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Nutritional status and neurodevelopmental levels in infants at high risk of cerebral palsy

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ABSTRACT

Importance: Nutrition is associated with neurodevelopment. Infants at high risk of cerebral palsy (CP) usually suffer from undernutrition, yet the relationship between nutritional status and neurodevelopmental levels is unclear.

Objective: To describe the nutritional status characteristics of infants at high risk of CP, and to explore the relationship between neurodevelopmental levels and nutritional status.

Methods: This single-center cross-sectional study enrolled infants at high risk of CP, with corrected age from 0 days to 12 months. Weight and height were measured and calculated into z-scores, which were used to classify the nutritional status based on the World Health Organization growth charts and American Society for Parenteral and Enteral Nutrition standards. The Bayley Scales of Infant and Toddler Development were used to evaluate the developmental levels of gross motor, fine motor, cognition, receptive communication, and expressive communication.

Results: A total of 479 infants at high risk of CP were recruited, with 43.4% classified as undernutrition. Compared to those with normal neurodevelopment, the odds of moderate and severe undernutrition were about 1.8 and 3.9 times higher in gross motor delay, 2.2 and 3.1 times higher in fine motor delay, 2.5 and 9.4 times higher in cognition delay, 2.2 and 3.9 times higher in receptive communication delay, and 3.0 and 5.6 times higher in expressive communication delay. There were significant positive correlations between nutritional status and neurodevelopmental levels ($P < 0.001$).

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Interpretation: Undernutrition and neurodevelopmental delays are prevalent among infants at high risk of CP. Worse nutritional status was correlated with lower neurodevelopmental levels.

KEYWORDS
Cerebral palsy, Infant, High risk, Nutrition, Neurodevelopment

INTRODUCTION

Cerebral palsy (CP) constitutes a major global cause of childhood physical disability, with an incidence of 2‰–3‰, imposing a significant burden on both families and society.[1,2] As Novak et al.[3] have established criteria for the early diagnosis of CP, an increasing number of research endeavors are concentrating on high-risk infants with CP. Motor dysfunction is a significant functional impairment in infants at high risk of CP, who may also suffer cognitive, communication, and swallowing impairments.[4] Evidence indicated that early specific intervention could maximize neuroplasticity as well as improve functional outcomes of infants with high risk of CP.[5] Additionally, a considerable amount of research had demonstrated that nutrition is also a crucial factor influencing early neurodevelopment.[6,7] A good nutritional status is the foundation for the construction of neural networks.

A considerable number of children diagnosed with CP and infants at risk of CP suffer from spasticity, dysphagia, and gastrointestinal dysfunction, which may be the risk factors of undernutrition.[8,9] It was found that undernutrition has negative impacts on brain structural and functional pathology as well as neurodevelopment.[10] Growth failure is regarded to be highly correlated with developmental delay in extremely preterm children.[11] Furthermore, malnutrition was correlated with an increasing risk of comorbidities in neurological impairments.[12,13] The prevalence of malnutrition in children with CP is about 50.8% in China, but few studies reported the nutritional status or correlation between neurodevelopment and nutritional status in infants at high risk of CP.[14] However, the nutritional status characteristics of infants at high risk of CP are still unclear.

Therefore, this study aims to describe the nutritional status and characteristics of infants at high risk of CP and to explore the relationship between neurodevelopmental levels and nutritional status.

METHODS

Ethical approval

This study obtained approval from the Ethics Committee of Guangzhou Women and Children's Medical Center (2022-020B01). Informed consent forms were signed by parents or guardians of all the participants before the recruitment.

