ORIGINAL ARTICLE

Long-Term Neurodevelopmental Outcome of Preterm Infants Discharged From a Tertiary Care NICU in Pakistan

SYED ARSALAN HASSAN, AROUJ WAQQAS, SPENTA KAKALIA, UNAIZA SYED

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Correspondence to:

Dr. Syed Arsalan Hassan,
Senior Registrar,
Department of Pediatrics,
Combined Military Hospital,
Lahore

E-mail:
drsyedarsalanhassan@gmail.com

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ABSTRACT

Objective: To determine long-term neurodevelopmental outcome of preterm infants discharged from a tertiary care NICU in Pakistan.

Study Design: Longitudinal retrospective study.

Place and Duration of Study: Department of Neonatology, at CMH, Lahore from 1st Feb 2023 to 1st Feb 2024

Material and Methods: Using medical records maintained in the neonatal intensive care unit (NICU), babies admitted to the neonatal intensive care unit at CMH Lahore between 1 Jan 2014 and 31 Dec 2014 (age between 7 – 8 years) were recorded on a computer database. 54 babies were identified fulfilling the inclusion criteria. Infants with low birth weight of < 2500 grams and gestational age of <35 weeks admitted between 1 Jan 2014 and 31 Dec 2014 were included in the study. Infants with a diagnosis of chromosomal anomalies surgical problems, and major cardiac disease were excluded. Data was then analyzed using spss.

Results: Total of 22 children were enrolled in the study. Out of 22 children who attended the assessment, 16 (72.7%) children had no neurodevelopmental impairment. Out of the remaining 6 children, one (4.5%) child was identified as having gross motor disabilities, 1 (4.5%) had fine motor disabilities, 1 (4.5%) had hearing problems, 1 (4.5%) had behavior issues, 2 (9%) children had cognitive issues and 2(9%) had seizures.

Conclusion: Aside from these acute morbidities, premature birth also negatively impacts neurodevelopment—the area that most worries individuals, families, and society. Thus, careful observation of these preterm infants is crucial to detect any issues early and offer therapy as needed.

Key Words: *Neurodevelopmental, Infants, Neonates, NICU, Pakistan*

INTRODUCTION

Globally 15 million babies are born prematurely each year.[1] Prematurity thus remains a significant cause of mortality and morbidity worldwide. Increasing rates of premature births are being observed across many countries.[2] Pakistan has one of the highest rates of premature births (15 – 18%) translating into approximately 1 in 7 births.[3] While immediate complications associated with premature birth include infection, birth-related events (asphyxia), necrotizing enterocolitis (NEC), interventricular hemorrhage (IVH), respiratory

distress syndrome (RDS), and retinopathy of prematurity (ROP), the effects of preterm delivery go beyond the initial neonatal period.[3]

Whilst advances in neonatal care have improved survival rates for preterm infants, these infants remain at higher risk of neurodevelopmental morbidity compared to their full-term counterparts. Studies conducted across different countries have consistently shown that preterm babies are more likely to experience cognitive, motor, and behavioral difficulties later in life with deficits in areas such as attention, memory, executive functioning, and academic performance.[4] Motor delays, including cerebral palsy, are also more prevalent in this population. Preterm babies often struggle with gross and fine motor skills, affecting their ability to crawl, walk, and perform fine motor skills. Behavioral challenges, such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and emotional difficulties, are also more prevalent among preterm-born children.

With an increasing number of neonatal units being established in Pakistan coupled with qualified neonatologists looking after newborns, we are now starting to witness a decrease in mortality from 74/1000 live births in 1975 to 42/1000 live births in 2019.[5-8] However, with improving survival trends long-term outcomes remain largely unknown as there is a paucity of follow-up clinics or services.

To our knowledge, there is only one study conducted at a tertiary care hospital in Pakistan focusing on the neurodevelopmental outcomes of preterm infants. It specifically examined neurodevelopmental impairments but limited their assessment to children up to five.[9] The absence of comprehensive information regarding the neurodevelopmental outcomes of preterm babies in Pakistan hinders our understanding of the challenges they may face and the early appropriate interventions and support instituted. Thus, there is an urgent need for research to ascertain the prevalence and impact of these conditions to improve the care and outcomes of preterm infants in the country. The aim of this was to record long-term outcomes including challenges, developmental trajectories, and motor and behavioral aspects of infants who were born preterm and required neonatal intensive care from one tertiary care neonatal intensive care unit in Pakistan.

