ORIGINAL ARTICLE

Correlation Between Perfusion Index and Clinical Risk Index for Babies II Score in Preterm Sick Neonates: A Prospective Cohort Study

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ABSTRACT

Objective: This study aims to investigate the correlation between perfusion index (PI) and Clinical Risk Index for Babies (CRIB) II score in sick preterm neonates < 37-week gestation admitted to neonatal intensive care unit (NICU).

Methods: This observational study was conducted over period of 18 months in a tertiary care centre. All eligible preterm neonates admitted to NICU were examined. The PI and CRIB II score for each neonate were documented. The primary outcome of the study was correlation between PI and CRIB II scores at admission.

Results: 383 neonates were enrolled in the study. Mean gestation of neonates was 32 weeks. A strong correlation between PI and CRIB II scores at admission was noted ($P = 0.01$). We demonstrated a strong association between PI at admission and predischarge mortality of neonates with 92.9% sensitivity and 70% specificity. Lower PI was associated with need of inotropes and invasive ventilation and longer duration of hospital stay. Combined use of PI and CRIB II predicted mortality with 83.3% sensitivity and 80.5% specificity.

Conclusions: The perfusion index is a potential bedside measure that correlated well with the CRIB II score, which is a validated tool to assess sick preterm neonates. Preductal PI at admission was associated with predischarge mortality, length of hospital stay, inotrope requirement and need for ventilator support in preterm neonates.

Keywords: *Clinical Risk Index for Babies (CRIB), Mortality, Perfusion index, Perfusion, Preterm*

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INTRODUCTION

The early neonatal period is the most vulnerable time of life when most of the newborn deaths occur. The maximum number of neonatal deaths are caused by birth injuries, low birth weight, infections, hypoxia, and preterm birth [1]. The severity of a newborn sickness must be determined to identify it immediately and initiate medical interventions on time. Early detection of neonatal illness severity facilitates resource allocation and triaging.

Perfusion Index (PI) is a simple, non-invasive method that measures the ratio of infrared light absorbed by the pulsatile elements like arterial blood to that absorbed by non-pulsatile elements like the venous or capillary blood, bone, and connective tissue [2]. It is derived from the plethysmography signal generated by pulse oximeters and reflects the real-time changes in peripheral blood flow [3]. Peripheral perfusion, cardiac output, and stroke volume have all been demonstrated to correlate with PI, making it an objective marker of hemodynamic changes [4,5]. This could facilitate the start of treatment early and lower the illness related morbidity and death rate. Previous research has demonstrated that PI is a predictor of high illness severity in infants [6] and may identify possible perinatal inflammatory diseases such as subclinical chorioamnionitis early on [7].

Several severity indices for newborn illnesses have been validated in the literature as potential predictors of predischarge mortality. Strong research comparing the prognostic power of individual severity scores for predischarge morbidity and death is lacking. When determined during the first hour of arrival, the CRIB II (Clinical Risk Index for Babies II) score is a validated indicator of the severity of the illness [8]. It helps in the identification of high-risk newborns and triage. A study by Marete et al demonstrated a strong correlation between CRIB II and hospital mortality, cost of health care, length of hospital stay and worse outcomes [9]. Compared to other newborn illnesses, a recent systematic analysis showed that the CRIB II strongly predicted hospital mortality in very low

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birth weight (VLBW) and very preterm neonates (< 32 weeks) [10].

The present study aims to investigate the relationship between PI and the CRIB II score in sick preterm newborns, as well as to ascertain the prediction accuracy of PI with respect to hospital mortality. Our goal is to deploy non-invasive scoring systems, such as CRIB II and PI to improve neonatal outcomes, prognosticate parents, and help prioritize and use health resources in a resource-limited setting.

METHODS

This prospective cohort study was conducted in a tertiary care centre over a period of 18 months after obtaining approval from the institutional ethics committee. Preterm neonates admitted to the NICU between January 2020 and June 2021 were evaluated for eligibility and enrolled after obtaining informed consent from either of their parents at the time of admission.

Preterm neonates between 28 and 36^{+6} weeks of gestation requiring respiratory support (continuous positive airway pressure, non-invasive ventilation, or invasive ventilation) for stabilization, circulatory compromise necessitating inotropes, convulsions, and moderate or severe hypothermia (<36°C) were included. Neonates with major congenital malformations (including congenital heart disease), those who left against medical advice or who were more than seven days postnatal age at admission or whose gestational age was unknown, were excluded.