Study design and participants

This study was a cross-sectional survey study, which was part of a random control trial (ChiCTR2200057897). Figure 1 shows the flow chart of this study. the participants were recruited from the rehabilitation clinic at the Guangzhou Women and Children's Medical Center. With corrected ages ranging from 0 to 12 months, infants diagnosed as high risk of CP following the criteria established by Novak et al.,[3] were recruited into this study. According to Novak's criteria, infants at high risk of CP refers to an interim clinical diagnosis used for infants suspected of having CP but not definitively diagnosed. Infants at high risk of CP must have motor dysfunction which was diagnosed by using the Prechtl Qualitative Assessment of General Movements, the Hammersmith Infant Neurological Examination, and the Alberta Infant Motor Scale in this study. The infants must meet at least one of the additional criteria, which includes abnormal neuroimaging and clinical history indicating risk for CP. Infants were excluded if they had other diseases that could affect energy metabolism and growth, or were clinically unstable. In addition, infants who had been diagnosed with CP were also excluded. The subjects were recruited during their initial outpatient visit. After recruitment, nutritional status assessment and neurodevelopmental assessment were conducted by trained research professionals. If the infants were identified as undernourished, they were recommended for nutritional intervention.

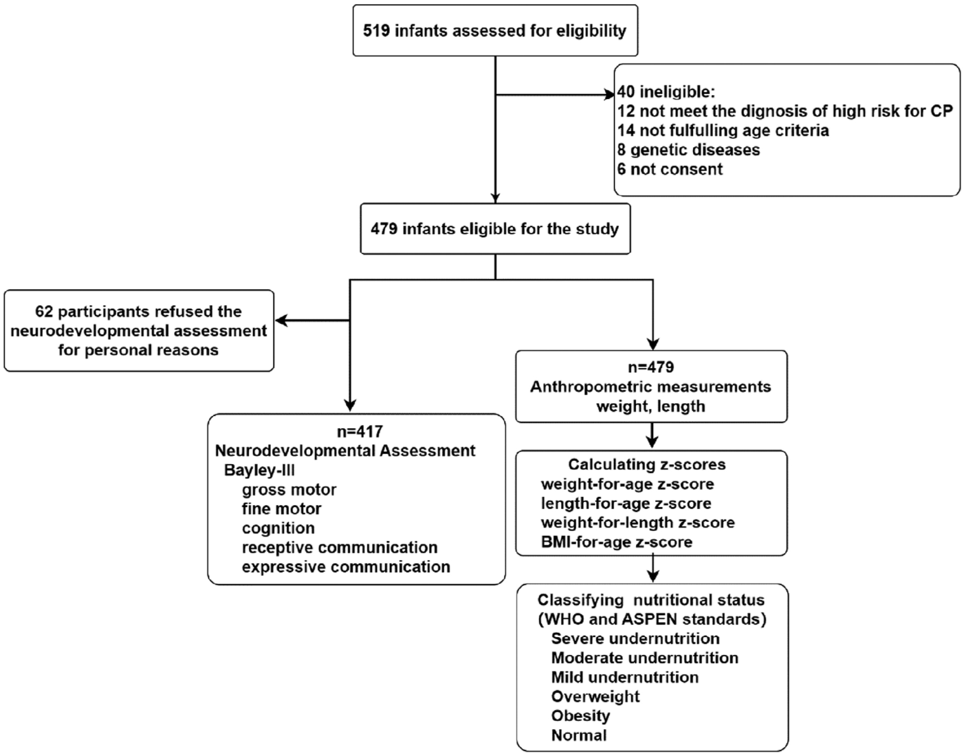

FIGURE 1 Flow chart of the overall research. ASPEN, American Society for Parenteral and Enteral Nutrition; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; CP, cerebral palsy; WHO, World Health Organization.

Data collection

The participant's gender, age in months, corrected age in months, gestational age, and birth weight were collected. Corrected age in months was recorded for participants with a gestational age of less than 37 weeks, and the formula used for calculating was: Corrected age in months = [Chronological age in days − (40 weeks × 7 days/week − Gestational age in days)] / 30. Based on gestational age, we divided the participants into four groups: full-term group (≥37 weeks), moderate to late preterm group (33–36 weeks), very preterm group (29–32 weeks), and extremely preterm group (<29 weeks). According to birth weight, infants were also classified into a low-birth-weight group (<2.5 kg) and normal-birth-weight group (≥2.5 kg). What's more, subjects were divided into the following three categories: small for gestational age (SGA) (birth weight <10th percentile), appropriate for gestational age (AGA) (birth weight between the 10th and 90th percentiles), and large for gestational age (LGA) (birth weight >90th percentile). In conformity with standards proposed by the World Health Organization (WHO) child growth and the American Society for Parenteral and Enteral Nutrition (ASPEN), we categorized the nutritional status of the participants into mild undernutrition, moderate undernutrition, severe undernutrition, normal, overweight, and obesity.[15,16] Two research professionals, who have received standardized training, conducted the neurodevelopmental assessment, using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III).

