Peripheral Perfusion Index as a Marker of Sepsis in Preterm Neonates

Jasmine Singh
Government Medical College and Hospital https://orcid.org/0000-0001-8478-9544
Suksham Jain (dr.sukshamj@gmail.com)
Government Medical College and Hospital https://orcid.org/0000-0002-1230-2992
Deepak Chawla
Government Medical College and Hospital
Shivani Randev
Government Medical College and Hospital
Supreet Khurana
Government Medical College and Hospital

Research Article

Keywords: Diagnostic accuracy study, Neonatal sepsis, Non-invasive marker, Perfusion Index

Posted Date: June 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-596749/v1

Version of Record: A version of this preprint was published at Journal Of Tropical Pediatrics on January 1st, 2022. See the published version at https://doi.org/10.1093/tropej/fmac014.

Abstract

Background: Neonatal sepsis is a major contributor to neonatal mortality in India. Blood culture, the gold standard for the diagnosis of sepsis takes 48-72 hours while the serological markers have suboptimal diagnostic test characteristics. Perfusion Index (PI) is a real time, non-invasive marker that can detect microcirculatory changes before other clinical manifestation of sepsis.

Objective: To determine the diagnostic accuracy of PI in detecting hospital-acquired sepsis before overt clinical manifestations.

Material and Methods: A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital.

Participants: Term and preterm neonates admitted to NICU.

Methods: PI was continuously monitored in all enrolled neonates. Clinical sepsis was defined using the Neonatal Krankenhaus-Infektions-Surveillance-System (NeoKISS). PI below 1.24 and 0.88 for term and preterm neonates, respectively, was defined as low PI. The time of fall of PI below this value and time of clinical sepsis as per NeoKISS was noted and the difference was calculated.

Results: Among 72 neonates (gestational age:32.2±3.2 weeks, birth weight:1420, IQR 1100-1855 g), a total of 93 events of suspected sepsis were noted, of which 70 were sepsis screen positive. 16 events were associated with culture positive sepsis. Using a cut off of 0.88 in preterm neonates, PI yielded a sensitivity of 89.47% (95% CI 78.48% to 96.04%), specificity of 56% (95% CI 34.93% to 75.60%), positive predictive value of 82.26% (95% CI 74.70% to 87.92%), and negative predictive value of 70% (95% CI 50.36% to 84.29%) in detection of hospital acquired sepsis. The positive and negative likelihood ratios came to be 2.03 (95% CI 1.30 to 3.19) and 0.19 (95% CI 0.08 to 0.43), respectively.

Conclusion: This study shows that PI might serve as an early, non-invasive marker of hospital acquired sepsis in preterm neonates.

What Is Already Known?

PI can detect high illness severity, subclinical chorioamnionitis, shock and congenital heart disease in neonates.

What This Study Adds?

PI can serve as a non-invasive and early marker for detection of sepsis in preterm neonates before the appearance of clinical signs.

Introduction

The neonatal period carries higher risk of mortality than any other period in the childhood. The current Neonatal Mortality Rate of India is 21.7 per 1000 live births.[1]Systemic infection accounts for about one-third of neonatal deaths globally and are the third most common underlying cause of neonatal death preceded only by preterm birth and intrapartum complications.[2, 3]Blood culture remains the gold standard for the diagnosis of neonatal bacteremia. However despite the high burden of sepsis, culture proven sepsis is seen only in 31.8% of cases.[2] The high incidence of false negativity can be attributed to low level of bacteremia[4], small volumes of blood inoculated[5] and laboratory factors.[6]

A variety of biochemical markers are being used for detection of neonatal sepsis. The most widely used is C-reactive protein (CRP). It has been included as a component of sepsis screen comprising of five parameters including total leucocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil ratio and micro-erythrocyte sedimentation rate (ESR). Presence of two abnormal parameters in a screen has been shown to have a sensitivity of 93–100%, specificity of 83% and a negative predictive value of 100 %.[7] However, high CRP values is also seen in intraventricular hemorrhage, meconium aspiration syndrome, respiratory distress syndrome, and transient tachypnea.[8]Procalcitonin, IL 6 and bacterial DNA PCR are among the other biochemical markers of sepsis that have been put to use. [9, 10]