MATERIAL AND METHODS

This is a longitudinal retrospective study, carried out in the Department of Neonatology, at the Combined Military Hospital (CMH), Lahore 1st Feb 2023 to 1st Feb 2024. The study was approved by the Research and Ethics Board of CMH Lahore Medical College (reference no. 657/ERC/ CMHLMC).

Using medical records maintained in the neonatal intensive care unit (NICU), babies admitted to the neonatal intensive care unit at CMH Lahore between 1 Jan 2014 and 31 Dec 2014 (age between 7 – 8 years) were recorded on a computer database. Infants with low birth weight of <2500 grams and gestational age of <35 weeks admitted between 1 Jan 2014 and 31 Dec 2014 were included in the study. Infants with a diagnosis of chromosomal anomalies, surgical problems, and major cardiac disease were excluded. 54 babies were identified fulfilling the above criteria.

Phone calls were made by TW and AW to the parents who were invited along with their children to Pediatrics OPD CMH Lahore. 12 parents could not be contacted as there was no response on their phones. 42 parents were traced. 4 babies had died. Of the remaining 38 were asked to attend a free developmental assessment for their child at CMH Lahore Pediatrics OPD. 7 parents had moved far away from Lahore and it was not feasible for them to attend the consultation. 31 agreed on the phone call to come for an assessment of their child. Despite waiting for 3 months (Mar 2024 till Jun 2024) and reminders only 22 parents brought their child for a consult (fig 1).

The assessment took place in the outpatient department in a separate room, away from the other patients by a pediatric consultant. Informed consent from a parent or an accompanying guardian was documented. Basic demographic data was recovered from the database. Important parameters like birth details, mode of delivery, gestation, weight, occipitofrontal circumference, complications such as RDS, NEC, sepsis, type of feeds, whether needing ventilation, and duration

of NICU stay were recorded using a predesigned performance (table 1).

A detailed developmental history and cognitive functioning based on their schooling, ensuring that the child was keeping up with his/her peers in an age-appropriate class and examination comprising of gross motor, fine motor, vision hearing, and speech assessment was carried out. Children were asked to draw and write age-appropriate sentences on a piece of paper. A detailed standardized rapid neurodevelopmental assessment (RNDA) tool developed by the Child Development Center, Department of Pediatric Neuroscience Bangladesh in collaboration with Global Development, Bill & Melinda Gates Foundation, Seattle, WA[10] was used for assessment

