Research Square

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Faltering growth in surviving preterm infants in Indonesia

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Abstract

Background:

The Cohort of Indonesian PreTerm infants for long-term Outcomes (CIPTO) study is an ongoing prospective cohort study studying preterm infants born at the Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. The usefulness of three indicators to define faltering growth, i.e., decline in weight-for-age, length-for-age and head circumference z-scores ≥ 1.2 were assessed.

Methods:

We recruited 1,227 appropriate for gestational age preterm infants < 37-week gestational age born between 2020–2023 who had survived and discharged from the neonatal unit of the Cipto Mangunkusumo General Hospital. Tested indicators were used to investigate the relationships between comorbidities and faltering growth between relatively healthy (without severe comorbidities) and less-healthy preterm infants. We defined faltering growth as declines in weight-, length-, and head circumference-for-age z-score ≥ 1.2 from birth to discharge.

Results:

The risk of faltering growth increased in lower gestational age infants. Preterm infants were more likely to have faltering growth for weight, length, and head circumference (24.1%, 22.7%, 33.1%) when they had neonatal morbidities than those without (4.3%, 3.3%, 14.2%). Comorbidities associated with faltering growth were late-onset neonatal sepsis and bronchopulmonary dysplasia.

Conclusion:

Preterm infant declines in weight-for-age, length-for-age and head circumference-for-age z-scores ≥ 1.2 were associated with lower gestational age and neonatal morbidities.

Introduction

The advancement of perinatal medicine has supported more surviving infants born prematurely during the past decades.[1] Preterm birth remains a substantial burden in Indonesia, with risk factors including adolescent pregnancy, smoking, eclampsia, bacterial vaginosis, and micronutrient deficiencies.[2] Preterm infants are very susceptible to malnutrition, in which the nutritional deficit can result in faltering growth and subsequently poor neurocognitive development.[3] The phrases “extrauterine growth restriction” and “postnatal growth failure” have been frequently used to identify preterm infants whose weights were below the 10th percentile (z-score < − 1.28) at discharge or around 36–40 weeks’ postmenstrual age,[4]

suggesting that preterm infants should weigh ≥ 10th percentile by approximately term age, irrespective of their birth weight centile, in order to achieve good neurocognitive development.[5] However, those are not approved diagnostic terms as both the Committee on Nutrition of the American Academy of Pediatrics and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition do not recommend that preterm infants' weight percentiles must return to any specific percentiles by discharge or term-equivalent age to ensure good neurocognitive development.[5–7] Furthermore, there is no evidence showing that infants with weights below the 10th ,[8,9] 7th ,[10] even 3rd or 2nd percentiles[8,9,11,12] at 36–40 weeks post-menstrual age have lower cognitive scores than infants with higher weights. Taken together, the diagnosis of extrauterine growth restriction/postnatal growth failure is problematic and a better indicator(s) is required to identify malnourished preterm infants with faltering growth.

There was a recent proposed definition of malnutrition, proposed as a screening tool for faltering growth in preterm infants. The proposed primary indicators in preterm infants included declines in weight-for-age z-score, slow weight gain velocity to maintain growth rate, or duration of consecutive days of protein/energy intake ≤75% of estimated needs.[3] It had been reported that among selected healthy preterm infants with uncomplicated postnatal adaptation transitioned to a growth pattern parallel to the Fenton 2013 growth chart had an average weight-for-age z-score of 0.8 standard deviation (SD) below their birth z-score.[13] The decline in weight-for-age z-score of 0.8–1.2, > 1.2-2.0 and > 2.0 SD were recommended as the cutoffs for mild, moderate and severe faltering growth, in which the cutoffs incorporate the expected weight change among preterm infants.[3] The proposed secondary indicators (requiring 2 or more indicators) included days to regain birthweight, slow linear growth velocity to maintain expected growth rate, or decline in length-for-age z-score.[3] These indicators may be superior to the conventional weight-based 10th percentile cutoff because additional features of faltering growth, such as length growth are considered as well.

