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Postnatal weight loss and neurodevelopmental outcomes at age 3 years in extremely preterm infants: a cohort study

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Abstract

Background Previous research has suggested a correlation between postnatal maximum weight loss (MWL) and both neonatal mortality and morbidities in extremely preterm infants. However, the relationship between MWL and neurodevelopmental outcomes remains underexplored.

Methods In a single-center, retrospective cohort study at Okayama Medical Center, we evaluated data from extremely preterm infants admitted to the neonatal intensive care unit from 2010 to 2020. Infants who died within the first 10 days of life were excluded. MWL in the first 10 days was the main exposure, categorized into three groups: >15%, 5–15%, and < 5%. The primary outcome evaluated was the occurrence of death or neurodevelopmental impairment (NDI) at age 3 years, defined as developmental impairments (developmental quotient [DQ] < 85), cerebral palsy, hearing impairments, or visual impairments. Data analysis involved robust Poisson regression, adjusted for perinatal confounders, with a restricted cubic spline function to examine the dose-response relationship. We also conducted a sensitivity analysis using a DQ of < 70 to define developmental impairment.

Results Among 135 infants assessed for neurodevelopmental outcomes, 40 were in the > 15% MWL group, 71 in the 5–15% group, and 24 in the < 5% group. Median gestational ages and birth weights were 25.9 weeks and 821 g for > 15% MWL; 26.1 weeks and 818 g for 5–15% MWL; and 26.0 weeks and 734 g for < 5% MWL. Compared with the 5–15% MWL group, the < 5% group exhibited a higher risk of death or NDI at age 3 years (62.8% vs. 80.8%, risk ratio [RR] 1.36, 95% confidence interval [CI] 1.04–1.79) and NDI alone (59.2% vs. 79.2%, RR 1.43, 95% CI 1.06–1.94). Furthermore, higher risks of developmental impairment were also noted in the > 15% (RR 1.32, 95% CI 1.00–1.75) and < 5% (RR 1.46, 95% CI 1.08–1.98) groups. These associations were confirmed by spline analyses. In contrast, the associations between MWL and neurodevelopmental outcomes using a DQ of < 70 were not apparent.

Conclusions MWL within the first 10 days of life may be associated with increased risks of NDI and developmental impairments by age 3 years in extremely preterm infants.

Keywords Weight loss, Neurodevelopment, Extremely preterm, Mortality, Developmental impairment

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Background

Infants born extremely preterm, defined as those delivered between 22 and 27 weeks of gestation, face a significant risk of neonatal mortality and morbidity. Recent advancements have improved the short-term outcomes for these infants [1, 2]. However, severe neurodevelopmental disorders remain a significant long-term issue [3, 4]. Factors such as gestational age, being small for gestational age, and sex are crucial in predicting neurological outcomes in these infants [5].

Physiological weight loss is a crucial aspect of the newborn adaptation. However, the threshold at which physiologic weight loss becomes problematic is unclear, even in term infants. It is recognized that preterm infants often face physiological challenges and require medical interventions. Notably, the lower the gestational age, the higher the volume of extracellular fluid [6]. Extremely preterm infants are particularly vulnerable to excessive weight loss in their first week of life, which can be attributed to an immature skin barrier, respiratory distress, significant postnatal diuresis, and immature renal function [7]. Excessive early postnatal weight loss has been associated with an increased risk of extrauterine growth restriction, which may lead to poorer neurodevelopmental outcomes [8]. Research also suggests a correlation between maximum weight loss (MWL) and neonatal mortality and morbidities, including bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis [9–11]. A retrospective analysis of the Preterm Erythropoietin Neuroprotection Trial revealed that an MWL ranging from 5 to 15% during the first week of life was associated with a decreased likelihood of necrotizing enterocolitis compared with an MWL exceeding 15% in extremely preterm infants born between 2013 and 2016 [9]. This finding suggests that an MWL of 5–15% might represent an optimal range for these infants. However, few studies have examined the association between MWL and neurodevelopmental outcomes in this population.

This study aimed to examine the association between MWL during the first 10 days of life and neurodevelopmental outcomes at the age of 3 years in extremely preterm infants.

Materials and methods

Study cohort

We conducted a retrospective cohort study at a single center to investigate perinatal information related to infants born extremely preterm between January 2010 and December 2020. These infants were admitted to our tertiary neonatal intensive care unit (NICU). We excluded infants born outside our hospital, those with major congenital anomalies, those who died within the first 10 days of life, or those without weight data beyond birth during the initial 10 days. We extracted perinatal data from discharge summaries and cross-verified it using admission charts.