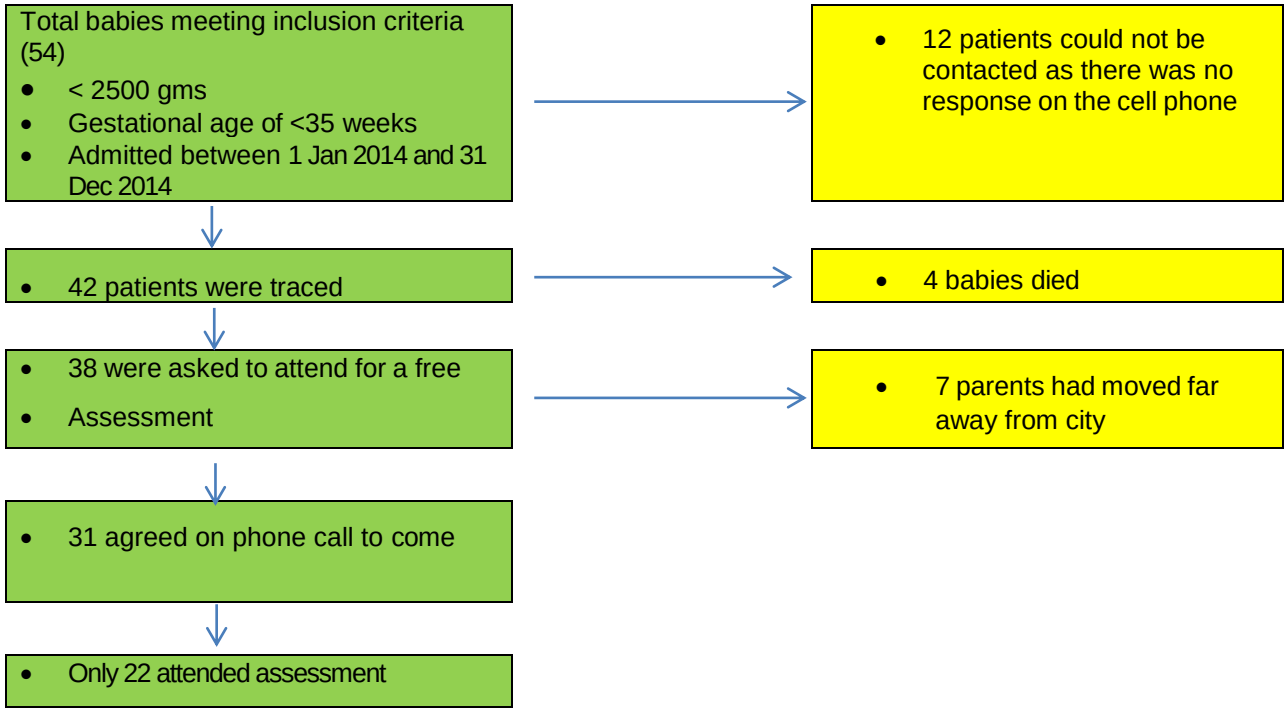

Fig 1: Flowchart depicting recruitment process

To be administered to the caretakers of all children 2 through 9 years living in household. interviewer : i would like to ask if any children in the household 2 through 9 years has any of the health conditions i am going to mention you

1	Compared with other children, does or did (name) have any serious delay in sitting, standing or walking?	Yes…..	1
		No…….	2
2	Compared with other children, does (name) have difficulty seeing, either in the daytime or at night?	Yes…..	1
		No…….	2
3	Does (name) appear to have difficulty hearing? (uses hearing aid, hears with difficulty, completely deaf)	Yes…..	1
		No…….	2
4	When you tell (name) to do something, does he/she seem to understand what you are saying?	Yes…..	1
		No…….	2
5	Does (name) have difficulty in walking or moving his/her arms or does he/she have weakness and/or stiffness in the arms or legs?	Yes…..	1
		No…….	2
6	Does (name) sometimes have fits, become rigid, or lose consciousness?	Yes…..	1
		No…….	2
7	Does (name) learn to do thing like other children his/her age?	Yes…..	1
		No…….	2
8	Does (name) speak at all (can he/she make him or herself understood in words; can say recognizable words)?	Yes…..	1
		No…….	2

9	(For 3-9 years olds): is (name)'s speech in any way different from normal (not clear enough to be understood by people other than the immediate family)?	Yes….. 1 No……. 2
	B. (For 2 years olds): can (child) name at least one object (for example ,an animal, a toy, a cup ,a spoon)?	Yes….. 1 No……. 2
10	Compared with children of the same age, does (name) appear in any way mentally backward, dull or slow?	Yes….. 1 No……. 2
11	Overall do you think that child has difficulties in one or more of the following areas: emotions, concentrations, behaviour or being able to get on with other people?	Yes….. 1 No……. 2