We are currently conducting a prospective cohort study (the Cohort of Indonesian PreTerm infants for long-term Outcomes [CIPTO] study) on preterm infants delivered at the Cipto Mangunkusumo General Hospital, Jakarta, Indonesia (an academic medical center with a facility of level III NICU), to ascertain the long-term outcomes of ex-preterm infants and establish an evidence-based framework for preterm care to ensure optimal outcomes.[14] We had reported that the decline in weight-for-age z-score ≥ 1.2 was a better indicator in identifying Indonesian preterm infants with faltering growth than common one-time weight-for-age indicators (i.e., weight-for-age z-score below either − 1.28 [< 10th percentile] or − 1.5 [< 7th percentile] at discharge).[15] Thus, decline in z-score ≥ 1.2 was selected as the cutoff to define faltering growth for all tested indicators in this study. Hereby, we describe the prevalence and associated morbidities with three potential indicators of faltering growth among preterm infants, i.e., decline in weight-for-age z-score ≥ 1.2, decline in length-for-age z-score ≥ 1.2, as well as decline in head circumference-for-age z-score ≥ 1.2. We evaluated its usefulness by comparing the incidence of faltering growth between relatively healthy (without severe comorbidities) and less-healthy preterm infants, including its association with comorbidities.

Methods

Study design

The CIPTO is a prospective cohort study.[14]

Study population

The inclusion criteria were preterm infants < 37-week gestational age appropriate for gestational age born between 2020–2023 who survived and were discharged from the neonatal unit. We excluded small for gestational age and large for gestational age infants as they might have had different growth patterns and have received different nutritional care. The exclusion criteria were multiple congenital anomalies (based on clinical syndrome and/or chromosomal abnormality), unwillingness to participate, or their parents were planning to relocate from Jakarta in the upcoming 2 years. The drop-out criterion was discharge against medical advice. Participating infants were followed from birth until discharge. All patients care at the Cipto Mangunkusumo General Hospital were financially covered by the national health insurance, thus avoiding potential selection bias due to the socioeconomic status.

All infants received standardized neonatal care according to the hospital guidelines, including access to surfactant, parenteral nutrition, antibiotics, intravenous immunoglobulin and imaging studies. The Hospital implemented a nutritional guideline in 2017 to improve nutritional intakes for all infants through parenteral and enteral nutrition (Supplementary Fig. 1). This study as a part of the CIPTO study[14] was approved by Ethical Committee Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo General Hospital, Jakarta (Protocol number 19-03-0228). Parental or legal guardian consents were obtained from all subjects.

Outcomes

In this analysis, we used a decline > 1.2 z-scores for weight, length and/or head circumference as cutoffs for faltering growth. The anthropometric measurements were performed using calibrated tools and the z-scores were calculated according to the Fenton 2013 growth chart for preterm infants[16]. The criteria for hospital discharge were weight > 2,000 grams, no longer needing intravenous access, and parents or guardians were judged capable to provide care at home. Diagnoses of the comorbidities, including early-onset sepsis, late-onset sepsis (confirmed by positive blood or body fluid culture), necrotizing enterocolitis grade II or III according to Bell's criteria, intraventricular hemorrhage grade III-IV, bronchopulmonary dysplasia (any grade) and history of invasive ventilation (comprising conventional and high-frequency oscillation ventilation), were diagnosed by the attending neonatologists based on the current criteria.[17–21] We defined preterm infants as " healthy" if they did not have any of the mentioned comorbidities. Full feeding was defined as days from birth to full enteral feeding (≥ 150 mL/kg). Duration of parenteral feeding was defined as days infants received parenteral nutrition (excluding dextrose-only

infusion). Enteral nutrition, based on our guideline, was mothers' breast milk as the first choice, followed by donor breast milk and formula. The choice of standard or preterm formula milk was according to the Indonesian Pediatric Society guideline: Preterm formula was used for infants below 32 weeks or 1500 gram. We used human milk fortification to increase breast milk's nutrient density from approximately 0.67 kcaL/mL to 0.81 kcaL/mL for all preterm < 32 weeks after breast milk feeding volume reached 100 ml/kg or for infants ≥ 32 weeks that had insufficient weight gain (less than 25–30 g/kg/day).

