Assessment of Neurodevelopmental Status and Risk Factors for Adverse Neurodevelopmental Outcome in Late Preterm Infants at 6 Months Corrected Age : An Prospective Observational Study

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Abstract

Background: Late Preterm (LP) infants, previously considered low risk, have been identified to be at risk of developmental problems in infancy and early childhood. There is limited information on the outcome of these infants in low and middle income countries. This study was aimed to assess the neurodevelopmental status of LP born neonates and to determine factors associated with adverse neurodevelopmental outcome in a tertiary hospital of Chattogram, Bangladesh.

Materials and methods: In this prospective observational study, 108 LP (34 to <37 completed weeks gestation at birth) infants were enrolled from the Special Care Neonatal Unit (SCANU) Chittagong Medical College Hospital (CMCH) from June 2018 to May 2019. Neurodevelopmental assessment was done by Rapid Neurodevelopmental Assessment (RNDA) at 1, 3, and 6 months of Corrected Age (CA).

Results: Of the 108 enrolled children, 30 (27.8%) attended all 3 follow-up, 69 (63.9%) had incomplete follow-up, and 9 (8.3%) died. At final follow-up, out of 30 infants, 25 (83.3%) had no abnormality in all 8 domains of RNDA. Three infants (10.0%) had abnormalities in one domain and 2 (6.7%) had abnormalities in 5 domains. Gross motor abnormality was most common abnormality (13.4%), followed by speech (10.0%), and cognition (6.7%). Small for gestational age was found to be the only independent predictive factor for Neurodevelopmental Abnormality (NDA) in LP infants.

Conclusion: This study demonstrates that 16.7% of the LP infants had evidence of neurodevelopmental impairment at 6 months of corrected age. SGA was an important risk factor of adverse neurodevelopmental outcome. Thus, LP infants in Bangladesh require long-term follow-up to monitor developmental outcome.

Key words: Late Preterm; Neurodevelopmental assessment; Neurodevelopmental abnormality.

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Introduction

Late Preterm Infants (LPI) are born between 34 and <37 completed weeks and among singleton live births 3% to 6% are LPI across countries.[1] Although data from Low- and Middle-Income Countries (LMIC) are sparse, Bangladesh is one of the 10 countries with the greatest number of preterm births in the world.[2]

Until recently, LPI were considered at low risk of morbidity and developmental problems. There is, however, increasing evidence that LPI are at increased risk of neonatal problems and poor neurodevelopmental function, in comparison to their term counterparts.[3-6] The incidence of problems increases as gestational age decreases. Several studies suggested that elective preterm delivery should therefore be discouraged, LPI should be discharged 48 hours after birth and have appropriate long term follow up.[3,4,6] Despite of accumulating evidence in the literature, data from Bangladesh and other LMICs are limited due to a lack of follow-up programs for high-risk infants in general and for preterm infants in particular.[7]

Information on neurological outcomes is crucial for both policy making and future planning for healthcare, social and educational services and for counseling caregivers about expected outcomes following preterm birth.[8] Therefore, we examined neurodevelopmental outcomes in a hospital-based cohort of LPI discharged from a Neonatal Intensive Care Unit (NICU) using the Rapid Neurodevelopmental Assessment (RNDA) tool at 1, 3 and 6-months Corrected Age (CA).[9] We also estimated the prevalence of abnormal neurological examination and attempted to assess risk factors for poor outcome.

Materials and methods

This prospective observational study was conducted at the SCANU at Chittagong Medical College Hospital, in Chattogram city, one of the largest tertiary centers responsible for critical care of newborns in southeastern Bangladesh. The SCANU has 30 beds and 1200 admissions annually, of which the vast majority are transferred from healthcare facilities providing obstetric care and the others are admitted from home via the emergency room. The study was approved by the Ethical Review Committee of Chittagong Medical College and written parental consent was obtained for each study participant.

All late preterm newborns of 34 to <37 completed weeks gestation admitted to SCANU from June 2018 to May 2019 were eligible for enrolment except those with perinatal asphyxia, meningitis, culture positive sepsis, hyperbilirubinemia >20 mg/dl or requirement of exchange transfusion, major morbidities such as intraventricular hemorrhage, major congenital malformation, congenital hypothyroidism.

Demographic data were obtained at enrollment including living place, maternal factors (Age, educational level, and occupation) and monthly family income.Antenatal, perinatal, neonatal and relevant postnatal information included Comorbid maternal condition during pregnancy, Neonatal condition, Parity, Gestatioal age, Antental care, Mode of delivery, Place of delivery, Birth weight, Gestational weight, Length of stay in hospital and Multiple pregnancy were recorded.

