

# NEURODEVELOPMENT OUTCOME AMONG PRETERM INFANTS ADMITTED IN NEONATAL INTENSIVE CARE UNIT

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## Abstract

**Introduction:** With increasing the survival rates of premature babies, the management of long-term complications, especially neurodevelopmental disorder is becoming an important issue for a better life.

**Aims:** To assess the factors associated with adverse neurodevelopment outcome among preterm infants admitted in Neonatal Intensive Care Unit (NICU).

**Methods and Material:** This prospective cohort study was conducted in Department of Neonatology, BSMMU, Dhaka, Bangladesh. Premature infants (<34 weeks) discharged from the NICU were enrolled and followed up for neurodevelopmental assessment at 6 months of age. Prenatal, perinatal, and postnatal features of the babies were recorded. The Bayley-III scale was used to assess the composite scores. Continuous variables were analyzed using an independent t-test and categorical variables with chi-square test. Logistic regression analysis was performed to find out the relationship of risk factors with neurodevelopmental scores.

**Results:** A total 47 patients were analysed at 6 months of age using Bayley scale III. Mean birth weight and gestational age was 1595.11 ± 377.17g and 32.43 ± 1.48 weeks respectively. Mean cognitive, motor and language score were 80.79±14.51, 82.87±14.53 and 82.98±13.72 respectively. Despite the fact that all mean scores were normal, 27.7% of infants in cognition, 23.4% in motor, and 31.9% in language had a BSID-III value < 70. Variables like gestational age < 30 weeks, birth weight <1500 grams, and convulsion have been linked to poor neurodevelopmental outcomes. However, regression analysis revealed none of them were significant.

**Conclusions:** In our study, at six months of age, the cognitive, language, and motor scores of preterm newborns (less than 34 weeks of gestation) were within normal limits. Of the newborns, we observed that 27.7% had cognitive delay and 31.9% experienced language delay.

**Key-words:** Preterm, Neurodevelopment, Outcome, Bayley-III, Cognition, Motor, Language.

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## Introduction

Preterm birth is one of the leading causes of child death in almost all high- and middle-income countries. The complications associated with preterm delivery are considered to be

responsible for 35% of all neonatal deaths globally each year.<sup>1</sup> Recent improvement in NICU technology have led to a decrease in morbidities among premature infants.

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Despite the increasing survival of preterm neonates, these babies are associated with a wide range of neurodevelopmental impairments. Autism Spectrum Disorders (ASD), Attention Deficit Hyperactivity Disorder (ADHD), anxiety, depression, hearing loss and delayed development are the most common neurological impairments.<sup>2</sup>

About a third of preterm survivors have serious long-term neurological impairments such as cerebral palsy or mental retardation.<sup>3</sup> Though the survival rate of preterm babies are increasing in developing countries, long-term neurodevelopmental impairment is still high. Even with that, of the neonates born at 22-24 weeks of gestation, only 20% in the USA,<sup>4</sup> 34% in England,<sup>5</sup> and 42% in Sweden<sup>6</sup> survived without neurodevelopmental impairment.

For evaluating the neurodevelopment, several screening tools have been developed. One of the most widely used tools for evaluating the development of newborns and toddlers is the Bayley Scales of Infant and Toddler Development (BSID). The Bayley Scales of Infant and Toddler Development (Bayley-III is the most recent edition), originally created by psychologist Nancy Bayley, are primarily used to evaluate the development of babies and toddlers between the ages of one and forty-two months. Nancy Bayley initially published the scale in 1969.<sup>7</sup> Neurodevelopmental assessment was done by using the composite score of the BSID-III. The composite score varies by institution and country. The majority of the research considers a composite score of >85 as normal, 84-70 as at risk and 70 as delayed.<sup>8</sup>

The importance of neurodevelopmental evaluation for neonates weighing less than 1500 grams is highly addressed by the American Academy of Pediatrics.<sup>9</sup> In many countries, early screening and early intervention for developmental abnormalities are recommended.<sup>10</sup>

Bangladesh has achieved millennium development goal-4 (MDG-4), but still, preterm-related mortality is one of the major causes of neonatal mortality and accounts for 67% of all under-5 deaths.<sup>11</sup> Screening and interventions to reduce prematurity-related complications, especially neurodevelopmental impairment, are

still a concern in developing countries. Thus, this study was conducted to evaluate neurodevelopmental outcomes among preterms in our context.

### **Subjects and Methods**

This prospective cohort study was conducted in the Department of Neonatology, BSMMU, Dhaka, Bangladesh over a period of 8 months. Premature Neonates (< 34 weeks) who were discharged from the NICU were included in this study. After taking informed written consent from parents and ethical clearance from institute, a total of 60 preterm infants less than 34 weeks were enrolled. Infants with congenital anomalies, syndromic manifestations or chromosomal malformations, suspected inborn errors of metabolism were excluded from the study.

