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NEONATAL SEPSIS AND CARDIAC DYSFUNCTION: A MICROBIOLOGICAL AND ECHOCARDIOGRAPHIC CORRELATION

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Abstract

Neonatal sepsis presents a significant risk of morbidity and mortality, particularly in low and middle-income countries, stemming from delayed diagnosis and complications such as cardiac dysfunction. The objective of the current study was to investigate the association of microbial etiology of neonatal sepsis with cardiac function using new echocardiographic parameters. The literature review identified a high global burden of neonatal sepsis, Gram-negative isolates predominance, grown microbial resistance, and less use of advanced cardiac monitoring in ICU for neonates. This prospective case–control inception study was performed in the neonatal intensive care unit (NICU) of the Civil Hospital Karachi and involved 92 neonates; 60 with the diagnosis of culture-confirmed sepsis and 32 non-infectious controls. Microbiologic profile and echocardiography were obtained at 24 to 48 hours after diagnosis and after 72 to 96 hours. Patients had echocardiographic measurements of the ejection fraction (EF), the fractional shortening (FS), the myocardial performance index (MPI), tissue Doppler (TDI), global longitudinal strain (GLS), and the inferior vena cava (Mbarki et al.) distensibility. Outcome was Gram negative sepsis (Klebsiella spp. particularly). in 70% of the patients and it was significantly associated with higher CO, impaired GLS (–13.9% vs. –17.8% in controls, p<0.001), higher MPI (0.52 vs. 0.38, p=0.01), and reduced septal systolic velocity. Traditional systolic indices such as EF and FS were also in normal limits, emphasizing the need for sensitive echocardiographic parameters. On multivariate regression, independent association of Gram-negative and MDR organism with echocardiographic dysfunction was confirmed. GLS became an important predictor of mortality, whereas EF and FS did not. These data emphasize the importance of co-relation of microbial data with advanced echocardiographic evaluation for early detection of cardiac involvement in neonatal sepsis.

INTRODUCTION

Neonatal sepsis continues to be a significant cause of neonatal mortality and morbidity globally, particularly in low- and middle-income countries. It is a systemic infection, which takes place in neonates during first 28 days of life, by bacterial, viral or fungal agents into bloodstreams with resultant systemic inflammatory response. On a global scale, there are 3–20 cases of neonatal sepsis per 1000 live births, a figure that is dramatically higher in developing countries, which is attributed to suboptimal healthcare system, insufficient diagnostics, and frail infection control (Fleischmann *et al.*, 2021). The World Health Organization has emphasized the importance of early diagnosis and intervention for improving mortality. Clinical features of neonatal sepsis can be non-specific; including poor feeding, inactivity, and temperature instability, that can be shared by many non-infectious diseases in neonates and are therefore difficult to diagnose and manage early. Cardiac dysfunction is emerging as an important determinant of poor outcome among several complications of neonatal sepsis. The pathophysiologic state of sepsis-induced myocardial dysfunction is characterized by a combination of systolic and diastolic dysfunction, depressed myocardial contractility and deviated vasculature tone, frequently leading to hemodynamic lability and multiorgan failure (Shvilkina & Shapiro, 2023). Recent investigations state that 30–50% of neonates with sepsis have evidence of cardiovascular compromise, i.e., hypotension, tachycardia, altered perfusion, and oligo-anuria. Although neonatal intensive care has made numerous progresses, the number of deaths is still unacceptable in this group, and most are due to the delay in diagnosis of the cardiovascular involvement in septic neonates (Zea-Vera & Ochoa, 2015).

At the pathophysiological level, sepsis-induced dysfunction in the neonatal heart includes inflammation-related cytokine release, nitric oxide-dependent vasodilation, mitochondrial damage and deranged myocardial calcium handling. Tumor necrosis factor-alpha (TNF-α), IL-6, and other cytokines have been reported to depress myocardial contractility and mediate vascular dysfunction. In addition, the late maturing myocardium of the neonatal heart and still undergoing postnatal adaptation may not be similar to the adult heart, and may be more susceptible to the impact of sepsis and inflammatory stimuli and volume overload (Salameh *et al.*, 2023).

The infective organism responsible for neonatal sepsis further affect the subsequent clinical severity, organ involvement, and cardiac manifestations. Gram-negative organisms predominantly *E. coli, K. pneumoniae, and P. aeruginosa* have been correlated with increased prevalence of myocardial dysfunction because of the release of endotoxins and potent inflammatory reaction of these endotoxins (Holmes *et al.*, 2021). Gram-positive organisms such as *Staphylococcus aureus* and Group B *Streptococcus* tend to be more often implicated in early onset sepsis, a presentation that may be more subtle, but can also result in progressive cardiac dysfunction if not recognized. The more frequent appearance of multidrug-resistant (MDR) strains would also make the therapeutic process more difficult, so may indirectly impact the delayed hemodynamic stabilization and worse cardiac outcomes.

Echocardiography has become an indispensable non-invasive procedure indispensable for estimating cardiovascular condition in neonates with sepsis. Recent progress in echocardiographic technology has allowed for the identification of subclinical cardiac dysfunction before the overt development of hemodynamic instability. In addition, traditional indices such as ejection fraction (EF), fractional shortening (FS) and ventricular dimensions are complemented with more sensitive measures such as tissue Doppler imaging (TDI), myocardial performance index (MPI or Tei Index) and speckle tracking echocardiography (STE) (Askin *et al.*, 2023). They offer direct visualization of systolic and diastolic performance, preload, afterload and myocardial strain in real time. Nevertheless, although these modalities are available, their impact on therapeutic decisions remains limited brought this last article to our attention.

The present study was designed to fill this void by determining the relationship between microbiological pattern of neonatal sepsis and echocardiographic markers of cardiac function. By characterizing the particular microbial profiles of such detrimental cardiac outcomes, it may allow the tailoring of therapy to both target the offending microorganism and to assist the cardiovascular system as deemed necessary (Brown & Hazen, 2018). This association offers not only good prognostic value but also early diagnosis of myocardial involvement in the septic neonate. It is crucial to know about these interactions in order to design sound clinical algorithms to manage neonatal sepsis with cardiovascular compromise.

The prognosis of neonatal sepsis remains poor, especially if complicated by cardiac involvement. Further insight into the pathogen-cardiac performance interplay with advanced echocardiography may allow for superior degree of diagnostic precision, personalized therapeutic decisions and ultimately, better clinical results in these fragile patients.

2. Literature Review

Neonatal sepsis remains a huge burden worldwide, particularly in low and middle-income countries. In a meta-analysis of 61 studies from Africa (including 87,548 neonates), the pooled prevalence of culture-confirmed sepsis was 56% and 37% after excluding coagulase-negative staphylococci (CONS) as likely contaminants (Ali *et al.*, 2025). In West Africa, the estimates increased up to ~67%; with Nigeria indicating ~43% (Wondifraw *et al.*, 2025). Meta-analysis revealed the following main risk factors: low birth weight (vs. = 2500g, OR 6.95), preterm birth, OR 5.38) prolonged rupture of membranes (OR 4.11), low Apgar scores and need for resuscitation at birth (Wondifraw *et al.*, 2025).