At the time of discharge, parents or guardians were advised to come for follow-up at one, three, and six months of CA.[10] Periodic reminder were sent to parents through telephonic calls to improve follow-up. Neurodevelopmental assessment was done at each follow-up by RNDA tool. RNDA tool previously was shown to have acceptable reliability and validity in Bangladeshi children.[9, 11] All tests were conducted by the principal investigator at the hospital in a quiet room, and the results were recorded on standard assessment forms. Standard treatment was provided to the babies and appropriately intervened in the follow-up whenever required.

Data were analyzed with the help of a computer software package (SPSS, version 23). Summary statistics are presented as mean (SD) or median (IQR) for continuous variables, and in absolute counts and percentages for categorical variables. To compare the continuous data between two groups'Independent samples t-test Or Mann-Whitney U test and between three groups, ANOVA test or Kruskal Wallis Test was as appropriate. Chi-square test was used for group comparisons of categorical variables. Risk factors for adverse neurodevelopmental outcomes were analyzed by logistic regression analysis. Results were shown by Odds Ratio (OR) with 95% Confidence Interval (CI). Statistical significance was defined as $p \leq 0.05$.

Results

Out of 108 LPIs who were enrolled in the study during the follow-up period, 9 (8.3%) infants died, 69 (63.9%) didn't complete F/U or were lost to follow-up, and 30 (27.8%) were available in all three follow-ups.

Table I Characteristics of the late preterm infants stratified by their retention in the study (n=108)

Characteristics (Unit)	Complete F/U (n=30)	Incomplete F/U or Lost (n=69)	Died (n=9)	p value
Maternal age (Years)	24 (22-28)	24 (21-26)	25 (20-25)	0.430‡
Maternal education[a]	10 (8-12)	10 (9-10)	10 (8-10)	0.653‡
Mother work outside	4 (13.3)	2 (2.9)	0 (0)	0.086*
MFI [b] (1000 BDT)	20 (15-30)	20 (15-27)	10 (9-20)	0.064‡
Resides in Rural area	16 (53.3)	47 (68.1)	6 (66.7)	0.533*
Parity	2 (1-3)	2 (1-2)	1 (1-3)	0.940‡
Had ANC	30 (100)	69 (100)	8 (88.9)	0.415*
Home delivery	18 (60.0)	34 (49.3)	6 (66.7)	0.442*
Delivered by CS	1 (3.3)	2 (2.9)	0 (0)	0.558*
Male infant	11 (36.7)	28 (40.6)	3 (33.3)	0.877*
Gestational age (Weeks)	35 (34-35)	35 (34-36)	36 (34-36)	0.214
Birth weight (kg)	1.95±0.32	1.76±0.30	1.51±0.11	<0.001†
SGA	11 (36.7)	37 (53.6)	9 (100.0)	0.004*
Neonatal sepsis	18 (60.0)	33 (47.8)	4 (44.4)	0.495*
RDS	3 (10)	4 (5.8)	4 (44.4)	0.001*
LOS	12 (7-17)	9 (7-14)	8 (6-19)	0.286‡

Data are expressed either as frequency (Percentage) Median (IQR: Interquartile Range) or Mean (±SD) as appropriate, p values are derived from *Chi-square test or †from ANOVA t test or ‡: Kruskal Wallis Test as appropriate, [a]: Years of schooling, [b]: Monthly family income, ANC: Antenatal Care, CS: Cesarean Section, SGA: Small for Gestational age, RDS: Respiratory Distress Syndrome, LOS: Length of Stay in hospital.

Sociodemographic, antenatal, perinatal, neonatal, and other variables were compared across those who completed Follow-Up (FU) till 6 months, those who didn't complete F/U or were lost to follow-up and those who died (Table I).

Significant differences were found in birth weight (Was lowest among those who died) proportion of small for gestational age (Was highest among those who died) and proportion of respiratory distress syndrome (Was highest among those who died).

Table II Frequency distribution of disability grade in different domains of RNDA at 1, 3, and 6 months of corrected age in 30 late preterm infants completed FU

