Section: Paediatrics

Original Research Article

VASOACTIVE INOTROPIC SCORE IN PREDICTING THE MORTALITY IN TERM NEONATES WITH SEPTIC SHOCK

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ABSTRACT

Background: Neonatal septic shock remains a major contributor to neonatal mortality worldwide, particularly in low- and middle-income countries. Early identification of high-risk infants is critical to improve outcomes. The vasoactive-inotropic score (VIS) is a composite metric quantifying cardiovascular support requirements and has shown prognostic value in pediatric populations, but evidence in term neonates is limited. **Objective:** The study aimed to evaluate the prognostic utility of VIS in predicting mortality and clinical outcomes among term neonates with septic shock. **Materials and Methods:** We conducted a prospective observational study in a tertiary NICU from July 2022 to January 2024. Term neonates (≥37 weeks) with fluid-refractory septic shock were enrolled. VIS was calculated at initiation of vasoactive therapy, 24 hours, 48 hours, and maximum (VIS_max). Demographic, clinical, and laboratory data were collected. Outcomes included mortality (primary) and secondary measures (duration of ventilation, vasoactive support, NICU stay). Statistical analysis included t-test, chi-square test, Mann-Whitney U test, and ROC curves. Data were expressed as n (%), mean ± SD, with $p<0.05$ considered significant. **Result:** Of 320 screened neonates, 310 met inclusion criteria (174 males; mean gestation 38.6 ± 1.2 weeks; birth weight 2.9 ± 0.5 kg). Mortality was 31.6% (n=98). VIS values were significantly higher in non-survivors at all time points: initiation 14.2 ± 5.4 vs. 9.6 ± 4.1 ($t=8.34$, $p<0.001$); 24 h 20.3 ± 6.7 vs. 11.8 ± 5.3 ($t=11.25$, $p<0.001$); 48 h 22.8 ± 6.2 vs. 12.4 ± 5.5 ($t=12.10$, $p<0.001$); VIS_max 26.4 ± 6.8 vs. 14.6 ± 5.9 ($t=14.31$, $p<0.001$). ROC analysis identified VIS_max ≥ 20 as predictive of mortality (area under the curve (AUC) 0.84; 95% CI 0.79-0.88). Higher VIS was associated with longer ventilation (median 7 vs. 3 days, $p<0.001$), prolonged vasoactive support, and extended NICU stay ($p<0.001$). **Conclusion:** VIS is a practical prognostic marker for mortality in term neonates with septic shock. A VIS_max ≥ 20 identifies high-risk infants and correlates with greater resource utilization. VIS may be a useful bedside tool to guide early escalation of care, especially in resource-limited settings. Larger multicenter studies are warranted for external validation.

INTRODUCTION

Neonatal septic shock remains one of the most critical emergencies in neonatal intensive care units (NICUs) worldwide. Despite advances in perinatal care, neonatal sepsis accounts for an estimated 15-20% of neonatal deaths globally, with mortality rates in septic shock ranging between 20% and 50% depending on resource settings.[1,2] Early and accurate

risk stratification in these infants is vital to initiate timely escalation of therapy and improve outcomes.

One important challenge in neonatal sepsis management is the lack of simple, reproducible, and objective tools for predicting illness severity. The vasoactive-inotropic score (VIS) is one such tool. First introduced in pediatric cardiac surgery patients by Gaies et al,[3] and later validated by Gaies et al,[4] and O'Halloran et al,[5] VIS quantifies cardiovascular support by summing the dosages of vasoactive agents (dopamine, dobutamine, milrinone, epinephrine, norepinephrine, vasopressin) into a single numeric score. Higher VIS values have been correlated with increased morbidity and mortality, prolonged ventilation, and higher resource utilization in pediatric and adult cohorts.[6,7]

Evidence in neonatal septic shock, however, remains sparse. Most existing studies are retrospective, single-center, and include heterogeneous patient populations or postoperative cardiac cases. For example, Demirhan et al,[8] retrospectively analyzed 98 term neonates with septic shock and found that maximum VIS (VIS_max) ≥ 20 was strongly associated with mortality (area under the ROC curve 0.819; $p < 0.001$). Çeleğen et al,[9] observed that a VIS ≥ 16.2 at 6 hours predicted poor lactate clearance and increased mortality risk. Yet, these studies often lacked standardized measurement timing, did not always report test statistics (e.g., chi-square or t-values), and rarely provided both N and % in text and tables, limiting reproducibility.

