4 has shown that MAPSE, TAPSE, ESD, ESV are significantly affected among septic patients ($P<0.05$). The confidence level taken for the study is 95%. Therefore, the p-values obtained less than the level of significance ($\alpha=0.05$) are considered significant.

5- Discussion

Neonatal myocardial dysfunction (NMD) is conventionally linked to intrinsic conditions like inborn errors of metabolism, mitochondrial disorders, or neuromuscular diseases. However, it may also arise secondarily in the context of systemic insults, most notably NS. In the present research, approximately one-third of full-term neonates with NS demonstrated evidence of myocardial dysfunction despite the absence of structural cardiac anomalies. The underlying mechanisms contributing to this phenomenon remain incompletely understood. It is possible that myocardial impairment represents a component of the systemic inflammatory response syndrome (SIRS) triggered by infection. Alternatively, the dysfunction may reflect the relative immaturity of the neonatal immune system, which is overwhelmed by infectious stimuli. Another potential mechanism involves the downregulation of β-adrenergic receptors at the cardiomyocyte level, mediated by various bacterial products collectively referred to as myocardial depressant factors (MDFs) [(8)].

It is important to note that immune profiling was not performed in the current research, limiting the ability to clarify the relative contributions of immune dysregulation versus direct myocardial insult. Moreover, the possibility that affected neonates harbored undiagnosed metabolic, mitochondrial, or neuromuscular disorders cannot be excluded, as no systematic neonatal metabolic or genetic screening was conducted [(9)]. Additional factors, like drug- or toxemia-induced mitochondrial membrane injury, may also have contributed to myocardial compromise.

Hemodynamic responses to sepsis in neonates differ markedly from those observed in older children and adults, exhibiting considerable variability and unpredictability [(10)]. Early recognition and prompt, aggressive supportive therapy for sepsis-associated myocardial dysfunction are critical in reducing neonatal morbidity and mortality [(11)]. In this research, RV function, assessed using TAPSE, and LV function, measured by MAPSE, were significantly impaired among septic neonates. Interestingly, the

myocardial performance index (Tei index) for both ventricles did not differ significantly between septic and control groups.

In agreement with our results Nguyen and co-authors (15) further reported that early-onset NS is associated with increased HR variability during stationary monitoring periods, suggesting autonomic and hemodynamic perturbations occur early in the septic course. septic neonates demonstrated significantly higher LV Tei index and lower TAPSE and MAPSE values compared with controls, indicating both systolic and diastolic dysfunction. These findings are consistent with the work of Abtahi and co-authors (13) exhibited significantly elevated RV and LV Tei indices in septic neonates. In contrast, to merak and co-authors (12) reported marked reductions in LV diastolic function, as indicated by a diminished E/A ratio, without significant alterations in EF or FS, in line with Abdel-Hady and co-authors (14) demonstrated that tissue Doppler imaging (TDI) indices of global myocardial function (RV and LV Tei) were significantly increased, while atrioventricular annular systolic velocities were markedly reduced in septic infants. These findings underscore the sensitivity of echocardiography in detecting subtle myocardial dysfunction. our data highlighted a more comprehensive pattern involving both systolic and diastolic dimensions, as shown by significantly increased EDD, ESD, EDV, and ESV. This discrepancy may be attributed to differences in disease severity, timing of echocardiographic assessment, and the use of functional parameters such as TAPSE and MAPSE, which are not universally evaluated in previous reports.

Clinical Implications

The observed alterations underscore the value of f-Echo as a bedside tool to detect early and subtle cardiovascular dysfunction in septic neonates. Elevated Tei index and reduced annular plane excursions may serve as red flags to guide fluid resuscitation, the initiation of inotropes, and careful avoidance of fluid overload. Based on our findings, we propose a structured protocol in which f-Echo is performed at baseline (diagnosis), post-resuscitation, and during clinical deterioration to guide real-time individualized therapy. Such an approach could complement conventional monitoring and potentially improve survival outcomes in this vulnerable population.