Statistical analysis

Data analyses were performed using the StataCorp. 2017 (Stata Statistical Software: Release 15 College Station, TX: StataCorp LLC). Statistical difference in categorical variables by the premature categories (late, moderate, very, and extremely),[22] as well as various characteristics of discharged preterm infants in Table 1, were calculated using the chi-square test or Fisher exact test when the data did not meet the assumption for chi-square test. We determined a statistical significance if the p value < 0.05. Bivariate and multivariate analyses were conducted using logistic regression to investigate risk factors of faltering growth. The regression outcome was faltering growth based on decline in weight-for-age, length-for-age, or head circumference-for-age z-score ≥ 1.2, in which various comorbidities were considered as potential risk factors for faltering growth. Possible effect modifiers were analysed in this study by conducting a stratified analysis based on gestational age groups (late, moderate, and very-to-extreme preterm) due to different distributions of preterm-related comorbidities and nutritional approaches (e.g. indication of parenteral nutrition) according to our unit guideline.

Results

A total of 1,227 appropriate for gestational age preterm infants were recruited during the study period (Table 1). The mean gestational age was 33.2 (± 2.4) weeks and the mean birth weight was 2,033 (± 522) grams. Based on the World Health Organization prematurity categories, there were 651 (53.1%), 317 (25.8%), 222 (18.1%) and 37 (3.0%) late, moderate, and very to extremely preterm infants, respectively.[22] The average birth weight, birth length, and birth head circumference z-scores of the subjects were slightly below the growth chart mean (-0.39, -0.80, and – 0.20, respectively) (Table 1). The majority of subjects received either a combination of breast milk and formula (828/1,227; 67.5%) or exclusively breast milk (306/1,227; 24.9%). The rates of each morbidity were higher among the lower gestational age infants. The most and least frequent comorbidities were early-onset sepsis (426/1,227; 34.7%) and bronchopulmonary dysplasia (66/1,227; 5.4%).

Table 1
Characteristics of discharged preterm infants

	Late preterm n = 651	Moderate preterm n = 317	Very preterm n = 222	Extremely preterm n = 37
Infant characteristics				
Female sex, n (%)	296 (45.5)	148 (46.7)	116 (52.3)	17 (45.9)
Birth weight in grams, mean ± SD	2,400 ± 323	1,860 ± 243	1,386 ± 247	947 ± 125
Infant anthropometrics at birth				
Weight in z-score, median (IQR)	-0.50 (-0.88 to 0.00)	-0.30 (-0.74 to 0.20)	-0.10 (-0.50 to 0.35)	0.06 (-0.33 to 0.30)
Length in z-score, median (IQR)	-0.90 (-1.46 to -0.30)	-0.90 (-1.50 to -0.10)	-0.60 (-1.10 to 0.17)	-0.43 (-1.00 to 0.00)
Head circumference in z-score, median (IQR)	-0.20 (-0.70 to 0.30)	-0.20 (-0.90 to 0.50)	0.00 (-0.69 to 0.60)	-0.10 (-0.40 to 0.70)
Postmenstrual age at discharge in weeks, mean ± SD	36.0 ± 1.5	35.4 ± 1.7	35.6 ± 2.1	36.9 ± 3.2
Infant anthropometrics at discharge				
Weight in grams, median (IQR)	2,430 (2,010 to 2,389)	2,165 (2,010 to 2,389)	2,235 (2,090 to 2,445)	2,245 (2,040 to 2,450)
Weight z-scores, median (IQR)	-0.70 (-1.20 to -0.20)	-0.90 (-1.50 to -0.40)	-0.80 (-1.40 to -0.40)	-1.10 (-2.20 to -0.60)
Length in cm, median (IQR)	45 (44 to 46)	44 (43 to 45)	44 (42 to 45)	44 (42 to 44)
Length z-scores, median (IQR)	-0.80 (-1.50 to -0.30)	-1.00 (-1.70 to -0.20)	-1.30 (-2.00 to -0.40)	-2.00 (-2.90 to -0.80)
Head circumference in cm, median (IQR)	33 (32 to 33)	31 (30 to 32.5)	30 (28 to 32)	31 (25 to 32)