Following admission, neonates who fulfilled the eligibility criteria underwent a detailed evaluation to ascertain the need for prompt clinical intervention. Baseline measurements such as blood pressure, axillary temperature, heart rate, respiration rate, and capillary refill time were noted. The first day of the last menstrual period (LMP) or first-trimester scan was used to calculate the gestational age; for mothers who were unable to recall their LMP, gestational age of the neonate was determined using the Expanded New Ballard Scoring (ENBS) for a period up to seven days neonatal age. Arterial blood drawn from the radial artery or umbilical artery catheter was promptly analyzed using an automated blood gas analyzer.

CRIB II parameters were scored appropriately (maximum score 27) [11]. Levels 1 through 4 were used to categorise newborns according to the severity of illness. Scores of 0 to 5, 6 to 10, 11 to 15 and ≥ 16 were considered as level 1, level 2, level 3 and level 4, respectively. Higher severity levels were defined as level 3 or more. A sensor was placed on the right wrist of each neonate (Masimo set, Radical-7) and PI was recorded at the preductal site. PI values were obtained after a sustained pulse wave was observed for at least twenty seconds, and five such values were recorded. An average of these five values was taken into consideration for each individual case. Data on demographic and general maternal characteristics, the newborn's gender, birth weight, gestational age, and anthropometric data recorded at the time of birth were collected from clinical records. Neonates were followed up from admission until discharge or death within the same hospitalization. For in-hospital mortality, we considered first 28 days of life as the cutoff. Vital parameters, general status and new events were recorded and followed up every day till outcome. The pediatrician who followed up the cases till the outcome, was unaware of the CRIB II scores and PI values.

The primary outcome was the correlation between the PI and CRIB II scores in preterm sick neonates. Secondary outcomes of the study were the predictive accuracy of PI and the combined use of PI and the CRIB II score in sick preterm neonates regarding in-hospital mortality.

The sample size was calculated with reference to a previous similar study which evaluated predictive value of PI for morbidity and mortality, and association with CRIB II score [12]. Considering the specificity of 54.5% and sensitivity of 81.8%, the level of precision was set at 0.05 and the level of confidence at 95%, the sample size was calculated to be 383.

Statistical analysis: Data were entered in an Excel spreadsheet (Microsoft Excel 2016) and analyzed by SPSS version 25.0 (Armonk, NY; IBM Corp.). Continuous variables were expressed as mean (SD), and categorical variables as proportions (%). Independent t test or Chi square test was used appropriately. Post-hoc analysis was carried out to determine the differences in PI between CRIB II levels. ROC curves were constructed to ascertain the cutoff values for PI for predicting morbidity and mortality. $P < 0.05$ was deemed significant. Multiple regression analysis was applied to evaluate the effect of various factors on the outcome.

RESULTS

Out of 433 admissions in NICU during the study period, 383 were included and analyzed for outcomes as shown in **Fig. 1**. The baseline neonatal and maternal characteristics are shown in **Table I**. Male neonates made up 59.3% of the entire study group. The median age of enrollment was 2 days. The average birth weight was 1602 grams, and the mean (SD) gestational age was 32.41 (2.8) weeks. The mean (SD) CRIB score was 5.32 (3.18), and the mean PI was 0.81 (0.65).

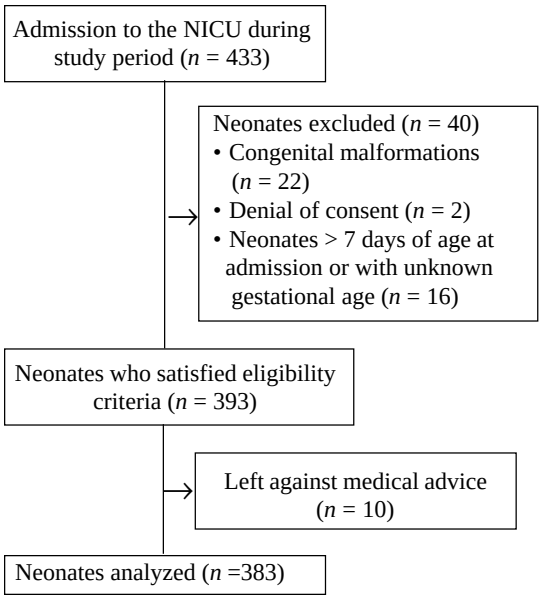

Fig. 1 Flowchart depiction of enrolment of study participants

We observed a statistically significant decline in PI values with an increase in the CRIB II levels (**Table II**). On further analysis, PI varied significantly between CRIB II levels 1 and 2, and ≥ level 3, respectively. Post-hoc analysis (**Table III**) was carried out to evaluate the differences between each level, which revealed significant differences in PI values between various CRIB II levels. A significant inverse correlation was observed between PI and CRIB II score (Spearman's rho = -0.604, $P = 0.01$).

