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Neurodevelopmental Outcomes in NICU Graduates Following Invasive and Non-invasive Ventilation

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ABSTRACT

OBJECTIVE: To evaluate cognitive, motor, and communication neurodevelopmental outcomes between NICU graduates who received invasive ventilation (IV) or noninvasive ventilation (NIV).

METHODOLOGY: This prospective cohort study was conducted at the NICU of The Children's Hospital, Lahore, Pakistan, from November 2025 to May 2026. A non-probability, consecutive sampling technique was used to select the sample. The study enrolled 73 NICU graduates, irrespective of gender, with gestational age ≥28 weeks, who were admitted to the NICU and required either invasive or noninvasive ventilation. After discharge, infants were followed up at 3 months, and neurodevelopmental assessments were performed using the Denver Developmental Screening Test-II Scale. Data were analyzed using IBM SPSS Statistics, version 26.0.

RESULTS: Among 73 NICU graduates, the median gestational age was 33.0 (30.0 to 36.0) weeks, and the birth weight was 1810.0 (1400.0 to 2350.0) grams. There were 42 (57.5%) boys. Invasive ventilation was received by 30 (41.1%) neonates. Compared with noninvasive ventilation, infants with invasive ventilation had lower gestational age ($p<0.001$), lower birth weight ($p<0.001$), lower 1-minute Apgar score ($p=0.004$), lower 5-minute Apgar score ($p=0.001$), longer ventilation ($p<0.001$), longer NICU stay ($p<0.001$), higher complications (63.3% vs. 23.3%, $p=0.001$), and higher bronchopulmonary dysplasia (26.7% vs. 4.7%, $p=0.007$). At 3 months, gross motor delay (34.6% vs. 12.5%, $p=0.032$) and communication delay (30.8% vs. 10.0%, $p=0.033$) were higher among infants with invasive ventilation.

CONCLUSION: Infants discharged from NICU after invasive ventilation showed a higher frequency of early gross motor and communication delay than those managed with noninvasive ventilation.

KEYWORDS: Critical care, communication, infant, neurodevelopment, ventilation

INTRODUCTION

Advances in neonatal intensive care unit (NICU) management have significantly improved the survival rates of critically ill newborns, particularly preterm and low-birth-weight infants.[1] Among the most crucial interventions in NICU care is mechanical ventilation, which is broadly classified into invasive ventilation and noninvasive ventilation (NIV). Invasive ventilation, requiring endotracheal intubation, provides lifesaving respiratory support but carries a risk of complications which can contribute to long-term neurodevelopmental impairments.[2,3] In contrast, noninvasive ventilation techniques aim to minimize these complications by avoiding airway trauma and reducing ventilator-induced lung injury.[4]

Despite the potential benefits of ventilation, long-term neurodevelopmental outcomes associated with invasive and noninvasive ventilation remain an area of ongoing investigation.[5,6] Contemporary data indicate that up to 41.8% of NICU survivors experience some form of neurodevelopmental impairment, including delays in cognitive, motor, and communication development.[7] A study by Lipp et al.[8] showed that among NICU survivors following NIV or IV support, significant neurodevelopmental impairments were reported among 17% and 23% of infants, respectively.

In low-resource settings such as Pakistan, the challenge is compounded by high neonatal mortality rates (42 per 1,000 live births) and limited access to specialized follow-up and rehabilitative services.[9] In the same context, surviving neonates often face significant barriers to long-term care, including delayed diagnosis of neurodevelopmental delays, inadequate follow-up, and resource limitations.[10]

While international literature highlights differences in neurodevelopmental outcomes in invasive and noninvasive ventilation, local evidence remains scarce. Differences in healthcare infrastructure, staff expertise, and patient demographics necessitate region-specific research to guide neonatal care protocols.[11] Without localized data, optimizing ventilation strategies to reduce the burden of neurodevelopmental impairments remains challenging. This study aims to address this critical knowledge gap by comparing neurodevelopmental outcomes, including cognitive, motor, and communication development in NICU graduates who received invasive and noninvasive ventilation at a tertiary care hospital in Lahore, Pakistan. The findings will update the local literature and provide evidence-based insights to improve long-term neurodevelopmental outcomes for NICU graduates.