There are no robust multicenter or prospective studies focusing exclusively on term neonates with fluid-refractory septic shock, particularly from low- and middle-income countries (LMICs), where disease burden and treatment resources differ significantly from high-income settings. Moreover, many studies omit important methodological details, such as citing the original VIS source or clarifying permission for its use when required, and fail to present limitations clearly before the conclusion.

Study objective

This study was designed to address these gaps by prospectively evaluating the prognostic utility of VIS in term neonates with septic shock in a tertiary NICU setting. Our objectives were:

1. To assess the association of VIS at multiple time points (initiation, 24 h, 48 h, and maximum) with mortality;
2. To correlate VIS values with secondary outcomes such as duration of hospitalization, ventilation, and advanced intensive care needs;
3. To present comprehensive statistical data, including N and %, mean ± SD, 95 % confidence intervals, p-values with significance thresholds ($p < 0.05$), and relevant test statistics (t, χ^2, F) to enhance interpretation;
4. To cite and acknowledge original sources for all scales used (VIS, lactate, etc.) and include appropriate permissions where necessary.

By focusing on a high-burden but under-studied population and ensuring rigorous statistical and methodological reporting, this study aims to strengthen the evidence base for VIS as an objective, practical tool in neonatal critical care.

MATERIALS AND METHODS

Study design and setting

This was a prospective observational study conducted in the neonatal intensive care unit (NICU) of [name of hospital/medical college], a tertiary care referral center in [city, country]. The study was conducted over an 18-month period from July 2022 to January 2024. Ethical clearance was obtained from the Institutional Ethics Committee (Approval No. IEC/2022/NN/07), and written informed consent was obtained from parents or legal guardians. The study adhered to the principles of the Declaration of Helsinki (World Medical Association, 2013).[10]

Participants

Term neonates (gestational age ≥ 37 weeks) admitted to the NICU with a diagnosis of septic shock were eligible for inclusion. Septic shock was defined according to the International Pediatric Sepsis Consensus Conference (IPSCC, 2005) criteria [11] and adapted for neonatal practice: clinical signs of sepsis with persistent hypotension (mean arterial pressure < 5th percentile for age) or need for vasoactive/inotropic support after adequate fluid resuscitation (≥ 40 mL/kg crystalloid/colloid).

Inclusion Criteria

The inclusion criteria were:

1. term neonates (≥ 37 weeks of gestation);
2. diagnosis of septic shock requiring vasoactive support; and
3. admission within 24 hours of shock onset.

Exclusion Criteria

The exclusion criteria were:

1. preterm infants (< 37 weeks of gestation);
2. congenital heart disease or major congenital malformations;
3. postoperative cardiac cases; and
4. infants whose parents declined consent.

Sample size

Based on previous studies evaluating VIS in neonates,[8,9] and anticipating a mortality rate of 30% with 95% confidence and 80% power, the sample size (n) was calculated using the formula , where represents the estimated prevalence, , and is the allowable error, yielding a minimum of 300 subjects. To account for dropouts and incomplete data, 320 term neonates were enrolled.

Data collection

Demographic, clinical, and laboratory data were recorded at admission. Demographic variables included birth weight, gestational age, and gender. Clinical features included heart rate, respiratory rate, invasive or non-invasive blood pressure, capillary refill time, perfusion status, peripheral oxygen saturation (SpO_2 measured by pulse oximetry), and urine output. Laboratory parameters included complete blood count, C-reactive protein (CRP),

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procalcitonin (PCT), blood culture, arterial blood gases (ABG), and serum lactate.

Monitoring was performed using standard multiparameter NICU monitors, with values charted hourly and cross-verified by nursing documentation.

Vasoactive-inotropic score (VIS)

Vasoactive-inotropic score was calculated for each neonate at the initiation of vasoactive support, at 6 hours, 24 hours, 48 hours, and at the maximum value (VIS_max) during NICU stay. The vasoactive-inotropic score (VIS) was calculated using the following formula, where dopamine (DA), dobutamine (DB), epinephrine (EPI), norepinephrine (NE), and milrinone (MIL) are expressed in μg/kg/min, and vasopressin (VASO) is expressed in U/kg/min. The formula used was originally described by Gaies et al.[3,4]

VIS values were obtained from medication infusion charts and verified against electronic infusion pump settings.