Conclusion:

Sepsis-induced cardiovascular dysfunction constitutes a major contributor to morbidity and mortality in the neonatal population. Despite its clinical relevance, knowledge regarding the epidemiology, pathophysiology, and prognostic implications of this condition remains limited, partly due to the lack of standardized definitions for NS and its cardiovascular complications. Functional echocardiography provides a sensitive and non-invasive tool for early detection, and timely supportive management remains essential for improving outcomes in this vulnerable population. Ongoing research is warranted to elucidate the mechanisms underlying myocardial dysfunction in NS and to develop standardized diagnostic and therapeutic protocols.

Limitations:

Small sample size, single center design, short follow up (limited to sepsis resolution, no long-term cardiac outcomes)

Supplementary Materials

No supplementary materials were associated with this research.

Author Contributions

- **Dr. Mostafa Abdel Azim** conceptualized the research, designed the research methodology, and provided overarching supervision throughout the project. He offered expert guidance in formal data analysis and maintained the scientific rigor and integrity of the research process.
- **Dr. Omima Abdel Hai** played a pivotal role in developing the research framework, refining methodological approaches, and overseeing analytical procedures. Her supervisory input was critical in ensuring the research objectives remained clinically relevant and scientifically robust.
- **Dr. Eman Amer** was primarily responsible for data collection, execution of experimental procedures, and conducting clinical investigations. She led the statistical analyses, ensuring that the results were interpreted accurately and systematically.

- **Walaa Abdallah Saleh** contributed substantially to the validation phase, performed key clinical procedures, and actively participated in drafting and editing the manuscript. Her editorial efforts significantly enhanced the clarity, readability, and overall coherence of the final manuscript.

All authors have carefully reviewed, revised, and approved the final version of the manuscript and accept full responsibility for its accuracy and integrity.

Declaration of Competing Interest

The authors declare that there are no financial, personal, or institutional conflicts that could have influenced the research outcomes. This declaration underscores the objectivity, independence, and transparency of the research.

Ethical Approval and Consent to Participate

This research was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Benha University. Prior to participation, all participants or their legal guardians provided written informed consent after receiving a comprehensive explanation of the research's objectives, procedures, potential benefits, and associated risks.

Consent for Publication

No individual-level data, images, or identifiable information are included in this manuscript. Therefore, specific consent for publication was not required beyond the general informed consent obtained for research participation.

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Conflicts of Interest

The authors declare that no conflicts of interest exist.

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Table 1: Anthropometric measures among the studied groups

	Control (n=45)		Cases (n=45)		t-statistic	P
	Mean	SD	Mean	SD		
Weight in kg	3	0.5	2.9	0.3	6.25	<0.001*
Head circumference in cm	34.13	1.56	31.85	2.36	6.26	<0.001*
Length in cm	48.10	3.15	43.30	4.35	6.92	<0.001*
Abdominal girth in cm	31.52	3.09	27.67	3.49	6.40	<0.001*

Table 2: Vital signs concerning mortality among cases

	Survivors (n=60)		None Survivors (n=30)		t-statistic	P
	Mean	SD	Mean	SD		
HR (beat /min)	140.53	11.94	141.27	27.77	-0.10	0.92
RR (cycle/ min)	52.69	4.63	60.33	14.98	-1.95	0.07
SBP (mmHg)	62.36	7.51	46.20	5.65	8.79	<0.001*
DBP (mmHg)	42.42	6.27	30.31	4.44	7.84	<0.001*

HR: heart rate, **RR:** respiratory rate, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure

Table 3: Complications in relation to mortality among cases

	Survivors (n=60)		None Survivors (n=30)		X^2 statistic	P
	No.	%	No.	%		
DIC	0	0.00	6	40.00	36.44m	<0.001
NEC	0	0.00	2	13.33		
Septic shock	1	2.22	3	20.00		
None	44	97.78	4	26.67		

DIC: disseminated intravascular coagulopathy, **NEC:** necrotizing enterocolitis.