Owing to the high mortality and morbidity associated with sepsis, there is a place for a non-invasive and early marker of sepsis. In 2003, Griffin et al showed that abnormal heart rate characteristics can be used to predict sepsis 12–24 hours before the onset of symptoms.[11] In 2005, Can Ince established that the pathophysiological effects of sepsis can be localized to its effect on microcirculation, the ultimate motor of sepsis. Sepsis induced damage to endothelial cells of microvasculature impair signaling, causing decreased perfusion in the peripheries. This is earliest site of damage and begins much before involvement of vital organs. Being the main prerequisite for adequate tissue oxygenation and thus organ function, impairment of this regulation causes heterogeneity in blood causing some capillaries to be under-perfused while others over-perfused. Unlike autoregulatory mechanism in brain, heart and kidney, cutaneous perfusion is devoid of autoregulation causing decreased perfusion and consequently decreased skin temperature in sepsis. The effect of sepsis on microcirculation serves the basis for non-invasive markers of sepsis such as perfusion index (PI).[12, 13]

Peripheral PI is derived from the photoelectric plethysmography signal of pulse oximetry and has been used as a noninvasive measure of peripheral perfusion. It reflects the real-time changes in peripheral blood flow and would be expected to be affected by changes in the arterial circulation.[14] PI provides an unambiguous value and can provide easy, noninvasive and unattended monitoring of illness severity in neonates.[14, 15] PI has been established as a marker of high illness severity in neonates, vasopressor requirement, detection of perinatal inflammation and congenital heart malformations.[15–18]PI has been evaluated as an early predictor of sepsis in asymptomatic newborn with antenatal risk factors for infection. However, it has not been previously studied in hospital-acquired sepsis. In this study, we have attempted to determine the diagnostic accuracy of PI in detection of hospital-acquired sepsis among neonates admitted in the Neonatal Intensive Care Unit (NICU).

Material And Methods

This prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital in north India from June 2018 to July 2019 after obtaining approval from Institute Ethics Committee. A written informed consent was obtained from either parent of the enrolled neonates.

All the term and preterm babies admitted to NICU were assessed for inclusion in the study. All neonates with a baseline PI of more than 0.88 in preterm and more than 1.24 in term neonates, who developed clinical sepsis after 48 hours of life, were included in the study. For including a repeat episode of sepsis in the same baby or babies receiving antibiotics for early onset sepsis, a period of at least 48 hours “off antibiotics” was considered for including the event. Neonates with major congenital malformations, structural congenital heart disease (except patent ductus arteriosus), HIV positive mothers, suspected inborn errors of metabolism, and cardiogenic shock were excluded.

The demographic details, perinatal history and general physical examination were recorded in a predesigned format. A Score for Neonatal Acute Physiology Perinatal Extension (SNAPPE II) was calculated for all enrolled neonates within 12 h of admission to NICU. PI was monitored continuously using a pulse oximeter or multiparameter monitor with Signal Extraction Technology (Masimo Corp., Irvine, CA, USA) and was recorded every 20 minutes. The data from Masimo device was directly transferred into computer via data transfer cable while that from multi-parameter screen display was captured as a photograph and later typed into a Microsoft® Excel worksheet. When the value of PI persisted below 0.88 in preterm babies and 1.24 in term babies for more 45 minutes, the time was noted. We used German Surveillance System for hospital-acquired neonatal sepsis, Neo-KISS (Neonatal Krankenhaus-Infektions-Surveillance-System) for defining clinical sepsis in both term and preterm neonates.[19] In laboratory parameters, CRP of > 10 mg/dl, TLC of less than 5000/mm^3or ANC abnormal as per Manroe [20] and Mouzinho [21] charts were considered to be sepsis screen positive. A minimum of 1 ml of blood was withdrawn for culture from a fresh venipuncture site, under all aseptic precautions, prior to starting antibiotics. Sending of sepsis screen and blood culture samples was decided clinically. The correlation with perfusion index was analyzed subsequently. Vitals in the form of heart rate, respiratory rate, blood pressure and temperature were monitored on hourly basis. All the babies were continuously monitored for perfusion index and oxygen saturation through an attached monitor. The babies with positive sepsis screen were considered to have sepsis while those with negative sepsis screen were considered to have no sepsis.

Statistical analysis:93 events achieve 91% power to detect a change in sensitivity from 0.5 to 0.8 using a two-sided binomial test and 100% power to detect a change in specificity from 0.5 to 0.8 using a two-sided binomial test. The target significance level is 0.05. Statistical analysis was done using SPSS version 19. All categorical variables were compared using chi-square test and continuous variables using Student’s t-test. Perfusion index was analyzed using repeated measures ANOVA test. Due to the effect of patent ductus arteriosus (PDA) on perfusion index, babies with PDA at the time of sepsis were excluded from analysis.

Results

The study flow is depicted in figure I. The mean maternal age was 25.5 ± 4.9 years. 34 (47.2%) of the mothers were primigravida. Pregnancy induced hypertension (PIH) and eclampsia were seen in 14 (19.4%) and eight (11.1%) mothers, respectively. Premature rupture of membranes was present in 29 (40.2%) cases. Mode of delivery was caesarean section in 42 (58.3%) patients.

