Correlation of Serum Lactate Levels, Perfusion Index and Plethysmography Variability Index With Invasive Blood Pressure in Late Preterm and Term Infants With Shock

SHYAM SUNDAR SHARMA, NATARAJAN CHANDRA KUMAR, C SHANMUGASUNDARAM, VAANATHI HEMENTHA KUMAR, GIRIRAJ KUMAR

Department of Neonatology, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu.

Correspondence to:
Dr Chandra Kumar Natarajan,
Head of Department,
Department of Neonatology,
Kanchi Kamakoti CHILDS Trust
Hospital, Nageshwara Road,
Nungambakkam, Chennai,
Tamil Nadu.
drchandrakumr@gmail.com
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Objective: To study the correlation of objective parameters for diagnosing shock viz., perfusion index (PI), plethysmography variability index (PVI) and serum lactate (SL) with invasive blood pressure in late preterm and term infants with shock. **Methods**: Prospective observational study (diagnostic test) conducted at the neonatal intensive care unit of Kanchi Kamakoti CHILDS Trust Hospital, Chennai between June, 2018 and May, 2020. Term and late preterm neonates with shock were included in the study. PI, PVI, SL, SpO2 and heart rate were monitored. PI, PVI and SLL were recorded at 0,12, 24 and 72 hours of onset of shock. All the babies were followed up till discharge or death. **Results**: Total 78 neonates were enrolled in the study. At 0 hour, SL and PVI had negative correlation (*P*=0.002 and *P*=0.003) while PI had a weak-to-moderate positive correlation (*P*=0.002) with invasive blood pressure. SL ≥4.65 had a sensitivity of 75% and specificity of 75.8%, and PI <0.455 had a sensitivity of 65%, and specificity of 58.6% for predicting invasive hypotension. PVI ≥23.5 had a sensitivity of 90% and specificity of 63.8% in predicting invasive hypotension. **Conclusion**: PI has moderate positive correlation while SL and PVI have moderate negative correlation with invasive blood pressure. The cutoff values of SL ≥4.65, PI <0.45 and PVI ≥23.5 can predict invasive hypotension with good sensitivity and negative predictive value.

Keywords: *Hemodynamic support, Hypotension, Management, Prediction.*

Shock in neonates is clinically assessed by monitoring heart rate, blood pressure, capillary refilling time, acid-base status and urine output [1-4]. The clinical parameters are liable to subjective variation, so there is a need for an objective parameter for diagnosing shock, which is less invasive, such perfusion index (PI), plethysmography variability index (PVI) and serum lactate (SL).

PI is an assessment of pulsatile strength, and it is an indirect measure of peripheral perfusion [5]. The signal comprises two components, one of which is arterial and pulsatile and the other, which is non-pulsatile and origi-nates from connective tissue, bone, and venous blood. PVI has recently been proposed to predict fluid respon-siveness. It is an automatic measure of the dynamic changes in PI occurring during the respiratory cycle [6]. Serum lactate gives information on metabolism capacity at cellular level and reflects true perfusion and oxygenation status [7]. The combination of measurement of PI, PVI and SL could help in early recognition of hemodynamic instability and thus initiate prompt treatment. Hence, we investigated the correlation of PI, PVI and SL with invasive blood pressure in our study.

METHODS

This prospective observational study (diagnostic test) study was conducted at a tertiary care level 3 neonatal intensive care unit (NICU) of Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu from June, 2018 to May, 2020. Ethics approval was obtained from the institute's ethics committee. Term and late preterm neonates, who were admitted in the NICU and fulfilling the case definition of shock [8], were enrolled in the study.