	Late preterm n = 651	Moderate preterm n = 317	Very preterm n = 222	Extremely preterm n = 37
Infant characteristics				
Head circumference z-scores, median (IQR)	0.00 (-0.70 to 0.70)	-0.70 (-1.70 to -0.10)	-1.10 (-2.70 to -0.20)	-2.20 (-5.60 to -0.40)
Feeding characteristics				
Days to reach full feed, median (IQR)	8 (5 to 9)	11 (5 to 15)	18 (9 to 24)	22 (19 to 37)
Days on parenteral nutrition, median (IQR)	1 (0 to 2)	3 (0 to 7)	8 (4 to 14)	11 (7 to 20)
Type of milk received				
Breast milk only, n (%)	165 (25.3)	83 (26.2)	50 (22.5)	8 (21.6)
Breast milk and formula, n (%)	416 (63.9)	218 (68.8)	166 (74.8)	28 (75.7)
Formula only, n (%)	70 (10.8)	16 (5.0)	6 (2.7)	1 (2.7)
Morbidities				
Early-onset sepsis, n (%)	145 (22.3)	119 (37.5)	137 (61.7)	25 (67.6)
Late-onset sepsis, n (%)	36 (5.5)	54 (17.0)	90 (40.5)	19 (51.4)
Necrotizing enterocolitis, n (%)	14 (2.2)	18 (5.7)	35 (15.8)	14 (37.8)
History of invasive ventilation, n (%)	21 (3.2)	27 (8.5)	63 (28.4)	20 (54.1)
Bronchopulmonary dysplasia, n (%)	0 (0.0)	11 (3.5)	33 (14.9)	22 (59.5)
Intraventricular hemorrhage grade III-IV, n (%)	13 (2.0)	28 (8.8)	36 (16.2)	15 (40.5)
Any morbidity	159 (24.4)	132 (41.6)	167 (75.2)	32 (86.5)

Table 2 shows the subsequent stratification based on the tested indicators of growth faltering, i.e., decline of > 1.2 weight-for-age, length-for-age and head circumference-for-age z-scores by category of preterm birth. As expected, faltering growth based on weight and length was least prevalent among late and moderately preterm and more frequent among the extremely preterm. Compared to the late and

moderate preterm groups, more infants had faltering head growth in the very (50.9%, 113/222) to extremely (59.5%, 22/37) preterm groups ($p < 0.001$).

Table 2
Incidence of faltering growth among preterm infants who were appropriate for gestational age

Preterm category	Decline in weight-for-age z-score		Decline in length-for-age z-score		Decline in head circumference-for-age z-score	
	< 1.2	≥ 1.2	< 1.2	≥ 1.2	< 1.2	≥ 1.2
Late (n = 651)	614 (94.3)	37 (5.7)	630 (96.8)	21 (3.2)	613 (94.2)	38 (5.9)
Moderate (n = 317)	275 (86.7)	42 (13.2)	290 (91.5)	27 (8.5)	223 (70.3)	89 (29.6)
Very (n = 222)	167 (75.3)	55 (24.8)	158 (71.2)	64 (28.9)	109 (49.1)	113 (50.9)
Extremely (n = 37)	21 (56.7)	16 (53.2)	14 (37.8)	23 (62.1)	15 (40.5)	22 (59.5)
Data reported as n (%)						

Stratified based on their health status, the majority of the late preterm infants were in the healthy group (75.6, 492/651), whereas more than three-quarters of very and extreme preterm were in the with morbidity group (76.8, 199/259) (Table 3). Also, a close association between medical complications of prematurity and faltering growth was observed in the with morbidity group, as there were more infants with faltering growth in the with morbidity groups, across all categories of preterm. In addition, more with morbidity preterm infants had faltering growth in the categories of very and extremely preterm, absolutely than the categories of late and moderately preterm ($p < 0.001$).

Similar relationships were noted between the healthy and with morbidity preterm infants and the declines in length-for-age z-score (Table 3). Proportionally, both healthy and with morbidity subjects had more infants with faltering growth in the categories of very and extremely preterm. Similarly, the decline in head circumference-for-age z-score identified more subjects with faltering growth in the categories of very and extremely preterm, both in healthy and with morbidity groups (Table 3).

