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Neurodevelopment and physical measurements in infants with birthweight of 500 grams or less

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Abstract

Background: In infants born weighing ≤500 g, little has been studied about the association between neurodevelopmental prognosis and growth. This study aimed to evaluate the association between neurodevelopmental impairment (NDI) and *z*-scores of physical measurements in infants born weighing ≤500 g.
Methods: A single-center, retrospective cohort study in a level IV neonatal intensive care unit in Japan. Infants born weighing ≤500 g between 2010 and 2019 were eligible. *Z*-scores in weight, length/height, and head circumference at birth, due date (or discharge), 6 and 18 months of corrected age, and 3 years of age were compared between infants with and without NDI at 3 years of age. Three infants with severe intraventricular hemorrhage or periventricular leukomalacia were excluded from the comparison analyses. NDI was defined as having a developmental quotient of ≤70, cerebral palsy, visual impairment, or hearing impairment.
Results: Of 22 eligible infants, the incidence of NDI at 3 years of age was 54.5%. The *z*-score was significantly smaller in the NDI group (n = 10) than that in the non-NDI group (n = 9) in head circumference at birth (median, −1.94 vs. −0.75; Z = 0.54; p = 0.020), and in height at 18 months of corrected age (median, −2.84 vs. −1.79; Z = 0.58; p = 0.013) and 3 years of age (median, −2.02 vs. −1.21; Z = 0.47; p = 0.046).
Conclusions: NDI at 3 years of age was associated with a small head circumference *z*-score at birth, height at 18 months of corrected age, and height at 3 years of age in infants born weighing ≤500 g.

KEYWORDS
500 g, development, extremely low birthweight, extremely preterm, growth

INTRODUCTION

The number of neonates born with a birthweight ≤ 500 g has increased over the last few decades,[1] and their survival rates have improved.[2] However, a nationwide study showed that 59.1% of them had neurodevelopmental impairment (NDI) at 3 years of age.[3] Thus, the goal is becoming not only to save their lives but also to improve long-term prognosis. NDI was shown to be associated with male sex, severe intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), severe necrotizing enterocolitis, need for patent ductus arteriosus ligation, and small head circumference *z*-score at 3 years of age.[3] Weight and height at 3 years of age and birthweight did not have an association with NDI. However, to our knowledge, little has been studied about the association between neurodevelopmental prognosis and *z*-scores of physical measurements, especially head circumference in infants born weighing ≤500 g.

Head circumference is one of the prognostic factors for neurodevelopmental outcomes in full-term and preterm infants. Smaller head circumference *z*-score at birth was associated with poor neurodevelopment.[4–7] Moreover, compared to weight or length, head circumference at birth was more strongly associated with intelligence.[8–10] This study aimed to evaluate the association between NDI at 3 years of age and z-scores of physical measurements at birth or later points in infants born weighing ≤500 g. Additionally, little is known about the necessity of special medical care at 3 years of age. This study also aimed to evaluate neonatal morbidities, conditions at discharge, and long-term outcomes at 3 years of age to fill in the knowledge gaps.

METHODS

Study design, population, and protocol

This was a single-center, retrospective cohort study. The study setting was a level IV neonatal intensive care unit of a regional perinatal center in Japan. Eligible patients were infants born weighing ≤500 g between January 1, 2010, and December 31, 2019, and whose clinical course was available in the electronic medical records. The following patients were excluded: stillbirths, out-born infants, or infants whose follow-up assessment had not been completed at analyses.

Individual informed consent was not required because of the anonymity of the data. The ethical approval and the study permission were given on April 27, 2021, by the Ethics Committee of the hospital where this study was conducted (board approval no.: S-03-3).

Outcome measures

The primary outcomes were z-scores of physical measurements at birth, due date, 6 and 18 months of corrected age (CA), and 3 years of age. Physical measurements included weight, length/height, and head circumference. Physical measurements at discharge were used instead of those at the due date if the infant was discharged before the due date assessment. In addition, conditions at discharge and 3 years of age were also evaluated: death, NDI, developmental retardation, cerebral palsy (CP), visual and hearing impairment, growth impairment, the need for home oxygen therapy, tracheostomy, tube feeding and gastrostomy, and the need for at least one rehospitalization until 3 years of age.