Shock was defined as the presence of at least two of the six criteria [1,9,10]: Heart rate >180 per min, decrease in blood pressure (mean arterial pressure (MAP) <5th centile for gestational age for age), oliguria <0.5 mL/kg/h for preceding 6h, CRT (capillary refilling time) >3s, central to peripheral temperature difference >3°C, and metabolic

acidosis (base deficit (BD) >5 or lactate >2 times upper normal) [11]. Hypotension was defined as mean blood pressure (MBP) value below the 5th centile for the gestational age and postnatal age of the baby [12-14]. Informed consent was obtained from parents in their own language. Gestational age was assigned either by first trimester ultrasonogram or last menstrual period. A detailed structured form, which included demographic data, etiology, risk factors, examination findings and investigation results, was completed. All neonates enrolled in the study had undergone baseline investigations as per the NICU protocol. A 4 Fr umbilical artery catheter or peripheral arterial line was placed for invasive blood pressure (IBP) monitoring by the doctor on duty. Heparin stock solution infusion was started to maintain the arterial line patency. IBP monitoring was done by using Edward kit transducer and pressure bag, and Dash 4000 multipara monitor.

PI and PVI and SL were recorded at 0,12, 24 and 72 hours of onset of shock. PI, PVI, SpO_2 and heart rate were monitored using new generation pulse oximeter (Masimo Rainbow Rad87; Masimo Corp). Pulse oximeter probe was placed on the right hand (preductal) of the subjects soon after diagnosis of shock. PI and PVI values were recorded every 20 seconds for 10 minutes duration during each pre-specified assessment points [15]. Average of lowest and highest PI reading was taken each time to eliminate the bias of considering lowest values. Lactate values were obtained from the arterial blood gas (ABG) analysis (Radiometer ABL 700 automated blood gas analyzer). All the babies were followed-up till discharge from the hospital or death.

PI, PVI and SL values were assumed to have strong correlation coefficient value of 0.9 with IBP in neonates with shock. To have 90% power and 95% confidence interval, the required sample size was calculated as 78 neonates undergoing invasive blood pressure monitoring.

Statistical analysis: Statistical analyses were performed using SPSS 22.0. Statistical significance was assumed for *P* value <0.05. Pearson correlation was performed to identify correlation between PI, PVI and SL and invasive blood pressure. We constructed a 2 × 2 table by taking SL as more than or equal to 4.65, PI less than 0.455 and PVI more than or equal to 23.50 as an index test and presence or absence of shock by invasive hypotension as a reference test. Sensitivity, specificity, positive and negative predictive values were calculated for PI, PVI and SL to predict invasive hypotension. Cutoff values for PI, PVI and SL were derived using ROC curves.

RESULTS

A total of 724 neonates were admitted during the study period, of which 478 were late preterm and term neonates.

All late preterm and term neonates were examined for features of shock. Eighty-nine neonates were found to be eligible and 78 were enrolled in the study, and followed-up till discharge or death (**Fig. 1**). Among the study population, 65% participants were male, and 63% babies belonged to term gestational age. Mean gestational age was 37.5 (1.89) weeks, median (IQR) postnatal age was 6 (2, 23.75) days and mean (SD) birth weight was 2.67 (0.67) kg. Out of 78 neonates, 26% required intubation and 15% PPV (**Table I**). The various shock parameters are given in **Web Table I**, and values of PI, PVI, SL, SBP, DBP and mean IBP at the onset of shock (0 hours) and when shock recovered (72 hours) are shown in **Web Table II**.

At 0 hour, SL and PVI had a significant negative correlation while PI had a significant weak-to-moderate positive correlation with IBP. SL ≥4.65 had sensitivity of 75% and specificity of 75.8%, PI <0.455 had sensitivity of 65 % and specificity of 58.6%, and PVI ≥23.5 had a sensitivity of 90% and specificity of 63.8% in predicting invasive hypotension (**Table III**).