Seven (9.7%) babies were more than 37 weeks of gestation, 34 (47.2%) babies between 32 to 36 weeks of gestation and 31 (43%) babies were less than 32 weeks of gestation. Of the 93 events of sepsis, seven were recorded in term neonates and 86 were recorded in preterm neonates. Mean PI at enrollment was 0.92 and 0.96 in term and preterm neonates, respectively. (Table I)

According to NeoKISS criteria, clinical sepsis was present in 77 (82.7%), non-coagulase negative *Staphylococcus* (CONS) sepsis in 12 (12.9%) and CONS sepsis in 4 (4.3%) of the events. In the no CONS group, blood culture showed Acinetobacter in 4 events, Klebsiella in 3 events, E. coli and methicillin-resistant *Staphylococcus aureus* (MRSA) in 1 event each and culture positive meningitis in 4 events (Enterococcus in 3 events and E. coli in 1 event).

Among the clinical parameters, new or more frequent apnea was most frequently encountered, that is, in 38(41%) events. This was followed by prolonged capillary filling time in 31(33.3%) events, heart rate variability in 26 (28%) events, temperature instability in 21 (22.6%) events, unexplained metabolic acidosis in 5(5.4%) events and new onset hyperglycemia in 4 (4.3%) events. Other signs of blood stream infection were seen in 65 (70%) of events.

Sepsis screen positivity, as defined by CRP of > 10 mg/dl, TLC of less than 5000/mm^3 or ANC abnormal as per Manroe [20] and Mouzinho [21] charts, was seen in 70 (75.2%) of clinical events with median value of CRP being 27 mg/L (IQR 12–73), TLC being 11450/μL (IQR 5900–18250) and ANC being 5541/μL (IQR 2370–9708). Meningitis was present in 13 (13.9%) events. 4 events were associated with culture positive meningitis. Taking 0.88 cut off for preterm babies and 1.24 for term babies, in 67 (72%) events perfusion index was below the cut-offs prior to clinical detection of sepsis. The median time difference between detection of sepsis with fall in perfusion index as compared to clinical sepsis was 268 minutes (IQR 120–459) or 4.5 hours (IQR 0.25–22.4). (Table II)

Of the sixty-seven cases with low PI, 11 (12.3%) had negative sepsis screen while 56 (62.9%) cases had sepsis screen positive. Of the twenty-two cases where PI did not fall below the cut off, 15 (16.8 %) had positive sepsis screen while 7 (7.8%) had negative sepsis screen. Four cases, which were being treated for PDA at the time of detection of sepsis, were not included in analysis due to the possibility of PI being falsely high secondary to PDA.

The median PI in term babies at the time of sepsis came to be 1.5 which was same as median PI at admission, hence deferring its utility in diagnosing hospital acquired sepsis in term neonates. For detection of hospital acquired sepsis in preterm babies, PI showed a sensitivity of 89.47% (95% CI 78.48–

96.04%), specificity of 56% (95% CI 34.93–75.60%), positive predictive value of 82.26% (95% CI 74.70–87.92%), and negative predictive value of 70% (95% CI 50.36–84.29%) in detection of sepsis in preterm neonates. The positive likelihood ratio of the test is 2.03 (95% CI 1.30 to 3.19) while the negative likelihood ratio is 0.19 (95% CI 0.08 to 0.43). The diagnostic accuracy of PI for diagnosis of sepsis is 79.27% (95% CI 68.89–87.43%). (Table III)

When the events associated with fall in PI and those in which PI did not fall before sepsis were compared, heart rate, respiratory rate and SNAPPE II scores at admission showed no significant difference in both the groups, however, the low PI group showed significantly lower values of temperature (p value = 0.0441) and PI (p value = 0.0048) at the time of admission to NICU. However, the median age at sepsis was 7 days or 268 hours and the median age at NICU admission was 8 hours, this seems to be a chance occurrence. (Table IV)

A one-way ANOVA was conducted to determine if there was any significant difference in the values of perfusion index 24 hours before sepsis, during sepsis and 24 hours after starting antibiotics. In both term and preterm neonates there was significant difference between the perfusion indices among three time periods ($p < 0.001$). The values of PI were significantly lower values in the sepsis period as compared to pre-sepsis period in both term ($p < 0.05$) and preterm ($p < 0.05$) neonates. In addition, preterm neonates showed significantly higher values of PI in the period 24 hours after starting antibiotics indicating positive response to starting treatment. The median value of PI during clinical sepsis in term and preterm neonates came out to be 1.5 (IQR 1.09–2.21) and 0.9 (IQR 0.58–1.5), respectively.