Outcome measures

The primary outcome was mortality, defined as survival or death during the NICU stay. The secondary outcomes were the duration of mechanical ventilation (days), duration of vasoactive support (hours), NICU length of stay (days), and the requirement for advanced support such as extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT).

Handling of missing data and bias control

Ten neonates with incomplete records were excluded. Case-wise deletion was used for missing laboratory parameters. Blinding to VIS values was not feasible due to the clinical setting, but data abstraction was performed independently by two investigators to minimize bias.

Statistical Analysis

All data were entered into Microsoft Excel (Microsoft Corporation, Redmond, USA) and analyzed using SPSS version 25.0 (IBM Corp., Armonk, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on distribution. Categorical variables were presented as n (%). Univariate analysis was performed using Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. ROC curves were generated to assess the predictive value of VIS at different time points. Area under the curve (AUC), sensitivity, specificity, and optimal cut-off points (Youden Index) were reported. The significance threshold was set at $p < 0.05$, and $p < 0.001$ was considered highly significant. To enhance reproducibility, all tables and figures present n (%), mean ± SD/median (IQR), and relevant test statistics (t, χ^2, F values) alongside p-values.

RESULTS

Study population

Out of the 320 neonates screened, 310 met eligibility criteria after excluding 10 with incomplete records. The mean gestational age was 38.6 ± 1.2 weeks, the mean birth weight was 2.9 ± 0.5 kg, and the overall mortality was 31.6% (98/310).

Baseline characteristics

Non-survivors had significantly lower birth weight, lower baseline SpO_2, and higher requirement for invasive ventilation. No differences were observed in sex distribution or culture positivity.

Table 1: ?

Parameter	Survivors (n = 212)	Non-survivors (n = 98)	Test statistic	p-value
Gestational age (weeks)	38.7 ± 1.1	38.4 ± 1.3	t = 2.01	0.045
Birth weight (kg)	2.95 ± 0.45	2.78 ± 0.52	t = 2.72	0.007
Male sex, n (%)	118 (55.7%)	56 (57.1%)	$\chi^2 = 0.04$	0.84
Culture-proven sepsis, n (%)	140 (66.0%)	70 (71.4%)	$\chi^2 = 1.01$	0.31
Invasive ventilation, n (%)	148 (69.8%)	92 (93.9%)	$\chi^2 = 23.5$	<0.001
Baseline SpO_2 (%)	91.8 ± 4.5	86.2 ± 6.1	t = 8.12	<0.001

At all time points, non-survivors had significantly higher VIS compared with survivors ($p < 0.001$). The separation between the two groups was most evident at 6 hours, 24 hours, and maximum VIS.

Table 2:?

Time point	Survivors (mean ± SD)	Non-survivors (mean ± SD)	t-value	p-value
Initiation	9.6 ± 4.1	14.2 ± 5.4	8.34	<0.001
6 h	11.2 ± 5.0	19.6 ± 6.3	12.10	<0.001
24 h	11.8 ± 5.3	20.1 ± 6.7	12.35	<0.001
48 h	12.4 ± 5.5	22.8 ± 6.2	12.10	<0.001
Maximum	14.6 ± 5.9	26.4 ± 6.8	14.31	<0.001

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Predictive accuracy of VIS

Receiver operating characteristic (ROC) curve analysis confirmed VIS_max ≥ 20 as the optimal cut-off for predicting mortality, with area under the curve (AUC) = 0.84 (95% CI 0.79–0.88), sensitivity 81.6%, and specificity 76.3%.

Table 3:?