Table 3
Incidence of faltering growth between healthy versus with morbidity preterm infants based on declines in weight, length, and head circumference-for-age z-scores

Preterm category	Healthy (n = 737)		With morbidity (n = 490)	
	< 1.2	≥ 1.2	< 1.2	≥ 1.2
Declines in weight-for-age z-scores				
Late (n = 651)	482 (98.0)	10 (2.0)	132 (83.1)	27 (16.9)
Moderate (n = 317)	170 (92.9)	15 (8.1)	105 (79.6)	27 (20.5)
Very (n = 222)	49 (89.1)	6 (10.9)	118 (70.7)	49 (29.4)
Extremely (n = 37)	4 (60.0)	1 (20.0)	17 (53.1)	15 (46.9)
Declines in length-for-age z-scores				
Late (n = 651)	487 (99.0)	5 (1.0)	143 (89.9)	16 (10.1)
Moderate (n = 317)	177 (95.7)	8 (4.3)	113 (85.6)	19 (14.4)
Very (n = 222)	48 (87.2)	7 (12.7)	110 (65.9)	57 (34.2)
Extremely (n = 37)	1 (20.0)	4 (80.0)	13 (40.6)	19 (59.4)
Declines in head circumference-for-age z-scores				
Late (n = 651)	478 (97.2)	**14 (2.8)**	135 (84.9)	24 (15.1)
Moderate (n = 317)	127 (68.6)	58 (31.4)	96 (72.7)	36 (27.3)
Very (n = 222)	25 (45.5)	30 (54.5)	84 (50.3)	83 (49.7)
Extremely (n = 37)	2 (40.0)	3 (60.0)	13 (40.7)	19 (59.4)
Data reported as n (%)				

Healthy, infants without severe comorbidities (early-onset sepsis, late-onset sepsis, necrotizing enterocolitis, intraventricular hemorrhage, bronchopulmonary dysplasia and history of invasive ventilation (comprising conventional and high-frequency oscillation ventilation); With morbidity, infants with any of the mentioned comorbidities.

The p-value between healthy and with morbidity groups for each preterm category were < 0.001.

Finally, multivariate analyses were conducted to analyze various comorbidities as risk factors of faltering growth, as defined by decline in weight, length and head circumference (Table 4). The decline in weight for-age z-score ≥ 1.2 identified three comorbidities as the risk factors, i.e., early-onset neonatal sepsis, late-onset neonatal sepsis, and bronchopulmonary dysplasia. The decline in length-for-age z-score ≥ 1.2 and the decline in head circumference-for-age z-score ≥ 1.2 identified four comorbidities as the risk

factors, i.e., late-onset neonatal sepsis, necrotizing enterocolitis, history of invasive ventilation and bronchopulmonary dysplasia. In sum, two comorbidities were identified as the common risk factor of faltering growth among preterm infants across all tested indicators, i.e., late-onset neonatal sepsis and bronchopulmonary dysplasia.

Table 4
Multivariate analysis of various comorbidities as risk factors for faltering growth (z-score ≥ 1.2) among late preterm infants

Risk Factor	Decline in weight-for-age z-score ≥ 1.2		Decline in length-for-age z-score ≥ 1.2		Decline in head circumference-for-age z-score ≥ 1.2	
	RR	95% CI	RR	95% CI	RR	95% CI
Late preterm (n = 651)						
Early-onset neonatal sepsis	4.06	1.95–8.48	1.09	0.31–3.79	1.16	0.48–2.81
Late-onset neonatal sepsis	4.05	1.87–8.75	41.34	10.45-163.58	12.29	4.79–31.56
Necrotizing enterocolitis	1.56	0.64–3.83	1.59	0.59–4.32	1.54	0.62–3.83
History of invasive ventilation	2.15	0.97–4.78	1.37	0.41–4.51	1.74	0.66–4.63
Bronchopulmonary dysplasia	-	-	-	-	-	-
Intraventricular hemorrhage	0.49	0.11–2.17	0.88	0.19–4.21	0.61	0.14–2.77
Moderate preterm (n = 317)						
Early-onset neonatal sepsis	1.32	0.62–2.78	0.61	0.22–1.71	0.53	0.30–0.92
Late-onset neonatal sepsis	3.64	1.62–8.19	5.83	1.91–17.86	2.04	1.03–4.08
Necrotizing enterocolitis	2.01	0.84–4.81	1.02	0.33–3.16	1.68	0.67–4.22
History of invasive ventilation	0.76	0.31–1.91	2.17	0.77–6.09	1.55	0.69–3.46
Bronchopulmonary dysplasia	1.85	0.66–5.18	2.01	0.66–6.16	1.24	0.44–3.47
Intraventricular hemorrhage	0.56	0.20–1.51	0.90	0.34–2.42	1.31	0.67–2.57
Very and extreme preterm (n = 259)						
Early-onset neonatal sepsis	1.37	0.60–3.12	0.83	0.38–1.78	0.83	0.52–1.32