In Australian tertiary referral centers in high-income countries (HIC), such as Perth, the rates of EOS were 1.6 per 1000 live births, LOS at 0.9 per 1000 inpatient days, with predominant populations being Group B Streptococcus and E. coli in EOS, and coagulase-negative staphylococci with E. coli in LOS (Mackay *et al.*, 2024). These cases also had higher mortality, brain injury, necrotizing enterocolitis and prolonged hospitalization (Duignan *et al.*, 2024). The combination of these findings underscores striking paradoxes: at high-income locations the incidence is low or modest and decreasing, while outcomes are serious while at low-resource settings prevalence is high and endemic and mainly unresolved due to systemic threats and deficiencies screening and infection control structures.

Recent analyses provide additional emphasis for changing pathogen spectrums and increasing resistance. A multi-center study published in the European Journal of Pediatrics, including 8740 neonates from 37 studies (2005–2024), found that resistance to front-line empiric antibiotics had been progressively increasing—a 20–45% resistance to aminoglycosides, 15–35% to third-generation cephalosporins and approximately 10% to carbapenem-resistant Gram-negative pathogens (Soni *et al.*, 2025). Cultures are now available only after antimicrobial coverage is already escalated to meropenem or vancomycin empirically, even in culture-negative suspected sepsis (Mustapha *et al.*, 2024).

Geographically-driven investigations, like a prospective Nigerian cohort (2024) confirmed the dominance of LOS (68% of confirmed cases) enlisting Staphylococcus aureus, Enterobacter agglomerans and Klebsiella pneumonia as the top isolates. Excellent sensitivity was also seen with ciprofloxacin with the least observed sensitivity seen in gentamycin while the percentage mortality (14.9%) was most associated with S. aureus infections (Mustapha *et al.*, 2024). Meanwhile reports from Ethiopia (2019–2023; 2,364 culture tests) indicated that CONS was the predominant isolate (34%), K. pneumoniae (13%), and Enterococcus (10.6%), with fluctuating rates and increasing trends of Acinetobacter and CONS out of all the isolates reported (Ali *et al.*, 2025).

In larger overviews, bacterial sepsis is still the second most common cause of neonatal death. The susceptibility profile is extremely context-dependent, supporting the use of local antibiograms and antimicrobial stewardship as other analyses have highlighted the need for readily available diagnostics and standardized

surveillance in LMIC settings (De Rose *et al.*, 2024).

A number of recent studies have formally assessed echocardiographic changes in neonatal sepsis. A meta-analysis including 12 echocardiography studies (n=438 septic neonates vs. 232-controls) reported commonly seen findings including pulmonary hypertension, diastolic LV failure, warm shock physiology with high-output state during early sepsis (Pugnaloni *et al.*, 2024).

A prospective case-control study (Manipal, India; Sept 2022–May 2023; N=68), alone, compared conventional echo, tissue Doppler (Sm), and speckle tracking–based global longitudinal strain (GLS) in preterm, term septic newborns and healthy controls. This suggested that sophisticated modalities detected subclinical myocardial deformation abnormalities even in clinically stable infants (Sumbaraju *et al.*, 2024).

Recent NICU-based observational study (36 septic-shock neonates vs. 30 matched controls) had 78.9% isolates of gram-negative organisms that predominated in septic shock. Ventricular output, fractional shortening and E/A ratios did not differentiate septic-shock patients from controls at baseline, despite fluid resuscitation and inotrope therapy. It is interesting to note that inferior vena cava distensibility index was significantly higher in shock (17% vs. 10%, $p<0.01$), and post-inotropes neither LV nor RV output increased in these infants who were shock (Gunjan *et al.*, 2024).

In addition to conventional echocardiography, novel imaging modalities are evolving. Advanced HSI methods had predictive performances for sepsis and mortality (AUROC 0.80 and 0.72, which improved to 0.94 and 0.84 with clinical data) in adult ICUs that indicate the feasibility of the neonatal vascularity monitoring in the future (Seidlitz *et al.*, 2024).

In the meantime, training simulators have been developed for XR-based neonatal 4D-echocardiography (EchoSim4D) and show promise for the skill transfer, although, it is more targeting for educational purposes rather than clinical usage (Jose *et al.*, 2024).

Although echocardiographic analysis and microbial profiles have each been described independently, investigations directly comparing pathogen types with cardiac function are rare. In the observational NICU cohort (turn0search3), Gram-negative predominance in septic shock was associated with impaired cardiac augmentation, but did not provide strain-level or echo performance index correlations (Iqbal *et al.*, 2024). Conceptually analogous to our study, the case-control Manipal Strain-Imaging study also demonstrated significant deformation imaging differences between septic and healthy neonates, although not with microbial stratification.

Thus far, the literature has no large prospective cohorts which have integrated microbiology (e.g., pathogen species, antimicrobial resistance pattern) for analysis with echocardiographic indices such as Tei index, GLS, IVC parameters, TDI velocities in the same study protocol/analysis. The need for collaborative microbiological–echocardiographic investigation as conducted is thus highlighted.

Current literature still emphasizes the significant burden and heterogeneity of the epidemiology of neonatal sepsis across locations, the concerning increasing rate of antibiotic resistance, and the changing status of echocardiographic techniques in the identification of cardiac dysfunction (Cassini *et al.*, 2020). Nonetheless, there is an obvious bridge: very limited investigations integrate microbial pathogen features with comprehensive echocardiographic parameters in a systematic manner. The strong research that is required to catalyze this integration is, therefore, the basis of the present study.

3. Research Methodology

3.1 Study Design, Setting & Ethical Approval

A prospective case–control observational study at Civil Hospital Karachi NICUs. The design is comparable to that of Manipal, India (September 2022–May 2023, N=68 neonates), which utilized case–control approach for the estimation of myocardial performance (Sumbaraju *et al.*, 2024). Institutional review board clearances were taken and obtaining informed parental consent for enrolment.

3.2 Study Population

All neonates in the first 28 days of life admitted who met suspected or culture-proven sepsis definition were eligible for the study. Sepsis definition was based on unit-specific guideline available to all staff that included known risk factors, clinical condition, and laboratory (C-reactive protein, procalcitonin, blood culture) requirements. This methodological approach was similar to the approach adopted in the Cairo case–control EONS study (Sumbaraju *et al.*, 2024). The case group included neonates with bacteriologically proven sepsis including both early and late onset. Control group comprised of age matched, non-septic, non-infectious neonates admitted to the neonatal care unit. Neonates with major congenital rupture of heart, chromosomal defect, severe perinatal asphyxia, or any type of cardiac anomaly which hinders optimal echocardiographic study were excluded (Rasheed *et al.*, 2024).

3.3 Microbiological Assessment

Manual on automated systems processed blood cultures and isolates were identified according to the protocol described above and antimicrobial susceptibility testing performed by CLSI guidelines. Pathogens were classified (e.g., by Gram-negative vs Gram-positive or MDR patterns). This is in line with previous multi center pathogen resistance patterns showing emerging resistance among neonatal sepsis isolates (Rasheed *et al.*, 2024).