SL and PVI had negative correlation with IBP (SBP, DBP and MBP) at 0 hour (*P*<0.05) (**Table II, Fig. 2**). SL and PVI values were high initially in the neonates with hypotensive shock at the time of admission, which came
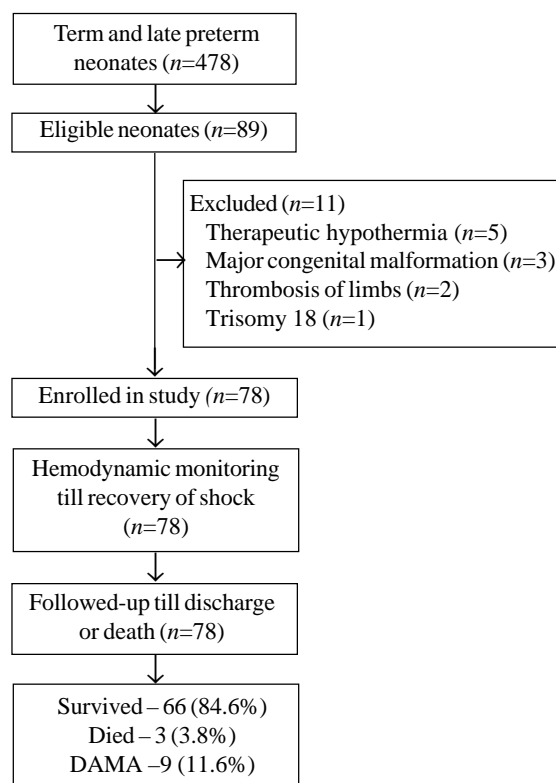
DAMA: discharge against medical advice.

Fig. 1 Study flow chart.

Table I Demographic Characteristics of the Study Population (*N*=78)

Characteristics	Value
Antenatal risk factors	
Urinary tract infection	3 (3.8)
Maternal fever < 24 h of delivery	3 (3.8)
Meconium stained amniotic fluid	4 (5.1)
Premature rupture of membranes	6 (7.7)
Neonatal characteristics	
Male sex	51 (65)
Gestation category	
Late preterm	29 (37)
Term	49 (63)
Cesarean delivery	62 (79)
Resuscitation required	
PPV	12 (15)
Intubation	20 (26)
No	46 (59)
Gestational age (d)[a]	37.5 (1.89)
Birth weight (kg)[a]	2.7 (0.67)
Postnatal day at admission[b]	6 (2, 23.7)
Final outcome	
Survived	66 (84.6)
Discharge against medical advice	9 (11.6)
Death	3 (3.8)

Values expressed as n (%),[a]mean (SD), or [b]median (IQR).

down when blood pressure improved after correction of shock (negative correlation). PI had a positive correlation with invasive blood pressure **(Table II, Fig 2)**. The PI values were low initially when blood pressure was low, which increased when it improved after correction of shock (P <0.05).

Table II Correlation Between Invasive Blood Pressure and Serum Lactate, Perfusion Index and Plethysmography Variability Index at Admission in Neonates (*N*=78)

Parameter at admission	Correlation coefficient	P value
Serum lactate		
Systolic blood pressure	-0.314	0.005
Diastolic blood pressure	-0.349	0.002
Mean blood pressure	-0.350	0.002
Perfusion index		
Systolic blood pressure	0.273	0.016
Diastolic blood pressure	0.341	0.002
Mean blood pressure	0.325	0.004
Plethysmography variability index		
Systolic blood pressure	-0.28	0.013
Diastolic blood pressure	-0.34	0.003
Mean blood pressure	-0.324	0.004

Table III Predictive Ability of Serum Lactate (SL), Perfusion Index (PI) and Plethysmography Variability Index (PVI) in Predicting Shock by Measuring Invasive Blood Pressure in Neonates (*N*=78)

Predictors	SL (≥4.65 mmol/L)	PI (<0.455)	PVI (≥23.5)
Sensitivity	75%	65%	90%
Specificity	75.8%	58.6%	63.8%
PPV	51.7%	35.1%	29%
NPV	89.79%	82.9%	87.5%

PPV: positive predictive value, NPV: negative predictive value.