Amongst 72 neonates, 56 (77.7%) were discharged from the hospital, 7 (9.7%) took leave against medical advice, 1 (1.3%) was referred to higher center for surgical intervention and in 8 (11%) cases the outcome was death. The mean length of NICU stay was 24 (16.8) days and that of hospital stay was 41 (22.5) days.

The median enrolment PI of the babies who died was 0.65 (IQR 0.6–0.76, 95% CI 0.58–0.87) and those who survived was 0.8 (IQR 0.69–1.1, 95% CI 0.77–0.84) (p value = 0.0161) hence indicating that the babies with lower PI at the time of enrolment are predisposed to a poor outcome.

A positive association was seen between SNAPPE II score and duration of NICU stay, that is, higher SNAPPE II scores were associated with prolonged duration of NICU stay. (Correlation coefficient, $r = 0.3774$, p value = 0.0002)

Discussion

In this prospective observational study conducted in NICU of a tertiary care hospital, 93 events of hospital acquired sepsis were studied. In 72% events of sepsis, PI was found to fall below cut off prior to sepsis. The median value of PI at the time of sepsis in term neonates came out to be 1.5 while in preterm neonates it was 0.9. This value could be used as a threshold for detecting sepsis in preterm neonates.

However, in term neonates, the median admission PI and median PI at the time of sepsis was 1.5. Thereby, PI does not seem to have a role in detecting hospital acquired sepsis in term newborn babies.

As compared to laboratory markers, fall in PI helped in detecting sepsis early by a margin of 4.5 hours (IQR 0.25–22.4 hours). In our study, PI yielded a sensitivity of 89.47% (95% CI 78.48–96.04%), specificity of 56% (95% CI 34.93–75.60%), positive predictive value of 82.26% (95% CI 74.70–87.92%), and negative predictive value of 70% (95% CI 50.36–84.29%) in detection of sepsis in preterm neonates. These indices were arrived at after excluding babies with PDA, at the time of sepsis, to account for the effect of PDA on PI.

The major strengths of our study were inclusion of both term and preterm neonates; continuous monitoring of PI and being the first study to evaluate PI as a marker of neonatal sepsis. However, a small number of term babies, is a major limitation and the variation of PI during sepsis in term babies would require validation on a larger sample size.

In a study by Felice et al, one minute PI ≤ 1.74 and five minute PI ≤ 2.18 showed 100% sensitivity and specificity in discriminating histological chorioamnionitis (HCA) positive from HCA negative cases.[17] Rasmy et al recorded perfusion indices for 36 neonates. A PI ≤ 0.3 had a sensitivity and specificity of 100% and 93%, respectively for determining vasopressor requirement. Also, a concomitant rise in serum lactate levels was seen.[16] A PI value of 1.24 has been shown to be associated with high illness severity in neonates.[15]

In a cohort study on extremely low gestational age newborns, Van laere et al concluded that low values and reduced short-term variability of PI on day 1 are associated with adverse outcomes.[22] In a cross sectional study design to evaluate correlation between PI and Clinical Risk Index for Babies (CRIB) score in sick neonates, Mathew et al found that the median PI of babies with shock and without shock was 0.63 (0.43, 0.84) and 1.58 (1.19, 2.41), respectively, with p value < 0.001.[23]

PI has also shown good correlation with occurrence of clinical shock.(24) Also PI is significantly correlated with left ventricular output and can be an important tool in the diagnosis of congenital heart defects.[18, 25]

The limitation of using PI as a marker of neonatal sepsis is that it can be affected by multiple factors including shock[16], heart disease[26] or perinatal inflammation[17]. However, based upon the findings of this study, we can conclude that PI can be used for early detection of sepsis in preterm neonates with a critical cut off value of 0.9 but it has no role in detecting sepsis in term neonates.

Abbreviations

ANC	Absolute Neutrophil Count
CONS	Coagulase-negative *Staphylococcus*

CRIB	Clinical Risk Index for Babies
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
HCA	Histological Chorioamnionitis
MRSA	Methicillin-Resistant *Staphylococcus aureus*
Neo-KISS	Neonatal Krankenhaus-Infektions-Surveillance-System
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus Arteriosus
PI	Perfusion Index
PIH	Pregnancy Induced Hypertension
SNAPPE II	Score for Neonatal Acute Physiology Perinatal Extension II
TLC	Total Leukocyte Count

Declarations

Sources of funding: No funding was received for conducting this study.

Competing interests: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article.