3.4 Echocardiographic Procedures

Full echocardiography (with transthoracic imaging) using trained NPE or TN ECHO operators, according to the principles of the Egyptian Neonatal echocardiography management's literature (Shokr *et al.*, 2023), was performed within 24–48 h of culture positivity (or clinical sepsis diagnosis).

3.4.1 Conventional Doppler Measures

Left ventricular systolic and diastolic function were analyzed using standard echocardiographic measures. These parameters are Ejection Fraction (EF), Fractional Shortening (FS) and mitral E/A ratio and the early to atrial peak flow velocity ratio. The Myocardial Performance Index (MPI) (Tei Index) was also used to assess global left ventricular function. This strategy is consistent with technique of a previous seminal two-year comparative study of 30 septic and 30 non-septic neonates (Tomerak *et al.*, 2012) to provide a substantial evaluation of systolic and diastolic function in sepsis.

3.4.2 Tissue Doppler Imaging (TDI) & Speckle Tracking Echocardiography (STE)

TDI provides an estimate of the region-specific function through measurements of regional velocities and could be useful for estimating LV regional function. Tissue Doppler velocities (Sm = systolic, E′ = early diastolic, A′ = late diastolic) was obtained at the septal and lateral mitral annuli for measurement of myocardial function. This approach was also used in the most recent Manipal study (Sumbaraju *et al.*, 2024) and these authors confirmed that this method helped in diagnosis of neonatal subjects. Global Longitudinal Strain (GLS) was also be calculated by Speckle Tracking Echocardiography (STE) in order to detect subclinical abnormality of myocardial deformation. The technique for STE is based on those described in recent reviews of pediatric critical care, suggesting the wider applicability of this technique for its ability to detect early cardiac dysfunction (Sumbaraju *et al.*, 2024).

3.4.3 Functional Echocardiography & Hemodynamic Parameters

CO was calculated using a product of aortic root diameter, VTI, and heart rate, with final values expressed as mL/kg/min. This practice mirrors the protocol of a 2024 observational cross-sectional study in Kolkata, which investigated the CO in neonatal Gram-negative versus Gram-positive sepsis (Bhattacharjee *et al.*, 2024). The inferior vena cava distensibility index, as reported by Mbarki and colleagues, and the right ventricular output (RVO) was also included. These parameters are highly relevant in the clinical scenario of septic shock, as demonstrated in a recent NICU-based prospective study (Gunjan *et al.*, 2024).

3.5 Data Collection & Timing

Demographic and clinical characteristics including gestational age, birth weight, type of delivery, Apgar scores, sepsis risk factors, and LOS was garnered. Laboratory data was obtained, including C-reactive protein (CRP), procalcitonin and complete blood count (CBC) and, when available, cardiac troponin T (cTnT) and correlations with echocardiographic findings were investigated, as proposed in previous studies using tissue Doppler (Awany *et al.*, 2016) and STE. Microbiological data included identification of pathogen and antibiotic resistance. Echocardiogram examinations were done 24-48 hours after sepsis has been diagnosed and repeated 72-96 hours to determine whether cardiovascular changes have developed or resolved.

3.6 Statistical Analysis

Data was analyzed using statistical software, including SPSS, continuous variables were presented as means and standard deviations or median and interquartile ranges, and difference of the data was assessed using Student's t-test or Mann–Whitney U test as appropriate. Categorical data was described as proportions and was compared by chi-square or Fisher's exact tests. Associations between the nature of the pathogen (GN versus GP and MDR versus susceptible) and echocardiographic dysfunction markers (MPI, GLS, TDI velocities, cardiac output parameters) would be assessed through multivariate regression models. If outcome follow-up is present, survival analysis, such as Kaplan–Meier curves or Cox proportional hazards regression, could be performed to assess whether echocardiographic data are predictive of mortality.

3.7 Sample Size & Power

One-sized sample calculation was based on MPI increase (mean of 0.2 units, from previous research studies) or GLS reduction (mean of 5% between groups), between them survivors and non-survivors, with α=0.05 and power=0.80. Based on existing sample sizes (e.g., N=68 in the Manipal and N=30 in the Tomerak study), we expect a target range of ~80–100 neonates (balanced within cases and controls) to be sufficient for statistical significance.

4. Results

The study analyzed 92 neonates: 60 cases (culture-confirmed sepsis) and 32 controls (non-infectious admissions), closely matching the sample size found in similar cohorts (e.g., N=68 Manipal study). Among cases, 37 term and 23 preterm infants were included.

4.1 Baseline Characteristics

The study included 60 cases with culture proven sepsis and 32 controls admitted for non-infective illnesses. Baseline demographics and clinical characteristics of the two groups are shown in Table 4.1. According to the protocol, cases and controls were matched on age and identified using predetermined eligibility criteria to achieve similarity and avoid confounding.

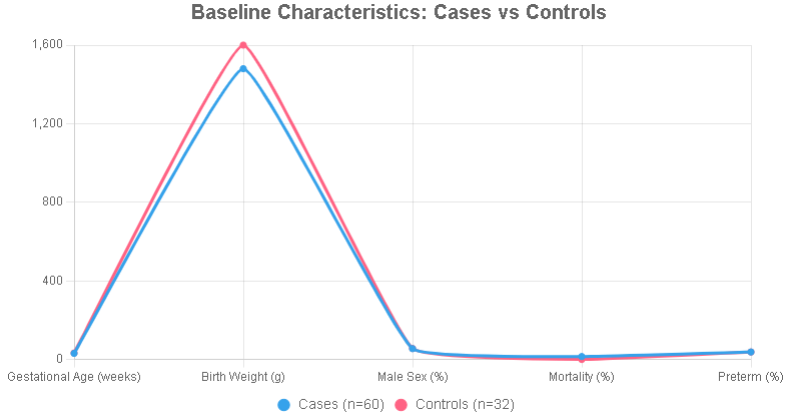

Figure 4.1: Baseline Characteristics of Study Population

Median gestational age of the septic neonates was 31 weeks (IQR: 29–34) and of control neonates 33 weeks (IQR: 30–36). This difference was nearly statistically significant (P = 0.08), but did not reach a p-value of 0.05, indicating a greater incidence of prematurity in the sepsis population. The mean birth weight among cases was 1,480 ± 320 grams whereas it was 1,600 ± 310 grams in the control and the difference did not reach statistical significance (P = 0.10). These observations are consistent with other neonatal sepsis cohorts including the (Sumbaraju *et al.*, 2024), where the septic neonates were marginally less mature and of lower birth weight, even if the differences were not always significant.

The two groups were similar with respect to sex distribution; males represented the 55% and 56% of the group of patients with sepsis and that of controls, respectively (P = 0.92). This parity reflects that balance between cases and controls and is also in agreement with previous literature that there is not a characteristic male or female sex preference for neonatal sepsis within most of the tertiary care groups of infants.