Study definitions

Gestational age was estimated using the last menstrual period, embryo transfer, ovulation, or ultrasound examination. NDI was defined as having at least one of the following conditions: cognitive impairment, CP, visual impairment, or hearing impairment. Cognitive impairment was defined as a developmental quotient (DQ) score of ≤70 assessed using the Kyoto Scale of Psychological Development. This assessment method is well correlated with Bayley III.[11] A DQ of ≤70 is considered moderate-to-severe developmental retardation. Visual impairment was defined as unilateral or bilateral blindness or any other condition requiring corrective lenses and diagnosed by an ophthalmologist. Hearing impairment was defined as unilateral or bilateral hearing loss that required a hearing aid. Hearing loss was diagnosed by otolaryngologists using auditory steady-state response. CP was defined as any type of CP with a Gross Motor Function Classification System level of ≥ II.[12]

Those who required ≥30% oxygen therapy or mechanical respiratory support at 36 weeks of gestation were defined as having severe bronchopulmonary dysplasia.[13] Patent ductus arteriosus was diagnosed by neonatologists using echocardiography, and the need for surgery was determined by pediatric cardiologists and pediatric cardiovascular surgeons. IVH was diagnosed by neonatologists using a head ultrasound examination. Severe IVH was defined as grade III or IV, according to the classification by Papile et al.[14] PVL was diagnosed using head ultrasonography and/or magnetic resonance imaging by the presence of typical cyst formations in the periventricular white matter. Sepsis was defined as septicemia or bacteremia diagnosed by positive blood culture results. Retinopathy of prematurity was diagnosed, and its necessity for treatment was assessed by an ophthalmologist. Z-scores of physical measurements were calculated using the Japanese neonatal anthropometric charts and growth standards.[15,16]

Statistical analyses

Eligible infants were classified into two groups after excluding those with severe IVH or PVL. Those with NDI at 3 years of age were classified into the NDI group, while the others were in the non-NDI group. The primary outcomes were compared between the groups. The other outcomes were evaluated for all eligible infants.

The differences between the two groups were calculated using Fisher's exact test (categorical variables) or Wilcoxon's rank sum test (continuous variables). Analysis was conducted using R,[17] version 4.1.2 with the R packages of tidyverse,[18] version 1.3.1, and epitools,[19] version 0.5-10.1. The R package ggplot2,[20] version 3.3.5, was used for visualization. P-values < 0.05 were considered statistically significant.

RESULTS

A total of 22 infants were identified as eligible. The demographics of the mothers and neonates are summarized in Table 1. The median gestational age at birth was 24 2/7 weeks (range, 22 0/7–29 2/7 weeks), and the median birthweight was 428 g (range, 258–498 g). Table 1 also shows the neonatal morbidities and the conditions at discharge.

TABLE 1 Demographics, morbidities, and conditions in the NICU.

	Total (*n*=22)	NDI group (*n*=10)[d]	Non-NDI group (*n*=9)[d]
Maternal demographics			
Maternal age, median (IQR), years	30 (20, 42)	28 (24, 33)	31 (29, 37)
Japanese ethnicity, *n* (%)	22 (100)	10 (100)	9 (100)
Singleton, *n* (%)	15 (68)	9 (90)	5 (56)
Antenatal corticosteroid, *n* (%)	16 (73)	9 (90)	5 (56)
Cesarean delivery, *n* (%)	16 (73)	8 (80)	6 (67)
Neonatal demographics at birth			
Gestational age, median (range), weeks$^{(days)}$	$24^{2/7}$ ($22^{0/7}$, $29^{2/7}$)	$24^{6/7}$ ($22^{2/7}$, $29^{2/7}$)	$23^{2/7}$ ($22^{0/7}$, $25^{3/7}$)
Weight, median (range), g	428 (258, 498)	415 (258, 486)	449 (273, 497)
Small for gestational age, *n* (%)[a]	17 (77)	8 (80)	7 (78)
Male sex, *n* (%)	10 (46)	6 (60)	2 (22)
Apgar score<7 at 5min, *n* (%)	14 (64)	5 (50)	7 (78)
Major congenital anomalies, *n* (%)[b]	0 (0)	0 (0)	0 (0)
Morbidities in NICU			
Death in NICU, *n* (%)	0 (0)	0 (0)	0 (0)
Severe BPD, *n* (%)	21 (96)	10 (100)	8 (89)
PDA surgery, *n* (%)	1 (5)	0 (0)	1 (11)
Severe IVH (Grade≥III), *n* (%)	2 (9)	–	–
PVL, *n* (%)	1 (5)	–	–
NEC, *n* (%)	0 (0)	0 (0)	0 (0)
Sepsis, *n* (%)	9 (41)	4 (40)	3 (33)
ROP treatment, *n* (%)	17 (77)	8 (80)	6 (67)
Conditions at discharge			
Length of hospital stay, median (IQR), days	174 (147, 216)	193 (159, 216)	148 (145, 181)
Postmenstrual age, median (IQR), weeks	49.1 (45.7, 54.2)	51.9 (49.6, 54.2)[c]	45.7 (43.3, 47.9)[c]
Home oxygen therapy, *n* (%)	7 (32)	4 (40)	2 (22)
Tracheostomy, *n* (%)	1 (5)	0 (0)	0 (0)