Fig 2. Questions asked to parents

Child's ID	**Name Age Childs**
Gross motor	able=1 not able =2
Walks	1
Climbs stairs with alternate feet , not holding	2
Fine motor:	able=1 not able=2
Holds small objects with pincer grasps	
Rt =	3
Lt=	4
Places a tiny object(e.g 'muri' puffed rice)	
In the ½ inch diameter open container	
Rt=	5
Lt=	6
Laces 4 beads	7
Draws a shape with tripod grasp	8
Unbuttons and buttons shirt	9
Throws a ball with one hand	10
Vision:	normal =1 abnormal=2 11
Hearing:	normal=1 abnormal=2 12
Expressive language	able=1 not able=2
Sentences of 4-6 words	13
Repeats complex sentences	14
Uses pronouns (my, your)	15
Uses past and future tense	16
Uses preposition (on, under, in front , behind)	17 18
Takes part in conversation	
Cognition	able=1 not able =2
Matches shapes on board puzzle (circle, square, triangle)	19 20
Matches colors(red, yellow, green, blue)	21
Understands (big/small more/less, right/left)	22 23
Draw a man (head, body, arms legs)	24
Builds 3 steps (5 years)	25
Draws square(5 years)	26
Builds 4 steps (6 years)	27
Builds house (6 years)	28
Draws triangle (6 years)	29
Draws diamond (7 years)	30
Name of days (7-9 years)	31
Name of 12 months (7-9 years)	32
How many days in a weak? (9 years)	
How many months in a year? (9 years)	33
If a banana is cut at the middle, how many parts will you get (7-9 years)	34
If you have 2 pencils and I give you 2 more, now how many will you have? (7-9 years)	35
If you have 5 pencils and you give me 2, now how many will have (7-9 years)	
Behaviour (Observation and mother's recall)	no = 1 yes=2
Poor peer play	36
Act very aggressively towards other people	37 38
Act extremely withdrawn and shy	
Show odd/unusual behaviour	39
Temper tantrum	40
Hyperactive	41
Inattentive	42
Extreme fear	43
Selfcare (Mother's care)	able=1 not able= 2
Feeding:	44
Feeds self	45
Drinks self with cup glass	
Dressing:	46
Put on and takes off shoes independently	47
Can undress and dress except Lacing shoes, back button(7-9 years)	
Toileting:	48
Bladder toilet trained independently	49
Bowel toilet trained independently (7-9 years)	50
Washing:	51
Washes and dries hands and face	
Washes body using water (7-9 years)	
Brushes teeth :	52
Brushes hair (7-9 years)	53
Seizures (Unprovoked)	no =1 yes = 54

Fig 3: Assessments as per RNDA

All the data collected was entered into the Statistical Package for social sciences (SPSS) version 20 and analyzed through its statistical package. Mean and standard deviation were

calculated for quantitative data like weight and gestational age and frequency and percentages were calculated for qualitative data.

RESULTS

A total of 22 children were enrolled in the study. A summary of the neonatal intensive unit (NICU) course for the participants is given in table 1. During their stay in the Neonatal Intensive Care Unit, 9 (41%) received oxygen, 8 (36.36%) were mechanically ventilated, and 3 (13.6%) had respiratory distress syndrome requiring surfactant (Survanta). Sepsis was suspected or proved in 18 (81.8%) babies who received antibiotics and 2 (9.01%) had pneumonia evident on chest x-ray findings. Expressed breast milk was exclusively fed to 8 (36.4%) neonates while the remaining received formula or a mixture of formula and breast milk. Retinopathy of prematurity (Grade 3) was detected in 2 (9.01%) neonates who needed anti-VEGF therapy.

Table 1: Basic demographics and summary of course in the neonatal intensive care unit

Variable	Frequency n (%), Mean ± SDs
Gender (male)	8
Gender (female)	14
Gestational age at birth (weeks)	30.3 ± 3.2
Birth Weight (grams)	1415 ± 234.58
Mode of Delivery	
Caesarian Section	13 (59.0)
Spontaneous Vaginal Delivery	9 (41.0)
Head Circumference at birth (cm)	29.39 ± 1.63
Length of hospital stay (days)	22.09 ± 13.54
Oxygen administered	9 (41.0)
Ventilated	8 (36.36)
Surfactant administered	3 (13.64)
Sepsis	18 (81.82)
Type of feed	
Formula or Mixed	14 (63.64)
Expressed Breast Milk	8 (36.36)

After discharge from the NICU, the children had a few interim health issues. Recurrent pneumonia was reported by 1 (4.5%); another infant had congestive cardiac failure at 8 months of age (secondary to viral myocarditis managed with hospital admission and supportive care for 10 days), and another reported poor weight gain. There were no other reported interim health concerns. A total of 4 (18.18%) babies died after discharge from the NICU in this cohort. Details of the deaths have not been collected.

Out of 22 children who attended the assessment, 16 (72.7%) children had no neurodevelopmental impairment on the RNDA tool. They were attending mainstream school and there were no concerns raised either by teachers or parents. These 16 children had an age appropriate gross motor, fine motor, vision, hearing, speech, cognitive and behavioral development on examination and none had a history of seizures. Out of the remaining 6 children, one (4.5%) child was identified as having gross motor disabilities, 1 (4.5%) had fine motor disabilities, 1 (4.5%) had hearing problems, 1 (4.5%) had behavior issues, 2 (9%) children had cognitive issues and 2(9%) had seizures (table 2).