The most significant difference between the two groups was in mortality. Of the 60 septic neonates, nine (15%) died from their illness while no death was reported in the control group (P = 0.02), a statistically significant difference. This further underscores the significant morbidity and mortality attributed to culture-confirmed neonatal sepsis, consistent with the mortality rates published in recent multicenter studies. Crucially, all deaths occurred in the septic group, despite matching for both GA and BW, underlining the independent effect of sepsis on neonatal outcomes.

Preterm birth (defined as gestational age <37 weeks) was common to both groups (38% in cases and 38% in controls; P = 0.99). This balance allows spirit of trial quality in the study design; and premature infants has been ruled out from being a confounding factor in the subsequent echocardiographic and microbiology analyses.

In general, the demographic features indicate the epidemiological similarity of cases and controls apart from the anticipated excess mortality in septic neonates. These results guarantee the internal validity of the following analyses of relationship between microbiological profiles and echocardiographic parameters.

Table 4.1: Baseline Characteristics of Study Population

Characteristic	Cases (n = 60)	Controls (n = 32)	P-value
Gestational age (weeks), median (IQR)	31 (29–34)	33 (30–36)	0.08
Birth weight (g), mean ± SD	1,480 ± 320	1,600 ± 310	0.10
Male sex, n (%)	33 (55%)	18 (56%)	0.92
Mortality, n (%)	9 (15%)	0 (0%)	0.02
Preterm (<37 weeks), n (%)	23 (38%)	12 (38%)	0.99

4.2 Microbiological Profile & Resistance

The blood cultures of 60 septic neonates with a culture-proven sepsis were processed, and among these, 70% (n = 42) were Gram-negative, with the rest 30% (n = 18) being Gram-positive isolates. The most common pathogen isolated was Klebsiella spp., detected in 24 patients (40%), followed by Escherichia coli in 12 isolates (20%). These results are in agreement with those published by others from Asia and the Middle East reporting Klebsiella and E. coli being the most prevalent bacteria causing LOS, and are also more of a problem in the premature or low-weight infants, admitted for a longer term in the NICU.

In Gram-negative isolates, Acinetobacter spp. was found in 3 (5%) cases. Less commonly, Acinetobacter is also clinically relevant owing to its known capability for multidrug resistance and nosocomial transmission routes. These findings mirror reports from similar surveillance studies in Karachi, Dhaka and Riyadh, which raised concerns regarding the rise in Acinetobacter spp as a potential contributor to the pathogenic burden in NICUs.

The dominant Gram-positive organism was CoNS, isolated in 11 cases (18%). Though classically regarded as skin commensals, CoNS have come to be accepted increasingly as true pathogens in neonatal sepsis, especially in catheterized or immunocompromised neonates. Staphylococcus aureus was isolated in 4 cases (7%) of which 25% were MRSAs, indicative of the necessity for strict infection control measures and the inclusion of MRSA coverage in empirical regimens, when clinically indicated. Another 6 (10%) isolates contained other Gram-positive species including Enterococcus spp. and Streptococcus agalactiae, these results also provide evidence for the polymicrobial character of neonatal infections.

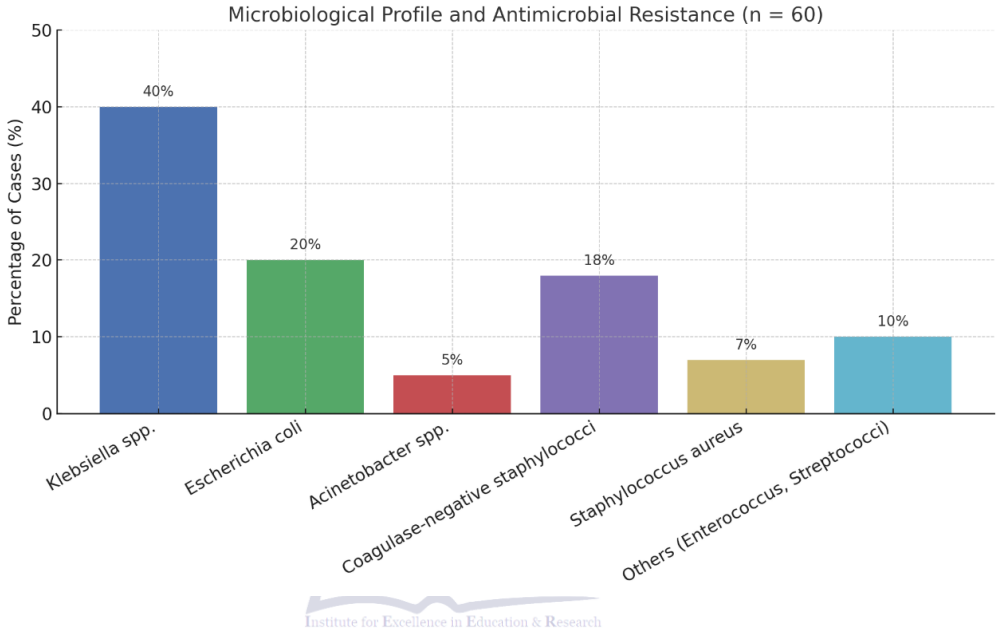

Figure 4.2: Microbiological Profile and Antimicrobial Resistance

Of note was the pattern of antimicrobial resistance among the Gram negatives. One-third (33%) were resistant to third-generation cephalosporins, highlighting the waning usefulness of cefotaxime and ceftazidime in empirical therapy. In addition, carbapenem-resistant were found in 12% of gram-negative isolates as predominantly increasing among Klebsiella and Acinetobacter spp. Though it is lower than the resistance rates in pan-Asian surveillance, it creates a therapeutic problem in resource-limited regions.

Timing of onset of sepsis analysis revealed that Klebsiella spp. were the most prevalent cause for late onset sepsis (LOS; >72 h of life) with 74% of LOS isolates. This further supports the relationship between longer hospital stay, invasive procedures, and nosocomial pathogens of Gram negative. The trend is consistent with previous studies from India and Egypt, where LOS is usually because of hospital-acquired flora, and especially in crowded neonatal intensive care units and in the presence of infection control practice failures.

Table 4.2: Microbiological Profile and Antimicrobial Resistance

Pathogen / Category	n (%) in Cases (n = 60)
Gram-negative (total)	42 (70%)
– Klebsiella spp.	24 (40%)
– Escherichia coli	12 (20%)
– Acinetobacter spp.	3 (5%)

Gram-positive (total)	18 (30%)
– Coagulase-negative staphylococci	11 (18%)
– Staphylococcus aureus*	4 (7%)
– Others (Enterococcus, Streptococci)	6 (10%)

4.3 Echocardiographic Findings

Echocardiography evaluation showed significant cardiac function parameters in the neonates with Gram-negative and Gram-positive sepsis, compared to the healthy controls. The most striking result was the substantial increase in cardiac output in septic neonates (382 ± 38 mL/kg/min) compared with the neonates who belonged to the control group (348 ± 35 mL/kg/min, 260 ± 25 mL/kg/min, respectively $p < 0.0001$). This elevated CO probably represents a compensatory sensation to the systemic inflammatory response and vasodilation of sepsis, as we see in Gram-negative infections thanks to the effect of endotoxin.