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; IQR, interquartile range; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a]Small for gestational age is defined as having a birthweight below the 10th percentile.

[b]A major anomaly is defined as a congenital condition that necessitates extensive medical or surgical treatment, significantly impacts health and development, or has a notable cosmetic effect.

[c]The difference between the NDI group and the non-NDI group is statistically significant ($p<0.05$).

[d]Three infants were excluded from the comparison analyses: two had severe IVH and one had PVL.

No infants died in the neonatal intensive care unit. The morbidity rate of severe bronchopulmonary dysplasia was 96%; patent ductus arteriosus requiring surgery, 5%; severe IVH, 9%; PVL, 5%; necrotizing enterocolitis, 0%; sepsis, 41%; and retinopathy of prematurity requiring treatment, 77%. The median length of hospital stay was 174days (interquartile range [IQR], 147–216). The long-term outcomes at 3years of age are summarized in Table 2. No infant died during the follow-up period to 3years of age. The proportion of those having NDI was 55%. The morbidity rate of moderate-to-severe developmental retardation (DQ ≤70) was 46%. This rate also included two infants who were not applicable for the usual assessment method. One of them was diagnosed with CP and PVL and required tracheostomy, while the other was estimated to have developmental delays equivalent to a year and four months based on a quick test. The proportions of those in need of special medical care at 3years of age were 9% on home oxygen therapy, 27% on tube feeding, and 9% on gastrostomy. Of those, 50% required at least one rehospitalization from discharge to 3years of age.

Of 22 eligible infants, 10 were classified into the NDI group and nine into the non-NDI group. Three infants were excluded from the comparison analyses: two had severe IVH and one had PVL. The NDI group had a later gestational age (median, 24 6/7 vs. 23 2/7 weeks) and more boys (60% vs. 22%) than the non-NDI group, whose difference was not significant. The median postmenstrual age at discharge was later (51.9 vs. 45.7weeks) in the NDI group than those in the non-NDI group ($p=0.05$).

TABLE 2 Long-term outcomes at 3 years of age.

n **(%)**	**Total (*n*=22)**
Death	0 (0)
NDI[a]	12 (55)
Moderate–severe developmental retardation (DQ ≤ 70)[b]	10 (45)
CP	1 (5)
Visual impairment	4 (18)
Hearing impairment	2 (9)
Growth	
Weight *z*-score < −2	10 (46)
Length *z*-score < −2	7 (32)
Head circumference *z*-score < −2[c]	5 (25)
Other conditions	
Home oxygen therapy	2 (9)
Tracheostomy	1 (5)
Tube feeding	6 (27)
Gastrostomy	2 (9)
Rehospitalization[c]	10 (50)

Abbreviations: CP, cerebral palsy; DQ, developmental quotient; NDI, neurodevelopmental impairment.

[a]NDI is defined as having at least one of the following conditions: cognitive impairment, CP, visual impairment, or hearing impairment. Cognitive impairment is defined as a DQ of ≤70 using the Kyoto Scale of Psychological Development.

[b]Two patients whose DQ was not evaluated was considered having moderate-to-severe retardation.

[c]Missing data in two patients.

Otherwise, the demographics, neonatal morbidities, and conditions at discharge were comparable between the two groups (Table 1).