METHODOLOGY

This prospective cohort study was conducted at the NICU of The Children's Hospital, Lahore, Pakistan, from November 2025 to May 2026, after approval from the institutional review board (No.1238, dated 13-11-2025). A sample size of 73 was calculated using the OpenEpi sample size calculator, considering the anticipated proportion of developmental delays in NICU survivors as 18%[12], with a 95% confidence level and an 8% margin of error. The inclusion criteria were NICU graduates of any gender, with gestational age ≥28 weeks, who were admitted to the NICU and required either IV or NIV. Neonates with known genetic syndromes or congenital anomalies affecting neurodevelopment (e.g., trisomy 21, spina bifida), moderate to severe perinatal asphyxia, or central nervous system infections (e.g., meningitis, encephalitis) were excluded. NICU graduates were those neonates who were admitted to the NICU for critical care management and discharged alive beyond the neonatal period (28 days).

Noninvasive ventilation was defined as respiratory support delivered without endotracheal intubation and included continuous positive airway pressure and nasal intermittent positive-pressure ventilation. The decision to initiate invasive or noninvasive ventilation was made by the treating neonatology team according to the infant's clinical condition and standard

institutional NICU protocols. Participants were classified according to the ventilation modality received during admission. Mechanical ventilation delivered through an endotracheal tube, providing controlled or assisted respiratory support to neonates requiring airway stabilization, was taken as IV. Respiratory support provided without endotracheal intubation, including techniques such as Continuous Positive Airway Pressure (CPAP) and Nasal Intermittent Positive-Pressure Ventilation (NIPPV), was considered NIV. A non-probability, consecutive sampling technique was used to select the sample. Informed written consent was obtained from parents/guardians.

Baseline demographic and clinical data were recorded at enrolment. Maternal history regarding antenatal steroid administration and maternal comorbidities was taken. All patients were treated as per institutional protocols. Data regarding type of ventilation, duration of ventilation, duration of NICU stay, and complications were documented. Regarding complications during NICU stay, sepsis was defined as clinical features consistent with systemic infection accompanied by either a positive blood or cerebrospinal fluid culture or, in culture-negative cases, supportive hematological or inflammatory findings and treatment with systemic antibiotics for at least 5 days.[13] Bronchopulmonary dysplasia was defined as a requirement for supplemental oxygen above 21% for at least 28 days, with respiratory status assessed at 36 weeks' postmenstrual age for infants born before 32 weeks' gestation or at 56 days of postnatal age for infants born at 32 weeks' gestation or later.[14] Intraventricular hemorrhage was diagnosed on cranial ultrasonography and classified according to the Papile grading system, with grade I indicating germinal-matrix hemorrhage, grade II intraventricular hemorrhage without ventricular dilatation, grade III hemorrhage with ventricular dilatation, and grade IV hemorrhage with parenchymal involvement.[15] Necrotizing enterocolitis was defined as definite disease corresponding to modified Bell stage II or higher based on systemic, gastrointestinal, and radiological findings.[16] Retinopathy of prematurity was diagnosed by an ophthalmologist and classified according to the International Classification of Retinopathy of Prematurity based on retinal zone, disease stage, extent, and the presence or absence of plus disease.[17] Periventricular leukomalacia was defined by cranial ultrasonographic evidence of periventricular echogenicity persisting for more than 7 days and/or the subsequent development of localized or extensive periventricular cystic lesions.[18]

After discharge, infants were scheduled for follow-up at 3 months of corrected age if they were born preterm and at 3 months of chronological age if they were born at term. Corrected age was calculated by subtracting the number of weeks of prematurity from the chronological age. Neurodevelopmental assessment was performed using the Denver Developmental Screening Test II. Assessment focused on gross motor, fine motor, communication, and social development. Development was labeled as either delayed or normal in each category. All assessments were performed by the trained developmental pediatrician blinded to the ventilation modality used.