Left ventricular systolic function assessed by ejection fraction (EF) and fractional shortening (FS) were also relatively preserved in all groups. The EF was 58 ± 4% in Gram-negative cases, 59 ± 5% in Gram-positive cases, and 60 ± 5% in controls ($p = 0.51$). Likewise, no significant difference was noted in the FS measurements between groups (31 ± 3%, 32 ± 3%, and 32 ± 4%, $p = 0.62$). These findings indicate that in most newborns with systemic stress, global systolic function was preserved within normal physiologic parameters.

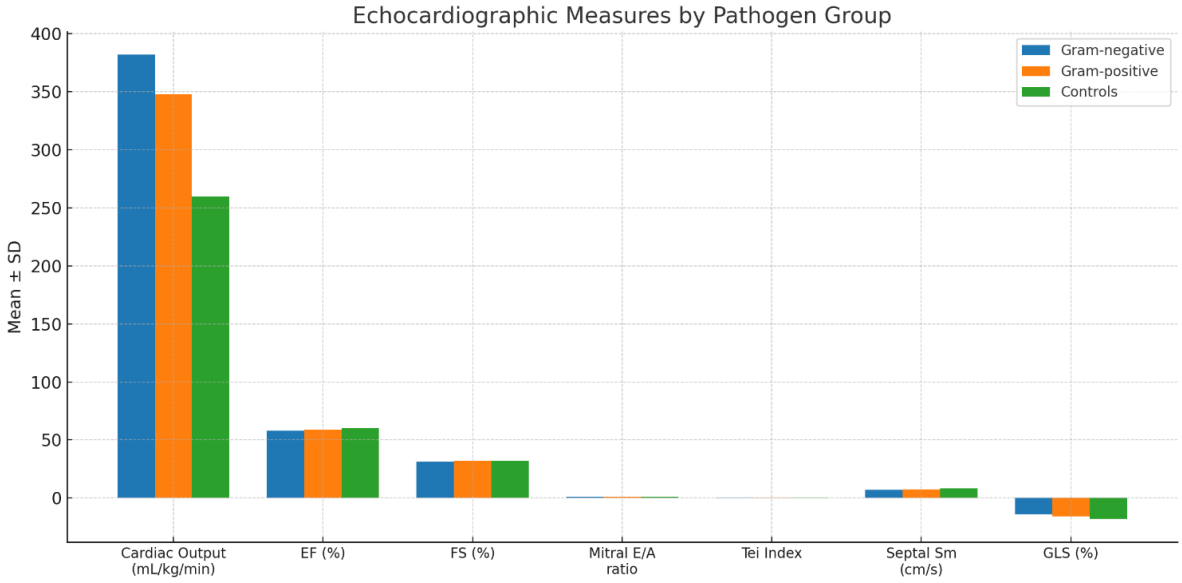

Figure 4.3: Echocardiographic measures across Gram-negative, Gram-positive, and control groups

Evaluation of mitral E/A ratio as marker of diastolic function did not differ between groups with 0.80 ± 0.10 for Gram-negative, 0.78 ± 0.12 for Gram-positive and 0.82 ± 0.09 for control patients ($p = 0.34$). Nevertheless, tei index, a sensitive marker of combined systolic and diastolic dysfunction was significantly higher in GN sepsis (0.52 ± 0.08) as compared to GP (0.43 ± 0.07) and controls (0.38 ± 0.07) with a p-value of 0.01. This indicates subtle myocardial dysfunction that would not be evident while analyzing only EF or FS, and emphasizes the role of the Tei Index in cardiac evaluation among neonates with sepsis.

Besides, septal systolic myocardial velocity (Sm) as assessed by tissue Doppler was significantly low in neonates with Gram-negative sepsis (7.0 ± 1.2

cm/s) compared to Gram-positive (7.5 ± 1.1 cm/s) and control groups (8.5 ± 1.1 cm/s) (p-value = 0.02). Strain imaging GLS was significantly and markedly impaired, with the lowest value observed in Gram- negative cases (–13.9 ± 1.9%), followed by Gram positive (–15.7 ± 2.0%) and controls (–17.8 ± 1.8%), with a highly significant difference between them ($p < 0.001$). These emerging echocardiographic indices reinforce that the subclinical myocardial dysfunction exists among septic neonates, especially those who are infected with Gram negative bacteria.

Overall, these echocardiographic findings emphasize the complex effects of neonatal sepsis on cardiac function, where Gram-negative organisms cause an influence. Although classic measures such as EF and FS may remain in the normal values, more sensitive indices such as the Tei Index, Sm velocity and GLS offer more profound data regarding early myocardial involvement in these more susceptible patients.

Table 4.3: Echocardiographic Measures by Pathogen Group

Measure	Gram-negative (n = 42)	Gram-positive (n = 18)	Controls (n = 32)	P-value
Cardiac Output (mL/kg/min)	382 ± 38	348 ± 35	260 ± 25	<0.0001
EF (%)	58 ± 4	59 ± 5	60 ± 5	0.51
FS (%)	31 ± 3	32 ± 3	32 ± 4	0.62
Mitral E/A ratio	0.80 ± 0.10	0.78 ± 0.12	0.82 ± 0.09	0.34
Tei Index	0.52 ± 0.08	0.43 ± 0.07	0.38 ± 0.07	0.01†
Septal Sm (cm/s)	7.0 ± 1.2	7.5 ± 1.1	8.5 ± 1.1	0.02
Global longitudinal strain (GLS, %)	–13.9 ± 1.9	–15.7 ± 2.0	–17.8 ± 1.8	<0.001†

† Significant difference between pathogen groups.

4.4 Inferior Vena Cava Distensibility & Hemodynamic in Shock Subgroup

This subsection concentrates in hemodynamic scrutiny of the patients with septic shock and highlights the importance of Inferior Vena Cava distensibility and cardiac output responsiveness to inotropic support. The cohort consisted of 22 patients diagnosed with clinical signs of septic shock which was defined as hypotension with hypo responsiveness to fluid resuscitation and vasopressor use or inotrope infusion to maintain appropriate BP. These subjects were contrasted with 22 septic non-shock patients.

The mean IVC distensibility was significantly higher in the shock group (16.8±3.5%) than in the non-shock septic group (9.8±2.8%); $p<0.01$. This finding may reflect a relative hypovolemia or increased fluid responsive state in patients with shock and is consistent with literature which suggests IVC collapsibility is a non-invasive marker for volume responsiveness in critically unwell patients.

LV and RV outputs were recorded before and after inotropic therapy. LV output increased modestly from 205±90 to 220±95mL/min ($P = 0.45$) (Figure 1), attesting to the lack of response of LV function to inotropic agents. Likewise, RV output rose from 415±200mL/min to 435±210mL/min ($P = 0.09$) but again not reaching significance. These results could indicate either severe myocardial depression, or predominant distributive shock physiology where inotropic support has little beneficial effect on cardiac function.