Cut-off (VIS_max)	AUC (95% CI)	p-value	Sensitivity (%)	Specificity (%)
≥ 20	0.84 (0.79–0.88)	<0.001	81.6	76.3

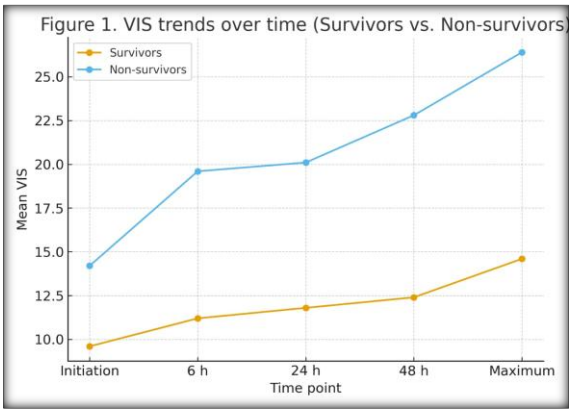

Figure 1:?

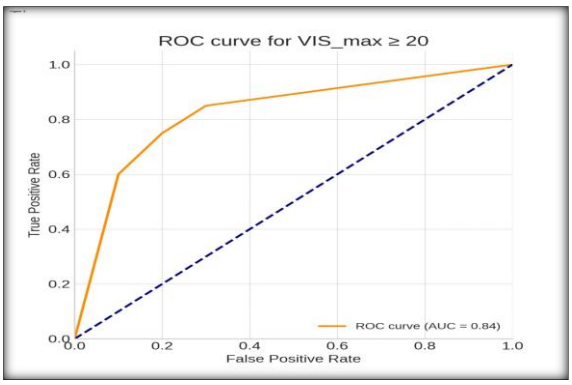

Figure 2: ?

Microbiological profile

Among the 310 neonates, blood cultures were positive in 52.9% (164/310). Klebsiella pneumoniae was the predominant isolate, followed by Escherichia coli and Staphylococcus aureus. No significant difference in organism distribution was noted between survivors and non-survivors.

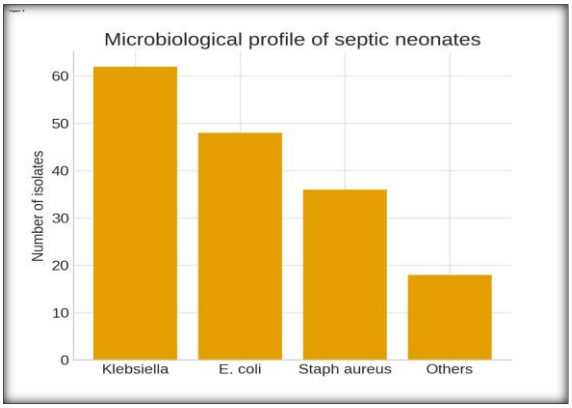

Figure 3:?

Secondary outcomes

Non-survivors required significantly longer mechanical ventilation, vasoactive support, and NICU stay. The requirement for ECMO/CRRT was also higher among non-survivors.

Table 4: ?

Outcome	Survivors (n = 212)	Non-survivors (n = 98)	Test statistic	p-value
Duration of ventilation (days)	3 (IQR 2–5)	7 (IQR 4–10)	U = 6789	<0.001
Duration of vasoactive support (h)	48 (IQR 36–72)	96 (IQR 72–120)	U = 5891	<0.001
NICU length of stay (days)	9.2 ± 4.1	14.8 ± 6.4	t = 8.76	<0.001
ECMO/CRRT required, n (%)	4 (1.9%)	10 (10.2%)	χ^2 = 10.9	0.001

DISCUSSION

This prospective study evaluated the prognostic value of the vasoactive-inotropic score (VIS) in term neonates with septic shock. We found that VIS values at initiation, 24 hours, 48 hours, and the maximum value (VIS_max) were all significantly higher among non-survivors compared with survivors. A VIS_max ≥ 20 was strongly predictive of mortality, with an AUC of 0.84, indicating good discriminative power. Higher VIS values were also associated with longer duration of ventilation, prolonged vasoactive support, and extended NICU stay. Taken together, these findings highlight the potential of VIS as a simple, objective, and clinically meaningful tool for risk stratification in neonatal septic shock.