Receiver operating characteristic curve (ROC curve) was constructed to predict invasive hypotension from SL, PI and PVI. Area under the ROC curve was 0.813, 0.666 and 0.707, respectively with a narrow confidence interval (**Web Fig. 1**).

DISCUSSION

In this study, we tried to identify objective parameters for assessment of shock, which are commonly available at the bedside of a sick neonate that would help clinician in the diagnosis of shock and assess the response to its treatment. We found that at 0 hour, SL and PVI had negative correlation while PI had a weak-to-moderate positive correlation with invasive blood pressure.

Increase in serum lactate levels in infants with shock and negative correlation with invasive blood pressure have been reported in previous studies on neonates receiving therapeutic hypothermia and neonates who had septic shock [16,17]. We also found a negative correction of lactate with invasive blood pressure. We found a moderate positive correlation between PI and invasive blood pressure, which is consistent with other studies. PVI as an indicator of volume-responsive hypotension in newborn infants during surgery has been studied and was observed to have negative correlation with arterial blood pressure [18]. Other studies have identified a weak positive correlation between inferior vena cava collapsibility index and PVI [8].

Our study was a prospective observational study conducted in an exclusively out born level 3 NICU. We studied three easily available parameters at point of care to draw a correlation with clinical shock and the invasive blood pressure in a comparatively adequate sample size. Our study was conducted in an extramural unit where more of the sick cases are referred, so results of our study cannot be extrapolated to intramural units. Frequently, babies with shock have already received fluid boluses or inotropes, before referral, which may have disturbed the real values of SL, PI and PVI. We did not evaluate the role of these
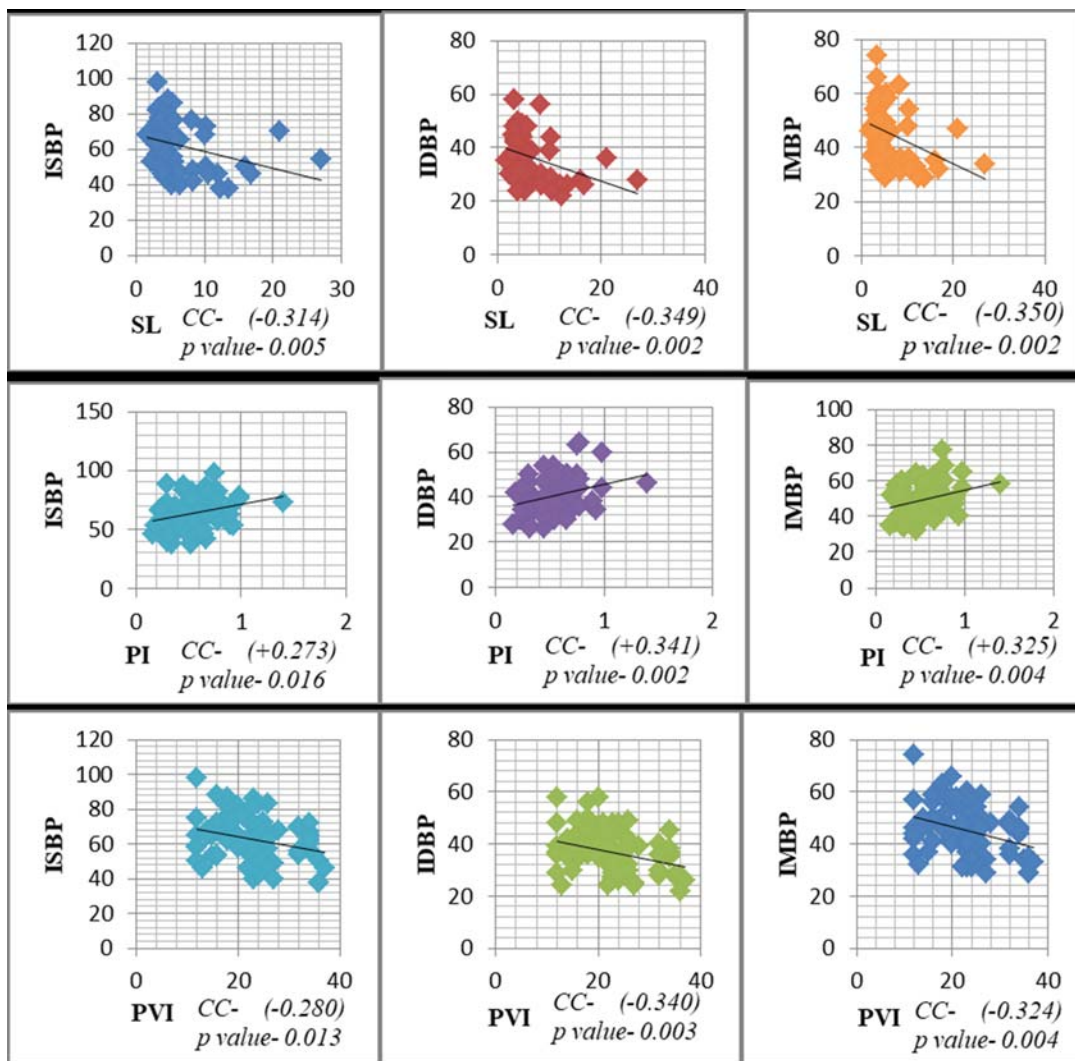
Fig. 2 Correlation between invasive blood pressure (BP) (systolic, SBP; diastolic, DBP; and mean, MBP) and serum lactate (SL), perfusion index (PI) and plethysmography variability index (PVI) at admission. *CC - Correlation coefficient.*