In the present study, a significant correlation was noted between PI at admission and in-hospital mortality. At a threshold of 0.5, the PI predicted mortality with a sensitivity of 92.9%, a specificity of 70%, a negative predictive value (NPV) of 98.8%, a positive predictive value (PPV) of 27.7%, and an area under curve (AUC) of 0.876 (95% CI 0.825, 0.926) (**Table IV**). **Fig. 2** depicts the ROC curve for PI for predicting mortality. Further-more, PI [mean (SD)] was significantly lower in infants who needed inotrope support [0.37 (0.31) vs. 0.82 (0.65)], ventilator support [0.49 (0.3) vs. 0.89 (0.68)], and an ICU stay longer than thirty days [0.52 (0.24) vs. 0.88 (0.7)] than those who did not. After adjusting for potential confounding factors that might affect PI, the CRIB II score was found to have a statistically significant association with PI (**Table V**).

Table II CRIB II Levels in Relation to Perfusion Index and Mortality

Levels of CRIB II	*No. of infants*[b]	*Perfusion index* [a]	*Death*[b]
1	226 (59.01)	1.04 (0.75)	10 (4.4)
2	122 (31.85)	0.52 (0.25)	16 (13.11)
≥ 3	35 (9.14)	0.40 (0.25)	11 (31.42)

$P < 0.001$
Values expressed as [a]mean (SD) or [b]n (%)

Table I Baseline Neonatal and Maternal Characteristics ($n = 383$)

Characteristics	*Value*
Neonatal characteristics	
Day of enrolment[a]	2 (1, 5)
Males[b]	227 (59.27)
Gestation (weeks)[c]	32.41 (2.79)
Birth weight (grams)[c]	1602 (475)
Apgar score at 1 min[a]	6 (6, 7)
Apgar score at 5 min[a]	8 (7, 9)
Hospital stays (days)[a]	18 (10, 31)
Follow up duration for in hospital mortality (days)[a]	7 (5, 14)
Respiratory support	
CPAP[b]	193 (50.39)
Ventilation[b]	89 (23.42)
Indication of blood gas	
Hemodynamic instability in first 24 hours[b]	65 (16.54)
Ventilation[b]	89 (23.42)
Seizures in first 24 hours[b]	86 (22.63)
Moderate hypothermia[b]	269 (70.23)
Severe hypothermia[b]	26 (6.79)
Mean temperature at admission (^{0}C)[c]	35.50 (4.48)
Levels of CRIB II[b]	
1	226 (59.01)
2	122 (31.85)
3	35 (9.14)
CRIB II score[c]	5.32 (3.18)
PI[c]	0.81 (0.65)
Outcome	
Discharge[b]	346 (90.3)
Death[b]	37 (9.7)
Maternal characteristics	
Age of the mother (years)[c]	25.30 (4.74)
Hemoglobin (g/dL)[c]	10.61 (1.44)
LSCS delivery[b]	200 (52.22)
Amniotic fluid characteristics	
Meconium-stained amniotic fluid[b]	50 (13.05)
Foul smelling liquor[b]	10 (2.61)
Bleeding PV[b]	31 (8.09)
Leaking PV > 24 hours[b]	29 (7.57)
Fetal distress[b]	154 (40.21)
Antenatal steroids[b]	115 (30.02)

Values expressed as [a]median (IQR), [b]n (%), [c]mean (SD)
PI Perfusion index, CRIB Clinical Risk Index for Babies, CPAP Continuous positive airway pressure, LSCS Lower segment ceserean section, PV Per vaginum