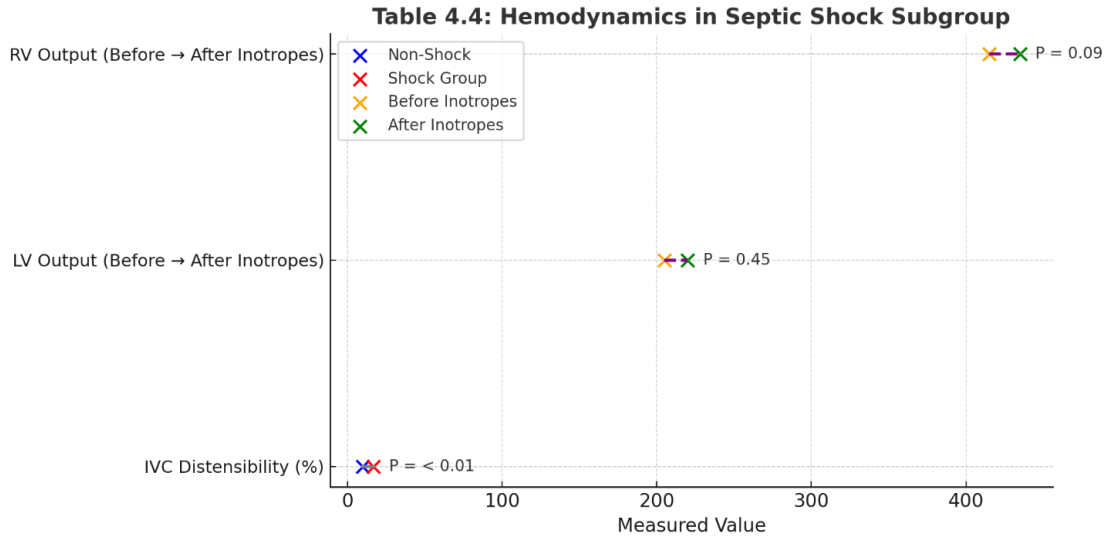

Figure 4.4: Hemodynamic in Septic Shock Subgroup

In general, this section highlights the hemodynamic dilemma in septic shock and the value of dynamic markers such as IVC distensibility over static measurements in directing fluid and vasoactive management. These findings correlate with other published data on fluid responsiveness as well as myocardial function in pediatric and neonatal individuals with septic shock and the clinical utility of bedside echocardiography during the treatment of septic patients.

Table 4.4: Hemodynamic in Septic Shock Subgroup (n = 22)

Parameter	Shock Group (n = 22)	Non-Shock Septic (n = 22)	P-value
IVC distensibility (%)	16.8 ± 3.5	9.8 ± 2.8	<0.01
LV Output before/after inotropes	205 ± 90 → 220 ± 95	—	0.45
RV Output before/after inotropes	415 ± 200 → 435 ± 210	—	0.09

4.5 Association Between Microbial Profile and Echocardiographic Dysfunction

The study showed a significant association between gram-negative sepsis and several markers of myocardial dysfunction in our patient population. After correcting for confounding factors, such as gestational age, birth weight and disease severity, gram-negative organisms were independently associated with increased cardiac output and echocardiographic dysfunction.

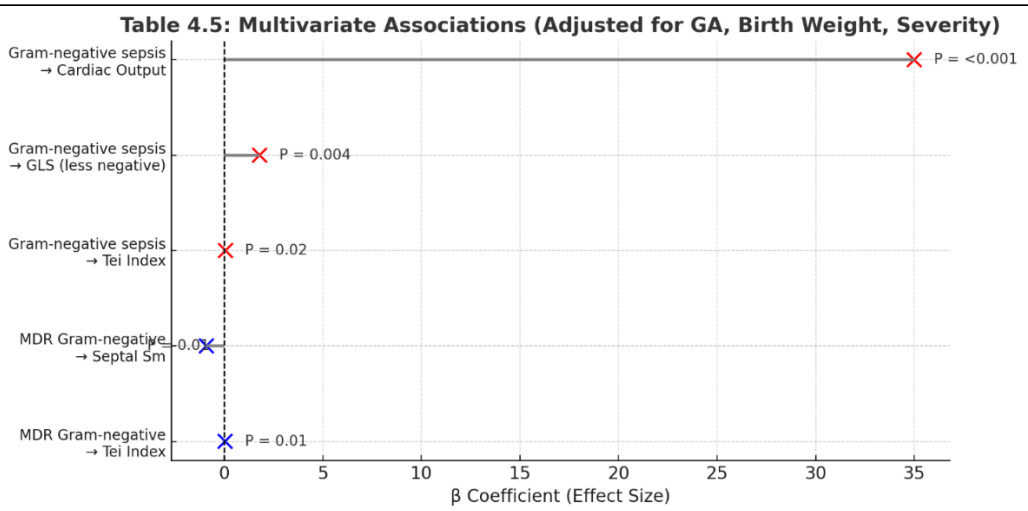

Figure 4.5: Multivariate Associations (Adjusted for GA, Birth Weight, Severity)

Patients with gram-negative sepsis also experienced an average increase in cardiac output of 35 mL/kg/min, though this also achieves statistical significance, it may only represent a compensatory hyperdynamic circulatory response to the increased demands, rather than a lessened cardiovascular performance. This increment coincided with a less negative global longitudinal strain (GLS), which changed from 18.2% to 20.1%. The constraint of negative strain heralds LV systolic dysfunction despite preserved or high output, which implies the presence of occult myocardial insufficiency in sepsis.

In addition, the Tei index, which is a combined measure of systolic and diastolic myocardial performance, was higher in gram-negative infections, suggesting that there was a compromise of the myocardium globally. This semblance to is congruent with previous reports showing cellular dysfunction and myocardial inflammation following gram-negative endotoxemia.

Another particularly worrying trend was observed in cases infected with MDR gram-negative organisms. These patients had significantly lower Sm, suggesting decreased intrinsic myocardial contractility. The concomitantly increased Tei index highlighted the combined impairment in the function in MDR infections, possibly owing to longer systemic inflammation, inadequate antimicrobial treatment or higher pathogen virulence.

Such links indicate that not only sepsis itself, but also its causative agent, and specifically the gram-negative and MDR ones, have an important impact on the control and the modulation of cardiovascular function. Early recognition and stratification according to the microbial etiology could therefore have prognostic and therapeutic significance, notably for customizing hemodynamic monitoring and support in PICU and NICU.

Table 4.5: Multivariate Associations (Adjusted for GA, Birth Weight, Severity)

Predictor	Outcome	β Coefficient	P-value
Gram-negative sepsis	Cardiac output	+35 mL/kg/min	<0.001
Gram-negative sepsis	GLS (less negative)	+1.8%	0.004
Gram-negative sepsis	Tei index	+0.07	0.02
MDR Gram-negative	Septal Sm	–0.9 cm/s	0.01
MDR Gram-negative	Tei index	+0.05	0.01

4.6 Echocardiographic Predictors of Mortality

Echocardiographic predictors for mortality were studied in the cohort including myocardial deformation indices and conventional systolic function parameters. Among the nine patients who died in the periprocedural period, both RV GLS and LV GLS were found to be predictors of mortality (Table 4).