Table4: Cardiac echocardiographic assessment in sepsis cases versus controls

	Control (n=45)		Cases (n=45)		P
	Mean	SD	Mean	SD	
SA (m^2)	0.21	0.02	0.20	0.01	0.177
RV Tei	0.31	0.03	0.30	0.03	0.240
LV Tei	0.36	0.03	0.36	0.03	0.695
TAPSE (cm)	1.98	0.34	1.71	0.33	0.004*
MAPSE (cm)	2.09	0.36	1.82	0.35	0.005*
EDD (cm)	2.32	0.07	2.31	0.05	0.230
EDV (ml)	12.57	1.12	12.21	0.78	0.146
ESD (cm)	1.54	0.03	1.62	0.04	<0.001*
ESV (ml)	3.62	0.22	4.18	0.19	<0.001*

***:** significant **SA**: surface area, **RV Tei**: right ventricular Tei index, **LV Tei:** left ventricular Tei index, **TAPSE:** tricuspid annular plane systolic excursion, **MAPSE:**

mitral annular plane systolic excursion, **EDD:** end diastolic diameter, **EDV:** end diastolic volume, **ESD:** end systolic diameter, **ESV:** end systolic volume.

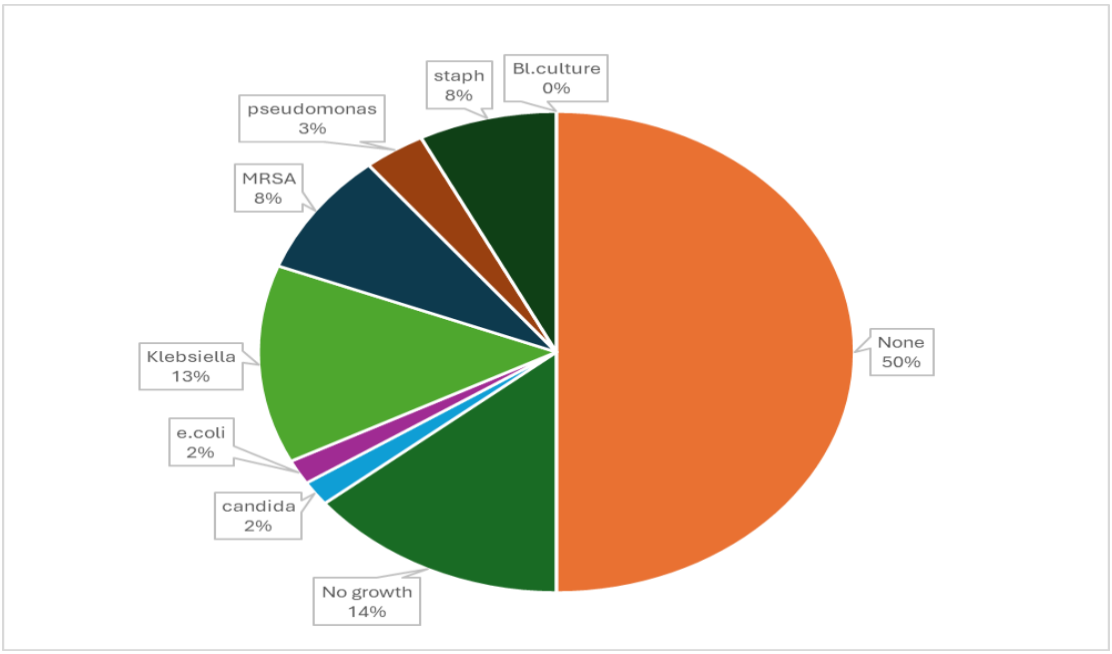

Figure (1) Distribution of microorganisms in blood culture.