Code availability: N/A

Contribution of each author:

Conceptualization and methodology by SJ and DC

Data collection by JS

Data curation and formal analysis SJ and DC

Provision of resources by SJ, DC and SK

Supervision/oversight by SJ, DC and SR

Ethics approval: Obtained from Institute's Ethics Committee.

Consent to participate: Written informed consent was obtained from the parents of enrolled neonates.

Consent for publication: N/A.

Acknowledgement: We thank our patients and their parents for their cooperation.

References

1. Sankar MJ, Neogi SB, Sharma J, Chauhan M, Srivastava R, Prabhakar PK et al (2016) State of newborn health in India. J Perinatol 36:S3–S8
2. Fleischmann C, Reichert F, Cassini A et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis [published online ahead of print, 2021 Jan 22]. Arch Dis Child. 2021;archdischild-2020-320217
3. Hug L, Alexander M, You D, Alkema L, UN Inter-agency Group for Child Mortality Estimation (2019 Jun) National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. Lancet Glob Health 7:e710–e720
4. Kellogg JA, Ferrentino FL, Goodstein MH, Liss J, Shapiro SL, Bankert DA (1997) Frequency of low level bacteremia in infants from birth to two months of age. Pediatr Infect Dis J 16:381–385
5. Neal PR, Kleiman MB, Reynolds JK, Allen SD, Lemons JA, Yu PL (1986 Sep) Volume of blood submitted for culture from neonates. J Clin Microbiol 24:353–356
6. Zea-Vera A, Ochoa TJ (2015) Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr 61:1–13
7. Patel U, Kumar Patel V, Prasad Patel N, Verma J, Kumar Ratre B, Verma S. C-Reactive Protein and other Hematological parameters for diagnosis of Neonatal Sepsis. Int J Med Res Rev [Internet]. 2014Aug.31;2:311–8
8. Forest JC, Larivière F, Dolcé P, Masson M, Nadeau L (1986) C-reactive protein as biochemical indicator of bacterial infection in neonates. Clin Biochem 19:192–194
9. Vouloumanou EK, Plessa E, Karageorgopoulos DE, Mantadakis E, Falagas ME (2011) Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. Intensive Care Med 37:747–762
10. Ganesan P, Shanmugam P, Sattar SBA, Shankar SL (2016) Evaluation of IL-6, CRP and hs-CRP as Early Markers of Neonatal Sepsis. J Clin Diagn Res JCDR 10:DC13–D17
11. Griffin MP, O'Shea TM, Bissonette EA, Harrell FE, Lake DE, Moorman JR (2003) Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. Pediatr Res 53:920–926
12. Ince C (2005) The microcirculation is the motor of sepsis. Crit Care Lond Engl 9:S13–S19

13. Hasanin A, Mukhtar A, Nassar H (2017) Perfusion indices revisited. J Intensive Care 5:24
14. Aoyagi T, Miyasaka K (2002) Pulse oximetry: its invention, contribution to medicine, and future tasks. Anesth Analg 94:S1–S3
15. De Felice C, Latini G, Vacca P, Kopotic RJ (2002) The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 161:561–562
16. Rasmy I, Mohamed H, Nabil N, Abdalah S, Hasanin A, Eladawy A et al (2015) Evaluation of Perfusion Index as a Predictor of Vasopressor Requirement in Patients with Severe Sepsis. Shock Augusta Ga 44:554–559
17. De Felice C, Del Vecchio A, Criscuolo M, Lozupone A, Parrini S, Latini G (2005) Early postnatal changes in the perfusion index in term newborns with subclinical chorioamnionitis. Arch Dis Child Fetal Neonatal Ed 90:F411–F414
18. Granelli A, de-Wahl, Ostman-Smith I (2007) Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr Oslo Nor 1992 96:1455–1459
19. Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen > NEO-KISS [Internet]. [cited 2019 Aug 3]. Available from: https://www.nrz-hygiene.de/en/surveillance/hospital-infection-surveillance-system/neo-kiss/
20. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R (1979) The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr 95:89–98
21. Mouzinho A, Rosenfeld CR, Sánchez PJ, Risser R (1994) Revised reference ranges for circulating neutrophils in very-low-birth-weight neonates. Pediatrics 94:76–82
22. Van Laere D, O'Toole JM, Voeten M, McKiernan J, Boylan GB, Dempsey E (2016) Decreased Variability and Low Values of Perfusion Index on Day One Are Associated with Adverse Outcome in Extremely Preterm Infants. J Pediatr 178:119–124.e1
23. Mathew J, Bada Shekarappa C, Padubidri Nanyam Rao S (2019) Correlation between Perfusion Index and CRIB Score in Sick Neonates Admitted to a Tertiary Center. J Trop Pediatr 1:65:84–89
24. Sivaprasath P, Mookka Gounder R, Mythili B (2019) Prediction of Shock by Peripheral Perfusion Index. Indian J Pediatr 86:903–908
25. Corsini I, Cecchi A, Coviello C, Dani C (2017) Perfusion index and left ventricular output correlation in healthy term infants. Eur J Pediatr 176:1013–1018
26. Khositseth A, Muangyod N, Nuntnarumit P (2013) Perfusion index as a diagnostic tool for patent ductus arteriosus in preterm infants. Neonatology 104:250–254