Anthropometric measurements

Following internationally recognized standard protocols, anthropometric data was collected, encompassing weight and length. Infants' weight was assessed by a digital weight scale, with an accurate measurement value of 0.1 kg.[17] Infants' length was assessed by an anthropometer, with an accurate measurement value of 0.1 cm. All participants were requested to remove heavy clothing and shoes before the measurements.

Classification of nutritional status

The nutritional status of each participant was determined with z-score, including weight-for-age z-score (WAZ), length-for-age z-score (LAZ), weight-for-length z-score (WLZ), and BMI-for-age z-score (BAZ). These scores were calculated by the WHO Anthro software for children under the age of 5 years (version 3.2.2). In this study, nutritional status was categorized as follows: mild undernutrition (–2 < WHZ/BAZ ≤ –1), moderate undernutrition (–3 < WAZ/LAZ/WLZ/BAZ ≤ –2), severe undernutrition (WAZ/LAZ/WLZ/BAZ ≤ –3), overweight (WLZ/BAZ > 2), obesity (WLZ/BAZ > 3), and normal, based on the WHO growth charts and ASPEN standards.[15,16]

Neurodevelopmental assessment

The Bayley-III is a standardized assessment tool for children aged 16 days to 42 months, evaluating the development of motor, cognition and language, adaptive behavior, and social-emotional development. In Bayley-III, motor development is divided into gross motor skills and fine motor skills, while language development is divided into receptive communication and expressive communication. The Bayley-III has been confirmed to possess good reliability and validity.[18] In our study, we collected and analyzed scores for gross motor, fine motor, cognition, receptive communication, and expressive communication. According to the standard scores, we categorized the neurodevelopmental levels of the subjects into three levels, including severe delay (1–3 scores), mild delay (4–6 scores), and typical development (7 scores or higher). In order to investigate the potential impact of varied nutritional statuses on neurodevelopment, we combined severe and mild delays into one group for comparative analysis.

Statistical analysis

Continuous variables were presented as mean (standard deviation, SD), while categorical variables were expressed as numbers and percentages. Ordinal data were analyzed by using the χ^2 test or Fisher's exact test. The statistical differences between the categories of neurodevelopmental levels and nutritional status were assessed by odds ratios with a 95% confidence interval calculated using the Mantel-Haenszel test. The associations between nutritional status and neurodevelopmental levels, corrected age in months, gestational age as well as birth weight by Spearman correlation. Significance was defined at a P-value < 0.05, and the statistical analyses were executed using SPSS software (IBM SPSS Statistics for Windows, version 26.0).

RESULT

Participants' characteristics

A total of 479 infants at high risk of CP (303 males and 176 females) were enrolled from April 2022–2023, all participants got a nutritional assessment while 417 participants received a neurodevelopmental assessment. The corrected ages of subjects ranged from 0 days to 12 months while ages ranged from 12 days to 14.9 months. Over half of the participants were under the corrected age of 6 months. The mean corrected age of these infants was 5.2 months.