Note: adjusted for total duration of parenteral nutrition. BPD among late preterm subgroup was omitted during analysis due to low incidence.

Risk Factor	Decline in weight-for-age z-score ≥ 1.2		Decline in length-for-age z-score ≥ 1.2		Decline in head circumference-for-age z-score ≥ 1.2	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Late preterm (n = 651)						
Late-onset neonatal sepsis	1.56	0.75–3.24	1.79	0.87–3.69	0.69	0.41–1.16
Necrotizing enterocolitis	0.57	0.25–1.28	1.54	0.88–2.69	1.03	0.62–1.72
History of invasive ventilation	1.32	0.74–2.38	1.67	0.97–2.87	1.17	0.74–1.85
Bronchopulmonary dysplasia	2.01	1.09–3.68	1.91	1.09–3.32	1.22	0.73–2.03
Intraventricular hemorrhage	1.57	0.84–2.91	1.12	0.62–2.04	1.04	0.61–1.79
Note: adjusted for total duration of parenteral nutrition. BPD among late preterm subgroup was omitted during analysis due to low incidence.						

RR, relative risk; CI, confidence interval. Bold letters indicate p value < 0.05.

Discussion

Our findings from the CIPTO study could be summarized into three points. First, all tested indicators showed that proportion of faltering growth was associated with preterm categories, i.e., there were more preterm infants with faltering growth in categories of very and extremely preterm. Intriguingly, the decline in head circumference-for-age z-score ≥ 1.2 identified more preterm infants with faltering growth (n = 267), across all categories of prematurity, than by decline in weight-for-age z-score ≥ 1.2 (n = 150) and in length-for-age z-score ≥ 1.2 (n = 135). Taken together, this suggests that the tested indicators of faltering growth would identify more subjects at risk if they belonged to more extreme case of prematurity.[3] Our data showed lower weight, length, or head circumference-for-age z-score at birth among higher gestational age infants (Table 1) as they were delivered mostly due to abnormal fetal growth rather than only maternal risk factors (e.g., intrauterine infection), as seen in previous studies.[23,24] Thus, using declines in weight, length, or head circumference-for-age z-scores to define faltering growth would be more appropriate than one-time indicator.

Second, we observed that there were more preterm infants with faltering growth in the with morbidity group than in healthy group. The only exception was observed for moderate preterm infants as defined by decline in head circumference-for-age z-score ≥ 1.2, in which there were similar proportions of preterm infants with faltering growth in healthy group as compared to in with morbidity group. Taken

together, these findings support an association between comorbidities and risk of malnourished preterm infants to have faltering growth.[3]

Third, certain comorbidities were observed to correlate with faltering growth among preterm infants. Of note, late-onset neonatal sepsis and bronchopulmonary dysplasia were identified as risk factors of faltering growth, as defined by all indicators (weight, length and head circumference) of faltering growth. Sepsis has been associated by others with the occurrence of faltering growth, in which a recent publication also suggested that a deficit in weight gain could occur several weeks after the onset of sepsis.[25] Bronchopulmonary dysplasia with its higher need of energy intake to sustain breathing, hence it was expected that this co-morbidity increased the risk of faltering growth.[26] Interestingly, decline in length-for-age and in head circumference-for-age z-scores ≥ 1.2 identified two other comorbidities that correlated with faltering growth as well, i.e., necrotizing enterocolitis and history of invasive ventilation. Necrotizing enterocolitis need prolonged parenteral nutrition and increased a risk of faltering growth.[18,27,28] A prolonged history of invasive ventilation reflects respiratory morbidity,[20,29] which others have noted was associated with faltering growth.[20,30]