Domain	Status	Disability grade	Corrected age of assessment At 1st month	At 3rd month	At 6th month
Gross motor	Normal		25 (83.3%)	25 (83.3%)	26 (86.7%)
	Abnormal	Mild	3 (10.0%)	4 (13.3%)	2 (6.7%)
		Moderate	1 (3.3%)	1 (3.3%)	2 (6.7%)
		Severe	1 (3.3%)	0 (0%)	0 (0%)
Fine motor	Normal		29 (96.7%)	29 (96.7%)	29 (96.7%)
	Abnormal	Severe	1 (3.3%)	1 (3.3%)	1 (3.3%)
Vision	Normal		28 (93.3%)	28 (93.3%)	29 (96.7%)
	Abnormal	Mild	0 (0%)	1 (3.3%)	1 (3.3%)
		Moderate	2 (6.7%)	1 (3.3%)	0 (0%)
		Severe	0 (0%)	0 (0%)	0 (0%)
Hearing	Normal		28 (93.3%)	27 (90.0%)	29 (96.7%)
	Abnormal	Mild	2 (6.7%)	1 (3.3%)	0 (0%)
		Moderate	0 (0%)	2 (6.7%)	0 (0%)
		Severe	0 (0%)		1 (3.3%)
Speech	Normal		26 (86.7%)	27 (90.0%)	27 (90.0%)
	Abnormal	Moderate	4 (13.3%)	1(%)	2 (6.7%)
		Severe	0 (0%)	2 (6.7%)	1(3.3%)
Cognition	Normal		24 (80.0%)	25 (83.3%)	28 (93.3%)
	Abnormal	Mild	3 (10.0%)	3 (10.0%)	0 (0%)
		Moderate	3 (10.0%)	2 (6.7%)	0 (0%)
		Severe	0 (0%)	0 (0%)	2 (6.7%)
Behavior	Normal		26 (86.7%)	28 (93.3%)	29 (96.7%)
	Abnormal	Mild	3 (10.0%)	1 (3.3%)	0 (0%)
		Moderate	1 (3.3%)	1 (3.3%)	0 (0%)
		Severe	0 (0%)	0 (0%)	1 (3.3%)
Seizure	Normal		30 (100.0%)	30 (100.0%)	30 (100.0%)

Data were expressed as frequency (Percentage).

Out of 108 included infants, only 30 had complete follow-up at 6 months of CA. Among them, at 1 month of CA, number of infants with abnormal domain were gross motor-5 (16.7%) fine motor-1 (3.3%) vision-2 (6.7%) hearing-2 (6.7%) speech-4 (13.3%) cognition-6 (20.0%) and behavior- 4 (13.3%). At 6 months of CA, number of infants with abnormal domain were gross motor-4 (13.3%) fine motor-1 (3.3%) vision-1 (3.3%) hearing-1 (3.3%) speech-3 (10.0%) cognition-2 (6.7%) and behavior- 1 (3.3%) (Table II).

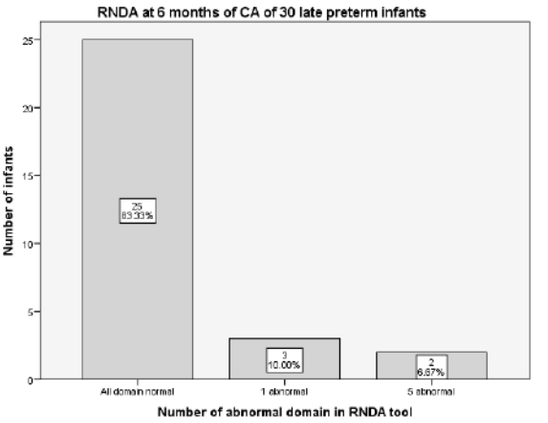

Fig 1 Clustering of the abnormal domains in RNDA at 6 months of CA (n=30)

At final follow-up (6 months of CA), out of 30 infants, 25 (83.33%) had no abnormality in all 8 domains of RNDA tool. Three infants (10%) had abnormalities in one domain and 2 (6.7%) had abnormalities in five domains (Figure 1).

Table III Association between socio-demographic, antenatal, perinatal, neonatal, and other relevant characteristics with developmental disability at 6 months corrected age in 30 late preterm infants

Characteristics (unit)	RNDA assessment at 6 month Normal (n=25)	Abnormal (n=5)	p value
Maternal age (Years)	24 (22-28)	22 (20-31)	0.627‡
Maternal education[a]	10 (8-13)	10 (9-12)	0.829‡
Mother work outside	4 (16.0)	0 (0)	1.0*
MFI [b] (1000 BDT)	20 (11-35)	20 (15-30)	0.957‡
Resides in rural area	13 (52.0)	3 (60.0)	1.0*
Maternal HTN/PET/Eclampsia	4 (16.0)	1 (20.0)	1.0*
Had ANC	25 (100)	5 (100)	NA
Home delivery	0 (0)	1 (20.0)	0.167*
Delivery by CS	16 (64.0)	2 (40.0)	0.164*
Male infant	15 (60.0)	4 (80.0)	0.327*
Gestational age (Weeks)	35 (34-35)	35 (34-35)	0.947‡
Birth weight (kg)	1.98±0.33	1.82±0.31	0.126†
SGA	7 (28.0)	4 (80.0)	0.037*
Neonatal sepsis	14 (56.0)	4 (80.0)	0.622*
RDS	4 (16.0)	1 (20.0)	1.0*
LOS (Days)	12 (7-17)	12 (7-18)	0.957‡
Not exclusively breast fed	23 (92.0)	4 (80.0)	0.138*

Data are expressed either as frequency (Percentage), Median (IQR: Interquartilerange) or Mean (±SD) as appropriate, p values are derived from *Chi-square test or †from Independent sample t test or‡: Mann-Whitney U test as appropriate, [a]: Years of schooling, [b]: Monthly

family income; ANC: Antenatal Care, CS: Cesarean Section; SGA: Small for Gestational Age, RDS: Respiratory Distress Syndrome, LOS: Length of Stay in hospital.