TABLE 1 Demographic and clinical characteristics of participants (n = 479)

Characteristics	*n* (%)
Sex	
Female	176 (36.7)
Male	303 (63.3)
Gestational age	
<37 weeks	250 (52.2)
33–36 weeks	120 (25.1)
29–32 weeks	80 (16.7)
<29 weeks	50 (10.4)
≥37 weeks	229 (47.8)
Birth weight	
<2.5 kg	225 (47.0)
≥2.5 kg	254 (53.0)
Age group	
<6 m	316 (66.0)
≥6 m	163 (34.0)
Birth weight and gestational age	
SGA	108 (22.5)
AGA	317 (66.2)
LGA	54 (11.3)

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

Among the participants, over half of them were born prematurely (gestational age <37 weeks), while fewer than half had a low birth weight (<2.5 kg). More than half of infants were appropriate for gestational age. Table 1 presents the demographic and clinical characteristics of the participants.

Nutritional status and neurodevelopment levels

In general, infants at high risk of CP exhibited an increased prevalence of undernutrition, with 208 (43.4%) subjects classified as undernourished and only six (1.3%) as overnourished. The most prevalent neurodevelopmental delay occurred in gross motor (50.6%), followed by receptive communication (47.0%), cognitive function (46.0%), fine motor (38.1%), and expressive communication (23.7%).

The prevalence of undernutrition progressively increased with the developmental levels of gross motor skills (Figure 2). From the group of typical development to the group of mild delay and severe delay in gross motor skills, the prevalence of undernutrition is respectively 35.4%, 40.5%, and 60.0%. Similarly, this trend of prevalence was also found in other domains. In infants at high risk of CP,

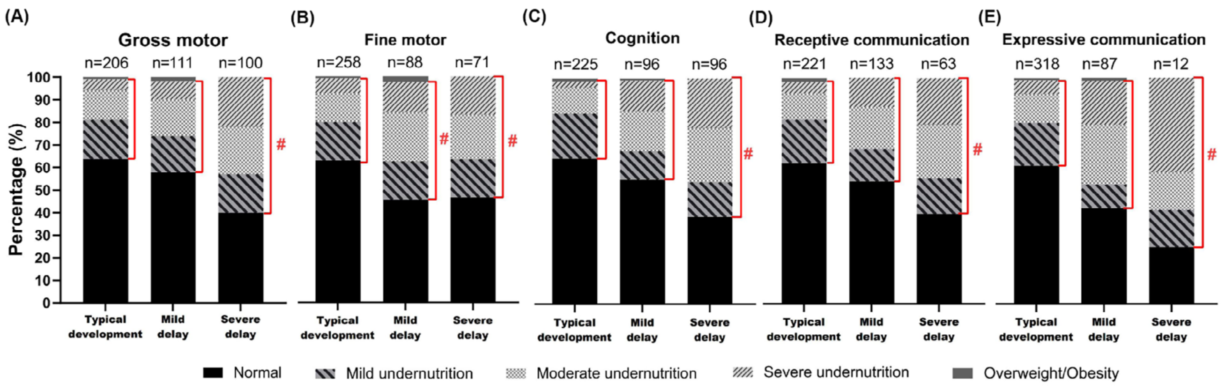

FIGURE 2 The prevalence of each nutritional status in different levels of (A) Gross motor, (B) Fine motor, (C) Cognition, (D) Receptive communication, and (E) Expressive communication. The red line indicates the undernutrition proportion. $^{\#}P < 0.05$ compared with the typical development level in each domain.