Preterm infants are prone to suffer from nutritional deficits, hence are at higher risk to contract faltering growth, which could be caused by malnutrition or medical complications of prematurity or both.[3,31] Several anthropologic parameters could be used to identify faltering growth among preterm infants, including changes in weight, length, head circumference, body composition, body mass index, mid-upper arm circumference and nutrition-focused physical examination.[3] Among those, weight measurement is the most common indicator as preterm infants with adequate nutrition should gain weight rapidly.[3] However, it is important to keep emphasizing that weight measurement alone might not accurately identify infants who had weight gain disproportionally to their growths in length and head circumference.[32,33] This reinforces encouragement to use various parameters to define preterm infants with faltering growth.

As malnutrition among preterm infants could cause faltering growth, higher nutrient intakes are known to lessen short-term morbidities and to improve long-term outcomes. Pertaining to the energy intake for preterm infants with birthweight < 1,800 grams, the 2022 ESPGHAN Committee on Nutrition consensus-based recommendations stated that a reasonable range of total energy intake for most healthy growing preterm infants is 115–140 kcal/kg/day.[34] Energy intakes can be subsequently increased > 140 kcal/kg/day when the growth is below the recommended range but should not be provided unless protein and other nutrient sufficiency has been ensured.[34] In addition, a protein to energy ratio of 2.8–3.6 g/100 kcal is recommended, when that energy and protein intakes are within the recommended ranges.[34] It is important to note that these recommendations do not consider changes in energy needs related to acute illness or chronic disease states.[34] In addition, we had recently reported that irrespective of the mode of enteral feeding, timely initiation of enteral feeding with adequate calories was the important factor to prevent faltering growth among preterm infants.[15] If exclusive breast milk feeding is not possible or is insufficient for optimal growth and development of preterm infants, the mode of breast

milk plus formula feeding or the nutrient fortification of breast milk would allow those infants to receive the multiple benefits of breast milk as well as of the formula.[7,24,35]

A limitation of our study is that it was a single-center study design with a small number of infants born at 26–27 weeks (i.e., extremely preterm). Nonetheless, our study consisted of relatively high numbers of infants in categories of late, moderate and very preterm. In addition, our cohort did not have preterm infants born below 26 weeks, hence our findings might not be suitable to be extrapolated to extremely preterm infants.

Conclusion

We provided supporting evidence that the decline in weight-for-age, length-for-age and head circumference-for-age z-scores ≥ 1.2 corroborated each result in defining faltering growth among preterm infants. These faltering growth indicators are also associated with preterm-related morbidities and have specific associations in certain preterm category groups. Our findings suggest using those indicators for weight, length and head circumference simultaneously. This practice could provide reassurance for local pediatricians to start using these indicators to identify preterm infants with faltering growth.

Abbreviations

BPD – Bronchopulmonary Dysplasia

CI – Confidence Interval

CIPTO – Cohort of Indonesian PreTerm infants for long-term Outcomes

CMH – Cipto Mangunkusumo Hospital

ESPGHAN – European Society for Paediatric Gastroenterology, Hepatology and Nutrition

IQR – Interquartile Range

IVH – Intraventricular Hemorrhage

NEC – Necrotizing Enterocolitis

NICU – Neonatal Intensive Care Unit

RR – Relative Risk

SD – Standard Deviation

WHO – World Health Organization

Declarations

Conflict of interest

The authors declare no conflict of interests.

Ethics approval and consent to participate

The study was a part of the CIPTO study and had been approved by Ethical Committee Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo General Hospital, Jakarta (Protocol number 19-03-0228). The research was conducted in accordance with the Declaration of Helsinki. Parental or legal guardian consents were obtained from all subjects.

Consent for publication

Not applicable.

Clinical trial number

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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Author contributions

RR and HGH were the primary investigators and contributed equally to this study. RR and HGH coordinated data collection. RR, HGH, and TRF conducted the data analysis. All authors (RR, HGH, TRF, MARS, ATPI, PMTM, RDR, DS, AK, RWB, and NLS) contributed to the interpretation of the findings. HGH

drafted the initial manuscript, and all authors reviewed, revised, and approved the final version of the manuscript.

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