Tables

Table I: Baseline characteristics in neonates with late onset neonatal sepsis

Variable	n=72
Gestational age(weeks) *	32.2 (3.2)
Birth weight(grams)+	1420 (1100-1855)
Small for gestational age#	21 (29%)
Male gender#	40 (55.5%)
Apgar score at 1 min+	7.3(1-9)
Apgar score at 5 min+	8.1(3-9)
Hours of life at NICU admission+	8 (5-12)
Heart Rate at the time of admission to NICU (beats per minute) +	141 (135-156)
Temperature at the time of admission to NICU (ºC)*	36.1 (0.8)
Respiratory rate at the time of admission to NICU (breaths per minute) +	64 (60-70)
Perfusion Index at the time of admission to NICU (Term)+	1.5 (1.25-1.6)
Perfusion Index at the time of admission to NICU (Preterm)+	1.1 (0.9-1.4)

Values represent *mean (SD) or #number (percentage) or +Median (Inter-quartile range)

Table II: Profile of perfusion index and clinical sepsis noted in 93 events of late onset neonatal sepsis

Variable	n=93
Perfusion index at enrollment (term)*	0.92 (0.53)
Perfusion index at enrollment (preterm)*	0.96 (0.56)
Hours of life at NICU admission+	8 (5-12)
Age at clinical sepsis (hours of life)+	160 (87.9-254.9)
Time difference between detection of sepsis with fall of PI vs. clinically (minutes)+	268 (120-459)
Time difference between detection of sepsis with fall of PI vs. clinically (hours)+	4.5 (0.25-22.4)
Perfusion index below cut off of 1.24 in term and 0.88 in preterm prior to sepsis#	67 (72%)

Values represent *mean (SD) or #number (percentage) or +Median (Inter-quartile range)

Table III:Diagnostic Accuracy of perfusion index in detecting sepsis in preterm neonates

	Sepsis n (%)	No Sepsis n (%)	
PI low	51 (62%)	11 (13.4%)	62 (73.1%)
PI not low	6 (7.3%)	14 (17.1%)	20 (24.4%)
	57 (69.5%)	25 (30.4%)	82
		VALUE	95% CI
Sensitivity		89.5%	78.5% to 96%
Specificity		56%	34.9% to 75.6%
Positive likelihood ratio		2	1.3 to 3.2
Negative likelihood ratio		0.2	0.1 to 0.4
Positive predictive value		82.3%	74.7% to 87.9%
Negative predictive value		70%	50.4% to 84.3%
Accuracy		79.3%	68.9% to 87.4%

Note: Seven term neonates and four cases of patent ductus arteriosus (PDA) who were receiving treatment for PDA at the time of sepsis have been excluded from analysis.

Table IV: Comparison of factors in neonates with PI below the cut off value prior to sepsis and those with PI above the cut off during late onset neonatal sepsis

Variable	PI below cut off group(n=67)	PI above cut off group (n=26)	p value
Male gender[#]	34 (50.7%)	15 (57.6%)	0.54
Preterm[#]	63 (94%)	24 (92.3%)	0.76
Small for gestational age[#]	21 (31.3%)	9 (34.6%)	0.76
Maternal age (years) [+]	25 (22-28)	27 (23-30)	0.138
Caesarian Section[#]	35 (52.2%)	18 (69.2%)	0.14
Chronic Hypertension[#]	1 (1.5%)	2 (7.7%)	0.13
Anemia (Hb<10g/dl) [#]	6 (8.9%)	3 (11.5%)	0.7
Eclampsia[#]	6 (8.9%)	4 (15.4%)	0.37
IUGR[#]	6 (8.9%)	4 (15.4%)	0.37
Oligohydramnios[#]	13 (19.4%)	2 (7.69%)	0.17
Preterm Premature Rupture of membranes[#]	31 (46.2%)	9 (34.6%)	0.31
Gestational age (weeks) [+]	31.4±3	32.8±3.1	0.058
Weight (grams) [+]	1200 (1000-1560)	1600 (1000-2000)	0.073
Apgar score at 1 minute[+]	9 (6-9)	9 (6-9)	0.132
Apgar Score at 5 minutes[+]	9 (8-9)	9 (8-9)	0.436
Heart rate at admission (beats per minute) [+]	149 (137-156)	138 (135-152)	0.165
Respiratory Rate at admission (per minute) [+]	64 (60-68)	62 (60-70)	0.445
Temperature at admission (^{0}C) [+]	36.2 (35.6-36.6)	36.5 (36-36.8)	0.0441
Perfusion Index at admission[+]	1.1 (0.9-1.37)	1.3 (1-2.03)	0.0048
SNAPPE 2 score[+]	20 (10-35)	21.5 (5-28)	0.525
CRP (mg/dl) [+]	31 (13.9-82.5)	24.8 (7.1-43)	0.097
PDA needing treatment[#]	17 (25.3%)	6 (23%)	0.81
Intraventricular hemorrhage[#]	12 (17.9%)	3 (11.5%)	0.32