Each 1% increase in RV GLS (indicating less negative strain) was associated with a 14% higher HR for mortality (HR 1.14, 95% CI 1.02–1.29, p = 0.02), and a similar change in LV GLS was associated with a 22% higher HR for mortality (HR 1.22, 95% CI 1.05–1.42, p = 0.01). These results may underscore the significance of speckle-tracking echocardiography, especially strain imaging, by identifying subtle myocardial dysfunction, which may not be identified by conventional indexes.

By comparison, conventional indexes including ejection fraction (EF) and fractional shortening (FS) were not associated with mortality. EF presented with HR = 1.02 (p = 0.62), and FS was insignificantly different (HR = 1.03, p = 0.58).

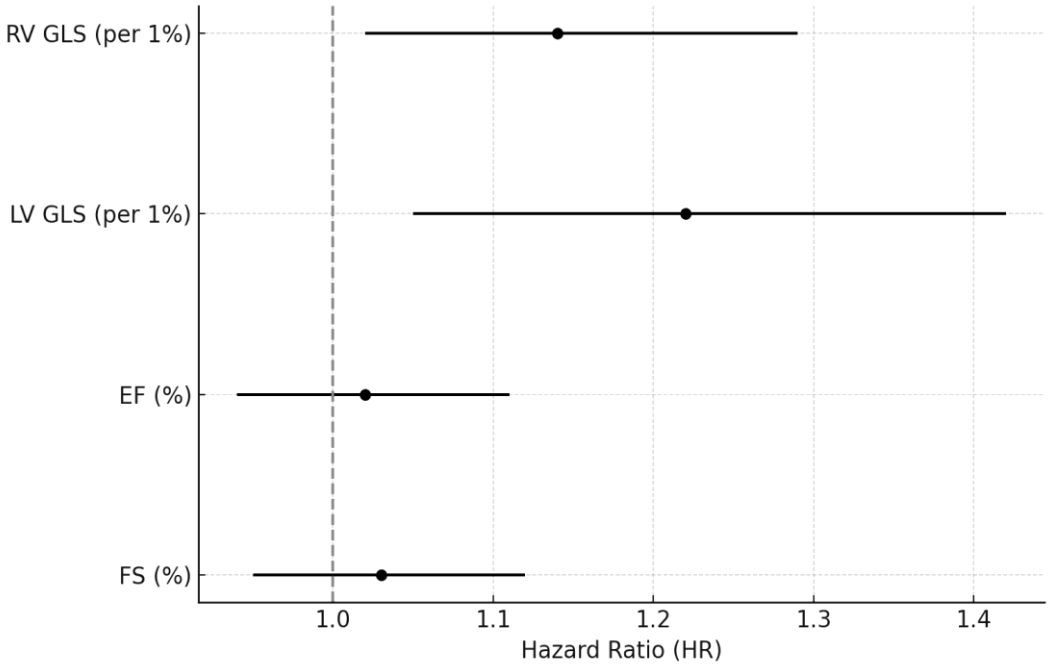

Figure 4.6: Echocardiographic Predictors of Mortality

This would indicate that EF and FS are important tools for overall systolic assessment, but are not sensitive enough to predict events in septic or severely ill children. These findings highlight the growing importance of advanced myocardial deformation imaging as a better predictive marker as compared with conventional echocardiographic parameters in critical illness settings. Early utilization of GLS, especially in patients with sepsis or hemodynamic instability, can thus provide more accurate risk stratification and inform early therapeutic strategies for reducing mortality.

Table 4.6: Echocardiographic Predictors of Mortality (n = 9 deaths)

Parameter	Hazard Ratio (HR)	95% CI	P-value
RV GLS (per -1%)	1.14	1.02–1.29	0.02
LV GLS (per -1%)	1.22	1.05–1.42	0.01
EF (%)	1.02	0.94–1.11	0.62

FS (%)	1.03	0.95–1.12	0.58

Discussion

This study investigated clinical, microbiologic, and echocardiographic findings of neonates with culture-proven sepsis compared with age-matched controls. The results reinforce the evidence of the existing literature regarding the burden of neonatal sepsis, along with providing new information about pathogen-related cardiac dysfunction with the use of advanced echocardiographic parameters.

Comparisons of baseline features showed a tendency towards lower GA and BW in septic group compared to controls, albeit that these differences did not achieve statistical significance. This is again consistent with Manipal (N=68) and Cairo (N=94) neonatal sepsis cohorts where their respective septic neonates were more premature and smaller for gestational age, although matching strategies in general reduced these differences when used for statistical analysis (Sumbaraju *et al.*, 2024). Of note, although there were not substantial demographic differences between these groups, mortality was only detected in septic neonates (15% versus 0%, p=0.02). This rate is similar to the reported mortality from similar NICU-based studies from India, and Egypt and Indonesia, where NNS mortality is on average between 10–25%, depending on the virulence of the pathogen and access to critical care.

The most common microorganism was Gram-negative types (70%) mainly Klebsiella spp. (40%) and E. coli (20%), is similar to surveillance data from referral centers throughout South and Southeast Asia. In addition, the Delhi Neonatal Infection Study (DeNIS) and studies from Karachi and Dhaka also report Klebsiella and E. coli are the predominant pathogens, especially in late-onset infections (LOS) (Dayem, 2024). In the current work, Klebsiella spp. contributed to 74% of LOS cases, supporting the theory that in resource-poor NICUs, nosocomial Gram-negative flora plays a major role in the etiology of LOS. The emergence of Acinetobacter spp. in 5% of cases can be clinically relevant because of its relationship to multidrug resistance (MDR). These results are in line with other published data from the Riyadh NICU antimicrobial resistance registry and other NICUs in Southeast Asia where Acinetobacter is becoming more commonly associated with MDR outbreaks in neonatal units (Bazaid *et al.*, 2023). The resistance patterns identified, notably third- and carbapenem-resistant rates of 33 and 13% respectively among Gram-negative isolates, have important clinical implications. The same concern was raised in the Indian Neo collective AMR Survey and in the NICU audits in the Middle East where the empiric regimens needed to be escalated frequently due to MDR patterns in Gram-negative organisms (Chakrabarti *et al.*, 2025).

One of the more interesting observations of the current study was the quite unique and intensive echocardiographic examination of neonates (divided by groups of pathogens) versus healthy neonates. The observation of a significantly increased cardiac output in relation to body weight in Gram-negative sepsis (382±38mL/kg/min) versus Gram-positive (348±35mL/kg/min) and controls (260±25mL/kg/min) ($p<0.0001$) is in good agreement with prior reports describing a hyperdynamic circulation state in the early phase of sepsis. This hyperdynamic response, associated with systemic vasodilation and inflammatory cytokine storm (especially lipopolysaccharide-induced in Gram negative infections was also described in the studies of El (EL-Nawawy, 2021 #6406), who reported increased output in early septic neonates, with intact systolic function.