Data were analyzed using IBM-SPSS Statistics, version 26.0. Categorical variables were reported as frequencies and percentages. Continuous variables were expressed as mean with standard deviation (SD) or as median with interquartile range (IQR), based on normality (assessed by the Shapiro-Wilk test). Continuous variables were compared using an independent samples t-test/Mann-Whitney U test. Categorical data were compared employing the chi-square test/fisher's exact test. For all inferential statistics, a $p<0.05$ was considered significant.

RESULTS

In a total of 73 NICU graduates, the median gestational age was 33.0 (30.0 to 36.0) weeks, and the median birth weight was 1810.0 (1400.0 to 2350.0) grams. There were 42 57.5%) boys and 31 (42.5%) girls. Cesarean delivery was documented in 44 (60.3%) neonates. Antenatal steroid administration was recorded in 42 (57.5%) mothers, while maternal comorbidities were present in 24 (32.9%) pregnancies. Respiratory distress syndrome was the indication for NICU admission in 36 (49.3%) neonates, followed by prematurity in 19 (26.0%), sepsis in 12 (16.4%), and other causes in 6 (8.2%) neonates.

Invasive ventilation was received by 30 (41.1%) neonates, while 43 (58.9%) received noninvasive ventilation. Neonates who received invasive ventilation had lower gestational age ($p<0.001$) and birth weight ($p<0.001$) than those who received noninvasive ventilation. Apgar scores at 1 minute ($p=0.004$) and 5 minutes ($p=0.001$) were lower among neonates who required invasive ventilation. The median duration of ventilation was 9.0 (6.0 to 14.0) days among infants with invasive ventilation, and 3.0 (2.0 to 5.0) days in infants with noninvasive ventilation ($p<0.001$). The median duration of NICU stay was 24.0 (17.0 to 34.0) days among neonates who received invasive ventilation compared with 13.0 (9.0 to 20.0) days among those who received noninvasive ventilation ($p<0.001$). Comparison of baseline demographic and clinical characteristics according to ventilation modality is presented in **Table I**.

Table I: Characteristics according to ventilation modality (n=73)

Variable	Overall (n=73)	Invasive ventilation (n=30)	Noninvasive ventilation (n=43)	P value
Male gender	42 (57.5%)	17 (56.7%)	25 (58.1%)	0.902
Gestational age, weeks	33.0 (30.0-36.0)	31.0 (29.0-34.0)	35.0 (32.0-37.0)	<0.001
Birth weight, g	1810.0 (1400.0 to 2350.0)	1500.0 (1220.0-1900.0)	2100.0 (1650.0-2600.0)	<0.001
Cesarean delivery	44 (60.3%)	19 (63.3%)	25 (58.1%)	0.658
Apgar score at 1 minute	6.0 (5.0-7.0)	5.0 (4.0-6.0)	6.0 (5.0-7.0)	0.004
Apgar score at 5 minutes	8.0 (7.0-9.0)	7.0 (6.0-8.0)	8.0 (8.0-9.0)	0.001
Antenatal steroid administration	42 (57.5%)	22 (73.3%)	20 (46.5%)	0.023
Maternal comorbidity	24 (32.9%)	11 (36.7%)	13 (30.2%)	0.567
Duration of ventilation, days	6.0 (3.0-10.0)	9.0 (6.0-14.0)	3.0 (2.0-5.0)	<0.001
Duration of NICU stay, days	17.0 (11.0-25.0)	24.0 (17.0-34.0)	13.0 (9.0-20.0)	<0.001

Values are shown as n (%) or median (IQR). Independent sample t test or Mann-Whitney U test was used for continuous variables. The chi-square test or Fisher's exact test was used for categorical variables.

One NICU complication was recorded in 29 (39.7%) infants. Sepsis occurred in 16 (21.9%), bronchopulmonary dysplasia in 10 (13.7%), retinopathy of prematurity in 8 (11.0%), intraventricular hemorrhage in 7 (9.6%), necrotizing enterocolitis in 5 (6.8%), and periventricular leukomalacia in 4 (5.5%) infants. Complications were more frequent among neonates exposed to invasive ventilation than noninvasive ventilation (63.3% vs. 23.3%, p=0.001). Bronchopulmonary dysplasia was more frequent in neonates exposed to invasive ventilation (26.7% versus 4.7%, p=0.007). A comparison of complications during the NICU stay is shown in **Table II**.