MWL

In our NICU, we routinely perform non-birth weight measurements on extremely preterm infants. Although we did not have a protocol to eliminate interobserver variability, our NICU nurses weighed extremely preterm infants in the incubator at the request of physicians, using a regularly maintained ATOM Infant Weighing Scale NS-616 hanging type (ATOM Medical Corporation, Tokyo, Japan). These assessments typically occur daily or every few days after 72 h of life. However, for infants with unstable respiratory and circulatory status, the evaluation of non-birth weight measurements could be delayed until after 96–120 h of life. We calculated the MWL using the formula: MWL = (birth weight − minimum weight other than birth weight) × 100/birth weight. We categorized the percentage of MWL within the first 10 days of life into three groups: MWL > 15%, between 5% and 15%, and < 5%, including cases with no weight loss. This classification aligns with the one used in the cohort study mentioned in the introduction [9]. All infants underwent consistent initial and subsequent fluid treatments according to our hospital's protocol (60 mL/kg on the first day, 70–80 mL/kg on the second day, and 80–90 mL/kg on the third day). The fluid regimen was adjusted as necessary in response to changes in the infant's electrolyte levels. Additionally, all infants were kept in incubators with a high-humidity environment (90–95%). Since March 2012, our NICU has adopted a revised protocol for the administration of amino acids to extremely preterm infants. Previously, the protocol required an increase in amino acid dosage of 0.5 g/kg/day every three days after birth. Following the revision, the protocol was adjusted to include a daily increase of 0.5 g/kg/day for the first three days after birth, followed by an increase of 0.5 g/kg/day every two days, up to a maximum of 2.5 g/kg/day.

Neurodevelopmental outcomes

Neurodevelopmental assessments were conducted at age 3 years. We defined cerebral palsy as abnormal muscle tone in one or more extremities, along with atypical control of movement and posture [12]. Cognitive function was evaluated using the Kyoto Scale of Psychological Development (KSPD) [13]. Certified psychologists administered the KSPD 2001 assessment. The KSPD is an individualized face-to-face test that assesses a child's development in the following three domains: Cognitive-Adaptive (non-verbal reasoning or visuospatial perceptions assessed with materials), Language-Social (interpersonal relationships, socialization, and language skills), and Postural-Motor (fine and gross motor

functions) [14]. Each score for these three domains and the sum of the scores were converted to represent each developmental age and the overall developmental age. The developmental quotient (DQ) was calculated by dividing the developmental age by the chronological age and multiplying the quotient by 100. In the Japanese protocol for the follow-up of VLBW infants, the developmental function was classified as "delayed" if the overall DQ was <70, "subnormal" if it was 70–84, and "normal" if it was ≥85. A comparative study in Japan demonstrated that an overall DQ of <70 in the KSPD is equivalent to a Bayley III cognitive score of <85 [13]. Hearing impairment and visual impairment were respectively defined as the requirement for amplification devices and the lack of functional vision in one or both eyes. Neurodevelopmental impairment (NDI) was defined as developmental impairment, cerebral palsy, hearing impairment, or visual impairment. We further classified mild and moderate to severe NDI based on the degree of developmental impairment, with mild NDI characterized by an overall DQ score of less than 85 and moderate to severe NDI by an overall DQ score of less than 70. The primary outcome measured was the incidence of death or mild NDI at age 3 years, with secondary outcomes including the individual components of the primary outcome.

Statistical analyses

To evaluate the impact of loss to follow-up, we initially examined the baseline characteristics of survivors with and without neurodevelopmental data at age 3 years. Additionally, we compared these characteristics among extremely preterm infants who had neurodevelopmental data at age 3 years, stratified by MWL categories: >15%, 5–15%, and <5%. Subsequently, we employed Poisson regression models with robust variance estimators to explore the associations between MWL categories and both primary and secondary outcomes. After adjusting for potential confounders, we calculated the risk ratios (RRs) and 95% confidence intervals (CIs) for the main outcomes using the MWL 5–15% category as the reference. Our selection of potential confounders was based on prior research and included gestational age (categorized as 22–23, 24–25, and 26–27 weeks), sex (dichotomous), small for gestational age (dichotomous), antenatal corticosteroids (dichotomous), Clinical Risk Index for Babies (CRIB) II score (categorized as ≤9, 10–14, and ≥15), birth following changes to the amino acid dosage protocol (dichotomous), and intraventricular hemorrhage (dichotomous) [9, 15–17]. As a sensitivity analysis, we performed a Poisson regression analysis for moderate to severe NDI and developmental impairment using the cutoff of an overall DQ score of 70.