Shock[#]	40 (59.7%)	10 (38.4%)	0.0667
Length of NICU stay (days)[+]	18 (12-34)	19 (14-33)	0.592

Values represent *mean (SD) or [#]number (percentage) or +Median (Inter-quartile range)

Figures

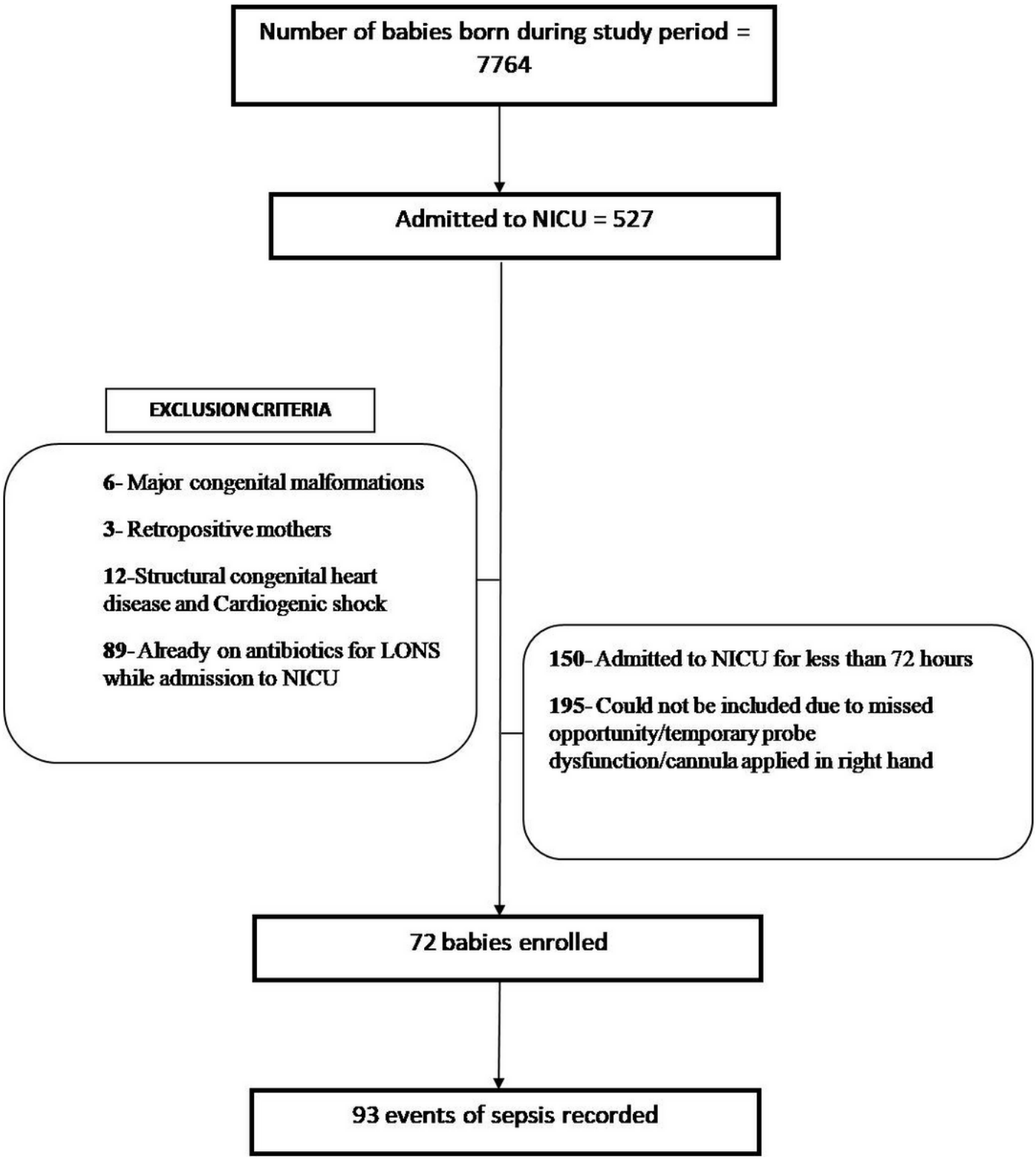

Figure 1

The Study Flow