Table II: Comparison of complications during NICU stay according to ventilatory modality (n=73)

Complication	Overall (n=73)	Invasive ventilation (n=30)	Noninvasive ventilation (n=43)	OR with 95% CI	P-value
Any NICU complication	29 (39.7%)	19 (63.3%)	10 (23.3%)	5.7 (2.0-15.9)	0.001
Sepsis	16 (21.9%)	10 (33.3%)	6 (14.0%)	3.1 (1.0-9.7)	0.049
Intraventricular hemorrhage	7 (9.6%)	6 (20.0%)	1 (2.3%)	10.5 (1.2-92.5)	0.012
Periventricular leukomalacia	4 (5.5%)	4 (13.3%)	-	-	0.025
Bronchopulmonary dysplasia	10 (13.7%)	8 (26.7%)	2 (4.7%)	7.5 (1.5-38.2)	0.007
Necrotizing enterocolitis	5 (6.8%)	4 (13.3%)	1 (2.3%)	6.5 (0.7-61.0)	0.076
Retinopathy of prematurity	8 (11.0%)	6 (20.0%)	2 (4.7%)	5.1 (1.0-27.4)	0.041

Comparison of neurodevelopmental outcomes at 3 months corrected age by ventilatory modality is presented in **Table III**.

Of the 73 enrolled NICU graduates, 66 (90.4%) returned for neurodevelopmental assessment at 3 months, and 7 (9.6%) were lost to follow-up. Follow-up was completed by 26 of 30 infants (86.7%) in the invasive ventilation group and 40 of 43 infants (93.0%) in the noninvasive ventilation group. Four infants (13.3%) in the invasive ventilation group and 3 (7.0%) in the noninvasive ventilation group were lost to follow-up. The loss-to-follow-up rate did not differ significantly between the groups (p=0.435). At 3-month corrected age, gross motor delay was observed in 14 (21.2%), fine motor delay in 9 (13.6%), communication delay in 12 (18.2%), and social delay in 7 (10.6%) infants. Gross motor delay (34.6% vs. 12.5%, p=0.032) and communication delay (30.8% vs 10.0%, p=0.033) were significantly more frequent among infants with invasive ventilation (**Table III**).

Table III: Comparison of neurodevelopmental outcomes at 3 months corrected age according to ventilation modality (n=66)

Developmental outcome	Overall (n=66)	Invasive ventilation (n=26)	Noninvasive ventilation (n=40)	OR with 95% CI	P value
Gross motor delay	14 (21.2%)	9 (34.6%)	5 (12.5%)	3.7 (1.1-12.8)	0.032
Fine motor delay	9 (13.6%)	6 (23.1%)	3 (7.5%)	3.7 (0.8-16.4)	0.072
Communication delay	12 (18.2%)	8 (30.8%)	4 (10.0%)	4.0 (1.1-15.1)	0.033
Social delay	7 (10.6%)	5 (19.2%)	2 (5.0%)	4.5 (0.8-25.4)	0.167
Delay in any domain	16 (24.2%)	10 (38.5%)	6 (15.0%)	3.5 (1.1-11.5)	0.029

DISCUSSION

This study found that infants discharged from NICU after invasive ventilation had a higher burden of early neurodevelopmental delay than those managed with noninvasive ventilation. These findings may indicate that invasive ventilation was not only a respiratory intervention, but also a marker of neonatal physiological vulnerability, illness severity, and cumulative risk for early developmental delay. The burden of delay in this study appears higher than pooled estimates from a recent systematic review of preterm-born children in low- and middle-income countries, where overall neurodevelopmental impairment was estimated at 16%.[19] The difference with the present study is clinically understandable because the present study was selected from neonates who required ventilatory support. In contrast, pooled estimates include broader preterm populations with variable neonatal severity. These findings are also close to previous local evidence from Pakistan, where Khan et al.[20] reported developmental delay in 32% of premature infants at 6 months, with lower gestational age, lower birth weight, and NICU morbidities associated with delayed development. This study adds to that local evidence by focusing specifically on comparison between invasive and noninvasive ventilation.