Gestational age was determined using ultrasound during the first trimester and the date of the last menstrual period. Small for gestational age was defined as a birth weight below the 10th percentile for gestational age, according to standard Japanese neonatal anthropometric charts [18]. The term "antenatal steroids" refers to any corticosteroid dose administered to the mother before delivery. The CRIB II score was computed using five variables assessed at NICU admission: sex, gestational age, birth weight, base excess, and body temperature [19]. Base excess was obtained from the initial blood gas analysis during a retrospective chart review. Intraventricular hemorrhage was diagnosed by head ultrasound performed daily during the acute phase and confirmed by head magnetic resonance imaging before discharge. Periventricular leukomalacia was diagnosed by head ultrasound or magnetic resonance imaging. Bronchopulmonary dysplasia was defined as the need for supplemental oxygen or positive pressure ventilation at 36 weeks of postmenstrual age [20]. Necrotizing enterocolitis was determined by radiographic or surgical findings and Bell's criteria (stage 2 or greater) [21]. The diagnosis and treatment of retinopathy of prematurity were based on the criteria proposed by the Task Force of the Ministry of Health, Labor and Welfare of Japan. The diagnosis of sepsis was based on positive blood culture results.

Furthermore, we conducted a restricted cubic spline analysis to evaluate the relationship between MWL and the primary and secondary outcomes. This analysis controlled for the same covariates as in the original categorical analyses. From the spline analyses, we derived the adjusted RR and 95% CI for each MWL category, using 10% MWL as a reference. For all statistical analyses, we utilized Stata SE version 18 (Stata Corp LLC, College Station, TX, USA).

Ethics statement

This study received approval from the Institutional Review Board of Okayama Medical Center (RINKEN 2023-080) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was waived given the retrospective nature of the study (Institutional Review Board of Okayama Medical Center, RINKEN 2023-080).

Results

Between 2010 and 2020, a total of 211 extremely preterm infants were admitted to our NICU. Of these, 27 infants were excluded for various reasons: out-of-hospital birth ($n=6$), congenital anomalies ($n=6$), death within the first 10 days of life ($n=7$), and lack of weight data during the initial 10 days ($n=8$). Among the remaining 184 infants, 7 died before NICU discharge, 2 died following NICU discharge, and 40 were lost to follow-up for neurodevelopmental assessment at the age of 3 years. We successfully collected neurodevelopmental data for 40 infants in