Table 3 summarizes the association between NDI at 3 years of age and the *z*-scores of weight, length/height, and head circumference at each time point. The head circumference *z*-score at birth was significantly smaller in the NDI group than that in the non-NDI group (median, −1.94 vs. −0.75; $Z=0.54$; $p=0.02$). Additionally, the height *z*-score was significantly smaller in the NDI group than that in the non-NDI group at 18 months CA (median, −2.84 vs. −1.79; $Z=0.58$; $p=0.01$) and at 3 years of age (median, −2.02 vs. −1.21; $Z=0.47$; $p=0.05$). The other time points or physical measurements showed no significant difference between the two groups. Trends in the median (IQR) *z*-score of each measurement in each group are demonstrated in Figure 1. The *z*-scores of physical measurements remained lower than the normal level until 3 years of age. The *z*-score of physical measurements remarkably decreased from birth to due date, except for that of the head circumference in infants without NDI at 3 years of age. The difference in *z*-score between the two groups remained at the same level throughout the period in weight and length/height, whereas the difference widened at the due date and caught up later in head circumference. The difference in median *z*-score between the two groups was greatest in head circumference at the due date although it was not statistically significant.

DISCUSSION

In this cohort study of infants born weighing ≤500 g, NDI at 3 years of age was associated with a small *z*-score of head circumference at birth, height at 18 months CA, and height at 3 years of age. This study also emphasized that about half of the infants born weighing ≤500 g suffered from NDI or growth impairment at 3 years of age.

Our finding that, at birth, only head circumference was associated with later NDI was in line with that of some previous studies on preterm infants. A longitudinal cohort study on preterm infants showed that small head circumference, or microcephaly, at birth was associated with delayed development at 4 years of age.[5] A nationwide cohort study using infants born at 22–45 weeks of gestation showed an association between microcephaly at birth and poor reading and mathematics skills at school age.[4] Another population-based cohort study on male preterm infants found that microcephaly at birth was associated with poor intellectual performance in adulthood.[9] Some studies also showed the superiority of head circumference as a prognostic factor of later prognosis compared to weight or length. In a population-based cohort study, a *z*-score of birthweight was not associated with later intellectual performance after adjusting *z*-scores of length and head circumference.[9] A Mendelian randomization study reported that a small head circumference *z*-score at birth was significantly associated with poor intelligence performance, and the association was not significant in weight or length *z*-score.[8] Additionally, especially in preterm births, the measurement technique of head circumference is easier and more accurate than that of length.[21,22]

The association between microcephaly at birth and poor neurodevelopmental prognosis could be explained by the epidemiology and mechanisms of microcephaly. In studies involving children with microcephaly, 29% had genetic causes and 27% had perinatal brain damage,[23] both are possibly related to NDI. Additionally, extreme insufficiency of the placenta, which was included in the unknown cause,[23] can also cause NDI through a small head circumference *z*-score at birth.[24] When a fetus does not receive sufficient nutrition, blood flow to the brain is usually preserved even during growth restriction.[25] However, if malnutrition in the uterus continues for a long time, the brain cannot be protected, resulting in microcephaly with brain damage.[26]

This study also showed the association between short stature at 18 months CA or 3 years of age and NDI at 3 years of age. A cohort study on boys born preterm showed a significant but weak positive correlation between height and intelligence quotient at seven years.[27]

TABLE 3 Physical measurements *z* score in the NDI and non-NDI groups.