Associations of developmental disability with socio-demographic, antenatal, perinatal, neonatal, and other relevant characteristics are presented in Table III. Only SGA had a significant association with developmental disability at 6 months. Significantly higher number of LPI with developmental disability had a history of SGA (p= 0.037) compared to the LPI with normal development.

Table IV Independent predictors of developmental abnormalities by RNDA in 30 late preterm infants who came for neurodevelopment follow-up at 6 months

Variables (unit)	Odds ratio	95% CI for OR		p value
		Lower	Upper	
Delivery by CS	0.07	0.04	1.94	0.102
Home delivery	1.04	0.291	47.78	0.312
Small for gestational age	5.14	1.11	16.22	0.041
Birth weight, kg	0.14	0.026	1.673	0.142
Not exclusively breast fed	1.21	0.416	7.47	0.442

To determine the independent effect of NDA, the variables which had a p value of 0.1 were subsequently entered into a logistic regression model. After adjustment of other variables, only SGA was found to be as an independent factor. Infants having SGA were 5.14 times more likely to have NDA than the infants with Appropriate for Gestational Age (AGA) {p=0.041}.

Discussion

Our study reports neurodevelopmental outcomes for Bangladeshi LPIs at 6 months CA and contributes to the evidence of adverse outcomes for LPIs in LMICs.[11,12] We found that 16.67% of LPIs had abnormal neurodevelopment in one or more of the seven domains (Gross motor, fine motor, vision, hearing, speech, cognition and behavior). All infants had normal development in the seizure domain. Among the neurodevelopmental abnormality, the most prevalent was in the gross motor domain followed by speech, cognition and other domains.

The results of the current study are in agreement with other research, who report that LPI are at increased risk of neurodevelopmental disability in comparison to term infants.[4,6,13] In a large population-based study, Johnson et al found that LPI were at twice the risk of neurodevelopmental disability, primarily in the cognitive domain.[5] Researchers in Thailand and China also found developmental delay at the age of 12 months in LPI.[14,15] In a previous study from Bangladesh where RNDA tool was used among preterm infants, it was observed that more than one domain was affected in 34.9% infants and the single largest category of NDA was gross motor abnormality which is greater at 3 months of age than previously in the neonatal period. In contrast, other abnormal domains have come down to a lower levels.[12]

Similar to Ramdin et al., the current study did not find any association between developmental status and neonatal or obstetric factors, except SGA.[16] Other reports have found male sex, maternal preeclampsia, low socio-economic status, emergency caesarean section delivery, and lack of breastfeeding on discharge to be associated with worse developmental outcome.[5,17]

Limitations

The prospective design is one of the strengths of our study and the considerable size of the initial cohort. Furthermore, the assessment tool RNDA that we used had been previously adapted and validated for Bangladeshi infants. On the other hand, we acknowledge several limitations. The study lacked a full-term peer control group. Furthermore, nearly 70% of the infants were lost to follow-up, potentially resulting in bias.

Conclusions

The current study is the first report of developmental outcomes in LPI in this area of Bangladesh and found a rate of neurodevelopmental abnormality of 16.67% in these infants. These findings are in agreement with reports from high-income settings and confirm that LPI are an at-risk population which requires close long-term follow-up, including neurodevelopmental. In addition, small for gestational age was an independent predictor for neurodevelopmental abnormalities in these babies.

Recommendations

Currently, the burden of morbidity of LPIs is largely undetected and unaddressed throughout the developing world. Our study suggests the consideration of long-term neonatal follow-up programmes in Bangladesh that could assist in ensuring this vulnerable group of children fulfills their potential.

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Contribution of authors
TH-Conception, design, acquisition of data, manuscript writing & final approval.
PKC-Design, interpretation of data critical revision & final approval.
FUA-Data analysis, interpretation of data, critical revision & final approval.
SKB-Design, critical revision & final approval.
SHH-Acquisition of data, data analysis, drafting & final approval.
MD-Acquisition of data, drafting & final approval.

Disclosure
The authors declared no competing interests.

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