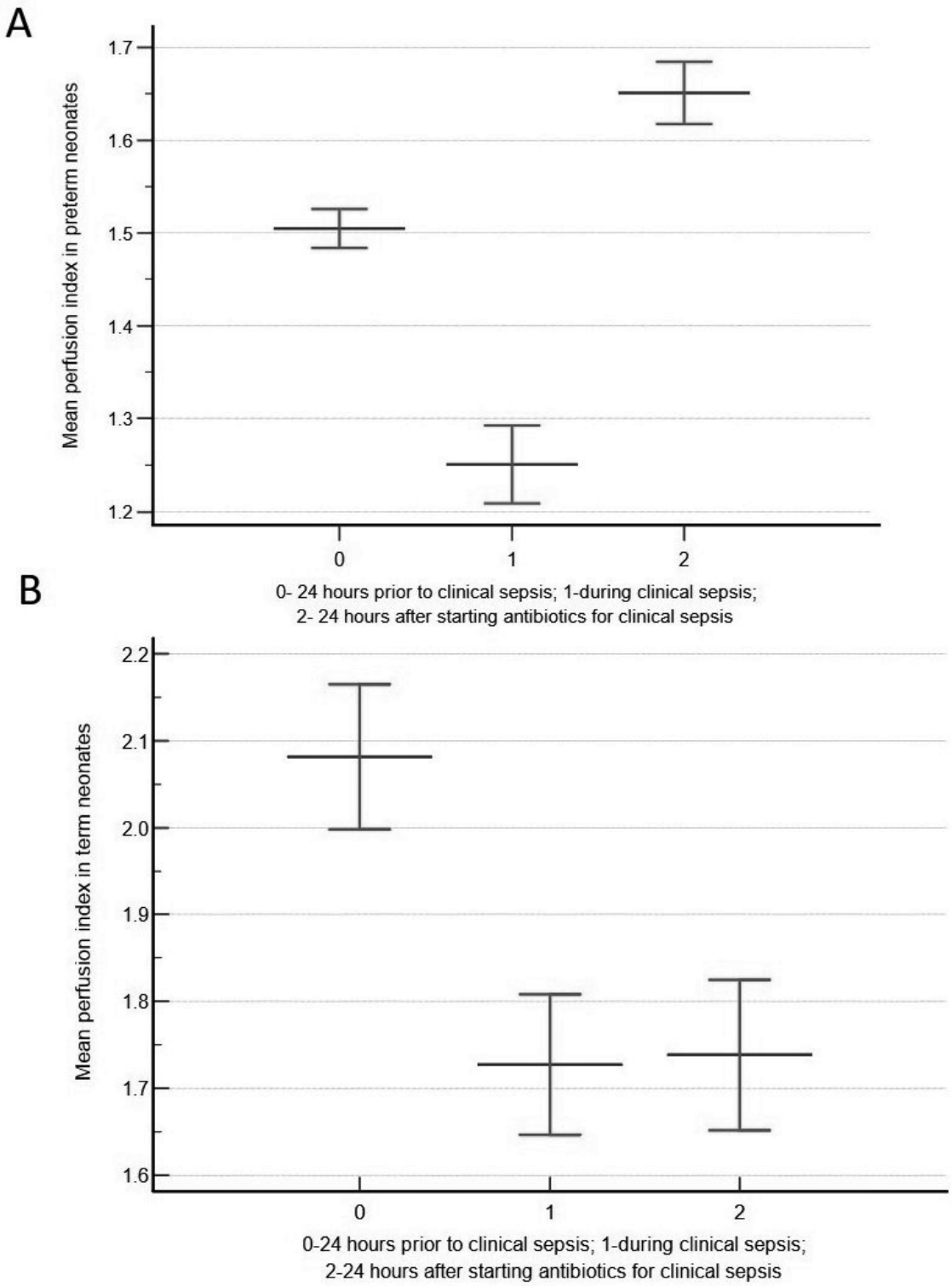

Figure 2

The box and whisker plot showing mean perfusion index 24 hours prior to sepsis, at the time of clinical sepsis and 24 hours after starting antibiotics for clinical sepsis in preterm (A) and term (B) neonates.