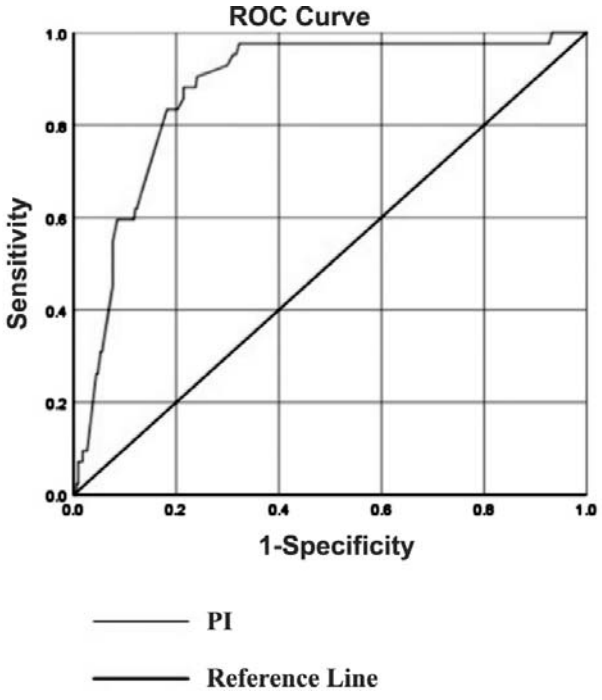

Fig.2 ROC curve illustrating the predictive accuracy of Perfusion Index in relation to predischarge mortality

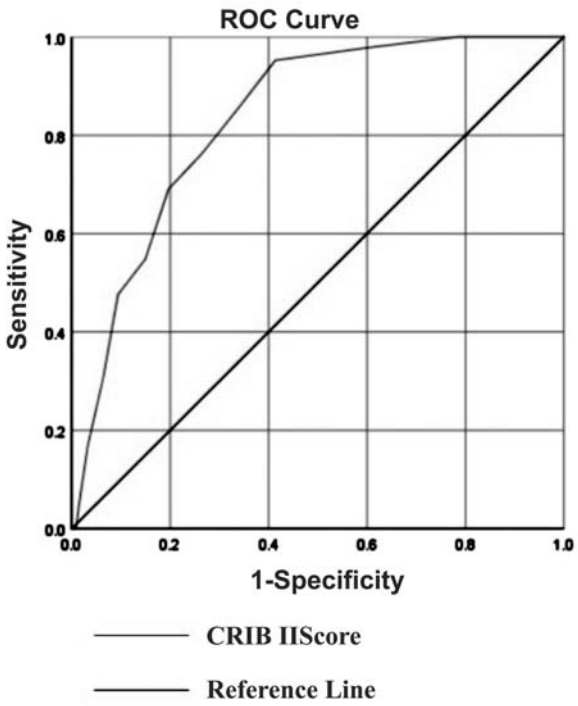

Fig. 3 ROC curve illustrating the predictive accuracy of CRIB II score in relation to pre discharge mortality

Table III Post-hoc Test (Games-Howell Test) For Comparison of PI Between Various Levels of CRIB II Scores

Levels of CRIB	*MD of PI between the levels of CRIB*	*P value*
Level 1 and Level 2	0.491	< 0.001
Level 1 and ≥ Level 3	0.611	< 0.001
Level 2 and ≥ Level 3	0.120	0.042

MD Mean difference, PI Perfusion index

Nevertheless, we noticed that, for the prediction of mortality, the CRIB II score cutoff of 5.5 resulted in an AUC of 0.834 (95% CI 0.781, 0.886), sensitivity of 85.7%, NPV of 97.4%, specificity of 65.8%, and PPV of 23.7% (**Fig. 3**). A higher level of CRIB II score was linked to lower PI and higher mortality.

When the CRIB II score and PI, with the cutoff specified by the current investigation, were combined to predict mortality, we observed a sensitivity of 83.3%, a specificity of 80.4%, a PPV of 34.3%, and a NPV of 97.5% (**Table IV**).

DISCUSSION

The current study found a strong association between preductal PI and CRIB II scores in sick preterm newborns warranting NICU admission assessed within the first hour of admission. Furthermore, there was a statistically significant difference in PI between each level of CRIB II. Additionally, the severity of illness as determined by CRIB II score increased with a decline in PI. Even after adjusting for potential confounding factors, a lower PI was strongly associated with higher CRIB II scores. The present study

Table IV Predictive Ability of Perfusion Index and CRIB II Scores for Mortality in Neonates

Parameters	*Cutoff*	*Sn (%)*	*Sp (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*
PI	≤ 0.5	92.9	70.1	27.7	98.8	72.5
CRIB II	≥ 5.5	85.7	65.8	23.7	97.4	67.6
Combined (PI + CRIB II)	≤ 0.5 and ≥ 5.5	83.3	80.4	34.3	97.5	80.6

CRIB II Clinical Risk Index for Babies, NPV Negative predictive value, PI Perfusion index, PPV Positive predictive value, Sn Sensitivity, Sp Specificity

WHAT THIS STUDY ADDS?