Median (IQR)	Total (*n* = 22)	NDI group (*n* = 10)[d]	Non-NDI group (*n* = 9)[d]	Effect size (*Z*)[a]	*p*[a]
Weight *z* score					
Birth	−2.18 (−3.90, −1.47)	−3.70 (−4.45, −1.65)	−1.68 (−2.68, −1.51)	0.38	0.11
Due date[b]	−3.82 (−5.29, −3.49)	−4.61 (−6.31, −3.65)	−3.71 (−4.51, −2.63)	0.28	0.24
6 months CA	−3.28 (−3.96, −2.70)	−3.73 (−4.46, −3.25)	−3.09 (−3.46, −2.44)	0.38	0.11
18 months CA	−2.34 (−2.87, −1.77)	−2.78 (−3.11, −2.19)	−2.14 (−2.55, −1.66)	0.28	0.24
3 years of age	−1.92 (−2.57, −1.52)	−2.21 (−2.88, −1.73)	−1.82 (−2.28, −1.23)	0.30	0.21
Length/height *z* score					
Birth	−1.94 (−3.42, −1.05)	−2.98 (−3.92, −1.42)	−1.84 (−2.46, −0.13)	0.36	0.13
Due date[b]	−5.57 (−6.69, −4.13)	−5.87 (−6.90, −4.52)	−4.78 (−5.65, −3.22)	0.30	0.21
6 months CA	−3.61 (−5.23, −2.31)	−4.39 (−5.69, −3.49)	−3.26 (−3.88, −2.17)	0.36	0.13
18 months CA	**−2.25 (−2.98, −1.74)**	**−2.84 (−3.57, −2.24)**	**−1.79 (−2.07, −1.48)**	**0.58**	**0.01**
3 years of age	**−1.47 (−2.52, −0.90)**	**−2.02 (−3.02, −1.34)**	**−1.21 (−1.48, −0.88)**	**0.47**	**0.05**
Head circumference *z* score					
Birth	**−0.67 (−0.86, −0.57)**	**−1.94 (−2.53, −1.16)**	**−0.75 (−0.87, −0.58)**	**0.54**	**0.02**
Due date[b]	−2.71 (−4.30, −0.75)	−4.17 (−4.61, −3.27)	−1.22 (−2.34, −0.38)	0.43	0.07
6 months CA	−1.23 (−2.33, −0.28)	−1.55 (−2.78, −1.24)	−1.08 (−2.23, −0.23)	0.41	0.08
18 months CA	−1.34 (−2.45, −0.75)	−1.61 (−2.85, −0.60)	−1.00 (−1.67, −0.92)	0.08	0.77
3 years of age[c]	−1.03 (−2.05, −0.18)	−1.50 (−2.47, −0.20)	−1.13 (−2.00, −0.47)	0.09	0.72

Abbreviations: CA, corrected age; IQR, interquartile range; NDI, neurodevelopmental impairment.
[a]Effect sizes and *p*-values of the comparison between the NDI and non-NDI group.
[b]Measured at discharge if the infant was discharged home before due date.
[c]Missing head circumference data of two patients in the NDI group.
[d]Three infants were excluded from the comparison analyses: two had severe IVH and one had PVL.

Another population-based cohort study indicated that short stature in adulthood was associated with higher intellectual performance.[7] A literature review has summarized an important association between compromised length growth and later neurodevelopment in preterm infants.[28] The mechanism of the association between short stature and NDI is not known. One of the possible mediators is intrauterine growth restriction. It was associated with poor neurodevelopmental prognosis[29] and with a low serum level of insulin-like growth factor-1.[30] A low serum level of insulin-like growth factor-1 possibly leads to short stature.[31] This mechanism might also be influenced by other perinatal factors that are associated with inflammation.[28] Further evaluation is awaited to understand the association between short stature and neurodevelopmental prognosis or its mechanism.

We would also like to mention the head circumference *z*-score at discharge. Although not significant possibly because of the small number of patients, the difference in *z*-score between those with and without NDI was greatest in head circumference at discharge. This might indicate the importance of head growth between birth and discharge. However, it is still not clear if the brain damage could be reduced by head growth promotion or if microcephaly at discharge is simply a result of the brain damage. Our nutrition strategy during the study period can be summarized as follows: the total target calories for parenteral nutrition were 100–120 kcal/kg/day with 3.5 g/kg/day of protein and 2.0 g/kg/day of lipid, while for enteral nutrition, it was 140–150 kcal/kg/day with 160–170 mL/kg/day of fortified breast milk. Further studies are needed to understand the mechanisms of microcephaly and brain damage, as well as how a nutrition strategy can aid in the recovery from such damage.

Our results regarding severe morbidities should also be mentioned. The morbidity rates of severe neonatal complications in this study differed compared to those in previous reports: higher rates of bronchopulmonary dysplasia (96% vs. 53%–66%)[2,32–34] and retinopathy of prematurity requiring treatment (77% vs. 7%–44%),[2,34–38] and a lower rate of patent ductus arteriosus requiring surgery (5% vs. 13%–50%).[2,33,39,40] The incidence of NDI is difficult to compare among the studies because they used different definitions. A large cohort study in Japan using the same definition as ours showed that the incidence of NDI at 3 years of age was 83%, which was higher than that in this study.[3] The incidence of CP in this study was lower than that in the other studies that were conducted on participants at 3 years of age (5% vs. 14%–33%), but the incidence of visual or hearing impairment was comparable.[3,37,41] The incidence of growth impairment was lower in this study than that of a large cohort study in Japan: 46% versus 70% in weight, 32% versus 70% in height, and 25% versus 41% in head circumference.[3] No previous data exists regarding the other conditions at 3 years of age, except for the need for gastrostomy: the incidence was 9%