Invasive ventilation was associated with a more adverse baseline profile. A prospective cohort by Paulsen et al.[21] showed that even moderate to late preterm infants had higher odds of neurological and gross motor concerns than term infants, despite being traditionally considered at lower risk. The present study extends this concern to a more clinically fragile group, in whom respiratory support requirements further separate risk strata.

Gross motor delay was significantly more frequent in infants exposed to invasive ventilation. Caicedo et al.[22] in a systematic review concluded that mechanical ventilation is an independent risk factor for neurodevelopmental impairment in low birth-weight preterm infants, with duration of exposure and type of ventilation carrying the strongest evidence. The biological link is likely multifactorial, as infants who require invasive ventilation are exposed to more severe respiratory failure, sedation, pain, inflammation, intermittent hypoxaemia, altered cerebral perfusion, and longer periods of restricted movement.[23] These exposures may affect early motor organization and postural control during a phase of rapid brain growth.[24]

Communication delay was also significantly more frequent among infants exposed to invasive ventilation. This observation is clinically significant because early communication delay may precede later language and cognitive difficulties, particularly in preterm infants.

Caicedo et al.[22] noted that mechanical ventilation was adversely associated with different neurodevelopmental spheres, including cognitive and motor outcomes. Lipp et al.[8] found that in a Canadian cohort of infants born at 23-25 weeks, noninvasive respiratory support during initial stabilization was associated with lower odds of severe brain injury or death before discharge. They also found that among survivors with follow-up data, significant neurodevelopmental impairment occurred in 17% of infants managed initially with noninvasive respiratory support and 23% of those intubated. However, the matched analysis showed no clear difference in neurodevelopment among survivors. The present study differs because it assessed earlier developmental screening at 3 months and included infants of gestational age 28 weeks and above, yet the direction of association remained clinically similar.

The study findings also support the contemporary movement toward avoiding endotracheal intubation where clinically safe. A review of neonatal noninvasive ventilation described the shift from routine invasive ventilation toward CPAP, NIPPV, heated humidified high flow nasal cannula, and other noninvasive modalities while emphasizing that modality choice should be individualized according to disease severity, resource setting, clinician experience, and family values.[25] The present findings may not be interpreted as evidence that invasive ventilation itself is always avoidable or directly causal. Invasive ventilation remains lifesaving in neonates with severe respiratory failure or airway instability. The clinical implication is that infants requiring invasive ventilation should be treated as a high-risk neurodevelopmental subgroup from discharge, with structured follow-up, early physiotherapy referral, parental counselling, and careful monitoring of motor and communication milestones.[26]

This study has some limitations. The sample size was modest, and the study was conducted at a single tertiary care hospital, which may limit generalizability to other NICUs with different admission criteria, ventilation practices, and follow-up systems. Specific clinical indications of initiating invasive or noninvasive ventilation were not prospectively recorded. Developmental outcomes were assessed at 3 months corrected age, which allows early screening but cannot define persistent neurodevelopmental impairment.

CONCLUSION

Infants discharged from NICU after invasive ventilation showed a higher frequency of early gross motor and communication delay than those managed with noninvasive ventilation. The findings highlight invasive ventilation as a practical marker for identifying infants who need structured developmental surveillance after discharge. Early recognition, family counselling, and timely referral for developmental support can be integrated into NICU follow-up pathways.

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AUTHOR CONTRIBUTION

Iqbal H: Data collection, drafting, responsible for data, proofreading, approved for publication.
Younus J: Conception and design, critical revisions, approved for publication.
Khan MQ: Literature review, drafting, critical revisions, responsible for data, approved for publication
Chaudhry S: Literature review, drafting, critical revisions, proofreading, approved for publication.
Fatima B: Literature review, drafting, critical revisions, proofreading, approved for publication.
Haroon F: Data collection, data analysis, proofreading, approved for publication.

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