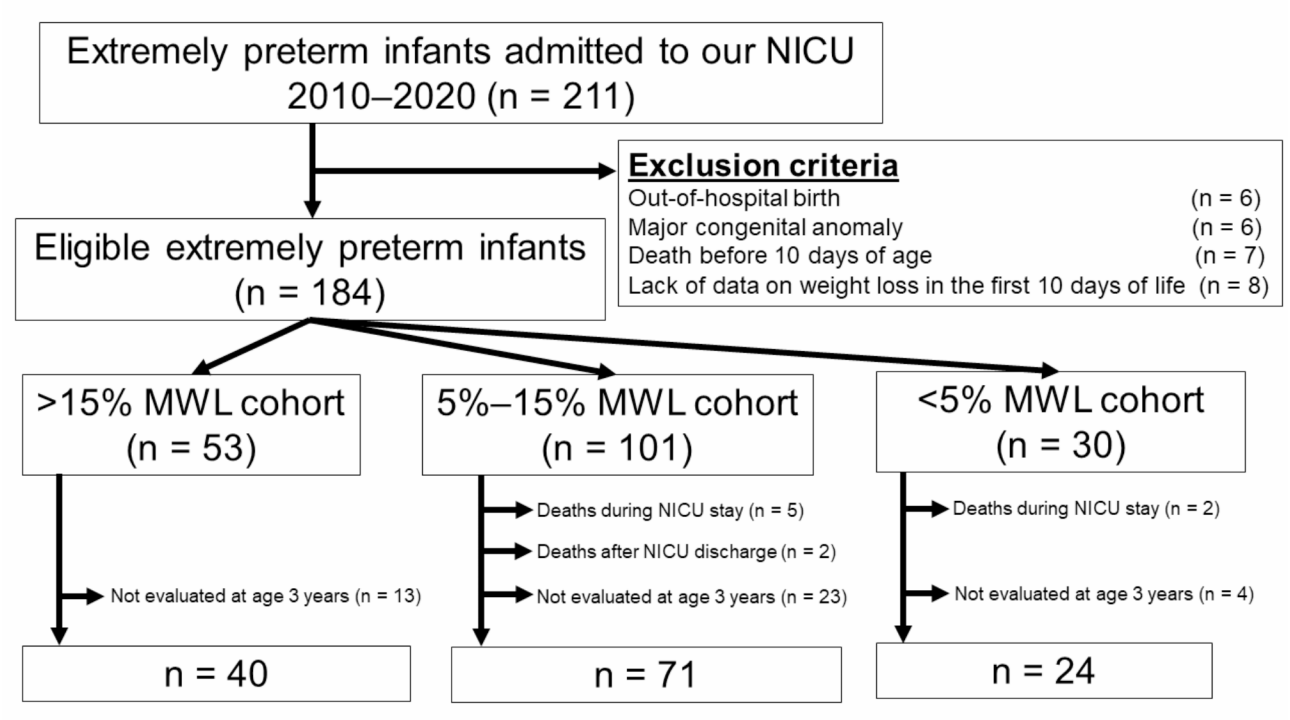

Fig. 1 Study flowchart. Abbreviations: NICU, neonatal intensive care unit; MWL, maximum weight loss

Table 1 Characteristics of survivors with and without neurodevelopmental data at age 3 years

	With neurodevelopmental data at age 3 years	Without neurodevelopmental data at age 3 years
	n = 135	*n* = 40
Gestational age, weeks	26.0 (24.9–27.0)	25.7 (24.4–26.9)
Birth weight, g	796 (636–922)	764 (660–878)
Small for gestational age	20 (14.8)	5 (12.5)
Sex, male	71 (52.6)	25 (62.5)
Antenatal corticosteroids	122 (90.4)	36 (90.0)
CRIB II score	11 (9–13)	12 (9–13.5)
Births after amino acid dosage protocol changes	104 (77.0)	32 (80.0)
Intraventricular hemorrhage	36 (26.7)	18 (45.0)
MWL category		
>15%	40 (29.6)	13 (32.5)
5–15%	71 (52.6)	23 (57.5)
<5%	24 (17.8)	4 (10.0)

Abbreviations: CRIB, Clinical Risk Index for Babies; MWL, maximum weight loss

Note: Data are expressed as *n* (%) or median (interquartile range)

the MWL > 15% cohort, 71 infants in the MWL 5–15% cohort, and 24 infants in the MWL < 5% cohort (Fig. 1).

Infants who did not have neurodevelopmental data at age 3 years tended to have a younger gestational age, lower birth weight, male sex, and a higher CRIB II score, as shown in Table 1.

Outlines the characteristics of extremely preterm infants, grouped by MWL category. Infants in the MWL < 5% category generally had a lower birth weight, a higher incidence of being small for gestational age, female sex, a later start date for measurements other than birth weight, and a later age at MWL assessment.

Table 3 Presents the associations between MWL categories and the primary and secondary outcomes in extremely preterm infants. None of the infants with follow-up data exhibited hearing or visual impairments. After adjusting for potential confounders, infants in the MWL < 5% category exhibited higher incidences of death or mild NDI at age 3 years (80.8%) compared with those in the MWL 5–15% category (62.8%, adjusted RR 1.36, 95% CI 1.04–1.79). Similarly, the incidence of mild NDI (79.2% vs. 59.2%, adjusted RR 1.43, 95% CI 1.06–1.94), as was the incidence of developmental impairment (79.2% vs. 57.7%; adjusted RR 1.46, 95% CI 1.08–1.98). In contrast, infants in the MWL > 15% category showed a higher incidence of developmental impairment (70.0% vs. 57.7% in the MWL 5–15% category; adjusted RR 1.32, 95% CI 1.00–1.75). Despite slight overlaps in the 95% CIs, a comparable pattern was noted for mild NDI between the MWL > 15% and 5–15% categories (70.0% vs. 59.2%; adjusted RR 1.29, 95% CI 0.98–1.70). No associations were observed between the individual DQ scores of the three domains (i.e., cognitive-adaptive, language-social, and postural-motor) of the KSPD and the MWL categories.