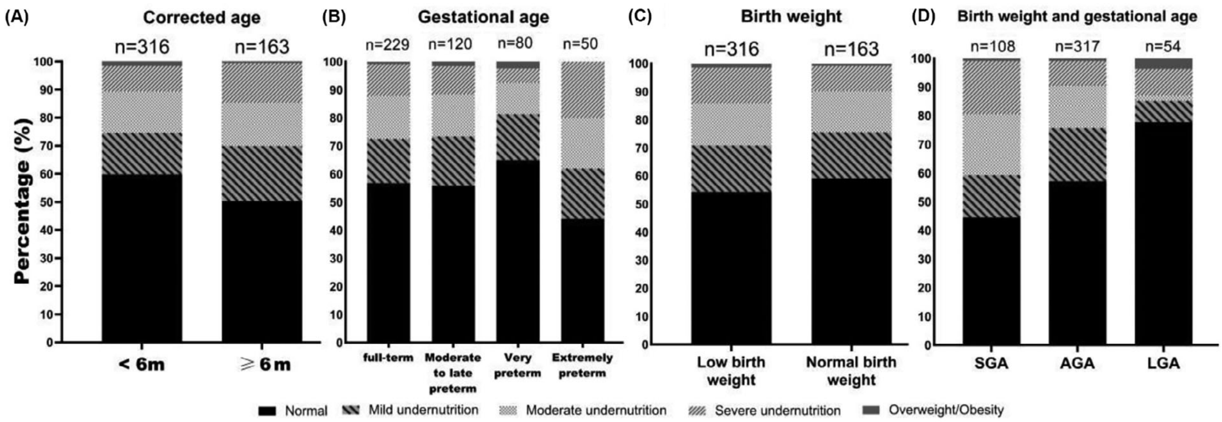

FIGURE 3 Bar charts showing the prevalence of each nutritional status in different groups in (A) Corrected age, (B) Gestational age, (C) Birth weight, and (D) Birth weight and gestational age. SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

undernutrition rates vary by development level. For fine motor skills, the prevalence is 36.4% in typical development, 52.3% in mild delay, and 53.5% in severe delay. In cognition, the rates are 34.2% for typical, 43.8% for mild delay, and 61.5% for severe delay. Regarding receptive communication, it's 35.8% in typical, 45.9% in mild, and 60.3% in severe. For expressive communication, these figures are 37.7% in typical development, 56.3% in mild delay, and 75.0% in severe delay. Figure 3 shows the nutritional status in different groups on corrected age, gestational age, and birth weight. According to the corrected age, infants were classified into two groups 0–6 months and 6–12 months. The rate of undernutrition in a group of 6–12 months (40.1%) was slightly higher than that in a group of 0–6 months (38.6%), but the difference was not significant ($P > 0.05$). The rates of undernutrition were 56.0%, 32.5%, 42.5%, and 42.4% in the extremely preterm group, very preterm group, moderate to late preterm group, and full-term group separately, with no significant difference ($P > 0.05$). The prevalence of undernutrition in the low-birth-weight group (44.1%) was slightly higher than in the normal-birth-weight group (40.0%), while the disparity did not reach statistical significance.

Odds of undernutrition in different groups of birth weight and gestational age and neurodevelopmental levels

Compared to the AGA group, infants at high risk of CP in the SGA group had a 1.7 times higher probability of malnutrition, while the probability of malnutrition was lower in the LGA group (Table 2).

The rate of undernutrition in infants at high risk of CP with neurodevelopmental delay was much higher than in those with typical development (Table 3). The probability of encountering moderate and severe undernutrition was elevated among infants with neurodevelopmental delay in contrast to those with typical development, and this distinction was more pronounced in the case of severe undernutrition than moderate undernutrition.

TABLE 2 Odds ratio of malnutrition in infants at high risk of cerebral palsy among groups of birth weight and gestational age

Birth weight and gestational age	Normal nutrition, *n* (%)	Malnutrition, *n* (%)	OR (95% CI)	*P*
AGA	181(57.1)	136 (42.9)	Reference	–
SGA	48 (44.4)	60 (55.6)	1.7 (1.1–2.6)	0.023
LGA	42 (77.8)	12 (22.2)	0.4 (0.2–0.8)	0.004

Abbreviations: AGA, appropriate for gestational age; CI, confidence interval; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.

TABLE 3 Odds ratio of malnutrition in infants at high risk of cerebral palsy between the typical development group and the neurodevelopmental delay group