parameters in various types of shock in neonates; even though, majority had septic shock.

Serum lactate levels and PVI had negative correlation while PI had a positive correlation with invasive blood pressure in late preterm and term neonates with shock.

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WHAT THIS STUDY ADDS?

- Trends of changes in serum lactate levels, perfusion index and plethysmography variability index values have good correlation with invasive hypotension in late preterm and term neonates with shock.

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Web Table I Indicators of Shock in Neonates Enrolled in the Study (*N*=78)

Indicators of shock	No. (%)
Heart rate >180/min	78 (100)
Capillary refilling time >3 s	76 (97)
Core-to- periphery difference >3°C	74 (95)
Base deficit >5 meq/L in blood gas	32 (42)
Elevated lactate >2-times	48 (62)
Hypotension	20 (26)
Oliguria	5 (6.5)
Weak peripheral pulses	62 (80)

**Web Table II Parameters of Shock at Various Time Points of Assessment**

Hemodynamic assessment	At admission	12 h	24 h	72 h
Mean heart rate (bpm)	189 (9)	164 (7)	148 (6)	142 (4)
Invasive BP				
ISBP (mm of Hg)	62.73 (13.04)	66.95 (10.92)	69.79 (9.47)	72.03 (8.58)
IDBP (mm of Hg)	36.90 (8.14)	40.31 (7.60)	42.63 (6.56)	44.79 (7.04)
IMBP (mm of Hg)	45.24 (9.64)	49.33 (8.69)	52.28 (7.68)	54.53 (7.17)
Non invasive BP				
SBP (mm of Hg)	68.89 (12.66)	72.07 (11.48)	75.82 (9.73)	76.667 (8.76)
DBP(mm of Hg)	39.69 (9.59)	43.25 (7.87)	46.53 (8.02)	49.00 (7.36)
MBP(mm of Hg)	49.36 (9.92)	53.21 (9.15)	56.68 (8.40)	59.16 (7.82)
Perfusion index	0.52 (0.23)	0.77 (0.27)	1.02 (0.35)	1.52 (0.42)
PVI	22.91 (6.89)	15.6 (4.65)	13.86 (4.95)	12.13 (2.91)
S. lactate	5.71 (2.25)	4.21 (1.93)	2.83 (1.37)	2.16 (1.05)
Base excess	-8.012 (3.97)	-5.017 (2.25)	-3.61 (1.54)	-2.21(1.34)