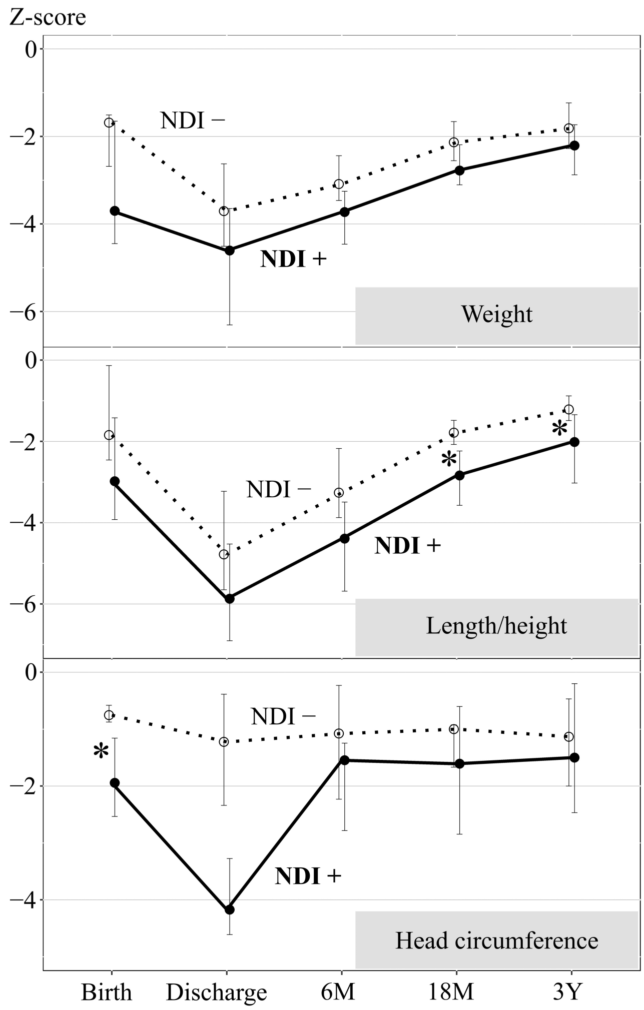

FIGURE 1 Trends in the z-score of weight, length/height, and head circumference in infants with or without neurodevelopmental impairment (NDI) at 3 years of age. White circles (○) with dashed lines and error bars indicate the trends of median (interquartile range) in infants without NDI at 3 years of age; black circles (●) with solid lines and error bars indicate the trends of median (interquartile range) in infants with NDI at 3 years of age. NDI, neurodevelopmental impairment; 6M, 6 months of corrected age; 18M, 18 months of corrected age; 3Y, 3 years of age. $*p<0.05$.

in this study, and 11% and 38% in the previous studies.[37,39] The reason for the better outcomes in this study might be attributed to the difference in sample size and fetuses' condition: mothers with fetuses in a poor condition might not have been referred to our hospital.

This study had some limitations. First, it was a single-center study with a small sample size. The small sample size undoubtedly contributed to the uncertainty of our results, especially in the comparison test. Second, this study may have a potential selection bias. Stillbirths were excluded from the analyses, and mothers of fetuses with poor conditions were usually not referred to our hospital. Third, multivariable analyses were not conducted to adjust for existing risk factors of NDI. The fact that more male infants were included in the NDI group may have affected the results. In addition, infants having a small head circumference z-score also tend to have a small weight z-score, which may have mediated the association with the NDI. Despite these limitations, our study was valuable in that it examined the prognosis of infants born weighing ≤500 g, a group that is few in number.

To conclude, NDI at 3 years of age was associated with a small z-score of head circumference at birth and height at 18 months CA and 3 years of age in infants born weighing ≤500 g. Microcephaly at birth and short stature after discharge home might be able to predict NDI. Although the survival rate of infants born weighing ≤500 g has improved over time, they are still at high risk of neurodevelopmental and growth impairment and other medical issues.

AUTHOR CONTRIBUTIONS

R.I., A.O., and R.O. contributed to the conception and design of this study; R.I. and T.Y. collected and cleaned the data; R.I. performed the statistical analyses; A.O., R.O., T.Y., T.H., and T.N. gave suggestion for the statistical analyses; R.I., drafted the manuscript; A.O., R.O., T.Y., T.H., and T.N. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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