Before discharge from the NICU, demographic and perinatal characteristics, such as gestational age (GA), birthweight, sex, neonatal medical problems, and maternal problems were recorded. Neonatal medical problems were classified as pulmonary disease (respiratory distress syndrome, pneumonia, TTN etc.), cardiac disease, sepsis, seizure, and others. Prenatal maternal problems were classified as intrauterine problem (premature rupture of membranes, placenta previa etc.), maternal medical disease (hypertension, diabetes mellitus etc.) and others.

After discharge from the NICU, infants were followed up at 6 months of age for neurodevelopmental assessment. To evaluate neurodevelopment, Bayley Scales of Infant Development-III (BSID-III), was administered in a calm environment by the appropriately trained clinical psychologists, who were blinded to the child's neonatal information. We used the BSID-III scale to assess 5 domains in neurodevelopmental scale, such as: cognitive development, expressive and receptive language, fine and gross motor development. Composite score was analysed. In this study, we classified neurodevelopment as "normal" if the Bayley-III composite score was above 70 and "delayed" if the score was below 70 on any of the language, cognitive, or motor scales.

Before follow up, communication was done with the parents / legal guardian over phone. Patients condition, feeding status were assessed and neurodevelopmental status with therapy if needed were advised when came for follow up. At 6 months of age 47 infants returned for BSID-III assessment.

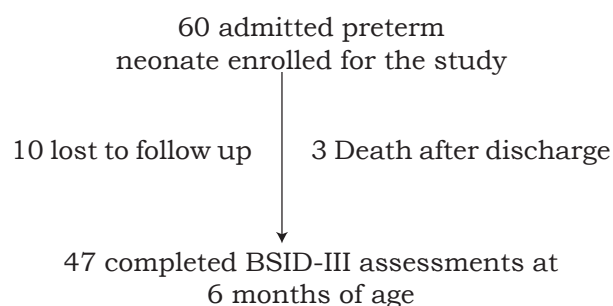
Maternal and neonatal variables like ACS exposure, mode of delivery, socioeconomic status, gestational age, birth weight, complications during NICU stay with support along with mode of feeding, early stimulation etc also were evaluated to find relationship with neurodevelopmental composite scores.

**Statistical analysis:**

All statistical analyses were performed using SPSS ver. 20.0. Baseline quantitative variable were described by mean ± standard deviation. Continuous variables were analyzed using an independent t-test and frequency (%). Categorical variables were analyzed with chi-square test. The relationship between perinatal and neonatal risk factors and Bayley-III scores was calculated. The Bayley-III results were presented as the composite cognitive, language, and motor scores. P-values of 0.05 were considered statistically significant. Logistic regression analysis was performed to find out the relationship of statistically significant outcome variables with neurodevelopmental scores.

**Results**

A total of 60 preterm infants who were admitted in NICU were enrolled for this study during neonatal period. Among them ten infants lost to follow up and 3 infants died at home due to complication of sepsis (2 cases) and aspiration pneumonia (1 case). At 6 months of age 47 infants completed follow up visit for neurodevelopmental assessment. (Figure- 1)



**Fig.-1:** Enrolment of premature infants for Bayley-III assessment.

**Table I**

*Baseline characteristics of enrolled premature infants (n= 47)*

Variable	n (%)
<b>Maternal characteristic</b>	
<b>Maternal age</b>	
<20 years	3 (6.4)
>20 years	44 (93.6)
<b>ACS exposure</b>	
Yes	26 (55.3)
No	21 (44.7)
<b>Mode of Delivery</b>	
NVD	7 (14.9)
LUCS	40 (85.1)
<b>No. of gestation</b>	
Singleton	41(87.2)
Multiple	6(12.8)
<b>Socioeconomic status</b>	
Low class	9(19.1)
Mid class	38(80.9)
High class	0
Maternal GDM	15(31.9)
Maternal hypertension	26(55.3)
<b>Infants characteristic</b>	
Gestational age (weeks) mean ± SD	32.43 ± 1.48
Birth weight(g) mean ± SD	1595.11± 377.17
<b>Place of birth</b>	
Inborn	30 (63.8)
Outborn	17(36.2)
<b>Gender</b>	
Male	23 (48.9)
Female	24 (51.1)
<b>SGA</b>	
SGA	15 (31.9)
<b>Apgar score at 5th minute</b>	
>7	43(91.5)
<7	4(8.5)
<b>Early stimulation</b>	
Early stimulation	13(27.7)
<b>Exclusive breast feeding</b>	
Exclusive breast feeding	24 (51.1)
<b>Mixed feeding</b>	
Mixed feeding	23(48.9)

Continuous data are presented as mean±SD and categorical data as number and percentage (%)

Table I showing the baseline characteristics of mother and neonates. The mean birth weight of the infants was 1595.11 ± 377.17 gram and the mean gestational age was 32.43 ± 1.48 week. Gender distribution was near about equal between male and female. The majority of children were inborn (63.8%) and 85.1% were born by LUCS. Only 15 neonates were SGA (31.9%). APGAR score was >7 in 43(91.5%) neonates. Neonates with exclusive breast feeding was about 51.1%. About 55.3% mother received antenatal corticosteroids.