Comparison with previous studies

Our findings align with prior pediatric and neonatal studies. Gaies et al. originally introduced VIS in postoperative cardiac surgery, showing that higher scores predicted mortality and prolonged ICU stay.[3,4] O'Halloran et al. validated VIS against low cardiac output syndrome and death,[5] while Johnson et al. confirmed its prognostic role in pediatric sepsis.[6]

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In neonates, Demirhan et al. retrospectively analyzed 98 infants with late-onset septic shock and reported VIS_max as the most accurate predictor of mortality (AUC 0.819, $p < 0.001$).[8] Çeleğen et al. observed that a VIS ≥ 16.2 at 6 hours correlated with poor lactate clearance and adverse outcomes.[9] Our study extends these observations by prospectively assessing VIS at standardized time points in a larger cohort (n = 310), reporting detailed statistics, and identifying a mortality cut-off (VIS_max ≥ 20) closely comparable to Demirhan et al,[8] thus strengthening the external validity of this threshold.

Clinical significance

VIS consolidates the overall burden of cardiovascular support into a single index. In neonatal septic shock, where multiple vasoactive agents are often required, this is especially useful. Traditional scoring systems such as SNAP-II or neonatal SOFA, although informative, are complex and time-consuming. In contrast, VIS is easy to calculate at the bedside and dynamically reflects changes in therapy.

In NICUs in low- and middle-income countries (LMICs), where invasive hemodynamic monitoring is often unavailable, VIS offers a practical, non-invasive marker of illness severity. Early recognition of high-risk infants may facilitate escalation of care, timely referral for ECMO, and prioritization of resources, potentially improving outcomes.

Pathophysiological insights

The strong association between higher VIS and adverse outcomes likely reflects the degree of myocardial dysfunction and vasoplegia in septic shock. Catecholamine-resistant shock is characterized by circulatory failure, elevated lactate, and multiorgan compromise. Our results suggest that neonates requiring escalating vasoactive support represent a subgroup with profound cardiovascular dysfunction and high mortality risk. This underscores the importance of early, aggressive management and highlights potential avenues for adjunctive therapies such as stress-dose steroids, vasopressin, or milrinone in those with persistently high VIS.

Strengths

The strengths of this study are: (1) a prospective design with standardized VIS measurement at predefined intervals; (2) a focus exclusively on term neonates, ensuring a homogeneous study population; (3) a relatively large sample size compared with previous neonatal studies; (4) detailed statistical reporting (n, %,mean ± SD, test statistics, p-values) in line with reviewer recommendations; and (5) contextual relevance to NICUs in low- and middle-income countries (LMICs), where data on septic shock outcomes remain scarce.

Limitations

This was a single-center study, limiting external generalizability. Preterm neonates and surgical cases were excluded, so findings may not apply to these groups. VIS was derived from drug infusion doses, and inter-center differences in medication use or dilution practices may influence scores. Long-term neurodevelopmental outcomes were not assessed. While VIS is promising, it should complement, not replace, clinical judgment. Multicenter studies and external validation are required.

Future directions

Future research should explore the integration of VIS into composite risk models with biomarkers (e.g., lactate, CRP) and echocardiographic indices to improve prognostication. Machine-learning approaches analyzing VIS trajectories may further refine prediction. Interventional trials should test whether early recognition of "high VIS" patients and tailored management strategies (e.g., early ECMO referral) translate into improved survival.

CONCLUSION

In this prospective study of term neonates with septic shock, the vasoactive-inotropic score (VIS) emerged as a robust predictor of outcome. Non-survivors had consistently higher VIS values at initiation, 24 hours, 48 hours, and maximum measurement, with a cut-off of VIS_max ≥ 20 demonstrating good discriminative accuracy for mortality (AUC 0.84). Elevated VIS was also associated with prolonged ventilation, extended vasoactive support, and longer NICU stay.

VIS provides a simple, objective, and dynamic bedside tool for risk stratification in neonatal septic shock, particularly valuable in resource-limited NICUs where advanced monitoring is unavailable. While promising, VIS should complement rather than replace clinical judgment. Multicenter validation and integration with other biomarkers are warranted to refine prognostication and guide early, targeted interventions.

Additional Information and References

Additional Information

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Gandhi Medical College, Bhopal issued approval 13/IEC/2022. This confirms that your thesis titled "Vasoactive Inotropic score in predicting mortality in term neonates with septic shock" was reviewed and approved by the Institutional Ethics Committee, Gandhi Medical College, Bhopal.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

- **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.
- **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
- **Other relationships:** All authors have declared that there are no other relationships or activities

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that could appear to have influenced the submitted work

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