Table 2 Characteristics of extremely preterm infants with neurodevelopmental data at age 3 years by MWL category

	MWL category		
	> 15% MWL	5–15% MWL	< 5% MWL
	n = 40	*n* = 71	*n* = 24
Gestational age, weeks	25.9 (24.4–27.1)	26.1 (24.9–26.9)	26.0 (25.6–26.9)
Birth weight, g	821 (607–918)	818 (648–922)	734 (633–872)
Small for gestational age	1 (2.5)	11 (15.5)	8 (33.3)
Sex, male	20 (50.0)	42 (59.2)	9 (37.5)
Antenatal corticosteroids	38 (95.0)	63 (88.7)	21 (87.5)
CRIB II score	11 (9–13)	11 (9–12)	11 (10–13)
Births after amino acid dosage protocol changes	31 (77.5)	55 (77.5)	18 (75.0)
Age at the start of non-birth weight measurement, days	4 (3–5)	4 (3–5)	5.5 (5–7)
Age at MWL, days	5.5 (4–7)	5 (4–7)	6.5 (5–9)
Intraventricular hemorrhage	9 (22.5)	21 (29.6)	6 (25.0)
Periventricular leukomalacia	0 (0.0)	1 (1.4)	0 (0.0)
Bronchopulmonary dysplasia	12 (30.0)	18 (25.4)	8 (33.3)
Patent ductus arteriosus requiring surgery	1 (2.5)	2 (2.8)	2 (8.3)
Necrotizing enterocolitis	1 (2.5)	7 (9.9)	0 (0.0)
Sepsis	5 (12.5)	7 (9.9)	4 (16.7)
Retinopathy of prematurity requiring treatment	21 (52.5)	22 (31.0)	9 (37.5)

Abbreviations: CRIB, Clinical Risk Index for Babies; MWL, maximum weight loss

Note: Data are expressed as *n* (%) or median (interquartile range)

The sensitivity analysis using moderate to severe NDI and developmental impairment defined as an overall DQ of less than 70 is shown in Table 4. The associations between MWL and neurodevelopmental outcomes at 3 years were not observed using this cutoff value for developmental impairment.

The results from the restricted cubic spline analysis are shown in Fig. 2 and the Supplementary Figure. This analysis identified a U-shaped association between MWL and the outcomes of death or mild NDI, isolated mild NDI, and developmental impairment defined as an overall DQ score < 85, with the lowest RR observed at an MWL rate of 10–12%.

Discussion

In our study, we investigated the association between MWL during the first 10 days of life and neurodevelopmental outcomes at age 3 years in extremely preterm infants. Infants in the MWL < 5% had a higher proportion of small-for-gestational-age infants with lower birth weights than the other groups, suggesting that more severely ill infants were more likely to be included in the MWL < 5% than in the other groups. We found that infants experiencing less than 5% or more than 15% MWL showed an elevated risk of mild NDI and other developmental impairments compared with those within the 5–15% MWL range. However, using developmental delay defined as a DQ of less than 70, the associations between MWL and neurodevelopmental outcomes at 3 years, including moderate to severe NDI, were not observed.

Several studies have explored MWL in preterm infants and its impact on short-term outcomes, such as neonatal mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis [9–11]. For instance, a retrospective cohort study from the United States involving 1,382 infants revealed that minimal weight loss during the initial 10 days of life was associated with higher risks of mortality or bronchopulmonary dysplasia in infants with extremely low birth weight born between 1999 and 2001 [10]. Similarly, another study in Turkey involving 126 infants demonstrated that either a weight loss below 3% or above 12% was associated with increased mortality, and a higher percentage of weight loss was linked to a greater risk of intraventricular hemorrhage [11]. Conversely, a Canadian study of 191 infants born between 23 and 28 weeks of gestation from 2015 to 2018 showed that maximum weight loss in the first 10 days, analyzed as a continuous variable, did not significantly affect the odds of death and bronchopulmonary dysplasia in this group [15]. A matched cohort analysis in Italy noted that MWL, categorized as either ≥ 10% or < 10%, had no significant impact on the 2-year neurodevelopment outcomes of 812 infants born between 24 and 31 gestational weeks from 2006 to 2019. These discrepancies in findings may be attributed to variations in sample size, outcome measures, and MWL thresholds. Indeed, in our study, there is also a difference in results between mild and moderate to severe NDI, which may be related to the small number of applicable cases for moderate to severe NDI. For our analysis, we adopted a simple MWL range of 5–15% as the reference category, aligning with a previous study [9]. The results of our spline analysis

Table 3 Associations between MWL and neurodevelopmental outcomes in extremely preterm infants