Nutritional status	Gross motor				Fine motor			
	Typical development, *n* (%)	Delay, *n* (%)	OR (95% CI)	*P*	Typical development, *n* (%)	Delay, *n* (%)	OR (95% CI)	*P*
Normal	131 (63.6)	104 (49.3)	Reference	–	162 (62.8)	73 (45.9)	Reference	–
Mild under-nutrition	36 (17.5)	35 (16.6)	1.2 (0.7–2.1)	0.455	44 (17.0)	27 (17.0)	1.4 (0.8–2.4)	0.273
Moderate undernutri-tion	27 (13.1)	39 (18.5)	1.8 (1.1–3.2)	0.033	33 (12.8)	33 (20.7)	2.2 (1.3–3.9)	0.004
Severe under-nutrition	10 (4.8)	31 (14.7)	3.9 (1.8–8.3)	<0.001	17 (6.6)	24 (15.1)	3.1 (1.6–6.2)	0.001
Overweight /Obesity	2 (1.0)	2 (0.9)	1.3 (0.2–9.1)	0.819	2 (0.8)	2 (1.3)	2.2 (0.3–16.1)	0.418

Nutritional status	Cognition				Receptive communication			
	Typical development, *n* (%)	Delay, *n* (%)	OR (95% CI)	*P*	Typical development, *n* (%)	Delay, *n* (%)	OR (95% CI)	*P*
Normal	145 (64.4)	90 (46.9)	Reference	–	138 (62.4)	97 (49.5)	Reference	–
Mild under-nutrition	45 (20.0)	26 (13.6)	0.9 (0.5–1.6)	0.798	42 (19.0)	29 (14.8)	1.0 (0.6–1.7)	0.948
Moderate undernutri-tion	26 (11.6)	40 (20.8)	2.5 (1.4–4.3)	0.001	26 (11.8)	40 (20.4)	2.2 (1.3–3.8)	0.005
Severe under-nutrition	6 (2.7)	35 (18.2)	9.4 (3.8–23.2)	<0.001	11 (5.0)	0 (15.3)	3.9 (1.9–8.1)	<0.001
Overweight /Obesity	3 (1.3)	1 (0.5)	0.5 (0.1–5.2)	0.587	4 (1.8)	0	0.4 (0.0–3.2)	0.096

Nutritional status	Expressive communication			
	Typical development, *n* (%)	Delay, *n* (%)	OR (95% CI)	*P*
Normal	195 (61.3)	40 (40.4)	Reference	–
Mild undernutrition	60 (18.9)	11 (11.1)	0.9 (0.4–1.9)	0.762
Moderate undernutrition	41 (12.9)	25 (25.3)	3.0 (1.6–5.4)	<0.001
Severe undernutrition	19 (6.0)	22 (22.2)	5.6 (2.8–11.4)	<0.001
Overweight/Obesity	3 (0.9)	1 (1.0)	1.6 (0.2–16.0)	0.675

Notes: Mantel-Haenszel test was used.
Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 4 Spearman correlation between nutritional status and neurodevelopmental levels, corrected age, gestational age, and birth weight

Items	Nutritional status	Gross motor	Fine motor	Cognition	Receptive communication	Expressive communication
Nutritional status	–	–	–	–	–	–
Gross motor	0.221***	–	–	–	–	–
Fine motor	0.186***	0.653***	–	–	–	–
Cognition	0.276***	0.565***	0.683***	–	–	–
Receptive communication	0.209***	0.465***	0.543***	0.595***	–	–
Expressive communication	0.247***	0.493***	0.483***	0.496***	0.547***	–
Corrected age	−0.155*	−0.434***	−0.289***	−0.083	0.003	−0.202***
Gestational age	0.004	−0.137**	−0.158**	−0.143**	−0.153**	−0.121*
Birth weight	0.146**	−0.098*	−0.108*	−0.089	−0.093	−0.093

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Correlation among nutritional status and neurodevelopmental levels, corrected age, gestational age, and birth weight

Nutritional status was significantly positively correlated with neurodevelopmental levels ($P < 0.001$). In addition, there was a negative association between age and worse nutritional status ($P < 0.05$). Worse nutritional status was correlated with lower birth weight ($P < 0.05$). However, nutritional status and gestational age did not show a correlated relationship ($P > 0.05$) (Table 4).

DISCUSSION

To our knowledge, this is the first study to systematically investigate the nutritional status of infants at high risk of CP. We found that the prevalence of undernutrition in these infants was pretty high. In addition, the nutritional status was positively associated with neurodevelopmental levels, which may help to guide clinical management.