Table II showing the complications and duration of NICU stay among enrolled neonates. Twenty-one neonates developed respiratory morbidities during neonatal period. Among them 25.5% developed RDS, 10.6% developed pneumonia,7 infants needed ventilatory support. About 59.6% infants had sepsis and 14.9% developed convulsion. Mean duration of NICU stay was 14.53±9.24 days. 21.3% infants needed readmission to hospitals.

**Table II**

*Preterm newborns with gestational age less than 34 weeks: neonatal problems and interventions (n=47)*

Complications and procedures	n (%)
Respiratory morbidity	21(44.7)
Respiratory distress syndrome	12(25.5)
Neonatal pneumonia	5(10.6)
Ventilatory assistance	7(14.7)
Congenital heart disease	10(21.3)
Sepsis	28(59.6)
Convulsion	7(14.9)
Duration of NICU stay-day, mean (SD)	14.53±9.24
Need for readmission in hospital	10 (21.3)

All values are presented No. (%)

Table III showing Composite scores of BSID III at 6 months of age. The mean cognition, motor and language score were 80.79±14.51, 82.87±14.53 and 82.98±13.72 respectively.

**Table III**

*Mean composite scores of BSID-III at 6 months follow up (n=47)*

BSID III scales	Mean ±SD
Cognition	80.79±14.51
Motor	82.87±14.53
Language	82.98±13.72

All values are presented as mean±SD

At 6 months of chronological age, 34(72.3%) infants had cognitive score >70, 36 infants in motor score (76.6%) and 32 infants in language (68.1%) had >70 scores. (Table IV).

**Table IV**

*Rates of developmental delay according to BSID-III composite scores at 6 months follow up (n=47)*

BSID III scales	Score >70	Score <70
	N (%)	N (%)
Cognition	34(72.3)	13(27.7)
Motor	36(76.6)	11(23.4)
Language	32(68.1)	15(31.9)

All values are presented as No. (%)

Table V showing comparison of maternal and neonatal demographic factors with BSID-III composite scores. Gestational age, birth weight (in cognition and motor) and convulsion were significantly associated with impaired neurodevelopmental outcome.

**Table V***Comparison of maternal and neonatal demographic characteristics with the Bayley-III composite scores*

Variables	No.of patient (n-47)	Cognition	p-value	Motor	p-value	Language	p-value
Gestational age							
<30 weeks	11	66.33± 13.5	.048	70.83±14.4	.023	71.33±15.2	.036
>30 weeks	36	84.93±21.6		85.0±13.6		84.29±13.4	
Birth weight							
<1500grm	27	76.78±14.46	.032	79.52±14.02	.041	79.81±12.88	.115
>1500grm	20	90.35±27.12		88.15±13.69		86.45±15.39	
ACS exposure							
Mode of delivery	26	83.15±14.12	.835	85.77±14.75	.175	83.58±15.05	.620
NVD							
LUCS	7	86.29±12.40	.626	80.14±12.95	.549	86.57±10.40	.434
APGAR at 5 min							
>7	43	83.42±22.10	.374	83.93±14.60	.253	83.44±14.21	.208
<7	4	73.25±14.56		75.25±9.91		74.0±13.11	
Socioeconomic status							
Low class	9	77.671±2.78	.457	76.33±12.45	.113	73,89± 10.50	.059
Middle class	38	83.71±23.22		84.82±14.48		84.79±14.32	
Respiratory morbidity							
Ventilator support	21	84.19± 29.0	.646	84.05±15.89	.718	85.10±14.23	.293
Sepsis	6	75.0±14.49	.366	77.50±18.05	.305	81.0±15.60	.766
Convulsion	28	82.57±26.21	.994	81.75±14.26	.411	83.14±13.70	.772
Early stimulation	4	64.71±8.49	.016	71.0±10.11	.013	72.71±11.02	.044
Exclusive breast feeding	13	93.69±31.95	.117	84.62±16.73	.680	84.77±13.10	.532
	24	86.38±26.65	.220	86.88±14.99	.073	85.96±14.18	.103