	N case/N total	(%)	Crude RR	(95% CI)	Adjusted RR	(95% CI)[a]
Death before age 3 years or mild NDI[b]						
>15% MWL	28/40	(70.0)	1.11	(0.85–1.45)	1.22	(0.94–1.59)
5–15% MWL	49/78	(62.8)	1	(reference)	1	(reference)
<5% MWL	21/26	(80.8)	1.29	(1.00–1.66)	1.36	(1.04–1.79)
Death before age 3 years						
>15% MWL	0/40	(0)	NE		NE	
5–15% MWL	7/78	(9.0)	1	(reference)	1	(reference)
<5% MWL	2/26	(7.7)	0.86	(0.19–3.89)	0.69	(0.18–2.58)
Mild NDI[b]						
>15% MWL	28/40	(70.0)	1.18	(0.89–1.57)	1.29	(0.98–1.70)
5–15% MWL	42/71	(59.2)	1	(reference)	1	(reference)
<5% MWL	19/24	(79.2)	1.34	(1.01–1.78)	1.43	(1.06–1.94)
Developmental impairment, overall DQ score < 85[c]						
>15% MWL	28/40	(70.0)	1.21	(0.91–1.61)	1.32	(1.00–1.75)
5–15% MWL	41/71	(57.7)	1	(reference)	1	(reference)
<5% MWL	19/24	(79.2)	1.37	(1.03–1.83)	1.46	(1.08–1.98)
Cognitive–Adaptive DQ score < 85[c]						
>15% MWL	24/40	(60.0)	1.09	(0.78–1.52)	1.16	(0.84–1.60)
5–15% MWL	39/71	(54.9)	1	(reference)	1	(reference)
<5% MWL	14/24	(58.3)	1.06	(0.71–1.58)	1.22	(0.80–1.85)
Language–Social DQ score < 85[c]						
>15% MWL	26/40	(65.0)	1.15	(0.85–1.57)	1.21	(0.89–1.66)
5–15% MWL	40/71	(56.3)	1	(reference)	1	(reference)
<5% MWL	17/24	(70.8)	1.26	(0.90–1.75)	1.28	(0.89–1.84)
Postural–Motor DQ score < 85[c]						
>15% MWL	12/40	(30.0)	0.82	(0.47–1.44)	0.82	(0.47–1.43)
5–15% MWL	26/71	(36.6)	1	(reference)	1	(reference)
<5% MWL	8/24	(33.3)	0.91	(0.48–1.74)	0.99	(0.50–1.98)
Cerebral palsy						
>15% MWL	1/40	(2.5)	0.44	(0.05–3.87)	0.61	(0.09–3.94)
5–15% MWL	4/71	(5.6)	1	(reference)	1	(reference)
<5% MWL	0/24	(0.0)	NE		NE	

Abbreviations: CI, confidence interval; DQ, developmental quotient; NDI, neurodevelopmental impairment; MWL, maximum weight loss; RR, risk ratio

Note: Data presented as the raw number (%) and RR (95% CI)

[a]Adjusted for gestational age, sex, small for gestational age, antenatal corticosteroids, Clinical Risk Index for Babies II score, birth after amino acid dosage protocol changes, and intraventricular hemorrhage

[b]Infants with developmental impairment (overall DQ score < 85), cerebral palsy, hearing impairment, or visual impairment

[c]Infants with a DQ score < 85 using the Kyoto Scale of Psychological Development

suggest that it is advisable to use the midpoint of MWL as a reference point.

Our findings indicate that infants with an MWL of 5–15% tend to exhibit more favorable neurodevelopmental outcomes at 3 years of age. We speculated that children with less weight loss may be more immature and exhibit unstable hemodynamics in the acute phase. In contrast, children with greater weight loss may experience excessive intrauterine growth restriction, potentially leading to poorer developmental outcomes [8]. This trend also suggests that extremely preterm infants with moderate edema rather than severe edema or malnutrition at birth may undergo moderate MWL during the acute phase, leading to a more favorable prognosis. Conversely, the poor prognosis of infants with either less or more weight loss may simply reflect their general condition at birth, whether due to excessive edema or malnutrition. In addition, the cumulative effect of short-term morbidities in infants with MWLs less than 5% and greater than 15% may influence their long-term prognosis. However, it is essential to recognize the inherent uncertainties associated with fluctuations in MWL during the critical early days of life. We speculate that MWL may serve as an indicator of prematurity rather than a directly modifiable determinant. Furthermore, asserting that an MWL of 5–15% is optimal for extremely preterm infants is challenging, given that the mortality rates observed in our study for the MWL 5–15% category were higher than

Table 4 Associations between MWL and neurodevelopmental outcomes using moderate to severe NDI and developmental impairment defined as a DQ score of < 70