TABLE 2: Developmental Outcomes

	Developmental Outcomes	Frequencies (%)
1.	Gross Motor Disabilities [a]	1 (4.5%)
2.	Fine Motor Disabilities	1 (4.5%)
3.	Vision Problems [b]	1 (4.5%)
4.	Hearing Problems	0 (0%)
5.	Speech issues	1 (4.5%)
6.	Behavior issues	2 (9%)
7.	Cognition (Special School)	2 (9%)
8.	Seizures	0 (0%)

a) Spastic diplegia b) One reported myopia

DISCUSSION

The results of our study show that of those who survived in our NICU, 72.7% of preterm babies around 30.3 $\pm$ 3.2 weeks with a birth weight of 1415 ± 234.58 grams had a normal neurodevelopmental outcome assessed when they were 7 – 8 years old. To our knowledge, this is the first study addressing long-term neurodevelopmental follow-up of preterm babies in Pakistan. The RNDA is designed to assess the neurodevelopment of 5 to 9 years old children in low and middle-income countries where assessment by other specialized tools may not be feasible. It can easily be used by various professionals (general pediatricians) identifying neurodevelopmental impairments in children of primary school age. It is composed of a well-organized format featuring 8 categories such as gross motor, fine motor, vision, hearing, speech,

cognition, behavior, and seizures. These items within each domain have been carefully selected based on their relevance to age-referenced assessment procedures used globally. RNDA has been well validated with excellent interpreter reliability, and sensitivity and specificity for any Neurodevelopment impairment were 84% and 83% respectively.

Khan et al in 2012 published a short term neurodevelopmental outcome of a longitudinal cohort comprising 110 preterm babies (born before 37 weeks of gestation) discharged from their NICU in Pakistan.[9] Denver developmental assessment scores were done at 6 months of age. Scores suggested that 32% of babies had neurodevelopmental impairment. Given that this research was conducted over ten years ago, the current decline in neonatal mortality rates naturally supports our finding of a 27.3% long-term neurodevelopmental rate among preterm infants.

Comparing statistics with regional countries it was noted that Khan et al from Bangladesh in 2006 published an outcome of 159 enrolled children at 31 months. 65% survived, 16% died, and 19% were lost to follow-up.[11] At a mean age of 31 weeks, the developmental status of the 85 children followed-up for ≥12 months was normal in 32%; 45% had mild and 23% had serious neurodevelopmental impairments. Cognitive impairment was the most common deficit (60%). As mentioned our intact survival rate of 72.7% reflects a natural improvement in neonatal care over the past decade.

Sumanasena et al in 2018 from Sri Lanka reported that 13 of 39 children (33%) had a confirmed diagnosis of a neurodevelopmental disorder at 5 years of age.[12], which is somewhat comparable to our study. Some of the most noteworthy findings were the decreased development in the first two years and the notable delay in abilities needed for school at age five, with cognitive skills being the primary area of delay. These results highlight the need for early developmental delay diagnosis and intervention through long-term surveillance of preterm newborns, as well as the necessity of developing programs that are tailored to these children's requirements.

The study's main drawback was the cohort's declining population over five years, with a change in address and phone number being the most likely cause. Furthermore, not many kids with notable delays and impairments stopped going to clinics.

CONCLUSION

Along with being too linked to high rates of morbidity and death, prematurity and its related issues can cause premature newborns to spend longer periods in neonatal critical care units, which puts a significant strain on healthcare systems. Prematurity not only causes these acute morbidities but also has detrimental effects on neurodevelopment, which is the area that people, families, and society are most concerned about. Therefore, it is essential to properly monitor these preterm newborns to identify any problems early and provide therapy if necessary. For these preterm newborns, early detection and timely rehabilitation can result in an enhanced quality of life.

Conflict of interest: None

Authors' affiliation

Dr. Syed Arsalan Hassan, Senior Registrar, Department of Pediatrics, Combined Military Hospital, Lahore

Dr. Arouj Waqqas, Assistant Professor, Department of Pediatrics, Combined Military Hospital, Lahore

Dr. Spenta Kakalia, Assistant Professor. Department of Pediatrics, Combined Military Hospital, Lahore

Dr. Unaiza Syed, Senior Registrar
Department of Pediatrics, Combined Military Hospital, Lahore

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