Chi-square test for categorical data. P < 0.05 w considered as significant. ACS- Antenatal corticosteroids. NVD-Normal vaginal delivery, LUCS-lower uterine caesarean section

Regression analysis of gestational age, birth weight and convulsion were done to see relationship with impaired outcome but none was found significant. (Table VI)

**Table VI***Logistic regression analysis to assess relationship between Bayley- III score and risk factors*

Variables	Cognition			Motor			Language		
	OR	95%CI	p value	OR	95%CI	P value	OR	95%CI	P value
Gestational age<30 weeks	.568	.086-3.736	.556	.612	.088-4.239	.619	.492	.079-3.088	.449
Birth weight <1500gm	2.086	.582-7.474	.259	1.740	.491-6.164	.319	-	-	-
Convulsion	.482	.089-2.599	.396	.536	.089-3.244	.498	.849	.161-4.488	.847

Statistical test by binary logistic regression

## Discussion

In this study, the mean composite score of cognitive, motor and language development at 6 months of age was normal as we took the cut off value  $> 70$  as normal and  $<70$  as delayed development. Mean composite score of cognition, motor and language were  $80.79 \pm 14.51$ ,  $82.87 \pm 14.53$  and  $82.98 \pm 13.72$  respectively. An important concern is whether early developmental evaluation during infancy is reliable enough to detect children with disabilities. Although this was not part of our research, Rademeyer and Jacklin noted that children evaluated between the ages of two and six months had higher Bayley- III scores than those tested at an older age where possible.<sup>12</sup>

We found about 34 infants in cognition (72.3%), 36 in motor (76.6%) and 32(68.1%) infants in language had normal neurodevelopment (score $>70$ ). A study conducted by Bulbul L in preterm babies  $>34$  weeks of gestational age, Bayley score was done at corrected age 18 to 24 months showing 13.5% cognitive delay, 19.8% language delay, and 33.3% motor delay.<sup>13</sup> In our study we also found 27.7 % cognitive delay and motor delay 23.4% though our study performed BSID-III at 6 months of age. By analysing the motor scale of 1376 babies at corrected age 18 months in extremely preterm neonates, Morgan-Feir et al.<sup>14</sup> found 22 percent delay in motor development which is consistent with our study.

A retrospective cohort study included 85 preterm infants in United States, neurodevelopmental performance was done at 8–12 months of age. In patterns of Bayley-III performance, mean language index and motor index were significantly lower than the cognitive index.<sup>15</sup> Our study supported the knowledge that language delay was more prevalent 31.9% in preterm infants followed by low cognition (27.7%)

Similarly, Fernandes et al. studied 58 Brazilian newborns born with very low birth weight. The researchers reported a higher rate of language delay (29.3%), and a low proportion of impaired motor and cognitive scores (both 6.9%).<sup>16</sup>

The present study also examined correlation between the perinatal and neonatal risk factors

with the Bayley-III composite scores. Our study result shows gestational age  $<30$  weeks was significantly associated with poor cognition, motor and language score. Birth weight  $<1500$ gm was associated with poor cognition and motor outcome but it has no association with language score. Convulsion is also associated with poor neurodevelopmental outcome in all domains. When regression analysis was done, no factor was found to be significantly related with poor neurodevelopmental outcome.

The neurodevelopmental delay rate increases when the GA and BW decrease.<sup>17</sup> In accordance with the literature, in our study, we found that Bayley-III composite scores decreased significantly as GA and BW decreased; though language score was not associated with low birth weight in this study.

According to several studies, extremely preterm infants have significantly lower cognitive, language, and motor functions than full-term infants.<sup>18,19</sup> Vohr BR<sup>20</sup> in their research found that very low birth weight were related to poor outcomes in neurodevelopment.

SH Ahn<sup>21</sup> in their study also showed that very low birth weight ( $<1,500$  g) was significantly related to low cognitive, language, and motor composite scores. Medical problems such as pulmonary disease, seizure, cardiac disease, and others were not significantly related to Bayley-III scales though in this study we found convulsion was associated with poor neurodevelopmental outcome.

Increasing evidence suggests that neonatal seizures are associated with adverse neurodevelopmental outcome, including epilepsy, cerebral palsy, developmental delay, and psychomotor deficits.<sup>22-24</sup>

## Conclusion

In our study, at six months of age, the cognitive, language, and motor scores of preterm newborns (less than 34 weeks of gestation) were within normal limits. Of the newborns, we observed that 27.7% had cognitive delay and 31.9% experienced language delay. Long-term follow-up is required for further evaluation.

### Limitation of the study

It was a single centered study and does not represent the whole population and sample size was small.

### Recommendation

Neurodevelopmental assessment should be incorporated in routine follow-up among preterms to reduce long term morbidities.

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### Conflicts of interest

There is no conflict of interest

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