	N case/N total	(%)	Crude RR	(95% CI)	Adjusted RR	(95% CI)[a]
Death before age 3 years or moderate to severe NDI[b]						
>15% MWL	8/40	(20.0)	0.62	(0.31–1.26)	0.85	(0.44–1.67)
5–15% MWL	25/78	(32.1)	1	(reference)	1	(reference)
<5% MWL	8/26	(30.8)	0.96	(0.49–1.86)	0.69	(0.35–1.35)
Moderate to severe NDI[b]						
>15% MWL	8/40	(20.0)	0.79	(0.38–1.65)	1.08	(0.52–2.22)
5–15% MWL	18/71	(25.4)	1	(reference)	1	(reference)
<5% MWL	6/24	(25.0)	0.99	(0.44–2.20)	0.70	(0.30–1.63)
Developmental impairment, overall DQ score < 70[c]						
>15% MWL	8/40	(20.0)	0.84	(0.40–1.77)	1.17	(0.56–2.42)
5–15% MWL	17/71	(23.9)	1	(reference)	1	(reference)
<5% MWL	6/24	(25.0)	1.04	(0.46–2.35)	0.70	(0.28–1.72)
Cognitive–Adaptive DQ score < 70[c]						
>15% MWL	13/40	(32.5)	1.28	(0.70–2.34)	1.66	(0.89–3.07)
5–15% MWL	18/71	(25.4)	1	(reference)	1	(reference)
<5% MWL	5/24	(20.8)	0.82	(0.34–1.98)	0.86	(0.36–2.08)
Language–Social DQ score < 70[c]						
>15% MWL	7/40	(17.5)	0.62	(0.29–1.34)	0.75	(0.35–1.58)
5–15% MWL	20/71	(28.2)	1	(reference)	1	(reference)
<5% MWL	7/24	(29.2)	1.04	(0.50–2.15)	0.82	(0.38–1.79)
Postural–Motor DQ score < 70[c]						
>15% MWL	8/40	(20.0)	1.18	(0.53–2.66)	1.20	(0.49–2.91)
5–15% MWL	12/71	(16.9)	1	(reference)	1	(reference)
<5% MWL	4/24	(16.7)	0.99	(0.35–2.78)	1.25	(0.43–3.66)

Abbreviations: CI, confidence interval; DQ, developmental quotient; NDI, neurodevelopmental impairment; MWL, maximum weight loss; RR, risk ratio

Note: Data presented as the raw number (%) and RR (95% CI)

[a]Adjusted for gestational age, sex, small for gestational age, antenatal corticosteroids, Clinical Risk Index for Babies II score, birth after amino acid dosage protocol changes, and intraventricular hemorrhage

[b]Infants with developmental impairment (overall DQ score < 70), cerebral palsy, hearing impairment, or visual impairment

[c]Infants with a DQ score < 70 using the Kyoto Scale of Psychological Development

those in the categories with MWLs greater than 15% or less than 5% (9.0% vs. 0% vs. 7.7%, respectively).

Our study, conducted in a NICU, provides accurate and comprehensive data but is subject to several limitations that must be acknowledged. The primary limitation is the relatively small sample size. Although we adjusted for potential confounders, the possibility of residual confounder effects could not be completely ruled out. The different results for mild and moderate to severe NDI may also be related to the lack of case numbers. Additionally, eligible infants were not weighed daily post-birth. Most were first weighed 72 h after birth, while those in unstable conditions were not weighed until 120 h post-birth. This delay could lead to an underestimation of MWL in these infants. For example, Table 2 shows that infants in the MWL < 5% category were older at the time of their first weight measurement post-birth compared with those in the MWL > 15% or 5–15% categories. Comparatively, a US cohort study found that the day of life for MWL measurement in extremely low birth weight infants was 5.5 ± 2.1 days (mean ± standard deviation) [22], suggesting that the timing of the first weight measurement in our study was appropriate for MWL assessment (Table 2). Another limitation is the loss of some cases to follow-up for neurodevelopmental assessments at 3 years. This loss was more frequent in the high-risk group, which includes infants with younger gestational age, lower birth weight, male sex, and higher CRIB II scores, thereby raising the possibility of selection bias that could inflate estimates of neurodevelopmental outcomes. This may be due to the early identification of developmental delays before 3 years, resulting in referral to and follow-up in rehabilitation facilities before our developmental assessment at 3 years. Furthermore, during the study period, our NICU revised the protocol for the administration of amino acids to extremely preterm infants. Although there was no notable difference in the number of cases between the three groups before and after the revised protocol, this could affect the results of our study. Finally, instead of the widely used Bayley Scales of Infant Development, Third Edition (Bayley III), we utilized the KSPD to assess developmental impairment. However, previous research has