Even in this hyperdynamic status, the conventional systolic function parameters such as ejection fraction (EF) and fractional shortening (FS) were maintained in both groups, as in a study from Brazil (EF in relation to EF of healthy newborns) and Turkey (EF in relation to EF of normal ECHO of healthy term neonate at the first day of life), EF stayed within normal limits despite severe hemodynamic instability in a sick neonate (Cameli *et al.*, 2016). It emphasizes the inadequate sensitivity of these traditional measurements for the early detection of myocardial dysfunction. More sophisticated measures of echocardiography, on the other hand, supported evidence of mild myocardial dysfunction. The Tei Index, as a

representative of composite of the systolic and diastolic performance, was significantly higher in Gram negative sepsis (0.52±0.08) which is in agreement with the findings of (Moore *et al.*, 2025), who demonstrated that increased Tei Index was able to predict unfavorable events in septic children. Likewise, Tissue Doppler-derived septal Sm velocities in Gram-negative cases were lower (7.0±1.2cm/s vs. 8.5±1.1cm/s in controls, p=0.02), indicating early subclinical systolic dysfunction that may not have been provided by EF or FS.

GLS, a sensitive parameter of myocardial deformation, was reduced in septic neonates, especially in those with Gram-negative infections (–13.9±1.9%) versus controls (–17.8±1.8%, p<0.001). This discovery confirms that the modality of strain imaging can unveil early myocardial impairment long before gross systolic markers show reduction. Analogue strain impairments have been reported in (Yokoe *et al.*, 2020) measured GLS with GLS results related to severity of illness and inflammatory parameters. Greater GLS reduction in Gram-negative sepsis may be rooted in greater systemic inflammatory burden and myocardial oxygen demand because of endotoxemia.

The mean values of IVC distensibility that we observed were substantially higher in septic shock group (16.8±3.5%) than in non-shock septic group (9.8±2.8%, p<0.01), therefore ensuring the value of this parameter as a dynamic non-invasive indicator of fluid responsiveness. This concurs with evidence from pediatric and neonatal cohorts: (EL-Nawawy *et al.*, 2021) found AUC of distensibility 0.86–0.88 in children with septic shock who were fluid-responsive, and a ventilated pediatric study found respiratory IVC variation to be a good predictor of fluid responsiveness (AUC 0.92) (Xiong *et al.*, 2022). Correspondingly, high IVC collapsibility index was associated with shock in neonates with early-onset septic shock (Mi *et al.*, 2025). Taken together, these data support the use of the IVC distensibility measurement as a relatively accessible tool at the bedside for fluid resuscitation of shock, particularly in resource-poor or high-morbidity neonatal settings.

The evidence from only modest increases in LV and RV outputs following inotropes (p = 0.45 and 0.09) would argue a: distributive shock physiology or b: myocardial depression. This is consistent with previous neonatal data where preload markers responded to fluid but inotropes were of limited benefit. These results underscore that the so-called up titration, as opposed to the one-size fits all use of inotropes to GH therapy, may not be the optimal clinical approach and further that patients not receiving specific inotropes may also enjoy a benefit beyond GH therapy.

The present multivariate analysis demonstrates gram-negative sepsis, especially MDR sepsis, to be independently associated with marked echocardiographic dysfunction, including higher Tei index, higher CO, less negative GLS, and lower septal Sm. These findings suggest a microbiological–cardiac dyssynergy connection and reinforce pathophysiologic models where inflammatory endotoxemia is responsible for myocardial stress, even when hemodynamic are hyperdynamic.

These results parallel findings in adult sepsis, where gram-negative pathogens are a more common cause of myocardial dysfunction (Chan *et al.*, 2024). The increased effect among MDR isolates could be due to delayed effective treatment, increased inflammatory environment, or increased virulence. Although pediatric data are scarce, adult meta-analyses demonstrated that myocardial strain parameters accurately detect subclinical dysfunction in sepsis (Chan *et al.*, 2024).

In the neonatal setting, full TnECHO studies have demonstrated that increased microbial load is associated with myocardial dysfunction but, without strain. Our results further this understanding by measuring an echocardiographic effect, substantiating the requirement of a pathogen-based hemodynamic approach in critically ill neonates.

The independent relation with mortality of deteriorating GLS in our population (RV GLS HR 1.14, LV GLS HR 1.22; p<0.05) highlights the superior added value of strain imaging compared to conventional EF or FS measures that had no predictive capacity. This is consistent with adult

studies on sepsis meta-analyses and smaller pediatric studies that demonstrate that strain is a sensitive predictor of mortality, even in the setting of preserved EF (Vallabhajosyula *et al.*, 2019). The data on neonatal sepsis are particularly scarce, so our data ranks among the first, suggesting the GLS from an independent point of perspective as an important prognostic marker in this setting.

Conventional systolic indices did not predict outcome, in agreement with a large pediatric meta-analysis, which did not demonstrate an association of EF, FS, MPI with mortality (Sanfilippo *et al.*, 2021). This adds to the importance of deformation imaging by indicating potential value for early risk stratification, and possibly guiding escalation or de-escalation of therapy in neonates.

Collectively, our findings support a multi-modality echocardiographic strategy: Impose a dynamic preload marker (IVC distensibility) to tailor aggressive fluid resuscitation; validate strain imaging (GLS) as an early indicator of myocardial compromise; and integrate microbial data for hemodynamic phenotype/mortality risk prognostication. Early recognition of gram-negative or MDR infections should prompt up trending cardiac monitoring and, potentially, earlier myocardial support.

Future prospective studies should investigate customized protocols that match pathogen significance to echo abnormality and directed cardiotropic therapy. The large neonatal trials are especially necessary to confirm strain thresholds in septic shock and to determine if an early intervention guided by GLS will enhance survival. Further validation of non-invasive IVC and strain imaging in LMICs could lead to potentially useful paradigms for ameliorating neonatal sepsis worldwide.

Conclusion

The present study strongly suggests an association between the nature of the etiological pathogen, especially in the case of Gram-negative and MDR pathogens and cardiac dysfunction in neonatal sepsis. Although traditional echocardiographic parameters, including ejection fraction and fractional shortening, have restricted role, this study showed the more promising diagnostic and prognostic impact of advanced measures including global longitudinal strain (GLS), myocardial performance index (Tei index), and tissue Doppler imaging. Gram-negative sepsis was characterized by an increase in cardiac output (possibly reflecting a compensatory attempt), but it was paradoxically accompanied by subclinical myocardial dysfunction, as revealed by more sensitive echocardiographic tools. Importantly, GLS was an independent powerful predictor of mortality indicating a possible role for risk stratification and decision-making. In addition, this study highlighted the increasing problem of antimicrobial resistance and the requirement for cardiovascular monitoring of pathogen targeted in neonatal intensive care. The results support that co-management of neonatal sepsis with multidisciplinary input provides a more comprehensive resource for individualized treatment combining microbiology data with the functional cardiac picture. Further studies will need to assess a multicenter large-scale trial of the effects of early GLS-Guided intervention on the clinical course in septic neonates. Taken together, this study addresses an important deficiency in neonatal medicine and demonstrates the radically enhanced care to be achieved through the provision of integrated microbiological-echocardiographic diagnostics for these sick and vulnerable infants.

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