In this study, the prevalence of undernutrition in infants at high risk of CP was 43.4%, which was lower than the prevalence in children with CP over 1 year old (50.8%).[14,19] Since CP is a chronic condition, the prevalence of undernutrition may come along with other dysfunctions as the child's age increases. Muscle spasticity, one of the main symptoms of CP, leads to sustained and slow increases in energy expenditure.[20,21] In addition, infants at high risk of CP might often suffer from swallowing disorders and gastrointestinal dysfunction, which could lead to insufficient intake of nutrients.[22] The continued accumulation of the above conditions leads to a gradual increase in the incidence of undernutrition with age. Moreover, this study showed that the prevalence of overnutrition in infants at high risk of CP (1.3%) was lower than that in children with CP over 1 year old (5.4%). This might be attributed to restricted mobility, low energy expenditure, and overfeeding in certain participants, particularly those who are unable to walk with normal swallowing function.[23] Hence, taking the nutritional status into account is essential for the health care of infants at high risk of CP.

The results of this study suggested that neurodevelopmental outcomes were associated with growth attainment. The current study also revealed that participants in moderate and severe undernutrition were more likely to have neurodevelopmental delay, compared with those in normal nutritional status. This is consistent with previous research findings on the relationship between nutrition and neurodevelopment.[24] The possible reason is that undernutrition leads to a lack of energy and essential substances required for the formation of the brain's neural structure and functional network composition.[25] Dabydeen et al.[26] found that providing 20% more protein and calories than the standard recommended amount in the early stage could promote the growth of the brain and corticospinal tracts in infants after perinatal brain injury. It was reported that nutritional intervention with high-calorie formula may be effective for improving gross motor dysfunction in children with CP from 1 year old to 10 years old.[27] Therefore, improving the nutritional status of infants at high risk of CP is important for their neurodevelopment, especially in the cases of undernutrition.

Gestational age seemed to have no association with nutritional status in this study, but the incidence of malnutrition is related to the categories of birth weight and gestational age. This contradicts the previous understanding that higher degrees of prematurity in infants were associated with more severe neurological impairment and poorer subsequent nutritional status.[28–30] We attributed this to the likelihood that it was associated with the majority of premature infants had received standardized care in the neonatal department or neonatal intensive care unit. Doctors and nurses conduct early nutritional monitoring and management for premature infants to facilitate their subsequent catch-up growth and development, especially during the first 1000 days of life. It also may be caused by the unequal participants' allocation in different degrees of prematurity which is led by cross-sectional design. The results of this study also suggested that the efforts of medical personnel had been very successful. Additionally, this may be also related to the changes in fat metabolism patterns in SGA and LGA compared to AGA.[31]

This study has some limitations: (i) the study did not gather or assess the severity of swallowing disorders or feeding difficulties; (ii) we couldn't conduct further analysis according to the level of CP risk due to the absence of standardized criteria; (iii) the low proportion in the group of over 6 months corrected age may not be representative; (iv) this study did not analyze the results of cranial imaging because some subjects underwent cranial ultrasound, some underwent cranial magnetic resonance imaging, and a small fraction did not undergo any examination; (v) this study did not analyze the confounding factors contributing to malnutrition and delayed neurodevelopment. Nevertheless, we conducted an initial analysis of the nutritional status and neurodevelopmental levels in infants at high risk of CP and their relationship. This may provide guidance for future research and clinical management related to the nutrition and neurodevelopmental outcomes of infants at high risk of CP.

In conclusion, undernutrition and neurodevelopmental delay are common in infants at high risk of CP, and worse nutritional status was correlated with severe neurodevelopmental delay. Moderate and severe undernutrition are much more common among infants at high risk of CP with neurodevelopmental delay. We should attach importance to the undernutrition in these infants and improve their nutritional status for better functional outcomes. Future studies need to analyze other nutritional indicators in this population and explore the impact of nutritional status on the long-term neurodevelopment of infants at high risk of CP.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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