Values expressed as mean (SD). SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure, PVI: Plethysmography variability index.
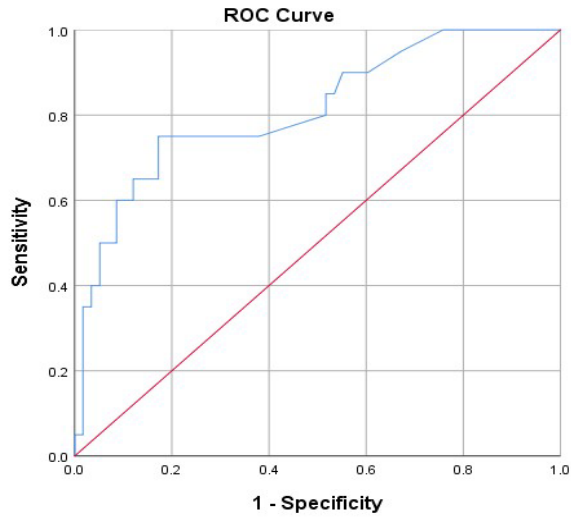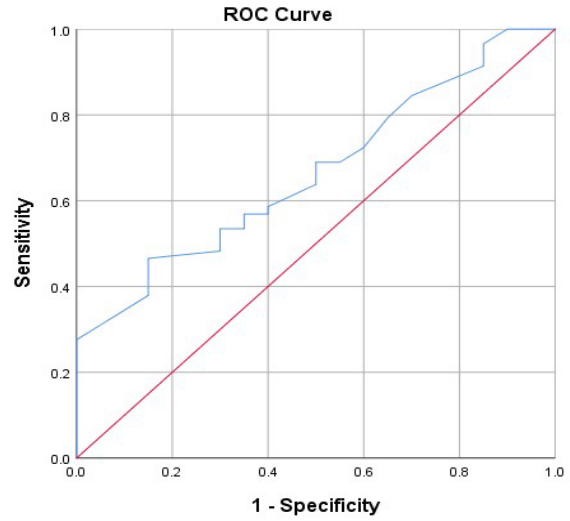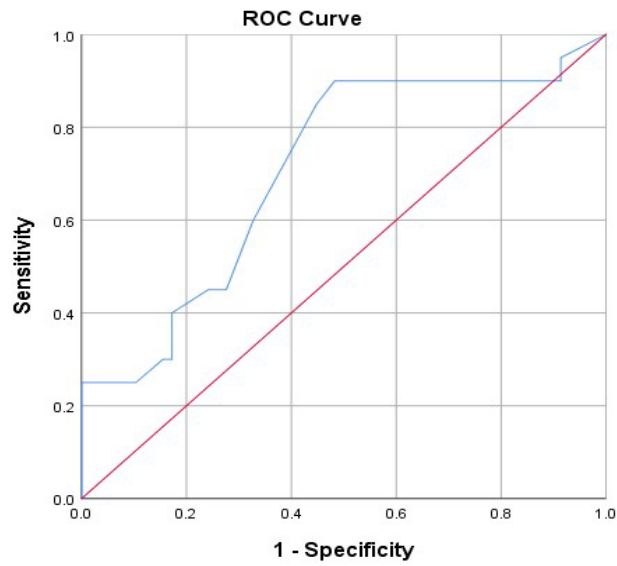
Fig A: SL

Fig B: PI

Fig C: PVI

Web Fig. 1 Receiver operating characteristic curve of serum lactate (SL) (Fig. A), perfusion index (PI) (Fig. B) and plethysmography variability index (PVI) (Fig. C) at admission in predicting hypotension by invasive blood pressure monitoring at admission.