- Combined use of CRIB II score and PI might aid in early detection of sick babies and with a better prediction of in-hospital mortality

Table V Multiple Regression Analysis Illustrating Relationship of Various Factors With Perfusion Index

	Pearson correlation	*Standardized coefficient β*	*P value*
Gestational age	0.264	-0.106	0.118
Birth weight	0.236	-0.114	0.074
Temperature	0.069	-0.007	0.883
CRIB II score	-0.429	-0.429	< 0.001

Dependent variable: Perfusion index (PI)
β Beta coefficients derived from binomial regression analysis after adjusting for gestation, birth weight, temperature and CRIB II, P< 0.05 considered as significant.

revealed that PI and CRIB II scores with cutoffs of ≤ 0.5 and ≥ 5.5, respectively, were associated with a more precise prediction of in-hospital mortality. When both were used in combination to predict mortality, this was achieved with 83.3% sensitivity, 80.4% specificity, and NPV of 97.5%. Furthermore, the PI was significantly lower at admission among neonates needing inotrope support, invasive ventilation, and longer NICU stay.

A study by Mathews et al also observed a decrease in PI values as the severity of newborn sickness increased as determined by the CRIB II score [13]. The mean PI values corresponding to CRIB levels 1, 2, and 3 were 1.5, 0.67, and 0.67, respectively. Available data suggests that CRIB II is the most discriminating tool for predischarge mortality prediction among all neonatal disease severity assessment tools studied so far [8,10,13].

The current study found that a cutoff of ≥ 5.5 for CRIB II score had better prediction of in-hospital mortality, although previously a cutoff ≥ 4 had been suggested [9].

Previous research indicated that lower PI values in sick neonates was substantially related to increased mortality [6]. In addition, Ibrahim et al investigated PI on days 1 and 3 in sick neonates and reported that lower PI at both time points showed a significant correlation with inotrope need and predischarge mortality, whereas PI on day 3 showed a significant inverse correlation with the duration of hospital stay [14]. It has been demonstrated by recent research that in both term and preterm newborns, preductal perfusion is superior to postductal perfusion [15,16]. This discrepancy was most likely caused by circulatory alterations during transition. But after the fifth postnatal day, this difference diminished, possibly as the preterm newborns' sympathetic nerve systems matured. In our investigation, we took the preductal PI into account to address these discrepancies.

In addition, differences in prediction accuracy of the combined use of PI and CRIB II as compared to individual parameters regarding mortality may have resulted from variability in the definition of cutoff values. The usefulness of combining PI and CRIB II scores in preterm infants has not been well studied so far. However, more robust research is advised to provide clarification.

The goal of the present study was to evaluate the relationship between PI and CRIB II scores in preterm neonates exclusively and to examine the potential advantage of using PI and CRIB II together to predict mortality prior to discharge. We excluded congenital heart disorders that substantially could affect PI. The clinicians who followed up the cases were not aware of the PI and CRIB II ratings and therefore this decreased any chances of observer bias. Our study did, however, have certain shortcomings. Most neonates in the present study had lower illness severity as defined by lower CRIB II scores. We did not analyze the comorbidities that the neonates developed during the course of NICU stay which could have impacted mortality in our study population. Furthermore, the impact of factors such as extreme prematurity and its complications on PI could not be investigated as the study population comprised less extreme preterm neonates. Comparison of outcomes with matched control group to reduce the bias was not feasible, as this study was conducted during COVID pandemic.

Therefore, further research involving sicker preterm and extreme preterm neonates is warranted to validate the findings of this study. A combined use of PI and CRIB II scores can aid in identifying preterm neonates at risk of dying to initiate aggressive management strategies.

Contributors: SSA: Collected and analyzed the data, drafted the initial manuscript; NHS: Supervised data collection, analyzed data, critical review and finalization of the manuscript; CA: Supervised data analysis, critical revision and finalization of the manuscript. All authors approved the final manuscript as submitted.

Ethics clearance: Institute's Ethics Committee of Indira Gandhi

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