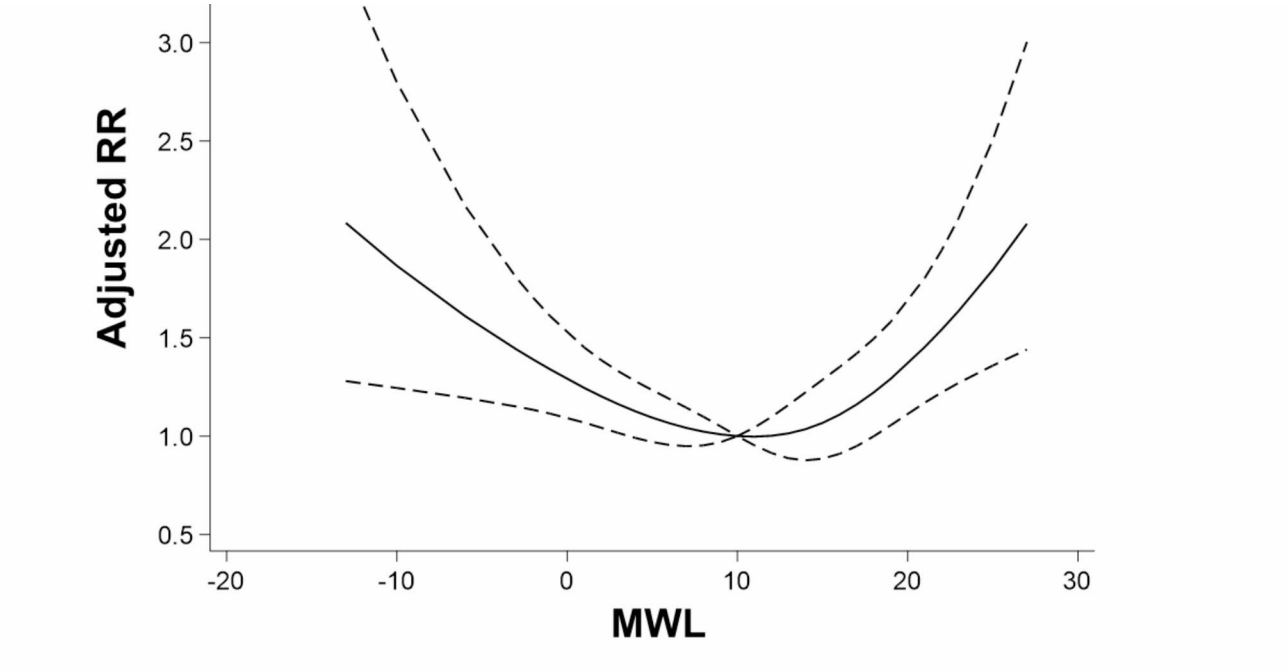

Fig. 2 Restricted cubic spline analysis. Adjusted RRs (solid lines) and 95% CIs (dotted lines) for the associations between MWL and the risk of death or mild NDI. An MWL below zero indicates infants who had no postnatal weight loss during the first 10 days of life. The analysis revealed that the lowest RR was associated with an MWL rate of 10–12%. Abbreviations: CI, confidence interval; MWL, maximum weight loss; NDI, neurodevelopmental impairment; RR, risk ratio

shown a strong correlation between the KSPD and Bayley III [13], validating our methodological choice.

Conclusions

Our study identified an association between MWL within the initial 10 days of life and mild NDI at 3 years of age in extremely preterm infants. In contrast, the associations between MWL and moderate to severe NDI were not apparent. Further research is needed to validate the association between MWL and neurodevelopmental outcomes in extremely preterm infants and to explore potential underlying mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05090-6.

Supplementary Material 1: Figure. Restricted cubic spline analysis. Adjusted RRs (solid lines) and 95% CIs (dotted lines) for the associations between MWL and secondary outcomes: (a) mild NDI and (b) developmental impairment defined as an overall DQ score < 85. An MWL below zero indicates infants who had no postnatal weight loss during the first 10 days of life. The analysis revealed that the lowest RR was associated with MWL rates of 10–12%. Abbreviations: CI, confidence interval; MWL, maximum weight loss; NDI, neurodevelopmental impairment; RR, risk ratio.

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Author contributions
K.T. contributed to the study design, data analysis and interpretation, and writing the first draft and revision of the manuscript. N.M. and T.Y. contributed to the study design, data analysis and interpretation, and revision of the manuscript. A.T., M.N., and M.K. contributed to the study design, provided important intellectual content, and revised the manuscript. All the authors mentioned above approved the final manuscript.

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Data availability
The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Okayama Medical Center (RINKEN 2023-080) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study (Institutional Review Board of Okayama Medical Center, RINKEN 2023-080).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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